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Distribution of Polybrominated Diphenyl Ethers Among Demographic Categories

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by

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List of Abbreviations and Acronyms

Agency for Toxic Substances and Disease Registry	ATSDR
Analysis of Variance	ANOVA
Aryl Hydrocarbon Receptor	AhR
Attention Deficit Hyperactivity Disorder	ADHD
Body Mass Index	BMI
Centers for Disease Control and Prevention	CDC
Center for the Health Assessment of Mothers and Children of Salinas	CHAMACOS
Centimeter	cm
Cytochrome P-450	CYP
Decabromo Diphenyl Ether	decaBDE
Dioxin-like Polychlorinated Biphenyl	dl-PCB
Environmental Protection Agency	EPA
Food & Drug Administration	FDA
Gas Chromatography	GC
Health Outcomes and Measures of the Environment Study	HOME
High Res. Gas Chromatography/Isotope-Dilution High-Res. Mass Spec.	HRGC/ID-HRMS
High Perf. Liq. Chromatography-Electro. Ionization Tandem Mass Spec.	HPLC-ESI-MS/MS
Integrated Risk Information System	IRIS
International Agency for Research on Cancer	IARC
Isotope Dilution Gas Chromatography High-Resolution Mass Spectrometry	GC/IDHRMS

Kilogram	kg
Limit of Detection	LOD
Low Density Lipoprotein	LDL
Methoxylated Polybrominated Diphenyl Ether	MeO-PBDE
Microliter	µL
Milligram per Kilogram per Day	mg/kg/day
Minimal Risk Level	MRL
Mobile Examination Center	MEC
Monobrominated Diphenyl Ether	monoBDE
Monobenzyl Phthalate	mBzP
Monobutyl Phthalate	mBP
Monocyclohexyl Phthalate	mCHP
Mono (3-carboxypropyl) Phthalate	mCPP
Mono (2-ethyl-5-carboxypentyl) Phthalate	mECPP
Mono (2-ethyl-5-hydroxyhexyl) Phthalate	mEHHP
Mono (2-ethylhexyl) Phthalate	mEHP
Mono (2-ethyl-5-oxohexyl) Phthalate	mEOHP
Monoethyl Phthalate	mEP
Mono-isobutyl Phthalate	miBP
Monomethyl Phthalate	mMP
Monoisononyl Phthalate	mNP
Monooctyl Phthalate	mOP
National Center for Health Statistics	NCHS

National Health and Nutritional Examination Survey	NHANES
National Institute for Occupational Safety and Health	NIOSH
Nanogram per Gram Lipid	ng/g lipid
Nanogram per Milliliter	ng/mL
NHANES Laboratory/Medical Technologists Procedures Manual	LPM
Nonabrobimated Diphenyl Ether	nonaBDE
Occupational Safety and Health Administration	OSHA
Octabromo Diphenyl Ether	octaBDE
Odds Ratio	OR
Part per Billion	PPB
Pentabromo Diphenyl ether	pentaBDE
Polybrominatted Diphenyl Ether	PBDE
Polychlorinated Biphenyl	PCB
Reference Concentration	RfC
Reference Dose	RfD
Selected Ion Monitoring	SIM
Statistical Analysis System	SAS
United States	US

Abstract

Polybrominated Diphenyl Ethers (PBDEs) are flame retardants widely used within the United States in various products such as plastics, electronics, textiles and furniture. With an increase in production and usage, PBDEs have recently emerged as a contaminant of concern. Due to their chemical structure, PBDEs have the propensity to bioaccumulate in mammals. In fact, elevated PBDE concentrations have been recorded in human breast milk. Due to the potential widespread exposure to PBDEs, this study investigates human blood concentrations of PBDEs generated through the 2003-2004 National Health and Nutrition Examination Survey. Through the use of statistical modeling, a comparison of mean PBDE concentrations in ng/g lipid is conducted based on age, gender and ethnicity. From a sample of 2337 individuals, the average blood concentration of PBDEs was approximately 81 ng/g lipid. The average PBDE concentration of males was significantly higher than females, using a 95% confidence level. In addition, PBDEs detected in human blood ranged approximately from 0.05 to 3676 ng/g lipid, with the highest concentrations found in black males. Also, a logistic regression analysis is conducted to determine whether an increase in background PBDE concentrations is a risk factor for obesity. Furthermore, the analyses of PBDEs are repeated for phthalates and polychlorinated Biphenyls for comparison. Finally, the measured concentrations of PBDEs are also compared to health outcome data known to show potential risk.

Chapter 1

Introduction

1.1 Flame Retardants

In 2009, the National Fire Protection Association reported an estimated 1,348,500 fires in the United States. These fires were responsible for approximately 17,050 civilian injuries, 3,010 civilian deaths and over $12 billion in property damage. Many of the casualties included children and the disabled. Unfortunately, the various threats of fires have always been a concern throughout history (American Chemistry Council, 2017). As a result, fire protection is a very important aspect of emergency planning. There are various methods of fire response and prevention. Within the United States, many entities share a responsibility to protect citizens from fire hazards. A city fire department is a popular example. However, a lesser-known yet very impactful entity includes the chemical industry. For many decades, the chemical industry has been responsible for generating compounds combat the progression of fire. These chemicals are called flame retardants (United States Environmental Protection Agency [USEPA], 2014).

The term "flame retardant" does not refer to a group of chemicals but, instead, refers to a function. Some chemicals with varying structures and properties can function as flame retardants and are sometimes combined for greater effect (American Chemistry Council, 2017; ATSDR, 2017; USEPA, 2014). Flame retardants are usually described as inorganic, halogenated compounds often containing bromine, chlorine, phosphorus or nitrogen. By lacing various consumer goods with flame retardants, the progression of fire is delayed or prevented. Generally,

ignition is prevented by increasing the threshold necessary to start a fire which delays flashover and reduces the spread of fire (American Chemistry Council, 2017).

Flame retardant use is an innovative way to protect ourselves from injury, death and prevent property damage. It is important to note that over three decades ago, American residents had approximately seventeen minutes to escape a house fire, while today, residents have three to four minutes. This is largely due to the types of materials used to build today's household furniture in comparison to thirty years ago. Then, more natural materials were used while today's furniture contain more synthetic material that are more flammable (Davis, 2016). This further accentuates the need for flame retardants in today's household goods.

The first flame retardants used in the United States were polychlorinated biphenyls (PCBs). However, due to human health concerns, PCB production was banned in 1979. PCBs have been classified as carcinogenic to humans (group 1) by the International Agency for Research on Cancer (IARC) and are known as persistent organic pollutants. As a result, PCBs were replaced as flame retardants by a compound with similar properties known as polybrominated diphenyl ethers (PBDEs) (Vonderheide et al., 2008). After 1979, PBDE compounds were the major group of flame retardants due to their cost effectiveness. In recent years, there has been a growing concern pertaining to the potential environmental and public health risks of background PBDE levels (Alaee et al., 2003; Aylward et al., 2013; Banasik et al., 2009; Birnbaum et al., 2004; Castorina et al., 2011; Turyk et al., 2009; Vasiliu et al., 2006).

1.2 Polybrominated Diphenyl Ethers

Polybrominated diphenyl ethers are flame retardants used in a variety of appliances, fixtures, furniture and other household goods. The use of these chemicals has increased tremendously since the ban of PCBs. Just as PCBs and PBDEs share similar flame retardant properties, they also share similarities in chemical structure. PBDEs are not covalently bonded to the polymer matrix within materials in which they are used. Therefore, these brominated compounds are known to readily leach into the surrounding environment where they have shown resistance to various forms of biodegradation. They have been shown to bioaccumulate in the food chain (Costa & Giordano, 2007; Kiviranta et al., 2004; Turyk et al. 2015; Viberg et al., 2003). Lower brominated congeners tend to be more persistent and bioaccumulate more than higher brominated congeners. BDE congeners differ in the orientation or total number of bromine atoms attached to the ether molecule (ATSDR, 2017).

There are 209 possible congeners. Of these, BDE-47 and BDE-99 make up 75% of the total brominated flame retardants in commercial mixtures. In comparison to BDE-47, there is twice as much BDE-99 in these commercial mixtures. When congeners contain the same number of bromine atoms, they are referred to as homologs. There are ten homologous groups of PBDEs; three of which are produced commercially. These three homologs are: decabromodiphenyl ether (decaBDE), octabromodiphenyl ether (octaBDE) and pentabromodiphenyl ether (pentaBDE). DecaBDE has been the most widely used homolog worldwide (USEPA, 2014).

At the end of 2004, pentaBDE and octaBDE mixtures were voluntarily phased out by their only U.S. manufacturers. According to the Environmental Protection Agency, as of January 2014,

PBDEs are no longer produced nor imported in the United States (ATSDR, 2017). However, levels of PBDEs in breast milk have significantly increased in the United States. In fact, just as usage of PBDEs continued to increase, so did the average concentration of PBDEs in humans. The latter occurs because PBDEs remain ubiquitous in various products, especially in indoor environments. Thus, despite being no longer produced or imported, PBDEs will persist for many years in our environment. In addition, PBDEs will likely be present in human tissue and body fluids at elevated levels for years to come (Darnerud et al., 2001; Frederiksen et al., 2009; Hooper & McDonald, 2000; Schecter et al., 2003).

Due to the relatively elevated levels of PBDEs found in human breast milk, in comparison to other regions such as Europe (*e.g.*, France, Germany, and Russia), there is increasing concern for pregnant mothers and nursing children as they may be more vulnerable to potential health effects of PBDEs, which are known to disrupt the body's endocrine system and thyroid hormone levels (Darnerud et al., 2001). Since they are lipophilic, PBDEs tend to accumulate in human fatty tissues (USEPA, 2014). As a result, it is important to investigate the level of association between their background concentrations and obesity. An investigation of the concentration and distribution of PBDEs in the American population is critical to characterizing levels of risk per demographic category.

1.3 Phthalates & Dioxin-Like Polychlorinated Biphenyls

There are dioxin-like and non-dioxin-like PCBs. Non-dioxin-like PCBs are often referred to as indicator-PCBs and include some mono-ortho-substituted biphenyls. Some PCBs are described as dioxin-like chemicals because they act in the body through similar mechanisms as

dioxins (ATSDR, 2000). As previously mentioned, PBDEs and PCBs (especially dioxin-like PCBs) share key similarities including their flame retardant properties and chemical structures. However, they also share other attributes along with phthalates. While American PBDE production and importation have reportedly ceased, and although PCBs have been banned in the United States, phthalates are still in use (ATSDR, 2000; ATSDR, 2002; ATSDR, 2017). Like PBDEs and dioxin-like PCBs (dl-PCBs), phthalates are ubiquitous in our surroundings. Phthalates are used in detergents, adhesives, lubricating oils, plastic clothing, containers and personal-care products, just to name a few (ATSDR, 2002). All three compounds can be found in household dust. Therefore, we are constantly exposed to these chemicals. In addition, PBDEs, dl-PCBs and phthalates are all known as potential endocrine disrupting compounds and are lipophilic. All three compounds have garnered significant attention concerning their potential human health effects (ATSDR, 2000; ATSDR, 2002; ATSDR, 2017; Aylward et al., 2013). Although this research primarily focuses on characterizing exposure levels and potential human health effects of PBDEs, it is also pertinent to compare results of PBDE analyses with those of PCBs and phthalates. The differences and similarities of these results will be discussed.

1.4 Objectives

This research study investigates the distribution of Polybrominated Diphenyl Ether concentrations in American blood using various demographic attributes through the 2003-2004 National Health and Nutrition Examination Survey (NHANES). The objectives of the current study are comprised of the following:

- Characterize the background concentrations of PBDEs in the blood of 2003-2004 NHANES participants.

- Compare the PBDE blood concentrations between various demographic groups including genders, age groups, ethnicities; and, genders *and* ethnicities (*e.g.*, Black Males vs. Mexican American Females).
- Since PBDEs have a strong affinity for lipids and bioaccumulate in human adipose tissue, investigate their association with obesity.
    - Similarly, the association between PBDE concentrations and being overweight is also investigated.
        - Repeat analyses for other lipophilic compounds including phthalates and dioxin-like PCBs.
        - Discuss results for the aforementioned objectives in relation to those of phthalates and dioxin-like PCBs.

PBDEs are a relatively new compound whose usage significantly increased over time (ATSDR, 2017). Much research remains to be done to fully understand their characteristics, distribution and potential human health effects. Therefore, these findings will provide a significant contribution to the overall body of knowledge for PBDEs.

1.5 Hypotheses

According to the objectives of this study, the following **hypotheses** will be tested:

1. Biomonitoring data obtained from the National Health and Nutrition Examination Survey indicates the presence of background biomarkers of PBDE, dl-PCB, and phthalate exposure in individuals from a sample of the general population.

2. Due to the bioaccumulative properties of PBDEs in the human body, increasing PBDE concentrations are significantly associated with increasing with age groups.
    a. Due to the bioaccumulative properties of dl-PCBs in the human body, increasing dl-PCB concentrations is significantly associated with increasing with age groups.
    b. Due to the bioaccumulative properties of phthalates in the human body, increasing phthalate concentrations is significantly associated with increasing with age groups.
3. Since PBDEs are ubiquitous in the environment, the average concentrations of its biomarkers are homogeneous across other sample subgroups including genders, ethnicities, and, genders *and* ethnicities; indicating that these subgroups are not at an increased risk of a negative health outcome.
    a. Similarly, average dl-PCB concentrations are homogeneous across other sample subgroups including genders, ethnicities, and, genders *and* ethnicities; indicating that these subgroups are not at an increased risk of a negative health outcome.
    b. Similarly, average phthalate concentrations are homogeneous across other sample subgroups including genders, ethnicities, and, genders *and* ethnicities; indicating that these subgroups are not at an increased risk of a negative health outcome.
4. Blood sample data from the National Health and Nutrition Examination Survey reveal that the background concentrations of PBDEs do not significantly increase the odds of obesity nor the odds of being overweight.

a. Blood sample data from the National Health and Nutrition Examination Survey reveal that the background concentrations of dl-PCBs do not significantly increase the odds of obesity nor the odds of being overweight.
b. Blood sample data from the National Health and Nutrition Examination Survey reveal that the background concentrations of phthalates do not significantly increase the odds of obesity nor the odds of being overweight.

5. Due to the similarities of PBDEs and dl-PCBs, average concentrations are not significantly different among demographic categories.
    a. Although distributions of phthalate concentrations can be discussed in relation to PBDEs, specific comparisons cannot be made due to a difference in measurement units (ng/g lipids for PBDEs and dl-PCBs vs. ng/mL for phthalates).

Chapter 2

Literature Review

2.1 Brominated Flame Retardant Use

The use of PBDEs began in the late 1970s. Their commercial production began largely as a response to the ban of PCBs, which were also used as flame retardants. Due to mounting environmental health concerns, PCBs were no longer produced in the United States. As a result, the production and usage of other flame retardants such as PBDEs became more prevalent. In fact, since the ban of PCBs, there has been a significant augmented use of PBDEs (ATSDR, 2017). In 2001, the global production rate of PBDEs was over 67,000 tons per year, as shown in Table 1 (Birnbaum, & Staskal, 2004). By 2003, approximately 98% of the global demand for pentaBDE occurred in North America (Hale et al., 2003). However, largely due to unsubstantiated public health concerns, PBDEs are also no longer in production in the United States. At the end of 2004, the only manufacturers of pentaBDEs and octaBDEs voluntarily phased out their production. As the only remaining PBDE mixture marketed for commercial products, decaBDEs experienced a similar fate. The only American manufacturers of decaBDEs were Albermarle Corporation and Chemtura Corporation; and their largest importer was ICL Industrial Products, Inc. In 2009, all three companies guaranteed a voluntary phase out of PBDE manufacture and importation for nearly all uses in America by December 31st of 2012. They also guaranteed a complete phase out of manufacture and importation for all uses of PBDEs in America by the end of the year 2013 (ATSDR, 2017).

Table 1. Major Brominated Flame Retardant Volume (metric tons) estimates by region in 2001 (Birnbaum & Staskal 2004).

BFR	Americas	Europe	Asia	Rest of world
TBBPA	18,000	11,600	89,400	600
HBCD	2,800	9,500	3,900	500
DBDE	24,500	7,600	23,000	1,050
OBDE	1,500	610	1,500	180
PentaBDE	7,100	150	150	100
Total PBDEs	33,100	8,360	24,650	1,330
Total BFRs by region	53,900	29,460	117,950	2,430

Data from BSEF (2001).

During periods of production, PBDEs were used as flame retardants in a variety of materials including thermos plastics. PBDEs were physically added to these materials instead of being chemically combined. Since PBDEs were not covalently bonded to many of the materials they were used for, these chemicals could easily diffuse out of the materials (Siddiqi et al., 2003). The furniture industry found great use in pentaBDEs as flame retardants (Standen, 2013). In fact, over 95% of pentaBDE commercial mixture usage was in furniture. Specifically, pentaBDEs were predominantly used in flexible polyurethane foams which are found in mattresses, sofas, carpets, etc. The majority of furniture treated with pentaBDEs were sold in California (ATSDR, 2017). It is the only state that required, by law, that upholstered products contain an approved level of ignition resistance (Standen, 2013). Only a small percentage of pentaBDEs were used for other materials like adhesives, printed circuit board components, hydraulic fluids, and rubber products. OctaBDEs were predominantly used as flame retardants in the plastic industry and specifically for acrylonitrile-butadiene-styrene terpolymers, often used in computer monitors and casings. DecaBDE mixtures were used as additive flame retardants for many polymer applications. The primary use of decaBDEs was high impact polystyrene often used as cabinet backs in the television industry (ATSDR, 2017; Watanabe & Sakai 2003).

2.2 Regulations & Guidelines

Although PBDEs are no longer being produced or imported in the U.S., the relatively limited US regulations and guidelines continue to apply since many products currently used still contain PBDEs. The Occupational Safety & Health Administration (OSHA) has not formulated any occupational regulations for these flame retardants. The US Food & Drug Administration (FDA) has not set any allowable bottled water limits for PBDEs. Also, the International Agency for Research on Cancer (IARC) has classified PBDEs as Group 3 toxicants - not classified as human carcinogens (Standen, 2013). The Agency for Toxic Substances and Disease Registry (ATSDR) has generated Minimum Risk Levels (MRLs) for these brominated flame retardants. Based on a no-observed-adverse-effect-level for thyroid hormone effects in rats, an intermediate-duration inhalation MRL of 0.006 mg/m^3 has been generated for lower-brominated congeners. Also, based on a lowest-observed-adverse-effect-level for endocrine effects in female rats, and neurobehavioral and reproductive effects in F1 offspring from several reports, the ATSDR has derived an acute-duration oral MRL of 0.00006 mg/kg/day for lower-brominated congeners (ATSDR, 2017). Moreover, based on a negligible lowest-observed-adverse-effect-level for decreased testosterone in rats, an intermediate-duration oral MRL of 0.000003 mg/kg/day was generated for lower-brominated PBDEs. The ATSDR has also derived an acute-duration oral MRL of 0.01 mg/kg/day for decaBDE due to a no-observed-adverse-effect-level for neurobehavioral health effects found in rats. In addition, based on a negligible lowest-observed-adverse-effect-level for increased serum glucose found in a study of rats, an intermediate-duration oral MRL of 0.0002 mg/kg/day was derived for decaBDE (ATSDR, 2017; Standen, 2013). The Environmental Protection Agency (EPA) has not assigned a reference concentration (RfC) for PBDEs. The EPA

has not generated drinking water standards for PBDEs. Instead, the US EPA has generated reference doses (RfDs) for PBDEs. The following are the current RfDs for BDE congeners. (IRIS, 2003; IRIS, 2004; IRIS, 2008a-d).

- Penta-BDE: $2x10^{-3}$mg/kg/day (IRIS, 2004)
- Octa-BDE: $3x10^{-3}$mg/kg/day (IRIS, 2003)
- Deca-BDE: $7x10^{-3}$mg/kg/day (IRIS, 2008a)
- 2,2',4,4'-tetraBDE: $1x10^{-4}$mg/kg/day (IRIS, 2008b)
- 2,2',4,4',5-pentaBDE: $1x10^{-4}$mg/kg/day (IRIS, 2008c)
- 2,2',4,4',5,5'-hexaBDE: $2x10^{-4}$mg/kg/day (IRIS, 2008d)

For all RfDs, potential effects to the nervous system is of significant concern, with a potential for neurobehavioral health effects; despite a relatively low level of confidence. Finally, mono-BDE congeners are regulated under the Comprehensive Environmental Response, Compensation, and Liability Act and Resource Conservation and Recovery Act (ATSDR, 2017).

2.3 Exposure Assessment

An exposure is defined as an interaction with the skin or eyes or contact through breathing or swallowing. This contact can be short-term or acute. On the other hand, it can also be long-term or chronic. It should be remembered that an exposure is only an opportunity for absorbing a substance. The types and duration of an exposure are key determinants of a significant dose. Then, if this dose is significant, there *may* be a health effect. Exposure assessment is the process of determining how someone may come into contact with a toxicant by considering the exposure route, frequency, duration and amount of the toxicant. There are several assessment methods which depend on the kind of exposure in question. Exposure assessments are commonly used in

environmental and occupational settings (Aylward et al. 2013; Lebeau, 2012). Passive air sampling may be conducted in a rural environment to evaluate environmental air quality (Jaward et al. 2005). In occupational settings, exposures to toxicants may be assessed through biomonitoring which measures the body burden of toxicants and their metabolites through the analysis of human fluids (*e.g.*, blood) (Lebeau, (2012).

2.4 Biomonitoring

Biomonitoring is the process of determining the presence of chemicals in the human body as a result of an exposure. Once a chemical has been absorbed due to an exposure to food, air water, dust, etc., and depending on the pharmacokinetics of the chemical, it may be measured in various biological media. These commonly include the sampling of urine, blood, breast milk, tissue, etc. The chemicals being analyzed in biological media are often referred to as biological markers. Measurable concentrations of the parent chemical and its intermediate or conjugate allows for the prediction of a human health effect (Centers for Human Health Assessment, 2017). A measured chemical concentration can also be used to determine previous health effects based on current levels in the body (Centers for Human Health Assessment, 2017; Lebeau, 2012). Their concentrations can be used to identify early physiological changes. In addition, based on key metabolic characteristics of certain individuals, biological markers can be used to determine health effects, given a level of exposure. Although, the presence of a chemical in a biological sample does not automatically indicate a health effect (Ames et al., 1990a,b).

In the process of biomonitoring, there are at least three factors that affect the detection of biological markers; one of which is half-life. Each chemical has a half-life, which is the time it

takes for a concentration of a chemical to decrease by half in the human body. If the chemical has a relatively brief half-life of one day, it is imperative to analyze the biological samples as quickly as possible. Thus, one must be aware of a chemical's half-life, as it is a key consideration in biomonitoring results. Other factors that affect the detection of biological markers include the physical characteristics of the chemical and the detection limits of the instrument being used (Aylward et al., 2013; Centers for Human Health Assessment, 2017; Lebeau, 2012).

As previously mentioned, there are various uses for biomonitoring. Biomonitoring is used to determine environmental (indoor or outdoor) and occupational exposures to toxicants. At the crux of biomonitoring is the need to understand if a population is at-risk after a chemical exposure. Thus, in the occupational setting for instance, biomonitoring is crucial if workers tend to work with chemicals at levels that are known to cause injurious health effects. Baseline levels of toxicants may be recorded for a group of workers. Over time, biological samples are taken from the workers on a routine basis. This allows us to determine whether concentrations of toxicants have increased significantly and may lead to a health effect (Lebeau, 2012).

On a regional or national level, biomonitoring serves as an important tool to gauge the background levels of people among various American demographic categories. Public health researchers use this biomonitoring data to determine if the reported levels of toxicants are associated with various human health effects. An example of regional biomonitoring includes studies of large populations in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study which is one of the longest running longitudinal birth cohort study of pediatric environmental exposures in a farmer community (Castorina et al., 2011; Eskenazi et

al., 2013). A similar study is the Health Outcomes and Measures of the Environment (HOME) Study in Cincinnati, Ohio from March 2003 to February 2006 which investigated the human health effects of low-level environmental toxicants (Vuong et al., 2015). On a much larger scale, scientists refer to the National Health and Nutrition Examination Survey (NHANES) to analyze biomonitoring data. NHANES biomonitoring data serves as the primary source of information for this dissertation research (Centers for Human Health Assessment, 2017).

NHANES is administered by the Centers for Disease Control & Prevention's National Center for Health Statistics. This biomonitoring program was started in the early 1960s and focused on specific populations and health topics (Centers for Human Health Assessment, 2017; Lebeau, 2012). In 1999, NHANES became a continuous biomonitoring program which changes focus based on several health and nutrition measurements that address emerging needs. A nationally representative sample of few thousand people are surveyed every year. Participants are from 15 counties throughout the country. NHANES data are released every two years. For biomonitoring specimens, participants are 6 years or older. Blood specimens are gathered from participants that are 12 years or older. It is important to note that the measured analytes cannot be used to estimate regional levels such as cities or states. They also cannot be used to generate estimates for populations with unusual exposures (Centers for Human Health Assessment, 2017).

2.5 Brominated Flame Retardant Exposure

2.5.1 Occupational Exposure

Polybrominated Diphenyl Ethers are ubiquitous in our environment because they are used as flame retardants in a variety of materials. When considering the most at-risk populations as a

result of their occupations, we must seriously consider workers involved in the production, distribution, handling and disposing of materials that contain PBDEs. Naturally, e-waste workers and dismantlers fit this category very well (Darnerud et al., 2001). According to Watanabe & Sakai, in Japan, hazardous waste incinerators and final disposal sites are some key sources of brominated flame retardant effluents (Watanabe & Sakai, 2003). Among disposed wastes, televisions and computers may serve as significant sources of PBDEs. In comparison to transportation materials, electrical appliances, building materials and others, electronics contained over half of the relative amounts of flame retardants, as shown in Figure 1 (Darnerud et al., 2001; Watanabe & Sakai, 2003). As a result, their research has shown that workers at electronics-dismantling facilities are among the most exposed individuals and appropriate measures should be taken to protect them along with those that handle other similar consumer waste products (Watanabe & Sakai, 2003).

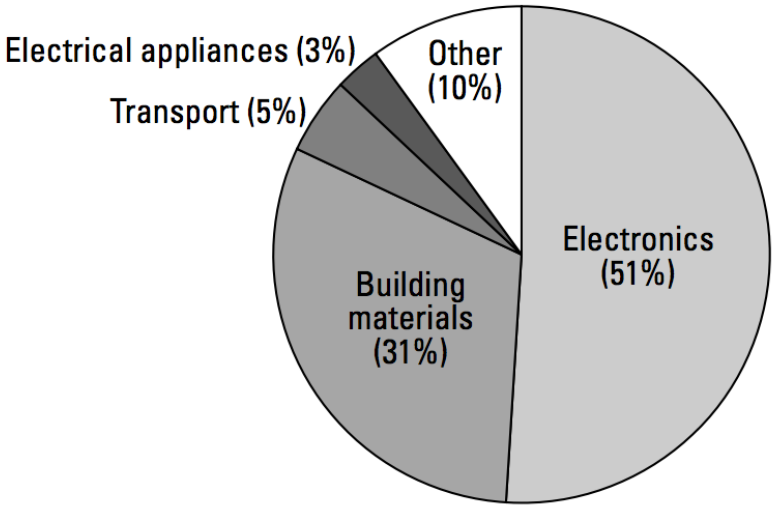

Figure 1. Relative amounts of flame retardants (including PBDEs) in various sectors (Darnerud et al., 2001).

Sjodin et al. conducted a study of PBDE levels among full-time workers at a computer screen facility and clerks from an electronics-dismantling plant with hospital cleaners as the

control group. Sjodin et al. reported significantly higher concentrations of PBDEs among workers at the electronics-dismantling plant in comparison to hospital cleaners. Through this research, despite the relatively small sample size, results suggest that those who handle computer parts may have increased exposures to PBDEs (Sjodin et al., 1999). Also, BDE-47 was among the most prevalent BDE congeners among workers according to a study of 52 office workers in Boston, Massachusetts (Makey et al., 2016).

Another potentially at-risk group of people due to the activities in which they partake include gymnasts. These athletes spend an inordinate amount of time with safety materials such as pit cubes and landing mats, which help to brace their fall during exercise. Because of their flame retardant content, materials used by gymnasts have been named as the primary culprits for the abnormally high concentrations of PBDEs found in these athletes. Research has also shown that apart from the materials, the facilities in which they train has been found to contain elevated levels of flame retardants in air and dust (Carignan et al., 2016). Carignan et al. have shown that these elevated levels of flame retardants corresponded with significantly higher concentrations of pentaBDEs in the blood serum of gymnasts. Concentrations were also significantly higher after practice in comparison to before practice, which suggests that elevated concentrations were likely due to contact with materials and dusts within the facility. Approximately 89% of foam samples from many training facilities contained flame retardants. Despite their interesting findings, this study was based on a relatively small sample of 53 participants; thus, leading to a relatively low statistical power (Carignan et al., 2016). However, it helps to identify another potentially at-risk group due to a specific type of activity or occupation. In general, further research should be conducted to determine the total PBDE body burden contribution of occupations in America.

2.5.2 Residential Exposure

Unlike some regions of the world, the primary source of PBDE exposure in America is the indoor environment; especially, residential exposure. It is difficult to discuss residential exposure to PBDEs without considering the impact of California's formerly strict flame retardant requirements. In 1975, Governor Jerry Brown signed the "Technical Bulletin 117" into law (Standen, 2013). This required all upholstered furniture to be injected with flame retardants like PBDEs. Since then, this law became a *de facto* national standard. Recently, California's Technical Bulletin 117 has been revised. Beginning in 2014, on his most recent stint as California's governor, Mr. Jerry Brown signed a revision to this law which no longer requires the injection of flame retardants into California's furniture. However, prior to this revision, many studies investigated the impacts of Technical Bulletin 117 on PBDE levels among American residents; especially Californians (Standen, 2013).

An increase of approximately one order of magnitude was reported for indoor air and dust concentrations of PBDEs in North America in comparison to Europe. The authors mention this disparity is likely due to a difference in fire standards between the two regions (Frederiksen et al., 2009). According to Castorina et al., on average, PBDE blood levels were approximately 20 times higher in the US in comparison to Europe (Castorina et al., 2011). The total range of PBDE levels in Americans was from 4.2 to 1380 ng/g lipid. The pentaBDE mixture was traced in over 97% of samples. Researchers found that the total PBDE concentrations in Americans significantly increased with the length of time someone has resided in the United States, and in women living in Californian homes containing at least 3 pieces of stuffed furniture. Specifically, the possession

of 3 or more stuffed furniture was significantly associated with nearly a 27% increase in women's blood concentrations of PBDEs (Castorina et al., 2011). A study by Harley et al. also indicated that the strongest predictor of PBDE concentrations among pregnant women living in a low-income mostly-Hispanic immigrant community in California, was residence time (Harley et al., 2010).

Zota et al. investigated the impacts of California's flammability standards. Comparisons were made between PBDE levels in household dusts from Californian homes and those from seven other regions in the United States. A significantly higher household dust level of PBDEs was found in Californian homes compared to other regions in America. Investigators also reported approximately a two-fold increase in blood serum concentrations of PBDEs; that is, a least square geometric mean of 73.0 vs. 38.5 ng/g lipid (Zota et al., 2008).

Frederiksen et al. indicated that although foodstuffs with a high fat content had relatively higher levels of PBDEs, diet alone cannot explain background levels of PBDEs among Americans. It was determined that the ingestion of indoor dusts contributed to the highest intake of BDE-209. Infants, often displaying crawling behaviors, tend to be exposed to a variety of chemicals. Toddlers were found to have ingested a significantly higher amount of PBDEs from indoor dusts in comparison to adults. Infants are also exposed to PBDEs via breast feeding. Overall, they have a higher body burden in comparison to adults (Frederiksen et al., 2009).

2.5.3 Dietary Exposure

Although diet is not the primary source of PBDE exposure in the United States, it remains a significant source. In many regions of the world diet is the primary source of exposure. When discussing diet, the main attribute of PBDEs to consider is their affinity to fat. Due to this lipophilicity, research has shown that foods heavy in fat like poultry, meat, and fish (especially from top predators) contain significantly higher levels of PBDEs in comparison to fruits and vegetables. In general, average dietary PBDE levels follow this trend: vegetables ≤ dairy<meat<fish. The PBDE content of North American meat was generally higher in comparison to other regions of the world (Frederiksen et al., 2009). Similarly, in a Finnish study of dietary PBDE intake, Kiviranta et al. found that approximately 53% of PBDE intakes were from Fish. These results were comparable to dietary PBDE intake studies in Sweden and Canada (Kiviranta et al., 2004).

Fromme et al. investigated various sources of PBDE exposure among 27 healthy females and 23 healthy males in Germany. Researchers found that dietary exposure was responsible for 97% of the average intake and 95% of the high intake of total PBDE intake in this adult population. Their findings coincide with other studies that have shown that diet is a significant exposure source in many European countries (Fromme et al., 2009).

Since Fish, especially top predators, are key dietary sources of PBDEs it is important to note that some fish and marine organisms contain what Teuten et al. have determined to be naturally produced PBDEs. The True's Beaked Whale is one such organism. Studies of these animals have found methoxylated polybrominated diphenyl ethers (MeO-PBDEs) which are

structurally-similar to synthetic PBDEs. Through methoxylation processes the PBDEs become MeO-PBDEs. Molecular-level C-14 analysis was used to determine the source of the halogenated compounds (Teuten et al., 2005). For example, a change of C-14 value of +90 per mil shows that the source was natural. On the other hand, a value of -990 per mil for Bromkal 70-5DE (a commercial mixture of PBDEs) indicated that the source was industrial. Just like their nonmethoxylated counterparts, MeO-47 and 68 showed a high propensity for bioaccumulation. The most likely source of exposure of MeO-PBDEs for the whales is dietary (*e.g.*, squid consumption). Microorganisms also naturally produce these compounds and the authors suggest that this may be a detoxification mechanism. The natural production of these compounds has been occurring before any known environmental release of industrial PBDEs. In fact, cytochrome p450 and other enzymes used in the metabolism of these compounds are believed to have existed for millions of years and probably arose originally as a response mechanism for naturally produced compounds in the environment (Teuten et al., 2005).

2.6 Polybrominated Diphenyl Ether Health Effects

2.6.1 Acute

Acute human health effects after PBDE exposure is poorly understood and currently being investigated. In general, most of the information related to acute health effects of PBDE exposure is from animal studies. Thus far, in animals, decaBDE mixtures have been shown to be relatively less toxic in comparison to lesser-brominated BDE congeners. In humans, decaBDEs are expected to have very little health effect. This is due to its much different toxicity in comparison to lesser-brominated congeners (ATSDR, 2017).

In animals, one of the most significant health endpoints has been PBDEs' potential effect on thyroid hormones. For example, rats and mice who were fed food laced with moderate amounts of lesser-brominated congeners for short periods had predominantly thyroid-related effects. However, it should be noted that thyroid disruption due to, short-term, small-to-moderate amounts of PBDE exposure is thought to be species-dependent. As a result, this suggests that similar effects are less likely to occur in humans. In addition, testing of animal offspring has also shown behavioral effects due to acute PBDE exposure (ATSDR, 2017). Once again, these behavioral effects are believed to be a result of changes in the thyroid since it is a major determinant of nervous system development. No additional birth defects have been recorded in animals after acute exposure. Much research is needed to determine if acute PBDE exposure has any reproductive health effects. Next, animal testing data of acute exposure has shown that some BDE congeners may affect the immune system and cause skin irritation if the animal's skin is lacerated (ATSDR, 2017). Furthermore, Darnerud et al. conducted studies pertaining to the clinical signs of toxicity after acute exposure. After rats were exposed to high doses of PBDEs, investigators reported the following clinical signs: diarrhea, red staining around the eyes and nose, reduced activity, continuous chewing, piloerection and clonic persistent tremors of forelimbs (Darnerud et al., 2001).

In humans, the only available data concerning acute PBDE health effects are from studies of decaBDE. In one skin sensitization study, involving 200 volunteers (120 females and 80 males) exposed to two decaBDE batches of unknown purity, no evidence of skin sensitization was observed. These participants were treated with nine induction patches every two days. For every treatment day, the test substance remained in contact with the participants' skin for 24 hours.

