BIOMONITORING STUDY

Utah Statewide Investigation of Neonatal Blood Cadmium 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

Cadmium 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. Pregnant women and newborns are not routinely screened. Elevated blood cadmium 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 cadmium in newborn infants. Two thousand, seven hundred and six (2,706) randomly selected blood spot cards submitted to the Utah Public Health Laboratory for the 2009 birth cohort were analyzed for blood cadmium 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 cadmium 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 cadmium in the blood spot and the amount of cadmium in the blood-free area of the card was considered to be the child's blood cadmium level. After rejecting results for administrative recording errors or because the blood-free area of the card was contaminated with more cadmium than the blood spot (resulting in a negative value difference), the results for 1,404 Utah newborns were aggregated and evaluated at the county level. The geometric mean for the state was 0.10 µg/L (maximum = 8.64 µg/L). Two children were found to have blood cadmium levels $\geq$ 5.00 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 cadmium 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 Cadmium? Cadmium ($_{48}$Cd) is a transition metal similar to zinc and mercury. Cadmium makes up about 0.1 ppm of the Earth's crust, and is found naturally in small quantities in air, water, and soil. In water, cadmium tends to sequester into the sediment layers under bodies of water. Because of its geochemical similarities, cadmium is often associated with zinc, lead, and copper ores. As a consequence, cadmium is produced mainly as a byproduct from mining, smelting, and refining sulfidic ores of zinc, and, to a lesser degree, lead and copper. The most common and industrially important form of natural cadmium is greenockite (CdS), which is nearly always associated with sphalerite (ZnS) (ATSDR 2012; EPA 2000; IPCS 2010).

Cadmium has many common industrial uses. The most important is in the nickel-cadmium rechargeable battery. Cadmium is used also to manufacture other electronic components, cadmium-based pigments and coatings, stabilizers in plastic production, and is commonly used in electroplating as an anti-corrosion agent (ATSDR 2012; EPA 2000; ICA 2014; IPCS 2010; Jarup 2003).

There is no significant recycling program for cadmium, and cadmium is released into the environment by incineration of household or industrial wastes, coal, and petroleum fuels. The smelting of zinc, lead, and copper ore also releases cadmium into the environment. Higher levels of cadmium are often found in surface soils and waters near smelters, incinerators, industrial areas, and hazardous waste sites. More than a third of all the superfund sites in the United States are contaminated with cadmium (ATSDR 2012; EPA 2000; ICA 2014; IPCS 2010).

Cadmium Exposure: Cigarette smoking is considered the most significant source of exposure for cadmium. Inhalation due to industrial emissions can be a significant exposure route for people who live in close proximity to the sources. Cadmium exposure may also occur as a result of ingesting contaminated food or water. Because of the high rates of soil-to-plant transfer, cadmium is a contaminant found in most plant-based foods. Thus diet is the most important source for cadmium exposure among non-smokers. Some dietary supplements are known to be a source (Bernhoft 2013; Bertin & Averbeck 2006; IPCS 2010; Guan et al. 2010; Hinwood et al. 2013; Jarup 2003; Satarug & Moore 2004; Satarug et al. 2009; Thompson et al. 2008).

Cadmium sequesters in the liver and kidney and has a 25-year half-life. Cadmium in the blood has a 75-day half-life on average. For adults, blood is not considered a good biological medium for measuring acute cadmium exposure (Bernhoft 2013).

Cadmium Toxicity: The toxicity of acute high-dose exposure to cadmium has been known since 1858 (Norberg 2009). Low-level chronic exposure to cadmium was found to be associated with a painful condition known as Itai-itai disease in Japan in 1957 (Bertin & Averbeck 2006; Norberg 2009).

Cadmium induces tissue damage through oxidative stress, leading to epigenetic changes in DNA expression and cellular and physiologic dysfunction (Bernhoft 2013; Bertin & Averbeck 2006; Filipic 2012; Fowler 2009; IPCS 2010; Jarup 2003; Joseph 2009; Mendez-Armenta & Rios 2007; Norberg 2009; Satarug & Moore 2004; Waisberg et al. 2003). Cadmium also interferes

with DNA repair (Bertin & Averbeck 2006; Filipic 2012; Giaginis et al. 2006; Waisberg et al. 2003). These two mechanisms of harm form the basis for cadmium toxicity and carcinogenicity. Because cadmium in the blood sequesters into kidney tissue, cadmium is particularly toxic to the kidneys. Other systems affected by cadmium toxicity include the neurologic system, the cardiovascular system, the immune system, the reproductive system, and bone tissue (Bernhoft 2013; Bertin & Averbeck 2006; Filipic 2012; Fowler 2009; IPCS 2010; Jarup 2003; Mendez-Armenta & Rios 2007; Norberg 2009; Satarug & Moore 2004; Thompson et al. 2008). Cadmium exposure is a known risk factor for developing insulin resistance (Bernhoft 2013). Exposure to cadmium in men has been shown to decrease lung function (Oh et al. 2014).

Children with low-level environmental cadmium exposure may have a higher risk for attention deficit hyperactivity disorder (ADHD) and learning disabilities (Ciesielski et al. 2012; Wang & Du 2013). However, not all researchers were able to find this effect (Kim et al. 2013). Female children have a higher risk for learning disabilities from cadmium exposure than male children (Llop et al. 2013).

