REPORT ON THE SELECTION OF PRIORITY CHEMICALS TO BIOMONITOR IN MICHIGAN RESIDENTS

Presented to the Michigan Environmental Science Board

by the

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INTRODUCTION

The following report includes a description of the process we followed to compile our list of chemicals in the Michigan environment that warrant human biomonitoring, as well as the list itself and our rationale for selecting individual chemicals. Biomonitoring is the measurement of environmental chemicals in the human body, specifically in blood, urine, serum, saliva, or tissues, as a means to evaluate the body burden or the internal, delivered or biologically effective dose of a chemical exposure. More specifically, biomonitoring is a method of determining exposure to chemicals found in the environment that have come in contact with a body surface, such as the respiratory tract, gastrointestinal tract or skin and have been absorbed into the body and into the circulation.

The first two sections, Stakeholders and Selection Criteria, describe the process we used to select the chemicals. The remaining sections review the scientific literature on each chemical as it pertains to the Selection Criteria.

STAKEHOLDERS

To obtain a statewide overview on the health issues associated with exposure to environmental contaminants, we chose to interview individuals from a variety of organizations across the state of Michigan. We began by listing the organizations, both local and national, that would have an interest in issues relating to health and the environment (see List of Organizations in the Appendix). From this list we identified individuals from these organizations to contact. At the same time, we constructed a questionnaire to be administered to these individuals, whom we considered potential stakeholders, soliciting their opinion as to which chemicals in the Michigan environment posed the greatest potential danger to the health of Michigan residents. We first interviewed employees of the State of Michigan who were in positions that dealt with public health issues involving environmental chemicals. For example, we interviewed the head of the Childhood Lead Program and the Deputy Director of the Department of Community Health. These early interviews lead us to modify the questionnaire from a fairly structured set of questions to four open-ended questions to allow the individuals to expand on areas that concerned them:

1. Which chemicals should be biomonitored and why?
2. What use will the information we collect have and for whom?
3. Would you be willing to work with us as we develop a biomonitoring plan for Michigan?
4. Can you suggest anyone else who might be interested in working with us?

Following these interviews, we contacted individuals from the organizations outside of state government (see List of People Interviewed in the Appendix) as well as those suggested by the interviewees. At the conclusion of these interviews, we had a preliminary list of chemicals of concern for Michigan residents. This list closely matched regional lists of chemicals of concern published by State-related and Federal agencies (see Comparative Chemical List in the Appendix).

From our lists of internal and external interviewees who indicated an interested in continuing to work with us on developing a biomontoring plan for Michigan, we selected a group of potential stakeholders. The potential stakeholders naturally fell into two groups: those with expertise in clinical laboratory management and analyses (Analytical Chemist Group) and those with other areas of expertise (Implementation Planning Group) (see the Appendix for a list of the Stakeholders Groups). All individuals were sent a letter of invitation to attend 3-4 meetings to be held at the Michigan Institute for Public Health (MPHI), Okemos, MI. Those who sent an email reply to the letter indicating that they wanted to participate became Stakeholders. Since we invited individuals with diverse backgrounds and wanted to make maximum use of their distinct perspectives, we hired a facilitator, Michelle Napier Dunnings, from Project Innovations, Detroit, MI. The core members of the Biomonitoring Planning Group (Frances Pouch Downes, David R Wade, John Riebow, Lori Cameron, Paul Loconto and Julie Wirth) initially met with Ms Napier Dunnings to acquaint her with the background on the Planning Grant and to develop the overall goals for the Stakeholders meetings. At the end of the meetings, we hoped to have a set of criteria for selection of chemicals to biomonitor, a list of chemicals to biomonitor and the justification for selecting

each chemical. Before each meeting, Ms Napier-Dunnings and the Core Group meet to determine the Desired Outcomes of each meeting and to decide on material to provide to the Stakeholders prior to or at the time of the meeting. Since the meetings were scheduled two weeks apart, we also meet immediately after each meeting to discuss the outcomes, assess progress and decide on the format for the following meeting. The Agendas in brief and formats for each meeting were as follows:

Meeting #1 – Possibilities; both groups met as one
Meeting #2 - Priorities; the two groups met separately with separate, but related Agendas
Meeting #3 – Setting Directions; both groups met as one.

The Stakeholders meetings accomplished the desired results: we have a list of criteria for chemical selection (see below for Selection Criteria) and a priority list of chemicals to biomonitor, including their ranking based on the criteria, and the status of the MDCH laboratory capacity to biomonitor them (see Priority Chemicals List in the Appendix). Lessons learned: we found it was extremely useful to have a highly skilled facilitator to moderate the discussion, to ensure all viewpoints were heard and taken into consideration, and to ensure that the overall goals were met. The Analytical Chemist Group has continued to provide opinions on various aspects of sample preparation as well as a proposed integrated scheme for laboratory biomonitoring. Their input continues to aid us as we prepare our final Biomonitoring Plan and the Implementation Grant.

CRITERIA FOR CHEMICAL SELECTION

The criteria for selecting the chemicals to biomonitor were arrived at through extensive discussion by members of both the Analytical Chemist Group and the Strategic Implementation Group during the second meeting. Highest consideration was given to chemicals associated with known or potential adverse health effects, with chemicals with known adverse human health effects given the highest numerical ranking. Recognizing, however, that several chemicals under consideration have not yet been investigated in epidemiological studies to evaluate their effects on human health, two other sub categories were created. Chemicals for which experimental animal or *in vitro* cell culture data indicated potential for adverse human health effects received a lower numerical score, while those with chemical structures similar to other chemicals with known adverse human health effects received the lowest score in this category.

The second criterion for chemical selection was the probability of human exposure. Within that heading, chemicals for which significant human exposure in terms of number of potentially exposed individuals has been documented were given the highest score. Those chemicals with more limited human exposure, for example chemical exposures associated with specific activities, but which were shown to bio-accumulate, received a lower numerical rank.

The third criterion, seriousness of health effect, was based on the length of life affected by the exposure and the severity of the effect, i.e. was it life threatening. Chemicals causing human cancer were highly ranked in this category. A chemical that affected the fetus via an *in utero* exposure would have a greater or more serious effect than a chemical exposure occurring later in life and was ranked higher. An adverse effect that was passed on from one generation to the next also received a somewhat lower score. In most instances, the distinction was used for chemicals that had not been examined in human epidemiological studies but had been tested in experimental animal studies. The numerical rankings were as follows:

Health Effect (range 0 to 5.0)

- Human health effect: 5.0
- Animal or other health effect: 4.5
- Structural similarities to chemical with know adverse human health effect: 4.0
- None of the above: 0

Probability of Exposure (range 0 to 3.5)

- Significant exposure: 3.5

- Bio-accumulation: 3.0
- None of the above: 0

Seriousness of Health Effect (range 0 to 2.5)
- Effect occurs early in life (in utero): 2.5
- Cancer: 2.5
- Multigenerational: 2.0
- Early in life *and* multigenerational: 4.5
- Other: 1.5
- None of the above: 0

REVIEW OF PRIORITY CHEMICALS

The complete table of the Priority Chemicals, which includes their ranking based on the chemical selection criteria described above, and the laboratory capacity for their analysis can be found in the Appendix. Below we provide the scientific rationale for their inclusion in the Priority Chemical List.

HEAVY METALS

The MDCH Analytical Chemistry Laboratory has the capacity to measure a panel of metals from a single sample, which enabled us to perform the analysis for several heavy metals that individually met the selection criteria without additional cost.

- **METHYLMERCURY**

Background
Inorganic mercury exists naturally in the environment and finds its way into the air through both natural processes and human activities. Power plants that burn fossil fuels, particularly coal, generate the greatest amount of mercury emissions. In Michigan, inorganic mercury in the atmosphere is deposited into the Great Lakes and into many of the freshwater inland lakes. In these waterbodies, it is converted to methylmercury, its most toxic form, by aquatic organisms. Methylmercury is then taken up by fish and bioaccumulates in the aquatic food chain biomagnifying to tens of thousands to millions of times the concentration found in water (EPA, 1997).

Probability of Exposure:
Consumption of mercury-contaminated food is the major source of methylmercury exposure (US EPA, 1999). In the Great Lakes region consumption of sport-caught fish is the greatest risk factor for methylmercury exposure (Zabik et al., 1995; DeVault et al., 2996). Approximately 2 million Michigan residents fish in Michigan waters each year and are potentially exposed, and often ignore fish consumption advisories (Johnson and De Rosa, 1999).

Methylmercury can accumulate if consumed at a greater rate than that excreted. It binds strongly to sulfhydryl groups in tissues and accumulates to higher concentrations in brain, muscle and kidney (National Academy of Sciences, 2000). Methylmercury easily crosses the blood-brain barrier where it is converted to inorganic mercury, which has a long half-life in brain tissue measured in years (Clarkson 1997; Davis et al. 1994; Pedersen et al. 1999). Total blood level of mercury is a good indicator of methylmercury exposure, but also includes small amounts of inorganic mercury (National Academy of Sciences, 2000).

The current U.S. Environmental Protection Agency (U.S. EPA) recommended reference dose (RfD) for blood mercury levels is 5.8 ug/L (Mahaffey and Rice, 1998). A recent study from an internal medicine practice in California with an excessive number of patients with neurological problems, evaluated all patients attending the clinic in a 1-year period for excess mercury using the current RfD (Hightower and Moore, 2003). Mercury levels ranged from 2.0 to 89.5 µg/L for 89 subjects. The mean for female patients was 15 ug/L and for men, 23 ug/L. A substantial fraction of patients had diets high in fish consumption; of

these, 89% had blood mercury levels exceeding the maximum level recommended by the U.S. EPA (5.8 ug/L). The mean level for women in this survey was 10 times that of mercury levels found in a recent population survey by the U.S. CDC (CDC, 1999) of 1.3 ug/l. Some children's levels were > 40 times the national mean. These results suggest that high fish consumption may pose a risk for exposure to methyl mercury levels above the current standard and that these levels may be associated with neurological problems.

Another recent report using data from the 1999-2000 National Health and Nutrition Examination Survey (NHANES) found that approximately 8% of the women had blood mercury levels above the US EPA RfD (Schober et al., 2003). Of concern was the finding that the mean mercury levels were almost 4-fold higher among women who ate 3 or more servings of fish in the past 30 days compared with women who reported eating no fish during that period. These results also suggest a possible association between fish consumption and blood levels of methyl mercury above the US EPA current standard.

Health Effects:
Public health concerns about methylmercury in edible fish began in 1969 when fish from Lake St. Clair bordering Michigan were found to have high levels. Since then many studies have shown that methylmercury is highly toxic and causes adverse effects in several organ systems through the life span of humans and animals. The major target for methylmercury is the central nervous system (US EPA, 2002; ATSDR, 1999). Studies of populations highly exposed to methylmercury, such as those in Japan (Harada et al., 1995) and Iraq (Bakir et al, 1973), have shown that methylmercury adversely affects cognitive, motor and sensory functions. A study on fish consumption in Finland found significant associations between mercury levels and cardiovascular disease (Salonen et al, 1995) and atherosclerosis (Salonen et a., 2000). Mercury effects on blood pressure regulation, heart rate variability and heart disease have also been reported (Frustaci et al., 1997).

Severity of Effects
Of particular concern are the effects of methylmercury on neurodevelopment. Both the Japan and Iraq outbreaks provided evidence that severe brain damage can occur from high prenatal methylmercury exposure (Bakir et al, 1973) as well as from mothers with mild symptoms (Harada et al., 1995). Subsequent studies on chronic low-dose prenatal methylcercury exposure from maternal consumption of fish have found subtle end points of neurotoxicity in children, including poor performance on neurobehavioral tests, particularly on tests of attention, fine-motor function, language, visual-spatial abilities and verbal memory (Meyers et al., 1995; Marsh et al., 1987). The National Academy of Sciences report on the Toxicological Effects of Methylmercury (National Academy of Sciences, 2000) concluded that perinatal exposure methylmercury is likely to result in an increase in the number of children with learning problems that may require remedial classes or special education.