Neither of the two undisclosed decaBDE batches had an effect on skin sensitization. In another study, the skin sensitization of a decaBDE mixture (decaBDE: 77.4%; nonaBDE: 21.8%; and, octaBDE: 0.8%) was assessed for 50 volunteers. A five percent suspension of decaBDE in petrolatum was spread over the participants' skin three times per week for a period of three weeks. Investigators did not find any skin sensitization among the participants (ATSDR, 2017). Finally, a study of workers involved in the manufacture of polybrominated biphenyls and polybrominated diphenyl ethers was conducted to investigate the acute health effects of PBDEs, including decaBDE. These workers were reported to have a higher prevalence of primary hypothyroidism and substantial reductions in conducting velocities in sensory and motor neurons than normal, after being acutely exposed to PBDEs at the workplace. However, no other dermatologic or neurologic changes were found (Darnerud et al., 2001).

2.6.2 Chronic

Similar to acute health effects, the chronic health effects of PBDEs are poorly understood and requires a significant amount of research. Most of the known chronic health effects of PBDEs are from animal studies. It is speculated that a long-term exposure to PBDEs has a higher chance of causing health effects in comparison to short-term low levels of exposure. This is partly due to the bioaccumulative property of PBDEs which occur over many years of exposure. Once again, in relation to chronic health effects, decaBDEs are expected to be generally less toxic than lesser-brominated counterparts. Of major importance to possible chronic health effects is the potential to cause cancer. Currently, it is unknown whether PBDEs can cause cancer in humans (ATSDR, 2017; USEPA, 2014).

Although, rats and mice that ingested PBDEs throughout their lives developed liver tumors. Overall, investigators have found a statistically significant increase in the incidence of carcinomas in the livers of male rats exposed to low and high doses, and of female rats exposed to high doses. Secondly, a significant increase in cases of hepatocellular adenoma or carcinoma was found in male mice after low dose exposure (National Toxicology Program, 2006). Next, a significantly increased incidence of follicular cell hyperplasia was found in male mice after being exposed to high and low doses of decaBDE. The latter is thought to be a precursor to thyroid tumors in mice. It is based on this relatively limited body of evidence that the EPA postulates that decaBDE may possibly be carcinogenic to humans (ATSDR, 2017; USEPA, 2014). On the other hand, the EPA describes lower-brominated congeners as not classifiable as human carcinogens (USEPA, 2014).

In case-control epidemiologic cancer studies, pancreatic cancer was not significantly increased with increased levels of lipid lower-brominated PBDEs. Next, in a study of women from California, of which were 78 cases and 56 controls, no significant association was found between adipose tissue concentrations of lower-brominated PBDEs and breast cancer. Third, a study of Alaskan women found no clear association between BDE-47 and breast cancer. In addition, blood concentrations of lower-brominated PBDEs were not significantly associated with thyroid cancer among participants from a large multicenter clinical trial in the U.S., which included 104 cases and 208 controls. Furthermore, in a study of Swedish men and women with 19 cases and 27 controls, BDE-47 exposure was not significantly associated with non-Hodgkin's lymphoma. Thus, from the relatively brief amount of human studies of cancer risks in relation to lower-brominated PBDE exposures, results have consistently shown that humans are not at significant risks to various forms of cancer (ATSDR, 2017).

2.6.3 Toxicokinetics

In general, toxicokinetic studies of PBDEs have indicated that the absorption, metabolism and elimination of polybrominated diphenyl ethers are all dependent upon the congener, species and gender. Also, animal studies have shown that pups have a higher body burden of PBDEs than adults. This is because while a significant amount of PBDEs are transferred from mothers to pups through breast feeding, the pups have a lesser capacity for PBDE elimination. Just as in animal studies, children have been shown to carry a higher body burden of PBDEs in comparison to their parents (Costa & Giordano, 2007). In humans, when comparing the amount of absorbed polybrominated diphenyl ethers, with polychlorinated dibenzodioxins, polychlorinated dibenzo furans and co-planar polychlorinated biphenyls from 1973 to 2000, human PBDE levels have increased significantly while these other toxicants have all significantly decreased. The three most common congeners in humans have been BDE-47, followed by BDE-153, then BDE-99 (Costa & Giordano, 2007).

2.6.3.1 Absorption

In general, lesser-brominated congeners are more likely to enter the human body through the lungs and stomach, and pass into the bloodstream than decaBDE. Also, during pregnancy, PBDEs have been shown to enter the bodies of unborn babies through the placenta. Oral absorption estimates are available for PBDEs and include the following. After forced administration of PBDEs in lipophilic vesicles, the most recent estimates, show a range of 70-75% for BDE-47, BDE-99, BDE-100, BDE-153, and BDE-154. An estimated range of 10-26% is expected for BDE-

209 (deca-BDE). The mechanisms of oral absorption, including active transport and protein binding, have not been determined (ATSDR, 2017).

To assess the bioavailability of PBDEs, studies of *in vitro* gastrointestinal models have been conducted. Yu et al. found that the most important factor impacting PBDE bioaccessibility was dietary fat; likely due to the lipophilicity of PBDEs. Further study of the bioaccessibility of lesser-brominated BDE congeners in flour, rice, meat, fish and vegetables yielded a range of 2.6 to 41.3% in foodstuffs. Bioavailability of PBDEs in food increased as fat, and carbohydrate content increased. On the other hand, bioavailability of PBDEs in food decreased with increasing protein and fiber content (Yu et al., 2009).

The bioavailability of PBDEs have also been investigated in dust; the largest source of PBDE exposure. Research by Lepom et al. found that the bioavailability of PBDEs found in ingested dust was approximately less than 50%. From this investigation, researchers also reported a bioavailability of 27 to 42% for lesser-brominated BDEs and approximately 10% for BDE-209 (Lepom et al., 2010). Similar results were found by Abdallah et al. Once again, the bioavailability of BDE-209 (14%) was much lower than that for lesser-brominated BDE congeners (32 to 58%) (Abdallah et al., 2012).

A few *in vitro* studies have been performed to investigate the diffusion potential of PBDEs across dermal barriers for rats, mice, and human. According to Staskal et al., female mice that were exposed to a dermal dose of 1 mg/kg ^{14}C BDE-47 had a dermal absorption efficiency of 62% (Staskal et al., 2005). Roper et al. reported that mean absorption efficiencies for ^{14}C BDE-47 was

14.58% in rat skin and 1.88% for human skin (Roper et al., 2006). Finally, Hughes et al. report a mean absorption efficiency range of just 0.07-0.34% from the ^{14}C decaBDE dose applied to mouse skin in vitro (Hughes et al., 2001).

2.6.3.2 Distribution

As previously mentioned, research has shown that infants have a higher body burden of PBDEs than their parents. One of the main reasons for the latter is due to PBDE absorption via breastmilk. However, research has also demonstrated that PBDEs are also distributed to the developing fetus from pregnant mothers via cord serum samples of non-occupationally exposed mothers (Li et al., 2013). The majority of congeners found in maternal, cord sera and breast milk samples have been tetraBDEs and pentaBDEs. Although, mounting evidence has shown the presence of hexaBDEs, octaBDEs and decaBDEs in cord sera and mothers' breast milk (ATSDR, 2017).

The distribution of PBDEs in animal and human tissues has also been investigated. In one study, animals that were exposed to ^{14}C-labeled BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, and BDE-209 (decaBDE) has shown that lower-brominated BDEs are distributed differently than decaBDE. Specifically, investigators found that after absorption and an initial wide distribution, lower-brominated congeners tended to accumulate more in adipose tissue. On the other hand, decaBDE tended not to be distributed in adipose tissue. Instead, decaBDE appeared to prefer highly perfused tissues, such as renal tissue, which are human tissues that circulate bodily fluids (ATSDR, 2017).

2.6.3.3 Metabolism

The primary metabolic pathway of PBDEs in humans and animals is oxidative hydroxylation and follows the following series of steps. Polybrominated diphenyl ethers are metabolized with phase I and phase II enzymes, forming hydroxylated PBDEs. Through this metabolic pathway, monohydroxylated OH-PBDEs are formed. Hydroxylated PBDEs have been found in samples of human blood and breast milk. These have also been found in the feces of rodents that were exposed to ^{14}C-labeled tetraBDEs, pentaBDEs, hexaBDEs and decaBDEs. The process of PBDE oxidative hydroxylation has been validated in studies of *in vitro* metabolic systems with primary hepatocytes or liver chromosomes in humans and rats (Cheng et al., 2008; Erratico et al., 2011; Erratico et al., 2012; Erratico et al., 2013). Other metabolic fate processes for PBDEs in mammals include the metabolic cleavage of the ether bond leading to a formation of brominated phenols and the debromination of lesser-brominated PBDEs (Cheng et al., 2008; Erratico et al., 2012; Erratico et al., 2013). Data from *in vivo* toxicokinetic studies of rodents exposed to PBDEs have been deemed adequate by the ATSDR to propose the likely involvement of cytochrome P450s in the formation of hydroxylated metabolites and hydroxylated debrominated metabolites. Furthermore, *in vitro* studies of human liver microsomes or hepatocytes and human recombinant CYP enzymes have shown that through hydroxylation and cleavage of the ether bond, CYP2B6-mediated metabolism of BDE-47, 99 and 100 generated several metabolites, as illustrated in Figures 2-4 respectively (Erratico et al., 2012; Erratico et al., 2013). Research of human liver microsomes or hepatocytes has not shown a production of hydroxylated metabolites of BDE-153 and BDE-209 (Lupton et al., 2009). Finally, it is interesting to note that there are

naturally occurring OH-BDEs and brominated phenols known to be produced by sponges and algae in marine environments (ATSDR, 2017).

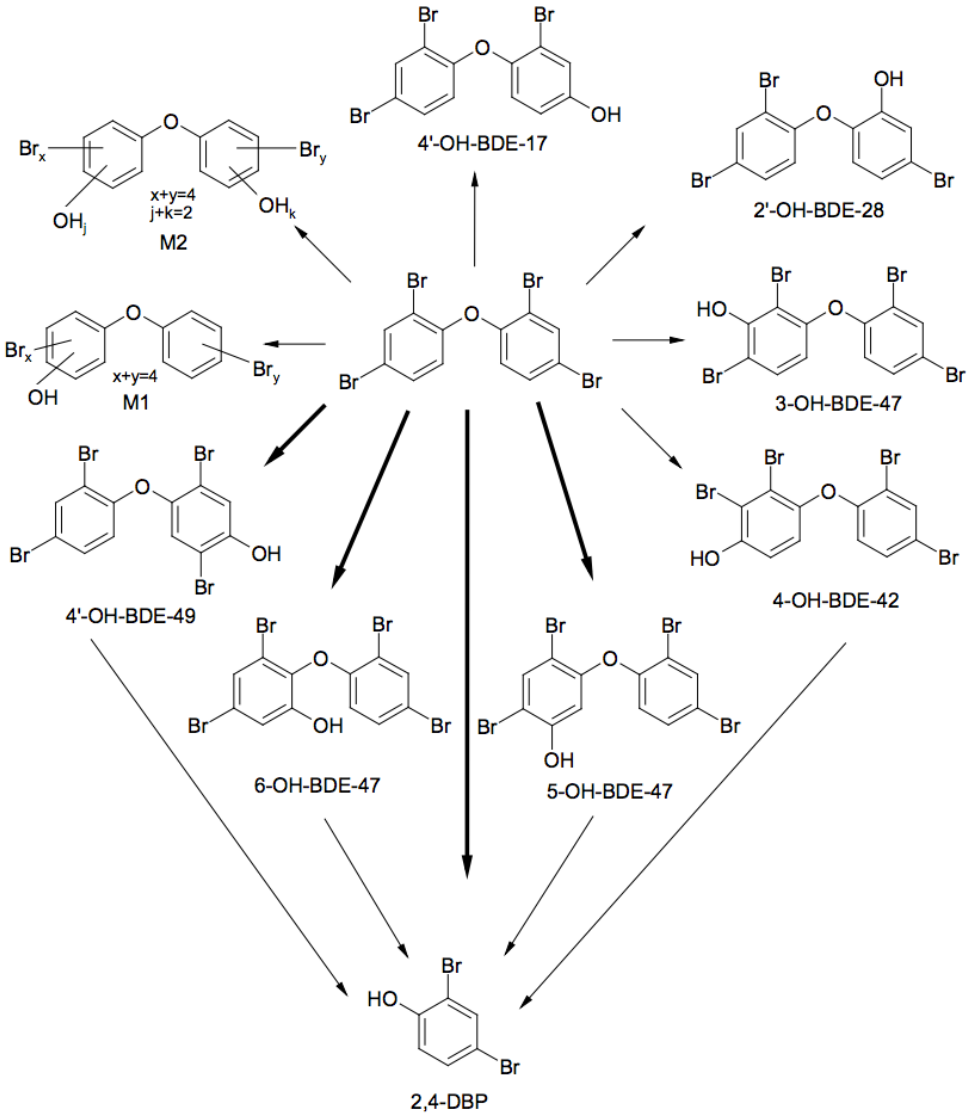

Figure 2. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE-47 Produced by Human Liver Microsomes (Erratico et al., 2013).

*M1 and M2 refer to general structures of unidentified hydroxylated and dihydroxylated tetrabrominated BDEs. Structures of other metabolites were determined with authentic chemical standards and ultra-performance liquid chromatography-mass spectrometry techniques. Bold arrows indicate major metabolites. CYP2B6 is proposed to be involved in production of all metabolites, based on inhibition of BDE 47 metabolism by a specific antibody to CYP2B6, and higher rates of BDE 47 metabolism in human liver microsomes incubated with specific human recombinant CYP2B6, compared with 11 other human recombinant CYPs.

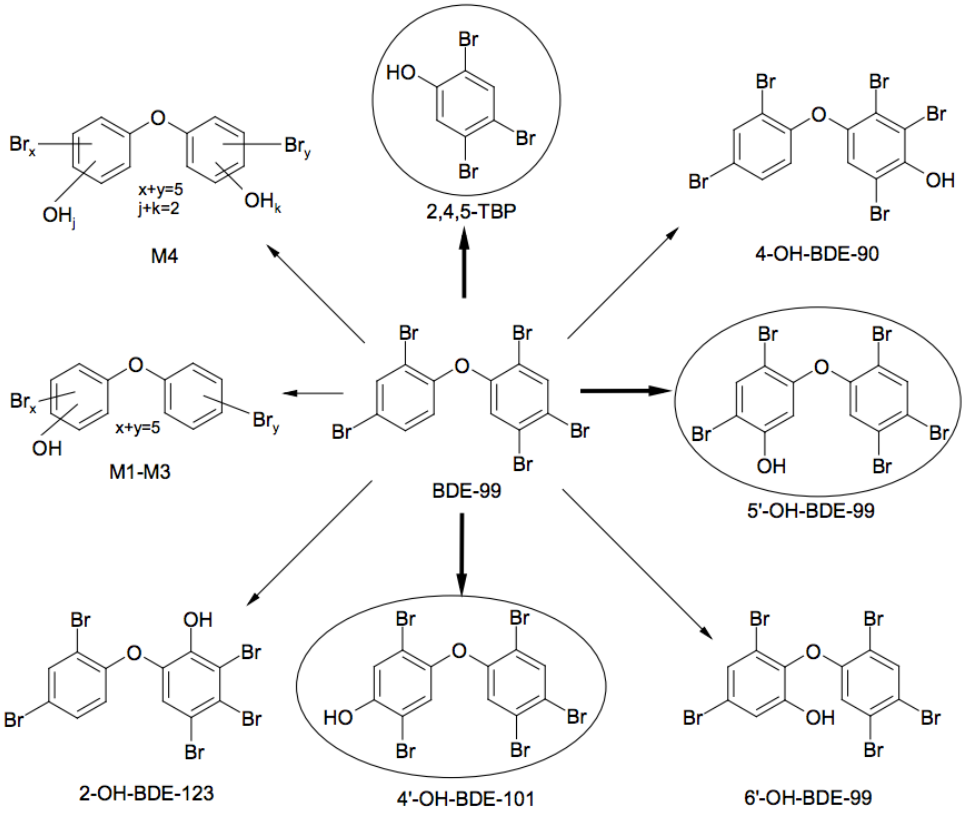

Figure 3. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE-99 Produced by Human Liver Microsomes (Erratico et al., 2012).

*M1-3 and M4 refer to general structures of unidentified hydroxylated and dihydroxylated pentabrominated BDEs. Structures of other metabolites were determined with authentic chemical standards and ultra-performance liquid chromatography-mass spectrometry techniques. CYP2B6 is proposed to be involved in production of all metabolites, based on inhibition of BDE 99 metabolism by a specific antibody to CYP2B6, and higher rates of BDE 99 metabolism in human liver microsomes incubated with human recombinant CYP2B6, compared with11 other human recombinant CYPs.

Source: Erratico et al. 2012

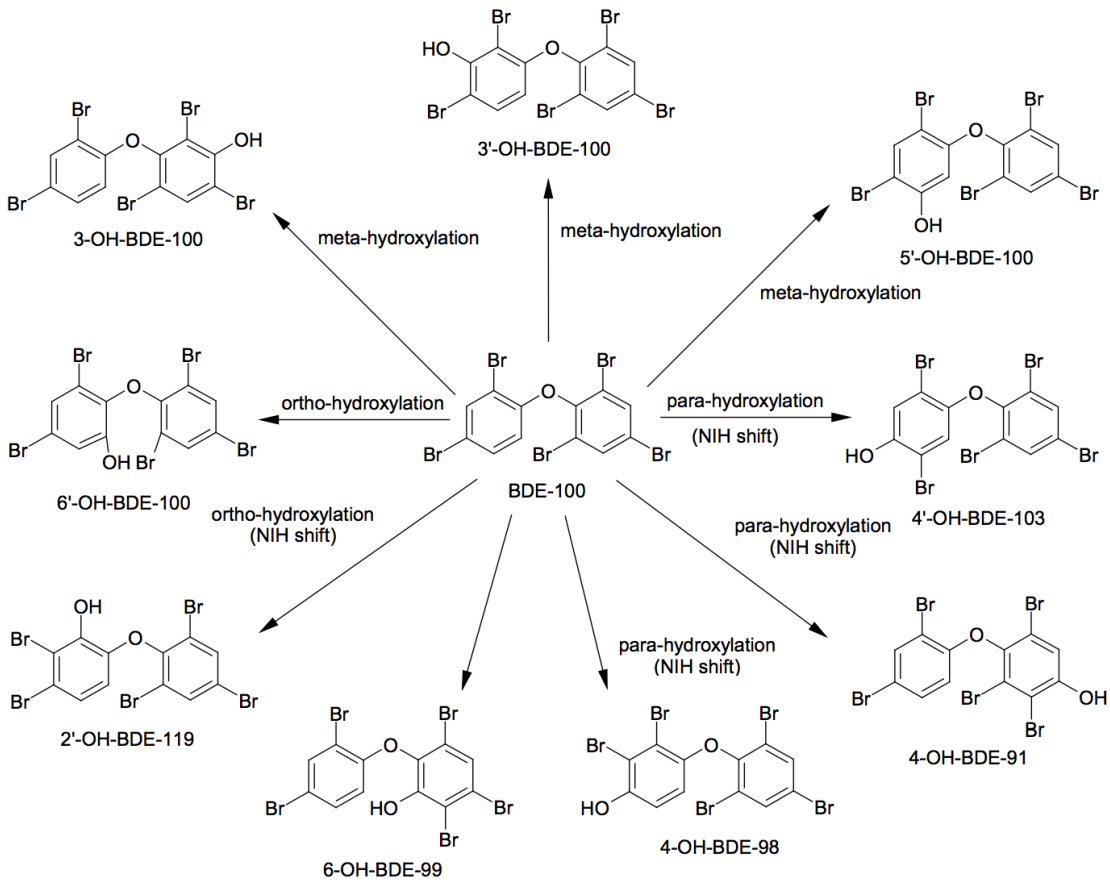

Figure 4. Structures and General Metabolic Scheme for Hydroxylated Metabolites of BDE-99 Produced by Human Liver Microsomes (ATSDR, 2017).

*Structures of 3-OH-BDE-100, 5'-OH-BDE-100, 6'OH-BDE-100, and 4'-OH-BDE-103 were determined using commercial reference standards and ultra-performance liquid chromatography-mass spectrometry techniques. The two remaining mono-OH-pentaBDE metabolites were hypothesized using mass spectral fragmentation characteristics of derivatized OH-BDEs. Additional information based on theoretical boiling point calculations using COnductor-like Screening MOdel for Realistic Solvents (COSMO-RS) and experimental chromatographicretention times were used to identify the hypothesized metabolites as 2′-hydroxy-2,3′,4,4′,6-pentabromodiphenyl ether (2′-OHBDE-119) and 4-hydroxy-2,2′,4′,5,6-penta-bromodiphenyl ether (4-OH-BDE-91), respectively. CYP2B6 is proposed to be involved in production of all metabolites, based on inhibition of BDE 99 metabolism by a specific antibody to CYP2B6, and higher rates of BDE 100 metabolism in human liver microsomes incubated with human recombinant CYP2B6, compared with nine other human recombinant CYPs.

Source: Gross et al. 2015

2.6.3.4 Elimination

Just as in the case of absorption, the elimination of PBDEs depends on the chemical structure of the BDE congener. In general, these flame retardants and their metabolites are

eliminated from the body mainly through feces. A relatively very small amount is eliminated in urine. DecaBDEs and their lower-brominated counterparts are all known to concentrate in human breast milk. Thus, breastfeeding may serve as an additional source of elimination for nursing mothers (Hooper et al., 2007; Jakobsson et al., 2012; Thomsen et al., 2010). The two general classes of congeners also differ in their half-lives within the human body. The half-life for lower-brominated BDE congeners is approximately 94 days. For decaBDEs, the approximate half-life is significantly less at 15 days. Thus, lower-brominated PBDEs have a much longer residence time in the body (ATSDR, 2017).

2.6.4 Mechanisms of Toxicity

Following exposure to PBDEs, the primary systems of concern in humans include the following: the liver, nervous, male reproductive, developing and mature endocrine systems. Although, the female reproductive, adult nervous system and the developing and mature immune systems are also of concern, the evidence that is available for these endpoints is incomplete. Many studies have been conducted to elucidate the likely mechanisms of toxicity for PBDEs. General mechanisms of toxicity, such as Aryl hydrocarbon receptor (AhR)-mediated effects and hepatic enzyme induction, and target-specific mechanisms have been investigated. Most mechanistic studies, for specific targets, have been focused on neurological effects and endocrine disruption. PBDEs share similar toxicological properties as PCBs likely due to their two-dimensional structural similarities. However, PBDEs are more coplanar in nature due to the ether bridge. This reduces the AhR binding affinity when compared to similar compounds. As a result, PBDEs are less sensitive to the influence of ortho substitutions that inhibit the AhR binding capability of PCBs (ATSDR, 2017; ATSDR, 2002). These attributes have implications on the nondioxin-like and

dioxin-like effects of PBDEs, which are mediated by the AhR pathway. Studies of the structure-activity of PBDEs have demonstrated that although some BDE congeners are able to bind to AhR, the binding affinities and induction of AhR-mediated responses are extremely weak or insignificant; especially for commercial PBDE mixtures (ATSDR, 2017). Finally, Dingemans et al. have reported that the toxicity of PBDEs should be investigated in conjunction with structurally similar compounds such as nondioxin-like polychlorinated biphenyls because there is evidence showing an additive effect when these two types of compounds are combined (Dingemans et al., 2016). Meng et al. also reported synergistic effects between polybrominated diphenyl ethers, polychlorinated biphenyls and organochlorine pesticides in a study of the association between asthma and persistent organic pollutants among children in Shanghai, China (Meng et al., 2016).

2.6.5 Toxicity Assessment

The assessment of polybrominated diphenyl ethers will be limited to select outcomes. This assessment concerns the most important public health risks, in addition to obesity; the primary health outcome concerning this dissertation research. Moreover, epidemiological studies will be presented, if available.

2.6.5.1 Developmental Effects

First, the neurodevelopment system is a target of concern in children for all PBDEs. According to various human studies, results suggest that PBDEs influence the neurodevelopment of children. In one cohort study, investigators found associations between maternal serum PBDE concentrations and decreased IQ, hyperactivity at age 5 and executive functions (mental control and self-regulation) deficits in those children from 5 to 8 years old (Braun et al., 2014; Chen et al.,

2014; Donauer et al., 2015; Vuong et al., 2016). Other studies have reported a correlation between cord serum PBDE concentrations in breast milk and adaptive behavior deficits in infants, mental and physical developmental deficits in toddlers, social development and language deficits in children (24 months old), increased impulsivity in toddlers, and attention deficit hyperactivity disorder at age 4. Secondly, despite the inconsistency of developmental endocrine system effect research, epidemiological data suggest that PBDEs can interact with the homeostasis of thyroid hormones in infants and children. Human research showed inconsistencies in the investigation of infant serum or cord blood thyroxine levels and PBDE developmental exposure. Results have also been inconsistent when researchers investigated infant serum or cord blood triiodothyronine levels and thyroid stimulating hormone in association with PBDE developmental exposure. In numerous studies of animals, results have shown a reduction in serum triiodothyronine and thyroxine levels in pups after receiving doses of pentaBDE or tetraBDE as low as 452 mg/kg/day in mice and 0.3 mg/kg/day in rats throughout gestation and lactation. Third, sufficient animal and limited human data has shown that oral exposure to PBDEs during development may potentially affect the male reproductive system (ATSDR, 2017). One study found, no relationships between maternal PBDE levels and hypospadias in boys, adipose tissue concentrations of PBDEs in children and cryptorchidism, or any measures of sexual maturation in girls (Carmichael et al., 2010). Yet, an American longitudinal cohort study found a significant association between blood levels of PBDEs for 6 to 8-year-old girls and delayed onset of puberty. However, more research is needed to determine if PBDE levels in infants and children can cause altered reproductive effects in adulthood. Last, limited animal and human data have shown that exposure to PBDEs may be able to cause low birth weight among other endpoints of human physical development. However, such

conclusions are relatively inconsistent (Costa & Giordano, 2007; Kuriyama et al., 2005; Lilienthal et al., 2006; Toms et al., 2009a,b; Viberg et al., 2003).

2.6.5.2 Endocrine Effects

Several epidemiologic studies have investigated possible endocrine system effects of PBDE exposure. First, many human studies have shown that PBDEs can disturb the endocrine system and hormone levels. In one study conducted by Hooper et al., 4 production workers out of a sample of 35 who worked at a decaBDE manufacturing plant presented with hypothyroidism (Hooper & McDonald, 2000). However, specific findings in human studies have been very inconsistent. Some studies have reported positive associations between thyroxine and PBDEs while others have reported negative or no associations (ATSDR, 2017). Similar inconsistencies exist for research concerning the association of thyroid stimulating hormone or triiodothyronine with PBDE concentration. Although, there is sufficient data supporting the ability for PBDEs to interact with the homeostasis of the thyroid hormone. Overall, current data from human and animal studies suggests that the thyroid is likely a target of concern for humans (Costa & Giordano, 2007; Hamers et al., 2006; Hooper & McDonald, 2000; Kim et al., 2012; Kovarich et al., 2011; Li et al., 2013; Lilienthal et al., 2006; Norrgran et al., 2017).

Finally, the pancreatic effects of PBDEs have been studied in humans and animals. Epidemiologic studies have been inconclusive. However, animal studies have shown that the pancreas may be a target of concern after an oral dose of PBDE is provided. For example, a study of male rats that were exposed to approximately 20 mg/kg/day to PBDEs in food for 70 days showed a reduction in serum glucose levels. However, it should be noted that the study did not

report the lowest dose at which point glucose levels were significantly lower in male rats. Another study, investigated insulin regulation and pancreatic morphology in male rats after being exposed to 0, 0.05, 1, or 20 mg/kg/day of decaBDE every day for a period of 8 weeks. Investigators reported that the rats exposed to 1 and 20 mg/kg/day had a significant 50-60% decrease of serum insulin. In addition, rats that were exposed to 0.05, 1 and 20 mg/kg/day had a significant increase of glucose levels by 12, 18, and 21%, respectively (ATSDR, 2017; Ernest et al., 2012).

2.6.5.3 Hepatic Effects

Currently, the potential human hepatotoxic effects of PBDEs is based primarily on animal data. There are no known animal studies of liver toxicity resulting from chronic lower-brominated PBDE exposure. Also, for decaBDEs, hepatotoxic effect research have been relatively inconsistent. Based on animal studies, acute exposure to lower-brominated BDE exposure is potentially toxic to the human liver. Furthermore, pups appear to be more susceptible to liver damage after decaBDE exposure, when compared to adult animals. Research has shown an increase in liver weights and diffuse liver cell hypertrophy with increased cytoplasmic eosinophilia in female rat pups that were exposed to ≥2 mg/kg/day and male rat pups exposed to 146 mg/kg/day of decaBDE. Research has also shown that fatty degeneration and elevated liver enzymes can occur in male rats after receiving a decaBDE dose that is ≥300 mg/kg/day (ATSDR, 2017).

2.6.5.4 Body Mass Index

A primary focus of this dissertation research is an investigation of the potential association of PBDEs and obesity. Studies in this area of research has been relatively limited and inconclusive. However, the following are some epidemiologic findings concerning the association of body mass

index (BMI) with PBDE levels. The Centers for Disease Control & Prevention defines obesity as having a BMI that is greater than 30. BMI is a calculation of an individual's weight in kilograms divided by the square of height in centimeters. In general, research shows that there is a moderate correlation between BMI and body fat (Centers for Disease Control & Prevention [CDC], 2015). This is important to remember due to the lipophilicity of PBDEs and their propensity to accumulate in the human body (Hooper & McDonald, 2000). First, in a study of Taiwanese mothers, investigators reported that children had low birth weight and height, and a decrease in Quetelet's BMI, after a daily intake of 20.6 ng/kg/day via breastmilk (Costa & Giordano, 2007). This dose is lower than the average levels of PBDEs found in American human breast milk (approximately 306 ng/kg/day) but higher than levels reported in the general Taiwan population in 2001 (Costa & Giordano, 2007). Other studies have reported no associations between PBDE exposure and the latter physical health endpoints in children. Next, a follow-up study of the Center for the Health Assessment of Mothers and Children of Salinas cohort was conducted to investigate the association between blood levels of BDE-47, 99, 100, and 153 with measures of obesity like obesity and overweight status, BMI and waist circumference. This investigation was conducted for 224 parents and 216 children from 2-7 years old. Investigators found no association between PBDE levels and measures of obesity. Although, once investigators adjusted for gender, significant effect modification was observed. Thus, investigators conducted the analyses separately, for each gender, and found a significant positive relationship between BMI z-score in 3.5-year-old boys and a 10-fold rise in PBDE levels. This suggests that PBDEs have potential obesogenic effects for in-utero exposure in male boys (ATSDR, 2017). On the other hand, a significant negative association was observed in 3.5-year-old girls. Interestingly, Vuong et al. have reported no significant association between PBDE levels in maternal blood, during the 16th week of pregnancy (geometric mean of

39.1 ng/g lipid), and weight or height of children from 1 to 8 years old. However, Vuong and colleagues found a negative association between BDE-153 and body mass index for children who were 2 to 8 years old. A lower percent of body fat was also found for 8-year-old children (Vuong et al., 2016). Finally, Agay-Shay et al. also found no significant associations between BMI z-scores or risk of being overweight in children and maternal PBDE colostrum levels. It should be noted that Agay-Shay et al. did not separate their analyses by sex as was done in the abovementioned Salinas cohort study (Agay-Shay et al., 2015).

Chapter 3

Methods

3.1 Data Source

The data analyzed for this research was generated from the 2003-2004 National Health and Nutritional Survey (NHANES). NHANES is a major data collection program of the National Center for Health Statistics (NCHS), which is a part of the Centers for Disease Control and Prevention (CDC). The primary goal of NCHS is to generate vital and health statistics for the country. Thus, the primary function of NHANES is to evaluate the health and nutritional status of American children and adults. In order to generate statistical data on the amount, type, and distribution of illnesses and disabilities within the United States, the National Health Monitoring Act of 1956 was created (CDC, 2012).

The NHANES program was officially operational in the early 1960s. Since then, it has conducted various surveys focused on different demographic groups and health topics. Prior to 1999, NHANES had been conducted periodically for periods of 2-4 years. However, there would be periods of 1-5 years where health data were not being collected. Since 1999, the NHANES program, now known as Continuous NHANES, has collected health and nutritional data on a yearly basis to address emerging health concerns (CDC, 2012; Donauer et al., 2015).

The NHANES program surveys a representative sample of the American population every year, amounting to approximately 5,000 people. These survey participants inhabit 15 counties

throughout the country, which NHANES visit on a yearly basis. NHANES intentionally oversamples minority populations (*e.g.*, African Americans, and Hispanics) and the elderly (60 years or older) to produce reliable statistics. As it relates to the elderly, NCHS is currently attempting to increase the knowledge concerning their health status. NHANES is a primary vehicle for this target. While all participants visit the physician, in general, the older the person the more extensive the examination tends to be. As it relates to minorities, oversampling is conducted because minority groups tend to have drastically different health status and characteristics in comparison to non-minorities (CDC, 2012; Donauer et al., 2015).

The current annual NHANES randomly selects approximately 7,000 American residents who have an opportunity to participate in the survey. It is also important to note that their participation is voluntary and confidential. Participants that are selected for the survey receive a standardized physical examination along with a personal interview. The health interviews are conducted in the homes of survey participants. The health examinations, on the other hand, are conducted in fully-equipped and specially-designed mobile examination centers (MECs) that travel across the nation during the survey period. These MECs are staffed with dietary and health interviewers, physicians, medical and health technicians. Many of the staff members are multilingual; especially in English and Spanish. In addition, the MECs uses a state-of-the-art computers system using high-end servers which efficiently processes the NHANES data while eliminating the use of manual coding or paper forms of data collection and reducing the potential for coding errors. When necessary, participants are provided vehicle transportation to and from the MECs. Surveyed individuals are provided a detailed summary of medical findings and are compensated for their participation (CDC, 2012; Donauer et al., 2015).

The collected data is published publically on the NHANES website and include the following subsets: Demographics, Dietary, Examination, Laboratory, Questionnaire, and Limited Access (NHANES, 2005a,b; NHANES, 2007; NHANES, 2008a,b). Demographics, Examination and Laboratory subsets were used for this dissertation research. From the Demographics subset, the Demographic Variables & Sample Weights XPT extension file was downloaded to include age, gender and ethnicity in the analytical models. From the Examination subset, the Body Measures XPT extension file was downloaded to include height (cm), weight (kg) and body mass index (BMI). From the Laboratory subset, the Brominated Flame Retardants XPT extension file was downloaded to include all the polybrominated diphenyl ether concentrations found in the blood serum of study participants. Also from the laboratory subset, the Cholesterol – Low Density Lipoprotein (LDL) & Triglycerides XPT was downloaded to include the LDL cholesterol and triglycerides. This process was repeated for comparative analyses of phthalates using the Phthalates – Urine XPT file, and Dioxin-Like PCBs using the Dioxins, Furans, & Coplanar PCBs XPT file. Each of the XPT extension files are attached with a word document which provide a description of the measured variable, limit of detection when necessary, sample requirements, sampling protocols and procedures, and other important information pertaining to the data.

3.2 Sampling

3.2.1 PBDE Sampling

Participants that were eligible for this research were 12 years or older; age-capped at 85 years old. This includes a total of 2337 individuals. For confidentiality and for cross-analyses of data, every individual was assigned a unique survey participant identifier (SEQN). Their PBDE

concentrations were determined from an extraction of blood serum and/or plasma from each participant. These specimens were collected in vials and stored under the appropriate frozen temperature of -20 °C as elicited in the NHANES Laboratory/Medical Technologists Procedures Manual (LPM). Once specimens were collected, they were processed and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for examination (CDC, 2012; NHANES, 2007).

The concentration of PBDEs are measured after sample cleanup and by using solid-phase extraction. First, samples are pretreated using a Gilson 215 liquid handler. This process involves the automated addition of internal standards, formic acid (denaturant) and water (diluent) and mixing in-between each addition by rotation. The use of formic acid allows for the extraction of the PBDEs from the samples. Next, during the extraction step, the analytes of interest of transferred from an aqueous medium to an organic solvent. Then, samples are cleaned up by removing co-extracted lipids through elution of the extract, using 8 mL of hexane, through a column of silica (0.1g) and 1 g of silica/sulfuric acid (33% by weight). PBDE samples are cleaned and extracted using an automated solid phase extraction workstation (Rapid Trace®, Caliper Life Sciences). In addition, samples are evaporated by controlling vacuum, temperature and vortex action using RapidVap® (LabConco) and transferred into gas chromatography vials for analysis (NHANES, 2007).