Cadmium is considered to be carcinogenic and is linked to breast, prostate, renal, lung, and pancreatic cancers, as well as non-Hodgkin lymphoma (Bernhoft 2013; Flowler 2009; Guan et al. 2010; IARC 1993; Jarup 2003; Joseph 2009; Satarug & Moore 2004; Waalkes 2003; Waisberg et al. 2003).

Maternal and Fetal Cadmium Exposure: Cadmium affects both maternal and fetal health (Hinwood et al. 2013). Maternal exposure to cadmium results in bioaccumulation of cadmium in the placenta tissue. The level of cadmium in the placenta can be several times higher than the maternal blood cadmium level (Esteban-Vasallo et al. 2012; Kippler et al. 2010; Kuhnert et al. 1982; Lin et al. 2010). The placenta acts as a partial barrier to fetal exposure to cadmium from the mother (Caserta et al. 2013; Esteban-Vasallo et al. 2012; Garcia-Esquinas et al. 2013; Gundacker & Hengstschlager 2012; Lauwerys et al. 1978; Lin et al. 2010).

Placental cadmium interrupts the transportation of micronutrients to the fetus, resulting in delayed fetal development and low birth weight (Casterta et al. 2013; Garcia-Esquinas et al. 2013; Gundacker & Hengstschlager 2012; Kippler et al. 2010; Lin et al. 2010; Menai et al. 2012; Ronco et al. 2009; Sun et al. 2014; Thompson et al. 2008). Cadmium can act as a metalloestrogen and an endocrine disrupter that deregulates fetal development (Henson et al. 2004; Kawai et al. 2002; Stasenko et al. 2010; Thompson et al. 2008). The effects of perinatal developmental delays can persist for the first several years of the child's life (Lin et al. 2010). Cadmium has also been found to pass from nursing mothers to their infants in the breast milk (Satarug & Moore 2004).

There is a strong correlation between smoking and maternal blood cadmium levels, placental bioaccumulation of cadmium, and fetal cadmium levels. Smoking results in dramatic increases in the cadmium levels of the placenta and fetus. Maternal smoking cessation is the most important preventive action that can be taken to protect the fetus from exposure to cadmium (Esteban-Vasallo et al. 2012; Falcon et al. 2002; Garcia-Esquinas et al. 2013; Kuhnert et al. 1982; Kutlu et al. 2006; Menai et al. 2012; Sikorski et al. 1988; Sun et al. 2014; Thompson et al. 2008). Maternal cadmium levels are lowered by iron and folic acid nutritional supplement intake

(Hinwood et al. 2013). The appropriate intake of dietary iron will also help reduce blood cadmium levels in children (Silver et al. 2013).

Reference Dose and National Exposure Levels: The U.S. Environmental Protection Agency (EPA) has not established a reference dose (RfD) for cadmium (EPA 1987, 2000; Taylor et al. 2014). Without a reference dose it is not possible to establish an elevated blood cadmium level (EBCL) equivalent.

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 cadmium concentration among women of childbearing age was 0.38 µg/L (1.80 µg/L maximum) (CDC 2009; Sanders et al. 2012). Some countries have set RfD values from which a blood reference dose can be calculated (Al-Saleh et al. 2011; Taylor et al. 2014). For example, in Germany the equivalent RfD for blood is 0.50 µg/L (Al-Saleh et al. 2011; Wilhelm et al. 2006). The Agency for Toxic Substances and Disease Registry (ATSDR) uses the guidance set by the American Conference of Governmental Industrial Hygienists (ACGIH), which is 5.00 µg/L (ATSDR 2012). This value has also been used by other investigators in the United States (Garcia-Esquinas et al. 2013; McKelvey et al. 2007).

Rocky Mountain Biomonitoring Consortium and the Utah Environmental Public Health Tracking Network 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 for cadmium from the 2009 birth cohort. 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 cadmium. The primary purpose of this

review is to develop an understanding of the geographic distribution of epidemiologic risk associated with EBCL among the newborn population in Utah. A secondary purpose is to consider the utility of blood spot biomonitoring for conducting prospective blood cadmium 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 blood cadmium levels (BCL) 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 EBCL 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 BCL among Utah newborns. However, statistical reviews lack the power to link EBCL 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 biomonitoring of infants born in Utah by testing randomly selected blood spot cards by the UPHL. The Newborn Screening Program (NSP) maintains custody of all blood spots submitted to the UPHL and randomly selected 2,706 cards from the 2009 birth year cohort. These cards represent five percent of the total number (53,750) of children born in Utah during that year. 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 cadmium 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 during 2009. Records of birth with maternal addresses outside of Utah or of undetermined sex were excluded from the tabulation.

Blood Spot Sampling Data: Two thousand seven hundred and six (2,706) samples were randomly drawn from all newborn blood spots collected from Utah children born during 2009, and were analyzed for whole-blood total cadmium. 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. One thousand two hundred and ninety-three (1,293; 47.8%) blood spot samples were from female infants and 1,423 (52.2%) samples were from male infants. The analytical result for each sample was geo-referenced to the mother's county of residency using the ZIP code provided to the lab with the blood spot. Seventeen samples lacked a ZIP code and could not be geo-referenced to a Utah county. These samples were excluded from the final analysis.

Each infant's BCL was calculated as the difference between the cadmium level measured in the blood spot minus the cadmium level for the paper blank from the same blood spot card (Funk et al. 2013). Three hundred and forty-seven (347) cards (13% 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 cadmium levels from a single card was 0.78 µg/L (standard deviation [SD] = 3.69 µg/L, maximum difference = 52.30 µg/L).

