BIOMONITORING STUDY

Utah Statewide Investigation of Neonatal Blood Mercury Levels Using Newborn Blood Spot Specimens

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Prepared by the

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ACKNOWLEDGMENT

This investigation is a biomonitoring demonstration project for the Utah Environmental Public Health Tracking Network (UEPHTN). The UEPHTN is funded by a grant from the Centers for Disease Control and Prevention (CDC), Environmental Public Health Tracking Branch. The current UEPHTN award numbers are U50CCU822437, 1U38EH000954, and 5U38EH000182 (UEPHTN 2012).

EXECUTIVE SUMMARY

Mercury poisoning has been recognized as a serious threat to public health for many years. In Utah, health care providers screen children based on clinical history and symptoms, therefore pregnant women and newborns are not routinely screened. Elevated blood mercury levels can cause several adverse health effects including impaired neurological development.

This pilot project investigated the use of newborn blood spots as a sample media to conduct surveillance for blood mercury in newborn children. Six thousand and sixty-eight (6,068) randomly selected blood spot cards submitted to the Utah Public Health Laboratory for the 2007, 2008, and 2009 birth cohorts were analyzed for blood mercury levels. From each card, a sample of the blood spot and a sample of a blood-free area of the card were digested and analyzed for mercury using inductively coupled plasma mass spectrometry. Quality control samples were analyzed with every batch of blood spot samples to assure laboratory data quality. The difference between the amount of mercury in the blood spot and the amount of mercury in the blood-free area of the card was considered to be the child's blood mercury level. After rejecting results for administrative recording errors or because the blood-free area of the card was contaminated with more mercury than the blood spot (resulting in a negative value difference), the results for 5,915 Utah newborns were aggregated and evaluated at the county level. The geometric mean for the state was 0.79 µg/L (maximum = 381.62 µg/L). The blood mercury level equivalent to the current U. S. Environmental Protection Agency reference dose is 5.8 µg/L. Thirty-eight children were found to have blood mercury levels ≥ 5.8 µg/L. However, this finding is based on a testing methodology that has not been validated and the estimates of performance were less than ideal. The Environmental Epidemiology Program does not recommend any change to current public health action or policy related to blood mercury surveillance based on these results.

Biomonitoring is being explored nationally as a better way to understand the true exposure people experience which may contribute to adverse health effects. Before neonatal blood spots can be used as a routine screening media, additional work needs to be conducted to determine the sensitivity, specificity, and predictive value positive of this testing methodology. Prior to any decision leading to implementing this testing methodology as part of Utah's current public health surveillance activities, consideration with respect to cost, alternative methods, and case follow-up should occur.

INTRODUCTION

What is Mercury? Mercury ($_{80}$Hg) is a metal that occurs naturally in several forms. These include metallic (or elemental) mercury, inorganic mercury, and organic mercury. Metallic mercury (also called quicksilver) exists as a liquid above -38^{o} F, vaporizes at a low temperature, and conducts electricity well. Because of these features, there have been many industrial and electronic uses. Metallic mercury has a high affinity for gold and silver making it useful in the mining and metal industries. Inorganic mercury compounds occur when mercury combines with elements such as chlorine, sulfur or oxygen to form mercury salts. Organic mercury results when mercury combines with carbon containing compounds. Inorganic and organic mercury compounds are used to make pigments, thimerosal (a medical preservative), and dental amalgams. Historically, mercury has had other medicinal uses (ATSDR 1999; Bernhoft 2012; NRC 2000).

In the environment, mercury comes from both natural and industrial sources. Mercuric sulfide, or cinnabar, is the main natural form of mercury. The concentration of mercury in the environment varies depending on location and natural history. Mercury is easily mobilized and is found in the air, water, and soil (ATSDR 1999; Bernhoft 2012; Jarup 2003; NRC 2000).

Maternal and Fetal Eexposure During Pregnancy: Sources of exposure include contaminated environments (soil, water, and air); contaminated foods, mainly seafood; vaccines containing thimerosal; dental fillings; and for some people the use of traditional remedies, or practices. Consumption of contaminated fish is consistently the most common source of population exposure. Mercury can enter the body through ingestion, inhalation, and transdermal absorption (Al-Saleh et al. 2011; Bose-O'Reilly et al. 2010; Caserta et al. 2013; Counter and Buchanan 2004; Esteban-Vasallo et al. 2012; Garcia-Esquinas et al. 2013; Hinwood et al. 2013; Jarup 2003; Myers and Davidson 1998). There is no known safe level of exposure (Bose-O'Reilly et al. 2010). The biological half-life (i.e., the time it takes for half the initial dose to be excreted from the body) depends on the form of mercury and ranges from 1 to 3 months (Counter and Buchanan 2004).

The fetus is exposed through transplacental absorption (Al-Saleh et al. 2011; Bose-O'Reilly et al. 2010; Caserta et al. 2013; Garcia-Esquinas et al. 2013; Gundacker and Hengstschlager 2012; Yoshida 2002). There is some evidence that mercury accumulates in the placenta resulting in a fetal blood mercury level (BML) that is higher than the mother's BML (Esteban-Vasallo et al. 2012).

Reference Dose and National Exposure Levels: The U.S. Environmental Protection Agency (EPA) reports that a BML of 5.8 micrograms per liter (5.8 µg/L) is the blood mercury equivalent of the current EPA reference dose (RfD) (EPA 2001, 2013; Jones et al. 2004; Mahaffery et al. 2004; NCR 2000). There is some disagreement about whether the EPA reference dose fully addresses all adverse health effects (Mahaffery et al. 2004; Rice 2004). New York state considered BML to be elevated when above 5.0 µg/L (McKelvey et al. 2007). Canada and Germany have set their blood mercury RfD at 4.6 µg/L (Brodkin et al. 2007). Germany has set its blood mercury RfD at 1.5 µg/L (Wilhelm et al. 2006). For this investigation, the EPA reference dose will be used to identify infants born with elevated blood mercury levels (EBML).