Isotope dilution gas chromatography high-resolution mass spectrometry (GC/IDHRMS) is used to determine the final concentration of PBDE congeners. GC/IDHRMS allows for the reduction or elimination of many interferences typically associated with low-resolution

measurement of organohalogen compounds. Serum concentrations are reported in a lipid weight basis (ng/g lipid) which is preferable due to PBDEs affinity for lipids and, thus, are distributed within the body according to the distribution of the tissues lipid content (NHANES, 2007).

3.2.2 DL-PCB Sampling

Participants that were eligible for this research were 12 years or older; age-capped at 85 years old. This includes a total of 1723 individuals. For confidentiality and for cross-analyses of data, every individual was assigned a unique survey participant identifier (SEQN). Their dl-PCB concentration was determined from an extraction of blood serum and/or plasma from each participant. These specimens were collected in vials and stored under the appropriate frozen temperature of -20 °C as elicited in the NHANES Laboratory/Medical Technologists Procedures Manual (LPM). Once specimens were collected, they were processed and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for examination (CDC, 2012; NHANES, 2008a).

Nine dL-PCBs were measured in serum using high resolution gas chromatography/isotope-dilution high-resolution mass spectroscopy (HRGC/ID-HRMS) and include the following: PCB 105, PCB 118, PCB 156, PCB 157, PCB 167, PCB 189, PCB 126, PCB 81, PCB 169. 5 to 10 mL serum specimens to be analyzed for dl-PCBs were spiked with ^{13}C-labeled ($^{13}C_{12}$) internal standards. Then, the analytes of interest were isolated in hexane using the C18 solid phase extraction which was followed by a Power-Prep/6 (Fluid Management Systems) automated cleanup and enrichment procedure using acidic, basic, and neutral multilayered silica gel and alumina columns coupled to an AX-21 carbon column. From carbon to toluene, Dl-PCBs are

isolated in the reverse direction. After sample cleanup, a Turbovap II (Caliper Life Sciences) was used to evaporate excess solvent to 350 μL. The remaining solvent was transferred to silanized auto sampling vials which contained 1 μL of dodecane "keeper" and was allowed to go to "dryness". Each vial was reconstituted with 5 μL $^{13}C_{12}$-labeled external standard before quantification. Then, sample extracts were analyzed for dl-PCBs by HRGC/ID-HRMS. Using a GC Pal (Leap Technology) auto sampler, 2μL were injected into an Agilent Technologies 6890 Gas Chromatograph operated in the splitless injection mode with a flow of 1 mL/minute helium through a DB-5ms capillary column (30 m × 0.25 mm × 0.25 μm film thickness) where analytes are separated prior to entering a Thermo Finnigan MAT95 XP (5 kV) magnetic sector mass spectrometer operated in EI mode at 40 eV, using selected ion monitoring (SIM) at 10,000 resolving power (10% valley) (NHANES, 2008a).

In order to calibrate the mass spectrometer response factor v. concentration, calibration standards containing known concentrations of each native ($^{12}C_{12}$) compound and its corresponding $^{13}C_{12}$ internal standard were used. Through interpolation from individual linear calibration curves the concentration of each analyte was derived and adjusted for sample weight. A variety of established criteria to evaluate the validity of all mass spectrometry data including: signal-to-noise ratio ≥ 3 for the smallest native ion mass, relative retention time ratio of native to isotopically labeled analyte within 3 parts per thousand compared to a standard, chromatographic isomer specificity index with 95% limits, instrument resolving power ≥ 10,000, response ratios of the two $^{12}C_{12}$ and $^{13}C_{12}$ ions within ± 20 % of their theoretical values and analyte recovery≥10 % and ≤ 120%. The method detection limit was calculated by correcting for sample weight and recovery, for each analyte. A summation method was used to estimate total lipid content of each

specimen from its total cholesterol and triglycerides values. Serum concentrations are reported in ng/g lipids (NHANES, 2008a).

3.2.3 Phthalate Sampling

In order to compare results with those of PBDE analyses, participants from 6 to 11 years old were removed from the data set. Participants that were eligible for this research were 12 years or older; age-capped at 85 years old. This includes a total of 2263 individuals. For confidentiality and for cross-analyses of data, every individual was assigned a unique survey participant identifier (SEQN). Phthalate concentration was determined from urine samples from each participant. These specimens were collected in vials and stored under the appropriate frozen temperature of -20 °C as elicited in the NHANES Laboratory/Medical Technologists Procedures Manual (LPM). Once specimens were collected, they were processed and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for examination (CDC, 2012; NHANES, 2008b).

High performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS) was used for the quantitative detection of the following phthalate metabolites in urine: mono(2-ethyl-5-carboxypentyl) phthalate (mECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (mEHHP), mono(2-ethyl-5-oxohexyl) phthalate (mEOHP), monoisononyl phthalate (mNP), monobenzyl phthalate (mBzP), monooctyl phthalate (mOP), mono (2-ethylhexyl) phthalate (mEHP), monocyclohexyl phthalate (mCHP), mono (3-carboxypropyl) phthalate (mCPP), mono-isobutyl phthalate (miBP), monobutyl phthalate (mBP), monoethyl phthalate (mEP) and monomethyl phthalate (mMP). Urinary samples were processed

using enzymatic deconjugation of the glucuronidated phthalate monoesters. This was followed by on-line solid phase extraction along with reversed phase HPLC-ESI-MS/MS. The incorporation of isotopically-labeled internal standards for each of the phthalate metabolites allowed the improvement of assay precision. Also, 4-methyl umbelliferone glucuronide was used to track deconjugation efficiency. Urinary concentrations are reported in ng/mL (NHANES, 2008b).

3.3 Data Analysis

Demographics, Examination and Laboratory XPT extension files were downloaded from the 2003-2004 NHANES. These laboratory subsets were uploaded and merged into SAS statistical software (Version 9.4) for preliminary analyses. Preliminary analyses included generating frequency distributions for all demographic groups and analytes (*e.g.*, PBDEs, dl-PCBs, Phthalates). For PBDEs, analyses were performed on a sum of 10 congeners and two of the most prevalent congeners, BDE-47 and BDE-99, representing 75% of PBDEs in commercial mixtures (NHANES, 2007.). For dl-PCBs, analyses were performed on 9 congeners (NHANES, 2008a). For Phthalates, analyses were performed on 13 phthalate metabolites (NHANES, 2008b). Descriptive statistics such as the mean, minimum, maximum, standard deviation and standard error were calculated for analyte concentrations given age, gender, and ethnicity. Microsoft Excel was also used to generate graphs and tables for data visualization and supplementary analysis.

During preliminary analyses of the concentration of analytes, it was determined that 562 observations did not have a recorded concentration for dl-PCBs; and 434 were missing for phthalates (NHANES, 2008b). These observations were removed from the analyses to reduce bias. In addition, 297 observations had concentrations which were below the limit of detection (LOD)

for PBDEs. The LOD of every BDE congener was identified from the NHANES Lab Manual for PBDEs. Following industrial convention, the missing values were replaced by LOD/Square root (2) (NHANES, 2007). There were other instances where the data of interest was missing. Specifically, some individual data was missing for height in kg, weight in cm, BMI, triglycerides, and LDL cholesterol. In these cases, the missing data were omitted to reduce the bias or misinterpretation of analytical results.

To investigate the validity of the research hypotheses, the following analyses were performed. Two major statistical procedures were utilized including analysis of variance (ANOVA) and logistic regression, when appropriate. First, ANOVA was calculated for any analysis that included dichotomous (or categorical) variables such as gender, age group or ethnicity. ANOVA was used to determine whether the average concentrations of analytes were significantly different among genders, age groups, ethnicities, and genders *and* ethnicities. A significance level of 0.05 (95% confidence level) was used for all ANOVA analyses. In other words, a resulting p-value less than 0.05 indicated a significant result.

In addition, a logistic regression was conducted for BMI, given quartiles of analyte concentrations. Quartiles of analyte concentration were generated for statistical significance. It should also be noted that the CDC generates BMI values for adults who are 20 years or older. Thus, the data analysis of BMIs excluded participants who were under the age of 20. Based upon guidelines set forth by the CDC, participants were categorized according to their BMI. Specifically, participants were marked as underweight (BMI<18.5), normal or healthy weight (BMI=18.5-24.9), overweight (BMI=25.0-29.9), or obese (BMI≥30) (CDC, 2015). The logistic

regression analyses were used to calculate odds ratios (OR) which determined whether higher concentrations of a given analyte led to a higher odd of being overweight or obese. These analyses incorporated age (20 years or older), gender, ethnicity, LDL cholesterol, triglycerides and analytes separated into quartiles. If the OR values are equal to 1, this signifies that there is no difference between comparative groups in relation to an outcome of interest. If OR is above or less than 1 than one of the two measure groups has a greater or lesser odd, respectively, of achieving an outcome in question. The further away from 1 the OR, the more drastic the difference between the two comparative groups (*e.g.*, males v. females). To account for precision of OR measurements, 95% Wald confidence limits are assigned for each calculation of OR point estimates. A point estimate outside of that confidence interval is deemed significant.

Lastly, analyte concentrations among demographic categories were specifically compared using a paired t-test in Microsoft Excel. For each analysis a 95% confidence interval was utilized, where a calculated p-value less than 0.05 indicated a significant result. Correlation coefficients were used to present the strength of association among analyte concentrations. In addition, correlation of determinations were generated to measure the percent of variation that could be explained by the regression equation.

Chapter 4

Results

Results are ordered by analyte(s); that is, BDE-47, BDE-99, sum of PBDEs, dl-PCBs, followed by phthalates. Analysis for each analyte(s) was conducted to determine the following:

- Frequency distribution of analytes, demographic categories and demographic categories per quartile.
- Average concentration of analytes for all individuals in the sample and per demographic category.
- Comparison of means for all demographic categories using ANOVA.
- Calculation of odds of being overweight and obese in association with analyte concentration compared to other factors, using logistic regression.
- Comparison of results using paired t-test.
- Summary of results.

4.1 Overall Detection Frequency

Analytes were detected in at least 85% of samples. Samples detected include values that were below the limit of detection, which were subsequently treated using LOD/Square root (2). These values could not be separated from the graph since they were not enumerated for dl-PCBs. The CDC automatically used the LOD/Square root (2) treatment for such analytes. Also, it should be noted that for the sum of all PBDEs, missing values from individual congeners were

automatically omitted in SAS and did not affect the final concentrations calculated for participants.

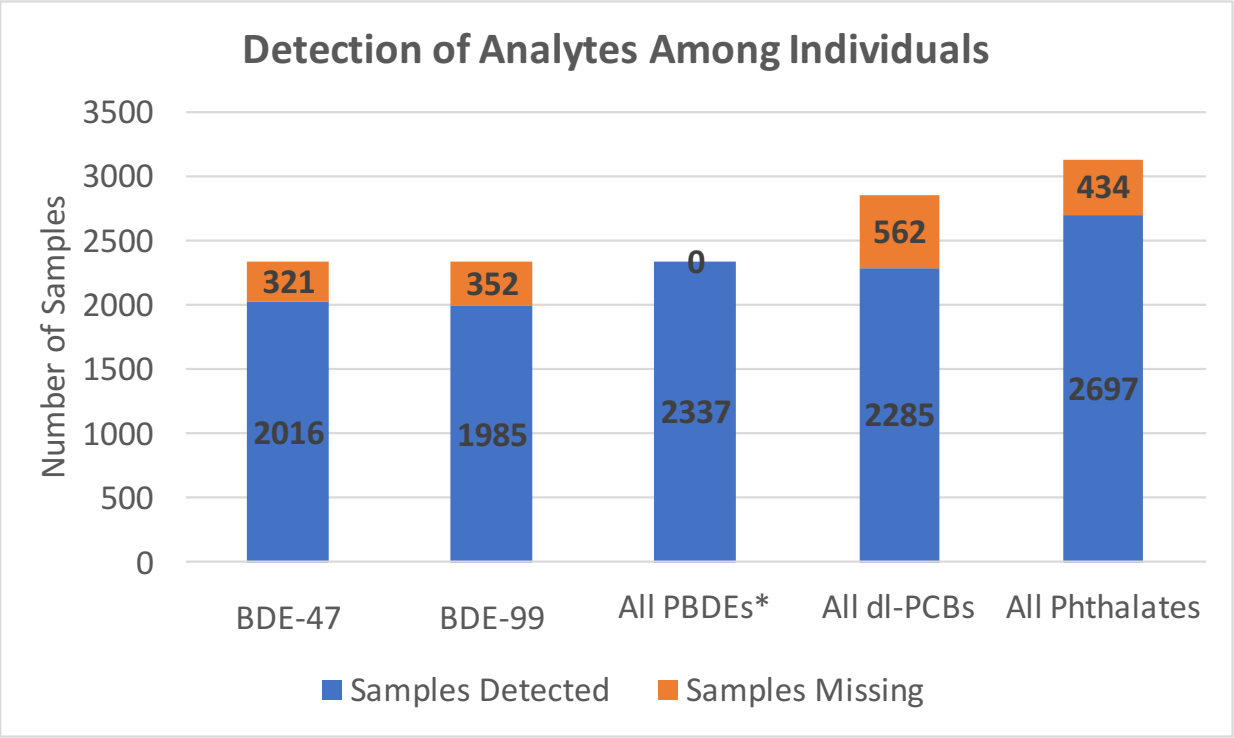

Figure 5. Number of samples detected.

Table 2. Detections among individuals in the dataset.

		BDE-47	BDE-99	All PBDEs*	All dl-PCBs	All Phthalates
Samples	Detected	2016	1985	2337	2285	2697
	Missing	321	352	0	562	434
	Percent Detected	86.26%	84.94%	100.00%	80.26%	86.14%
*Note: Although the sum of PBDEs contains some missing values, when calculating the sum of concentrations SAS automatically ignores missing values.						

4.2 Polybrominated Diphenyl Ethers

4.2.1 BDE-47

4.2.1.1 Frequency Distributions

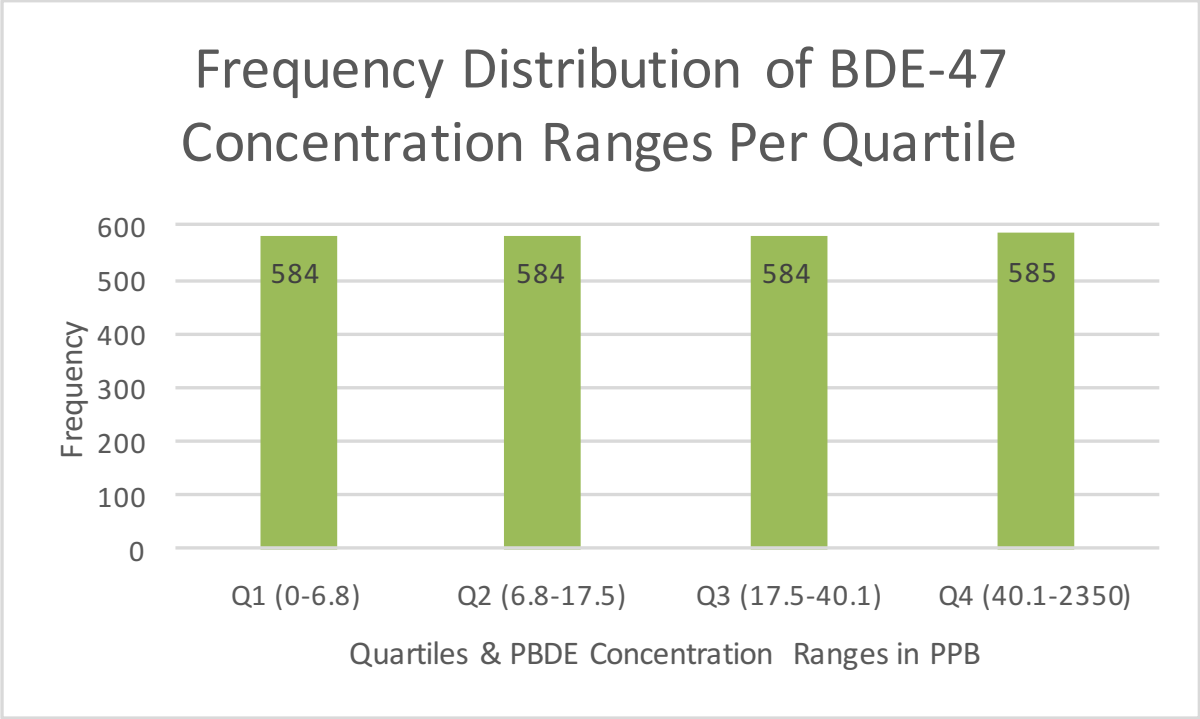

Figure 6. Frequency distribution of BDE-47 per quartile range.

Table 3. Frequency distribution table of BDE-47 per quartile range.

BDE-47 (Quartiles)				
Concentration Range	**Frequency**	**Percent**	**Min**	**Max**
Q1 (0-6.8)	584	24.99%	0.004384062	2350
Q2 (6.8-17.5)	584	24.99%		
Q3 (17.5-40.1)	584	24.99%		
Q4 (40.1-2350)	585	25.03%		

Table 4. Frequency distribution table of age ranges cross-referenced with BDE-47 quartiles. RIDAGEYR refers to age in years from the 2003-2004 NHANES Demographic dataset and LBXBR3LA refers to BDE-47 from the 2003-2004 NHANES Brominated Flame Retardants dataset.

The FREQ Procedure

Frequency
Percent
Row Pct
Col Pct

Table of RIDAGEYR by LBXBR3LA

RIDAGEYR(Age at Screening Adjudicated - Recode)	LBXBR3LA(2,2',4,4'-tetrabromphenyl ether lipid ad)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
12-18	163 6.97 24.70 27.91	135 5.78 20.45 23.12	177 7.57 26.82 30.31	185 7.92 28.03 31.62	660 28.24
19-30	84 3.59 19.76 14.38	96 4.11 22.59 16.44	133 5.69 31.29 22.77	112 4.79 26.35 19.15	425 18.19
31-50	127 5.43 23.92 21.75	172 7.36 32.39 29.45	120 5.13 22.60 20.55	112 4.79 21.09 19.15	531 22.72
51-84	186 7.96 28.27 31.85	172 7.36 26.14 29.45	142 6.08 21.58 24.32	158 6.76 24.01 27.01	658 28.16
85 & above	24 1.03 38.10 4.11	9 0.39 14.29 1.54	12 0.51 19.05 2.05	18 0.77 28.57 3.08	63 2.70
Total	584 24.99	584 24.99	584 24.99	585 25.03	2337 100.00

Table 5. Frequency distribution table of gender cross-referenced with BDE-47 quartiles. RIAGENDR refers to gender from the 2003-2004 NHANES Demographic dataset and LBXBR3LA refers to BDE-47 from the 2003-2004 NHANES Brominated Flame Retardants dataset.

The FREQ Procedure

Frequency
Percent
Row Pct
Col Pct

Table of RIAGENDR by LBXBR3LA

RIAGENDR(Gender)	LBXBR3LA(2,2',4,4'-tetrabromphenyl ether lipid ad)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
Male	260 11.13 23.09 44.52	295 12.62 26.20 50.51	265 11.34 23.53 45.38	306 13.09 27.18 52.31	1126 48.18
Female	324 13.86 26.75 55.48	289 12.37 23.86 49.49	319 13.65 26.34 54.62	279 11.94 23.04 47.69	1211 51.82
Total	584 24.99	584 24.99	584 24.99	585 25.03	2337 100.00

Table 6. Frequency distribution table of ethnicity cross-referenced with BDE-47 quartiles. RIDRETH1 refers to CDC-defined ethnicity from the 2003-2004 NHANES Demographic dataset and LBXBR3LA refers to BDE-47 from the 2003-2004 NHANES Brominated Flame Retardants dataset.

The FREQ Procedure

Frequency
Percent
Row Pct
Col Pct

Table of RIDRETH1 by LBXBR3LA

RIDRETH1(Race/Ethnicity - Recode)	LBXBR3LA(2,2',4,4'-tetrabromphenyl ether lipid ad) Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
Mexican_American	112 4.79 20.07 19.18	118 5.05 21.15 20.21	175 7.49 31.36 29.97	153 6.55 27.42 26.15	558 23.88
Other_Hispanic	13 0.56 17.57 2.23	23 0.98 31.08 3.94	21 0.90 28.38 3.60	17 0.73 22.97 2.91	74 3.17
NonHispanic_White	284 12.15 27.73 48.63	269 11.51 26.27 46.06	222 9.50 21.68 38.01	249 10.65 24.32 42.56	1024 43.82
NonHispanic_Black	149 6.38 25.47 25.51	146 6.25 24.96 25.00	144 6.16 24.62 24.66	146 6.25 24.96 24.96	585 25.03
OtherRace_IncludingMultiRacial	26 1.11 27.08 4.45	28 1.20 29.17 4.79	22 0.94 22.92 3.77	20 0.86 20.83 3.42	96 4.11
Total	584 24.99	584 24.99	584 24.99	585 25.03	2337 100.00

4.2.1.2 Comparative Statistics

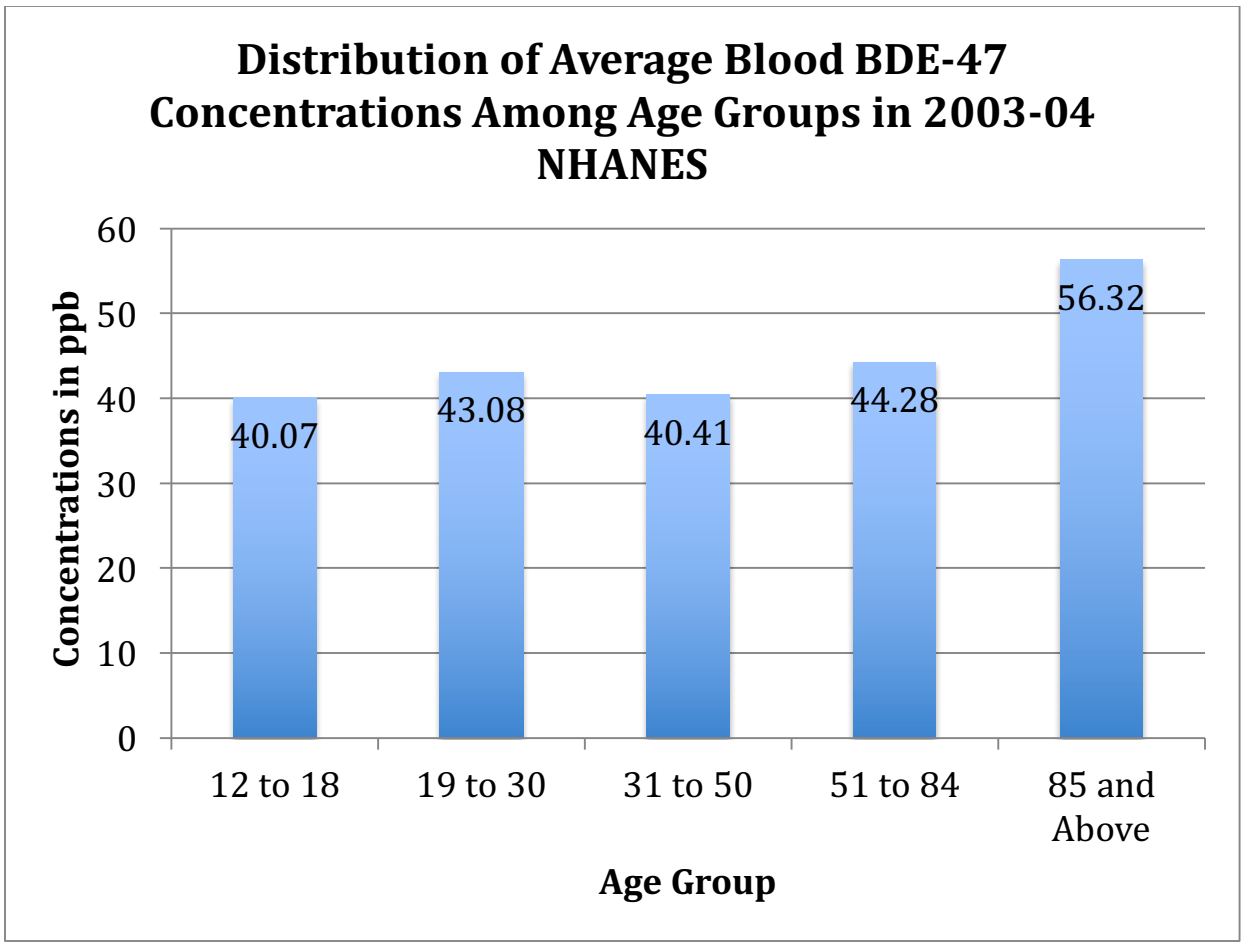

Figure 7. Comparison of average BDE-47 concentrations among age groups, in years. Difference in mean BDE-47 concentrations between age groups were insignificant; p-value >0.05.

Table 7. Comparison of average BDE-47 concentrations among age groups, in years.

Age Group, in years	12 to 18	19 to 30	31 to 50	51 to 84	85 and Above
Concentrations, in ng/g lipids	40.068	43.083	40.411	44.275	56.318

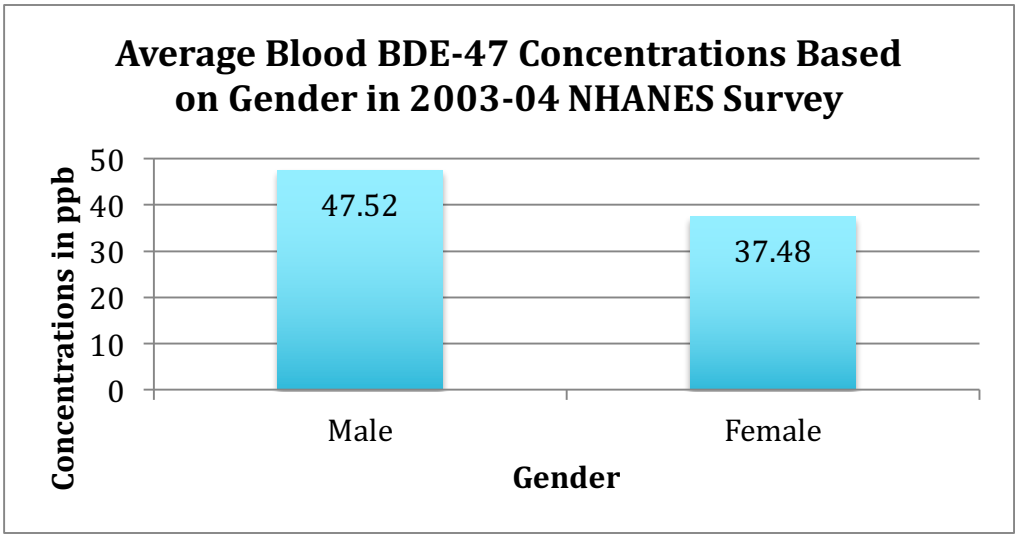

Figure 8. Comparison of average BDE-47 concentrations among genders. Difference in mean BDE-47 concentrations between genders were significant; p-value <0.05.

Table 8. Comparison of average BDE-47 concentrations among genders.

Gender	Male	Female
Concentrations, in ng/g lipids	47.524	37.476

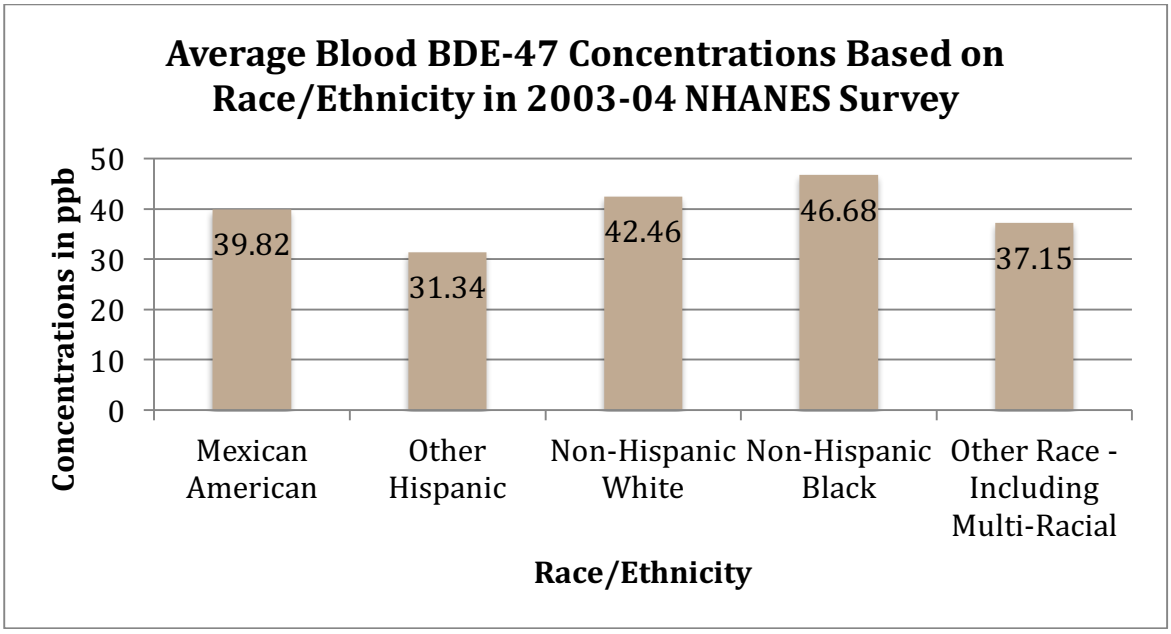

Figure 9. Comparison of average BDE-47 concentrations among ethnic groups. Difference in mean BDE-47 concentrations between ethnicities were insignificant; p-value >0.05.

Table 9. Comparison of average BDE-47 concentrations among ethnic groups.

Ethnicity	Mexican American	Other Hispanic	Non-Hispanic White	Non-Hispanic Black	Other Race - Including Multi-Racial
Concentrations, in ng/g lipids	39.819	31.341	42.463	46.681	37.145

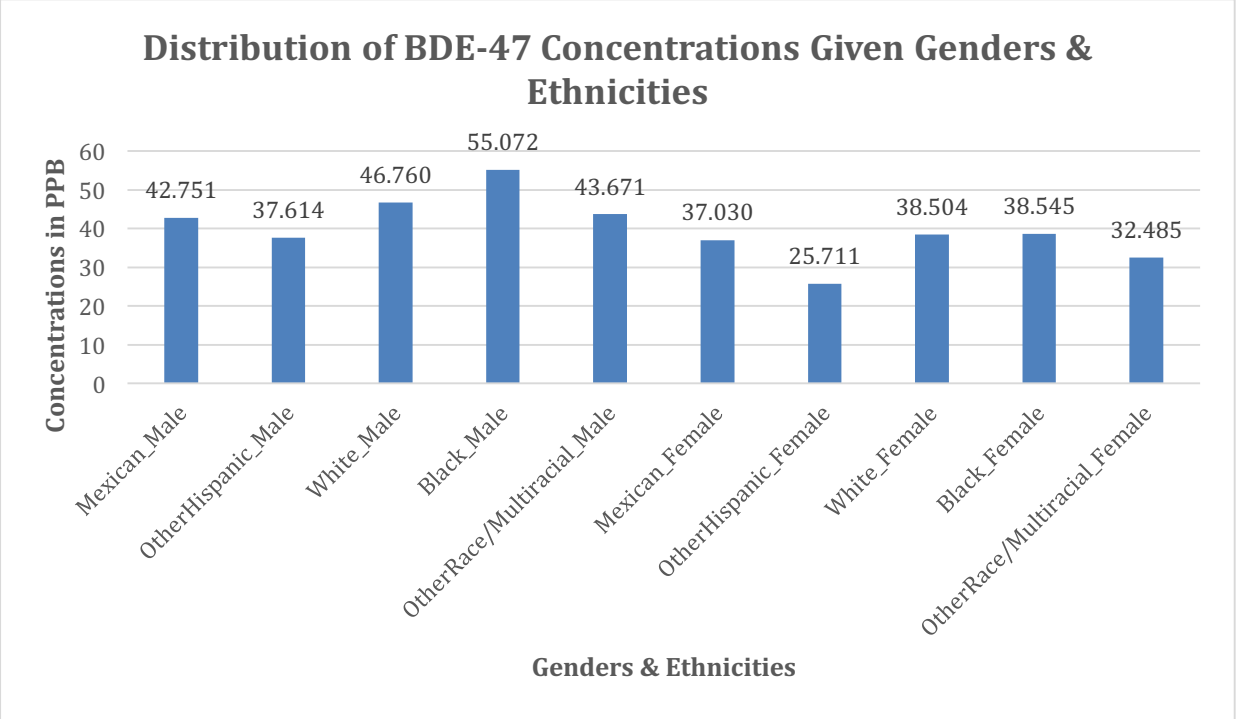

Figure 10. Comparison of average BDE-47 concentrations among gender and ethnicities. Difference in average BDE-47 concentrations is insignificant, given genders & ethnicities; p-value >0.05.

Table 10. Comparison of average BDE-47 concentrations among gender and ethnicities.

Ethnicity & Gender	**Concentrations, in ng/g lipids**
Mexican_Male	42.751
OtherHispanic_Male	37.614
White_Male	46.760
Black_Male	55.072
OtherRace/Multiracial_Male	43.671

Table 10. (continued).

Ethnicity & Gender	Concentrations, in ng/g lipids
OtherHispanic_Female	25.711
White_Female	38.504
Black_Female	38.545
OtherRace/Multiracial_Female	32.485

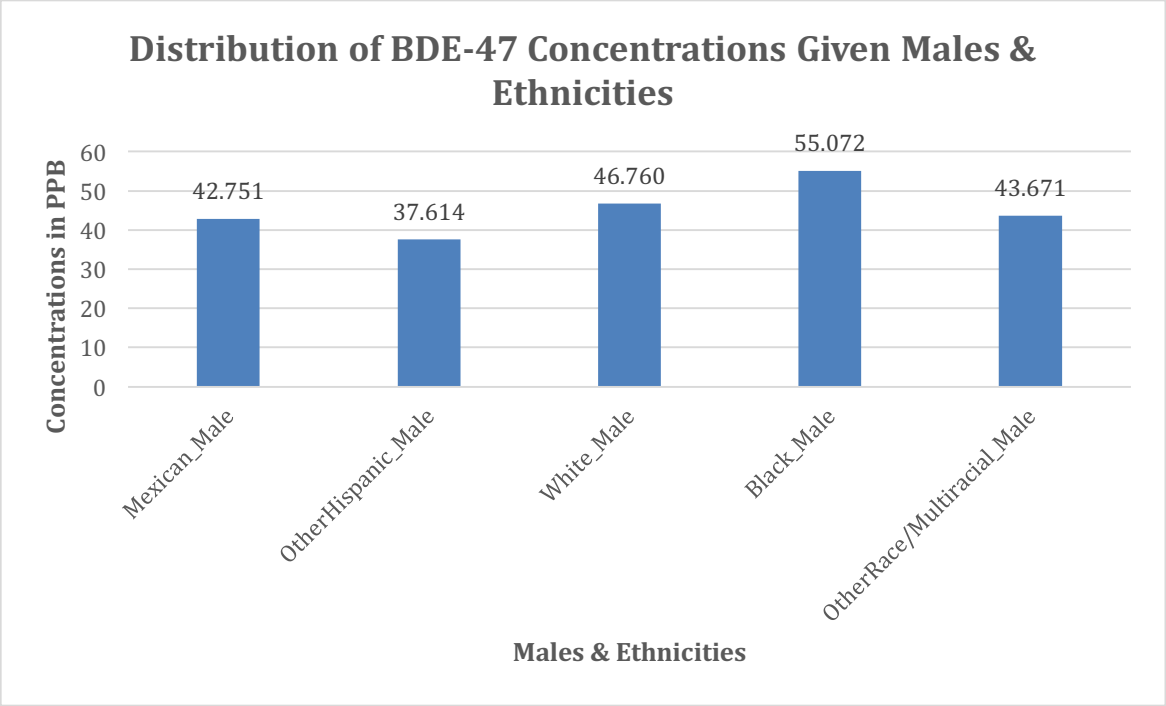

Figure 11. Comparison of average BDE-47 concentrations among males and ethnicities. Difference in average BDE-47 concentrations is insignificant, given males & ethnicities; p-value >0.05.

Table 11. Comparison of average BDE-47 concentrations among males and ethnicities.