Cards with a paper blank cadmium level higher than the blood spot cadmium level, resulting in a negative value calculated BCL, were not included in the final analysis. One thousand two hundred and eight-five (1,285; 47.5%) cards were excluded because the paper blank had a higher cadmium reading than the blood spot. The lowest positive calculated BCL for cards with multiple tests was used for the final analysis. The 1,302 (48.1%) cards excluded from final analysis included 17 cards missing administrative (ZIP code) data and 1,285 cards with negative calculated BCLs. After exclusion, 1,404 cards were analyzed for county level geometric mean BCL and for EBCL frequency.

The t-test was used to determine whether there were differences in the calculated BCLs between female and male children. The mean of the log-transformed cadmium levels was -2.24 (SD = 1.33) for females and -2.36 (SD = 1.30) for males. The test for equality of variance (F = 1.05 with 679 degrees of freedom, and the p-value = 0.53) suggested that the variances between female and male results were not statistically different. The pooled t-test suggested that there was no difference in the distribution of calculated BCLs for females and males (t-value = 1.71 with 1,393 degrees of freedom, and the p-value of the null hypothesis = 0.09). 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 cadmium 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. As discussed above, the number of children born with cadmium levels above the current ACGIH RfD for elevated blood cadmium (5.00 µg/L) was tabulated.

FINDINGS

For the 1,404 Utah newborns included in the final analysis of this investigation, the geometric mean BCL was 0.10 µg/L (range = 0.00 to 8.64 µg/L). These 1,404 children represent approximately 2.6% of the 53,750 children born in Utah in 2009. The geometric mean and maximum BCLs tabulated by sex and county are presented in **Tables 1** and **2**, respectively. The county was determined by the maternal residential ZIP code at the time of birth. There is no available information about the residential tenure of the mothers.

Two (2) newborns were identified with EBCLs ≥ 5.00 µg/L, with blood cadmium levels of 6.91 and 8.64 µg/L. These children were located in Duchesne and Grand counties. Based on this count, the rate of children with EBCLs would be approximately 1.42 children per 1,000 births using the current ACGIH 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 76 children could be born each year with EBCLs ≥ 5.00 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. In addition, there is no information regarding what level of cadmium should be considered elevated for children.

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, and the true specificity and sensitivity of the blood spot testing methodology cannot be determined. The UPHL has a policy that when an elevated cadmium value is detected, the sample is automatically confirmed by analysis of a replicate punch from the same blood spot. In this study, 13% of the cards (349 of 2,706 cards) were reanalyzed to confirm high cadmium 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 EBCL (≥5.00 µg/L), the specificity was estimated to be 97% and the predictive value

positive was estimated to be 40%. The sensitivity could not be estimated using this approach (German 2000). The mean difference between the lowest and highest test for the cards was 0.8 µg/L (maximum difference = 52.30 µg/L, standard deviation = 3.69 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 2**. The distributions of samples taken represented between 0.8% (Beaver County) and 30.0% (Grand County) of the children born per county during the project sampling period. The geometric mean ranged between 0.02 µg/L (Garfield County) and 0.22 µg/L (Duchesne and Wasatch counties). Although samples were taken for children born to Wayne county mothers, they were among those excluded and no Wayne County samples were analyzed. The summary statistics for Beaver, Daggett, and Rich counties are computed on two or less samples and are provided with the caution that the results are not stable.

DISCUSSION

Public Health Surveillance (Why Do Biomonitoring?): 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 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 EBCL 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 cadmium (i.e., factories that discharge cadmium into the atmosphere). 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 unintrusive 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 EBCLs 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 cadmium (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 cadmium 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 cadmium 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 cadmium 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 EBCLs and increased risk for adverse health outcomes. The data necessary to quantify the true epidemiologic specificity, sensitivity, and predictive value positive for this testing methodology were 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 96%, which is an acceptable level. However, the predictive value positive was estimated to be 40%. This level suggests that the use of blood spots may not perform well as a screening test for children born with EBCLs. 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 cadmium 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 cadmium 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 cadmium 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 cadmium, and there are few treatment options for newborns with EBCLs. Those options, such as chelation therapy, result in other health concerns and need to be used selectively (Bernhoft 2012). Preventive interventions, such as better choices regarding smoking, hand washing behaviors, and avoiding the use of cadmium-containing products, may reduce the mother's BCLs and thus fetal exposure.

The findings of this investigation suggest that as many as 76 children could be born each year in Utah with EBCLs (≥5.00 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. In addition, there is no definition of elevated blood cadmium levels for children, and it is uncertain that an occupational standard would be relevant. Currently, Utah does not have a policy regarding screening for women of childbearing age for blood cadmium. While the results of this investigation are informative about the spatial distribution of the blood cadmium levels in Utah

children, these results do not indicate a need to establish an adult screening policy. The geometric mean cadmium level of 0.10 µg/L is below the national geometric mean level of 0.41 µg/L (CDC 2014). Adult testing and treatment should be guided by a clinical presentation that suggests a need (Bernhoft 2012).

This pilot project used de-identified data to examine the efficacy of using blood spots as a means of conducting noninvasive blood cadmium screening among newly born children in Utah. Because the children were not identified, the results for the two children with EBCLs 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 cadmium 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 2009. 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 cadmium 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 cadmium among neonates was 1.42 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).

