A geospatial analysis of the role of lead exposure in substance use disorders.

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Individualized Studies (Western) Senior Project Proposal

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Introductory Statement:

This project investigates how the disproportionate exposure to lead (Pb), a hazardous neurotoxin, may result in the development of substance use disorders (SUDs) through a geospatial analysis of:

1. Discriminatory redlining strategies used by the Federal Housing Administration and Homeowners' Loan Corporation from the 1930s-1960s;
2. Elevated Blood Lead Level maps developed by city and county health departments from 2000-2020;
3. Maps of drug overdose events developed by city and county health departments from 2000-2020.

The objective of this project is to apply the Bradford-Hill criteria for causation, which is commonly used in environmental health exposure assessments, to determine whether Pb exposure can cause the development of SUDs.

If this project supports this theory, it can be used as evidence for action to hold governmental agencies accountable for providing safe and healthy environments to prevent the development of SUDs, instead of employing downstream combatants of policing efforts to address SUDs.

Project Background:

The Bradford-Hill criteria for plausible causality are guidelines for epidemiological studies investigating a specific condition and the proposed outcome. In this study, I will be applying these criteria to understand the role of Pb exposure in the development of SUDs through an interdisciplinary background review of the current literature and a proposed geospatial analysis. The background will provide evidence to support baseline plausibility to explain why a geospatial analysis of my chosen variables are appropriate. I recognize that the geospatial analysis may offer correlational evidence for this relationship that does not imply causation, so the background evidence will also serve to supplement the Bradford-Hill criteria that the geospatial analysis does not meet. See *Figure 1* in the appendix, which serves as a summary of how the background evidence and proposed project meet the Bradford-Hill criteria.

In the field of neuroscience, there have been a number of studies that investigate the effects of Pb on a biological, molecular, developmental, or behavioral level to provide detailed and standardized understandings of the role of Pb in SUD development. Many of these studies, particularly the preclinical studies that intersect Pb exposure and addictive-like behavior, provide the biological plausibility for conducting epidemiological studies under this topic.

To begin, Pb is a known neurotoxin that competes with calcium (Ca^{2+}) at the synapses between pre- and post-synaptic neurons, which interrupts healthy neuron communication (Bressler et al., 2002). Ca^{2+} is required for the release of neurotransmitters from the presynaptic cell, so if Pb blocks or mimics the function of Ca^{2+}, neurons cannot effectively relay critical messages within a neurocircuit (Bressler et al., 2002). Without healthy patterns of neuron firing, synapses can be underdeveloped or weakened, leading to various cognitive effects (Bressler et al., 2002). This is supported by magnetic resonance images (MRI) of brains exposed to Pb that

show decreased volumes of gray matter, which is composed of cell bodies, dendrites, and axon terminals, indicating that there are decreased levels of synapses in these brains (Cardenas-Iniguez et al., 2022).

Pb poisoning is a critical hazard to consider because its most drastic effects in humans occur in utero or early childhood (Cardenas-Iniguez et al., 2022). This is because during these critical development periods in utero and early childhood, synapses in the brain are forming, so any inhibition or interruption of Ca2+ function by Pb is highly impactful during these periods. Additionally, because Ca2+ is readily used for synapse and bone development in childhood, children are more vulnerable than adults to absorb Pb. After a meal, adults absorb about 20% of exposed lead while children absorb 50% (ATSDR, 2023). On an empty stomach, adults absorb 60-80% of exposed lead while children can absorb 100% (ATSDR, 2023). In humans, if Pb is not absorbed, then it can be excreted, and high-calcium diets are known to prevent this absorption by out-competing the ingested or inhaled Pb (CDC, 2022). Pb is absorbed in the blood and is associated with red blood cells, and then becomes stored in the bones and teeth (ATSDR, 2023). Pb stored in the bones can be mobilized back into the blood during periods of pregnancy when the pregnancy body requires Ca2+ for the developing fetus, and because Pb can pass through the blood-placenta barrier, generational effects of Pb exposure may occur (Banna et al., 2022). When culminating biological vulnerability with social and financial vulnerabilities, Pb toxicity is most harmful to those experiencing generational poverty, where families exposed to disinvested infrastructure containing Pb and insufficient calcium-based diets may have children that are most exposed to and readily absorbent to Pb.