Of particular concern for Michigan residents is the finding that high fish consumers have mercury levels close to those found in young children exposed in utero who have developed neurological problems (Davidson et al., 1998; Grandjean et al., 1999).

Why methylmercury should be biomonitored in Michigan:
- Methylmercury is a neurotoxin and the developing fetus is most sensitive to its effects
- Methylmercury is found in high levels in Michigan sport-caught fish
- Michigan has a significant number of sport fish consumers
- Methylmercury levels in MI sport fish consumers may reach levels where adverse effects occur for pregnant women

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- **LEAD**

Background
Lead is naturally-occurring element, but is often released into the environment from man-made sources such as mining and smeltering (Pirkle et al, 1998; Juberg, 2000). Lead has been used as an additive in paint and gasoline, and in leaded pipes, solder, crystal, and ceramics (ATSDR, 1999). Natural levels of lead in soil are usually low, but human activities have resulted in substantial increases in lead levels in the environment, especially near mining and smelting sites, near some types of industrial and municipal facilities, and adjacent to highways.
Lead particles in the environment can attach to dust and be carried long distances in the air (ATSDR, 1999; Juberg, 2000). Such lead-containing dust is often removed from the air by rain and deposited on surface soil, where it may remain for many years. In addition, heavy rains may cause lead in surface soil to migrate into groundwater and eventually into water systems. Lead and lead compounds have been found at more than half of the sites on the National Priorities List (NPL) of hazardous waste sites in the United States, although this number may change as more sites are evaluated by the EPA. There are also approximately 400 Superfund sites contaminated with elevated (above background) levels of lead.

Probability of Exposure
Given the widespread distribution of lead in the environment, everyone has a low background level of around 1.66 ug/dL (CDC, 2003). For adults the major pathways for lead exposure are largely inhalation of lead-containing dusts and fumes in occupational settings, particularly mining, smelting and refining operations or battery manufacturing and reclamation operations (Gittleman et al., 1994). Exposure to lead may also occur through drinking water contaminated with lead leached from lead-containing pipes and fixtures. For children, ingestion of lead-containing dust and paint chips remain the primary routes of exposure (Juberg, 2000; Bornschein et al., 1986).

The Third NHANES, phase 2 (1991-1994) measured blood lead levels in the US population and found that the US average for blood lead (BLL) was 2.9 µg/dL. For children 1-2 years of age, the most recent data show that the mean level is 3.1 µg/dL, all well below the CDC's action level of 10 µg/dL (Brody et al., 1994). This report also identified subpopulations who were at increased risk of lead exposure as non-Hispanic blacks or Mexican-American children aged 1-5 years, from lower-income families living in metropolitan areas with a population over 1 million, or living in older housing (MMWR, 1997). The risk for a BBL greater than or equal to 10ug/dl was higher among non-Hispanic black children living in housing built before 1946 (21.9%) or built during 1946-1973 (13.7%), among children in low-income households who lived in housing built before 1946 (16.4%) and among children in areas with populations greater than or equal to 1 million who live in housing built before 1946 (11.5%) when compared to children in other categories.

The Second National Report on Environmental Exposures, using the 1999-2000 NHANES data, found an over all decrease in BLL for the US population, 1.66 ug/dL (CDC, 2003). The highest levels, however were still found in children aged 1-5 years (2.7ug/dL), and 2.2% of those children had BLLs greater or equal to 10ug/dL. As in the previous NHANES, higher prevalences of elevated BLLs in US children occurred in urban settings, lower socioeconomic groups, and immigrants.

Health Effects
In adults, lead adversely affects the nervous system at both high and low levels, the hematopoetic system and the reproductive system (reviewed in Juberg 2000). Lead poisoning can cause irritability, poor muscle coordination, and nerve damage. It has been associated with kidney disease (Goyer, 1971) with chronic and excessive lead exposure progressing to end-stage renal disease (Weeden, 1992). Lead exposure has been associated with increased blood pressure (Hertz-Picciotto and Croft, 1993), hearing and vision impairment, and reproductive problems (ATSDR, 1999,reviewed in Juberg, 2000).

In children, lead poisoning can cause brain damage, mental retardation, behavioral problems, anemia, liver and kidney damage, hearing loss, hyperactivity, developmental delays, other physical and mental problems, and in extreme cases, death (Ernhart, 1992; reviewed in Juberg, 2000). Neurological effects including IQ deficits and *in utero* effects can occur at BBLs as low as 10ug/dl; hearing deficits at 20 ug/dl;

and peripheral neuropathy at 40 ug/dl (reviewed in Juberg, 2000). Hematological problems begin at 10 ug/dl and renal problems start at less than 30 ug/dl.

Children with even very low blood lead levels, below current CDC Guidelines, show poorer performance on tests of arithmetic skills, reading skills, nonverbal reasoning and short term memory (Lanphear et al., 2000). In a recent study of 240 children enrolled between 5 and 7 months for an unrelated study (Canfield et al., 2003). BLLs were obtained at 6, 12, 18, 24, 36, 48, and 60 months of age. BLL was inversely and significantly associated with IQ, with each increase of 10 µg per deciliter in the lifetime average blood lead concentration was associated with a 4.6-point decrease in IQ (P=0.004). Of greater concern was the finding that for the subsample of 101 children whose maximal lead concentrations remained below 10µg/dl, the change in IQ associated with a given change in lead concentration was greater than those children whose BLL were above 10ug/dl. IQ declined by 7.4 points as lifetime average BLLs increased from 1 to 10 µg/dl.

During 2001 as many as twenty percent of Michigan's children under age six were lead poisoned in some urban neighborhoods (Kent, 2001). Over 4700 Michigan children were lead poisoned and an additional 20,000 were found to have damaging blood lead levels of 5 to 9 ug/dl (MDCH, 2001). The total annual economic costs of childhood lead poisoning in Michigan could be some $1.4 billion (based on Michigan's portion of national economic cost estimates). Alone, Michigan's annual special education costs for the approximately 50 severely lead poisoned children, who require chelation therapy each year, are approximately $10 million (MDCH, 2002).

Severity of Effects
Although lead is an established carcinogen in experimental animals, it is classified only as a possible carcinogen in humans (IARC, 1987). Several epidemiological studies on cohorts of highly exposed workers have found only weak evidence of increased cancer mortality (Steenland and Bofetta, 2000). A recent study on the general US population found no association between BLL and increased risk of cancer (Jemal et al., 2002).

Why Lead should be biomonitored in Michigan:

- Lead is a neurotoxicant with adverse effects in children observed below 10ug/dl.
- Children living in urban areas, with lower socioeconomic status are at increased risk of exposure to high levels of lead
- According to Detroit Health Department and the Census, 73.9% of the City's housing was built before 1955 and, therefore, contains paint with a high proportion of lead. All children in the City of Detroit are considered at-risk by the State (Wayne State University, 2002-2003).
- The cost to Michigan for treatment of lead-poisoned children is in the millions of dollars annually.

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- **ARSENIC**

Background

Arsenic is a metalloid widely distributed in the earth's crust. It can exist in four valency states: -3, 0, +3, and +5. The most commonly found forms are arsenate (+5) and arsenite (+3) (reviewed in Gomez-Caminero et al., 2001). Arsenic and its compounds usually occur in trace quantities in all rock, soil, water and air. Concentrations may be higher in certain areas as a result of weathering and anthropogenic activities including metal mining and smelting, fossil fuel combustion and pesticide use. Other sources of contamination are the manufacture and use of arsenical pesticides and wood preservatives.

Probability of Exposure

In 1983, arsenical pesticides were one of the largest classes of biocontrol agents in the USA (Woolson, 1983). Annual historical applications of lead arsenate to orchards in the USA ranged from 32 to 700 kg As/ha. Residues in orchard soils as high as 2500 mg/kg have been reported, but they are more commonly in the range of 100-200 mg/kg.

General population exposure to arsenic comes from eating food, drinking water, or breathing air containing arsenic, breathing contaminated workplace air, breathing sawdust or burning smoke from wood treated with arsenic, living near uncontrolled hazardous waste sites containing arsenic and living in areas with unusually high natural levels of arsenic in rock (ATSDR, 2000).

High concentrations of naturally occurring arsenic have been detected in the groundwaters of southeast Michigan (Kolker et al., 1998; Haack and Trecanni, 2000) with values in some areas exceeding the current US Environmental Protection Agency (USEPA) maximum contaminant level (MCL) of 50 µg/l for drinking water (USEPA, 1982). More recently, groundwater samples taken from 73 wells in 10 counties of southeast Michigan (Huron, Tuscola, Sanilac, Lapeer, Genesee, Shiawassee, Livingston, Oakland, Macomb, and Washtenaw) in 1997 had arsenic concentrations in the range of 0.5 to 278 microg/L with the average being 29 microg/l. About 12% of these wells had arsenic concentrations that exceeded the USEPA's MCL. Most (53-98%) of the arsenic detected was arsenite [As(III)] and other environmental observations supported the arsenic species distribution (low redox potential and DO) (Kim et al., 2002).

Health Effects
Arsenic has been identified as a public health problem because it has serious toxic effects even at low exposure levels and is widespread in the environment (Hypenhayn and Smedley, 1996). As(III) is reported to be 25–60 times more toxic than As(V), and several hundred times as toxic as organic arsenicals (Morrison et al., 1989).

Arsenic exposure can have acute, short term effects. Ingestion of large doses of arsenic can lead to gastrointestinal symptoms, loss of blood pressure, multi-organ failure and ultimately death (Gomez-Caminero et al., 2001). A mass poisoning in Japan in which 12,000 infants were fed milk powder inadvertently contaminated with arsenic at concentrations of 15-24 mg/kg, resulted in 130 deaths (Hamamoto, 1955).

The effect of ingestion of arsenic in drinking water on adverse human health effects has been investigated in a number of epidemiological studies in Taiwan (reviewed in Gomez-Caminero et al., 2001). An endemic peripheral vascular disease (PVD) known as blackfoot disease, leading to progressive gangrene of the legs, has been known in Taiwan since the 1920's and has increased in prevalence since the 1950s. Artesian wells containing high concentrations of arsenic provided drinking water to a number of villages in an area in which black foot disease was prevalent. In an extensive report based on 126 analyses from 29 villages in the endemic area, the average arsenic concentration was 500 ug/L, with village averages varying between 54 and 831 ug/L; approximately 50% were between 400 and 700 ug/L (Kuo, 1968). National surveys from the 1970s found that about one third of the wells in the endemic area had arsenic concentrations over 50 ug/L and 5.2% had levels over 350 ug/L (Chen et al., 1985).

Results from the Taiwanese studies established a relationship between exposure to drinking water arsenic and the development of black foot disease (Chen et a. 1988b; Tseng et al., 1996). Continuing work with the arsenic exposed Taiwanese from the blackfoot endemic area found a significant excess in the mortality from cardiovascular disease and from ischaemic heart disease (Tsai et a., 1999). A study carried out in 30 counties in the USA with drinking water concentrations of arsenic greater than 5 ug/L found excess mortality rates due to diseases of the arteries, arteriole and capillaries especially for the highest exposure group (>20 ug/L)(Engel and Smith, 1994).

An association between long term exposure to inorganic arsenic and the prevalence of hypertension in the black foot disease areas of Taiwan has also been established (Chen, 1995). Similar results have been reported in populations from Bangladesh (Rahman et al., 1999a) and Denmark (Jensen and Hansen, 1998). An association between inorganic arsenic ingestion and diabetes mellitus has also been found for drinking water concentrations greater than 15 ug/L (Lai et al 1994; reviewed in Gomez-Caminero, 2001).

Seriousness of Effects
A significant association between arsenic exposure and lung cancer has been examined in occupational cohorts (reviewed in Gomez-Caminero, 2001).