Based on the 1999-2000 National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey of the non-institutionalized U.S. population, the geometric mean total blood mercury concentration among women of childbearing age was 1.02 µg/L (95% confidence limit [95% CI] = 0.85 to 1.20 µg/L). Approximately eight percent of women had total BMLs above the EPA recommended reference dose of 5.8 µg/L. In the same survey, children 1 to 5 years old had a geometric mean total BMLs of 0.34 µg/L (95% CI 0.30-0.39 µg/L) (Schober et al. 2003).

Toxicology of Mercury Exposure: The three main forms of mercury (metallic, inorganic, and organic) are all toxic, but differ in health effects and toxicity. Organic mercury is the most toxic, followed by inorganic mercury, with metallic mercury being the least toxic (ATSDR 1999, 2013; Bernhoft 2012; Bose-O'Reilly et al. 2010; Brousard et al. 2002; Clarkson et al. 2003; Counter and Buchanan 2004; NRC 2000; Nuttall 2004; Syversen and Kaur 2012). In this brief discussion, the adverse health effects of mercury are discussed without differentiating between the forms.

Mercury is lipophilic and is stored in fat. Mercury has a high affinity for certain parts of amino acids, thus interfering with cellular protein production and function (ATSDR 1999, 2013; Bose-O'Reilly et al. 2010; Brousard et al. 2002). In adults, high exposure to mercury has been associated with leukemia (ATSDR 1999; Bose-O'Reilly et al. 2010). Mercury may have a weak genotoxic or mutagenic potential (ATSDR 1999, 2013; Bose-O'Reilly et al. 2010).

In children, the main effects include impaired neurological development, kidney damage (nephrotoxicity), heart function alterations, and suppression of the immune system (immunotoxicity) (Aschner and Walter 2002; ATSDR 1999, 2013; Bose-O'Reilly et al. 2010; Clarkson et al. 2003; Kim et al. 2013). The fetus is particularly sensitive to the neurotoxic effects of mercury (ATSDR 1999, 2013; Castoldi et al. 2003; Clarkson et al. 2003; Myers and Davidson 1998; NRC 2000; Schober et al. 2003). However, the effects that have been associated with prenatal exposure to mercury may be confounded by concomitant exposure to polychlorinated biphenyls (PCBs) or other environmental contaminants (Nakai and Satoh 2002). In the case of fish consumption, some of the effects of mercury neurotoxicy may be countered by the neuroprotective nutrients also contained in fish tissue (Davidson et al. 2011; Williams and Ross 2007).

The supposed association between ethylmercury (a component of the thimerosal preservative used in some vaccines) and autism is unsubstantiated (Aschner and Walker 2002; Clarkson et al. 2003; DeStefano 2007; Hviid et al. 2003; Parker et al. 2004; Price et al. 2010; Schultz et al. 2010).

Rocky Mountain Biomonitoring Consortium (RMBC) and the Utah Environmental Public Health Tracking Network (UEPHTN) Biomonitoring Initiatives: In 2001, the Centers for Disease Control and Prevention (CDC) established the National Biomonitoring Program within its Division of Laboratory Sciences (APHL 2009, CDC 2008). Concurrent with that action, CDC awarded pilot money for state laboratory biomonitoring to develop and propose demonstration projects. At that time, the Utah Public Health Laboratory (UPHL) joined with the state laboratories of Arizona, Colorado, Montana, New Mexico, and Wyoming to form the Rocky Mountain Biomonitoring Consortium (RMBC). The RMBC had a number of goals, one of which

was to explore the ability of each state's laboratory to specialize in some of the laboratory service requirements and provide those services to the other states in the RMBC. The consortium identified and proposed nine demonstration projects, one of which was to use neonatal blood spots to conduct heavy metals biomonitoring. In 2003, the RMBC became one of three grantees to receive funding to implement their proposed demonstration projects (APHL 2009). With that support, the UPHL developed laboratory methodology and capacity to analyze neonatal blood spots for lead, mercury, and cadmium (Chaudhuri et al. 2009).

In 2003, the Environmental Epidemiology Program (EEP) within the Utah Department of Health (UDOH) was awarded funding to start developing the Utah Environmental Public Health Tracking Network (UEPHTN) (UEPHTN 2013). In collaboration with the RMBC, the UEPHTN acquired money specifically to conduct a biomonitoring demonstration project. The UEPHTN received supplemental funding to conduct neonatal blood spot monitoring in 2009, and again in 2012 and 2013. With that supplemental funding, the UEPHTN contracted with the UPHL to randomly select and test blood spots from the 2007, 2008, and 2009 birth cohorts. These cohorts were selected because they were available for testing.

Report Objectives: This report presents a statistical review of laboratory results provided by the UPHL to the EEP for newborn blood spot testing for mercury. The primary purpose of this review is to develop an understanding of the geographic distribution of epidemiologic risk associated with EBML among the newborn population in Utah. A secondary purpose is to consider the utility of blood spot biomonitoring for conducting prospective blood mercury surveillance.

Authority and Funding: This study was conducted as part of the UDOH Executive Director's responsibility to investigate public health concerns within Utah. The executive director delegates responsibility for environmental health investigations to the EEP. Biomonitoring, population, and geographic data for this investigation are collected, maintained, and made available by the UEPHTN. The UEPHTN also funds the SAS® and ArcGIS® analytical software application licenses that were used to conduct this investigation. The UEPHTN is funded by a grant from the CDC (UEPHTN 2013). Personnel time used to conduct this investigation was charged against state-funded Environmental Health Administrative funds.

Institutional Review Board: This investigation was reviewed and approved by the UDOH Institutional Review Board (IRB) on March 20, 2007 (IRB #151) for analysis of the 2007 birth cohort. An additional IRB approved an expansion of the project to include samples from the 2008 and 2009 birth cohorts issued on January 11, 2012 (IRB #330). The purpose of this investigation was to gain an understanding of the geographic distribution of BML and to explore the feasibility of using blood spots as a convenience sample for blood cadmium surveillance. The study protocol presented to the IRB did not allow the UPHL or EEP to have identifiable data for the infants whose blood spots were used in this investigation, nor did the study protocol include procedures for informing caretakers of infants with EBML about the laboratory findings. The use of blood spots for this kind of surveillance is new and information about the reliability of the results and the use of those results in guiding patient care and treatment is known.