By negatively impacting synapses, Pb poisoning can negatively affect general intelligence, memory, executive functioning and attention, processing speed, language, and

motor skills (Mason et al., 2014). The dopamine system is responsible for many of these cognitive functions, including motor activity, motivation and reward, mood, attention, and learning (Jones & Miller, 2008). High levels of Pb have been observed to negatively impact the dopamine (DA) system through alterations in dopaminergic neurotransmission, specifically increased synaptic clearance of DA by DA transporters and decreased DA levels (Jones & Miller, 2008). These effects of an over-stimulated DA system and low DA levels may explain why one of the most common diagnoses paired with Pb poisoning is attention-deficit/hyperactivity disorder (ADHD) (Jones & Miller, 2008; Cardenas-Iniguez et al., 2022). Studies with South Korean School-Age Children have found that environmental Pb exposure was associated with impulsivity behaviors related to ADHD (Hong et al., 2014).

Specific to the development of SUDs, Pb was found in multiple studies to sensitize the mesolimbic DA system, which is the neural reward circuitry tied to the rewarding effects of drugs, resulting increased dosage requirements to elicit desired effects of drugs in rodents (Jones & Miller, 2008; Fishbein et al., 2008). The parallels in brain regions and affected cognitive functions between these two disorders may explain the comorbidity of ADHD and SUDs, as well as how ADHD can be a risk factor for the development of SUDs (Wilens & Fusillo, 2007). However, ADHD is more commonly associated with chronic Pb exposure than SUDs.

Looking closer into the neural circuits that are associated with addiction, chronic developmental Pb exposure increases μ-opiate receptor (MOR) levels in the adolescent rat brain (Albores-Garcia et al., 2021). MORs play key roles in addictive disorders, as drug interactions with this receptor mediate the release of dopamine, which elicits the rewarding feeling paired with drug use. Increased MORs would heighten sensitivity to these rewarding feelings, and eventually would result in a dependence on drugs, resulting in a higher risk of SUDs.

The next scope in preclinical research is to investigate the behavior paired with these effects. In a study investigating adolescent rat cocaine seeking behavior and dopaminergic system effects, chronic developmental Pb exposure sensitizes adolescent male and female rats to the effects of cocaine, but not adult rats (Albores-Garcia et al., 2022). Chronic Pb exposure also significantly increased dopamine receptor levels in the brain regions are associated with goal-directed behaviors, reward, and addiction (Albores-Garcia et al., 2022). When mice were exposed to low-level developmental Pb exposure, Pb did not affect adult alcohol self-administration but did increased risk of relapse to alcohol (Rangel-Barajas et al., 2020). These low levels of Pb were to be representative of the Pb levels exposed to people in inner cities of the U.S., which provides translational evidence for clinical studies (Rangel-Barajas et al., 2020).

However, one issue with the Rangel-Barajas et al. (2020) study is the paradigm in which mouse behavior was measured. Within behavioral neuroscience, there are a few paradigms that can measure self-administration. In self-administration tasks, there is a quantity of a substance that subjects can consume, which is the alternative to investigators injecting a standard amount, so they can measure the amount of a substance that subjects are seeking. This seeking behavior can give critical information about the motivations a subject has towards a substance. When the substance is paired with a known aversive effect, such as bitter-tasting quinine, but a subject is still seeking the substance, then the subject is very motivated to resist aversion to that substance and is showing addictive behavior. Rangel-Barajas et al. (2020) used an operant conditioning task, in which subjects had to learn a set of motions, such as pulling a specific lever, to deliver an alcohol substance. The amount of lever pulls was a way to measure seeking behavior (Rangel-Barajas et al., 2020). However, a key factor of operant conditioning is the ability of subjects to learn a task, but it is known from clinical studies that Pb exposure results in the development of

learning disorders, such as ADHD (Cardenas-Iniguez et al., 2022). Because of this, I personally do not think that this paradigm choice was an effective way to measure alcohol addictive behavior in mice exposed to Pb.

With my involvement in behavioral neuroscience research at Miami University, I began my own independent study to measure fentanyl drinking behavior in mice that underwent low-level developmental Pb exposure. I modeled my treatments based on Rangel-Barajas et al. (2020), but I chose to use fentanyl instead of alcohol because it is more addictive, which may uncover nuanced addictive behaviors, and a different self-administration task called Drinking in the Dark (DID). DID occurs in the dark because mice are naturally nocturnal and more active in the dark. High levels of mouse activity are necessary because under this task, the mice have two hours to binge drink substances. Mice also have the choice between two bottles, water and fentanyl, so investigators can measure consumption of fentanyl and preference of fentanyl over water. The findings of my study were that Pb affected preference of fentanyl differently based on sex and over sessions of drinking. Additionally, after a two-day withdrawal period, male mice exposed to Pb had significantly more consumption than control males, indicating Pb plays a role in relapse-like behaviors in mice, which is also supported by Rangel-Barajas et al. (2020). These preclinical findings can help inform clinical studies that are investigating the role of Pb exposure in SUDs.