Why arsenic should be biomonitored in Michigan
- Arsenic exposure via drinking water has been a associated with several adverse outcomes including peripheral vascular disease, cardiovascular disease, hypertenstion, and diabetes.
- Several Michigan counties have levels of arsenic in their well water that have been associated with adverse heath outcomes in other studies.

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- **CADMIUM**

Background
Cadmium in the environment is found in combination with other elements. Most cadmium used in the U.S. is obtained as a by-product from smelting zinc, copper or lead ores. Cadmium obtained through this process is used mainly to produce nickel-cadmium batteries, used in a large variety of appliances, and for emergency power supplies and emergency lights (ATSDR, 1999). Several cadmium compounds are used as paint pigments. Cadmium is also used as a stabilizing compound in the plastics industry and in nuclear reactor control rods to dampen the nuclear reaction and keep the fission reactions under control.

In the environment, cadmium has been detected in air, surface water, ground water, soil and vegetation. Cadmium has also been detected in a variety of wildlife species, including some species of wild birds, eagles, fish, terrestrial mammals and marine mammals. Terrestrial animals and fish consume contaminated plants and accumulate it in their tissues. Cadmium is bioaccumulative, with a long half-life.

Probability of exposure
Human exposure in the general population primarily occurs through consumption of contaminated food, especially shellfish, liver and kidney meats (ATSDR, 1999). Since plants can accumulate high levels of cadmium even from low cadmium soils, consumption of vegetables poses a potential risk for cadmium exposure. Cigarette smoke, which contains high levels of cadmium is another source exposure for the general population (Shaham et al., 1996**)**. Occupational exposure to cadmium, through inhalation, can lead to high exposure levels. Exposure to cadmium in the jewelry industry is a significant source of occupational cadmium exposure (Wittman and Hu, 2002).

Data from NHANES (1999-2000) show mean cadmium blood levels in the general US population (aged 1 or older) of 0.412 ug/L, reflecting recent exposure, and urine levels of 0.307ug/g)(CDC, 2003). Occupational exposures can result in elevated cadmium blood and urine levels depending on the type of occupation, industry and protection measures. A New Jersey study reported values ranging between 5.0-29.0 µg/L, with a mean of 7.6 µg/L for occupationally exposed workers (New Jersey, 1997).

Health Effects
Cadmium is associated with nephrotoxic effects, particularly at high exposure levels (ATSDR, 1999). Studies suggest that cadmium is associated with several clinical complications, primarily renal dysfunction and bone disease, but also some cancers (Nordberg, 1984; reviewed in Jarup, 2002). Recent findings, however, indicate that changes in sensitive renal biomarkers may occur at lower urinary cadmium concentrations (greater than or equal to 1 ug/g) than previously estimated among populations exposed to environmental cadmium (Yamanaka et al., 1998). A recent study found that subjects with mean urinary cadmium levels of 0.23 µg/g creatinine had significant increases in indicators of renal damage (Noonan et al., 2002). Levels of cadmium, ranging between 30-50 µg/day, have been associated an increased risk of bone fracture, cancer, kidney dysfunction and hypertension (Satarug et al., 2003; Bakshi et al., 1994). The same study found increased mortality among individuals with signs of cadmium renal toxicity compared with those without such signs. A dose-response relationship between levels of cadmium in urine and blood of subjects environmentally exposed to cadmium and the prevalence of renal dysfunction has been reported (Jin et al., 2002A).

Cadmium accumulation in bone is associated with osteomalacia and osteoporosis, possibly associated with renal damage. A relationship between blood cadmium and tubular proteinuria and low bone mineral density has been shown (Alfven et al. 2002). Whether the problem is calcium deficiency, osteoporosis or osteomalacia, cases have been reported in workers occupationally exposed to high levels of cadmium. The effects on the bone only become apparent after the renal damage has occurred and are probably secondary to the changes in the vitamin D, calcium and phosphorus metabolism.

Emphysema and dyspnea have been reported after long-term exposure to cadmium. A significant relationship between cadmium occupational exposure and pulmonary emphysema was reported (Davison et al 1988). Furthermore, abnormalities of lung function were found to be greatest in those with the

highest cumulative cadmium exposure. Other studies have also reported chronic inflammation of the nose, pharynx and larynx (Rydzewski et al., 1998).

Seriousness of the Effects
Evidence on carcinogenesis and genotoxicity is limited. Although cadmium is currently considered to be a human carcinogen by the International Agency for Research and Cancer (IARC, 1987), some investigators have questioned the evidence supporting its role in human carcinogenicity (Satoh et al., 2002). In a longitudinal study of battery workers, Jarup et al. (1998) found an increased overall risk for lung cancer, but no exposure-response relationship between cumulative exposure to cadmium and risk of lung cancer. They also reported a highly significant increased risk of cancer of the nose and nasal sinuses, which may be caused by exposure to nickel or cadmium or a combination of both. Another study found no significant relationship between occupational exposure to cadmium oxide fume and mortalities from lung cancer and from chronic non-malignant diseases of the respiratory system (Sorahan et al. 1997).

Studies on animals showed reproductive effects of cadmium exposure (Waalkes et al, 1999) and a recent study found weak relationship between cadmium exposure during pregnancy and low birth weight (Nishijo et al., 2002). Evidence supporting an association with cadmium and adverse birth is inconclusive.

Why cadmium should be biomonitored in Michigan
- Cadmium exposure is associated with renal toxicity, hypertension, bone disorders and possibly cancer.
- Cadmium levels associated with these outcomes are those found in the general population.
- Both Michigan residents occupationally exposed to cadmium and the general population are at increased risk for adverse outcomes.

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- **MANGANESE**

Background
Manganese is a metallic element commonly found in minerals that is commonly used in alloying agent to improve the quality of steel, in dry cell batteries, in animal feed, as a plant fertilizer, and in black paints and purple glass as a coloring agent (ATSDR, 1999; Barceloux, 1999). More recently, the manganese-containing compound, methylcyclopentadienyl manganese tricarbonyl (MMT), is being used as an octane-improving additive to unleaded gasoline (Lynam et al.,1999 ; Zayed et al., 1999; Frumkin and Soloman, 2002). Manganese is also a required human micronutrient.

Probability of Exposure
Occupational settings pose the greatest risk of manganese poisoning. Manganese fumes from welding, steel manufacturing, mining, and railroad work can be absorbed through inhalation (ATSDR, 1999; Boojar and Goodarzi, 2002). Roads with high traffic levels provide additional higher risk for manganese exposure due to the re-suspension of road dusts by vehicles and to the products resulting from burning MMT in tailpipe emissions. Air in subway stations can reach very high levels of manganese possibly due also to poor ventilation. Another significant source of manganese is cigarette smoke, to which both smokers and passive smokers are exposed (Blum, 1982).

Health Effects
Acute manganese exposure may cause irritation of eyes, nose and throat, metallic taste and fever. Inhalation of dust may cause bronchitis and pneumonitis (ATSDR, 1999; Barceloux, 1999). The result of chronic exposure to high levels of manganese is a condition called manganism, with symptoms very similar to those that appear in Parkinson's disease (Barceloux, 1999; Lee 2000). Some of the symptoms include fatigue and weakness, sore and stiff muscles, lack of coordination, speech disturbances,

abnormal walk, tremors, muscle cramps and weakness (especially in the legs), fixed facial expression, impotence, difficulty swallowing and breathing, mental and emotional disturbances. Other chronic effects include an increased incidence of bronchitis and cough and increased susceptibility to pulmonary infections (Boojar and Goodarzi, 2002).

Chronic exposure to much lower doses of manganese, such as with occupational exposures, has been linked with deficits in the ability to perform rapid hand movement and some loss of coordination and balance along with an increase in reporting mild symptoms, such as forgetfulness, insomnia, and anxiety (ATSDR, 2000). The lower levels of manganese exposure that still cause adverse neurological effects are not known. Several epidemiological studies have found lower levels of neurotransmitters in children exposed to high levels of manganese in drinking water (Zhang et al, 1995) as well as neurobehavioral difficulties in children living near high-level-manganese sewage irrigation.(He et al., 1994).

Severity of Effects
No data is available on the effects of manganese and human cancer. It has been associated with a slightly increased incidence of pancreatic tumors in male rats and thyroid tumors in male an female rats (ATSDR, 2000). In animal experiments it was shown to cause birth defects after high maternal exposure. Large amounts of manganese affect fertility in mammals and are toxic to the embryo and fetus

Why manganese should be biomonitored in Michigan:

- At high levels manganese causes neurological problems but the effects of low level exposure are poorly understood. It carcinogenic potential for humans is also unknown.
- The increasing use of MMT coupled with the presence of several large cities and well-traveled highways raise the prospect of increasing low level manganese exposure in urban areas of Michigan.
- The evidence for biomonitoring manganese is currently less compelling than for the other reviewed metals.

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CHEMICALS

- **POLYCHLORINATED BIPHENYLS (PCBS)**

Background
PCBs are synthetic chlorinated hydrocarbon compounds that were intentionally manufactured as industrial insulators. PCBs are formed by the addition of chlorine atoms to the two biphenyl rings; the process yields variable levels of chlorination, producing a theoretical 209 congeners depending on the number and location of the chlorine atoms on the biphenyl rings. Because of their chemical stability, PCBs were used as hydraulic fluids, adhesives, plasticizers in paint, heat transfer fluids, wax extenders, dedusting agents, organic diluents, lubricants, flame retardants and as dielectric fluids in capacitors and transformers (Safe 1984). It is estimated that approximately 1.4×10^9 pounds of PCBs were manufactured in the USA from 1930 to 1975 under trades names such as Phenoclor, Kanechlor, Clophen, and, in the USA, Arochlor (Safe 1984). Manufacture of PCBs was banned in the USA in the late 1970's when high levels were detected in the environment and in wildlife.

As a consequence of atmospheric transport, however, PCBs have been detected in rivers, lakes and ocean sediments and their biota. Through the bioaccumulation of PCBs in water and soil sediments, they bioconcentrate in the food chain, with the highest levels found in fatty tissues of carnivores such as certain fish species, herring gulls and mink.

Probability of Exposure
Since PCB production ceased in 1977, reports indicate that levels found in the Great Lakes basin have declined (Stow et al. 1995) and will continue to decline although at a slower rate (Fensterheim 1993). According to the US EPA, however, the concentration of PCBs is well above safe water quality standards (EPAc, 1993), and the amount of PCBs in Lake Michigan alone is estimated at 80,000 kg (Wong 1993). Reports as recent as April 2000, indicate that PCBs are leaking into Lake Michigan, and probably into other sites in the Great Lakes, from point sources, spills and direct run off from urban an rural areas (Webber, 2000), resulting in locally high exposure levels. In particular, southeastern Michigan, the most heavily populated and industrialized area in Michigan, has been contaminated by historical point source discharges and ongoing nonpoint sources with heavy metals, PCBs, pesticides and other organics. The US EPA continues to classify two areas, the Rouge (EPA 2000a) and Clinton Rivers (EPA 2000b), as "areas of concern," due to the impact of these compounds on fish and wildlife (Canada 1991; Resources 2000).

Most people living in the Great Lakes region have low levels of PCB congeners with 80-90% of the exposure coming from consumption of sport-caught Great Lakes fish (deVault, 1996). Great Lakes fish consumers, such as anglers and fishing boat captains, have increased body burdens of PCBs and DDE compared to non- fish consumers (Hanrahan et al.1999, 1997). PCB levels in low or non-consumers of Great Lakes fish declined from 7 ppb in 1973-1774 to 2-3 ppb in 1994 (Falk et al 1999). However, research has shown that the decline has not been as great in anglers who consume their catch, whose levels changed from 20 ppb in 1973-1774 (Humphrey et al., 1996) to 23 ppb in 1979-1982 to 21 ppb in 1989-1993 (He et al., 2001). The number of potentially exposed people is not insignificant: approximately 2 million Michigan residents fish in Michigan each year (Resource 2000) and often with little regard for the fishing advisories (Johnson et al 1999a).