DATA AND METHODS

Study Design: This investigation is a retrospective statistical review of biomonitoring results for neonatal BML among Utah newborns. However, statistical reviews lack the power to link EBML incidence to putative risk factors (Jekel et al. 1996; Mann 2003). A statistical review is a tool used by the EEP to better understand the health status of a population, identify priorities for public health action, and assess public health activities.

This investigation funded testing of randomly selected blood spot cards by the UPHL for the biomonitoring of infants born in Utah. The Newborn Screening Program (NSP) maintains custody of all blood spots submitted to the UPHL and randomly selected 6,068 cards from the 2007, 2008, and 2009 birth year cohorts. These cards represent 3.70% of the total number (163,869) of children born in Utah during those years. This sample size is the result of funding and not based on the expected prevalence or a sample size and power calculation. After UPHL analyzed the cards for heavy metals, the results were submitted to the EEP for statistical analysis. The EEP evaluated the quality of the results and analyzed the data by county of residence.

Blood Spot Analysis: A detailed description is contained in the "Description of Laboratory Methodology" section later in this report. Briefly, two paper punches, called "dots" were taken; one from the blood spot area and one from the blood-free area of each blood spot specimen card. The blood-free area punches were used to determine the level of heavy metal contamination on the paper.

Heavy metals from each dot were extracted using an acid digestion, and the clarified extract was analyzed for mercury by inductively coupled plasma mass spectrometry (ICP-MS) (Chaudhuri et al. 2009).

Vital Records Birth Data: Vital records birth data were obtained from the Office of Vital Records and Statistics, UDOH. These data are standardized and made available through the UEPHTN (UEPHTN 2013). Vital birth records were used to quantify the total births occurring in Utah by county for the 2007 through 2009 study period. Records of birth with maternal addresses outside of Utah or of undetermined sex were excluded from the tabulation.

Blood Spot Sampling Data: Six thousand and sixty-eight (6,068) samples were randomly drawn from newborn blood spots collected from Utah children born during 2007, 2008, and 2009, and were analyzed for whole-blood total mercury. Data regarding the child's sex and mother's residential ZIP code were obtained from the NSP. When the UPHL received the cards, they were given an additional sample identification number specific to this project. The EEP was provided with only de-identified data that consisted of the project-specific sample identification number, and the child's birth year, sex, and ZIP code information. Two thousand nine hundred and thirty-seven (2,937; 48.5%) blood spot samples were from female infants and 3,124 (51.5%) samples were from male infants. Seven samples did not identify a sex, and five samples were missing birth year data. The analytical results for 6,032 samples were geo-referenced to the mother's county of residency using the ZIP code provided on the accession form. Thirty-six samples lacked a ZIP code and could not be geo-referenced to a Utah county. One of the samples missing

a ZIP code also was missing the birth year. In total 47 samples were missing the sex, birth year, and/or a valid Utah ZIP code and were excluded from the final analysis.

An infant's BML was calculated as the difference between the level of mercury measured in the blood spot minus the mercury level for the paper blank from the same blood spot card (Funk et a. 2013). The UPHL reporting limit for total mercury was 0.71 µg/L. UPHL data for the first year of this investigation used the "<0.71" code for blood mercury levels that were below the reporting limit. The UPHL reported the actual measurements for the second and third year. Because of this reporting discrepancy, tests that were reported with a measure or code indicating the measured value was below the reporting limit were set to 0.502 µg/L. This value is derived from the reporting limit divided by the square root of two (0.71 / √2) (Finkelstein and Verma 2001; Hornung and Reed 1990; Taylor 1987).

Six hundred and fifty-eight (658) cards (11% of the cards) were tested multiple times as part of the laboratory quality control process or to confirm elevated results. The average difference between the lowest and highest calculated mercury levels from a single card was 0.52 µg/L (standard deviation [SD] = 1.93 µg/L, maximum = 38.9 µg/L).

Cards with a paper blank mercury level higher than the blood spot mercury level, resulting in a negative value calculated BML, were not included in the final analysis. The lowest positive calculated BML for cards with multiple tests was used for the final analysis. After exclusion of cards for missing administrative data or for negative calculated BMLs, samples for 5,915 children with positive calculated BMLs were evaluated.

Data from two different funding cycles, the 2009 cycle and the 2012 cycle, were used for this pilot project. During the time between the cycles, changes occurred in UPHL staff and equipment used in this project. Before combining the data of the two funding cycles, it was necessary to ensure that there were not cycle-specific differences in the testing of samples and reporting of results that would invalidate the analytical results derived from combined data sets. The t-test was used to determine if the calculated BMLs for the 2009 and the 2012 funding cycles were done by the same laboratory testing and reporting methodology. The calculated BMLs were not normally distributed. The calculated Anderson-Darling test A2 value of 1,684 is well above the 99% critical value of 1.092, therefore, the log transformation of the calculated BMLs was used for the t-test. The variances of the data for the two funding cycles were not equal (the funding cycle 2009 mean was -0.38 for the log transformed calculated mercury levels, SD = 0.91; and the funding cycle 2012 mean was -0.41, SD = 0.80; tests for the equality of variance = 1.32 with 2,275 degrees of freedom, and the p-value for accepting the hypothesis of equal variance [the null-hypothesis] was <0.0001). The Satterthwaite t-test for unequal variance showed that the two sampling periods likely used the same testing and reporting methodology (t-value = 1.10, p-value = 0.27). Based on these results, the data from the sampling cycles were pooled for the final analysis.