Ethnicity & Gender	Concentrations, in ng/g lipids
Mexican_Male	42.751
OtherHispanic_Male	37.614
White_Male	46.760
Black_Male	55.072
OtherRace/Multiracial_Male	43.671

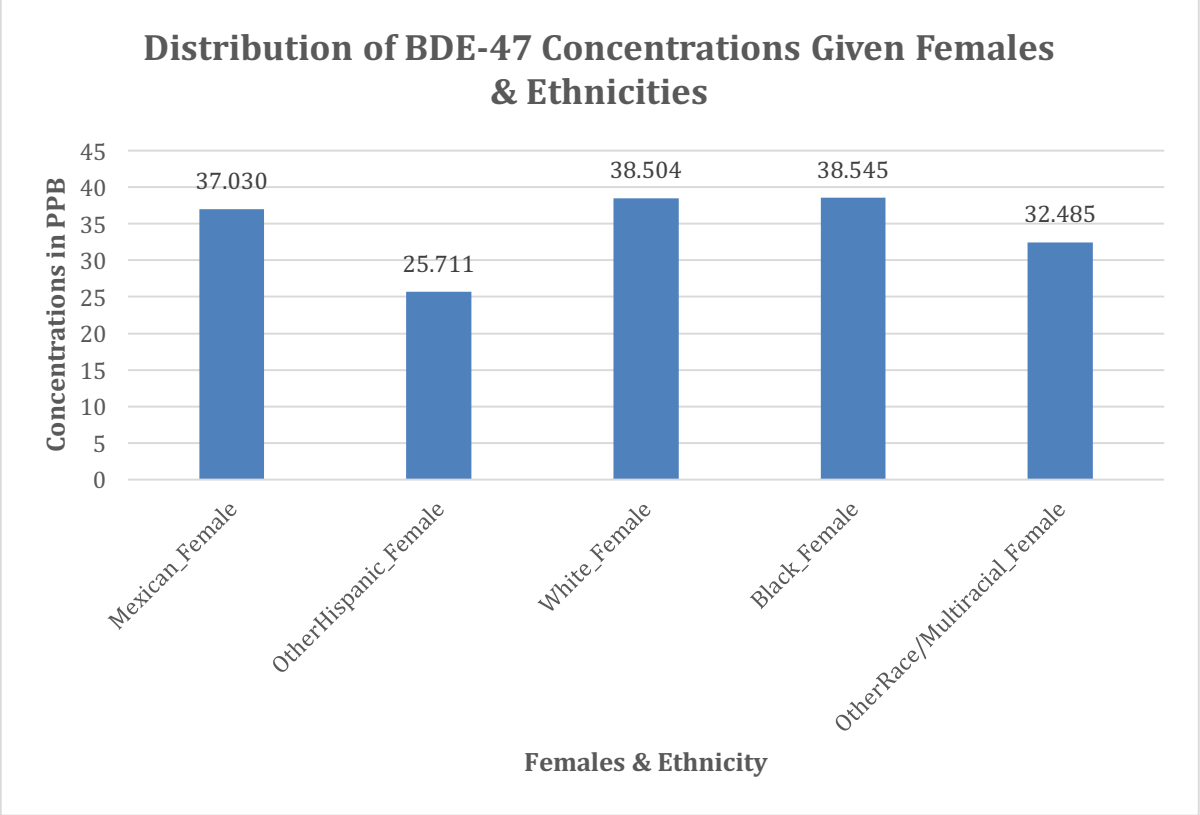

Figure 12. Comparison of average BDE-47 concentrations among females and ethnicities. Difference in average BDE-47 concentrations is insignificant, given females & ethnicities; p-value >0.05.

Table 12. Comparison of average BDE-47 concentrations among females and ethnicities.

Ethnicity & Gender	**Concentrations, in ng/g lipids**
Mexican_Female	37.030
OtherHispanic_Female	25.711
White_Female	38.504
Black_Female	38.545
OtherRace/Multiracial_Female	32.485

4.2.1.3 Logistic Regression Statistics

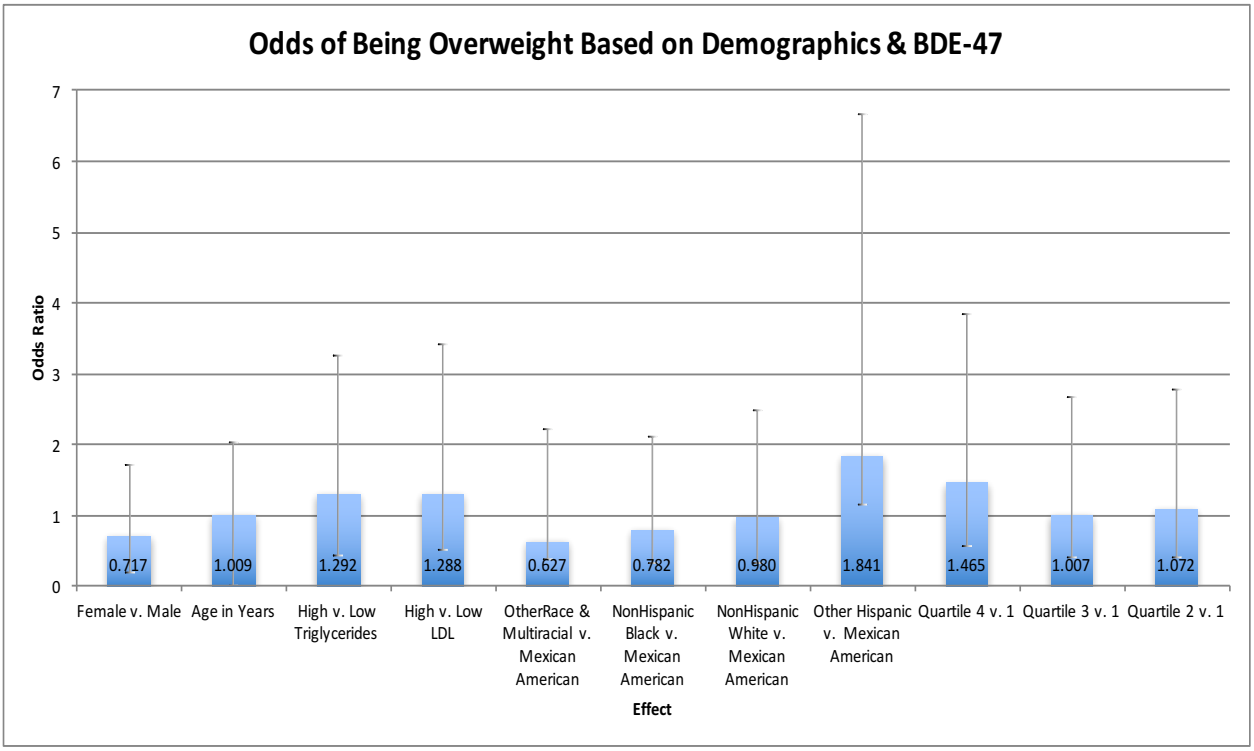

Figure 13. Odds of being overweight in relation to blood concentration of BDE-47. From a logistic regression model containing Gender, Age, Ethnicity and Quartiles as exposure variables and Overweight BMI as the outcome, Ethnicity is the only significant exposure variable which increases the odds of being overweight. Most interestingly is the 1.841 odds ratio produced for Other Hispanic (non-Mexican) Vs. Mexican categories.

Table 13. Odds of being overweight in relation to blood concentration of BDE-47.

Effect	**Odds Ratio**	**95% Confidence Intervals**	
Female v. Male	0.717	0.517	0.995
Age in Years	1.009	1.000	1.017
High v. Low Triglycerides	1.292	0.852	1.959
High v. Low LDL	1.288	0.784	2.116
OtherRace & Multiracial v. Mexican American	0.627	0.249	1.576
NonHispanic Black v. Mexican American	0.782	0.465	1.317
NonHispanic White v. Mexican American	0.980	0.644	1.491
Other Hispanic v. Mexican American	1.841	0.703	4.824

Table 13. (Continued).

Effect	Odds Ratio	95% Confidence Intervals	
Quartile 4 v. 1	1.465	0.898	2.389
Quartile 3 v. 1	1.007	0.611	1.661
Quartile 2 v. 1	1.072	0.673	1.707

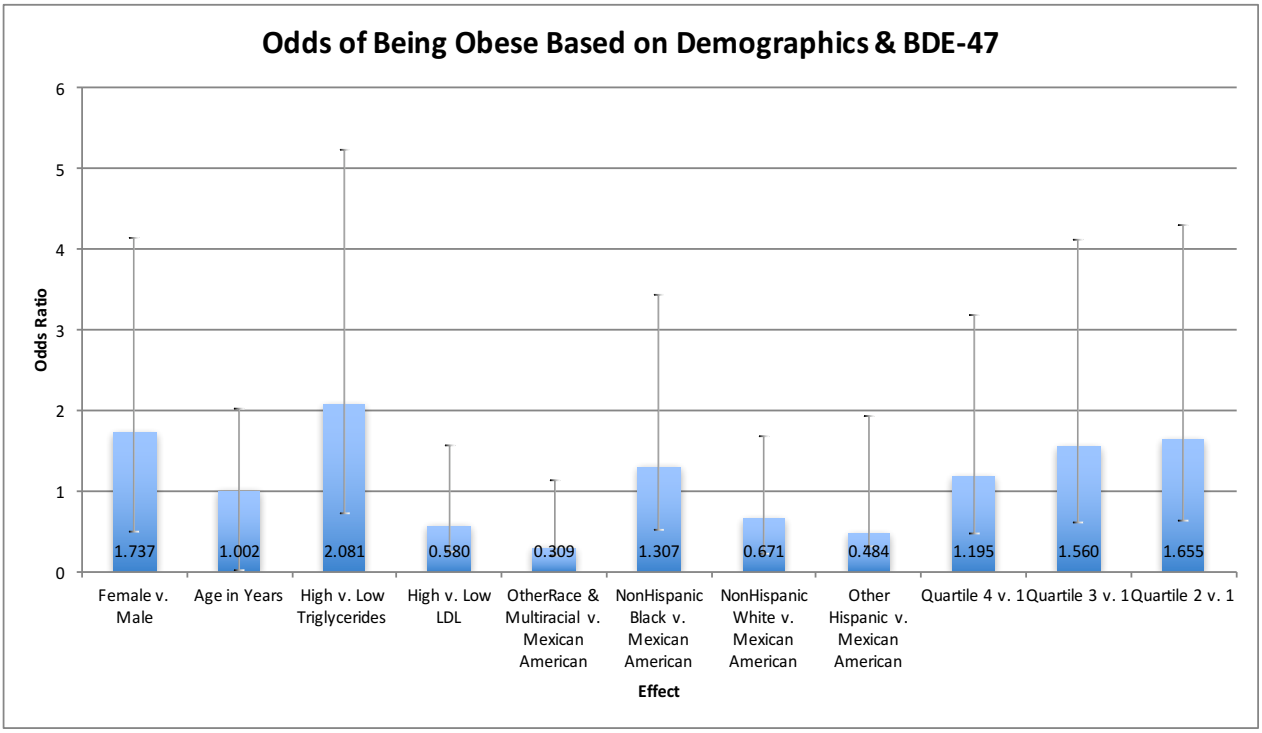

Figure 14. Odds of being obese in relation to blood concentration of BDE-47. No comparisons yielded significant odds of obese BMI.

Table 14. Odds of being obese in relation to blood concentration of BDE-47.

Effect	Odds Ratio	95% Confidence Intervals	
Female v. Male	1.737	1.251	2.412
Age in Years	1.002	0.993	1.011
High v. Low Triglycerides	2.081	1.371	3.159
High v. Low LDL	0.580	0.339	0.994
OtherRace & Multiracial v. Mexican American	0.309	0.116	0.820
NonHispanic Black v. Mexican American	1.307	0.800	2.136

Table 14. (Continued).

Effect	Odds Ratio	95% Confidence Intervals	
NonHispanic White v. Mexican American	0.671	0.443	1.017
Other Hispanic v. Mexican American	0.484	0.163	1.443
Quartile 4 v. 1	1.195	0.722	1.978
Quartile 3 v. 1	1.560	0.949	2.565
Quartile 2 v. 1	1.655	1.035	2.645

4.2.2 BDE-99

4.2.2.1 Frequency Distributions

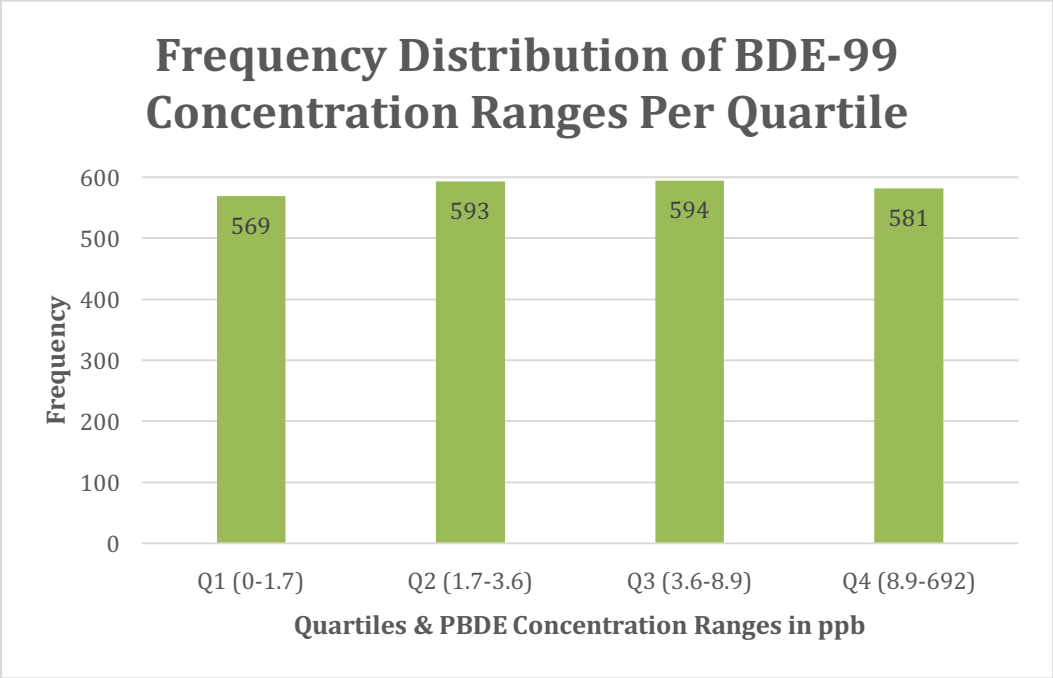

Figure 15. Frequency distribution of BDE-99 per quartile range.

Table 15. Frequency distribution table of BDE-99 per quartile range.

BDE-99 (Quartiles)				
Concentration Range	**Frequency**	**Percent**	**Min**	**Max**
Q1 (0-1.7)	569	24.35%	0.004949747	692
Q2 (1.7-3.6)	593	25.37%		
Q3 (3.6-8.9)	594	25.42%		
Q4 (8.9-692)	581	24.86%		

Table 16. Frequency distribution table of age ranges cross-referenced with BDE-99 quartiles. RIDADEYR refers to age in years from the 2003-2004 NHANES Demographic dataset and LBXBR5LA refers to BDE-99 from the 2003-2004 NHANES Brominated Flame Retardants dataset.

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of RIDAGEYR by LBXBR5LA				
RIDAGEYR(Age at Screening Adjudicated - Recode)	LBXBR5LA(2,2',4,4',5-pentabromphenyl lipid adj)				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
12-18	149 6.38 22.58 26.19	136 5.82 20.61 22.93	186 7.96 28.18 31.31	189 8.09 28.64 32.53	660 28.24
19-30	79 3.38 18.59 13.88	106 4.54 24.94 17.88	129 5.52 30.35 21.72	111 4.75 26.12 19.10	425 18.19
31-50	131 5.61 24.67 23.02	156 6.68 29.38 26.31	129 5.52 24.29 21.72	115 4.92 21.66 19.79	531 22.72
51-84	190 8.13 28.88 33.39	180 7.70 27.36 30.35	139 5.95 21.12 23.40	149 6.38 22.64 25.65	658 28.16
85 & above	20 0.86 31.75 3.51	15 0.64 23.81 2.53	11 0.47 17.46 1.85	17 0.73 26.98 2.93	63 2.70
Total	569 24.35	593 25.37	594 25.42	581 24.86	2337 100.00

Table 17. Frequency distribution table of gender cross-referenced with BDE-99 quartiles. RIAGENDR refers to gender from the 2003-2004 NHANES Demographic dataset and LBXBR5LA refers to BDE-99 from the 2003-2004 NHANES Brominated Flame Retardants dataset.

Levels of BDE99 in Parts Per Billion

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of RIAGENDR by LBXBR5LA				
	LBXBR5LA(2,2',4,4',5-pentabromphenyl lipid adj)				
RIAGENDR(Gender)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
Male	250 10.70 22.20 43.94	300 12.84 26.64 50.59	283 12.11 25.13 47.64	293 12.54 26.02 50.43	1126 48.18
Female	319 13.65 26.34 56.06	293 12.54 24.19 49.41	311 13.31 25.68 52.36	288 12.32 23.78 49.57	1211 51.82
Total	569 24.35	593 25.37	594 25.42	581 24.86	2337 100.00

Table 18. Frequency distribution table of ethnicity cross-referenced with BDE-99 quartiles. RIDRETH1 refers to CDC-defined ethnicity from the 2003-2004 NHANES Demographic dataset and LBXBR5LA refers to BDE-99 from the 2003-2004 NHANES Brominated Flame Retardants dataset.

The FREQ Procedure

Table of RIDRETH1 by LBXBR5LA

Frequency Percent Row Pct Col Pct	LBXBR5LA(2,2',4,4',5-pentabromphenyl lipid adj)				
RIDRETH1(Race/Ethnicity - Recode)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
Mexican_American	123 5.26 22.04 21.62	112 4.79 20.07 18.89	170 7.27 30.47 28.62	153 6.55 27.42 26.33	558 23.88
Other_Hispanic	16 0.68 21.62 2.81	16 0.68 21.62 2.70	21 0.90 28.38 3.54	21 0.90 28.38 3.61	74 3.17
NonHispanic_White	265 11.34 25.88 46.57	289 12.37 28.22 48.74	232 9.93 22.66 39.06	238 10.18 23.24 40.96	1024 43.82
NonHispanic_Black	138 5.91 23.59 24.25	146 6.25 24.96 24.62	152 6.50 25.98 25.59	149 6.38 25.47 25.65	585 25.03
OtherRace_IncludingMultiRacial	27 1.16 28.13 4.75	30 1.28 31.25 5.06	19 0.81 19.79 3.20	20 0.86 20.83 3.44	96 4.11
Total	569 24.35	593 25.37	594 25.42	581 24.86	2337 100.00

4.2.2.2 Comparative Statistics

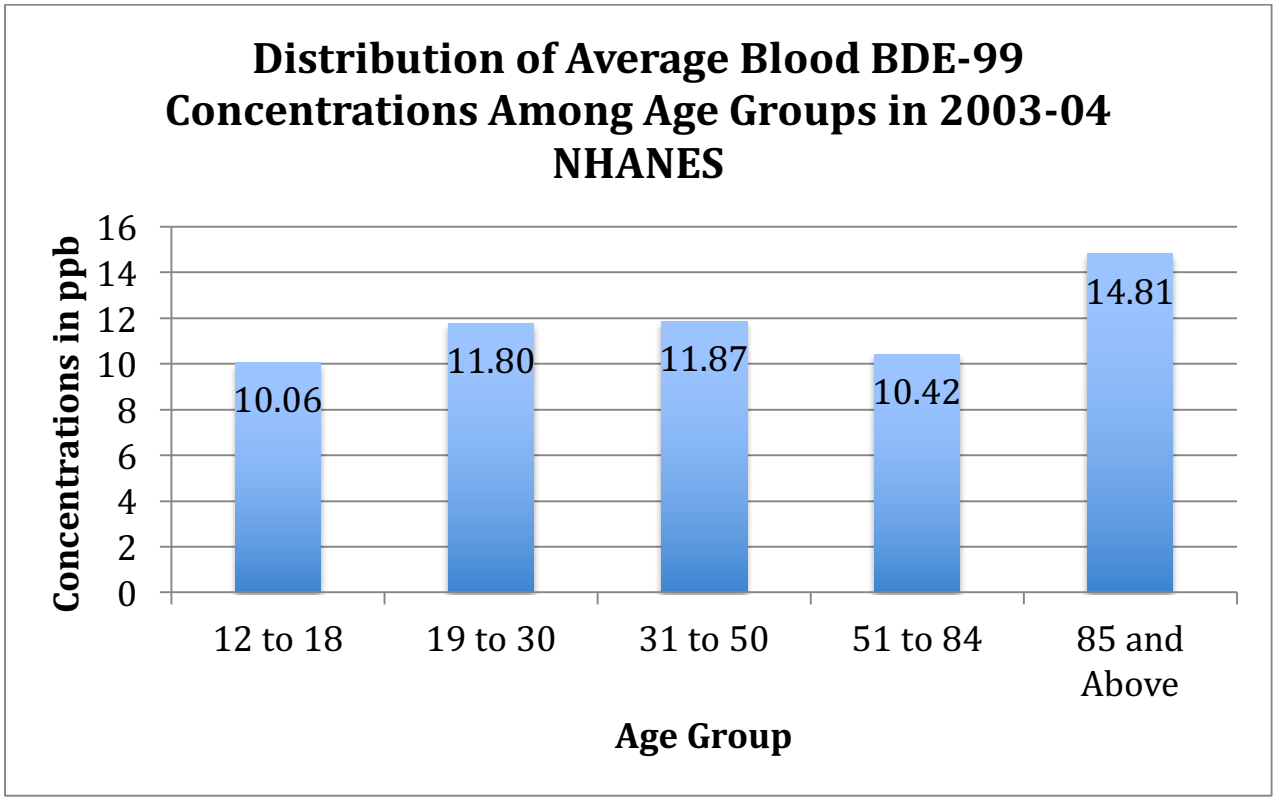

Figure 16. Comparison of average BDE-99 concentrations among age groups, in years. Difference in mean BDE-99 concentrations between age groups were insignificant; p-value >0.05.

Table 19. Comparison of average BDE-99 concentrations among age groups, in years.

Age Group, in years	12 to 18	19 to 30	31 to 50	51 to 84	85 and Above
Concentrations, in ng/g lipids	10.058	11.795	11.873	10.421	14.814

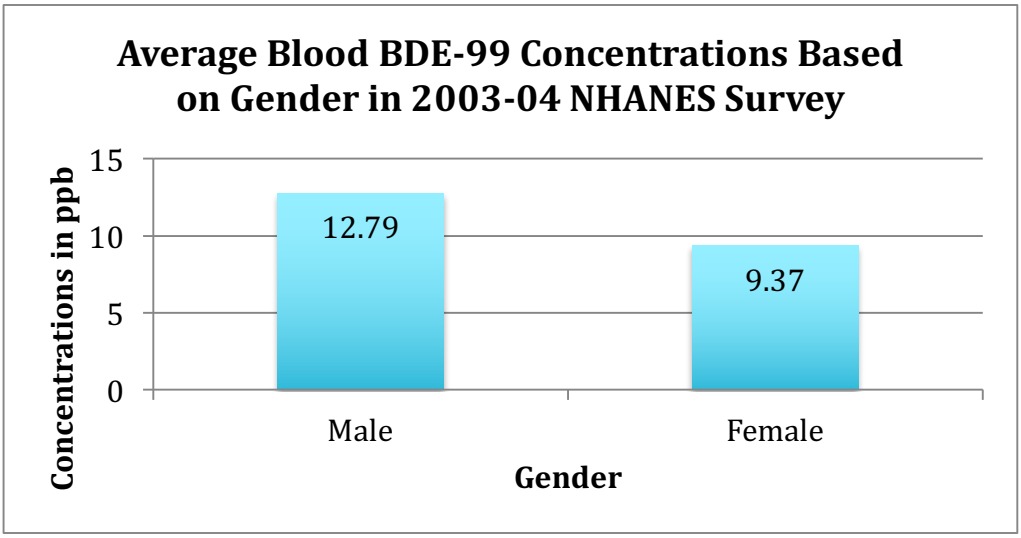

Figure 17. Comparison of average BDE-99 concentrations among genders. Difference in mean BDE-99 concentrations between genders were significant; p-value <0.05.

Table 20. Comparison of average BDE-99 concentrations among genders.

Gender	Male	Female
Concentrations, in ng/g lipids	12.793	9.365

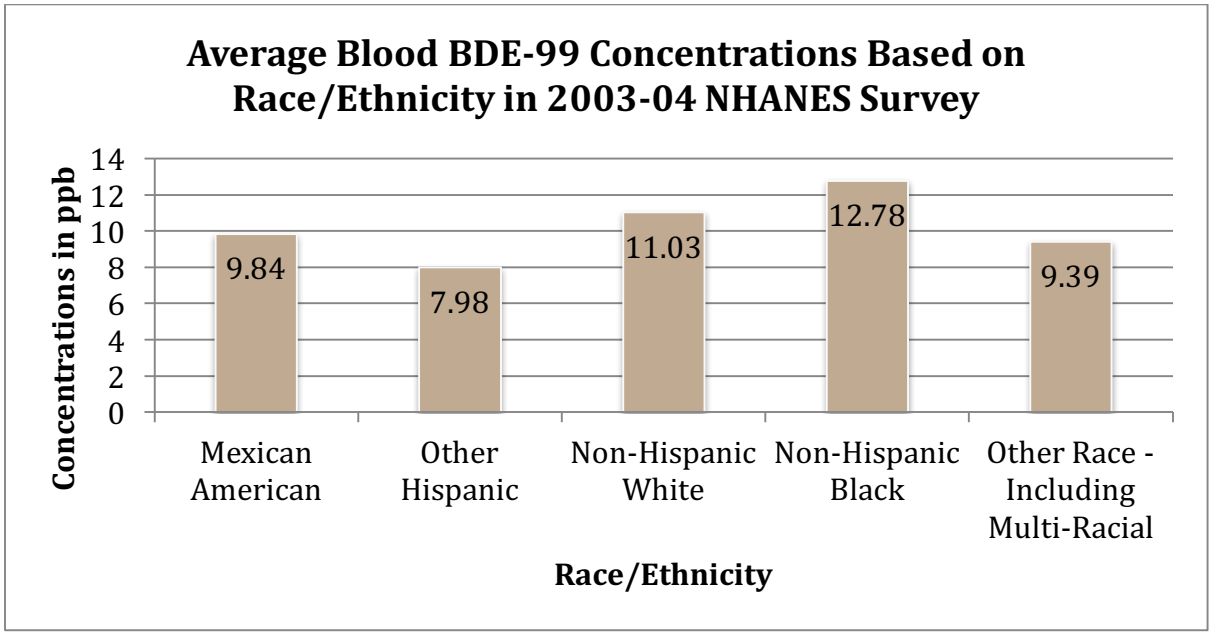

Figure 18. Comparison of average BDE-99 concentrations among ethnic groups. Difference in mean BDE-99 concentrations between ethnicities were insignificant; p-value >0.05.

Table 21. Comparison of average BDE-99 concentrations among ethnic groups.

Ethnicity	Mexican American	Other Hispanic	Non-Hispanic White	Non-Hispanic Black	Other Race - Including Multi-Racial
Concentrations, in ng/g lipids	9.840	7.984	11.025	12.776	9.387

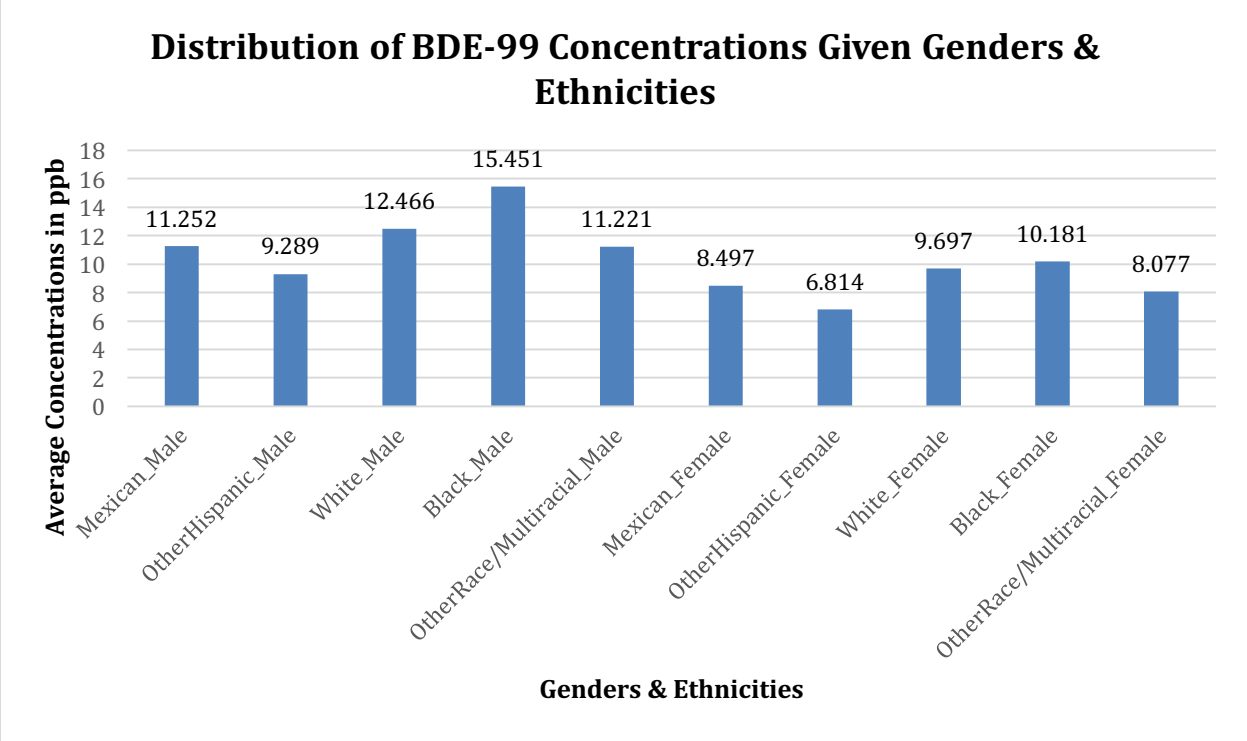

Figure 19. Comparison of average BDE-99 concentrations among gender and ethnicities. Difference in average BDE-99 concentrations is insignificant, given genders & ethnicities; p-value >0.05.

Table 22. Comparison of average BDE-99 concentrations among gender and ethnicities.

Ethnicity & Gender	**Concentrations, in ng/g lipids**
Mexican_Male	11.252
OtherHispanic_Male	9.289
White_Male	12.466
Black_Male	15.451
OtherRace/Multiracial_Male	11.221
Mexican_Female	8.497

Table 22. (Continued).

Ethnicity & Gender	Concentrations, in ng/g lipids
White_Female	9.697
Black_Female	10.181
OtherRace/Multiracial_Female	8.077

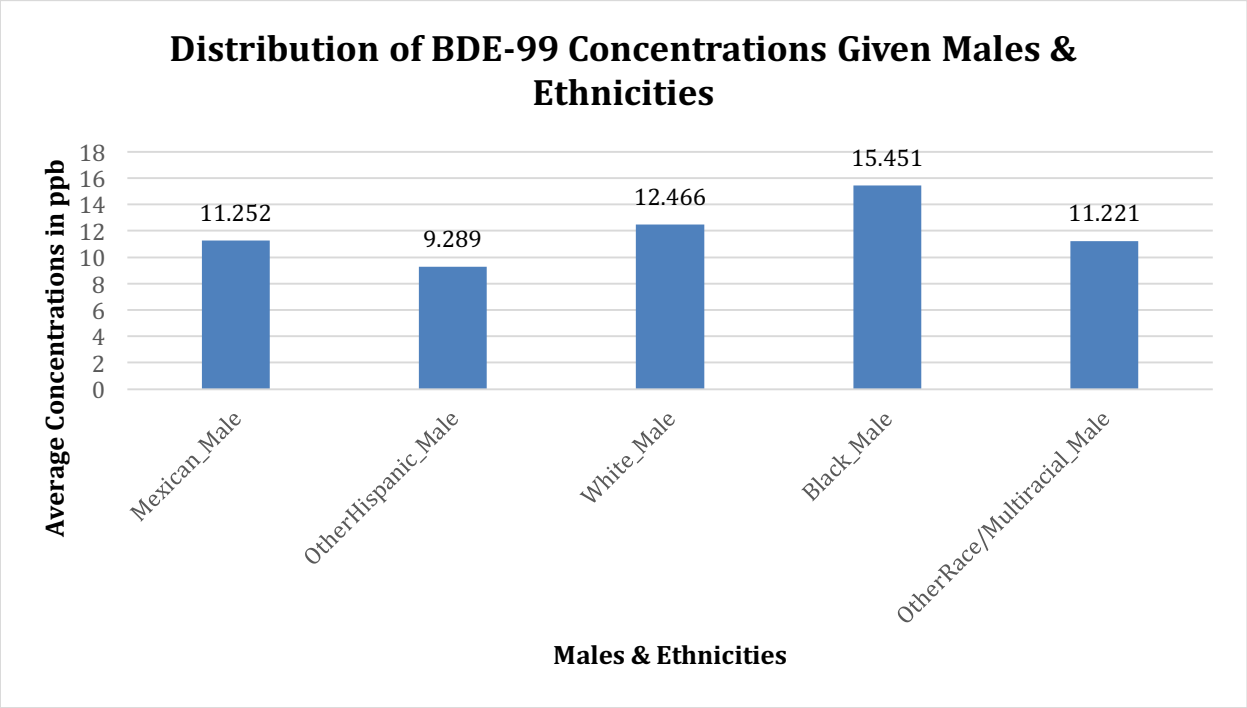

Figure 20. Comparison of average BDE-99 concentrations among males and ethnicities. Difference in average BDE-99 concentrations is insignificant, given males & ethnicities; p-value >0.05.

Table 23. Comparison of average BDE-99 concentrations among males and ethnicities.

Ethnicity & Gender	Concentrations, in ng/g lipids
Mexican_Male	11.252
OtherHispanic_Male	9.289
White_Male	12.466
Black_Male	15.451
OtherRace/Multiracial_Male	11.221

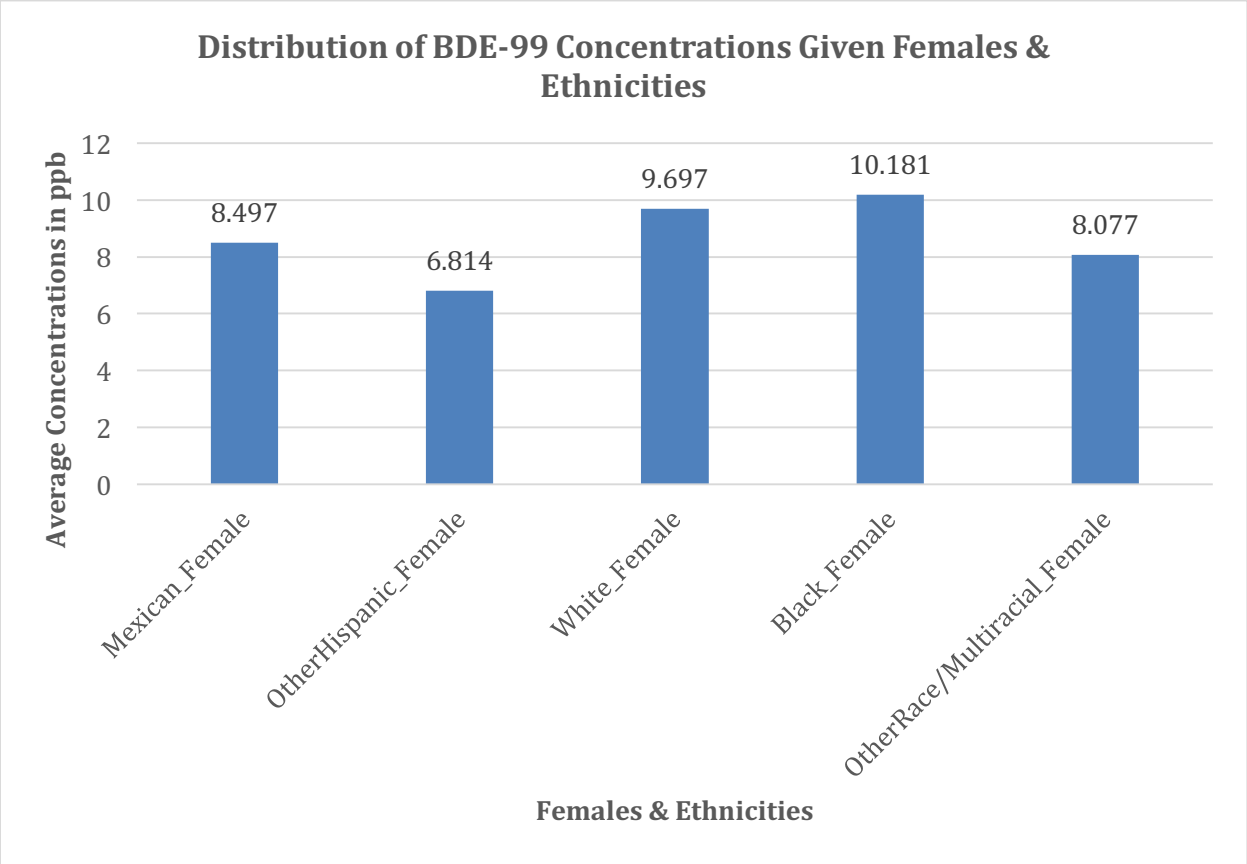

Figure 21. Comparison of average BDE-99 concentrations among females and ethnicities. Difference in average BDE-99 concentrations is insignificant, given females & ethnicities; p-value >0.05.