Health Effects
People exposed directly to high levels of PCBs, either via the skin, consumption or inhalation, or in the air, have experienced irritation of the nose and lungs, skin irritations such as severe acne (chloracne), rashes, and eye problems (ATSDR, 2000; Johnson et al. 1999b).

PCBs with only a few chlorine atoms can mimic the body´s natural hormones, especially estrogen. Women who consumed PCB-contaminated fish from Lake Ontario were found to have shortened menstrual cycles (Mendola et al, 1997). http://www.clearwater.org/news/ - refs PCBs may also play a role in reduced sperm counts, altered sex organs, premature puberty, and changed sex ratios of children (reviewed in Carpenter 1998). More highly-chlorinated PCBs (with more chlorine atoms) alter the

metabolism of sex steroids in the body, changing the normal levels of estrogens and testosterone (Arcaro et al.1999). PCBs are converted in the body and in the environment from more highly-chlorinated to lower-chlorinated forms, increasing their estrogenic effects.

In a study of adolescents Mohawk males in New York State, PCBs were shown to alter thyroid hormone levels, which may affect growth as well as intellectual and behavioral development (Schell et al. 2000).

PCBs bind to receptors that control immune system function, altering the number and distribution of immune cells such as lymphocytes and T cells (reviewed in Carpenter 1998). In a study of Dutch children, PCB levels were associated with an increased susceptibility to disease, including ear infections and chickenpox (Weisglas-Kuperus et al., 2000). Significant correlations were found between maternal serum PCB levels during pregnancy and the number and type of bacterial infections contracted by the breast-fed infant during the first four months of life and between the incidence of infections in the breast –fed infant and cumulative fish consumption by the mother (Swain, 1991).

Seriousness of Health Effect
The International Agency for Research on Cancer and the Environmental Protection Agency classify PCBs as a probable human carcinogen (IARC, 1978). Occupational studies and studies of environmentally exposed subjects found increased rates of liver, biliary tract, intestinal and skin (melanoma) cancer (Johnson et al.1999b; ATSDR, 2000). Environmental exposure to PCBs may be linked to breast cancer in a subset of women (Moysich et al 2002).

Women exposed to PCBs before or during pregnancy can give birth to children with significant neurological and motor control problems, including lowered IQ and poor short-term memory (reviewed in Faroon et al. 2000; Schantz et al. 2003). A group of children in Michigan whose mothers had been exposed to PCBs were found to have decreased birth weight and head size, lowered performance on standardized memory, psychomotor and behavioral tests, and lowered IQ. These effects lasted through at least 7 years (Jacobson and Jacobson, 1996) and at 11 years were also associated with poorer verbal IQ and reading comprehension (Jacobson and Jacobson, 2002). A group of women occupationally exposed to PCBs in upstate New York had shorter pregnancies and gave birth to children with lower birth weight (Taylor et al). Another study of the children of women who ate contaminated Lake Ontario fish found significant performance impairments on a standardized behavioral assessment test (Stewart et al, 2000).

Why PCBs should be biomonitored in Michigan:

- Despite overall decreasing levels, PCBs continue to be wide-spread in the environment and found in human samples.
- PCBs are endocrine disruptors, probable carcinogens and have been shown to adversely effect cognitive function in children exposed in utero.

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- **POLYBROMINATED BIPHENYLS (PBBs)**

Background
Polybrominated biphenyls (PBBs) are brominated cyclic hydrocarbons that were used as flame retardant additives for plastics, textiles, and other materials (reviewed in Di Carlo et al, 1978 and ATSDR 2002). Commercial production of PBBs began in 1970, but following a large contamination episode that occurred in Michigan in 1973 (Fries et al. 1985), ceased in 1979. Approximately 13.3 million pounds of PBBs were produced in the United States from 1970 to 1976. Due to their fat solubility and chemical stability, PBBs have a long half-life (years) and can bioaccumulate and biomagnify as they move up the food chain.

Probability of Exposure
PBBs were introduced into the environment through an accident that took place in Michigan in 1973, when a large quantity (approximately 4,000 kg) of a PBB mixture (commercial name Firemaster BP-6) was mistaken for a food additive and was mixed into cattle feed (Fries et al. 1985). Thousands of animals that consumed the contaminated feed were destroyed, but not before PBB-containing meats, butter, milk, eggs and cheese entered the human food chain. Michigan residents showed concentrations ranging from less than 1 to 3,150 µg/L with a geometric mean of 4.1 µg/L(28). Only 10% of the population did not have detectable blood PBB levels (US Dept HHS, 2002). Many farms were quarantined because of high soil PBB levels from the fecal excretion of the contaminated animals, which provided another source of PBB exposure. PBBs were also detected in the residues in and around former PBB production sites in St. Louis, MI. In 1976, sera from 524 dairy farm residents, 40 consumers of dairy products from quarantined farms and 55 workers at the Michigan PBB production company were analyzed for PBB levels (Wolf et al. 1978). Michigan farm residents had a mean level of 23.7 parts per billion (ppb), consumers of dairy products had 56.6 ppb and the chemical workers 123 ppb. A control group of Wisconsin farmers had nondetectable levels of PBBs. The half-life of PBBs in serum of the cohort members has been estimated to be between 12.0 and 18.5 years (Lambert et al 1990; Rosen et al 1995; Blanck et al. 2000).

Health Effects
Public concern prompted assessment of possible adverse health consequences in exposed individuals. A registry of exposed individuals was established in 1976 and enrollment began for a long-term study of human health effects of PBB exposure by the Michigan Department of Public Health (MDPH) (reviewed in Landrigan et al, 1997). The initial enrolment consisted of 4,127 persons in 1,073 families. Over 1,000 offspring of female cohort members have been added, for a current total of 5,219. Most of the known human health effects of PBB exposure have been established by studies on this cohort.

An early health survey conducted by MDPH found that subjects self-reported nausea, loss of appetite, abdominal pain, joint pain, fatigue, weakness, and skin color changes, but there was no set of symptoms that correlated with highly exposed persons (Senate report, 1975). This report has been challenged (Stadtfeld 1976) and a second study comparing Michigan residents with those of Wisconsin, found a significant increase in skin conditions (halogenacne) (Chanda et al.,1982).

A 1982 study on the hepatic effects of PBB ingestion found no consistent correlation between PBB serum levels and levels of several liver enzymes (Kreiss et al., 1982); the investigators, however, indicated a need for tests with higher sensitivity and specificity to assess the effects. Another study found that prevalence rates of PBB-exposed Michigan residents with abnormal liver-related enzymes were significantly higher than the rates for the unexposed control group in Wisconsin (Silva et al., 1979).

Immunological and lymphoreticular effects have been assessed but the data are inconsistent. In a 1978 report on 45 adult Michigan dairy farmers, peripheral blood lymphocytes reactivity to non-specific antigens was low (Bekesi et al., 1979). Another study found no relation between lymphocyte function and serum PBB levels (Silva 1979). A comparison of PBB-exposed farmers with high (mean, 787 ppb) and low (mean, 2.8 ppb) PBB levels found no difference with respect to peripheral lymphocyte function, T and B cell quantitation and in vitro responses to 3 nonspecific stimulants (Landrigan et al.,1979). On the other hand, Michigan farm residents with the highest exposure to PBB had significantly elevated levels of IgG, IgM and IgA compared to Wisconsin controls (Anderson 1979). A later study examined adult Michigan farm residents who typically consumed dairy products from their farms, general Michigan consumers, and

dairy farm residents in Wisconsin, who had not eaten PBB-contaminated food (Bekesi et al., 1987). Abnormalities in the Michigan groups included hypergammaglobulinemia, exaggerated hypersensitive response to streptococci, significant decreases in absolute numbers and percentage of T and B-lymphocytes, and increased number of lymphocytes with no detectable surface markers ("null cells"). Significant reduction of in vitro immune function was noted in 20-25% of the Michigan farm residents who had eaten food containing PBBs. It is difficult to reconcile these opposing results. While the quality of the earliest studies have questioned, it is also possible that the immune altering effects of PBBs were only seen in later studies because a prolonged duration of exposure is required to see the effects.

Seriousness of Effects
Recent reports indicated subtle in utero effects on the female offspring of PBB-exposed women in the PBB cohort. Breastfed daughters exposed to high levels of PBBs in utero had an earlier age at menarche (mean age 11.6 years) than breastfed daughters exposed to lower levels of PBBs in utero (mean age 12.2-12.6 years) (Blanck et al 2000). Perinatal PBB exposure was associated with earlier public hair stage in breastfed girls although no association was found with breast development. No effect on current height or weight was found in PBB exposed daughters (Blanck et al 2002). Animal studies have also indicated that perinatal exposure to PBBs can lead to adverse effects on the offspring including embryolethal effects, structural abnormalities, growth retardation, liver effects and neurological effects in the offspring (ATSDR 2002).

Several studies have determined the cancer incidence of the PBB cohort members. No association was found between serum PBB levels at time of enrolment and breast cancer (Anderson et al., 1979), but another study found a significantly increased risk for women with the highest serum levels (Hogue et al., 1998). The same study found significant risks for cancers of the digestive system and for lymphoma although the number of cases for any cancer was low. The cohort may be too young to accurately assess cancer incidence.

Why PBBs should be biomonitored in Michigan:

- The PBB contamination of Michigan dairy products was wide spread exposing thousands of people, many of whom still have detectable levels
- Recent reports indicate second generation endocrine disrupting effect of PBBs, increasing the scope of PBBs potential adverse effects

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- **DIOXINS AND FURANS**

Background

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are produced as unwanted by-products of many industrial combustion processes including the synthesis of PCBs and certain pesticides and the bleaching of wood pulp in paper mills (Second National Report, 2003; ATSDR, 1998). The best-studied and most toxic PCDD is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), commonly referred to as dioxin. TCDD is the most toxic chemical ever made. It is the prototype for a family of chemicals, including other PCDDs, PCDFs and dioxin-like PCBs, that have a common mechanism of action and spectrum of effects (reviewed in Hankinson, 1995; Safe, 1990). Due to these and other similarities, these compounds are assigned a toxic equivalency quotient (TEQ) that reflects their toxicity compared to TCDD, which has the highest TEQ of 1.

Probability of Exposure

Dioxins and furans are widespread in the environment and have been detected in soil, air, water, sediments, and food, especially in dairy products, meat, fish and shellfish. The highest levels are found in soil, sediments and food (Second National Report, 2003; ATSDR, 1998). Dioxins are resistant to degradation and, due to their lipophilic nature, bioaccumulate, and biomagnify at higher levels of the food chain. In the general population, ingestion of contaminated foods is the most likely source of TCDD, but accidental exposure has also occurred in the workplace, during wartime and as a result of industrial accidents (Safe, 1990, 1994; DiVito *et al*., 1995). A commonly used measure of the toxicity of TCDD and related compounds, including other PCDDs, PCDF, and certain PCBs, is the compound's toxic equivalency quotient (TEQ). The TEQ of a compound is based on specific assays for animal toxicity, mode of action, and distribution in the environment. TCDD has the highest TEQ of 1 (Safe, 1994; DiVito *et al*., 1995).

TCDD levels in the United States have been declining as a result of efforts to restrict emissions from manmade sources (Dioxin, 2000). However, a recent study showed that TCDD exposure through contaminated food is still high, and the estimated daily intake was higher than the recommended values (Schecter et al, 2001). A recent U.S. nationwide sampling of food items for dioxins, dibenzofurans, and dioxin-like PCBs, found that freshwater (farm fed) fish had the highest wet weight TEQ of all foods (1.7 ppt)(Schecter et al, 2001). Ocean fish, meat, poultry, sandwich meat, eggs, cheese as well as human milk had 0.33-0.51 dioxin-like TEQ. The highest estimated daily TEQ intake was 252 pg/day for breast-feeding infants. Daily intake for an infant is thus 42 pg/kg/d body weight, while that for adults range from 1.8 to 6.3 depending on gender and age. The US EPA has used a level of 0.0006/pg/kg/d as the acceptable daily intake of dioxin TEQ.