The t-test was also used to determine whether there were differences in the calculated BMLs between female and male children. The mean of the log-transformed mercury levels was -0.39 (SD = 0.88) for females and -0.39 (SD = 0.87) for males. The test for equality of variance (F = 1.02 with 1,735 degrees of freedom, and the p-value = 0.72) suggested that the variance between

female and male results were not statistically different. The pooled t-test suggested that there was no difference in the distribution of calculated BMLs for females and males (t-value = 0.01 with 3,560 degrees of freedom, and the p-value of the null hypothesis = 0.99). Therefore, the results of female and male children were pooled for the final analysis.

Data Analysis: After aggregating by sex, birth cohort, county and state groupings, the geometric mean and highest computed mercury level were used to summarize the data. The geometric mean is the preferred measure of central tendency, when the data are highly skewed toward and bounded by zero. The number of children born with mercury levels above the current EPA RfD for elevated blood mercury (5.8 µg/L) was tabulated.

FINDINGS

For the 5,915 Utah newborns included in the final analysis for this investigation, the geometric mean BML was 0.79 µg/L (standard deviation = 3.13 µg/L, range = 0.00 to 381.62 µg/L). These 5,915 children represent approximately 3.6% of the 163,869 children born in Utah between 2007 and 2009. The geometric mean and maximum BMLs tabulated by sex, birth year, and county are presented in Tables 1, 2, and 3, respectively. The county was determined by the maternal residential address at the time of birth. There is no available information about the residential tenure of the mothers.

One sample had a measured BML of 381.62 µg/L and two additional samples had BML greater than 90 µg/L. The fourth highest level was 16.68 µg/L. The measurements of the three samples with extreme EBML were verified by reanalysis. Without a confirmatory test using venous blood it is difficult to say what the actual BML is for those three children.

Thirty-eight (38) newborns were identified with EBMLs ≥ 5.8 µg/L. Based on this count, the rate of children with EBMLs would be approximately 6.42 children per 1,000 births using the current EPA RfD. Utah has approximately 53,000 births per year based on the number of births per year between 2007 and 2012 (UDOH 2013). These findings suggest that approximately 340 children could be born each year with EBMLs ≥ 5.8 µg/L. However, this testing methodology was not validated with a gold standard screening method, and no conclusions should be made that lead to a public health action or policy change, based on these results.

Validation of the blood spot results using paired venous blood samples from the infants would be necessary to assess the epidemiologic performance measures (specificity, sensitivity, and predictive values) used in evaluating screening methodology. Because this project relied on the availability of stored blood spots, this was not possible. Therefore the true specificity and sensitivity of the blood spot testing methodology cannot be determined. The UPHL has a policy that when an elevated mercury value is detected, the sample is automatically confirmed by analysis of a replicate punch from the same blood spot. In this study, 11% of the cards (658 of 6,088 cards) were reanalyzed to confirm high mercury concentrations. By categorizing the relationship of the lowest and highest positive test value with respect to whether the child represented by the card had an EBML (≥5.8 µg/L), the specificity was estimated to be 97% and the predictive value positive was estimated to be 55%. The sensitivity could not be estimated

using this approach (German 2000). The mean difference between the lowest and highest test for the cards was 15.0 µg/L (maximum difference = 1,411.7 µg/L, standard deviation = 69.2 µg/L). This estimation of epidemiologic predictive value positive was low indicating that the testing methodology does not perform well as a surveillance tool.

County data are presented geographically in Figure 1 and Table 3. The distributions of samples taken represented between 1.9% (Duchesne County) and 22.0% (Grand County) of the children born per county during the project sampling period. The geometric mean ranged between 0.45 µg/L (Garfield County) and 1.07 µg/L (Kane County). No summary statistics were computed for Daggett County because only two samples were from that county. Elevated mercury levels were found among the children of eight counties: Cache, Davis, Iron, Salt Lake, Tooele, Utah, Washington, and Weber. The highest level found was 381.62 µg/L in a child born in Utah County in 2007.

DISCUSSION

Public Health Surveillance (Why Do Bbiomonitoring?): Health is one of the most important assets a human being is given. It permits each person to fully develop their capacities thus allowing them to enjoy the highest quality of life. The mission of public health is to promote and protect people's health accomplished through ten essential public health services (Harrell and Baker 1994; IOM 1988). The first of these services is to "monitor health status to identify community health problems" (Stanbury et al. 2012). Public health surveillance is the systematic, ongoing, population-based collection of data that leads to early detection and response to public health concerns (Choi 1998; Thacker et al. 1996). This service helps public health officials and policymakers identify and assess communities with public health challenges; define public health priorities; develop and implement informed public health policy; monitor and evaluate public health actions; discover knowledge about public health concerns; and guide public health outreach, education, and intervention activities (Dicker 2002; Stanbury et al. 2012; Thacker 2000; Thacker et al. 2012). To conduct public health surveillance, environmental epidemiology collects data about environmental hazards, exposure, and adverse health outcomes (Malecki et al. 2008; Thacker et al. 1996).

Health outcomes (e.g., disease, disability, death, etc.) surveillance is the collection and registration of "cases." Ascertainment of cases is dependent on the willingness and timing of people seeking medical assistance and the capacity of health care to report conditions. This surveillance process has the advantage of involving the health care system, which is much larger and has more direct contact with people than public health agencies. The cost of health care registries varies depending on the level of active versus passive surveillance and the degree of additional data collection through abstraction or other linkages that occurs as part of the surveillance process. A drawback of health outcomes surveillance is that knowledge of cases is after the fact and the focus tends to be curative rather than preventive (Aldrich and Griffith 1993; Thacker et al. 1996).