Clinical studies investigating this relationship are limited in human populations due to the inability to control for confounding factors like adverse childhood experiences, genetic predisposition, and adverse social determinants of health that may also lead to SUDs, and the inability to ethically treat experimental groups with Pb to measure outcomes. In a study conducted with Inuit children from northern Québec, there were associations between childhood

Pb exposure and adolescent externalizing behaviors, binge drinking, and cannabis use (Desrochers-Couture et al., 2019). However, it should be noted that these associations were found to be indirect, signifying that childhood Pb exposure led to adverse childhood behaviors that mediated the consequent adolescent substance use, which is alternative to a direct association where childhood Pb exposure would directly lead to adolescent substance use (Desrochers-Couture et al., 2019). While epidemiological studies are sometimes limited by confounding social determinants within populations, the merit of this study is that an indirect relationship was uncovered and was due to social factors, which can tell us more than studies with animals.

Another cohort study with participants from the Midwest United States found that elevated BLL at age 4 was associated with higher likelihoods of developing substance use-related problems during adolescence (Min et al., 2022). In a similar fashion with the previously discussed study, this association was indirect and was fully mediated by childhood language skills (Min et al., 2022). The authors have concluded that elevated BLL in preschool years is a risk factor for adolescent substance use (Min et al., 2022). Based on the consistency of a mediating condition that leads Pb exposure to make children more vulnerable to adolescent substance use with the work by Min et al. (2022) and Desrochers-Couture et al. (2019), one prevention measure to prevent substance use-related problems is to hold behavioral and educational interventions in early childhood for those with elevated BLL. However, there are definite limitations of access to health interventions for families with Pb exposure.

The first pilot study with human populations investigating the relationship between Pb exposure and SUDs came about in 2008. This study measured tibial Pb concentrations, which is a measure of cumulative Pb exposure because Pb is eventually stored in the bones, in women

that were injection heroin users (Fishbein et al., 2008). These women had 1.8 times higher tibial Pb concentrations compared to women that did not use heroin (Fishbein et al., 2008). Even with this discovery, Fishbein et al. (2008) still recognized the limitations with defining appropriate control groups with "normal" tibial Pb concentrations. The women injection heroin users were from inner city Baltimore, where the Fishbein et al. (2008) describe the participants at high risk for Pb exposure due to economic disadvantage, disinvested infrastructure, and in access to quality healthcare and nutrition. This vulnerability to Pb exposure based on various social determinants is consistent amongst the current literature.

Social determinants of health (SDOH) are the conditions in the environments where people have community that affect a wide range of health, functioning, and quality-of-life outcomes (Office of Disease Prevention and Health Promotion). SDOH can include factors of economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context (Office of Disease Prevention and Health Promotion). So far in the literature search, some SDOH identified in the relationship between Pb exposure and SUD-related issues include: the community's context in how children with adverse behaviors are cared for, educational access for childhood language skills, and economic stability and the built environment (Desrochers-Couture et al., 2019; Min et al., 2022; Fishbein et al., 2008). The role of economic stability as an SDOH is complex, as it can serve as both a mediator for the development of SUDs after exposure to Pb, but also a determining factor in Pb exposure in the first place (Bellinger, 2008). This complex relationship is imbedded in the built environment, which are human-made structures that make up communities and are determined by one's economic stability. Discriminatory strategies in developing the built environment can result in disproportionate vulnerabilities to adverse health conditions.

While few studies of the built environment have integrated the relationship of Pb exposure and the development of SUDs, there are a plethora of studies that look at these variables independently. To understand who may be most vulnerable to Pb exposure, redlining maps could be analyzed from a perspective that integrates community context, economic stability, and built environment SDOH. Redlining was a deeply discriminating practice used by the Home Owners' Loan Corporation (HOLC) and the Federal Housing Administration (FHA) from 1936-1960s to characterize the risk potential home loan recipients. These appraisals were encoded with racial and ethnic terminology, with White individuals characterized with the least risk on returning a loan and non-White individuals of color characterized with the highest risk, regardless of education or income status (Ranganathan, 2016). Ultimately the non-White communities were outlined in red by FHA, and HOLC policies resulted in the critical disinvestment of these communities (Ranganathan, 2016).