Serum levels of TCDD in industrialized countries have been reported to be 1–5 parts per trillion (ppt, lipid-adjusted) and body burdens estimated at 25 ppt TCDD (lipid adjusted) TEQs in individuals with no overt exposure (Farland *et al*., 2000). In these populations, TCDD contributes approximately 15% of the body burden of total dioxins while dioxin-like PCDDs, PCDFs, and non-ortho and mono-ortho substituted PCBs comprise about 85% of the dioxin body burden (DeVito *et al*., 1995). The half life of TCDD is about seven year (Birnbaum and Tuomisto 2000).

The recently published Second National Report on Human Exposure to Environmental Chemicals attempted to determine TCDD levels in the general population (Second National Report, 2003) using samples collected in 1999-2000 from the Third NHANES. They reported that the mean serum lipid level of dioxins and furans for the general population was below the detection limit and that 95% of the sampled population had less than 16.8 ppt-TEQ in serum. However they also indicated that their ability to accurately measure levels of these chemicals was prevented by the low volume of serum available to them. These estimates are therefore likely to be under estimates.

Health effects
The human health effects of TCDD have been studied most extensively in three populations: those occupationally exposed, Vietnam veterans potentially exposed to Agent Orange and populations exposed to TCDD after the industrial accidents.

The immune system is a major target of TCDD toxicity (Birnbaum and Tuomisto 2000). A morbidity study following up BASF employees exposed to TCDD in a 1953 chemical reactor incident found a significant increase in the incidence of infectious and parasitic disease (intestinal and respiratory infections) in workers with severe chloracne (Zorber et al., 1994), a well documented effect of exposure to TCDD and PCBs (Kimbrough RD et al.1997; Pelclova et al. 2001).

A major accident involving TCDD occurred in 1976 in a residential area surrounding Seveso, Italy (Bertazzi and Di Domenico 1994). The exposure was acute, relatively pure, and affected more than 45,000 men, women, and children. Measurements of soil levels of TCDD within 5 weeks delimited three zones (A, B, and R) of decreasing contamination. Twenty years after the exposure, TCDD levels were still high in exposed persons, particularly in women. Plasma TCDD ranged between 9.8 and 89.9 ppt in individuals from zone A, 1.0-62.6 ppt in individuals from zone B, and 1.0-18.1 ppt in individuals from the noncontaminated surrounding area (non-ABR) (Landi et al. 1998). Children exposed during the Seveso accident showed subclinical changes in complement protein levels that correlated with the incidence of chloracne (Tognoni and Bonaccorsi, 2001). Another follow-up of the Seveso population nearly 20 years after the accident found significantly decreasing IgG levels with increasing TCDD plasma concentration (r = -0.35, p = 0.0002) in a random sample of the population in the most highly exposed zones (n = 62) and in the surrounding noncontaminated area (n = 58) (Baccarelli et al 2002). Median IgG concentration decreased from 1,526 mg/dL in the group with the lowest (< 3.5 ppt) TCDD levels to 1,163 mg/dL in the group with the highest (20.1-89.9 ppt) TCDD levels (p = 0.002).

Exposure to TCDD has also been associated with signs and symptoms of both central and peripheral nervous system damage that occur soon after exposure (Filippini et al, 1981, Pocchiari et al., 1979). In Seveso, early health assessments of the exposed populations found both signs of idiopathic subclinical neurologic damage and cases of clinically detectable idiopathic polyneuropathy in adults (Pocchiari et al.

1979). A 30 year follow-up of workers exposed to very high levels of TCDD in a herbicide production plant in the Czech Republic found significant correlations between neuropsychological variables and plasma levels of TCDD (Neuberger et al. 1999). In these workers, the current mean plasma level of TCDD was 256 pg/gm lipid (range = 14-760 pg/gm lipid), corresponding to an estimated concentration of approximately 5,000 pg/gm plasma fat that existed about 30 years.

Alterations of glucose metabolism and thyroid function have been reported. Vietnam veterans exposed to TCDD reported an increase in diabetes and elevated serum glucose levels (Henriksen et al., 1997). An increased incidence of thyroid disease was observed in a group exposed to dioxins following an accident at a chemical reactor (Zober et al. 1994). A mortality study of the Seveso cohort found a significant increase in deaths from diabetes among women exposed (Pesatori et al., 1998).

Several adverse reproductive effects have been reported including alterations in hormone levels (high luteinizing hormone and low testosterone levels) in male workers, (Egeland et al., 1994), an increased incidence of spontaneous abortion (Fosberg and Nordstrom, 1985), and altered sex-ratios in the offspring of the Seveso populations (Mocarelli et al., 1996).

The possible association between TCDD exposure and endometriosis has been investigated in several studies. Two hospital-based case-control studies produced conflicting results. One study (Mayani *et al*. 1997) reported that more infertile women with endometriosis had detectable serum TCDD concentrations compared to infertile women without endometriosis. Another study (Boyd *et al*. 1995), however, found similar levels of TCDD, dioxin-like PCDDs, and PCDFs in women with endometriosis and their control group (fertile women), but did not surgically confirm the absence of disease in the control group. A third study is currently investigating the incidence of endometriosis in TCDD-exposed women in Seveso (Eskenazi *et al*., 2000), but again a surgical definition of endometriosis was missing. Due to the current inability to define endometriosis without invasive surgery, the current human data neither confirm nor refute the hypothesis that environmental dioxins play a role in the development of endometriosis.

Seriousness of Effect

The International Agency for Research on Cancer classified 2,3,7,8, TCDD as a known human carcinogen in 1997 (IARC, 1997) and an increased risk of cancer in TCDD-exposed human populations has been reported in several studies. In a retrospective cohort study among workers exposed to TCDD, an increase in the standardized mortality rate for all cancers was observed (Fingerhut et al 1991). Another study found exposure to TCDD following the chemical reactor accident was related to the number of all cancer deaths, particularly deaths from digestive and respiratory cancers (Ott and Zober, 1996).

Studies on the Seveso population revealed significant increases in the risk of several types of cancer including hepatobiliary cancer, multiple myeloma in women, lymphoreticulosarcoma in men (residents of zone B) and soft-tissue sarcomas in men residents of zone R (Bertazzi et al, 1994,1997). A study on the children from the Seveso population found an increased risk for Hodgkin's lymphoma, myeloid leukemia and thyroid cancer (Pesatori et al., 1993). Cancer mortality studies on Vietnam veterans have been inconclusive to date, largely because of the small number of cancer cases and lack of accurate exposure data.

TCDD is reported to be developmental immunotoxicant in experimental animals, but this effect has not been documented in human studies (Van Loveren et al., 2003). In experimental animals, an important target organ of TCDD-mediated immunotoxicity is the thymus. Atrophy of the thymus and suppression of the thymus-dependent immune response is a major immunotoxic effect of TCDD and it is seen in all animal species tested (reviewed by Vos et al., 1980). TCDD adversely affected thymic epithelial cells, and inhibited maturation of thymocytes. The distribution of T lymphocyte subsets was also reported to be altered after TCDD exposure in rodents, mice, marmoset, and human thymus (Neubert et al. 1994; de Heer et al. 1995; De Waal et al.,1997).

Why TCDD should be biomonitored In Michigan:

- Heavy industrialization of much of the southeastern portion of Michigan and other parts of the state have resulted in the designation of 13 areas of Michigan including southeastern MI, the Saginaw Bay area and parts of the west coast (Kalamazoo River, Muskegon Lake, and White Lake) as Areas of Concern by the CDC (http://www.epa.gov/glnpo/aoc.html). These areas are so designated because they contain unacceptable levels of dioxins, heavy metals, PCBs, and pesticides.
- TCDD has been shown to cause a variety of adverse human health outcomes including cancer.
- To date there has not been an assessment of TCDD levels in Michigan residents to estimate exposure; thus there is no way to know if potential TCDD exposure is limited to industrial areas of it or posses a potential state-wide health risk.

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- **ORGANOCHLORINE PESTICIDES (OCP)**

Background
OCPs include a wide variety of chemicals, with different structures and activities. All however, share the common characteristics of bioaccumulation, bioconcentration and persistence and most of them have endocrine-disrupting properties. Because of their similarities, they will not be discussed individually. Instead, a brief synopsis of endocrine disruption is presented followed with in an depth review of DDT/DDE, the most wide-spread and best studied OCP.

Endocrine disrupting compounds (EDC) comprise a diverse group of compounds of anthropogenic origin that include OCPs. EDC are ubiquitous and persistent and, even at low environmental concentrations, appear to exert a range of adverse effects on animals of many species, including humans. Their effects include disruption of reproductive and immune systems and carcinogenicity (Rind, 2002). Specifically, several endocrine-disrupting pesticides appear to be involved in the development of several cancers and noncancer health risks in humans and wildlife.

Probability of exposure
The potential for human and animal exposure to such pesticides is very high. Farmers, as a group, may be particularly at risk, because they are subject to higher-than-average levels of exposure to pesticides over longer-than-average periods. Recent studies have shown that the incidence of hormone-related organ cancers, or hormonal cancers, is elevated among farmers. Exposure to endocrine-disrupting pesticides, particularly to DDT and phenoxy herbicides, is suspected of involvement in some of these hormonal cancers.

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- **DICHLORODIPHENYLTRICHLOROETHANE (DDT) AND DDE**

Background
DDT was originally produced for various purposes as early as the1890's. Its usefulness as an insecticide was realized in the 1930s and large-scale industrial production started in 1943 (Smith, 1991). The low price of DDT, of about $0.25 per pound in the mid-1950s (Dunlop et al.,1981), contributed to its worldwide use. While early use of DDT to control mosquitoes carrying the parasites responsible for malaria and typhus required small quantities of DDT, much larger quantities were used after 1945 for the control of agricultural and forest pests. In the early 1960s, about 400,000 tons of DDT were used annually worldwide (70-80% of which was used for agriculture) (Smith, 1991; IARC, 1974). Due to worldwide concern over the toxicity of DDT for wildlife (Cooper et al., 1991), several counties including the USA banned uses of DDT by 1975. In 1985, however, about 300 tons of DDT were still exported from the United States (IARC,1991). In 1990 DDT was produced by one company each in Italy, India, and Indonesia with a total worldwide production estimated at about 30 million pounds (IARC,1991; Thomson, 1997). DDT is still used in some developing countries for essential public health purposes, and it is still produced for export in the above mentioned three countries. In spite of banning its use in many countries, DDT and its metabolites are still found all over the world.

Probability of exposure
DDT is slowly biodegraded, persists for a long time in the environment, and accumulates in the food chain and in the tissues of living organisms. DDT is stored in all tissues, with the highest accumulation in fat, where repeated exposures, even at low concentrations, result in a particularly high storage (Smith, 1991). No living organism is considered DDT-free.

Human exposure to DDT and its metabolite, DDE, comes from consumption of contaminated foods. It has been calculated that it would take between 10 and 20 years for DDT to disappear from an individual if exposure would totally cease, but that DDE would possibly persist throughout the life span (Smith, 1991). The half-life of plasma DDE has been estimated to be approximately 10 years (Hunter et al., 1997). In the United States, storage of total DDT in body fat increased from 5 ppm in 1950 to 15.6 ppm in 1956, and decreased thereafter to 3 ppm in 1980 (Smith, 1991). Levels of DDE, which is ingested with food, in particular fish, however, remain constant or are decreasing only slightly.

Health effects
DDT is toxic to freshwater and marine microorganisms, fishes, amphibians, and birds. DDE has been found in the eggs of fish-eating birds, such as falcons, causing hatchability difficulties resulting in a severe population decline. In parallel, high levels of DDT in lakes were a cause of reproduction failure in certain fishes (Smith, 1991;WHO, 1989; Cooper et al., 1991).