Table 24. Comparison of average BDE-99 concentrations among females and ethnicities.

Ethnicity & Gender	**Concentrations, in ng/g lipids**
Mexican_Female	8.497
OtherHispanic_Female	6.814
White_Female	9.697
Black_Female	10.181
OtherRace/Multiracial_Female	8.077

4.2.2.3 Logistic Regression Statistics

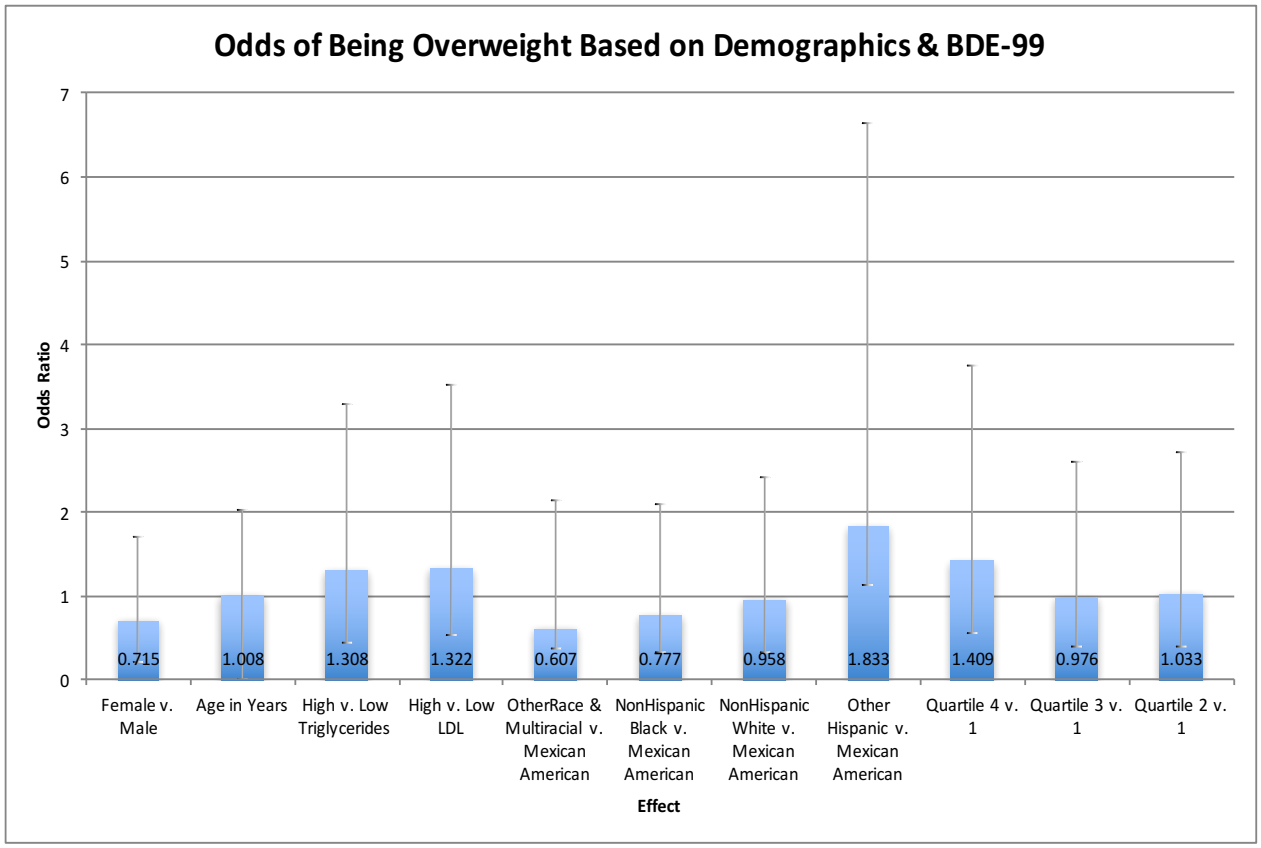

Figure 22. Odds of being overweight in relation to blood concentration of BDE-99. From a logistic regression model containing Gender, Age, Ethnicity and Quartiles as exposure variables and Overweight BMI as the outcome, Ethnicity is the only significant exposure variable which increases the odds of being overweight. Most interestingly is the 1.833 odds ratio produced for Other Hispanic (non-Mexican) Vs. Mexican categories.

Table 25. Odds of being overweight in relation to blood concentration of BDE-99.

Effect	**Odds Ratio**	**95% Confidence Intervals**	
Female v. Male	0.715	0.515	0.992
Age in Years	1.008	0.999	1.017
High v. Low Triglycerides	1.308	0.859	1.992
High v. Low LDL	1.322	0.799	2.188
OtherRace & Multiracial v. Mexican American	0.607	0.241	1.528
NonHispanic Black v. Mexican American	0.777	0.461	1.308

Table 25. (Continued).

Effect	Odds Ratio	95% Confidence Intervals	
NonHispanic White v. Mexican American	0.958	0.630	1.458
Other Hispanic v. Mexican American	1.833	0.699	4.804
Quartile 4 v. 1	1.409	0.849	2.338
Quartile 3 v. 1	0.976	0.590	1.615
Quartile 2 v. 1	1.033	0.638	1.673

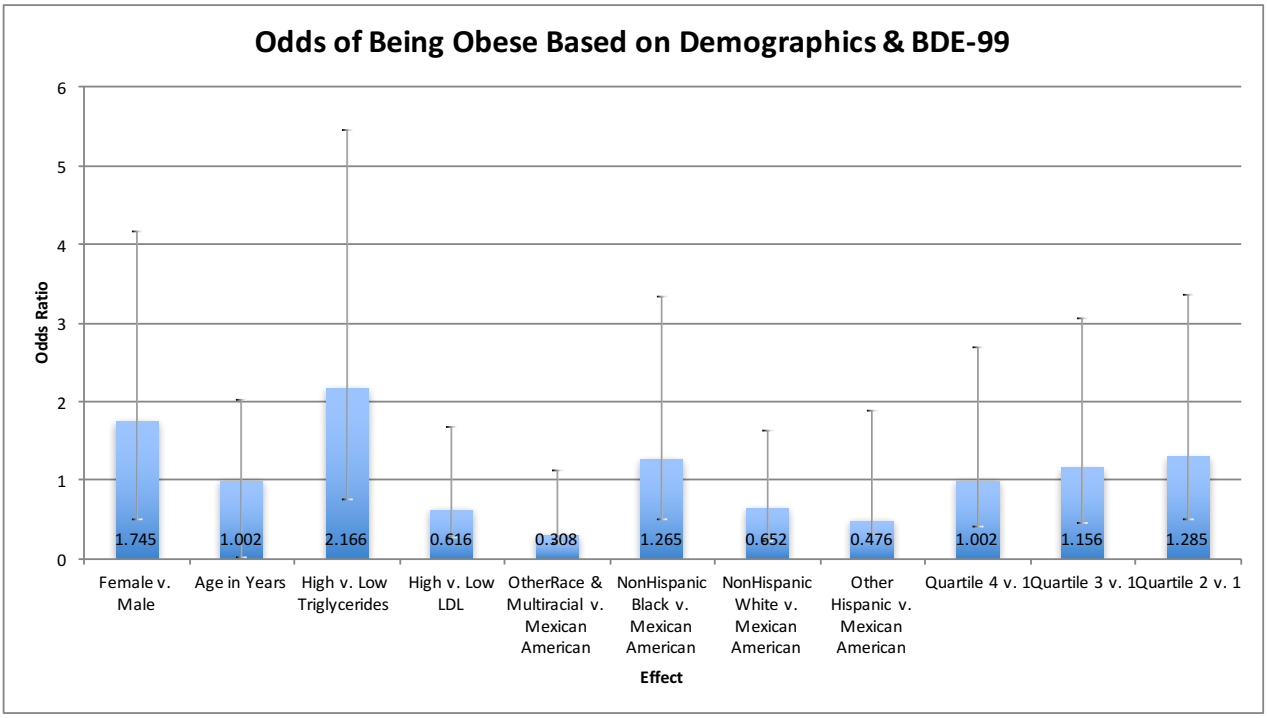

Figure 23. Odds of being obese in relation to blood concentration of BDE-99. No comparisons yielded significant odds of obese BMI.

Table 26. Odds of being obese in relation to blood concentration of BDE-99.

Effect	Odds Ratio	95% Confidence Intervals	
Female v. Male	1.745	1.257	2.423
Age in Years	1.002	0.993	1.010
High v. Low Triglycerides	2.166	1.422	3.301
High v. Low LDL	0.616	0.358	1.059

Table 26. (Continued).

Effect	Odds Ratio	95% Confidence Intervals	
OtherRace & Multiracial v. Mexican American	0.308	0.116	0.817
NonHispanic Black v. Mexican American	1.265	0.775	2.065
NonHispanic White v. Mexican American	0.652	0.430	0.987
Other Hispanic v. Mexican American	0.476	0.160	1.415
Quartile 4 v. 1	1.002	0.598	1.677
Quartile 3 v. 1	1.156	0.701	1.904
Quartile 2 v. 1	1.285	0.796	2.075

4.2.3 Sum of PBDEs

4.2.3.1 Frequency Distributions

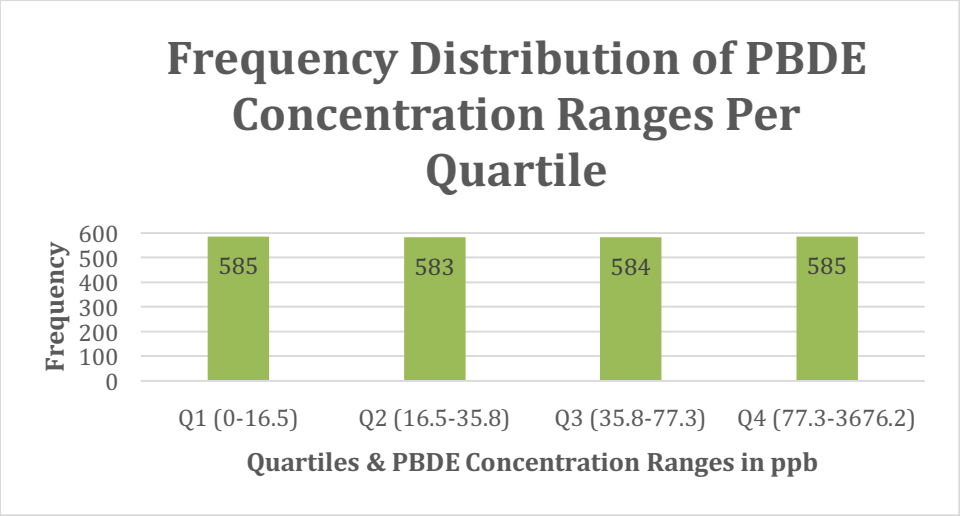

Figure 24. Frequency distribution of the sum of PBDEs per quartile range.

Table 27. Frequency distribution table of the sum of PBDEs per quartile range.

Sum of 10 PBDEs (Quartiles)				
Concentration Range	**Frequency**	**Percent**	**Min**	**Max**
Q1 (0-16.5)	585	25.03%	0.044901281	3676.204667
Q2 (16.5-35.8)	583	24.95%		
Q3 (35.8-77.3)	584	24.99%		
Q4 (77.3-3676.2)	585	25.03%		

Table 28. Frequency distribution table of age ranges cross-referenced with total PBDE quartiles.

The FREQ Procedure

Frequency
Percent
Row Pct
Col Pct

Table of RIDAGEYR by TotalPBDEs

RIDAGEYR(Age at Screening Adjudicated - Recode)	TotalPBDEs				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
12-18	149 6.38 22.58 25.47	141 6.03 21.36 24.19	193 8.26 29.24 32.99	177 7.57 26.82 30.31	660 28.24
19-30	82 3.51 19.29 14.02	105 4.49 24.71 18.01	130 5.56 30.59 22.22	108 4.62 25.41 18.49	425 18.19
31-50	136 5.82 25.61 23.25	161 6.89 30.32 27.62	116 4.96 21.85 19.83	118 5.05 22.22 20.21	531 22.72
51-84	195 8.34 29.64 33.33	164 7.02 24.92 28.13	137 5.86 20.82 23.42	162 6.93 24.62 27.74	658 28.16
85 & above	23 0.98 36.51 3.93	12 0.51 19.05 2.06	9 0.39 14.29 1.54	19 0.81 30.16 3.25	63 2.70
Total	585 25.03	583 24.95	585 25.03	584 24.99	2337 100.00

Table 29. Frequency distribution table of gender cross-referenced with total PBDE quartiles.

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of RIAGENDR by TotalPBDEs				
	TotalPBDEs				
RIAGENDR(Gender)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
Male	261 11.17 23.18 44.62	273 11.68 24.25 46.83	265 11.34 23.53 45.30	327 13.99 29.04 55.99	1126 48.18
Female	324 13.86 26.75 55.38	310 13.26 25.60 53.17	320 13.69 26.42 54.70	257 11.00 21.22 44.01	1211 51.82
Total	585 25.03	583 24.95	585 25.03	584 24.99	2337 100.00

Table 30. Frequency distribution table of ethnicity cross-referenced with total PBDE quartiles.

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of RIDRETH1 by TotalPBDEs				
	TotalPBDEs				
RIDRETH1(Race/Ethnicity - Recode)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
Mexican_American	115 4.92 20.61 19.66	133 5.69 23.84 22.81	171 7.32 30.65 29.23	139 5.95 24.91 23.80	558 23.88
Other_Hispanic	16 0.68 21.62 2.74	17 0.73 22.97 2.92	26 1.11 35.14 4.44	15 0.64 20.27 2.57	74 3.17
NonHispanic_White	283 12.11 27.64 48.38	254 10.87 24.80 43.57	223 9.54 21.78 38.12	264 11.30 25.78 45.21	1024 43.82
NonHispanic_Black	143 6.12 24.44 24.44	152 6.50 25.98 26.07	143 6.12 24.44 24.44	147 6.29 25.13 25.17	585 25.03
OtherRace_IncludingMultiRacial	28 1.20 29.17 4.79	27 1.16 28.13 4.63	22 0.94 22.92 3.76	19 0.81 19.79 3.25	96 4.11
Total	585 25.03	583 24.95	585 25.03	584 24.99	2337 100.00

4.2.3.2 Comparative Statistics

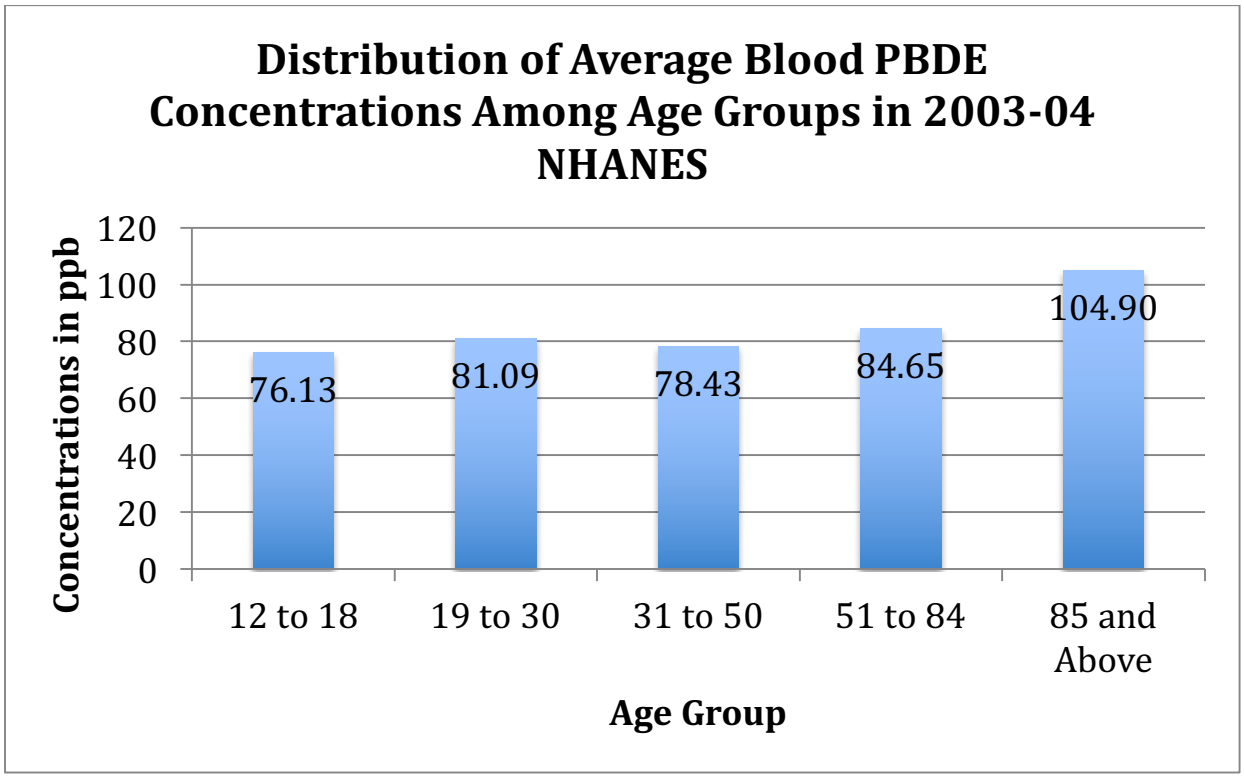

Figure 25. Comparison of average PBDE concentrations among age groups, in years. Difference in mean PBDE concentrations between age groups were insignificant; p-value >0.05.

Table 31. Comparison of average PBDE concentrations among age groups, in years.

Age Group, in years	12 to 18	19 to 30	31 to 50	51 to 84	85 and Above
Concentrations, in ng/g lipids	76.134	81.089	78.433	84.654	104.898

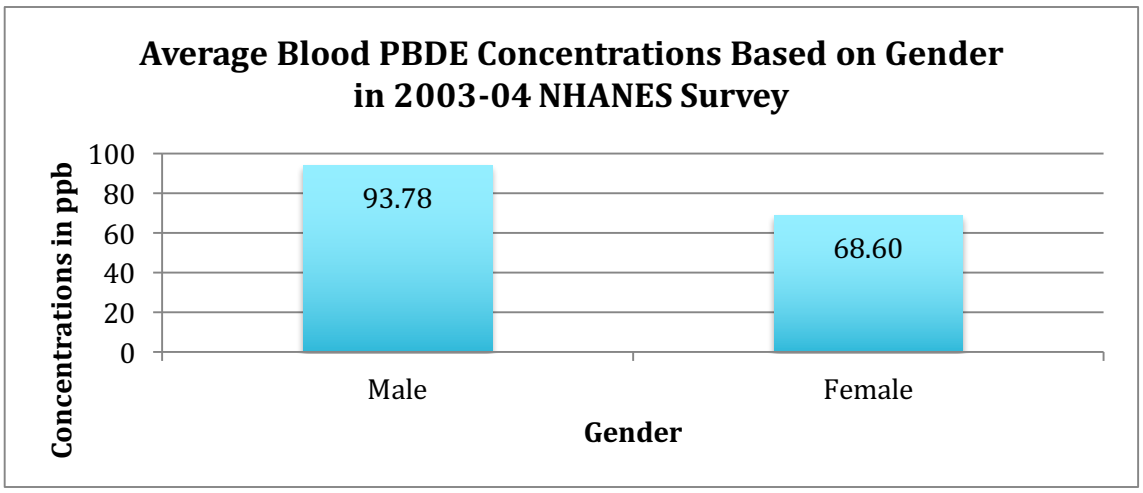

Figure 26. Comparison of average PBDE concentrations among genders. Difference in mean PBDE concentrations between genders were significant; p-value <0.05.

Table 32. Comparison of average PBDE concentrations among genders.

Gender	Male	Female
Concentrations, in ng/g lipids	93.780	68.599

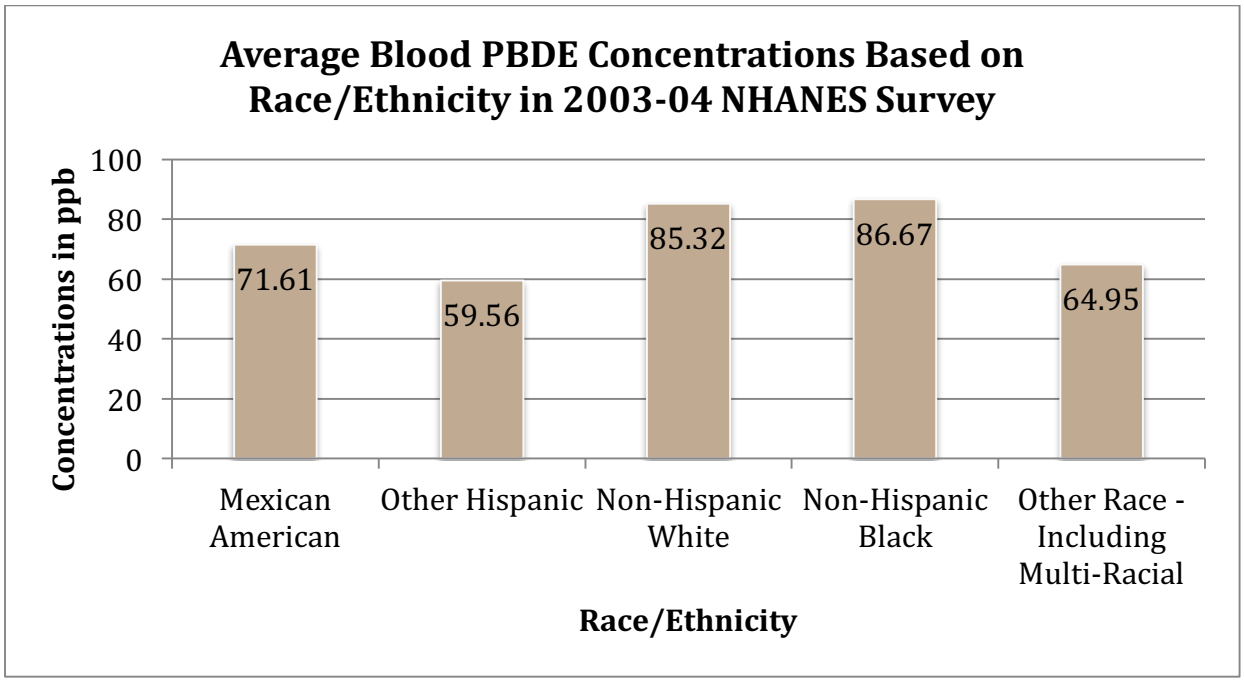

Figure 27. Comparison of average PBDE concentrations among ethnic groups. Difference in mean PBDE concentrations between ethnicities were insignificant; p-value >0.05.

Table 33. Comparison of average PBDE concentrations among ethnic groups.

Ethnicity	Mexican American	Other Hispanic	Non-Hispanic White	Non-Hispanic Black	Other Race - Including Multi-Racial
Concentrations, in ng/g lipids	71.607	59.555	85.321	86.671	64.954

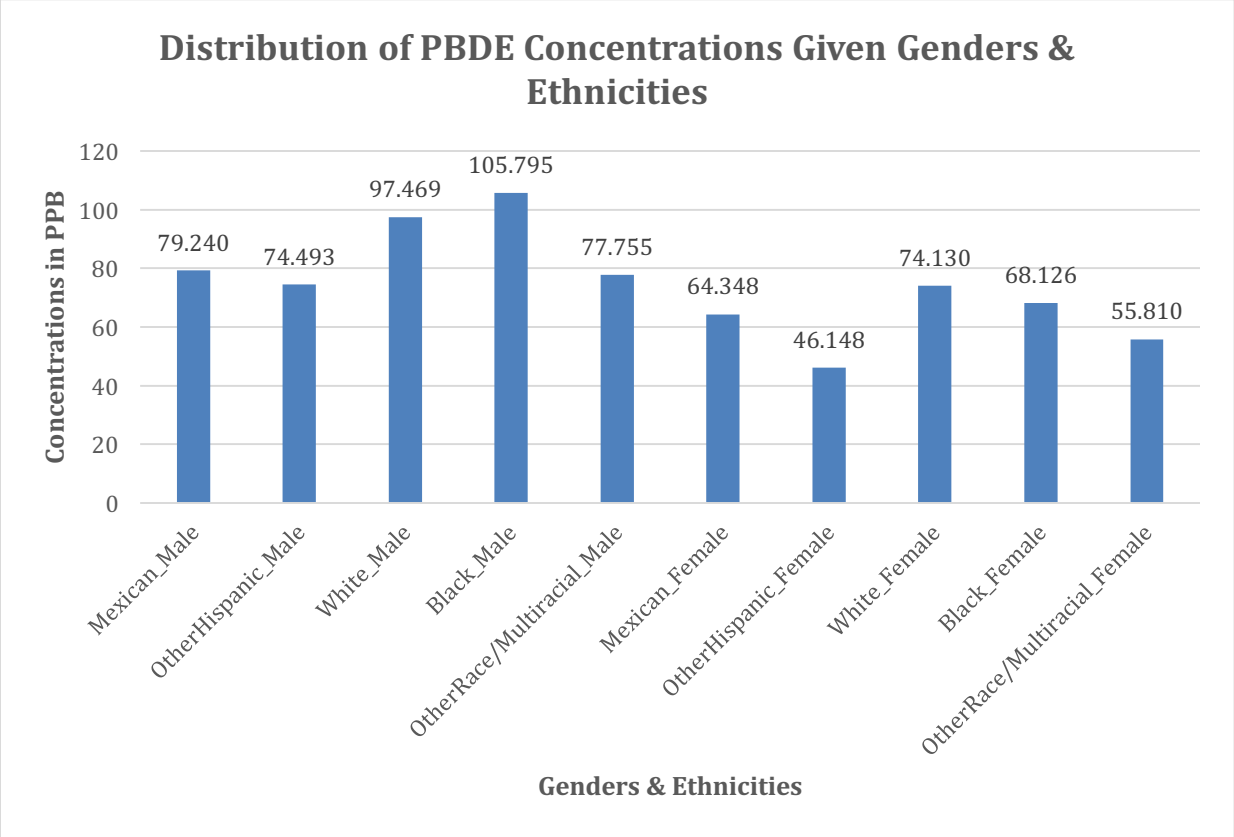

Figure 28. Comparison of average PBDE concentrations among gender and ethnicities. Difference in average PBDE concentrations is insignificant, given genders & ethnicities; p-value >0.05.

Table 34. Comparison of average PBDE concentrations among gender and ethnicities.

Ethnicity & Gender	Concentrations, in ng/g lipids
Mexican_Male	79.240
OtherHispanic_Male	74.493
White_Male	97.469
Black_Male	105.795
OtherRace/Multiracial_Male	77.755
Mexican_Female	64.348
OtherHispanic_Female	46.148
White_Female	74.130
Black_Female	68.126
OtherRace/Multiracial_Female	55.810

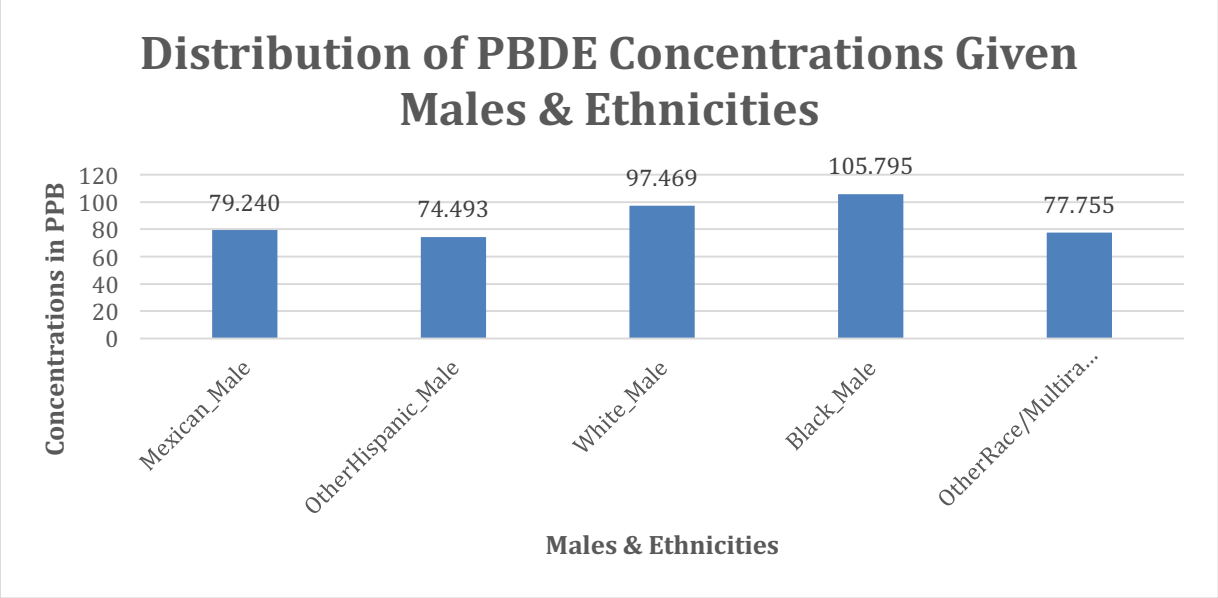

Figure 29. Comparison of average PBDE concentrations among males and ethnicities. Difference in average PBDE concentrations is insignificant, given males & ethnicities; p-value >0.05.

Table 35. Comparison of average PBDE concentrations among males and ethnicities.

Ethnicity & Gender	Concentrations, in ng/g lipids
Mexican_Male	79.240
OtherHispanic_Male	74.493

Table 35. (Continued).

Ethnicity & Gender	Concentrations, in ng/g lipids
Black_Male	105.795
OtherRace/Multiracial_Male	77.755

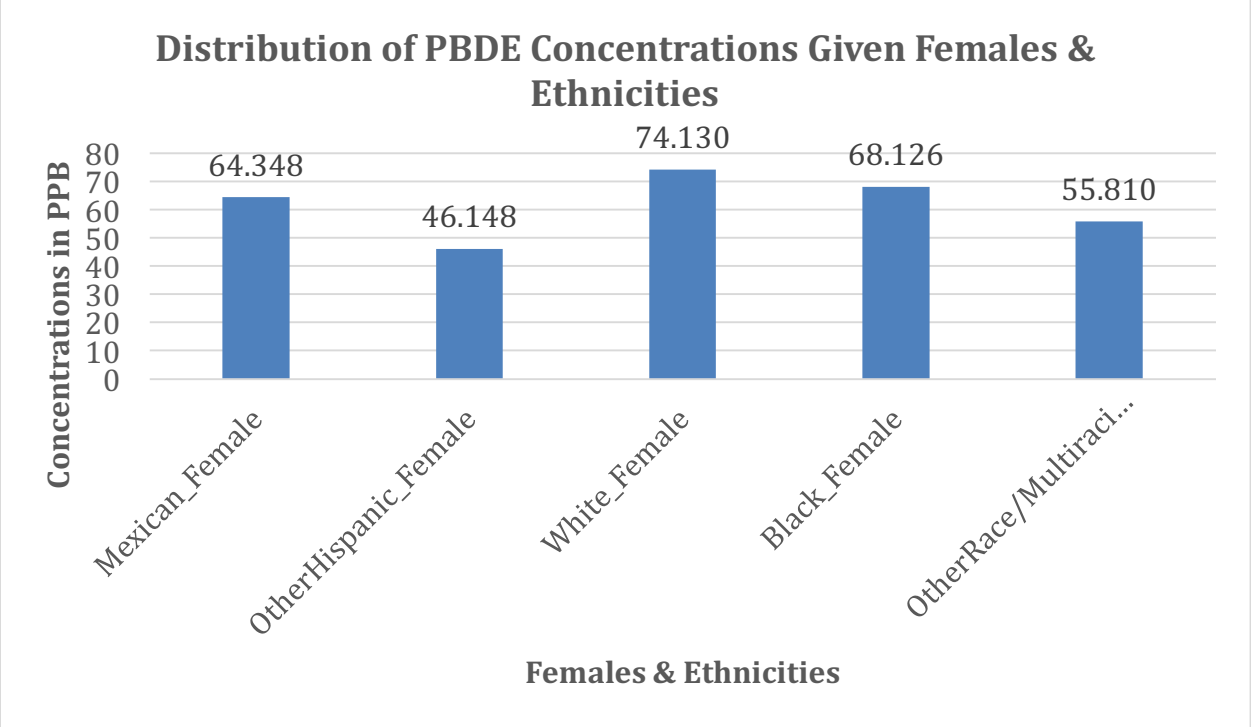

Figure 30. Comparison of average PBDE concentrations among females and ethnicities. Difference in average PBDE concentrations is insignificant, given females & ethnicities; p-value >0.05.

Table 36. Comparison of average PBDE concentrations among females and ethnicities.

Ethnicity & Gender	Concentrations, in ng/g lipids
Mexican_Female	64.348
OtherHispanic_Female	46.148
White_Female	74.130
Black_Female	68.126
OtherRace/Multiracial_Female	55.810

4.2.3.3 Logistic Regression Statistics

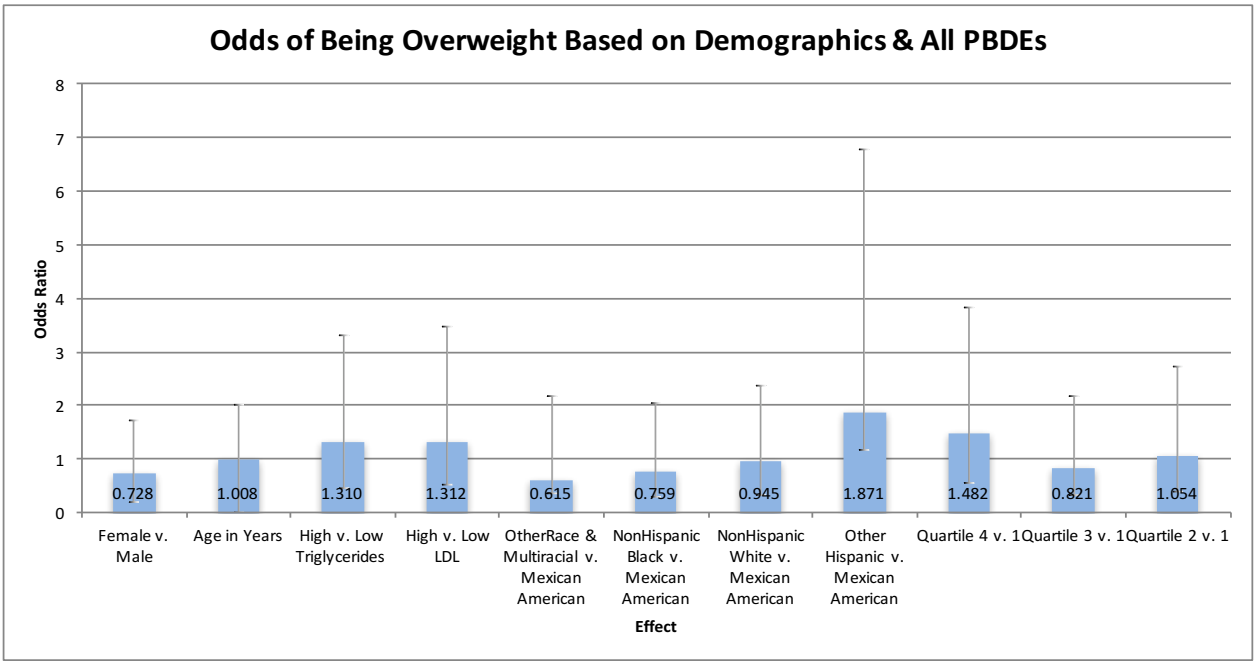

Figure 31. Odds of being overweight in relation to blood concentration of PBDEs. From a logistic regression model containing Gender, Age, Ethnicity and Quartiles as exposure variables and Overweight BMI as the outcome, Ethnicity is the only significant exposure variable which increases the odds of being overweight. Most interestingly is the 1.871 odds ratio produced for Other Hispanic (non-Mexican) Vs. Mexican categories.