While it should be noted that redlining does not directly result in Pb exposure, the underlying causes of redlining would also mediate the investment in environmental health protections that would result in disproportionate elevated BLL (Karp, 2023). Pb is commonly sourced in the paint of homes and buildings built before 1978 where if left unrenovated, the paint can deteriorate as chips that children may eat or dust that children may breathe (CDC, 2022). Pb can also be sourced in drinking water if the service lines connected to homes are made of Pb (CDC, 2022). The use of Pb-based paint was outlawed in 1978 and the use of pipes containing Pb was outlawed in 1986. With these inner-city neighborhoods that underwent disinvestment for generations, this could explain the association between redlining and elevated BLL that we still see today. And, because of these strong associations between discriminatory redlining and elevated BLL, we can characterize this association as a case of environmental racism. Thus,

redlining can be used as a mapped reference of disinvestment and racial segregation of a city that highlights disproportionate Pb exposures to people of color and with lower socioeconomic status.

When understanding the effects of the built environment on the development of SUDs, various methods of that incorporate epidemiological data, qualitative interviews, and spatial analyses can be applied. In a study with participants from an urban location, New York City, and a rural location, southern Illinois, Ezell et al. (2021) uncovered the specific features of the built environment that influence drug use behaviors, experiences, patterns, and risk factors within these locations. From qualitative interviews with participants, investigators concluded that the built environment mediates the social reproduction, specifically where people who use drugs (PWUD) chose to obtain and use those drugs (Ezell et al., 2021). Additionally, "stigma zoning," which is the cultural perceptions of behaviors that are undesirable or deviant, negatively affected the socio-geographic mobility, social conditions, and resources access of PWUD (Ezell et al., 2021). Because the built environment has influenced the physical place where PWUD are limited to gather as discussed by Ezell et al. (2021), this raises an inquiry of whether Pb exposure causes SUDs, or if SUDs make people more at risk to be in environments where Pb toxicity is greater. It is possible that Pb exposure may come first, second, or interspersed in this causality relationship, which is also similar to the role of economic stability in Pb exposure as discussed by Bellinger et al. (2008). While this may serve as a limitation to meet the temporality Bradford-Hill criterion, it should be noted that other studies that measured childhood BLL found substance use-related issues later in life during adolescence, so Pb exposure as the first agent in the relationship is still a valid theory (Desrochers-Couture et al., 2019; Min et al., 2022).

A spatiotemporal analysis of Cincinnati, Ohio using emergency medical calls regarding heroin-related incidents identified several features of the built environment and demographics

where calls were most associated (Li et al., 2019). These calls were positively associated with males and people aged 35-49 years, and parks, commercial areas, manufacturing areas, and downtown development zones within the urban setting of Cincinnati (Li et al., 2019). The calls were negatively associated with people with a bachelor's degree or higher and median household income, distance to hospitals, and distance to opioid treatment centers, showing that these incidents were not as likely to happen with people of a higher socioeconomic status or access to health care (Li et al., 2019). A global spatial analysis of Cincinnati by Choi et al. (2022) also had similar sociodemographic results when using emergency medical service response data, American Community Survey data, and health facilities datasets, where high heroin overdose rates occurred in neighborhoods with high crime rates, male populations, high poverty levels, lower education levels, and unequal access to overdose prevention centers.

From this interdisciplinary collection of background evidence that ranges from neurocircuitry to spatial analyses, the role of Pb exposure on the development of SUDs has met nearly all of the Bradford-Hill criteria necessary for plausible causality.

The neurocircuitry and behaviors involved with the development of SUDs that have been shown to be affected by Pb exposure give biological rationale for ***plausibility*** (Jones & Miller, 2008; Albores-Garcia et al., 2021; Mason et al., 2014; Albores-Garcia et al., 2022; Rangel-Barajas et al., 2020). Additionally, the cohort studies that measured elevated childhood BLL preceded the measurements of adolescent substance-use related issues, which give evidence for appropriate ***temporality*** for this relationship (Desrochers-Couture et al., 2019; Min et al., 2022). Furthermore, high childhood BLL was shown to result in more substance-use related issues, demonstrating a biological gradient for this relationship (Min et al., 2022).