Exposure surveillance, also called biomonitoring, is the monitoring of individual members of the population for the presence of an environmental agent or its subclinical or preclinical effects. Biomonitoring may occur in conjunction with health outcome surveillance (i.e., a child presents

with symptoms of EBML and is tested) or may occur by sampling otherwise healthy people (i.e., a child is tested as part of a screening requirement) (Albertini et al. 2006; Angerer et al. 2007; Thacker et al. 1996). Sampling usually involves collection of biological specimens (blood, urine, milk, saliva, hair, adipose, or other tissues) during a health care event (i.e., a routine physical) or through soliciting volunteers (Farmer et al. 1996; Needham et al. 2007). Biomonitoring has proven to be more costly and more difficult than health outcome or hazards surveillance. Hazards surveillance is the identification and characterization of environmental sources of hazardous material such as mercury (i.e., factories that discharge mercury into the atmosphere, etc.). Because of the cost and difficulty of obtaining samples, many investigations model exposure from hazards surveillance data rather than conducting exposure surveillance (Angerer et al. 2007). An advantage of biomonitoring is that these data provide a better understanding of exposure in the diseased and healthy populations. This concept is important in understanding thresholds (i.e., a dose-response curve) that contribute to the development, progression, and disposition of associated adverse health outcomes (Albertini et al. 2006; Angerer et al. 2007; Farmer et al. 1996, Needham et al. 2007).

One way to overcome sampling difficulties for biomonitoring is the use of samples collected for other purposes (Albertini et al. 2006). Blood spots, usually collected to look for a variety of adverse genetic conditions in newborns, are an efficient and un-intrusive method to conduct heavy metal surveillance for that population (Olshan 2007).

Pilot Biomonitoring Project: One of the objectives for this project was to assess the feasibility of using blood spots as a mechanism for conducting public health surveillance for EBMLs in Utah newborn children (Funk et al. 2013; Olshan 2007).

The value of a public health surveillance system can be assessed by understanding the usability of the information derived through surveillance and the reliability and efficacy of the surveillance methodology. The usefulness of the information can be evaluated by understanding its scientific basis, relevance, and ability to be translated into public health actions or policy (Malecki et al. 2008). Analytical soundness is usually measured by statistical comparisons of the surveillance methodology with a gold standard in terms of sensitivity, specificity, and predictive value positive (German 2000).

The UPHL used commercially prepared venous blood containing a standardized concentration of mercury (i.e., standard reference material) to spike blank blood spot papers that were included with each batch of newborn blood spots to assure quality of the laboratory analyses. Because the UPHL used commercially available standard reference material with known mercury levels that was spiked on to filter paper and included those spiked filter papers as part of the quality control, there is certainty about the ability of the UPHL to accurately and consistently test blood spots (Chaudhuri et al. 2009). In addition, the UPHL successfully participated in the Wisconsin State Laboratory of Hygiene proficiency testing program for filter paper blood mercury testing during the duration of this study, further demonstrating the utility and accuracy of the laboratory analytical method.

The laboratory specificity and sensitivity is the ability to accurately quantify the level of mercury from the same blood spot punch demonstrated by multiple tests of that sample. Epidemiologists

also use tests of specificity, sensitivity, and predictive value positive to quantify how well laboratory results correctly identify people with EBMLs and increased risk for adverse health outcomes. The data necessary to quantify the true epidemiology specificity, sensitivity, and predictive value positive for this testing methodology was not available. Instead, the EEP used the test results for those samples where two or more different punches from the same card were analyzed. Using those data, the specificity was estimated to be 97%, which is an acceptable level. However, the predictive value positive was estimated to be 55%. This level suggests that the use of blood spots may not perform well as a screening test for children born with EBMLs. To know for certain, a different kind of study would need to be conducted that allowed the matching of blood spot results to serological tests for mercury and to the children's health status.

Typically, a surveillance system would be founded on one or more surveillance objectives, such as quantifying and characterizing the magnitude of public health concerns in a population at risk; obtaining increased understanding of the epidemiology of a public health concern; empowering sound preventive or mitigating public health actions and policies; and evaluating those actions or policies. Justification for conducting surveillance requires balancing the costs, the collection of personal information, and the legal concerns against needs and strengths of the surveillance objectives. An effective surveillance system typically links laboratory analysis with additional data (Sneider and Stroup 2000; Stanbury et al. 2012; Teutsch 2000; Thacker et al. 1996; Thacker and Birkhead 2002).

This report presents data that attempt to quantify the magnitude of elevated blood mercury in newborn children. However, there is insufficient data to fully characterize the health concern or understand the epidemiology involved with respect to probable risk factors. To be useful, these data would have to be linked to other data collected about the mother and her pregnancy. For example, it would be important to know what the historical and current exposures to mercury are for the mother, and whether any of the current exposures can be mitigated.

Currently, there is no guidance on the testing and treatment of infants for blood mercury, and there are few treatment options for newborns with EBMLs. Those options, such as chelation therapy, result in other health concerns and need to be used selectively (Bernhoft 2012; Nuttall 2004). Preventive interventions, such as better choices regarding fish consumption, hand washing behaviors, and avoiding the use of mercury-containing products, may reduce the mother's BMLs and thus fetal exposure (Bose-O'Reilly et al. 2010).

The findings of this investigation suggest that as many as 340 children could be born each year in Utah with EBMLs (≥5.8 µg/L). However, this finding is based on a testing methodology that has not been validated and does not appear to have good predictive power. Currently, Utah does not have a policy regarding screening for women of childbearing age for blood mercury. While the results of this investigation are informative about the spatial distribution of the blood mercury levels in Utah children, these results do not indicate a need to establish an adult screening policy. The geometric mean BML was found to be 0.79 µg/L which is consistent to the national geometric mean BML level (also 0.79 µg/L) (CDC 2014). Adult testing and treatment should be guided by a clinical presentation that suggests a need (Bernhoft 2012; Nuttall 2004).

This pilot project used de-identified data to examine the efficacy of using blood spots as a means of conducting noninvasive blood mercury screening among newly born children in Utah. Because the children were not identified, the results for the 38 children with EBMLs were not reported to the health care provider or guardians of those children.

Methodology Limitations: The public often wants public health investigations to determine whether health risks can be linked to a putative environmental concern. The methods used in this investigation do not have the capability to definitively link the findings of elevated neonatal blood mercury exposure risk to any inherent or external risk factors, including environmental exposures. This kind of investigation is sometimes referred to as a "snapshot," and presents data about the health status of newly born children in Utah during the 2007-2009 time period. A concern with "snapshot" investigations is that the data in this report may be used to generate inferences leading to public health policy or action based on this single assessment. The environmental risks associated with those counties where significant results were found should be assessed before any change to public health policy or program actions are made regarding mercury poisoning in children (Meliker and Sloan 2011).

