Bone Lead Description and Population Comparison including by pXRF

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Lead is a known toxicant having wide ranging negative effects throughout the body with a particular impact on neurodevelopment. Even dating back to Roman times, lead's deleterious effects in the body were recognized. Lead used to be more ubiquitously used in paints and leaded gasoline, which led to serious exposures nationwide with many deaths attributable directly to lead. In the 1990's, many studies showed the drastic negative impacts lead was having on the population including serious effects such as cardiovascular disease (Navas-Acien, Guallar et al. 2007), neurodevelopmental deficits (Canfield, Henderson et al. 2003), and death (Weisskopf, Jain et al. 2009). There was a drastic public health intervention to reduce these known issues and improve health by removing lead from both paint and gasoline, which resulted in a drastic reduction in lead exposures nationwide (Dignam, Kaufmann et al. 2019). However, even after these reductions, it was determined that ever lower levels of lead exposure continued to show these drastic influences on neurodevelopment, particularly in children (Canfield, Henderson et al. 2003, Lanphear, Hornung et al. 2005, Jusko, Henderson et al. 2008, Lanphear, Rauch et al. 2018). Thus, communities still experiencing exposures outside of paint and leaded gasoline had continued health issues associated with lead. For this reason, the Centers for Disease Control reduced the actionable level of lead exposure from 10 ug/dL to 5 ug/dL (Dignam, Kaufmann et al. 2019) and most recently the reference level has been further reduced to 3.5 ug/dL. However, despite these reference values, the scientific community recognizes that there is no safe level of lead exposure.

Lead can be absorbed through oral ingestion, inhalation, and dermal absorption in the body. Children have been shown to be much more susceptible to ingested lead than adults with 40-50% of lead dose orally ingested ultimately being absorbed in the body (United States. Agency for Toxic Substances and Disease Registry. 2007). This typically leads to high exposures in children from hand-to-mouth exposures and lead accumulation in dust. However, water soluble lead actually increases the ability of the body to metabolize and ultimately absorb the ingested lead. Thus, lead in water is a particularly dangerous source of exposure during development (United States. Agency for Toxic Substances and Disease Registry. 2007).

The primary means of surveilling lead exposure in communities relies on widespread blood testing. Lead in blood, although taken as standard in these surveillance settings, has many situations in which its capabilities as a biomarker of exposure are severely lacking (Rabinowitz 1991). Blood lead is a biomarker that is highly linked with turnover of red blood cells in the body, as red blood cells are the primary carriers of lead in blood (O'Flaherty 1998). Thus, in adults, lead in blood has been repeatedly shown to only reflect recent exposures with a half-life of about 30 days (Nilsson, Attewell et

al. 1991). This means that if we measured an adult who was severely exposed one month ago, we would only be able to identify half of the exposure from our lagged measurement. This is further complicated when we look at children's biokinetics and blood lead turnover. Previous studies have shown children have a blood lead half-life of less than one week, so the measurement from blood is incredibly time sensitive (Specht, Lin et al. 2016, Specht, Weisskopf et al. 2018). This effect introduces a great deal of uncertainty into a single measurement of blood lead, as, in any given week, the blood lead could change by more than 50%. In order to properly assess the exposure to lead over time using blood lead, there would need to be serial measurements taken over many weeks at the known point of highest exposure.

Bone lead is the most valuable tool for accurately determining cumulative exposure to lead over years to decades. When lead gets in the body, it acts similarly to calcium, as they have similar binding properties (Rabinowitz 1991). As a consequence, lead can disrupt critical neural pathways reliant on calcium channels, as well as produce many other ill-effects throughout the body (Bressler and Goldstein 1991). Lead will also replace calcium in bone. Not only is lead in bone a good marker of overall exposure, but, since it is directly related to disruption in calcium metabolism, it is a proxy for lead's effects in the brain and throughout the body (United States. Agency for Toxic Substances and Disease Registry. 2007). This is what makes bone such an excellent marker of exposure. Additionally, since bone changes slowly in the body, studies have shown that lead measured from bone is reflective of years to decades worth of exposure due to the slow kinetic processes of bone remodeling (Nilsson, Attewell et al. 1991, Rabinowitz 1991, Barbosa, Tanus-Santos et al. 2005). Thus, a single measurement of bone lead reflects the lead exposure during a time period of potential exposure from an acute or chronic source in an individual's past (i.e., the water crisis). Thus, we can use bone lead to identify lead exposure that was missed due to the poor temporality, high uncertainty, and unavailability of widespread blood lead testing from years prior.