In this investigation, 47.5% (1,285 of 2,706) of the blood spot cards were found to be unusuable for surveillance purposes because the measured level of cadmium in the paper blank was higher than the measured level of cadmium in the blood spot. This limitation is a significant barrier to consideration of using blood spots as a means of conducting population surveillance for cadmium exposure.

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. EBCLs 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 cadmium that is considered safe. This study found that approximately 1.42 newborns per 1,000 live births, or as many as 76 children per year (where the 2007-2012 average birth year cohort is

53,000 births), may have EBCLs 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 cadmium exposure. The EEP does not recommend establishing a policy at this time.

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. BCL 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 cadmium 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 Cadmium 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 cadmium surveillance. Editorial and technical review was completed by UDOH certifying reviewers and program partners.

Approved by:

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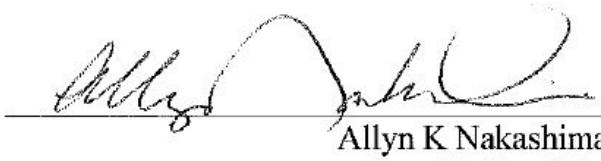

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REFERENCES

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

Albertini R, Bird M, Doerrer N, Needham L, Robison S, Sheldon L, Zenick H. 2006. The use of biomonitoring data in exposure and human health risk assessment. *Environmental Health Perspectives* 114(11):1755-1762.

Aldrich TE, Griffith J. 1993. Surveillance activities in disease and exposure situations. *In*: Environmental Epidemiology and Risk Assessment (Aldrich, TE, Griffith J, Cooke C, eds.). New York, NY: Van Norstrand Reinhold.

Al-Saleh I, Shinwari N, Mashhour A, Mohamed Gel D, Rabah A. 2011. Heavy metals (lead, cadmium and mercury) in maternal, cord blood and placenta of healthy women. *International Journal of Hygiene and Environmental Health* 214(2):79-101.

Angerer J, Ewers U, Wilhelm M. Human biomonitoring: state of the art. *International Journal of Hygiene and Environmental Health* 210(3-4):201-228.

APHL (Association of Public Health Laboratories). 2009. Moving forward: biomonitoring stories from the states. Silver Springs, MD: Association of Public Health Laboratories.

ATSDR (Agency for Toxic Substances and Disease Registry). 2012. Toxicological profile for cadmium. Atlanta, GA: ATSDR. For more information see: http://www.atsdr.cdc.gov/toxprofiles/tp5.pdf.

Bernhoft RA. 2013. Cadmium toxicity and treatment. *The Scientific World Journal*. 394652:7.

Bertin G. Averbeck D. 2006. Cadmium: cellular effects, modifications of biomolecules, modulation of DNA repair and genotoxic consequences (a review). *Biochimie* 88:1549-1559.

Caserta D, Graziano A, Lo Monte G, Bordi G, Moscarini M. 2013. Heavy metals and placental fetal-maternal barrier: a mini-review on the major concerns. *European Review for Medical and Pharmacological Sciences* 17(16):2198-2206.

CDC (Centers for Disease Control and Prevention). 2008. Division of Laboratory Sciences (brochure). NCEH Publication Number 4-1-08-57f94. Atlanta, GA: Centers for Disease Control and Prevention: National Center for Environmental Health. For more information see: http://www.cdc.gov/nceh/dls/pdf/dlsbrochure.pdf.

CDC (Centers for Disease Control and Prevention). 2009. Fourth National Report on Human Exposure to Environmental Chemicals. Atlanta, GA: National Centers for Environmental Health, Division of Laboratory Sciences.

Centers for Disease Control and Prevention (CDC). 2014. Fourth national report on human exposure to environmental chemicals, updated tables, August 2014. Atlanta GA: National Center

for Health Statistics. Found at: http://www.cdc.gov/exposurereport/pdf/fourthreport_updatedtables_aug2014.pdf [Accessed October 20, 2014].

Chaudhuri SN, Butala SJM, Ball RW, Braniff CT, Rocky Mountain Biomonitoring Consortium. 2009. Pilot study for utilization of dried blood spots for screening of lead, mercury and cadmium in newborns. *Journal of Exposure Science and Environmental Epidemiology* 19(3):298-316.

Choi BCK. 1998. Perspectives on epidemiologic surveillance in the 21st century. *Chronic Diseases in Canada* 19(4):145-151.

Ciesielski T, Weuve J, Bellinger DC, Schwartz J, Lanphear J, Wright RO. 2012. Cadmium exposure and neurodevelopmental outcomes in U.S. children. *Environmental Health Perspectives* 120(5):758-763.

CLSI (Clinical and Laboratory Standards Institute®). 2007. Blood collection on filter paper for newborn screening programs; approved standard 5th ed., Method LA4-A5, Vol. 27, No. 20. Wayne, PA: Clinical and Laboratory Standards Institute.

Dicker RC. 2002. A brief review of the basic principles of epidemiology. In: Field epidemiology, 2nd Ed. (Gregg MB, ed.). New York, NY: Oxford University Press.

EPA (U.S. Environmental Protection Agency). 1987. Cadmium (CASRN 7440-43-9) Integrated Risk Information System. Found at: http://www.epa.gov/iris/subst/0141.htm [Accessed June 2, 2014].

EPA (U.S. Environmental Protection Agency). 2000. Cadmium compounds website. Found at: http://www.epa.gov/ttn/atw/hlthef/cadmium.html [Accessed June 2, 2014].

