Emily L. Evans
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Uncertainty and Public Health Research Ethics

I. Introduction

Primary prevention efforts designed to reduce or eliminate exposure to environmental toxicants are critical to protecting the health of the population. Often, however, there is a lack of knowledge about which strategies will best accomplish the goals of primary prevention. Available public health interventions may be insufficiently supported by the evidence or known to be inadequate in important respects, and in some cases, there may be no intervention currently available. Public health intervention research is therefore necessary to develop "practical and feasible solutions" for reducing or eliminating the adverse health effects of environmental contaminants (Ryan 2006).[1]

As with all research involving human subjects, public health intervention research is subject to ethical and epistemic constraints. Yet traditional research ethics frameworks do not adequately address the scientific and ethical challenges presented by public health intervention research, which is conducted under decidedly non-ideal conditions. Most importantly, these frameworks fail to provide sufficient conceptual and practical guidance for analyzing the uncertainty assumed to justify the research. Because public health intervention research is designed to resolve uncertainty surrounding the scientific

[1] Public health interventions and research include, but are not limited to, environmental health interventions and research. Although I focus on environmental health interventions and research, I intend for my claims to apply to public health interventions and research broadly. In this paper, public health intervention research refers to "those studies, which have as their rationale and goals, the assessment of methodologies for reducing or eliminating the adverse impacts of environmental contaminants" (Mushak 2002).

and social value of interventions, evaluation of the research should *begin* by characterizing this uncertainty.

In contrast, approaches to determining whether such research is permissible generally begin the evaluation *later* in the research process – after the public health problem has been identified, the research question formulated, and the study designed. That is, a study proposal is isolated as the object of ethical analysis and evaluated against a mix of principles and regulations that are not always coherent or helpful in the context of public health intervention research.[2] The result is that ethical analysis is generally restricted to issues of informed consent, risk-benefit analysis, and subject selection (Mastroianni and Kahn 2002; Resnik, et al. 2005; Buchanan and Miller 2006). This is not to say that these issues are unimportant. Rather, discussion of these issues is premature without a more systematic understanding of the uncertainty assumed to justify the research.

In this paper, I argue that evaluations of public health intervention research must begin by characterizing this uncertainty. I examine both the epistemic aspects and ethical implications of uncertainty using the example of a recent study examining the effectiveness of treated sewage sludge in remediating lead-contaminated soil. This case study serves as a vehicle through which to explore and analyze (1) two fundamental aspects of uncertainty; (2) the conceptual parameters that should guide our understanding of uncertainty and evaluation of the research; and (3) ways in which these parameters

[2] For example, London argues that two main frameworks for assessing research risks suffer from fundamental deficiencies and consequently fail to provide sufficient practical guidance for conducting these assessments (2007b). Although London's criticisms are directed primarily at clinical research, they apply to public health intervention research, particularly insofar as approaches to public health research ethics are derived from methods used in the clinical research setting. Similarly, Kukla criticizes "traditional" understandings of the equipoise requirement, claiming that these fail to provide helpful guidance in determining whether research is ethically permissible in non-ideal conditions (2007).

might be operationalized in the context of a particular study. My goal is to provide a more robust understanding of uncertainty that can augment existing frameworks for ensuring that public health intervention research is both scientifically and morally sound.[3]

II. Background

The toxic legacy of leaded gasoline and paint affects millions of Americans. Although lead was banned as a gasoline additive in 1986, an estimated 4.5-5.5 million tons of the metal remain in soil and dust (Mielke and Reagan 1998; Stehouwer and Macneal 1999; Kitman 2000). Deposits from lead paint, which was used on approximately 75% of homes prior to 1978, further increase lead levels in soils (Stehouwer and Macneal 1999).

The problem is particularly acute for those living in urban areas, and children are disproportionately affected. Compared to adults, children are more likely to be exposed to lead and to be exposed at higher levels through frequent contact with contaminated soil via hand-to-mouth activities (Mielke, et al 1983; Stehouwer and Macneal 1999; ATSDR 2007). They absorb a larger proportion of ingested lead into their bloodstreams, and a greater proportion of this circulating lead is deposited in the brain (Lidsky and Schneider 2003; ATSDR 2007). Chronic exposure to lead in early childhood alters brain structure and impairs cognitive functioning and development (Canfield 2003; Lidsky and Schneider 2003).