Bone lead can be measured in a variety of ways, but the most successful and least invasive method is a tool utilizing x-ray fluorescence (XRF) (Wielopolski, Ellis et al. 1986, Hu, Milder et al. 1989, Todd, Moshier et al. 2001). In XRF, an X-ray source generates a photon beam that passes through the sample. The photon transfers the energy and displaces an electron from atoms in the sample. Displacement of this electron makes the sample atoms unstable and electrons jump from outer orbitals to lower orbitals releasing fluorescence, characteristic of the element of each atom. The fluorescence in the form of secondary X-rays is measured by a radiation spectrometer and the rate of determination of these secondary rays gives the elemental concentration present in the sample. XRF has been used for decades to determine the bone lead level of individuals from children to adults in a variety of different settings (Wielopolski, Ellis et al. 1986, Bleecker, Mcneill et al. 1995, McNeill, Stokes et al. 2000, Grashow, Spiro et al. 2013, Specht, Lin et al. 2018). Lead can be measured at multiple energies particular to the XRF device, the K- and L-shell. K and L are reflective of the electron orbitals in which the measurement arose. K-shell requires the use of a radioisotope source or a high energy radiation source. L-shell can be used with either radioisotope or x-ray tube sources. Both have been used successfully in measurement of bone lead (Wielopolski, Ellis et al. 1986, Hu, Milder et al. 1989, Todd, Moshier et al. 2001). There have been a number of iterations of these XRF devices to gradually make this measurement of bone lead easier through the years.

Measurement of bone lead has become much more convenient as the capabilities of the XRF technology has improved. The first devices to measure bone lead (K-shell) utilized a radioisotope source (cobalt-57 and cadmium-109), which made the devices themselves fairly difficult to obtain and operate (Hu, Milder et al. 1989). The measurement systems were also incredibly large, requiring

special high-purity germanium detectors with liquid nitrogen cooling in order to operate properly. Finally, the measurements were slow with each measurement taking 30 minutes to complete. Thus, the initial XRF bone lead measurement systems were incredibly large, difficult to obtain, difficult to operate, and took a significant amount of time for each measurement.

Improvements in low energy (L-shell) x-ray detection led to advancements of low energy XRF technology (Wielopolski, Ellis et al. 1986, Nie, Sanchez et al. 2011, Specht, Weisskopf et al. 2014). Previous L-shell measurement systems had similar long measurement times as the K-shell systems in order to reach detection limits needed for measurement of bone lead. In the early 2000's, low energy x-ray detector systems vastly improved in both the maximum counts per second (resolving time) and energy resolution, which would drastically lower the detection limits and, most importantly, the measurement times with these devices. The current standard L-shell XRF utilizes a portable form factor and boasts a 3-minute measurement time to achieve equivalent detection limits to conventional XRF devices (Specht, Weisskopf et al. 2014, Zhang et al. 2022). This allows for easy, convenient measurements of bone lead in field environments and the ability for widespread testing for cumulative lead exposure.

The current portable XRF measures the same bone lead measurement as has been done decades prior. This has been verified in theoretical, human, animal, and lab settings using multiple methodologies for validation (Nie, Sanchez et al. 2011, Specht, Weisskopf et al. 2014, Specht, Lin et al. 2016, Specht, Parish et al. 2018, Specht, Dickerson et al. 2019, Specht, Kirchner et al. 2019, Zhang et al. 2021). The device x-rays give a small radiation exposure, which is equivalent to that of standing outside for about 9 hours with natural cosmic sources of radiation or equivalent to 1/3rd of a single dental x-ray (Specht, Zhang et al. 2019).

Reference studies of bone lead have been completed in a few comparable groups for recent environmental exposures, legacy leaded gasoline exposures, and within groups of communities with known exposure sources from industry. Populations of adults that do not have blood lead levels typically considered elevated, can still have bone lead levels consistent with that of an elevated level of exposure. Bone lead in adults from a study in Toronto recently showed a level on average of about 3.4 µg/g bone mineral for those with an average age of 43 (McNeill, Fisher et al. 2017). From the same study, those with an average age of 29 years had a bone lead measurement of 0.9 µg/g bone mineral and those with average age of 56.5 years had 6.0 µg/g bone mineral (McNeill, Fisher et al. 2017). Correcting these levels to values reflective of general population bone lead measurements during the time of this case would change the values for ages of 29, 43, and 56 years to 0.5, 1.7, and 3.0 µg/g bone mineral (McNeill, Fisher et al. 2017).

For children, we have a couple of points for comparison. In a group of lead poisoned children in China (diagnosed as lead poisoned defined as blood lead levels >25 ug/dl) the median and standard deviation of bone lead was 12 ± 26 ug/g bone mineral (Specht, Lin et al. 2016, Specht, Weisskopf et al. 2018). The most highly exposed children from that population were directly ingesting 100% lead powder. The control group from that study had a median value of -1 ± 4 ug/g bone mineral (Specht, Lin et al. 2016, Specht, Weisskopf et al. 2018). Similarly a recent population survey of children between 6-19 years of age in Ontario, Canada found bone lead levels to be 0.63 ± 1.0 ug/g bone mineral (average ± standard deviation) (McNeill, Fisher et al. 2017). Populations of children that do not have blood lead levels typically considered elevated, can still have bone lead levels consistent with that of an elevated level of exposure.