Esteban-Vasallo MD, Aragonés N, Pollan M, López-Abente G, Perez-Gomez B. 2012. Mercury, cadmium, and lead levels in human placenta: a systematic review. *Environmental Health Perspectives* 120(10):1369-1377.

Falcón M, Viñas P, Osuna E, Luna A. 2002. Environmental exposures to lead and cadmium measured in human placenta. *Archives of Environmental Health* 57(6):598-602.

Farmer PB, Sepai O, Lawrence R, Autrup H, Sabro Nielsen P, Vestergård AB, Waters R, Leuratti C, Jones NJ, Stone J, Baan RA, van Delft JH, Steenwinkel MJ, Kyrtopoulos SA, Souliotis VL, Theodorakopoulos N, Bacalis NC, Natarajan AT, Tates AD, Haugen A, Andreassen A, Ovrebø S, Shuker DE, Amaning KS, Schouft A, Allul A, Garner RC, Dingley KH, Abbondandolo A, Merlo F, Cole J, Aldrich K, Beare D, Capulas E, Rowley G, Waugh APW, Povey AC, Haque K, Kirsch-Volders M, Van Hummelen P, Castelain P. 1996. Biomonitoring human exposure to environmental carcinogenic chemicals. *Mutagenesis* 11(4):363-381.

Filipic M. 2012. Mechanisms of cadmium induced genomic instability. *Mutation Research* 733:69-77.

Fowler BA. 2009. Monitoring of human populations for early markers of cadmium toxicity: a review. *Toxicology and Applied Pharmacology* 238:294-300.

Funk WE, McGee JK, Olshan AF, Ghio AJ. 2013. Quantification of arsenic, lead, mercury and cadmium in newborn dried blood spots. *Biomarkers* 18(2):174-177.

García-Esquinas E, Pérez-Gómez B, Fernández-Navarro P, Fernández MA, de Paz C, Pérez-Meixeira AM, Gil E, Iriso A, Sanz JC, Astray J, Cisneros M, de Santos A, Asensio A, García-Sagredo JM, García JF, Vioque J, López-Abente G, Pollán M, González MJ, Martínez M, Aragonés N. 2013. Lead, mercury and cadmium in umbilical cord blood and its association with parental epidemiological variables and birth factors. *BMC Public Health* 13:841.

German RR. 2000. Sensitivity and predictive value positive measurements for public health surveillance systems. *Epidemiology* 11(6):720-727.

Giaginis C, Gatzidou E, Theocharis S. 2006. DNA repair systems as targets of cadmium toxicity. *Toxicology and Applied Pharmacology* 213:282-290.

Greenland S. 2001. Ecologic versus individual-level sources of bias in ecologic estimates of contextual health effects. *International Journal of Epidemiology* 30(6):1343-1350.

Greenland S, Robins J. 1994. Ecologic studies – biases, misconceptions, and counter examples. *American Journal of Epidemiology* 139(8):747-760.

Guan H, Piao F-Y, Li X-W, Li Q-J, Xu L, Yokoyama K. 2010. Maternal and fetal exposure to for carcinogenic environmental metals. *Biomedical and Environmental Sciences* 23:458-465.

Gundacker C, Hengstschläger M. 2012. The role of the placenta in fetal exposure to heavy metals. *Weiner Medizinische Wochenschrift* 162(0-10):201-206.

Harrell JA, Baker EL. 1994. The essential services of public health. *Leadership in Public Health* 3(3):27-30.

Henson MC, Chedrese PJ. 2004. Endocrine disruption by cadmium, a common environmental toxicant with paradoxical effects on reproduction. *Experimental Biology and Medicine* 229(5):383-392.

Hinwood AL, Callan AC, Ramalingam M, Boyce M, Heyworth J, McCafferty P, Odland JØ. 2013. Cadmium, lead and mercury exposure in non smoking pregnant women. *Environmental Research* 126:118-124.

IARC (International Agency for Research on Cancer). 1993. Summaries and evaluations: cadmium and cadmium compounds (group 1). In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 58:119. Lyon, FR.

ICA (International Cadmium Association). 2014. Levels of cadmium in the environment. Found at http://www.cadmium.org [Accessed Jun 2, 2014].

IOM (Institute of Medicine). 1988. The future of public health. A report by the Committee for the Study of the Future of Public Health, IOM, Washington, DC: The National Academies Press.

IPCS (International Programme on Chemical Safety). 2010. Exposure to cadmium: a major public health concern. World Health Organization: Geneva, SZ.

Jarup L. 2003. Hazards of heavy metal contamination. *British Medical Bulletin* 68:167-182.

Jekel JF, Elmore JG, Katz DL. 1996. Epidemiology, biostatistics, and preventive medicine. Philadelphia, PA: WB Saunders Co.

Joseph P. 2009. Mechanisms of cadmium carcinogenesis. *Toxicology and Applied Pharmacology* 238:272-279.

Kawai M, Swan KF, Green AE, Edwards DE, Anderson MB, Henson MC. 2002. Placental endocrine disruption induced by cadmium: effects on P450 cholesterol side-chain cleavage and 3beta-hydroxysteroid dehydrogenase enzymes in cultured human trophoblasts. *Biology of Reproduction* 67(1):178-183.

Kim S, Arora M, Fernandez C, Landero J, Caruso J, Chen A. 2013. Lead, mercury, and cadmium exposure and attention deficit hyperactivity disorder in children. *Environmental Research* 126:105-110.