Excavating the contaminated soil and replacing it with clean soil can reduce these exposures (Farrell, et al. 1998). However, governmental agencies and property owners

[3] Although I think that certain [research ethics] frameworks have more to recommend them than others, my approach is applicable to and should enrich any framework that takes uncertainty to be relevant to determining the permissibility of research.

have rejected this method of soil lead abatement as too costly (Silbergeld 1997; Farfel, et al. 2005; KKI 2008). A 1990 study by the U.S. Environmental Protection Agency (EPA) found that the cost of abating residential urban soil in Baltimore ranged from $600 to $4,891.33 per house with an average cost of roughly $2,000 (EPA Baltimore 1993). Moreover, properly disposing of the lead-contaminated soil is difficult due to the decreasing number of disposal sites, such as landfills, willing to accept it (EPA Boston 1993). Public health researchers have begun to explore less expensive and more feasible alternatives for decreasing the risks associated with exposure to lead-contaminated soils, including sandboxes, barrier shrubs, and raised boxes with clean soil (Farfel, et al. 2005).

Another potential alternative involves the application of biosolids compost products rich in phosphate and hydrous iron (FE) oxides to reduce the bioavailability of lead in contaminated soil (Farfel, et al. 2005). Biosolids compost is produced from sewage sludge that has undergone additional treatment. Sewage sludge that meets the most stringent pollutant limits, pathogen reduction standards, and vector attraction reduction is classified as exceptional quality (EQ) sludge and can generally be applied "as freely as any other fertilizer or soil amendment to any type of land" (EPA 2008).[4] This is the type of biosolids compost used to remediate lead-contaminated residential soils.

There are two ways in which the use of biosolids compost may reduce the bioavailability of lead. Bioavailability refers to "the likelihood of [an individual] ingesting a sufficient dose of lead and the ability of the intestinal tract to absorb and retain lead" (Mielke and Reagan 1998). First, biosolids compost products can promote

[4] EQ sludge is also referred to as "landscape grade" or "Class A" sludge.

the formation of pyromorphite, a form of soil lead with low solubility and bioavailability (Farfel, et al. 2005). Second, biosolids can help promote the growth of vegetation cover, making it less likely that individuals will be exposed to lead in soil and soil dust (Farfel, et al. 2005). By reducing the bioavailability of soil lead, biosolids compost amendments might reduce the risks associated with exposure to soil lead.

In 2005, researchers from the Kennedy Krieger Institute (KKI) and the Johns Hopkins School of Public Health published the results of a pilot study examining whether a compost amendment of biosolids was effective in reducing hazards from lead-contaminated soil (Farfel, et al. 2005). Although this intervention was shown to be effective in reducing lead concentrations in the soil, the researchers' use of sewage sludge in a heavily impoverished, minority community sparked a public outcry. The "sludge study", as it came to be called, was denounced on the grounds that the researchers exposed individuals, particularly children, to unacceptable levels of risk; failed to adequately inform the participants of the risks involved; and exploited a vulnerable population (Baltimore Sun 2008).[5]

Absent from these debates is any discussion concerning the scientific and social legitimacy of the research question itself, namely whether the relevant uncertainty surrounding this method's ability to reduce exposure to soil lead hazards was sufficient to justify the research. In the next section, I argue that understanding the nature and the scope of the putative uncertainty is critical to determining the permissibility of a study.

III. The Nature and Scope of Uncertainty

[5] Most of the concerns focused on the risks associated with exposure to the treated sewage sludge, not the lead in the soil.

Uncertainty is a necessary condition for the sound moral and scientific conduct of research involving human subjects. If the expert public health community lacked uncertainty about the interventions under investigation, it would be unethical to knowingly (1) subject individuals to inferior or harmful interventions or (2) withhold effective interventions. Moreover, if the relative merits of the interventions were previously established, as indicated by the lack of uncertainty within the relevant expert community, the results of an additional trial would be of little, if any, scientific value.