One of the proposed hypotheses for DDT/DDEs toxicity is its ability to act as an endocrine disruptor (Keith, 1997; Longnecker et al., 1997). There is evidence that DDE is an androgen receptor antagonist, and it is possible that DDE may interact in an additive or multiplicative way with other endocrine-disruptive environmental pollutants (Kelce et al., 1995; Ramamoorthy et al., 1996). Indirect evidence of the hormonal activity of DDE in humans comes from the observed association between levels of DDE in maternal fat and earlier weaning (Rogan et al., 1987; Gladden and Rogan, 1995). Because a considerable proportion of all cancers in women are hormonally mediated, it has been proposed that xenoestrogenic substances, such as organochlorine insecticides, contribute to an increased cancer risk (Wolff et al., 1996).

Seriousness of effects
Early reports showed higher concentrations of DDT and DDE in fat tissue of individuals with mammary cancer (Wasserman et al., 1974), and an association between DDE blood levels and mammary cancer was reported in some epidemiologic studies (Wolff et al., 1993; Krieger et al., 1994). Subsequent studies provided conflicting results, with most of them not confirming the association (Longnecker et al., 1997). The analysis of five large studies carried out in the United States, which had the limitation of not considering occupational exposures nor exposures *in utero* or during adolescence, did not provide evidence to support a role of DDE in increasing the risk for breast cancer (Laden et al., 2001).

Recent epidemiological studies have reported an increased risk for pancreatic cancer after self-reported exposure to DDT (Garabrant et al., 1992, Frizek et al., 1997) and significant excess incidences of liver cancer and multiple myeloma were reported after occupational exposure to DDT (Brown et al.,1993; Cocco et al., 1997). The association with an increased risk for pancreatic cancer was not confirmed in a subsequent study, but the conditions of exposure were not comparable (Hoppin, 2000).

Subsequent investigations on the long-term adverse effects of DDE confirmed the association between the concentrations of this metabolite in adipose tissue and an increased risk for mortality from liver cancer but did not confirm an increased mortality rate from cancer of the pancreas or multiple myeloma (Cocco et al., 2000), nor from non-Hodgkin lymphomas (Baris, 2000).

In addition to a possible carcinogenic effect, DDT has been reported to affect neurobehavioral functions and to be associated with premature births (van Wendel et al., 2001; Longnecker et al., 2001). Prenatal exposure to DDT and other organochlorine insecticides in Inuits living in Greenland has been reported to affect the immune status of the children and increase their susceptibility to infections (Dewailly et al., 2000).

Why OCPs should be biomonitored In Michigan

- Due to their widespread use and persistence in the environment, many Michigan residents are likely to have measurable levels, especially of DDT/DDE
- OCPs have endocrine disrupting properties and are (DDT/DDE) or may be associated with cancer

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- **ORGANOPHOSPHATE PESTICIDES (OPPs)**

Background

The banning or restricted use of persistent OCPs has resulted in the expanded use of organophosphate pesticides. In general, these substances are less persistent in the environment than the OCPs but are more likely to acutely poison the people who use them or come in contact with them. Although they represent chemicals with a variety of structures, they share a common mechanism of action. OPPs affect the nervous system by reducing the ability of cholinesterase to control the levels of acetylcholine. Acetylcholine helps transfer nerve impulses from a nerve cell to a muscle or another nerve cell. If acetylcholine levels are not properly regulated, the nerve impulse to the neurons remain active longer than they should, overstimulating the nerve and muscles. The toxic effects of overstimulation include sweating, dizziness, vomiting, diarrhea, convulsions, cardiac arrest, respiratory arrest, and, in extreme cases, death (Sultatos, 1994). The OPPs have a range of inhibitory effects on acetylcholinesterase, which is reflected in the range of their individual toxicities. In its “Overview of the preliminary cumulative organophosphorus risk assessment,” the US EPA listed 30 cholinesterase-inhibiting OPPs registered by the EPA (EPA Summary, 2001), all of which can have acute and sub-acute toxicity.

OPPs are used to control a large variety of pests in most major crops (cotton, corn, and wheat) and most important minor crops. They are also used for mosquito control (EPA Organophosphates, 1999). Approximately 60 million pounds of organophosphates are applied to approximately 60 million acres of US agricultural crops annually. Nonagricultural uses account for about 17 million pounds per year (EPA Organophosphates, 1999).

OPPs are very efficiently absorbed from the skin, lungs and gastrointestinal tract. The absorption rate is higher if the skin surface is moist. Ingestion and inhalation are other routes of absorption (EPA Assessing, 1999).

Probability of Exposure

OPP exposure is quite common, especially in agricultural settings. Workers who apply and mix pesticides are at special risk of systemic pesticide illness. Both acute and chronic exposure can occur from spillage or by environmental contamination of clothing. In Michigan in 2001-2002, the top four OPPs applied to fruit crops, in thousands of pounds, were: phosmet, 179.3, azinphos-methyl (a dialkylphosphate (DAP)),

154.4, chlorpyrifos, 38.3, and malathion, 30.2 (Michigan Dept. Ag,). These numbers indicate substantial use in the fruit growing regions of Michigan.

Metabolites of the OPPs present in urine are markers of recent exposure (past 72 hours) (Lopez and Lopez,). The urinary concentrations of several commonly used OOPs in the US population above 12 years of age were determined using samples collected in 1999-2000 in NHANES III (CDC, 2003). Levels for malathion, parathion and diazinon metabolites were below the levels of detection, but the mean level for a chlorpyrifos metabolite was 1.58 ug/L creatinine. For the dialkyl phosphate pesticides (DAPs), including phosmet and azinphos-methy, measurements were made of the 6 possible urinary metabolites. Since several DAPs produced the same metabolite profile, there is no way to distinguish the level of a specific DAP. The 50^{th} percentile values for the 6 metabolites ranged from .074 to 2.12 ug/g creatinine. These national values may mask regional differences in OPP exposure.

Health Effects
In 1999, more than 13,000 cases of OOP poisoning were reported to US poison centers, with more than 3000 cases seen in the emergency department resulting in 83 fatalities (Riegel, 2003). The clinical picture after poisoning depends on the toxicity of the pesticide, the amount of pesticide involved in the exposure, the route of exposure (inhalation is fastest, followed by ingestion, then dermal), and the duration of exposure. There is also significant variability in the ability of the various OPPs to inhibit acetylcholinesterase. Some organophosphates such as diazinon and parathion have significant lipid solubility allowing fat storage with delayed toxicity due to late release. Some need to be metabolized to a more active form to produce toxicity. Chlorpyrifos and parathion need to be activated metabolically before producing toxicity (Riegel, 2003).

Symptoms of acute OPP poisoning include nausea, drooling, profuse sweating, headaches, dizziness, shivering, difficulty breathing, vomiting and diarrhea, although not all symptoms are present. Time until onset of symptoms is very short, from a few minutes to one-two hours for acute exposure (Eskenazi et al. 1999; Lifshitz et al., 1999).

Chronic exposure to low levels of OPPs can result in depressed serum cholinesterase levels sometimes accompanied by fatigue, headaches, giddiness, nausea, profuse sweating, difficulty sleeping, attention deficit and memory loss. Chronic exposure in adults may also cause peripheral nervous disturbances and alteration of short-term memory and anxiety (Levin and Rodnitzky 1976, London et al. 1998). Chronic exposure in children may be related to developmental impairment, as suggested by human adult and animal studies (reviewed in Eskenazi et al 1999).

More detailed studies on the effects chronic low level exposure to OPPs found slower reaction times(Fiedler and Kipen, 1997), impaired postural sway (Sack et al. 1993), decreased conduction velocities in motor and sensory nerves (Ruijten et al, 1994), wider two-point discrimination (Beach et al. 1996), as well as some neurobehavioral effects such as increased anxiety (Levin and Rodnitsky, 1976) decreased visuomotor speed (Ames et al,1995) and impaired short-term verbal memory (Chuwers et al, 1989). An influenza-like illness with symptoms like weakness, fatigue, anorexia and malaise has also been described in chronic low-level exposures (Morgan, 1982). No correlation was found between the severity of symptoms and the degree of cholinesterase inhibition.

Neuropsychologic effects including anxiety, depression, irritability, confusion, and impaired concentration and memory appear to be the sequels of acute exposure (Ngowi et al., 2001). Delayed neurotoxicity (characterized by moderate to severe peripheral neuropathies) has also been reported after acute or subacute exposures (Jamal, 1997).

A delayed peripheral sensorimotor neuropathy, called organophosphate-induced delayed neuropathy (OPIDN), may begin 10 - 14 days after exposure. The neuopathy may progress centrally and involve motor function leading to complete respiratory paralysis. An "intermediate syndrome" of lower limb muscle weakness (beginning with burning and tingling), cranial nerve abnormalities, and respiratory paralysis has been reported to occur 1-4 days after the initial cholinergic phase (Organophosphate, 2003).

Seriousness of Effects
A possible relationship between childhood leukemia and parental occupational exposure to pesticides was reported (Buckley et al 1989); however the association was not statistically significant and the sample size was small.

Animal studies suggest that OPP exposure during pregnancy and early life may lead to neurodevelopmental effects, as measured by impairment on maze performance, locomotion, and balance in young animals exposed *in utero* and postnatally to OPPs (Schultz et al. 1995; Spyker and Avery, 1977; Stamper et al., 1988).

Several studies reported decreased body weight in the offspring of rats exposed during the first period of gestation; at higher doses other effects were evident (shorter limbs, decreased head circumference (Muto et al. 1992). Decreased birth weight and slower weight gain postnatally were found as a consequence of exposure to chlorpyrifos (Chanda and Pope, 1996) or diazinon (Spyker and Avery, 1977) during gestation.

Why OPPs should be biomonitored In Michigan

- Due to the wide-spread use of certain OOPs in the fruit growing regions of Michigan, it may be advisable to biomonitor OOP levels in farm workers and farm families.

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- **BENZENE**

Background
Benzene is a volatile, polycyclic aromatic hydrocarbon that is used as an industrial solvent in the chemical and pharmaceutical industries. It is used in the synthesis of various other chemicals (styrene, cumene, cyclohexane) and as an additive for gasoline (ATSDR, 1999). Other uses include production of synthetic rubbers, gums, lubricants, dyes and pesticides. Production of benzene in the U.S. has been steadily increasing since 1980. The U.S. domestic benzene import for the year 2000 were 4,794,533,678 L (ITA, 2003).

As a consequence of its industrial uses and volatility, benzene is widespread in the environment. Since it is degraded in a matter of days in the atmosphere and on the ground, it not bioaccumulative (ATSDR, 1999).

The main route of benzene absorption is through inhalation and approximately 50% of the inhaled benzene is rapidly absorbed through the lungs (ATSDR, 1999; Report on carcinogens, 2002). Data on accidental or intentional benzene ingestion indicate that benzene can be absorbed through the gastrointestinal tract, and animal studies show that almost all ingested benzene is absorbed (Reese and Kimbrough, 1993). Liquid benzene is readily absorbed through skin (Wester and Maibach, 2000). Benzene is a lipophilic and distributes to the blood, brain, liver, kidney, stomach, and bile following inhalation exposure (ATSDR, 1999). Benzene also crosses the placenta into cord blood following inhalation exposure (Dowty et al,1976).

Probability of Exposure
Nearly 50% of benzene exposure in the general population is attributable to tobacco smoking (Wallace, 1990). The other major source of benzene exposure is through inhalation of air contaminated with

industrial benzene emissions and from automobile exhaust and fuel evaporation, especially in areas of heavy traffic. 50% of the entire U.S. population is exposed to benzene from industrial sources (ATSDR, 1999). Potential for exposure to benzene in the workplace can be high in certain industries, such as the production of paint and organic chemicals (Ayers et al., 1989).

Benzene has been identified in surface and ground water and consequently has also been detected in fish, eggs, dairy products, vegetables, fruits, nuts and beverages. Human exposure levels as measured in urine have been reported to be 25.8-1099.1 ng/l in thenon-smoking population (Perbellini et al., 2003).