Table 37. Odds of being overweight in relation to blood concentration of PBDEs.

Effect	**Odds Ratio**	**95% Confidence Intervals**	
Female v. Male	0.728	0.525	1.011
Age in Years	1.008	0.999	1.017
High v. Low Triglycerides	1.310	0.863	1.987
High v. Low LDL	1.312	0.798	2.157
OtherRace & Multiracial v. Mexican American	0.615	0.244	1.549
NonHispanic Black v. Mexican American	0.759	0.450	1.280
NonHispanic White v. Mexican American	0.945	0.621	1.438
Other Hispanic v. Mexican American	1.871	0.711	4.925
Quartile 4 v. 1	1.482	0.929	2.363

Table 37. (Continued).

Effect	Odds Ratio	95% Confidence Intervals	
Quartile 3 v. 1	0.821	0.501	1.347
Quartile 2 v. 1	1.054	0.665	1.672

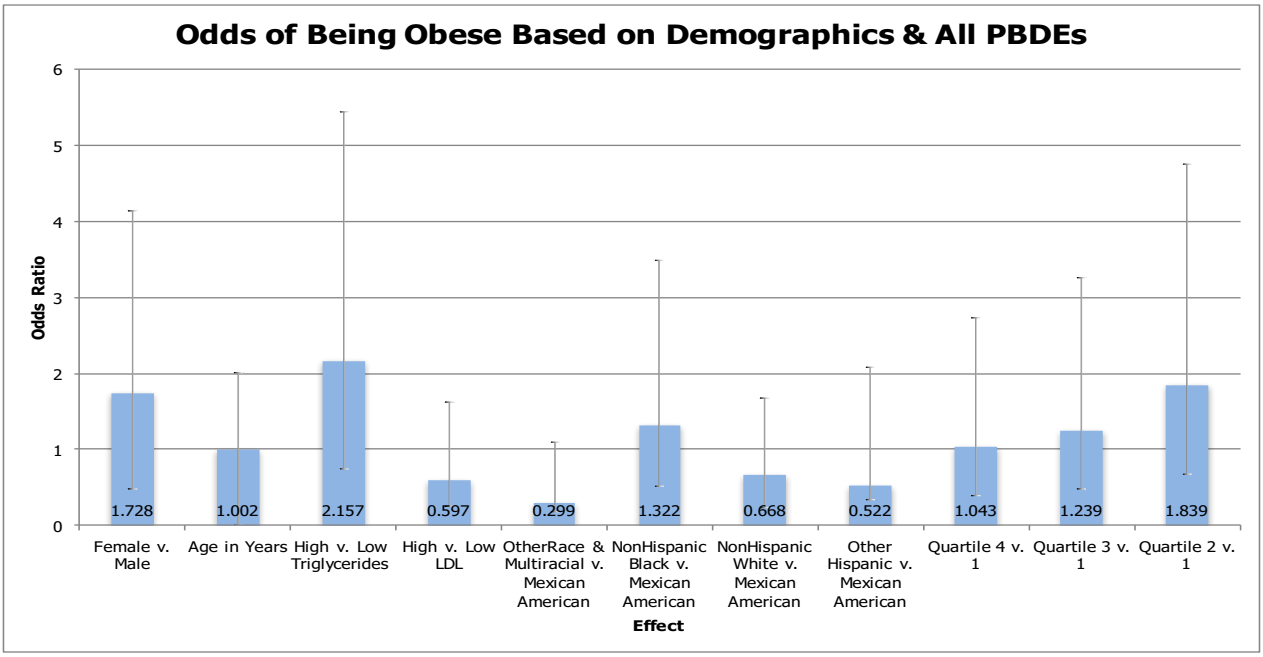

Figure 32. Odds of being obese in relation to blood concentration of PBDEs. No comparisons yielded significant odds of obese BMI.

Table 38. Odds of being obese in relation to blood concentration of PBDEs.

Effect	Odds Ratio	95% Confidence Intervals	
Female v. Male	1.728	1.243	2.402
Age in Years	1.002	0.993	1.011
High v. Low Triglycerides	2.157	1.418	3.281
High v. Low LDL	0.597	0.349	1.022
OtherRace & Multiracial v. Mexican American	0.299	0.112	0.796
NonHispanic Black v. Mexican American	1.322	0.807	2.165
NonHispanic White v. Mexican American	0.668	0.441	1.011
Other Hispanic v. Mexican American	0.522	0.175	1.558
Quartile 4 v. 1	1.043	0.643	1.694

Table 38. (Continued).

Effect	Odds Ratio	95% Confidence Intervals	
Quartile 3 v. 1	1.239	0.761	2.017
Quartile 2 v. 1	1.839	1.161	2.912

4.3 Dioxin-Like Polychlorinated Biphenyls

4.3.1 Frequency Distributions

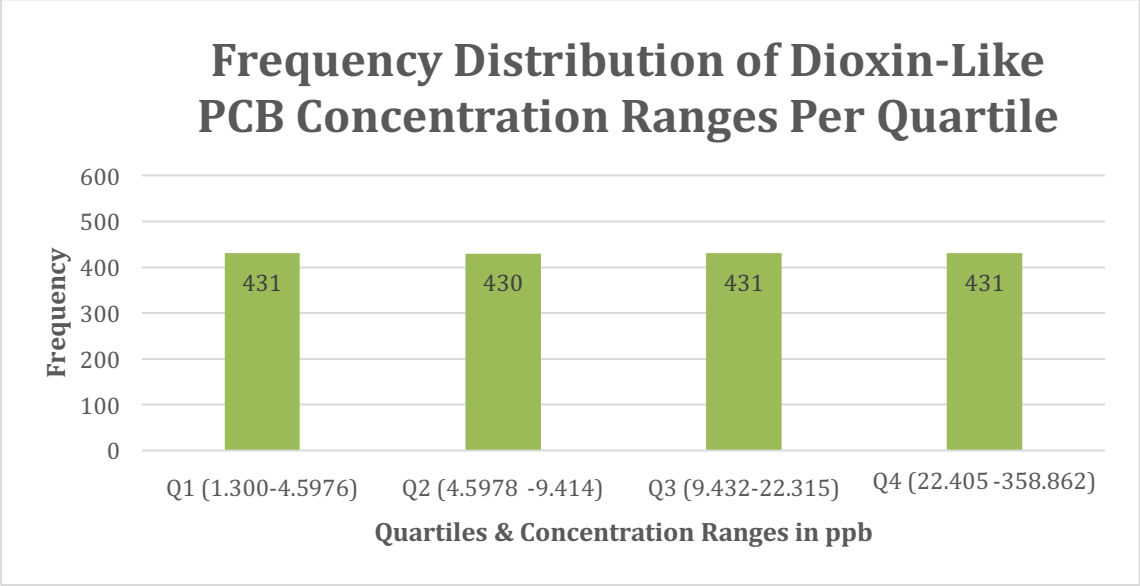

Figure 33. Frequency distribution of the sum of dl-PCBs per quartile range.

Table 39. Frequency distribution table of the sum of dl-PCBs per quartile range.

Sum of DL-PCBs (Quartiles)				
Concentration Range	**Frequency**	**Percent**	**Min**	**Max**
Q1 (1.300-4.5976)	431	25.01%	1.3001	358.8613
Q2 (4.5978 -9.414)	430	24.96%		
Q3 (9.432-22.315)	431	25.01%		
Q4 (22.405 -358.862)	431	25.01%		

Table 40. Frequency distribution table of age ranges cross-referenced with total dl-PCB quartiles.

The FREQ Procedure

Frequency
Percent
Row Pct
Col Pct

Table of RIDAGEYR by TotalDLPCBs

RIDAGEYR(Age at Screening Adjudicated - Recode)	TotalDLPCBs				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
12-18	258 14.97 55.60 60.00	148 8.59 31.90 34.34	52 3.02 11.21 12.06	6 0.35 1.29 1.39	464 26.93
19-30	137 7.95 42.95 31.86	134 7.78 42.01 31.09	40 2.32 12.54 9.28	8 0.46 2.51 1.86	319 18.51
31-50	32 1.86 8.06 7.44	129 7.49 32.49 29.93	174 10.10 43.83 40.37	62 3.60 15.62 14.39	397 23.04
51-84	3 0.17 0.59 0.70	20 1.16 3.91 4.64	164 9.52 32.03 38.05	325 18.86 63.48 75.41	512 29.72
85 & above	0 0.00 0.00 0.00	0 0.00 0.00 0.00	1 0.06 3.23 0.23	30 1.74 96.77 6.96	31 1.80
Total	430 24.96	431 25.01	431 25.01	431 25.01	1723 100.00

Table 41. Frequency distribution table of gender cross-referenced with total dl-PCB quartiles.

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of RIAGENDR by TotalDLPCBs					
		TotalDLPCBs				
	RIAGENDR(Gender)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
	Male	210 12.19 24.88 48.84	220 12.77 26.07 51.04	226 13.12 26.78 52.44	188 10.91 22.27 43.62	844 48.98
	Female	220 12.77 25.03 51.16	211 12.25 24.00 48.96	205 11.90 23.32 47.56	243 14.10 27.65 56.38	879 51.02
	Total	430 24.96	431 25.01	431 25.01	431 25.01	1723 100.00

Table 42. Frequency distribution table of ethnicities cross-referenced with total dl-PCB quartiles.

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of RIDRETH1 by TotalDLPCBs					
		TotalDLPCBs				
	RIDRETH1(Race/Ethnicity - Recode)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
	Mexican_American	179 10.39 46.02 41.63	87 5.05 22.37 20.19	82 4.76 21.08 19.03	41 2.38 10.54 9.51	389 22.58
	Other_Hispanic	13 0.75 25.49 3.02	16 0.93 31.37 3.71	11 0.64 21.57 2.55	11 0.64 21.57 2.55	51 2.96
	NonHispanic_White	120 6.96 15.09 27.91	171 9.92 21.51 39.68	238 13.81 29.94 55.22	266 15.44 33.46 61.72	795 46.14
	NonHispanic_Black	107 6.21 26.16 24.88	130 7.54 31.78 30.16	81 4.70 19.80 18.79	91 5.28 22.25 21.11	409 23.74
	OtherRace_IncludingMultiRacial	11 0.64 13.92 2.56	27 1.57 34.18 6.26	19 1.10 24.05 4.41	22 1.28 27.85 5.10	79 4.59
	Total	430 24.96	431 25.01	431 25.01	431 25.01	1723 100.00

4.3.2 Comparative Statistics

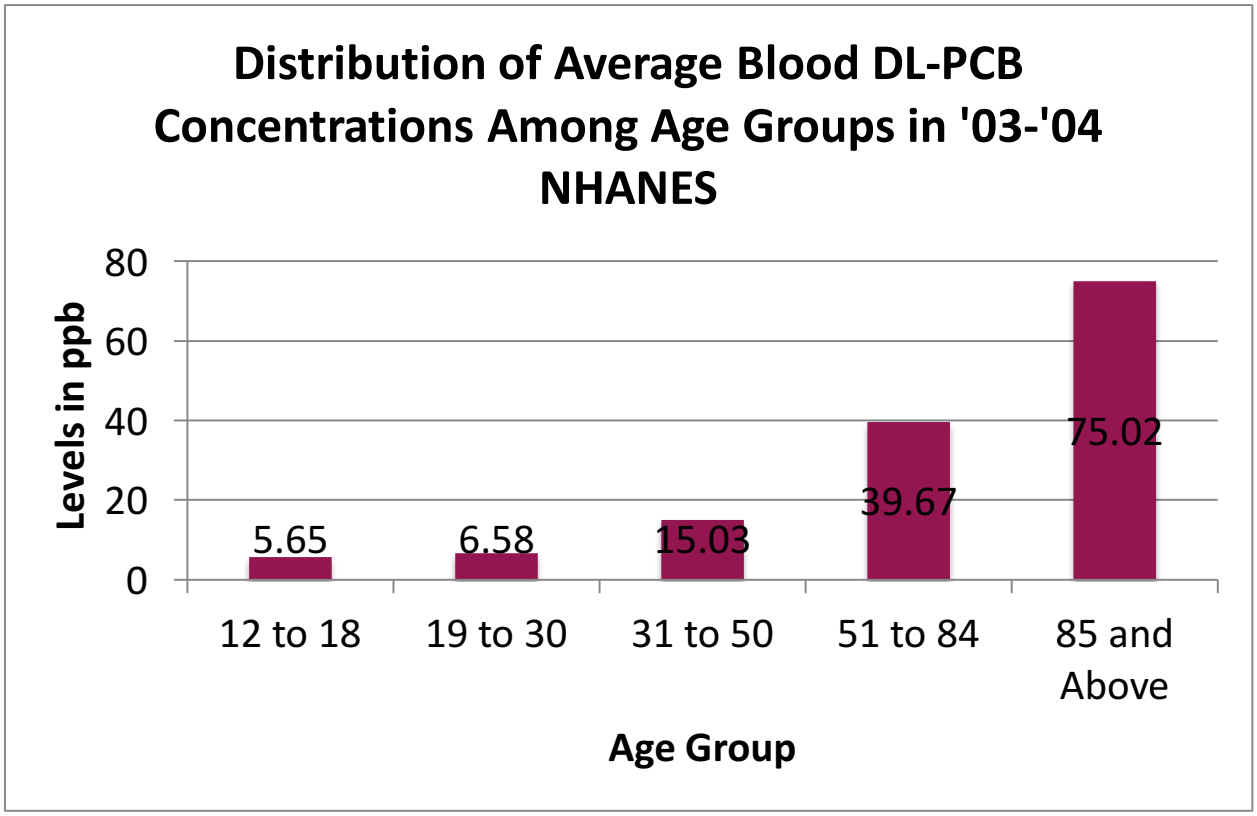

Figure 34. Comparison of average dl-PCB concentrations among age groups, in years. Difference in mean DL-PCB concentrations between age groups were significant; p-value <0.05.

Table 43. Comparison of average dl-PCB concentrations among age groups, in years.

Age, in years	12 to 18	19 to 30	31 to 50	51 to 84	85 and Above
Concentrations, ng/g lipids	5.652	6.578	15.025	39.665	75.020

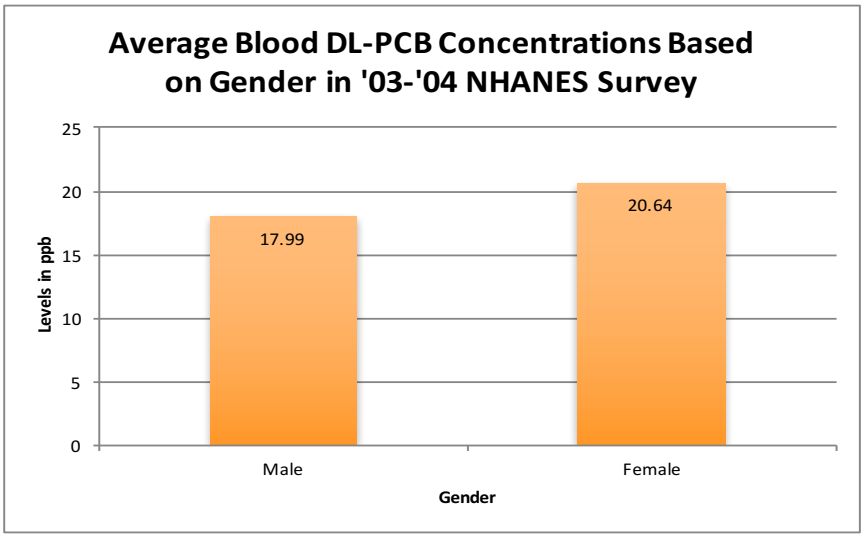

Figure 35. Comparison of average dl-PCB concentrations among genders. Difference in mean DL-PCB concentrations between genders were insignificant; p-value >0.05.

Table 44. Comparison of average dl-PCB concentrations among genders.

Gender	Male	Female
Concentrations, ng/g lipids	17.987	20.635

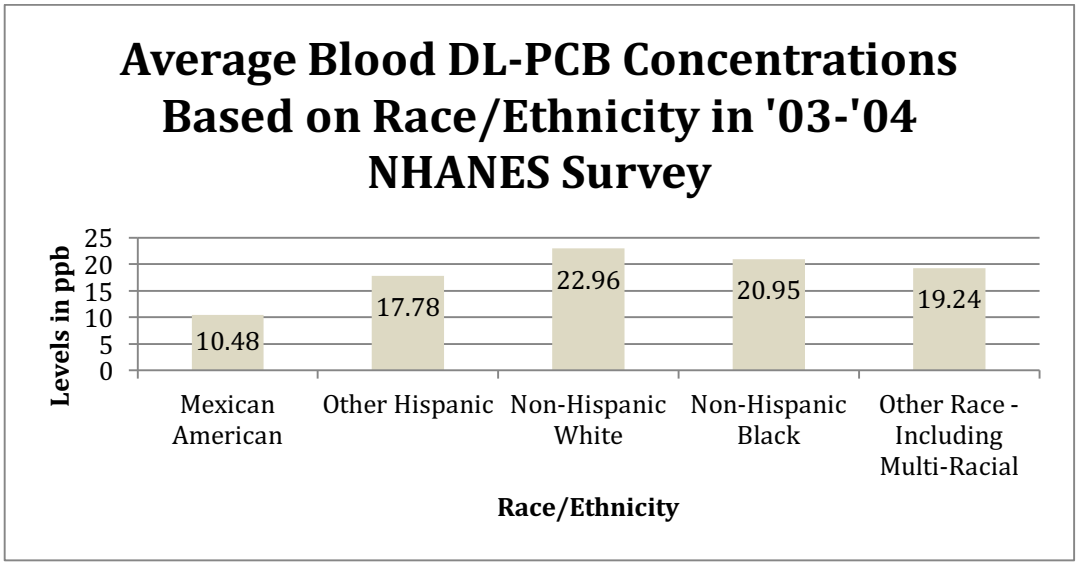

Figure 36. Comparison of average dl-PCB concentrations among ethnic groups. Difference in mean DL-PCB concentrations between races were significant; p-value <0.05. Non-Hispanic White vs. Mexican American and Non-Hispanic Black vs. Mexican American PBDE concentrations were the significant comparisons.

Table 45. Comparison of average dl-PCB concentrations among ethnic groups.

Ethnicity	Mexican American	Other Hispanic	Non-Hispanic White	Non-Hispanic Black	Other Race - Including Multi-Racial
Concentrations, ng/g lipids	10.477	17.784	22.957	20.946	19.235

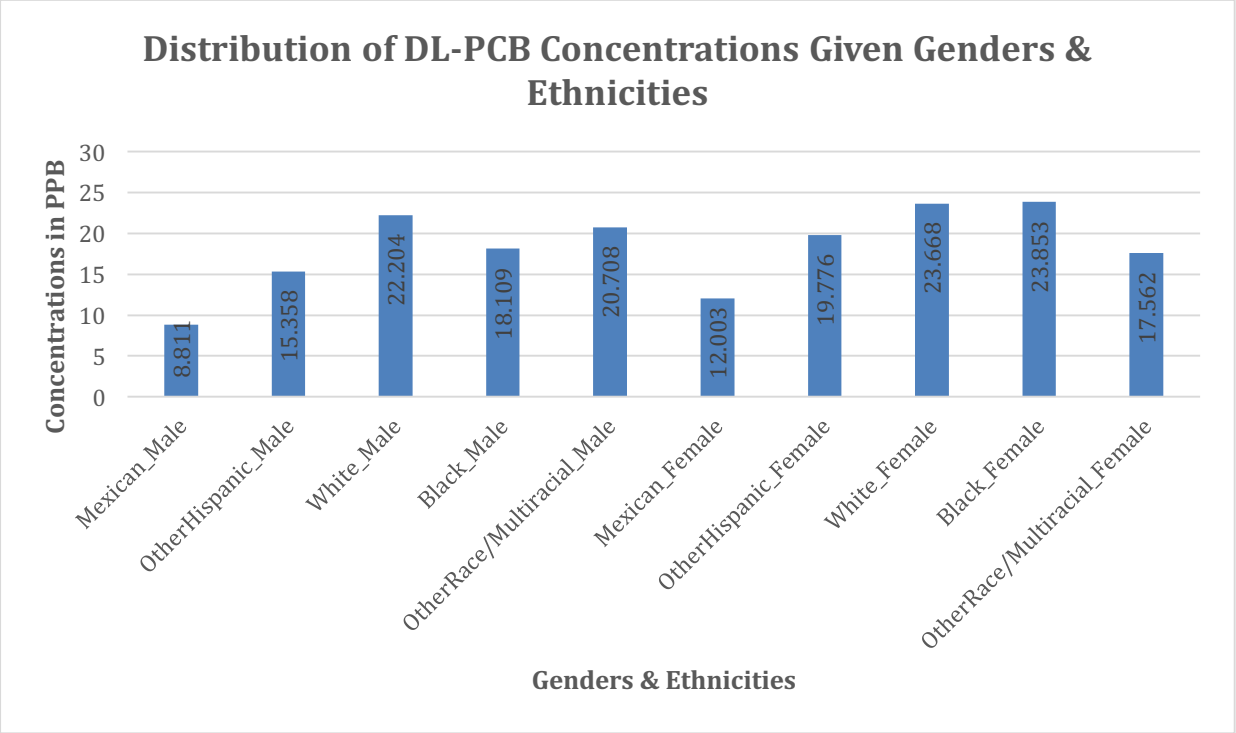

Figure 37. Comparison of average dl-PCB concentrations among gender and ethnicities. Difference in average DL-PCB concentrations is significant, among genders & ethnicities; p-value <0.05. According to Tukey's test, a comparison of average DL-PCB concentrations of White_Male v. Mexican_Male, and Black_Male v. Mexican_Male groups were significant and a comparison of average DL-PCB concentrations of Black_Female v. Mexican_Female, and White_Female v. Mexican_Female groups were significant.

Table 46. Comparison of average dl-PCB concentrations among gender and ethnicities.

Ethnicity	**Concentrations, ng/g lipids**
Mexican_Male	8.811
OtherHispanic_Male	15.358

Table 46. (Continued).

Ethnicity	Concentrations, ng/g lipids
Black_Male	18.109
OtherRace/Multiracial_Male	20.708
Mexican_Female	12.003
OtherHispanic_Female	19.776
White_Female	23.668
Black_Female	23.853
OtherRace/Multiracial_Female	17.562

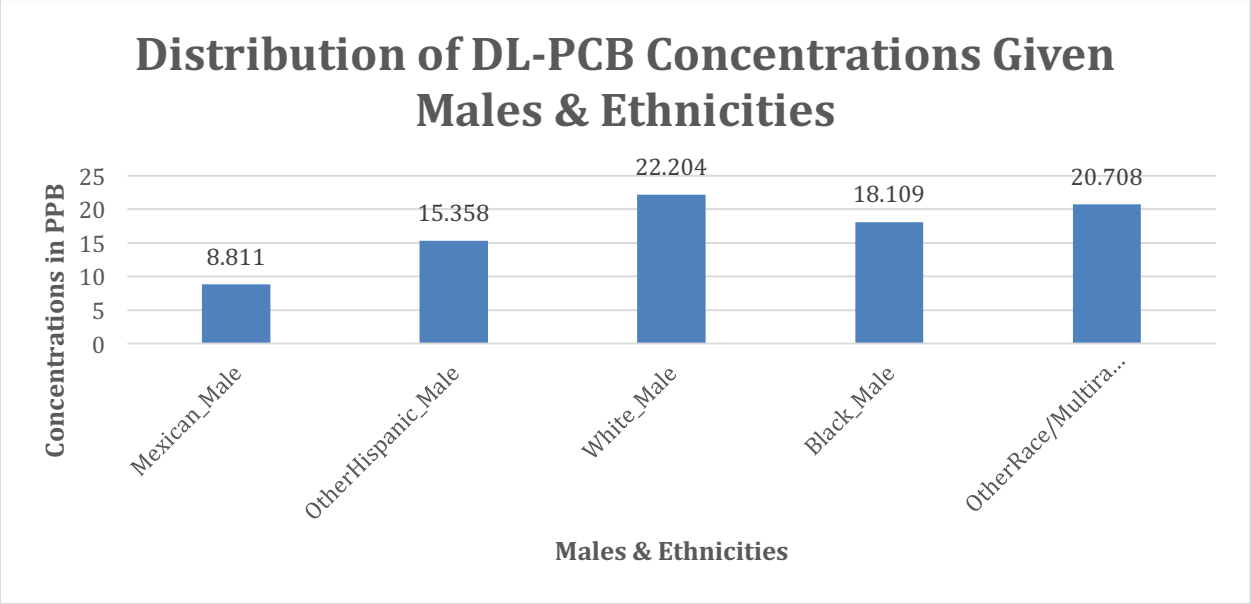

Figure 38. Comparison of average dl-PCB concentrations among males and ethnicities. According to Tukey's test, a comparison of average DL-PCB concentrations of White_Male v. Mexican_Male, and Black_Male v. Mexican_Male groups were significant.

Table 47. Comparison of average dl-PCB concentrations among males and ethnicities.

Ethnicity	Mexican_ Male	OtherHispanic_ Male	White_M ale	Black_M ale	OtherRace/Multiracia l_Male
Concentrations, ng/g lipids	8.811	15.358	22.204	18.109	20.708

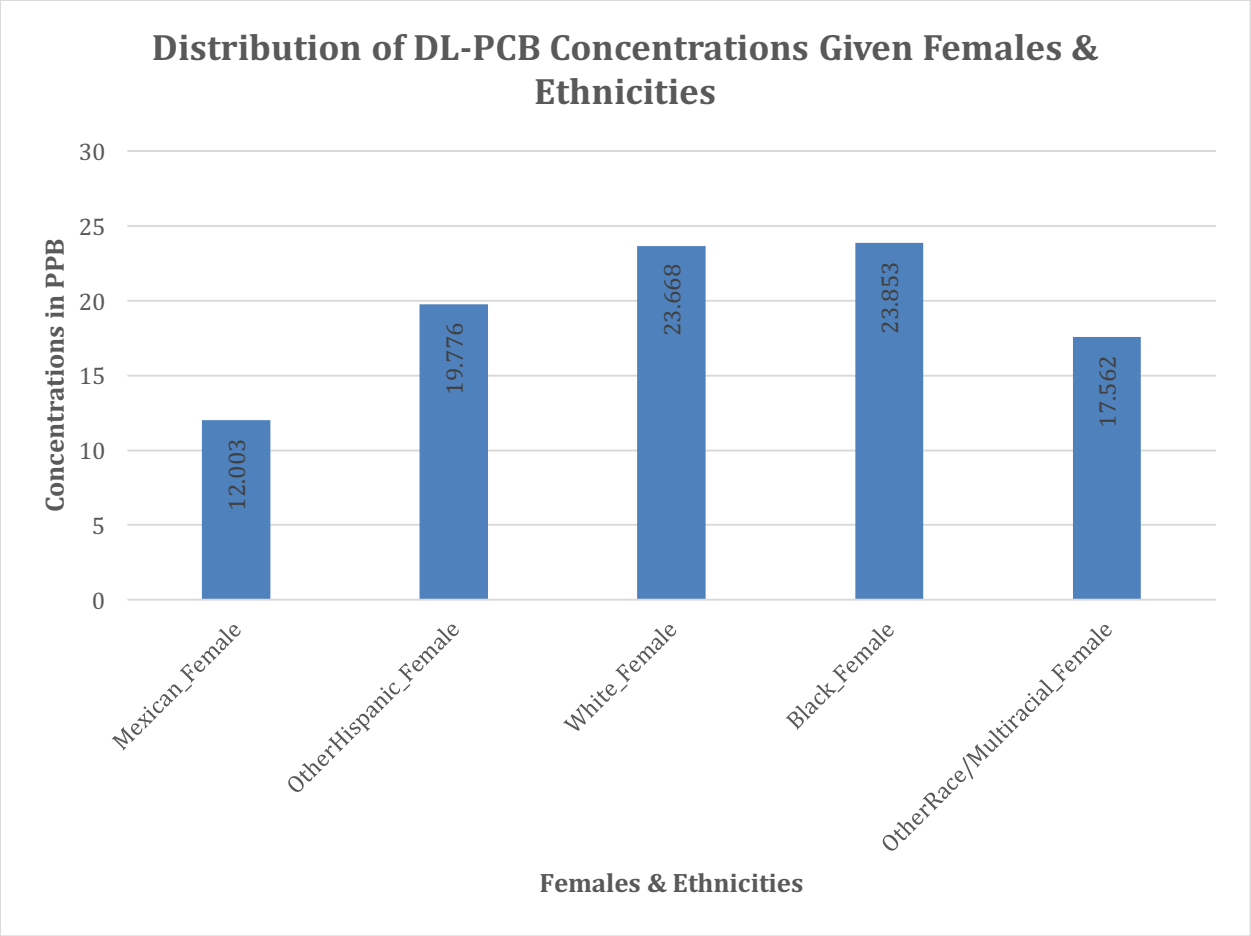

Figure 39. Comparison of average dl-PCB concentrations among females and ethnicities. According to Tukey's test, a comparison of average DL-PCB concentrations of Black_Female v. Mexican_Female, and White_Female v. Mexican_Female groups were significant.

Table 48. Comparison of average dl-PCB concentrations among females and ethnicities.

Ethnicity	Mexican_Female	OtherHispanic_Female	White_Female	Black_Female	OtherRace/Multiracial_Female
Concentrations, ng/g lipids	12.003	19.776	23.668	23.853	17.562

4.3.3 Logistic Regression Statistics

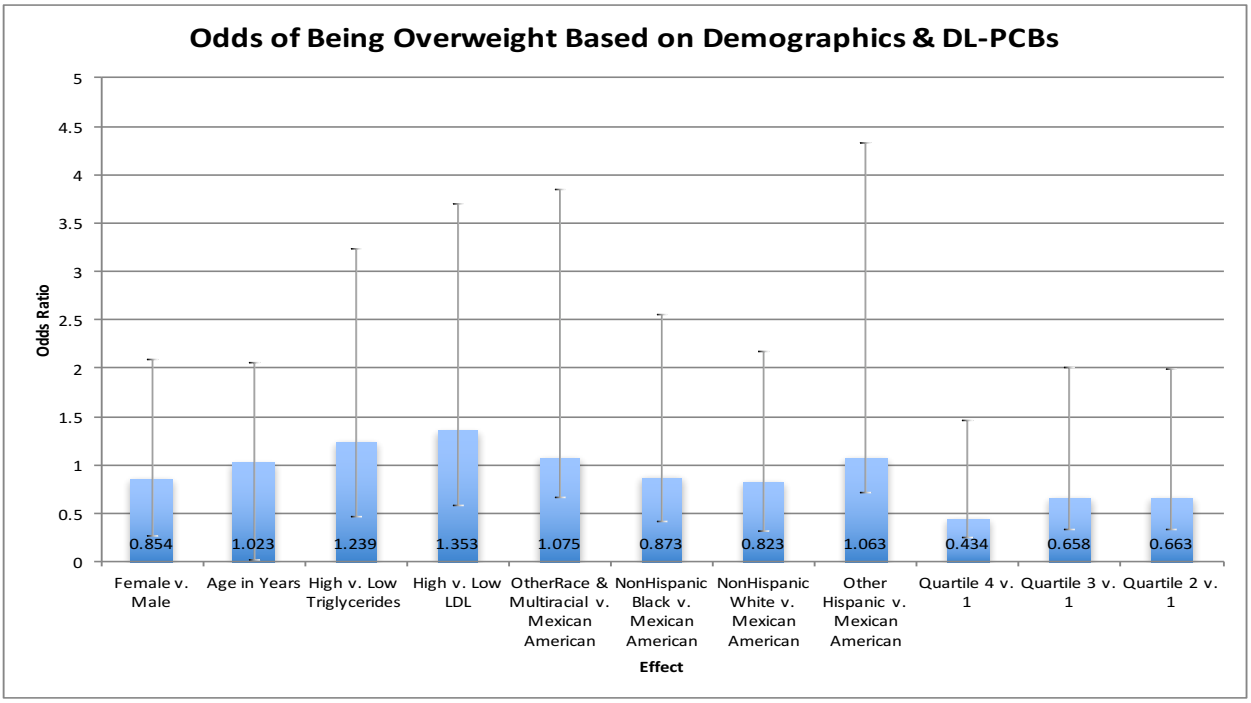

Figure 40. Odds of being overweight in relation to blood concentration of dl-PCBs. From a logistic regression model containing Gender, Age, Ethnicity and Quartiles as exposure variables and Overweight BMI as the outcome, Ethnicity and LDL Cholesterol (High vs Low) differences are significant in increasing the odds of being overweight. Most interestingly is the 1.063 odds ratio produced for Other Hispanic (non-Mexican) Vs. Mexican, 1.075 odds ratio produced for Other Race Vs. Mexican categories, and 1.353 odds ratio produced for High LDL Cholesterol Vs. High LDL Cholesterol.

Table 49. Odds of being overweight in relation to blood concentration of dl-PCBs.

Effect	**Odds Ratio**	**95% Confidence Intervals**	
Female v. Male	0.854	0.589	1.239
Age in Years	1.023	1.008	1.037
High v. Low Triglycerides	1.239	0.768	1.999
High v. Low LDL	1.353	0.778	2.352
OtherRace & Multiracial v. Mexican American	1.075	0.417	2.769
NonHispanic Black v. Mexican American	0.873	0.453	1.682
NonHispanic White v. Mexican American	0.823	0.503	1.348
Other Hispanic v. Mexican American	1.063	0.345	3.272
Quartile 4 v. 1	0.434	0.184	1.027

Table 49. (Continued).

Effect	Odds Ratio	95% Confidence Intervals	
Quartile 3 v. 1	0.658	0.319	1.358
Quartile 2 v. 1	0.663	0.331	1.326

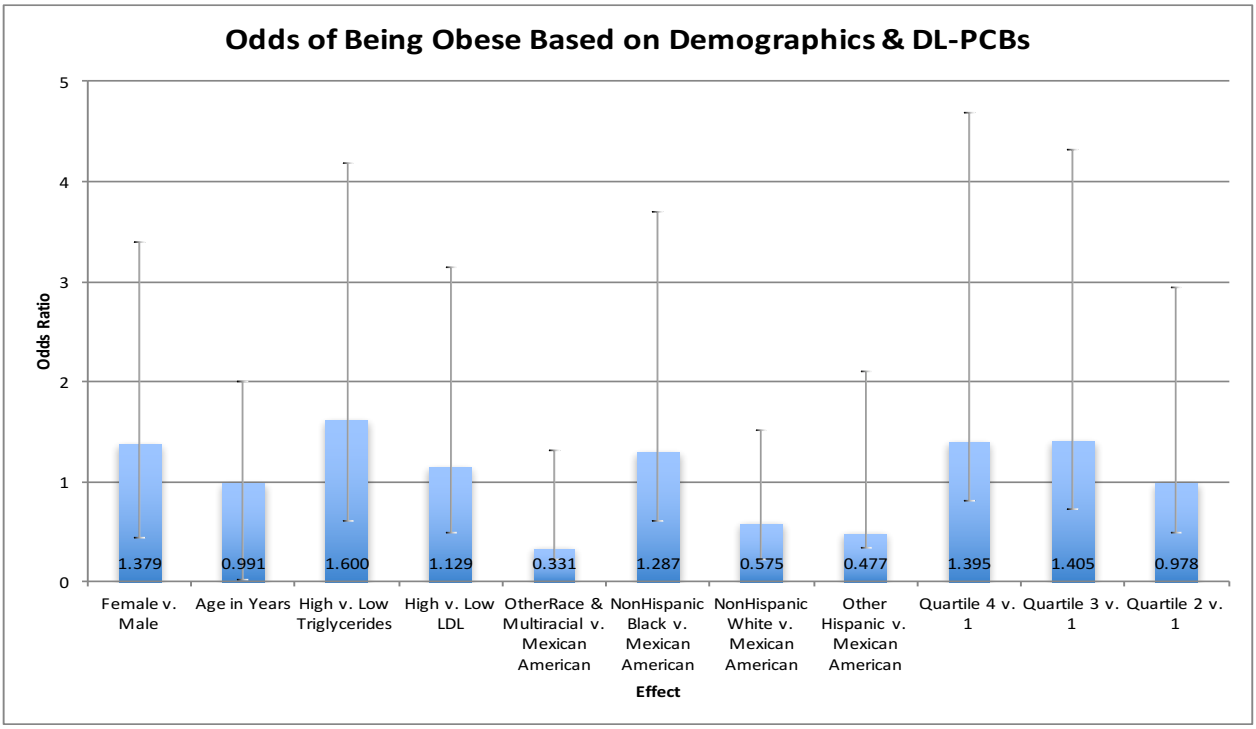

Figure 41. Odds of being obese in relation to blood concentration of dl-PCBs. No comparisons yielded significant odds of obese BMI.