Despite the foundational role that uncertainty plays in the formulation and conduct of research, the concept has been insufficiently explored in the research ethics literature.[6] To the extent that uncertainty is discussed, it is usually either in the context of uncertainty regarding the potential risks and benefits of a study or in debates about whose uncertainty permits individuals to enroll in research trials.[7] In neither case has there been a widespread effort to unpack the epistemic aspects of uncertainty and trace out the ethical implications.

Perhaps the most important considerations left unaddressed are (1) the nature or type of uncertainty and (2) the scope of uncertainty, namely, that about which we are uncertain. In what follows, I examine the ways in which uncertainty can be characterized

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[6] This criticism applies to the research ethics literature generally, but concomitant with the lack of attention to public health research ethics (compared to clinical research ethics), there has been even less examination of uncertainty in this context.

[7] Much of the original discussion on uncertainty centered on answering the question of *whose* uncertainty counted for determining whether it was permissible to offer patients the opportunity to enroll in a [clinical] trial (e.g. the participant, the physician or researcher, the expert community, or some combination of these). Indeed, the equipoise literature takes this issue as foundational to the framework. (For a more detailed discussion of how this question has been answered in the context of equipoise, see London 2007a.) Although the expert community is increasingly seen as the appropriate level at which the uncertainty should be situated, little progress has been made in exploring other aspects of uncertainty. (A few exceptions to this include London (2007a), Djulbegovic (2007), and Kukla (2007)). As it stands now, these approaches are of limited usefulness in the context of public health research. I try to distance my discussion of uncertainty from these traditional debates in order to focus attention on the particular scientific and ethical challenges posed by public health intervention research.

in terms of its nature and scope and how these characterizations are critical to analysis of public health intervention research. First, I show how the type of uncertainty affects the epistemic and ethical justifications for a proposed trial. Second, I illustrate how the scope of uncertainty reflects the ways in which available evidence, economic and social constraints, and institutional structures and capacity, will influence the choice of interventions to study and the metric by which they are measured

The nature of uncertainty is treated loosely in the research ethics literature. Uncertainty is glossed as agnosticism, indifference, and conflict, but these terms represent distinct states. In fact, from a decision-theoretic perspective, only agnosticism and conflict are properly understood as uncertainty. Yet agnosticism and indifference are often treated as interchangeable concepts. Agnosticism is properly understood as a state where one has not yet made an all things considered judgment about the relative merits of sets of interventions and serves as an impetus to further inquiry and analysis (Evans and London 2006). Indifference, on the other hand, is a state in which one has made such an all things considered judgment and deemed the sets of interventions equivalent in merit (Evans and London 2006). For example, the expert public health community is agnostic about the appropriate intervention to address a particular public health problem when its members have yet to make a decision concerning the relative merits of intervention A and intervention B, but indifferent between the two if they have decided that the interventions are equivalent for the purposes of addressing this particular public health problem (Evans and London 2006).

Conflict arises when there is a disagreement among the members of the expert community concerning the relative merits of sets of interventions. For example, the expert public health community is said to be conflicted when at least a reasonable minority of members have endorsed a competing assessment [to that of the majority's] regarding the relative merits of intervention A and intervention B. (Freedman 1987; Evans and London 2006; London 2007a).

Because public health intervention research should be designed to resolve uncertainty, the sound scientific and moral conduct of a trial requires that the nature of the uncertainty be precisely articulated. While agnosticism and conflict at the level of the expert public health community may justify the conduct of a trial, indifference will not (Evans and London 2006). In the latter case, the "uncertainty" present is more appropriately described as equivalence, and there is nothing for public health intervention research to resolve.[8] However, even when the expert public health community is agnostic or conflicted about the relative merits of sets of interventions, the uncertainty may not always justify the proposed research. If the expert public health community is in a state of agnosticism, there may be other ways to resolve this uncertainty, or at least reduce it to a level at which public health intervention research is justified.[9] When there is

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[8] Equivalence (or indifference) is not necessarily a permanent state; new evidence may emerge that forces the expert public health community into a state of agnosticism or conflict concerning the relative merits of sets of interventions. How easily the expert public health community's stance will be disturbed depends on the strength and quality of both the evidence on which the interventions were said to be equivalent and the new evidence. For example, if the public health community had determined that two interventions were equivalent on the basis of strong, high-quality evidence, preliminary findings from poorly designed studies should not greatly impact that position. On the other hand, strong, high-quality evidence will more easily disturb determinations of equivalence that were based on weak and/or low quality evidence. (These claims apply to states of agnosticism or conflict as well.) This approach is similar to a Bayesian model of prior and posterior probabilities. For a rigorous analysis of how Bayesian methods can be employed in research, see Kadane (1996).