Kippler M, Hoque AMW, Raqib R, Ohrvik H, Ekstrom E-C, Vahter M. 2010. Accumulation of cadmium in human placenta interacts with the transport of micronutrients to the fetus. *Toxicology Letters* 192:162-168.

Kuhnert PM, Kuhnert BR, Bottoms SF, Erhard P. 1982. Cadmium levels in maternal blood, fetal cord blood, and placental tissues of pregnant women who smoke. *American Journal of Obstetrics and Gynecology* 142(8);1021-1025.

Kutlu T, Karagozler AA, Gozukara EM. 2006. Relationship among placental cadmium, lead, zinc, and copper levels in smoking pregnant women. *Biological Trace Element Research* 114(1-3)7-17.

Lauwerys, R.R., J.P. Buchet, H.A. Roels, and G. Hubermont. 1978. Placental transfer of lead, mercury, cadmium, and carbon monoxide in women. I. comparison of the frequency distributions

of the biological indices in maternal and umbilical cord blood. *Environmental Research* 15:278-289.

Lin C-M, Doyle P, Wang D, Hwang Y-H, Chen P-C. 2010. Does prenatal cadmium exposure affect fetal and child growth? *British Medical Journal* 68:641-646.

Llop S, Lopez-Espinosa M-J, Rabagliato M, Ballester F. 2013. Gender differences in the neurotoxicity of metals in children. *Toxicology* 311:3-12.

Malecki KC, Resnick B, Burke TA. 2008. Effective environmental public health surveillance programs: a framework for identifying and evaluating data resources and indicators. *Journal of Public Health Management and Practice* 14(6):543-551.

Mann CJ. 2003. Observation research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal* 20(1):54-60.

McKelvey W, Gwynn RC, Jeffery N, Kass D, Thorpe LE, Garg RK, Palmer CD, Parsons PJ. 2007. A biomonitoring study of lead, cadmium, and mercury in the blood of New York City adults. *Environmental Health Perspectives* 115(10):1435-1441.

Meliker JR, Sloan CD, 2011. Spatio-temporal epidemiology: principles and opportunities. *Spatial and Spatio-temporal Epidemiology* 2(1):1-9.

Menai M, Heude B, Slama R, Forhan A, Sahuquillo J, Charles M-A, Yazbeck C. 2012. Association between maternal blood cadmium during pregnancy and birth weight and risk for fetal growth restriction: The EDEN mother-child cohort study. *Reproductive Toxicology* 34:622-627.

Mendez-Armenta M, Rios C. 2007. Cadmium neurotoxicity. *Environmental Toxicology and Pharmacology* 23:350-358.

Morgenstern H. 1982. Uses of ecologic analysis in epidemiologic research. *American Journal of Public Health* 72(12):1336-1344.

Morgenstern H. 1995. Ecologic studies in epidemiology: concepts, principles, and methods. *Annual Reviews of Public Health* 16:16-81.

Needham LL, Calafat AM, Barr DB. 2007. Uses and issues of biomonitoring. *International Journal of Hygiene and Environmental Health* 210(304):229-238.

Norberg GF. 2009. Historic perspectives on cadmium toxicology. *Toxicology and Applied Pharmacology* 238:192-200.

Oh C-M, Oh I-H, Lee J-K, Park YH, Choe B-K, Yoon T-Y, Choi J-M. 2014. Blood cadmium levels are associated with a decline in lung function in males. *Environmental Research* 132:119-125.

Olshan AF. 2007. The use of newborn blood spots in environmental research: opportunities and challenges. *Environmental Health Perspective* 115(12):1767-1779.

Rockhill B. 2005. Theorizing about causes at the individual level while estimating effects at the population level: implications for prevention. *Epidemiology* 16(1):124-129.

Ronco AM, Urrutia M, Montenegro M, Llanos MN. 2009. Cadmium exposure during pregnancy reduces birth weight and increased maternal and foetal glucocorticoids. *Toxicology Letters* 188:186-191.

Sanders AP, Flood K, Chiang S, herring AH, Wolf L, Fry RC. 2012. Toward prenatal biomonitoring in North Carolina: assessing arsenic, cadmium, mercury, and lead levels in pregnant women. *PLoS One* 7(3):e1354

Satarug S, Moore MR. 2004. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. *Environmental Health Perspectives* 112(10):1099-1103.

Satarug S, Garrett SH, Sens MA, Sens DA. 2009. Cadmium, environmental exposure, and health outcomes. *Environmental Health Perspectives* 118(2):182-190.

Sikorski R, Radomański T, Paszkowski T, Skoda J. 1988. Smoking during pregnancy and the perinatal cadmium burden. *Journal of Perinatal Medicine* 16(3):225-231.

Silver MK, Lozoff B, Meeker JD. 2013. Blood cadmium is elevated in iron deficient U.S. children: a cross sectional study. *Environmental Health* 12:117.

Snider DE, Stroup DF. 2000. Ethical issues. *In*: Principles and practices of public health surveillance, 2nd ed. (Teutsch SM, Churchill RE, eds). New York, NY: Oxford University Press.

Stanbury M, Anderson H, Blackmore C, Fagliano J, Heumann M, Kass D, McGeehin M. 2012. Functions of environmental epidemiology and surveillance in state health departments. *Journal of Public Health Management and Practice* 18(5):453-460.