An investigation that uses population-based summary data rather than individual-level data, such as the investigation presented in this report, is called an ecologic study by epidemiologists. An interpretation error commonly associated with ecologic studies is to apply population-level risk findings to the individual. This kind of interpretation error is called an "ecologic fallacy." For example, this study found the statewide risk for elevated blood mercury among neonates was 6.42 per 1,000 births. This risk metric should not be applied to individuals. An individual may have no risk or a risk several times higher than the overall statewide risk (Greenland 2001; Greenland and Robins 1994; Morgenstern 1982, 1995; Rockhill 2005).

CONCLUSIONS AND RECOMMENDATIONS

This report provides a description and findings of a pilot surveillance project using newborn blood spots as a possible sampling media to conduct surveillance for heavy metal exposure. EBMLs in the developing fetus or newborn child can cause a number of adverse health effects, including harm to neurological and hematological development. There is no level of blood mercury that is considered safe. This study found that approximately 6.42 newborns per 1,000 live births, or as many as 340 children per year (where the 2007-2012 average birth year cohort is 53,000 births), may have EBMLs at birth. However, this estimation is based on a testing methodology that has not been validated and statistical indications of performance were less than ideal. Utah does not currently have a policy regarding screening for women of childbearing age for mercury exposure. The EEP does not recommend establishing a policy.

Before neonatal blood spots can be used as a routine screening media, additional work would be needed to determine and improve the sensitivity, specificity, and predictive value positive of the testing methodology. BML results using newborn blood spot samples would need to be validated using venous blood from the same newborn. In addition, prior to any decision on whether to or how to implement this testing methodology as part of Utah's routine public health surveillance

activities, consideration with respect to the need for routine blood mercury surveillance in newborns, cost, alternative methods, and case follow-up should occur.

AUTHORSHIP, REVIEW AND CITATION

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CERTIFICATION

This report titled "Utah Statewide Investigation of Neonatal Blood Mercury Levels Using Newborn Blood Spot Specimens" was prepared by the Environmental Epidemiology Program, Utah Department of Health. This report describes the findings of a pilot surveillance project using newborn blood spots as a medium for conducting blood mercury surveillance. Editorial and technical review was completed by UDOH certifying reviewers and program partners.

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Web links for citations of government or organizational websites may wrap onto multiple lines.

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TABLES AND FIGURES

TABLE 1. Summary of Utah neonatal blood mercury levels by sex for children born between 2007 and 2009.

Sex	Total Births Statewide	Samples Tested	Geometric Mean Blood Mercury Level µg/L	Highest Observed Blood Mercury Level µg/L	Number Tests with Blood Mercury Levels Greater than 5.8 µg/L
Female	79,813	2,879	0.79	97.0	15
Male	84,056	3,036	0.79	381.6	23
Both	163,869	5,915	0.79	381.6	38

TABLE 2. Summary of Utah neonatal blood mercury levels by year for children born between 2007 and 2009.

Year	Total Births Statewide	Samples Tested	Geometric Mean Blood Mercury Level µg/L	Highest Observed Blood Mercury Level µg/L	Number Tests with Blood Mercury Levels Greater than 5.8 µg/L
2007	54,773	2,440	0.82	381.6	19
2008	55,346	828	0.63	13.8	12
2009	53,750	2,647	0.82	12.7	7

FIGURE 1. Geometric mean blood mercury levels by county in Utah among children born between 2007 and 2009. “C” is the number of newborn children tested in each county. “GM” is the geometric mean blood mercury level in µg/L. These findings are based on maternal residential address at the time of birth.