[9] For example, animal experiments or physiologically based pharmacokinetic (PBPK) models might be used to generate the evidence necessary for the design and conduct of a public health intervention study that is scientifically and ethically sound. In the clinical research literature, Djulbegovic takes a similar position, offering a "taxonomy of uncertainties" to guide the choice of clinical research design based on the underlying level of uncertainty (2007).

conflict, the permissibility of a public health intervention trial as a way to resolve the uncertainty is affected by who disagrees and to what extent.[10]

Similarly, the scope of the uncertainty affects the permissibility of the trial. Because public health intervention research is intended to resolve uncertainty surrounding the effectiveness of an intervention in achieving the desired outcome(s) under a given set of constraints, the scope of the uncertainty is multidimensional. That is, gaps in scientific knowledge are not the only considerations relevant to characterizing the uncertainty present; economic, social, institutional, and political conditions may influence our understanding of the uncertainty that a study must address.[11]

For example, researchers may be interested in whether "water kiosks" in remote African villages are able to adequately treat contaminated water in a manner that is sufficiently reliable, economically feasible, and sustainable.[12] Here, they are concerned not simply with whether the water treatment method works in an isolated laboratory setting, but whether the method is able to adequately address the public health problem as it occurs "on the ground."

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[10] A minority challenge to orthodoxy can represent legitimate conflict. Still, there will likely always be "residual" conflict among recalcitrant members of the expert public health community, particularly in cases where the definition of what constitutes an "expert" is broadened as part of efforts to create uncertainty. Although it is often the case that "more research is needed," the available evidence may justify going forward with the development and implementation of policies and programs. Further research is not precluded and may even be conducted concurrently with policy and program implementation. For example, suppose we are concerned about the adverse health effects of an environmental toxicant. If we know (1) the population exposure is x units and (2) the dose-response relationship between the exposure and outcome at x units, we do not need additional research on the dose-response relationship at much lower levels of exposure in order to implement measures to reduce the risks associated with exposure to this toxicant. At the same time, however, we can continue to gather additional information that will enable us to better understand the relationship between the toxicant and adverse health outcomes; this evidence will enable us to refine or revise existing policies if necessary. (I thank Dr. Thomas Burke for helpful discussion on this point.)

[11] Although as I note in the next section, the consideration given to such conditions in characterizing the uncertainty is not without limits.

[12] Economic concerns are also important in clinical research, particularly in understanding the comparative effectiveness of competing interventions. However, public health interventions are often more expansive and less controlled than targeted clinical treatments, and therefore their effectiveness must be measured against a larger set of parameters.

In accepting the multi-dimensional scope of uncertainty in public health intervention research, one recognizes that even if a "gold standard" intervention exists, public health intervention research may sometimes be justified in continuing to explore alternative methods for reducing the risks from environmental health hazards. Those who claim that it is unethical to provide anything less than the gold standard intervention, and that research on less costly or difficult interventions is therefore unjustified, fail to understand that the role of research in public health is tied to its capacities to successfully navigate complex problems arising from a combination of factors. Effective public health interventions are those that are "workable as well as protective in order to be implemented on a scale wide enough to provide meaningful benefits" (Ryan and Farr 2002).

Failure to evaluate public health interventions in "real public health settings" undermines our ability to protect the health of the population (Reijneveld 2009). The lack of public health intervention research leaves individuals at greater risk for adverse health outcomes, and in some cases, inadequate research may lead to the adoption of a "gold-standard" that is ineffective or harmful. Ryan and Farr note that "without such 'real world' research of health hazards…unproven and even dangerous interventions can gain acceptance in practice or regulations" (2002). For instance, traditional methods of removing lead paint, including power sanding or open flame burning, were shown to *increase* exposures to lead nearly 40 years after the practices were recommended or required by regulations (Farfel, et al. 1990; Ryan and Farr 2002). Had the scope of the original research question been broadened to include uncertainty about residual exposures (e.g. lead in dust) and health endpoints (e.g. blood-lead levels of workers and/or residents), this situation may have been avoided.