Health Effects
Acute exposure to benzene can cause dermal effects such as erythema, edema, burns and necrosis (ATSDR,1999). Ocular effects can be moderate conjunctival irritation and transient corneal damage. Acute exposure to inhaled benzene can cause death usually by asphyxia, respiratory arrest, central nervous system depression or cardiac collapse. Benzene ingestion causes serious disturbances of the gastrointestinal tract including congestive gastritis, intense toxic gastritis and pyloric stenosis, depending on the dose ingested and individual variations in metabolism (Bauer et al., 1993).

Exposure to benzene through any route can lead to adverse effects on the hematological system. Workers exposed to benzene solvents showed a range of hematotoxic effects including anemia, leucopenia, and thrombocytopenia (Snyder et al., 1975). Aplastic anemia has been linked to benzene exposure with a gradient of severity between the lowest exposed group compared to the unexposed subjects (Qu et al., 2002). Lack of platelets can lead to hemorrhagic complications, lack of leukocytes to an increased susceptibility to infections, and lack of erythrocytes to cardiac overload leading possibly to impaired cardiac function.

Seriousness of Effects
Benzene is one of the few known etiological factors identified for acute myelogenous leukemia in humans (AML) (Sanz et al., 1997), and is associated with a spectrum of lympho-hematopoietic cancers in humans and mice (Cronkite et al., 1989; Ferris et al., 1997). A study following a cohort of 74,828 benzene-exposed and 35,805 unexposed workers from 1972 to 1987 in 12 cities in China found a significantly increased risk for AML for the benzene-exposed workers along with an elevated risk for aplastic anemia (Yin et al., 1996). A 2001 review on benzene exposure and lymphohematopoietic malignancies in humans also provided further evidence for hematopoietic cancer risks at benzene levels substantially lower than had previously been established (Hayes et al., 2001).

Animal studies have linked benzene to developmental effects on the fetus, including low birth weight, bone marrow damage, and delayed bone formation (Saillenfait et al.,2003). Animal studies also show that inhalation of benzene vapors reduces the number of live fetuses as well as the incidence of pregnancy.

Why benzene should be biomonitored in Michigan
- Benzene levels in the environment are increasing
- Benzene has adverse effects on the hematopoetic system and is a risk factor for with AML and other hematopoietic cancers

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EMERGING CHEMICALS OF CONCERN

In this section we briefly review a group of chemicals that are of emerging concern, but have not yet been clearly associated with adverse human health outcomes. In all cases production of these chemicals has increased greatly in recent years and the chemicals have been found in the environment and/or in wildlife. All chemicals were rated highly by the Stakeholders, who voiced serious concern for their potential adverse effects on wildlife and humans.

- **PFOS (perflurooctanoic sulfate) and PFOA (perflurooctanoic acid)**

Background
PFOS and PFOA are two of a group of perfluorinated surfactants that, due to their unique surface active properties, have been used in industrial applications and consumer products (reviewed in Giesy and Kannan, 2001, 2002). They are found in surface-treatments of fabric and apparel for soil/stain resistance, paper coatings approved for contact with food, specialized applications such as fire fighting foams, insecticides, surfactants, plasticizers, lubricants, wetting agents and emulsifers. Approximately 37% of these compounds are used in surface treatment of fabrics (furniture, carpets, clothing) and about 42% are used in paper products. The Minnesota Mining and Manufacturing Company (3M) has been the major global producer of PFOS and related chemicals since 1948. PFOS was produced in at least three 3M plants: Decatur, AL; Antwerp, Belgium; and Sagamihara, Japan. Up until 2000, approximately 4,500 metric tons (10 million pounds) of PFOS-related chemicals were produced annually. In May 2000, 3M discontinued production of PFOS due to its own research on its toxicity in experimental animals.

Probability of Exposure
PFOS-related chemicals have been found in surface water, sediment downstream of a production facility, wastewater treatment plan effluent, sewage sludge and land fill leachate at a number of cities in the USA. PFOS and PFOA are very stable in the environment and are readily adsorbed by animals. In wildlife studies from several sites in the USA, these chemicals have been shown to bioconcentrate in fish and in birds and mammals that consume fish in the parts per billion (ppb) to parts per million (ppm) range (Kannan et al, 2002). PFOS has been detected in Carp from Saginaw Bay (~300 ng/g) Kannan, 2001, 2002).

Health Effects
Humans are exposed non-occupationally from environmental sources, consumer products or from indirect food additives. Levels in sera from human blood supply companies were reported to be 30-53 ppb. A survey of adults and children (2-12 years) in the USA found levels of approximately 43 ppb. Several studies have measured levels of PFOS in 3M perfluoro chemical workers from all three plants; values of approximately 1-2 ppm were found in 2000 (Olsen et al, 2003). The half life in men was found to be approximately 8 years.

Cross-sectional studies on chemical workers in Decatur and Antwerp found no consistent associations between workers' PFOS levels (<6 ppm) and certain hematological, hormonal and other clinical chemistry parameters in 1995 and 1997 (Ubel et al, 1980; Olsen et al., 2000). A re-analysis of combined data from both plants, however, found significantly elevated liver enzymes and thyroid hormone levels (T3) in workers with the highest PFOS serum level (1.69 – 10.06 ppm).

Longitudinal analysis of this data did not find statistically significant associations over time between PFOS and cholesterol, triglycerides, and other lipid and hepatic parameters. However the studies were limited by use of volunteer subjects, the small number of participating employees, the use of different analytical labs and techniques to quantitate PFOS at the different sites, and differences in PFOS levels, demographics and clinical chemistries between Decatur and Antwerp employees.

Morbidity was examined in employees that had worked at the plant from 1993 – 1998 using an "episode of care" analysis. An "episode of care" is a series of health care services provided from the start of a particular disease or condition until solution or resolution of that problem. Episodes of care were identified in the employees' health claim records. The study found increased risk for cancer of the male reproductive tract, especially for prostate cancer, overall cancers and benign growths and cancer of the gastrointestinal tract. The highest risk for employees with the highest and longest exposure levels.

A mortality study, which followed workers for 37 years, found a statistically significant risk of death from bladder cancer for workers that had worked for at least 15 years at the plant (SMR = 12.77, 95%CI = 2.63-37.35); only 3 deaths versus the expected 0.12 (Gilliand and Mandel, 1993).

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- **PHTHALATES**

Background
Phthalates are dialkyl or alkyl aryl esters of 1,2-benzenedicarboyxylic acid. They are important industrial chemicals used in the manufacture of a wide range of plastic and non-plastic products. They can be divided into two groups: those used as plasticizers for synthetic polymers that are incorporated into food wrap, medical tubing, and molded toys, including infant pacifiers; and those primarily used as nonpolymeric constituents of fixatives, detergents, and lubricating oils. They are found in consumer products such as varnishes, perfumes, nail polishes and insect repellants (Koo et al., 2002; Blount et al., 2000). In 1998 the USA imported 567,000 pounds of n-butyl phthalate (UNITC, 1998).

Probability of Exposure
Phthalates are found in a wide variety of extensively used products and are widespread ubiquitous environmental contaminants. The primary source of phthalate exposure is through direct contact with phthalate-treated consumer products. However, as a result of disposal of phthalate-containing products, there is considerable phthalate emission into the environment.

The primary route of human phthalate exposure to the general population is presumed to be ingestion. Phthalate diesters are metabolized in the gut to monoesters and to other oxidative products, which are glucuronodated and excreted through the urine and feces. Most of the phthalate dose is cleared in 24 hr and completely eliminated in 3-5 days. Despite their short half life, these metabolites are widely distributed in the body with the liver being the major initial repository organ. Lower molecular weight phthalates, such as the diethyl phthalates (DEP) and di-*n*-butyl phthalates (DNP) can be absorbed percutaneously and the more volatile ones can be inhaled (Koo et al., 2002).

The first study addressing exposure levels of the general population to commercially important phthalate diesters was published in 2000 (Blount et al., 2000). This study measured concentrations of 7 phthalate monoesters, responsible for animal reproductive and developmental toxicity, in urine of 289 people collected as part of the 1988-1994 NHANES III (NHANES). The means of the monoesters with the highest urinary levels were 345 ng/mL for monoethyl phthalate, 41.5 ng/mL for monobutyl phthalate, and 22.6 ng/mL for monobenzyl phthalate. These monoester levels reflect exposure to diethyl phthalate, dibutyl phthalate, and benzyl butyl phthalate. Women of reproductive age (20-40 years) were found to have significantly higher levels of monobutyl phthalate, a reproductive and developmental toxicant in rodents (Wine et al., 1997), than other age/gender groups. The selective effects on woman were supported by the finding that the estimated exposure values for women 20-40 years of age for monobutyl phthalate was approximately 5 times greater than the corresponding values for the other individuals in the study (Kohn et al., 2000). Koo et al. (2002), also using data from the 1988-1994 NHANES III, but with another statistical method, found approximately the same exposure levels as did Blount et al. (2000). The investigators further correlated higher levels of specific phthalates with demographic factors including education level, lower family income and gender.

Another study focused on African-American women, ages 35-49 years, residing in the Washington, DC area in 1996-1997 (Hoppin et al., 2002). Four phthalate monoesters were detected in all urine specimens. The median levels were 31 ng/mL for monobenzyl phthalate, 53 ng/mL for monobutyl phthalate, 211 ng/mL for monoethyl phthalate, and 7.3 ng/mL for monoethylhexyl phthalate.

A recent study measured plasma di-ethylhexyl phthalate (DEHP) and mono-ethylhexyl phthalate (MEHP) concentrations in 24 consecutive mother-infant pairs and found both compounds in over 70% of the mothers' plasma (Latini et al., 2003). DEHP and MEHP were found in 44% and 72% of cord samples, respectively. The mean DEHP concentrations in maternal and cord plasmas were 1.15 and 2.05 ug/mL, respectively; and mean MEHP concentrations were 0.68 and 0.68 ug/mL, respectively. This study indicates potential exposure of the developing fetus.

Health Effects
Little information is available concerning the human health effects of phthalates. A study examining the role of organic pollutants in premature breast development in Puerto Rican girls found significantly higher serum levels of dimethyl, dibutyl, diethyl and di-(2-ethylhexyl) and mono-(2-ethylhexyl) phthalates in girls with this condition compared to girls without it (Colon et al., 2000). The levels of di-(2-ethylhexyl) was almost 4 times higher in cases than controls (450 ppb versus 70 ppb). These results suggest a possible association between phthalates and endocrine disruption.

A recent study found that both di-butyl and di-iso-butyl-phthalate were genotoxic in human mucosal cells and lymphocytes in vitro (Keinsasser et al, 2001).

While the acute animal toxicity, as measured by the $LD_{50,}$ is low (0.7 to >20g/kg) (Autian, 1973), phthalates have been shown to be reproductive and developmental toxicants in experimental animals. Other observed effects of phthalates in experimental animals include changes in lipid metabolism (Ready et al., 1976), testicular atrophy (Creasy et al., 1983), alterations in xenobiotic metabolism (Walseth et al., 1982), liver peroxisome proliferation (Moody and Ready, 1978), and carcinogenicity (Kluwe et al., 1982).

Based on the experimental animal data alone, the US Department of Health and Human Services has determined that di-ethyl hexyl phthalate may reasonably be anticipated to be a carcinogen (ATSDR, 2002).

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- **POLYBROMINATED DIPHENYL ETHERS (PBDEs)**

Background
PBDEs are diphenyls structurally similar to PCBs, but have an ether linkage between the two phenyl rings. PBDEs are manufactured for commercial purposes as three products, each consisting of congeners of differing degrees of bromination (reviewed in Manchester-Neesvig et al., 2001). The deca-products consist of about 97% of the fully brominated DPE. These constitute about 82% of world PBDE demand and are employed on textiles and in plastics where flame retardancy is essential, such as in computers and television housings. The octa- product consists of 70-80% hepta and octa congeners, constituted less than 6% of the global PBDE marker in 1999 and are used largely in thermoplastics. The penta- product consists primarily of tetra- and penta-BDEs. They are used virtually exclusively as a fire retardant in polyurethane foam. Applications include furniture upholstery and padding in transportation-related products. They constitute about 12% of world demand. The 5-6 brominanted PBDEs are the most bioaccumulative, toxic and widely distributed in the environment and are the most frequently found in the USA. Global demand for the penta-product more than doubled between 1992 and 1999 from 4,000 to 8,500 tons. 98% of the global production was for applications in the USA.