Table 50. Odds of being obese in relation to blood concentration of dl-PCBs.

Effect	Odds Ratio	95% Confidence Intervals	
Female v. Male	1.379	0.941	2.020
Age in Years	0.991	0.976	1.005
High v. Low Triglycerides	1.600	0.989	2.589
High v. Low LDL	1.129	0.633	2.012
OtherRace & Multiracial v. Mexican American	0.331	0.112	0.980
NonHispanic Black v. Mexican American	1.287	0.685	2.418
NonHispanic White v. Mexican American	0.575	0.350	0.943

Table 50. (Continued).

Effect	Odds Ratio	95% Confidence Intervals	
Other Hispanic v. Mexican American	0.477	0.140	1.632
Quartile 4 v. 1	1.395	0.591	3.293
Quartile 3 v. 1	1.405	0.679	2.906
Quartile 2 v. 1	0.978	0.488	1.958

4.4 Phthalates

4.4.1 Frequency Distributions

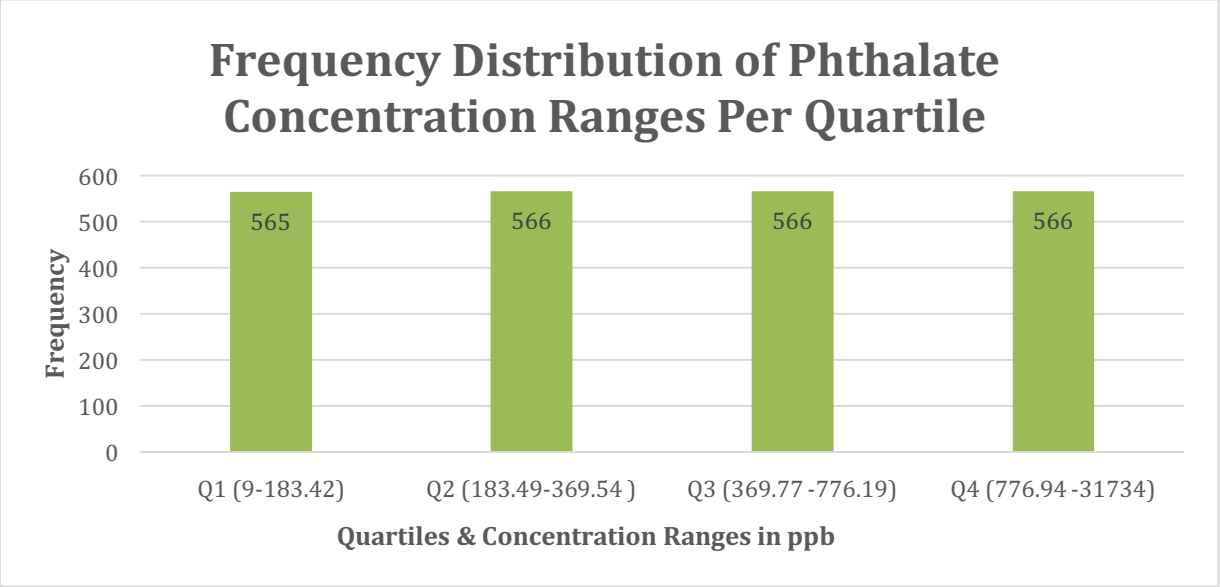

Figure 42. Frequency distribution of the sum of phthalates per quartile range.

Table 51. Frequency distribution table of the sum of phthalates per quartile range.

Sum of Phthalates (Quartiles)				
Concentration Range	**Frequency**	**Percent**	**Min**	**Max**
Q1 (9-183.42)	565	100.00%	9.282631811	31733.40514
Q2 (183.49-369.54)	566	0.00%		
Q3 (369.77 -776.19)	566	0.00%		
Q4 (776.94 -31734)	566	0.00%		

Table 52. Frequency distribution table of age ranges cross-referenced with total phthalate quartiles.

The FREQ Procedure

Frequency
Percent
Row Pct
Col Pct

Table of RIDAGEYR by TotalPhthalates

RIDAGEYR(Age at Screening Adjudicated - Recode)	TotalPhthalates				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
12-18	110 4.86 17.21 19.47	163 7.20 25.51 28.80	181 8.00 28.33 31.98	185 8.17 28.95 32.69	639 28.24
19-30	88 3.89 21.57 15.58	94 4.15 23.04 16.61	113 4.99 27.70 19.96	113 4.99 27.70 19.96	408 18.03
31-50	131 5.79 25.19 23.19	127 5.61 24.42 22.44	126 5.57 24.23 22.26	136 6.01 26.15 24.03	520 22.98
51-84	211 9.32 33.18 37.35	162 7.16 25.47 28.62	137 6.05 21.54 24.20	126 5.57 19.81 22.26	636 28.10
85 & above	25 1.10 41.67 4.42	20 0.88 33.33 3.53	9 0.40 15.00 1.59	6 0.27 10.00 1.06	60 2.65
Total	565 24.97	566 25.01	566 25.01	566 25.01	2263 100.00

Table 53. Frequency distribution table of gender cross-referenced with total phthalate quartiles.

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of RIAGENDR by TotalPhthalates					
		TotalPhthalates				
	RIAGENDR(Gender)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
	Male	249 11.00 22.87 44.07	277 12.24 25.44 48.94	265 11.71 24.33 46.82	298 13.17 27.36 52.65	1089 48.12
	Female	316 13.96 26.92 55.93	289 12.77 24.62 51.06	301 13.30 25.64 53.18	268 11.84 22.83 47.35	1174 51.88
	Total	565 24.97	566 25.01	566 25.01	566 25.01	2263 100.00

Table 54. Frequency distribution table of ethnicities cross-referenced with total phthalate quartiles.

Frequency Percent Row Pct Col Pct	Table of RIDRETH1 by TotalPhthalates					
		TotalPhthalates				
	RIDRETH1(Race/Ethnicity - Recode)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
	Mexican_American	125 5.52 22.81 22.12	148 6.54 27.01 26.15	148 6.54 27.01 26.15	127 5.61 23.18 22.44	548 24.22
	Other_Hispanic	22 0.97 30.56 3.89	12 0.53 16.67 2.12	21 0.93 29.17 3.71	17 0.75 23.61 3.00	72 3.18
	NonHispanic_White	312 13.79 31.61 55.22	268 11.84 27.15 47.35	212 9.37 21.48 37.46	195 8.62 19.76 34.45	987 43.61
	NonHispanic_Black	77 3.40 13.68 13.63	119 5.26 21.14 21.02	157 6.94 27.89 27.74	210 9.28 37.30 37.10	563 24.88
	OtherRace_IncludingMultiRacial	29 1.28 31.18 5.13	19 0.84 20.43 3.36	28 1.24 30.11 4.95	17 0.75 18.28 3.00	93 4.11
	Total	565 24.97	566 25.01	566 25.01	566 25.01	2263 100.00

4.4.2 Comparative Statistics

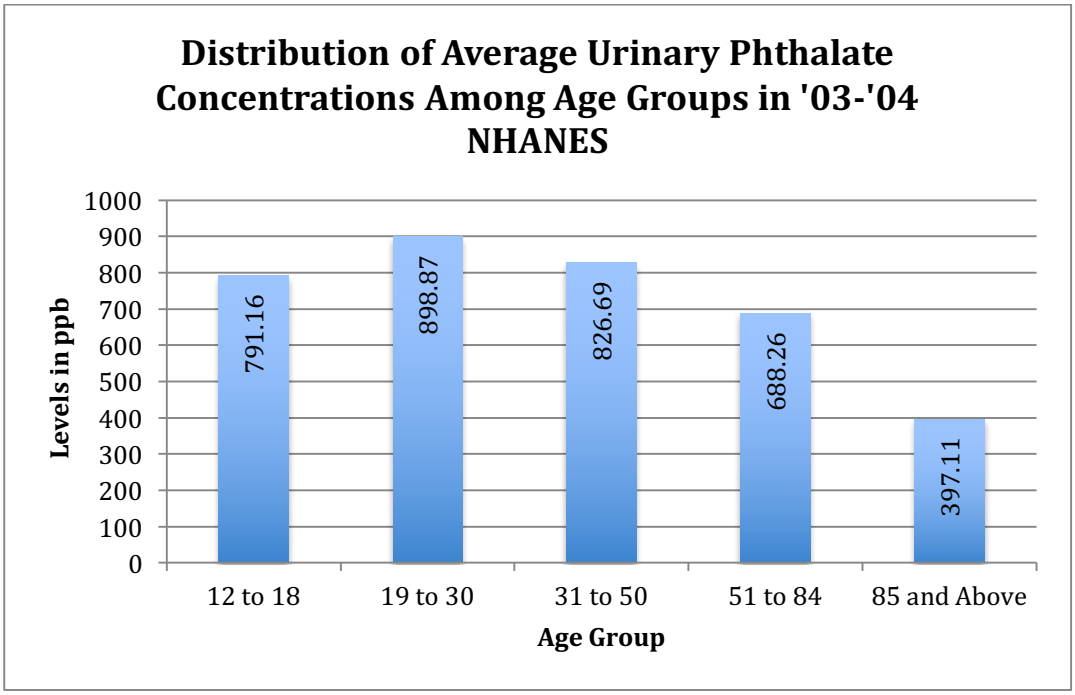

Figure 43. Comparison of average phthalate concentrations among age groups, in years. Difference in mean Phthalate concentrations between age groups were significant; p-value <0.05

Table 55. Comparison of average phthalate concentrations among age groups, in years.

Age Group, in years	12 to 18	19 to 30	31 to 50	51 to 84	85 and Above
Concentrations, in ng/g lipids	791.161	898.867	826.693	688.263	397.113

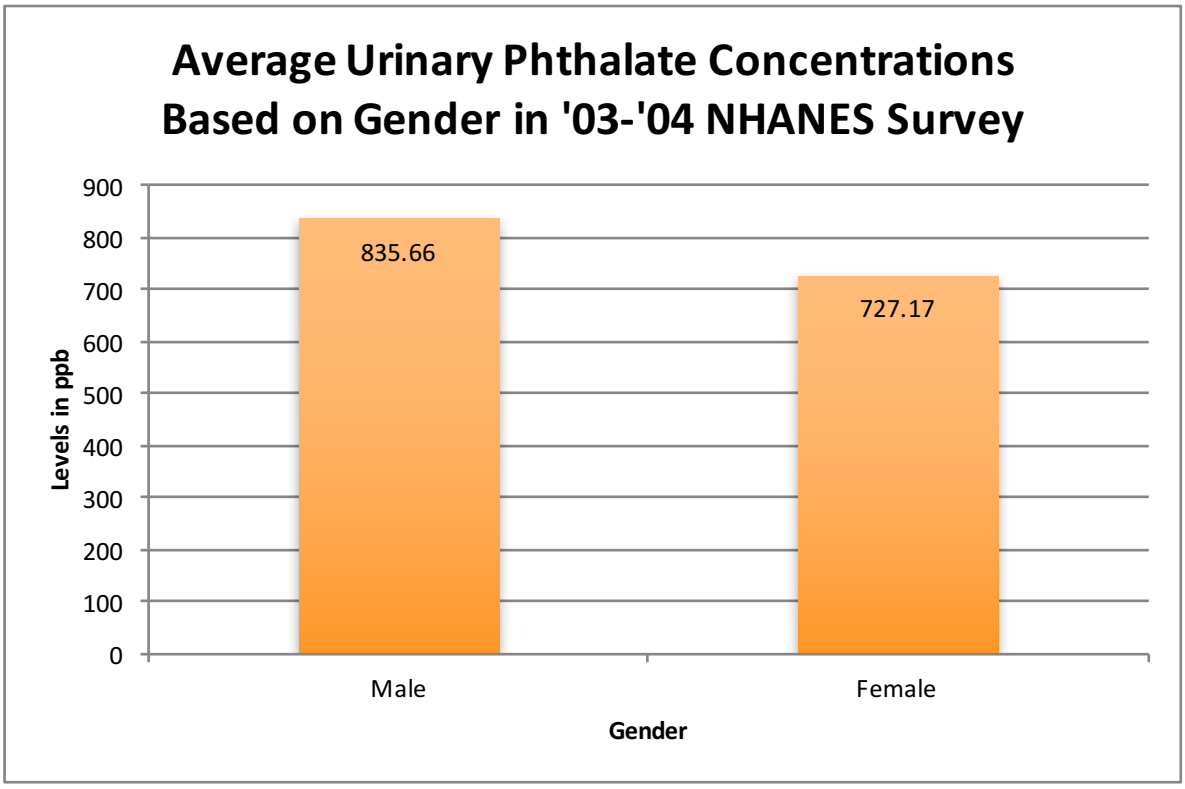

Figure 44. Comparison of average phthalate concentrations among genders. Difference in mean phthalate concentrations between genders were insignificant; p-value >0.05.

Table 56. Comparison of average phthalate concentrations among genders.

Gender	Male	Female
Concentrations, in ng/g lipids	835.662	727.169

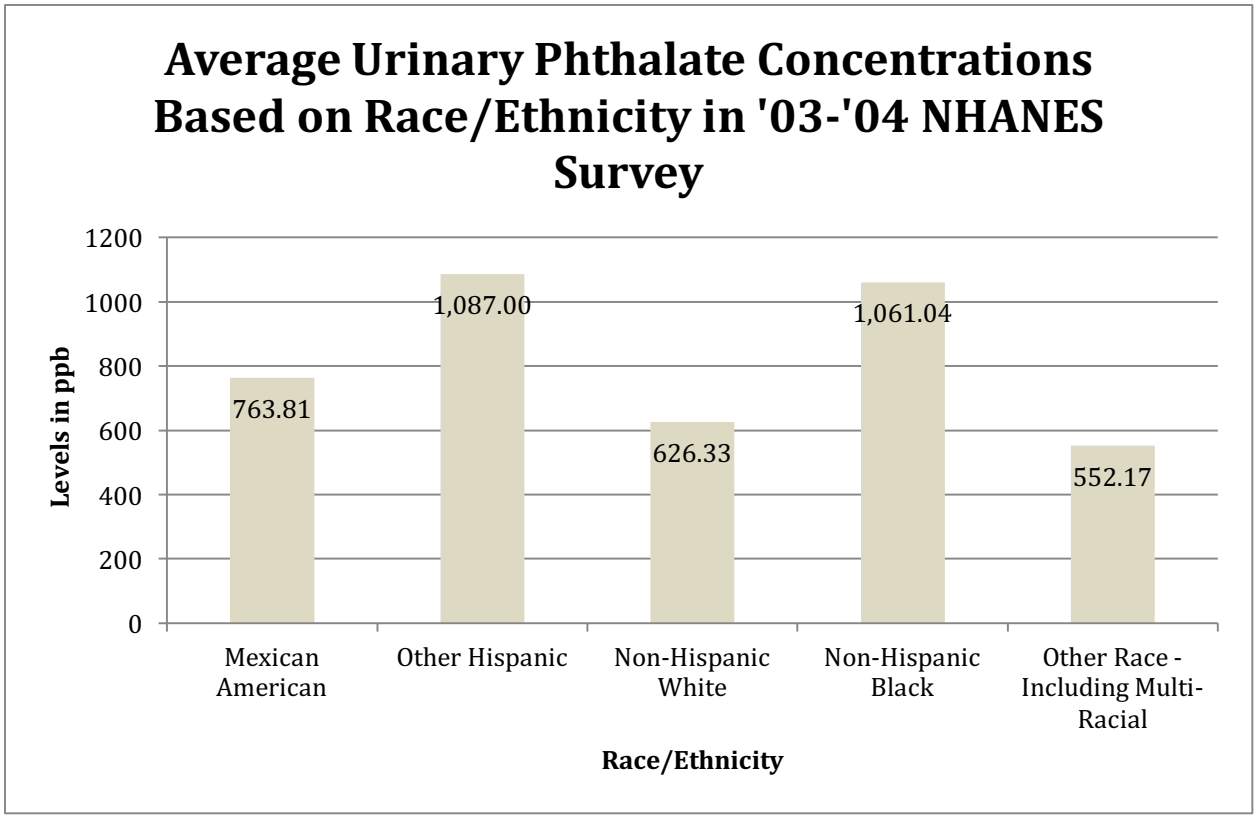

Figure 45. Comparison of average phthalate concentrations among ethnic groups. Difference in mean Phthalate concentrations between races were significant; p-value <0.05.

Table 57. Comparison of average phthalate concentrations among ethnic groups.

Ethnicity	Mexican American	Other Hispanic	Non-Hispanic White	Non-Hispanic Black	Other Race - Including Multi-Racial
Concentrations, in ng/g lipids	763.812	1086.998	626.326	1061.037	552.166

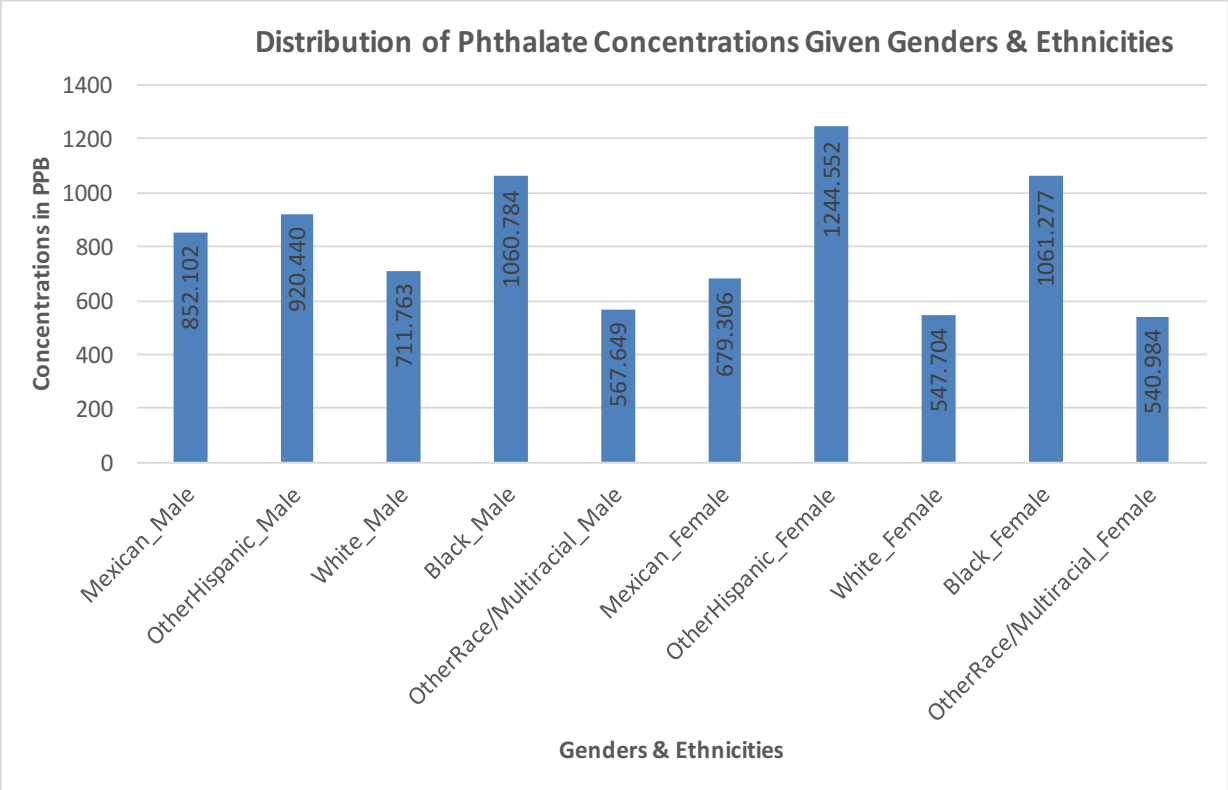

Figure 46. Comparison of average phthalate concentrations among gender and ethnicities. According to Tukey's test, a comparison of average phthalate concentrations of OtherHispanic_Male and Black_Male groups was significant and a comparison of average phthalate concentrations of OtherHispanic_Female and White_Female, Black_Female and Mexican_Female, Black_Female and White Female were significant.

Table 58. Comparison of average phthalate concentrations among gender and ethnicities.

Ethnicity	**Concentrations, in ng/g lipids**
Mexican_Male	852.102
OtherHispanic_Male	920.440
White_Male	711.763
Black_Male	1060.784
OtherRace/Multiracial_Male	567.649
Mexican_Female	679.306
OtherHispanic_Female	1244.552
White_Female	547.704
Black_Female	1061.277
OtherRace/Multiracial_Female	540.984

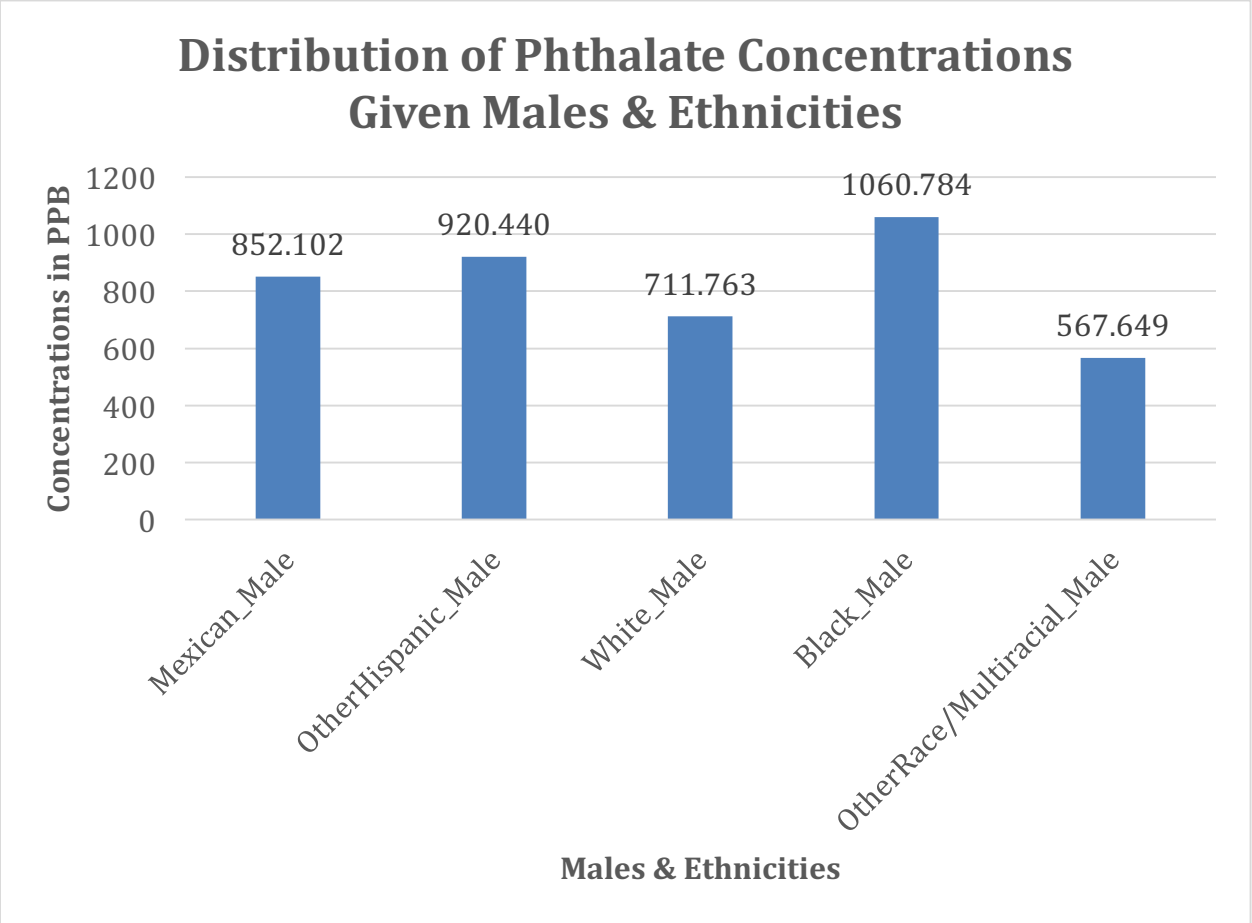

Figure 47. Comparison of average phthalate concentrations among males and ethnicities. According to Tukey's test, a comparison of average phthalate concentrations of OtherHispanic_Male and Black_Male groups was significant.

Table 59. Comparison of average phthalate concentrations among males and ethnicities.

Ethnicity	Mexican_Male	OtherHispanic_Male	White_Male	Black_Male	OtherRace/Multiracial_Male
Concentrations, in ng/g lipids	852.102	920.440	711.763	1060.784	567.649

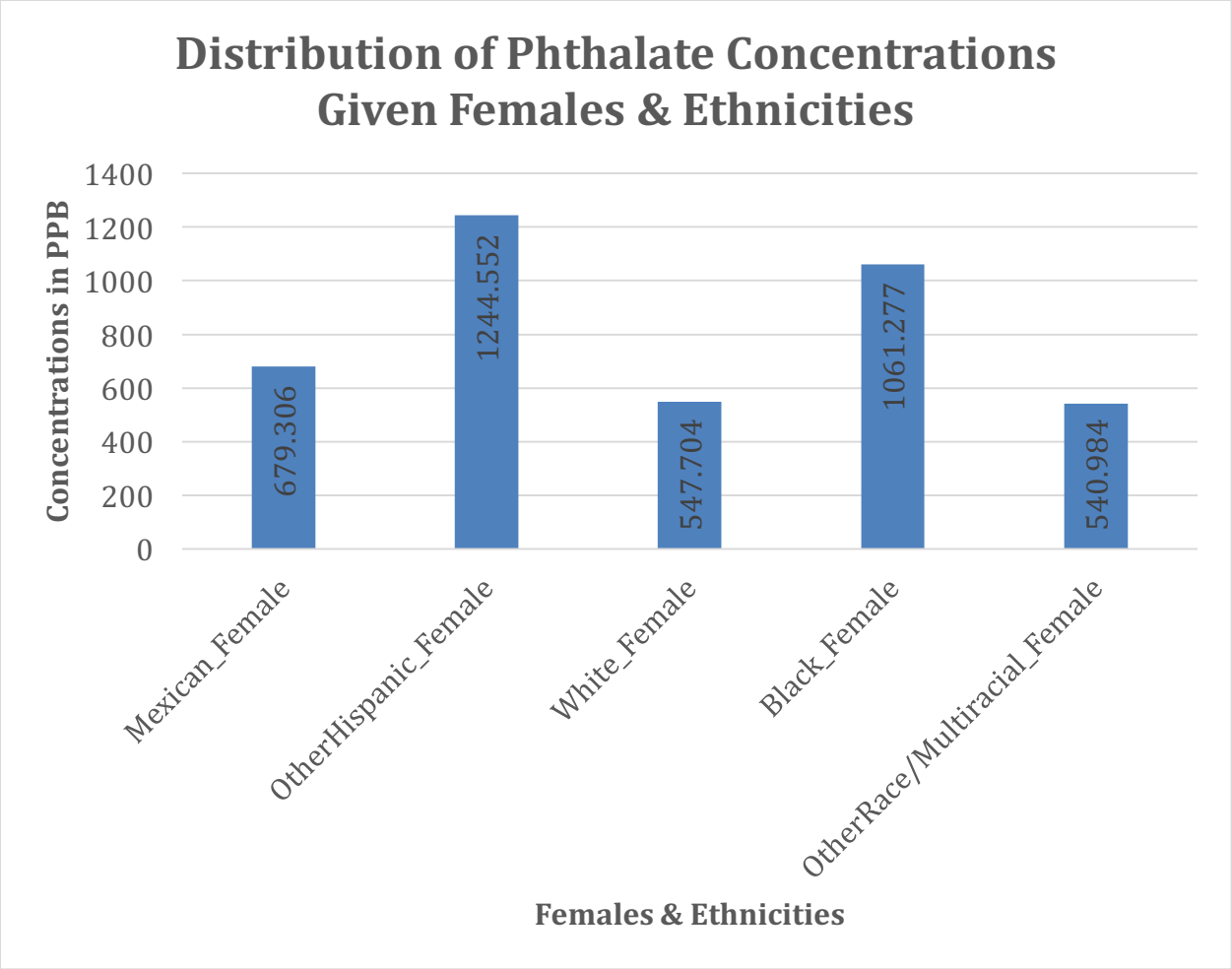

Figure 48. Comparison of average phthalate concentrations among females and ethnicities. According to Tukey's test, a comparison of average phthalate concentrations of OtherHispanic_Female and White_Female, Black_Female and Mexican_Female, Black_Female and White Female were significant.

Table 60. Comparison of average phthalate concentrations among females and ethnicities.

Ethnicity	Mexican_Female	OtherHispanic_Female	White_Female	Black_Female	OtherRace/Multiracial_Female
Concentrations, in ng/g lipids	679.306	1244.552	547.704	1061.277	540.984

4.4.3 Logistic Regression Statistics

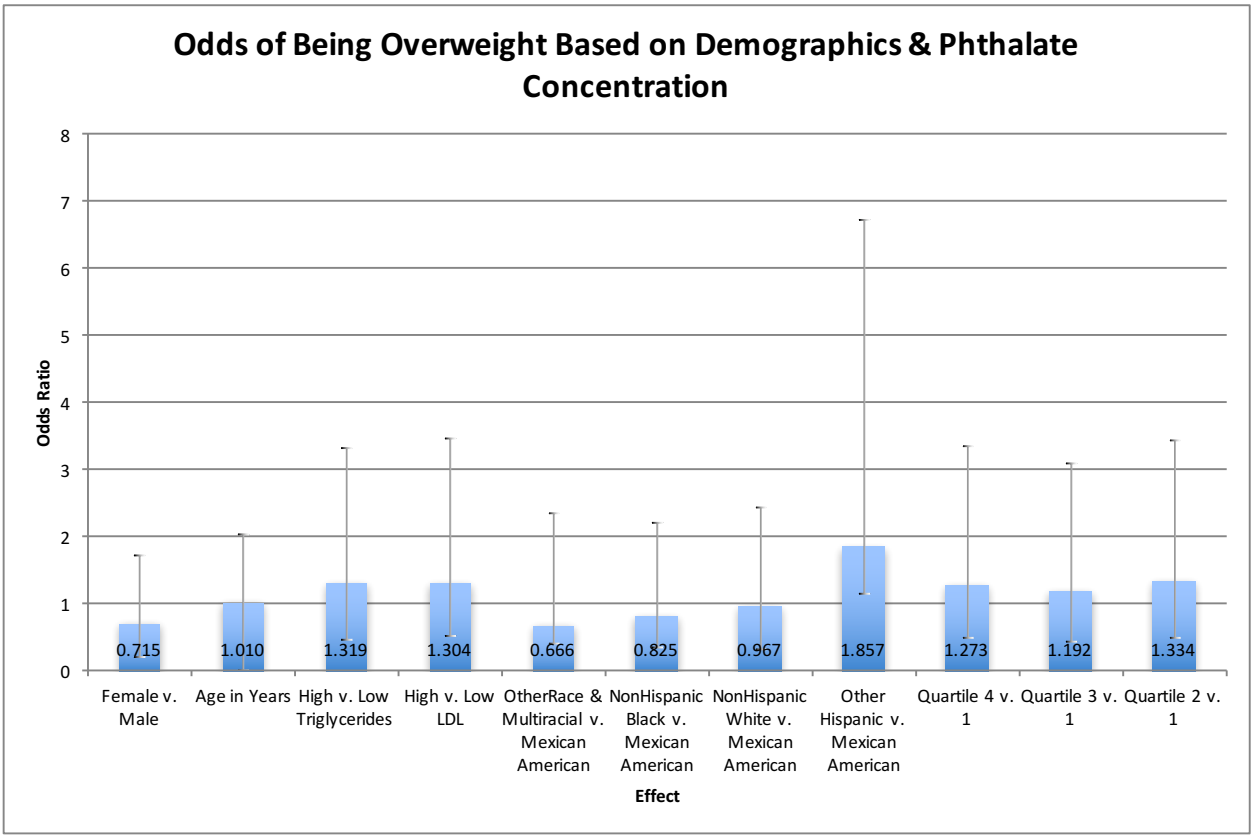

Figure 49. Odds of being overweight in relation to urinary concentration of phthalates.

Table 61. Odds of being overweight in relation to urinary concentration of phthalates.

Effect	Odds Ratio	95% Confidence Intervals	
Female v. Male	0.715	0.514	0.994
Age in Years	1.010	1.001	1.019
High v. Low Triglycerides	1.319	0.869	2.001
High v. Low LDL	1.304	0.790	2.152
OtherRace & Multiracial v. Mexican American	0.666	0.263	1.685
NonHispanic Black v. Mexican American	0.825	0.489	1.392
NonHispanic White v. Mexican American	0.967	0.636	1.472
Other Hispanic v. Mexican American	1.857	0.710	4.859
Quartile 4 v. 1	1.273	0.785	2.067
Quartile 3 v. 1	1.192	0.745	1.907
Quartile 2 v. 1	1.334	0.847	2.099

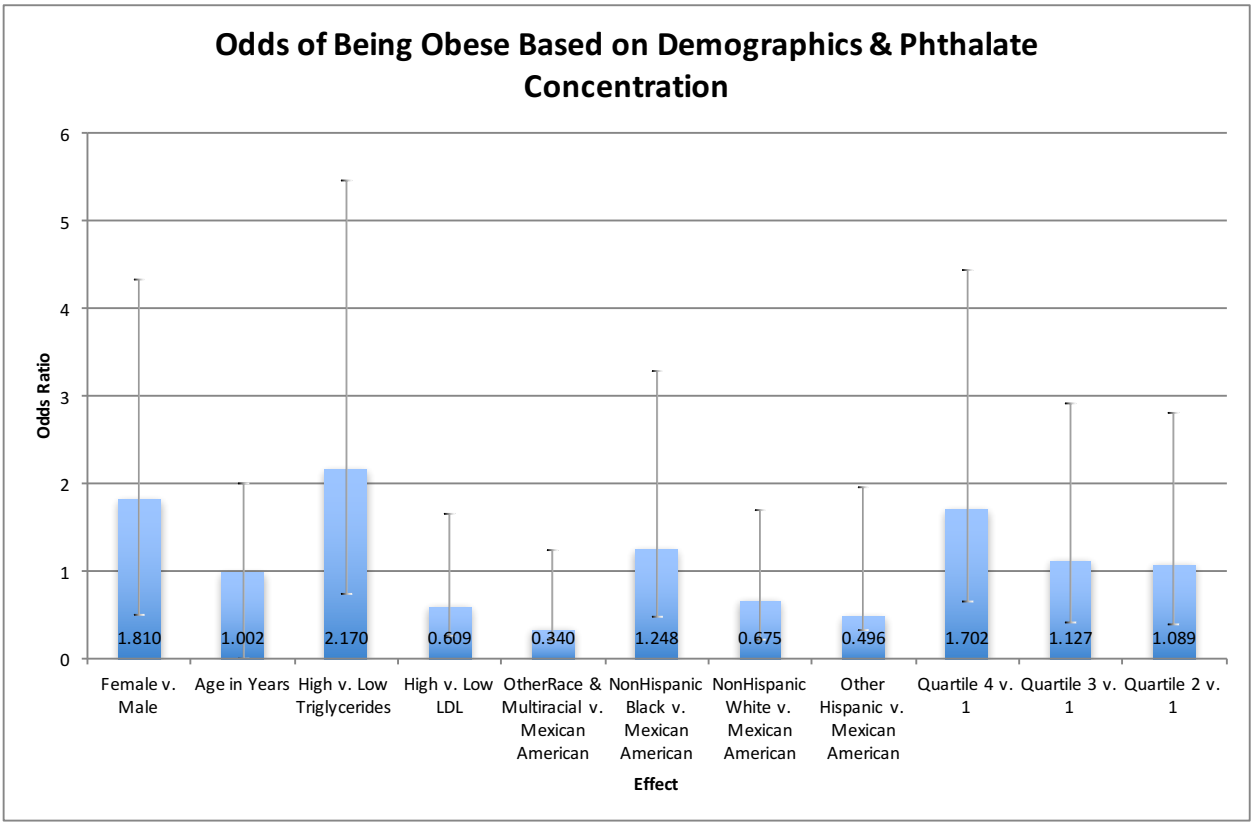

Figure 50. Odds of being obese in relation to urinary concentration of phthalates.