Of course, this is not to say that every "practical reality" should be understood as relevant to the uncertainty surrounding public health interventions; uncertainty can be manufactured out of any combination of factors.[13] The challenge, explored in the next section, is to determine what constitutes scientifically and ethically sound uncertainty in public health intervention research.

IV. Uncertainty and the Parameters of Ethically Permissible Research

The criteria against which the permissibility of public health intervention research is determined must reflect the significance of both the nature and the scope of uncertainty. In this section, I propose a preliminary framework for assessing the permissibility of public health intervention research with respect to uncertainty. I focus primarily on the scope of the uncertainty, as that was the predominant flashpoint in the "sludge study".[14] Before I address this issue, I want to make a few brief remarks about the connection between the nature of the uncertainty and study design.

Public health intervention research should be designed not simply to generate data but to provide evidence useful for addressing, if not resolving, the underlying uncertainty. The type and strength of evidence necessary for resolving uncertainty will differ depending on the nature of uncertainty. However, it is important to recognize that a

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[13] For a detailed and fascinating look at the ways in which uncertainty is inappropriately constructed and used as a putative justification for further research (and delayed public health action), see Michaels (2008).

[14] Technically, the term "sludge" refers to *un*treated sewage sludge and not the *treated* sewage sludge used in this study. The EQ sludge used in this study is commonly labeled and sold as regular "fertilizer" at many home improvement and gardening stores (Farfel, et al. 2005). Not surprisingly, critics of the study have dismissed the use of these more euphemistic labels. In this paper, I use the term sludge as a shorthand way of identifying the study as it has been described in the popular press and lay conversations.

single study may not fully resolve the uncertainty. The relevant uncertainty will persist until evidence emerges that is sufficient to create consensus within the expert public health community regarding the relative merits of the interventions (London 2006; Evans and London 2006; London 2007a; London 2007b).[15] Thus, it is critical that public health intervention research studies be designed in a way such that the results contribute to the body of evidence concerning the relative merits of the interventions, providing a sound basis for future research and public health policy.

Additionally, the evidence generated from public health intervention research must reflect the scope of the uncertainty surrounding the interventions of interest. Sound public health policy and practice require information concerning factors beyond basic efficacy, including, but not limited to, "real world" effectiveness, feasibility, sustainability, and cost. Public health intervention research must therefore target the parameters relevant to the public health problem of interest.

However, because there are multiple ways in which a particular public health problem can be formulated, there are multiple uncertainties that may be targeted by public health intervention research. Not all of these uncertainties (or the underlying problem formulations) are scientifically and ethically sound.[16] Public health intervention

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[15] Consensus need not imply unanimity. Again, there will likely always be residual conflict among members of the expert public health community. The question then is when should the uncertainty be considered sufficiently resolved (or the available evidence sufficiently informative) to take public health action, a question that space constraints do not permit me to properly address.

[16] Nor are they all the appropriate target of public health research. The research enterprise should be understood as one part of a morally appropriate social division of labor, and its use should be consistent with that role (London 2005). This raises the issue of how to determine when research should be employed in the service of public health problems. Oftentimes, there are interventions available to address the problem. However, these interventions are frequently deficient in certain aspects; they may be unreliable, marginally effective, too costly, or politically infeasible, among other things. The question then is whether we should devote resources to finding better interventions or continue to advocate, fund, and implement, to the extent possible, the established interventions. (London 2005; London 2007b; London 2008: Spriggs 2008). These are important issues in understanding the relationship between public health research, advocacy, and practice but are beyond the scope of this paper.

research should not focus on resolving such uncertainties.[17] At minimum, such research is a waste of scarce resources, and at worst, it significantly harms the interests of research participants (e.g., subjecting them to an intervention known to be harmful).