Stasenko S, Bradford EM, Piasek M, Henson MC, Varnai VM, Jurasovic J, Kusec V. 2010. Metals in human placenta: focus on the effects of cadmium on steroid hormones and leptin. Journal of Applied Toxicology 30(3):242-253.

Sun H, Chen W, Wang D, Jin Y, Chen X, Xu Y. 2014. The effects of prenatal exposure to low-level cadmium, lead, and selenium on birth outcomes. *Chemosphere* 108:33-39.

Taylor CM, Goulding J, Emond AM. 2014. Lead, cadmium and mercury levels in pregnancy: the need for international consensus on levels of concern. *Journal of Developmental Origins of Health and Disease* 5(1):16-30.

Teutsch SM. 2000. Considerations in planning a surveillance system. *In*: Principles and practices of public health surveillance, 2nd ed. (Teutsch SM, Churchill RE, eds). New York, NY: Oxford University Press.

Thacker SB. 2000. Historical development. In: Principles and practice of public health surveillance, 2nd Ed. (Teutsch SM, Churchill RE, eds.). New York, NY: Oxford University Press.

Thacker SB, Birkhead GS. 2002. Surveillance. *In*: Field epidemiology, 2nd ed. (Gregg MB, ed.). New York, NY: Oxford University Press.

Thacker SB, Qualters JR, Lee LM. 2012. Public health surveillance in the United States: evolution and challenges. *Morbidity and Mortality Weekly Report – Surveillance Summary* 61(Supplement):3-9

Thacker SB, Stroup DF, Parrish RG, Anderson HA. 1996. Surveillance in environmental public health: issues, systems, and sources. *American Journal of Public Health* 86(5):633-638.

Thompson J, Bannigan J. 2008. Cadmium: toxic effects on the reproductive system and the embryo. *Reproductive Toxicology* 25(3);304-315.

UDOH (Utah Department of Health). 2013. Utah's Indicator-Based Information System for Public Health website. Information: http://ibis.health.utah.gov/ [accessed December 15, 2013]. For birth count data use the following menu chain: "Dataset Queries," "Births, Fetal Deaths, and Infant Deaths," "Births," "Count, Birth and Fertility Rates," "Count," set "Step: 1: Select year" to include 2007 through 2012, then submit query.

UEPHTN (Utah Environmental Public Health Tracking Network). 2013. Utah Environmental Public Health Tracking Network website. Information: http://epht.health.utah.gov/epht-view/ [accessed October 1, 2013].

Waalkes MP. 2003. Cadmium carcinogenesis. *Mutation Research* 533:107-120.

Waisberg M, Joseph P, Hale B, Beyersmann D. 2003. Molecular and cellular mechanisms of cadmium carcinogenesis. *Toxicology* 192:95-117.

Wang B, Due Y. 2013. Cadmium and its neurotoxic effects. *Oxidative Medicine and Cellular Longevity* 2013:898034.

Wilhelm M, Schulz C, Schwenk M. 2006. Revised and new reference values for arsenic, cadmium, lead, and mercury in blood or urine of children: basis for validation of human

biomonitoring data in environmental medicine. *International Journal of Hygiene and Environmental Health* 209(3):301-305.

TABLES AND FIGURES

TABLE 1. Summary of Utah neonatal blood cadmium levels by sex for children born in Utah in 2009.

Sex	Total Births Statewide	Samples Tested	Geometric Mean Blood Cadmium Level µg/L (95% confidence limit)	Highest Observed Blood Cadmium Level µg/L	Number Tests with Blood Cadmium Levels Greater than 5.0 µg/L
Female	26,264	686	0.11 (0.03 – 0.18)	8.64	1
Male	27,486	718	0.10 (0.02 – 0.17)	6.91	1
Both	53,750	1,404	0.10 (0.05 – 0.15)	8.64	2