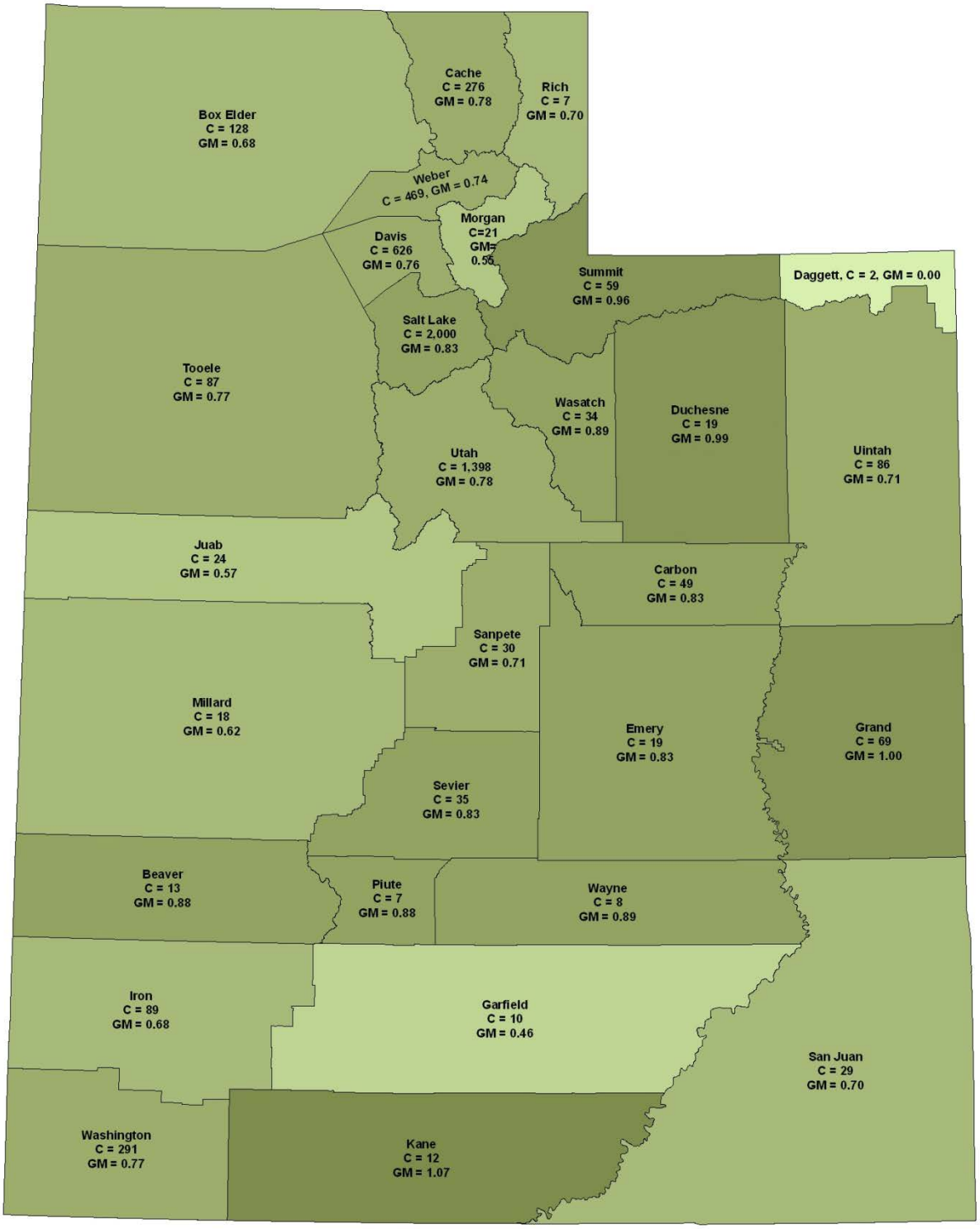

TABLE 3. Summary of Utah neonatal blood mercury levels by county for children born between 2007 and 2009. These data are based on the maternal residential address at the time of birth.

County	Total Births Statewide	Samples Tested	Geometric Mean Blood Mercury Level µg/L	Highest Observed Blood Mercury Level µg/L	Number Tests with Blood Mercury Levels Greater than 5.8 µg/L
Beaver	383	13	0.88	3.2	0
Box Elder	2,915	128	0.68	2.4	0
Cache	7,417	276	0.78	16.7	5
Carbon	967	49	0.83	3.0	0
Daggett	35	2			
Davis	18,367	626	0.76	12.7	2
Duchesne	982	19	0.99	4.5	0
Emery	576	19	0.83	2.9	0
Garfield	188	10	0.46	0.8	0
Grand	314	69	1.00	4.3	0
Iron	2,842	89	0.68	13.0	2
Juab	701	24	0.57	1.7	0
Kane	247	12	1.07	3.9	0
Millard	634	18	0.62	1.5	0
Morgan	554	21	0.55	1.2	0
Piute	67	7	0.88	0.4	0
Rich	106	7	0.70	1.1	0
Salt Lake	57,681	2,000	0.83	11.2	17
San Juan	540	29	0.70	2.0	0
Sanpete	1,181	30	0.71	1.5	0
Sevier	1,057	35	0.83	1.9	0
Summit	1,591	59	0.96	4.6	0
Tooele	3,198	87	0.77	9.8	1
Uintah	2,293	86	0.71	4.6	0
Utah	36,918	1,398	0.78	381.6	9
Wasatch	1,312	34	0.89	2.3	0
Washington	7,846	291	0.77	9.1	1
Wayne	108	8	0.89	2.7	0
Weber	12,849	469	0.74	8.6	1

DEFINITIONS

ArcGIS: A computer application that provides mapping and spatial analysis of spatially referenced data. ArcGIS is a product developed and available through ESRI. For more information see: http://www.esri.com or http://www.arcgis.com.

Biomonitoring: A way of measuring which substances humans have been exposed to and the level of exposure to those compounds, through analysis of body fluids (e.g., saliva, urine, or blood, etc.) or tissues (e.g., epithelial cells obtained by swabbing the mouth, or hair, or nail clippings, etc.) for those compounds or metabolites of those compounds.

Blood Spots: Drops of blood placed on a filter card and dried. Blood spot cards are prepared for infants by sampling the blood obtained by a heel stick.

BML: Blood mercury level. The amount of mercury in the blood, quantified as micrograms of mercury per liter of blood (µg/L). Blood mercury levels greater than or equal to 5.8 µg/L are considered elevated based on the current EPA reference dose.

CDC: Centers for Disease Control and Prevention. A federal agency within the U.S. Department of Health and Human Services responsible for investigating disease trends and causalities, and promoting best disease prevention practices. For more information see: http://www.cdc.gov/.

EBML: Elevated blood mercury levels. Blood mercury levels greater than or equal to 5.8 µg/L are considered elevated based on the current EPA reference dose.

EEP: Environmental Epidemiology Program. A program within the Bureau of Epidemiology, Division of Disease Control and Prevention, UDOH. The EEP was established in 1996 and is responsible for investigating diseases related to the environment. The program has two sections. One section conducts surveillance and data management activities, including managing the UEPHTN. The other section conducts health hazards risk assessment, including cancer investigations. The program is staffed by personnel with experience and expertise in environmental epidemiology, environmental sciences, toxicology, statistics, public health informatics and geomatics, and health education. For more information see: http://health.utah.gov/enviroepi/.

EPA: U.S. Environmental Protection Agency. The EPA is responsible for investigating environmental pollution and health hazards. For more information see: http://www.epa.gov/.

ESRI: ESRI (formally known as Environmental Systems Research Institute) is a leading developer and supplier of GIS software and geographically referenced data. ESRI is headquartered in Redlands, California. The EEP uses the ArcGIS software application developed by ESRI. For more information see: http://www.esri.com.

Geometric mean: A type of average or measurement of central tendency that uses the products of a set of numbers rather than the summation. The geometric mean of a data set $\{a_1, a_2, ..., a_n\}$ is given by $(\Pi a_i)^{1/n}$. The geometric mean is used to describe the average of blood mercury levels because the distribution of values in the data set is skewed towards zero, and no value can be less than zero.