Here, the main concern is that considerations of cost and political climate will be allowed to unduly influence the characterization of uncertainty, favoring research over practice and allowing unethical research to be carried out on vulnerable populations. That is, a lack of political will or unjust social structures should not permit research to be substituted for interventions deemed valid and necessary with respect to population health and social justice (Farmer and Campos 2004; Spriggs 2004; Miller and Buchanan 2006; Spriggs 2008).

In light of these concerns, what sorts of parameters should be considered relevant to articulating the scope of uncertainty surrounding public health interventions? How might these parameters be conceptualized in a way that is useful for determining whether scientifically and ethically sound uncertainty obtains? Below I sketch out what I take to be three categories of *prima facie* parameters for articulating the scope of uncertainty in public health intervention research.

The first category is **scientific concerns**. Here the issue is whether the available evidence suggests that this is a scientifically sound research question. The first parameter in this category is <u>background knowledge</u>. Evidence regarding the relative merits of the public health intervention may be currently lacking, conflicting, or insufficiently supportive of the relationship between the public health intervention and the outcome(s) of interest. We are interested in whether the evidence suggests that there is a

[17] Again, for instructive examples see Michaels (2008).

scientifically plausible connection between the intervention and the outcome(s) of interest, and if so, what risks and benefits are associated with this approach.

The next parameter is comparative effectiveness. Interventions that are known to be effective in the short-term may have questionable effectiveness in the long-term. There may also be a range of interventions available (and competing for funding) that differ with respect to effectiveness. Both sets of considerations are important when evaluating the permissibility of public health intervention research.

The final parameter in this category concerns the generalizability of existing research, namely whether biological factors or differences in the natural or built environment may modify the effect of an intervention between the original study population and the population of interest. For example, research on adults may not generalize to children. In some cases, a public health intervention may need to be evaluated in different populations and settings.

The second set of parameters relate to **issues of priority**. Do the risks associated with the public health problem require the development and evaluation of other interventions? Here, the main considerations are the urgency, magnitude, and severity of the problem. In terms of urgency, research might be necessary to identify more immediate or efficient ways of addressing public health problems. Similarly, the development and evaluation of new interventions might be necessary when the available methods are no longer adequate for addressing a problem due to its magnitude and severity.

The final category – **responsiveness to the public health problem(s)** – looks at whether the available evidence adequately reflects the health outcomes of interest. The parameter of interest is the choice of endpoint(s). For example, there may be other related, but as yet unstudied, endpoints of interest that might better reflect the impact of an intervention on the health of the population. Even if the relationship between exposure X and outcome Y is adequately understood, the relationship between exposure X and outcome Z might better reflect concerns regarding adverse health outcomes.

This is by no means an exhaustive list of relevant parameters,[18] and the order in which they are listed should not be understood to reflect absolute lexical importance. Rather, this list is intended to assist in characterizing the scope of uncertainty surrounding public health intervention research, thereby informing a more comprehensive analysis of such studies.

In the next section, I show how these parameters might be operationalized in the context of the sludge study and how they can guide our evaluation of its scientific and moral soundness.

V. Uncertainty and Ethics: Evaluating the "Sludge Study"

Any systematic evaluation of the sludge study should begin by examining the uncertainty assumed to justify the research. The relevant uncertainty is identified by the research question, namely whether the use of biosolids compost amendments was effective in reducing soil lead hazards. The question is whether this uncertainty was scientifically and ethically sound.

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[18] Factors relating to economic concerns and the political climate may also be relevant to characterizing the uncertainty. Any discussion of the influence these considerations should have over the scope of the uncertainty raises thorny questions concerning the relationship between public health research and practice, an issue that I leave aside for the purposes of this paper.

According to the researchers, the study was designed to investigate "the effectiveness of in situ treatment by incorporation of composted biosolids and grass into contaminated residential soils to reduce lead hazards" (Farfel, et al. 2005). More broadly, the goal of the research was to "find effective ways to prevent lead poisoning" by identifying "a simple low-cost" method to reduce exposure to soil lead hazards (KKI 2008). These statements clearly mark the sludge study as public health intervention research, which should be reflected in concerns over the nature and scope of the study.