Throughout this review, studies conducted with participants across various populations have shown ***consistency*** and ***coherency*** with results, including studies measuring Pb levels and substance use by Desrochers-Couture et al. (2019), Min et al. (2022), and Fishbein et al. (2008), and studies measuring the effects of the built environment on substance use by Ezell et al. (2021), Li et al. (2019), and Choi et al. (2022).

The ***strength*** of this relationship between Pb exposure and SUDs can be supported by studies showing affected neurocircuitry by Jones & Miller (2008) and Albores-Garcia et al. (2021) and studies that highlight the SDOH that make certain populations more vulnerable to Pb exposure and SUDs by Desrochers-Couture et al. (2019), Min et al. (2022), Fishbein et al. (2008), Bellinger (2008), Li et al. (2019), Choi et al. (2022), and Ranganathan (2016). The identified SDOH in this relationship include economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context, which are all the SDOH identified by the Office of Disease Prevention and Health Promotion.

The relationship between Pb exposure and SUDs as presented by background evidence is similar to the effects of Pb exposure on ADHD, and because SUDs have been shown to be comorbid with ADHD in part due to overlapping neurocircuits, an ***analogy*** of these relationships have been demonstrated (Wilens & Fusillo, 2007; Cardenas-Iniguez et al., 2022; Jones & Miller, 2008).

Various ***experiments*** using preclinical studies, including my own unpublished work, have supported this relationship (Albores-Garcia et al., 2021; Rangel-Barajas et al., 2020).

The final Bradford-Hill criteria unmet by this collection of background evidence is specificity, however I argue that because SUDs are complex diagnoses with many contributing

factors, and because Pb exposure can affect many other brain regions that result in other disorders, specificity is not possible with this relationship.

From the current literature, there is lacking epidemiological research using geospatial analyses that integrate Pb exposure, effects of the build environment and community context, and SUDs to offer additional evidence of this relationship. With a geospatial analysis of these three factors, the Bradford-Hill criteria aimed to be met include consistency, coherence, strength, and temporality.

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Appendix:

Criterion	Description	Background Evidence	Proposed Project	How?
Temporality	The cause must precede the outcome.	★	★	Cohort studies measured childhood BLL, then adolescent substance use (Desrochers-Couture et al., 2019; Min et al., 2022). Redlining and elevated BLL maps come before the overdose event maps.
Strength	Strong relationship between variables: high relative risk.	★	★	The neurocircuitry directly involved with SUDs is affected by Pb exposure (Jones & Miller, 2008; Albores-Garcia et al., 2021). Statistical analyses of these three factors will show risk.
Biological Gradient	Dose-response: more exposure leads to more outcome.	★		High doses of Pb result in more expression of disordered symptoms than low doses. Higher BLL resulted in more adolescent substance use issues (Min et al., 2022).
Consistency	The relationship is consistent in different studies and populations.	★	★	Participants from Baltimore, Québec, and the Midwest all had similar results (Fishbein et al., 2008; Desrochers-Couture et al., 2019; Min et al., 2022). Analyses of multiple cities and regions will be conducted.
Specificity*	Single cause for single effect.			*Not addressed because SUD development is very nuanced and can be caused by many factors. Pb also affects many other neurocircuits and can lead to many other disorders.
Plausibility	There is biological rationale for the relationship.	★		Neuroscience evidence for how Pb exposure affects neurocircuits and behaviors related to SUDs (Jones & Miller, 2008; Albores-Garcia et al., 2021; Mason et al., 2014; Albores-Garcia et al., 2022; Rangel-Barajas et al., 2020).
Coherence	Relationship is consistent with previous knowledge.	★	★	Geospatial analysis is a unique approach to study this, but this study can fit in current literature.
Analogy	The relationship is synonymous with other, similar relationships.	★		Pb exposure can lead to ADHD, and is often comorbid with SUDs of similar neurocircuits (Wilens & Fusillo, 2007; Cardenas-Iniguez et al., 2022; Jones & Miller, 2008)
Experiment	Randomly assigned treatment changes the clinical outcome: change in cause leads to change in effect.	★		My previous study with mice showing relapse behaviors after Pb exposure along with other studies. (Albores-Garcia et al., 2021; Rangel-Barajas et al., 2020).

Figure 1: The Bradford-Hill criteria for plausible causality. Star symbols indicate which criteria the background evidence has supported, and the proposed project may support in determining Pb exposure as a factor causing the development of SUDs. The background evidence collected effectively supplements the criteria not addressed by the proposed study, except for specificity*