GIS: Geographic Information Systems. A GIS includes computer software and geographically referenced data. The EEP uses ArcGIS as the computer software and obtains data from ESRI or AGRC.

ICP-MS: Inductively coupled plasma mass spectrometry. This is a laboratory methodology that is able to separate and quantify the amount of atoms or compounds present in a solution based on the mass of those atoms or compounds.

RMBC: Rocky Mountain Biomonitoring Consortium. The RMBC was a CDC-funded collaboration of the state laboratories of Arizona, Colorado, Montana, New Mexico, Utah, and Wyoming. The New Mexico Scientific Laboratory served as the grant coordinating laboratory and distributed funds from CDC to the other states within the consortium. Each state laboratory developed one or more biomonitoring analytical capabilities that could serve the needs of all of the states biomonitoring needs. Utah developed methodology for blood spot testing for heavy metals.

SAS: SAS (originally from "Statistical Analysis System") is a globally recognized system of integrated computer software products provided by SAS Institute Inc. The SAS system includes a large variety of data manipulation and statistical analysis processes. The EEP uses the desktop version 9.2. For more information see: http://www.sas.com.

UDOH: Utah Department of Health. The UDOH is one of the executive agencies within Utah state government. The UDOH strives to improve health in Utah by promoting healthy lifestyles, evidence-based interventions, creating healthy and safe communities, and eliminating health disparities. The EEP is a program within the UDOH. For more information, see: http://health.utah.gov/.

UEPHTN: Utah Environmental Public Health Tracking Network. The UEPHTN is a data warehouse that contains health outcomes, environmental, and supporting data. For more information see: http://epht.health.utah.gov/epht-view/.

µg/L: Micrograms per liter. A microgram is one millionth of a gram.

UPHL: Utah Public Health Laboratory. A part of the Unified State Laboratories. The UPHL provides laboratory support to other state agencies and to the public. For more information, see: http://health.utah.gov/lab/index.html.

DESCRIPTION OF THE LABORATORY METHODLOGY

Preparation of Samples and Internal Blanks: Filter paper punches, each ¼ inch (6.35 mm) in diameter, were punched from cards containing newborn dried blood spots directly into 15 mL polypropylene tubes (Stockwell Scientific #3220N, Scottsdale, Arizona). Two sets of dots (in duplicate) were punched. The first set was comprised of two dots from the card adjacent to the newborn's blood sample spots and is defined as the internal blank. The internal blank dots were assumed to have been exposed to the same environmental conditions as the actual blood samples and hence are utilized to assess extraneous environmental contamination from the hospital, contamination during transit to the laboratory, storage contamination, and contamination during laboratory handling. The second set of dots was comprised of two dots punched directly from the dried blood spots. An empty 15 mL polypropylene tube from the same lot as the other tubes was utilized as a control tube. This "blank" tube was filled with the same extraction solution as the tubes containing the actual samples and carried throughout the entire extraction procedure to assess contamination from the actual procedure.

The dots were extracted with a 2% hydrochloric acid solution (GFS Chemicals®, Columbus, Ohio) containing 0.05% 2-mercaptoethanol (Acros Organics, Thermo Fisher Scientific #12547-2500), 0.001% l-cysteine (Fluka, Milwaukee, Wisconsin), and 10 µg/L iridium and rhodium (Spex Industries Inc., Edison, New Jersey). The latter two elements served as internal standards. 1.5 mL of the extraction solution was added to each tube and then vortexed for 15 minutes. The tubes were then allowed to stand overnight (about 16-18 hours), then vortexed for another 15 minutes, and lastly, centrifuged for 5 minutes at 5,000 RPM in an Eppendorf 5804 centrifuge (Brinkman Instruments, Inc., Westbury New York). The tubes were then placed into the autosampler of the inductive coupled plasma mass spectrometer (ICP-MS) for analysis.

Quality Control and Quality Assurance: With each batch of blood spot samples (typically ten spots), the following quality control samples were analyzed at a minimum: a set of calibration standards; a blank control (negative) to assure the system is free of contamination from previous analyses; a positive control using commercially prepared standard reference material (SRM) to assess accuracy; and a set of duplicate samples to assess precision. The SRM samples were prepared from a freeze-dried human whole blood toxicology control (whole blood control lot 7984 and 8083) that were custom made for low level mercury and other heavy metals by Utak Laboratories, Inc. (Valencia, California). The material had a known, verified mean mercury concentration and an expected analytical range. The material was reconstituted by adding 3 mL of 18 mega ohm water with a volumetric pipette. The mixture was gently swirled for 5-10 minutes then allowed to stand for 1 hour for equilibration and subsequent warming to room temperature. The reconstituted blood was then spotted drop-wise with a Pasture pipette onto S&S (Keene, New Hampshire) 903, lot W011 filter paper. The blood was added until the dotted, printed circle was filled, which corresponds to a total blood volume of about 75 µL (CLSI 2007). This has also been calibrated during the present study. The spotted filter paper cards were dried

for several hours then placed in TearZone Safeguard Specimen bags, stored under refrigerated conditions, and analyzed in the same manner as patient samples.

The calibration curve was constructed using aqueous-based samples and calculated using ordinary linear regression methods. Weighting was not used and the intercepts were not forced through the origin.

Additional quality assurance was demonstrated by the UPHL's participation in the Wisconsin State Laboratory of Hygiene proficiency test program for filter paper blood analysis during the duration of this study. Every testing event was passed.

Analyis: The samples were analyzed utilizing ICP-MS. An Elan DRC II ICP-MS machine (PerkinElmer, Shelton, Connecticut) equipped with a Meinhard nebulizer and a quartz cyclonic spray chamber was used to make these readings. The dynamic reaction cell (DRC) was not utilized for this work. For mercury, the three isotopes scanned and summed were m/z 202, 200 and 199. Arithmetic isobaric correction equations were utilized and two replicate readings were taken for each m/z.

For a more detailed description of the methods briefly described here, see Chaudhuri et al. 2009.