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

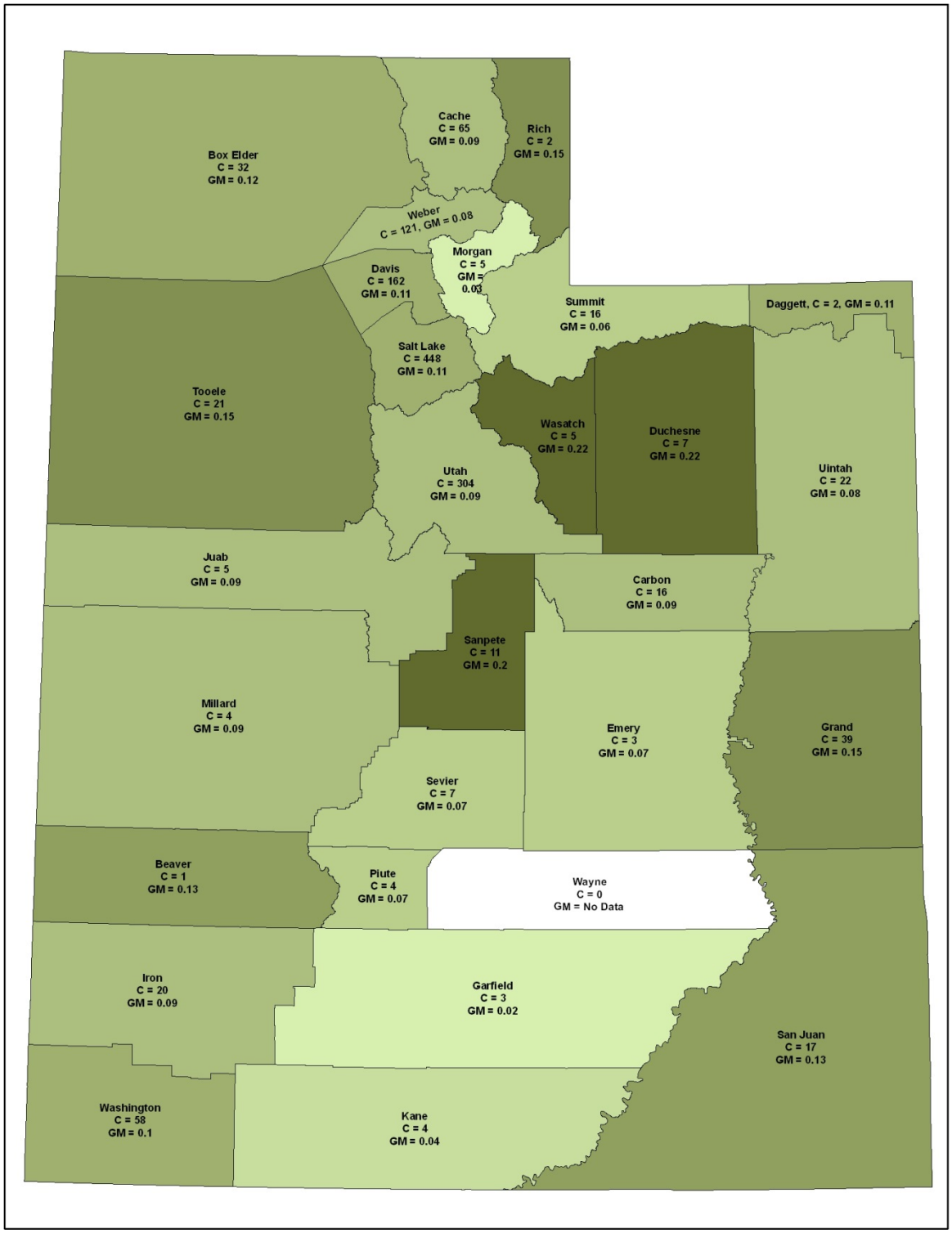

TABLE 2. Summary of Utah neonatal blood cadmium levels by county for children born in 2009. These data are based on the maternal residential address at the time of birth.

County	Total Births Statewide	Samples Tested	Geometric Mean Blood Cadmium Level µg/L (95% confidence level)	Highest Observed Blood Cadmium Level µg/L	Number Tests with Blood Cadmium Levels Greater than 5.0 µg/L
Beaver	131	1	0.13 (----- – -----)	0.13	0
Box Elder	992	32	0.12 (0.00 – 0.48)	0.60	0
Cache	2,520	65	0.09 (0.00 – 0.34)	1.22	0
Carbon	320	16	0.09 (0.00 – 0.64)	1.31	0
Daggett	12	2	0.11 (0.00 – 1.62)	0.13	0
Davis	6,041	162	0.11 (0.00 – 0.27)	1.31	0
Duchesne	300	7	0.22 (0.00 – 1.16)	8.64	1
Emery	187	3	0.07 (0.00 – 1.64)	0.21	0
Garfield	58	3	0.02 (0.00 – 1.38)	0.04	0
Grand	129	39	0.15 (0.00 – 0.48)	6.91	1
Iron	887	20	0.09 (0.00 – 0.56)	1.76	0
Juab	242	5	0.09 (0.00 – 1.16)	0.29	0
Kane	83	4	0.04 (0.00 – 1.21)	0.10	0
Millard	219	4	0.09 (0.00 – 1.36)	0.38	0
Morgan	210	5	0.03 (0.00 – 1.31)	0.09	0
Piute	26	4	0.07 (0.00 – 1.69)	0.33	0
Rich	42	2	0.15 (0.00 – 3.94)	0.60	0
Salt Lake	18,664	448	0.11 (0.02 – 0.21)	2.88	0
San Juan	200	17	0.13 (0.00 – 0.63)	2.15	0
Sanpete	363	11	0.20 (0.00 – 0.84)	0.70	0
Sevier	361	7	0.07 (0.00 – 0.87)	0.17	0
Summit	536	16	0.06 (0.00 – 0.61)	1.28	0
Tooele	1,033	21	0.15 (0.00 – 0.61)	0.91	0
Uintah	845	22	0.08 (0.00 – 0.52)	0.85	0
Utah	12,231	304	0.09 (0.00 – 0.20)	3.90	0
Wasatch	414	5	0.22 (0.00 – 1.36)	1.64	0
Washington	2,440	58	0.10 (0.00 – 0.37)	2.37	0
Wayne	26	0	----- (----- – -----)	-----	0
Weber	4,238	121	0.08 (0.00 – 0.26)	4.32	0

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.

BCL: Blood cadmium level. The amount of cadmium in the blood, quantified as micrograms of cadmium per liter of blood (µg/L). Blood cadmium levels greater than or equal to 5.0 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/.

EBCL: Elevated blood cadmium levels. Blood cadmium levels greater than or equal to 5.0 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 cadmium 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 lots 7984 and 8083) that were custom made for low level cadmium and other heavy metals by Utak Laboratories, Inc. (Valencia, California). The material had a known, verified mean cadmium concentration and an expected analytical range. The material was reconstituted by adding 3 mL of 18 megaohm 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.

Analysis: 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 cadmium, the three isotopes scanned and summed were m/z 111. No significant inference was observed at this m/z. 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.