Table 62. Odds of being obese in relation to urinary concentration of phthalates.

Effect	**Odds Ratio**	**95% Confidence Intervals**	
Female v. Male	1.810	1.297	2.525
Age in Years	1.002	0.993	1.011
High v. Low Triglycerides	2.170	1.427	3.298
High v. Low LDL	0.609	0.355	1.047
OtherRace & Multiracial v. Mexican American	0.340	0.127	0.913
NonHispanic Black v. Mexican American	1.248	0.761	2.048
NonHispanic White v. Mexican American	0.675	0.446	1.024
Other Hispanic v. Mexican American	0.496	0.167	1.470
Quartile 4 v. 1	1.702	1.057	2.740
Quartile 3 v. 1	1.127	0.705	1.800
Quartile 2 v. 1	1.089	0.690	1.721

4.5 Comparison of Analytes

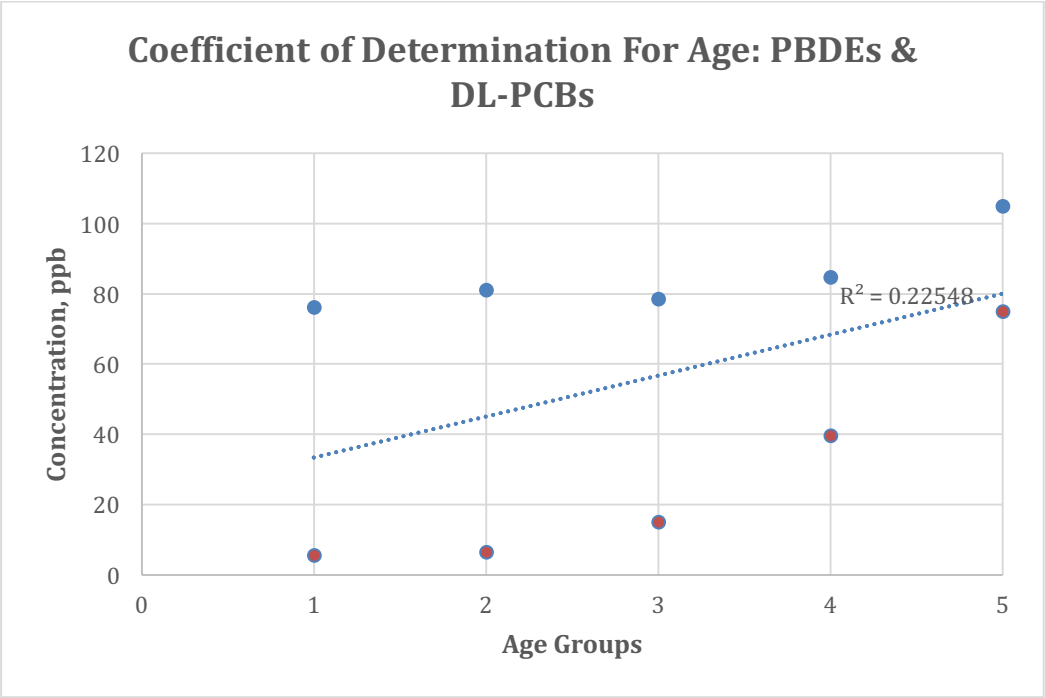

Figure 51. Comparison of average PBDE (in blue) and dl-PCB (in red) concentrations among age-groups. Approximately 22.5% of the total variation in y can be explained by the linear relationship between x and y (as described by the regression equation). A positive moderate association exists between concentrations of PBDEs and dl-PCBs among age groups; R=0.47. Finally, p-value<0.05; there is a significant difference in the average concentrations of PBDEs in comparison to dl-PCBs', among age groups.

Table 63. Comparison of average PBDE and dl-PCB concentrations among age-groups.

Age Groups	Ages	Mean PBDE Concentrations (ppb)	Mean dl-PCB Concentrations (ppb)
1	12 to 18	76.134	5.652
2	19 to 30	81.089	6.578
3	31 to 50	78.433	15.025
4	51 to 84	84.654	39.665
5	85 and Above	104.898	75.020

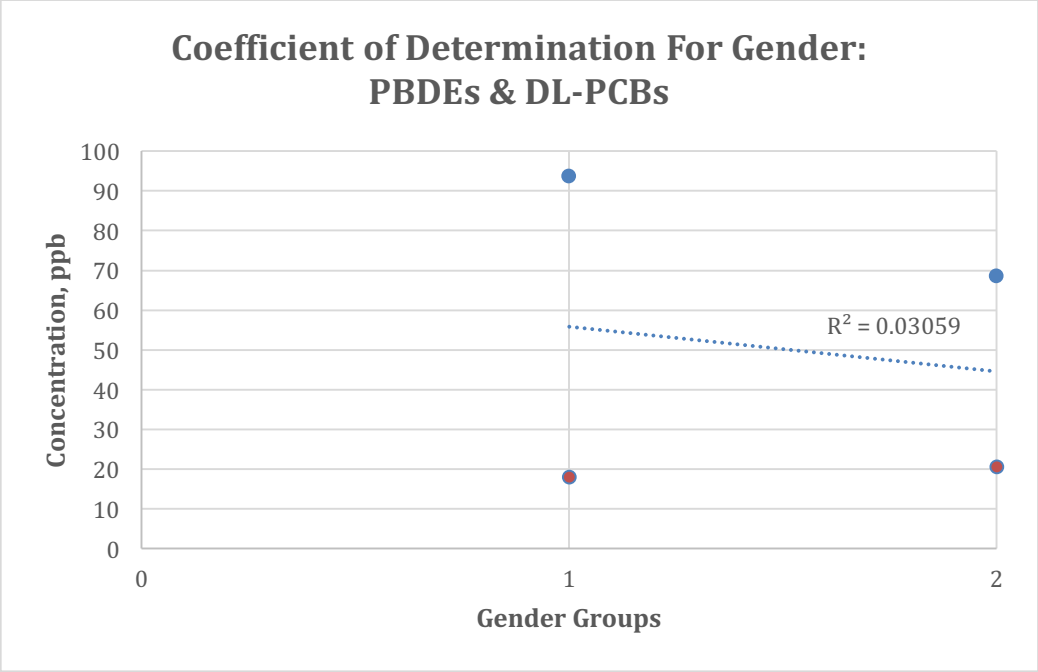

Figure 52. Comparison of average PBDE (in blue) and dl-PCB (in red) concentrations among genders. Approximately 3.1% of the total variation in y can be explained by the linear relationship between x and y (as described by the regression equation). A negative but very weak association exists between concentrations of PBDEs and dl-PCBs among genders; R=0.17. Finally, p-value>0.05; there is no significant difference in the average concentrations of PBDEs in comparison to dl-PCBs', among gender groups.

Table 64. Comparison of average PBDE and dl-PCB concentrations among genders.

Gender Groups	Genders	Mean PBDE Concentrations (ppb)	Mean dl-PCB Concentrations (ppb)
1	Male	93.780	17.987
2	Female	68.599	20.635

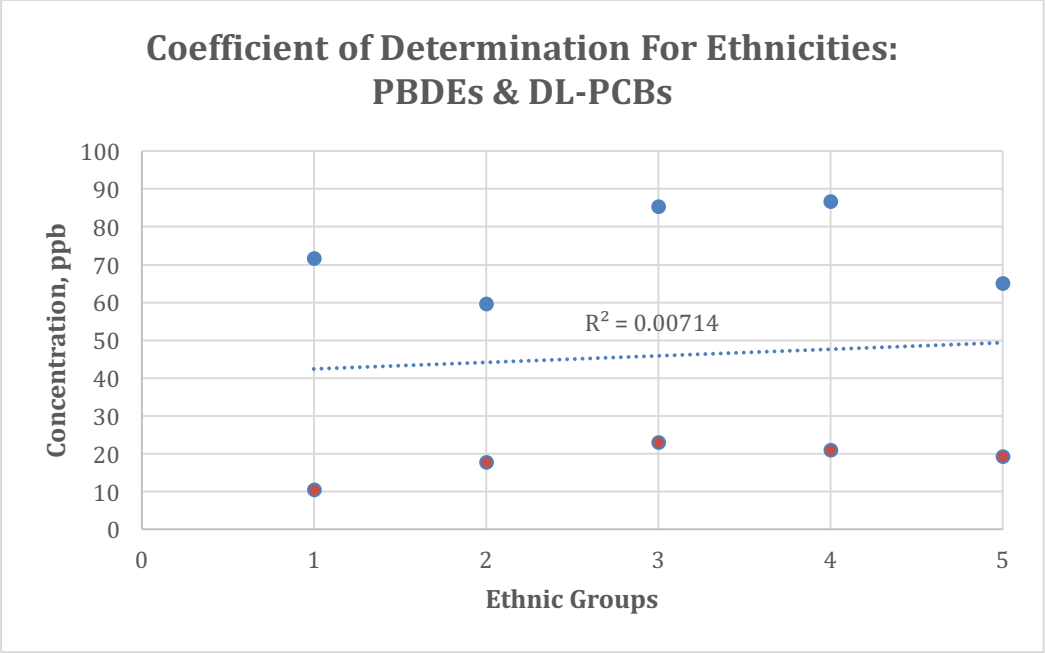

Figure 53. Comparison of average PBDE (in blue) and dl-PCB (in red) concentrations among ethnicities. Approximately 0.7% of the total variation in y can be explained by the linear relationship between x and y (as described by the regression equation). A positive but very weak association exists between concentrations of PBDEs and dl-PCBs among ethnicities; R=0.08. Finally, p-value<0.05; there is a significant difference in the average concentrations of PBDEs in comparison to dl-PCBs', among ethnic groups.

Table 65. Comparison of average PBDE and dl-PCB concentrations among ethnicities.

Ethnic Groups	Ethnicities	Mean PBDE Concentrations (ppb)	Mean dl-PCB Concentrations (ppb)
1	Mexican American	71.607	10.477
2	Other Hispanic	59.555	17.784
3	Non-Hispanic White	85.321	22.957
4	Non-Hispanic Black	86.671	20.946
5	Other Race/MultiRacial	64.954	19.235

4.6 Summary of Results

Summary of PBDE Results

- Mean PBDE concentrations are significantly different among genders
    - For sum, BDE-47, BDE-99
- Mean PBDE concentrations are not significantly different among age groups, ethnicities
    - For sum, BDE-47, BDE-99
- Based on categorical analysis,
    - Ethnicity is the only significant predictor of overweight BMI
    - Although, confidence intervals were generally large
    - No significant results were found for obesity analyses
- The difference in PBDE blood concentrations was insignificant when accounting for genders and ethnicities.

Summary of dl-PCB Results

- Mean PCB concentrations are significantly different among age groups and ethnicities
- Mean PCB concentrations are not significantly different among genders
- Based on categorical analysis
    - Ethnicity and LDL cholesterol are predictors of overweight BMI
    - Although, confidence intervals were generally large
    - No significant results were found for obesity analysis

- The difference in PCB concentrations were significant among gender and ethnicities, males and ethnicities, and females and ethnicities.

Summary of phthalate Results

- Mean Phthalate concentrations are significantly different among age groups and ethnicities.
- Mean Phthalate concentrations are not significantly different among genders.
- Based on categorical analysis,
    - Ethnicity is the only significant predictor of overweight BMI.
    - Although, confidence intervals were generally large.
    - No significant results were found for obesity analysis.
- The difference in Phthalate concentrations were significant among gender and ethnicities.

Summary of Analyte Comparison Results

- Mean concentrations among age groups, in parts per billion, differed significantly between PBDEs and dl-PCBs.
- Mean concentrations among genders, in parts per billion, did not differ significantly between PBDEs and dl-PCBs.
- Mean concentrations among ethnicities, in parts per billion, differed significantly between PBDEs and dl-PCBs.
    - Blood serum concentrations of PBDEs was generally higher than dl-PCBs in analyses of age groups, genders and ethnicities.

Chapter 5

Discussion

5.1 Evaluation of Research Hypotheses

The proposed hypotheses of this dissertation research will be examined below, to determine how well the results of this study supported the overall objectives of this research:

Hypothesis 1: Biomonitoring data obtained from the National Health and Nutrition Examination Survey indicates the presence of background biomarkers of PBDE, dl-PCB, and phthalate exposure in individuals from a sample of the general population.

Through the analyses that were conducted using the Demographic Variables & Sample Weights, Phthalates, and Dioxins, Furans, & Coplanar PCBs, there is evidence that PBDE, dl-PCB and Phthalate biomarkers are present in a sample of the US population. However, one must remember that the metabolism of pollutants can vary among study participants (Manno et al., 2010). The latter has an impact on the reported concentrations of each analyte. In addition, one should consider the impact of dilution on reported analyte concentrations, especially in the case of urinary phthalates.

Hypothesis 2: Due to the bioaccumulative properties of PBDEs in the human body, increasing PBDE concentrations is significantly associated with increasing with age groups.

- *Due to the bioaccumulative properties of dl-PCBs in the human body, increasing dl-PCB concentrations is significantly associated with increasing with age groups.*
- *Due to the bioaccumulative properties of phthalates in the human body, increasing phthalate concentrations is significantly associated with increasing with age groups.*

A comparison of the average concentrations of PBDEs among age groups reveal that concentrations of the sum of PBDEs, BDE-47, and BDE-99 are not significantly associated with increasing age groups. The opposite results were found in an analysis of the distribution of dl-PCB and phthalate concentrations among age groups. It is not known why such differences in distributions exist since all three compounds are known to accumulate in the body over time. In the case of dl-PCBs, an exponential increase in concentration with increasing age groups was observed which supports the notion that these contaminants have a relatively long half-life in comparison to PBDEs. In the case of phthalates, urinary concentrations generally decrease with age. Furthermore, participants aged 85 or older have urinary concentrations that are, on average, lower in comparison to other age groups. Additionally, it should be noted that the age groups were arbitrarily divided. Hence, different conclusions and trends could have been generated if much different age groups were selected. Also, since the dataset is limited to ages 12 – 85 years, it is not known whether different conclusions would have been generated if the NHANES survey of these contaminants included individuals of a broader age range (*e.g.*, including participants younger than 12 years old).

Hypothesis 3: Since PBDEs are ubiquitous in the environment, the average concentrations of its biomarkers are homogeneous across other sample subgroups including genders, ethnicities, and,

genders and ethnicities; indicating that these subgroups are not at an increased risk of a negative health outcome.

- *Similarly, average dl-PCB concentrations are homogeneous across other sample subgroups including genders, ethnicities, and, genders and ethnicities; indicating that these subgroups are not at an increased risk of a negative health outcome.*
- *Similarly, average phthalate concentrations are homogeneous across other sample subgroups including genders, ethnicities, and, genders and ethnicities; indicating that these subgroups are not at an increased risk of a negative health outcome.*

Concerning the analysis of other demographic categories, including gender, ethnicities and gender *with* ethnicities significant differences were observed for all analytes of interest. First, the average PBDE concentrations reported for the sum of PBDEs, BDE-47 and BDE-99 were significantly different among genders. In fact, males consistently had significantly higher average concentrations of the sum of PBDEs, BDE-47 and BDE-99. This is likely due to toxicokinetic (*e.g.*, absorption, metabolism and elimination) differences among genders. The opposite was found in the case of dl-PCBs and phthalates. Once again it is not known why PBDEs are distributed differently than dl-PCBs and phthalates, among genders. In fact, a similar difference was found when analyzing the concentrations of these analytes among ethnicities. Specifically, the average concentrations of the sum of PBDEs, BDE-47, and BDE-99 were not significantly different among ethnicities. On the other hand, significantly different concentrations of dl-PCBs and phthalates were observed among ethnicities. Moreover, based on an analysis of the average concentrations of PBDEs, BDE-47 and BDE-99, there is no significant difference among genders *and* ethnicities (*e.g.*, Black males v. Mexican American females). The latter supports part of the above-listed

hypothesis. However, when the analyses were conducted for the other contaminants, the opposite conclusions were found. Specifically, the difference in dl-PCB concentrations were significant among gender *and* ethnicities, males *and* ethnicities, and females *and* ethnicities. Also, the difference in phthalate concentrations were significant among gender and ethnicities; not for males *and* ethnicities, nor females *and* ethnicities. Tukey's Test was used to determine which specific groups had significantly different concentrations for dl-PCBs and phthalates, using a 95% confidence level. According to Tukey's test, a comparison of average dl-PCB concentrations of White_Male v. Mexican_Male, and Black_Male v. Mexican_Male groups were significant and a comparison of average dl-PCB concentrations of Black_Female v. Mexican_Female, and White_Female v. Mexican_Female groups were significant. Also, according to Tukey's Test, a comparison of average phthalate concentrations of OtherHispanic_Male and Black_Male groups was significant and a comparison of average phthalate concentrations of OtherHispanic_Female and White_Female, Black_Female and Mexican_Female, Black_Female and White Female were significant. The significant outcomes that were discovered in the analyses of dl-PCB and phthalate concentrations could have been due to the oversampling of minorities through the NHANES program. As mentioned in the Methods section, the NHANES program oversamples minorities and the elderly since they tend to have drastically different health statuses and characteristics of concern, in comparison to non-minorities (CDC, 2012). However, one must note that this oversampling could lead to an overestimation of true exposure. Thus, the significant differences of dl-PCB and phthalate concentrations found among age groups, ethnicities, and genders *with* ethnicities could have been nullified if elderly and minority groups were not given special attention. The reported data could be overestimating the actual concentration of the biomarkers when extrapolating results to the population. In fact, true population levels may be lower than

those reported in the NHANEs sample (Lebeau, 2012). Finally, as a result of the consistency of results that have been observed between analytes, one can conclude that PBDEs appear to be distributed differently among demographic categories in comparison to dl-PCBs and phthalates. In contrast, when considering the homogeneity or heterogeneity of average dl-PCB and phthalate concentrations among various demographic categories, significance of results is similar for both types of compounds. These results suggest pharmacodynamic differences for PBDEs in comparison to dl-PCBs and phthalates. Correspondingly, these results also suggest possible pharmacodynamic similarities between dl-PCBs and phthalates.

Hypothesis 4: Blood sample data from the National Health and Nutrition Examination Survey reveal that the background concentrations of PBDEs do not significantly increase the odds of obesity nor the odds of being overweight.

a. *Blood sample data from the National Health and Nutrition Examination Survey reveal that the background concentrations of dl-PCBs do not significantly increase the odds of obesity nor the odds of being overweight.*
b. *Blood sample data from the National Health and Nutrition Examination Survey reveal that the background concentrations of phthalates do not significantly increase the odds of obesity nor the odds of being overweight.*

According to a categorical analysis of PBDEs and obesity, PBDE background concentrations (higher vs. lower quartiles) did not significantly increase participants' odds of being obese. In fact, when considering age, gender, ethnicity, LDL cholesterol, triglycerides and PBDE quartiles in the logistic regression model no results were significant. In the case of overweight

status, ethnicity was the only significant predictor of overweight BMI. Next, analyses also show that the background concentrations of dl-PCBs did not significantly increase one's odd of being obese or overweight. Ethnicity and LDL cholesterol were the only significant predictors of overweight BMI, when considering age, gender, ethnicity, LDL cholesterol, triglycerides and PBDE quartiles in the logistic regression model. Finally, background concentrations of phthalates did not significantly increase participant's odds of obesity or of being overweight. Ethnicity was the only significant predictor of overweight BMI, when considering age, gender, ethnicity, LDL cholesterol, triglycerides and PBDE quartiles in the logistic regression model. Although, it should be noted that confidence intervals were generally large in all three sets of categorical analyses.

Hypothesis 5: Due to the similarities of PBDEs and dl-PCBs, average concentrations are not significantly different among demographic categories.

c. *Although distributions of phthalate concentrations can be discussed in relation to PBDEs, specific comparisons cannot be made due to a difference in measurement units (ng/g lipids for PBDEs and dl-PCBs vs. ng/mL for phthalates).*

First, it should be reiterated that a direct comparison cannot be made between PBDEs and phthalates because unlike PBDEs and dl-PCBs which were measured in serum and reported in ng/g lipid, phthalates were measured in urine and reported in ng/mL. In other words, the prior were reported in weight/weight ratio whereas the latter was reported in weight/volume ratio. Due to mathematical convention, a direct comparison cannot be made between these two types of units. As a result, while the distributions of all three analytes were investigated, direct comparative analyses could only be conducted for the sum of PBDEs and the sum of dioxin-like PCBs. Based

on paired t-test analyses, the average concentrations of PBDEs were significantly different from the average concentrations of dl-PCBs, when considering age groups and ethnicities. Next, average concentrations of PBDEs and dl-PCBs did not significantly differ when considering genders. In general, PBDE blood serum concentrations were higher than dl-PCBs in analyses of age groups, genders and ethnicities. These results are likely due to the 1979 ban on polychlorinated biphenyls. Although PCBs are persistent in our environments and despite their relatively long half-lives, and ability to accumulate in the body, PBDEs have been the dominant flame retardants of since (Vonderheide et al., 2008). Hence, their presence in our environments is likely to be much more pronounced.

5.2 Evaluation of Results

Overall, the average PBDE concentration among participants in the 2003-2004 NHANES was approximately 81 ng/g lipid with a range of 0.05 (LOD/√2) to 3676 ng/g lipid. These results are not clearly comparable with those of other studies for several reasons. First, unlike other studies, the 2003-2004 NHANES survey provides one of the largest samples used to investigate polybrominated brominate diphenyl ethers. Most comparable studies have much more limited sample sizes. As a result, investigators often report concentrations that are on generally less than those found in this dissertation research. The range of reported results are also much different. For example, according to a study of a sum of 10 PBDEs, Eskenazi and company reported a range of 4.2 to 1379.4 ng/g lipid in maternal serum and 6.9 to 1385.5 ng/g lipid in child serum, in a study of the neurodevelopment effects of PBDEs (Eskenazi et al., 2013). Investigators in this study and others often report the median as a measure of central tendency instead of the mean. This also makes it difficult to compare results of this study with others. Overall, comparisons are difficult to

make as a result in differences in congeners, statistical tests, sample size, sample medium (*e.g.*, blood, milk, food, etc.) and demographic categories considered. Most studies report PBDE concentrations (in various media) specifically in nursing mothers and children. Thus, the results of such studies are not representative of the US population.

Nonetheless, Schecter et al. conducted a 2003 study of the PBDE concentrations in American breast milk compared to women's breast milk in other countries. Investigators analyzed 13 PBDEs in 47 individual milk samples from Texan nursing mothers, aged 20 to 41 years old. Investigators reported a range of 6.2 to 419 ng/g lipid and a mean of 73.9 ng/g lipid. Furthermore, investigators postulate that their results are similar to concentrations found in American blood and adipose tissue from Indiana and California (including research by Zota et al.) which are 10 to 100 times greater than PBDE concentrations found in France, Germany, and Russia. They also mention that most of the women were Caucasian. Hence, it may be more appropriate to compare their results to PBDE concentrations of White_Females in this dissertation research who had a comparable average PBDE concentration of 74.1 ng/g lipid. It should also be mentioned that since their research contained participants who were mostly Caucasian, their results are selectively biased (Schecter et al., 2003).

5.3 Evaluation of Risk

In general, as a result of a lack of information pertaining to the dose, duration, exposure source and route biomonitoring data can be difficult to assume risk. The National Health and Nutrition Examination Survey does not provide such information, which can lead due to a misinterpretation of the results (Centers for Human Health Assessment, 2017; Lebeau, 2012;

Manno et al., 2010). Regardless of the latter, a reported concentration, even if it were above a permissible level, would not be sufficient evidence to suggest a health risk. In fact, some statistically significant results were observed when considering the average sum of PBDE, BDE-47 and BDE-99 concentrations among genders. Males had consistently higher levels than females, in all three analyses. These results could suggest that males may be more at-risk than females to the potential health effects of PBDEs. However, this conclusion would likely be incorrect since, not only do measured concentrations not necessitate risk, a specific health outcome may be dependent on the phenotypic or genotypic characteristics of individuals. Moreover, the measured background concentrations may not lead to any health effects in the American population. In addition, although reference doses have been generated for some BDE congeners, such reference doses cannot be used to predict risk (IRIS, 2003; IRIS, 2004; IRIS, 2008a-d). They are created to protect people from potential and often unknown health effects.

5.4 Limitations of the Research

This cross-sectional study using the NHANES survey yielded some significant results among various demographics, depending upon the contaminant of interest. Since risk assessment is a very important feature of toxicology, a longitudinal study would have been more appropriate for the assessment of health risks. A major benefit of the latter is that data would be gathered for the same subjects repeatedly over a period. This would allow us to monitor increases and decreases in PBDE concentration. On the other hand, the NHANEs cross-sectional study design only generates a snapshot of PBDE concentrations for different participants. In addition, since the 2003-2004 NHANES dataset contained the most recent PBDE concentration data among Americans, this data is relatively dated. It would be useful to analyze recent data. However, NHANES has not

produced such a dataset since then. Next, it is unknown whether low dose, chronic exposure to PBDEs can cause adverse health effects. This makes the evaluation of dose-response difficult. As previously mentioned, minorities and the elderly were oversampled in this research. This may have introduced sampling bias into the analyses. Furthermore, there were 297 values that were below the limit of detection. These values were treated by dividing the LOD/√2. Other treatment methods which could have been used include LOD=0 and LOD/2. The LOD/√2 treatment method was automatically applied by the CDC for the dl-PCB dataset. Hence, for comparison's sake, this method was also used for the other analytes in this dissertation research. It should also be mentioned that the all analyses for the sum of PBDEs, BDE-47 and BDE-99 were also performed using the LOD=0 and LOD/2 treatment methods for values that were below the detection limits of the analytical instruments. No significant differences were found among analyses. Finally, since electronic waste workers are often addressed as an occupational group with increased exposure to PBDEs, it would be worthwhile to assess their blood PBDE concentrations in addition to other demographics. However, these workers could not be categorized using the NHANES occupational subset due to the use of broad occupational and industry categories. In other words, electronic-waste workers could not be separated from NHANES' occupational or industry designations.

Chapter 6

Conclusion

Since the 1979 ban of polychlorinated biphenyls in the United States, production, importation and usage of polybrominated diphenyl ethers have grown tremendously due their cost effectiveness as flame retardants. However, PBDEs experienced a similar fate in December of 2013 when their only US manufacturers and importers guaranteed a complete phase out of these flame retardants. This phase out occurred largely as a result of unsubstantiated public health concerns based on inconsistent literature.

In fact, research pertaining to the most potential health effects of PBDEs have been very inconsistent. Most notably, previous studies have investigated measures of obesity in relation to PBDE exposure with a focus on pediatric populations. As mentioned in the Literature Review, the only applicable research is from Agay-Shay, Costa and Vuong et al. whose results have been conflicting at best. Moreover, no other study has focused primarily on the potential effects of PBDE exposure in relation to obesity and overweight status of American adults.

Therefore, to address current research gaps, this study investigated the human blood concentrations of PBDEs among demographic categories generated through the 2003-2004 NHANES. Analyses of this representative sample of the American population revealed detectable concentrations of PBDEs ranging from 0.05 to 3676 ng/g lipid. Among the various demographic categories that were analyzed, PBDE concentrations per gender yielded the only significant results

for the sum of PBDEs, BDE-47 and BDE-99. In addition, PBDEs did not lead to a higher odd of being obese or overweight. These analyses were repeated for dioxin-like polychlorinated biphenyls and phthalates. In general, analyses of dl-PCBs and phthalates among demographic categories produced similar significant results which opposed those of PBDE analyses. Overall, no analytes led to a significant odd of being obese or overweight.

Appendices

Appendix I – Polybrominated Diphenyl Ethers Sampled

PBDE Congeners in 2003-2004 NHANES

Name of Congener	Compound	SAS name (lipid-adjusted)	Limits of Detection in ppb (NHANES Manual)	LOD/√2*
BDE-17	2,2',4-tribromodiphenyl ether	LBXBR1LA	0.0025	0.00176776695
BDE-28	2,4,4'-tribromodiphenyl ether	LBXBR2LA	0.0025	0.00176776695
BDE-47	2,2',4,4'-tetrabromodiphenyl ether	LBXBR3LA	0.0062	0.00438406204
BDE-66	2,3',4,4'-tetrabromodiphenyl ether	LBXBR66L	0.0028	0.00197989898
BDE-85	2,2',3,4,4'-pentabromodiphenyl ether	LBXBR4LA	0.0164	0.01159655121
BDE-99	2,2',4,4',5-pentabromodiphenyl ether	LBXBR5LA	0.007	0.00494974746
BDE-100	2,2',4,4',6-pentabromodiphenyl ether	LBXBR6LA	0.0025	0.00176776695
BDE-153	2,2',4,4',5,5'-hexabromodiphenyl ether	LBXBR7LA	0.017	0.01202081528
BDE-154	2,2',4,4',5,6'-hexabromodiphenyl ether	LBXBR8LA	0.0025	0.00176776695
BDE-183	2,2',3,4,4',5',6-heptabromodiphenyl ether	LBXBR9LA	0.0041	0.0028991378

*There were 297 values below the limit of detection. These values were divided by the square root of two and manually inserted into the master dataset.

Appendix II – Dioxin-Like Polychlorinated Biphenyls Sampled

Dioxin-Like PCBs in 2003-2004 NHANES

Name of Congener	Chemical Name	SAS Name (Lipid Adjusted)*
PCB 105	2,3,3',4,4'-Pentachlorobiphenyl	LBX105LA
PCB 118	2,3',4,4',5-Pentachlorobiphenyl	LBX118LA
PCB 156	2,3,3',4,4',5-Hexachlorobiphenyl	LBX156LA
PCB 157	2,3,3',4,4',5'-Hexachlorobiphenyl	LBX157LA
PCB 167	2,3',4,4',5,5'-Hexachlorobiphenyl	LBX167LA
PCB 189	2,3,3',4,4',5,5'-Heptachlorobiphenyl	LBX189LA
PCB 126	3,3',4,4',5-Pentachlorobiphenyl	LBXPCBLA
PCB 81	3,4,4',5-Tetrachlorobiphenyl	LBXTC2LA
PCB 169	3,3',4,4',5,5'-Hexachlorobiphenyl	LBXHXCLA

*The variable named LBX___ provides the analytic result for that analyte. Analytical results which were below the detection limit, were automatically divided by the square root of 2 by the CDC. Units were originally in ng/g of lipid; except for PCB 126, PCB 81, PCB 169 which were originally in pg/g lipid. Their values were converted to ng/g lipid (parts per trillion to parts per billion). Also, 562 missing values were removed from the total sample.

Appendix III – Phthalates Sampled

Phthalate Metabolites in 2003-2004 NHANES

SAS Name for Metabolite	Compound	Typical Limits of Detection in PPB (NHANES Lab Manual) in ng/mL or ppb	LOD/√2*
URXECP	Mono-2-ethyl-5-carboxypentyl phthalate	0.25	0.1767766953
URXMBP	Mono-n-butyl phthalate	0.40	0.2828427125
URXMC1	Mono-(3-carboxypropyl) phthalate	0.16	0.113137085
URXMCP	Mono-cyclohexyl phthalate	0.402	0.284256926
URXMEP	Mono-ethyl phthalate	0.264	0.1866761902
URXMHH	Mono-(2-ethyl-5-hydroxyhexyl)	0.32	0.22627417
URXMHP	Mono-(2-ethyl)-hexyl phthalate	0.90	0.6363961031
URXMIB	Mono-isobutyl phthalate	0.26	0.1838477631
URXMNM	Mono-n-methyl phthalate	1.0	0.7071067812
URXMNP	Mono-isononyl phthalate	1.54	1.088944443
URXMOH	Mono-(2-ethyl-5-oxohexyl)	0.45	0.3181980515
URXMOP	Mono-n-octyl phthalate	1.68	1.187939392
URXMZP	Mono-benzyl phthalate	0.072	0.0509116882

*The variable named URX___ provides the analytic result for that analyte. These values were divided by the square root of two and manually inserted into the master dataset. Also, 92 missing values were removed from the sample.

Appendix IV – Residential Sources of PBDE Exposure

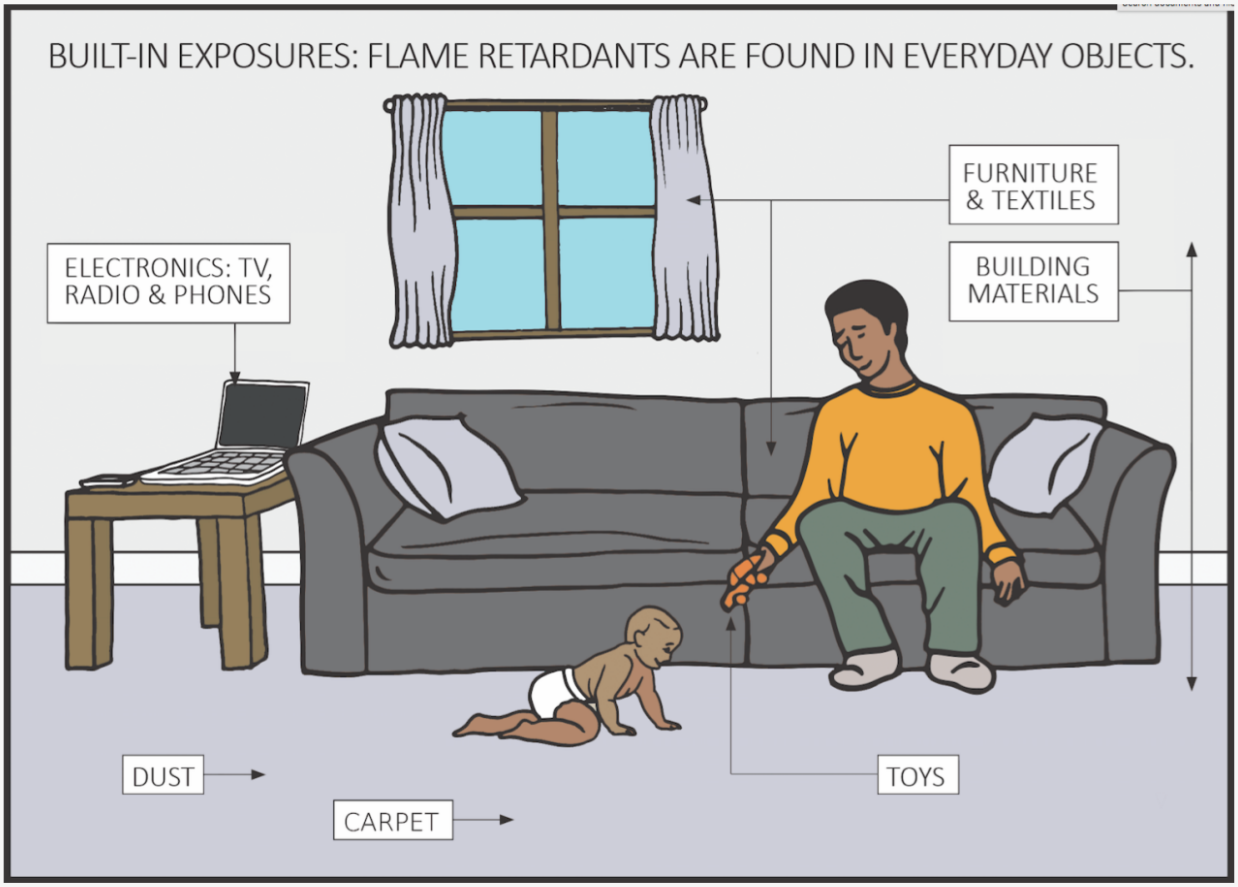

Image from Toxic By Design (2016) report. Illustration by Adam Cross. CC

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Mr. Giorvanni Merilis graduated with a Bachelor's of Science in Environmental Studies from the Florida State University Department of Geography (2011) and a Master's of Science in Environmental Sciences & Policy from the Johns Hopkins University School of Arts & Sciences (2014). In 2015, the Department of Environmental and Occupational Health at the University of South Florida's College of Public Health accepted Mr. Merilis into the doctoral of philosophy program. In addition, the Florida Education Fund awarded Mr. Merilis with a McKnight Doctoral Fellowship to support his scholastic endeavors. His degree program focused primarily on toxicology and risk assessment. Mr. Merilis has participated in research designed to assess the potential public health effects of background exposure to polybrominated diphenyl ethers among various demographic categories.