Probability of Exposure
There is growing concern over the apparent similarity between PBDEs and PCBs in terms of their prevalence in the environment and in humans and in their toxicology. Both compounds bioaccumulate in the aquatic environment with predatory fish and marine mammals having the highest concentrations. As with PCBs, PBDEs bind to lipids, persist, and have similar dispersion in the environment (Eriksson et al., 2001). Ingestion through consumption of contaminated fish appears to be the main route of exposure.

A major difference between PBDEs and PCBs, however, is that the levels of PBDEs detected in mother´s milk are increasing (Solomon and Weiss, 2002) while levels of other organohalogens are decreasing. PBDE concentrations in Swedish women have increased over the last 2 decades from 0.07 ng/g lipid weight in 1972 to 4.02 ng/g lipid weight in 1998 (Meironyté et al., 1999). The concentration in adipose tissue of a 74 year old Swedish man was 8,800ng/kg (Haglund et al. 1997).

More alarming are the PBDE levels detected in human milk samples collected in North America over the last ten years (Betts, 2001). Although the data are based on a limited number of samples and the collection methods differed, it suggests an exponential increase in PBDEs found in breast milk. A value of 200 ng/g lipid was found for the most recent samples collected in 2000. Analysis of breast adipose tissue samples from 23 women from the San Franciso Bay area found levels of PBDEs in the low ng/g fat range, with PBDEs 47, 153, 154, 99, and 100 as the major congeners (She et al., 2002). The average PBDEs (86 ng/g fat) in these California women were the highest human tissue levels reported to date. An inverse relationship between concentration of PBDEs and age was observed. PBDEs have been detected in Lake

Michigan salmon (Manchester-Neesvig, 2001) and trout (Luross et al., 2002) and in serum from Lake Michigan fish consumers (Mathew et al., 1996).

Health Effects
Available evidence suggests that the PBDE congeners that tend to bioaccumulate (i.e., those observed in human tissues and other biota) have the capacity to disrupt thyroid hormones and cause neurobehavioral deficits in laboratory animals (reviewed in MacDonald, 2002). The most sensitive end points of PBDE toxicity *in vivo* are effects on thyroid function, observed as induction of thyroid hyperplasia and alteration of thyroid hormone production (i.e., lowering of free and total thyroxine (T_4) concentrations) in rodents (Darnerud and Sinjari, 1996; Zhou et al., 2002). Consistent with these findings is the recent observation that several pure PBDE congeners were able to displace T_4 from transthyretin (a plasma transport protein of thyroid hormones) *in vitro* (Meerts et al., 2000). Similar activities have been observed with PCBs and their hydroxylated metabolites (Brouwer et al., 1998). PBDEs have also been shown to have agonist activity for both estrogen receptors (α and β) in in vitro assays using a human breast cell line (Ilonka et al., 2001).

PBDE congeners (PBDE 99 and PBDE 47) were found to affect cognitive functions in mice. Neonatal mice, treated with either of two of the most common human tissue PBDEs, had permanent aberrations in spontaneous behavior, evident at 2- and 4-months of age (Eriksson et al., 2001). This effect together with the habituation capability was more pronounced with increasing age, and the changes were dose- related. Furthermore, neonatal exposure to PBDE 99 also affected learning and memory functions in adult animals, developmental defects that have been previously detected after PCB treatment.

PBDEs are also Ah receptor-mediated inducers of cytochrome P450 1A1 and 1A2, a property shared with certain PCBs, PBBs and dioxin (Von Meyerinck et al.,1990), although they are not thought to be strong inducers (reviewed in Manchester-Neesvig et al., 2001). Recently several pure di- to hepta-brominated PBDE congeners were shown to act via this Ah receptor pathway *in vitro* as agonists and antagonists in a congener-specific manner (Meerts et al., 1998).

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APPENDIX

ORGANIZATIONS
(from which Stakeholders were drawn)

- *International Joint Commission on the Great Lakes*
- *Federal*
    - *US Environmental protection Agency*
    - **National Institute of Occupational and Safety Health**
    - **Federal Department of Agriculture**
    - **US Department of Agriculture**
    - **US Geographical Survey**
    - **Occupational and Safety Health Agency**
    - **National Institute of Environmental Health Science**
- *State of Michigan*
    - **Michigan Institute of Occupational Safety and Health Agency**
    - **Michigan Department of Environmental Quality**
    - **Michigan Department of Community Health**
    - **Department of Agriculture**
    - **Toxic Steering Committee**
    - **Poison Control Centers**
- *Local Government*
    - **County Environmental Health Officers**
    - **County Health Departments**
- *Native American/First Nation Tribes: Great Lakes Inter-Tribal Council*
- *Environmental Groups*
    - **Michigan Environmental Council**
    - **Clean Water Action**
    - **Michigan United Conservation Clubs**
- *Automotive companies*
    - **Ford Motors**
    - **GM**
    - **Chrysler/Daimler**
- *American Chemistry Council*
- *Pharmaceutical Companies*
    - **Parke-Davis (Pfizer)**
    - **Upjohn (Monsanto)**
    - **Dow Chemical Company**
- *Workers Unions: UAW*
- *Universities*
    - **Michigan State University**
        - Animal Health Diagnostic Lab
        - Center for Integrated Plant Systems
        - Epidemiology
        - Food Safety/Toxicology
        - Medicine
        - Agriculture
        - Zoology
    - **University of Michigan**
        - Toxicology
        - Epidemiology:
        - Occupational Medicine
    - **Wayne State University**
- *Hospitals/HMOs*
    - **Henry Ford Hospital**
    - **Spectrum Health Care**

People interviewed for the Biomonitoring Planning Grant

Internal (9)

Boulton, Matt: MDCH, Director, Bureau of Epidemiology
Bush, Chris: MDCH: occupational toxicologist
Chabut, Jean: MDCH, Director of Division of Chronic Disease & Injury Control
Hinkle, Carol: MDCH, Blood Lead Program
Johnson, Dave: MDCH, Director/Chief Medical Officer
Larsen, L: MDCH, Manager, Toxicology & Response Section
Scranton, R: MDCH, Director, Division of community Services
Scarpetta, Linda: MDCH, Manager, Childhood & Unintentional Injury Prevention Section
Stanbury, M: MDCH, occupational health

External (32)

Bell, D: MI United Conservation Clubs
Braselton, E: MSU Pharm Tox
Carlson, Dale: Ingham Hospital, Dept Medical Ed, Admin Director
Castro-Escobar, A; Dept. Ag-worker pesticide education
Chou, K: MSU PCBs in animals
Comai, A: UAW (works for Frank Mirer)
Cooper, Bill: MSU environmental engineering
Daughton, Christian: EPA Pharmaceuticals & personal care products (PPCPs)
Degenhardt: WI State Lab Hygiene PCB & PBDE analysis
De Rosa, Chris: ATSDR environmental chemical analysis
Dempsey, Dave: MI Environmental Council
Easthope, Tracey: Ecology Center
Fischer, Larry: MSU, Institute of Environmental Tox
Franzblau, Al: U of M, Occupational health
Giesy, John: MSU, environmental toxicologist
Haack, S: USGS, microbiologist
Harlow, Siobhan: U of M, epidemiologist
Harrison, Maria Lucy: Native American health issues
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PRIORITY CHEMICALS TO BIOMONITOR

Chemical	Strategic Implementation Group Scores				Analytic Status of MDCH Laboratory			
	Health effect	Exposure probability	Seriousness of effect	**Overall score**	A	B	C	D [~$K per instrument]
Metals panel including:						X		[200] Additional ICP-MS
Mercury	5.0	5.0	2.5	**12.5**	X			
Arsenic	5.0	3.5	2.5	**11.0**		X		
Lead	5.0	5.0	2.5	**12.5**	X			
Manganese	2.5	3.5	2.5	**8.5**		X		
Cadmium	5.0	5.0	1.5	**11.5**		X		
Arsenic speciation						X		[255] HPLC-ICP-MS
Dioxins & furans	5.0	5.0	2.5	**12.5**			X	[477] GC-HRMS
PCBs	5.0	5.0	2.5	**12.5**	X			
PBBs	5.0	5.0	2.5	**12.5**	X			
Brominated compounds	4.5	5.0	2.5	**12.0**	X			
Perfluro compounds	4.5	3.5	2.0	**10.0**		X		[410] LC-MS
Pesticides: OP	5.0	3.5	2.5	**11.0**		X		[410] LC-MS/335 GC-MS
Pesticides: OC	5.0	5.0	2.5	**12.5**	X			
Petroleum hydrocarbons-benzene	5.0	3.5	2.5	**11.0**		X		Additional PAL-GC-MS VOCs [140]
Phthalates	4.5	3.5	2.5	**10.5**		X		Additional LC-MS/MS 410

Chemical mixtures not evaluated because:

- Chemicals of concern in them probably fit in other categories
  - Non-regulated dietary supplements
  - Foods from unique sources
  - Neutraceuticals
- Probability of significant exposure low:
  - Chemical terrorist agent or metabolite
  - Chemicals used in meth lab
  - Human or veterinary drugs in water supply

Status of MDCH Laboratory Explanatory Notes:

A instrumentation, sample prep accessories *and* analytical methods currently available within MDCH

B instrumentation and sample prep accessories are currently available *while* analytical methods are in the process of being, or have not been, developed within MDCH

C instrumentation, sample prep accessories *and* analytical methods are not currently available within MDCH

D approximate cost (estimated from recent CDC information) for instrumentation and sample prep accessories to move the Bureau of Laboratories within MDCH from status C to B or A

CHEMICALS AND LISTS ON WHICH THEY APPEAR

CHEMICAL	LISTS									
	GL Quality Agree/1978	IJC Top 11/1985	US EPA Critical Contam/	BNS		LaMP 2000				ATSDR Top20 /2000
				Level I/1997	Level II/1997	Erie	Huron	Michigan	Superior	
PCBs	x	x	x	x		x	x	x	x	x
PBBs			x			x	x		x	
Dioxins			x	x		x	x	x	x	
Furans		x	x	x				x		
Aldrin/ dieldrin	x	x	x	x				x	x	x
Chlordane	x		x	x		x	x	x	x	x
DDT/DDE	x	x	x	x		x	x	x	x	x
Endrin	x				x					
Heptachlor	x				x					
Lindane	x									
Methyoxychlor	x									
Mirex	x	x	x	x		x				
Toxaphene	x	x		x				x	x	
PAHs					x	x		x		
AT					x	x				x
BAT						x				x
BbFA						x				x
BkFA						x				
Bpyl					x	x				
BaP		x		x		x				x
Cs						x				
DNPy					x					
FA						x				
Ipy						x				
OCS				x					x	
Pyl					x					
PA					x	x				
VOCs										
Benzene										x
Chloroform										x
HCB		x		x				x	x	
HCBu					x					x
HCCH					x					
PCB					x					
PCPh					x					
TCB					x					
TCE										x
VC										x
1,4DCB[4]					x					
3,3DCBZ[5]					x					
Metals										
As	x							x		x
Cd	x		x		x		x	x	x	x
Cr	x							x		x
Cu	x		x				x	x	x	
Pb	x	x	x	x			x	x	x	x
Mn										
Hg	x	x		x			x	x	x	x
Ni	x		x				x		x	
Se								x		
Tributyl tin					x					
Zn	x		x				x	x	x	
New										
alkyl phenol										
atrazine								x		
PBDEs										
PCB subs								x		

Perfluros										
PB naphth										
PPCP										
4,4MCA					x					
cyanide								x		