The first question is whether there was uncertainty to be resolved, and if so, what was the nature of this uncertainty? Here, the nature of uncertainty surrounding the use of biosolids compost amendments to reduce soil lead hazards is best understood as agnosticism. Prior research had produced mixed results concerning the effectiveness of complete soil abatement in reducing children's blood lead (PbB) levels (EPA Baltimore 1993; EPA Boston 1993; Farrell 1998; Mielke and Reagan 1998). At the time of the sludge study, researchers had begun to explore alternative methods to reduce soil lead hazards, including the use of biosolids compost amendment to reduce the bioavailability of lead in soil (Farfel, et al. 2005).

As the available evidence was tentative and superior alternatives had not yet emerged, the public health community had not made an all things considered judgment about the merits of biosolids compost amendment in reducing soil lead hazards. That is, they were agnostic about this public health intervention; this agnosticism served as the impetus for further inquiry and analysis, namely the sludge study. This study should thus be designed to disturb the agnosticism and provide evidence that, in conjunction with background knowledge, could lead the expert public health community to (1) favor or disfavor the use of biosolids compost amendments as an intervention for reducing soil lead hazards or (2) to disagree about the appropriateness of this intervention (i.e. conflict).[19] Importantly, the study was designed to meet these objectives and provide a sound basis for future research and public health policy.

The thornier issues involve the scope of uncertainty. In terms of background knowledge, the first parameter of interest, preliminary evidence suggested that the use of biosolids compost amendments had the potential to reduce the hazards from soil lead exposures. Animal experiments had shown that biosolids composts rich in phosphorus and iron reduced the bioavailability of lead in ingested soil (Farfel, et al. 2005). The application of biosolids compost amendments had reduced soil lead hazards at industrial sites and residential communities located near smelters (Farfel, et al. 2005). Additionally, biosolids compost amendments encouraged plant growth and cover, reducing the transfer of lead-contaminated soil and dust into homes (Mielke and Reagan 1998; Farfel, et al. 2005).

However, the risks associated with the intervention were unknown – and not addressed by the study. Although the EPA had approved – and at times promoted - the use of these biosolids compost amendments for residential use, significant concerns remained over the risks associated with exposure to treated sewage sludge (NRC 2002). EQ biosolids often contain toxic metals (including lead) and pathogens even after treatment. Moreover, at the time of the study, the National Research Council was in the process of conducting a review of the evidence and standards for the land application of biosolids (NRC 2002). The final report, issued in 2002, concluded that there was a

[19] Once agnosticism has been disturbed, the expert public health community may move to either a state of relative consensus or to a state of conflict concerning the merits of a particular intervention. In the latter case, further research is necessary to resolve the remaining uncertainties.

"critical need to update the scientific basis" of the regulations governing the land application of biosolids (NRC 2002).

Although the sludge study was designed to generate evidence concerning the relationship between biosolids compost amendments and soil lead hazards, it was not designed to examine the health risks associated with the use of these compost amendments. The exclusion of the latter relationship from the research question was putatively justified on the grounds that "the vast preponderance of scientific opinion shows that [the compost] did not then and does not now pose a known threat to human health" (KKI 2008). Yet the evidence available at the time of the study does not bear this claim out, and the NAS report published after the conclusion of the study underscores the ongoing uncertainty surrounding the health risks associated with biosolids and the need for more research (NRC 2002).

Still, in the context of this study, it would have been difficult to evaluate the health risks of biosolids compost amendments in a scientifically valid manner. The small sample size (9 households) and difficulties in attributing adverse health effects to exposure to the sludge itself would have greatly limited the usefulness of any data that might have been generated.

The sludge study fared better in terms of comparative effectiveness. At the time of the study, research into alternative methods of soil lead reduction was in its preliminary stages, and other interventions were not intended to have the same level of impact (e.g. raised boxes for gardening vs. remediation of the entire yard). As such, there was little evidence regarding the comparative effectiveness of these alternative methods. Moreover, the research concerning the "gold standard" – complete soil abatement – had produced mixed results concerning its ability to reduce exposure to soil lead hazards. What was known, however, was that primary prevention, not treatment (e.g. chelation therapy), was the more effective public health course of action; this favored efforts to identify effective preventive interventions. (Silbergeld 1997; Needleman 1998; Mielke and Reagan 1998).

With respect to the generalizability of existing research, the assessment is equivocal. A previous EPA study in Baltimore had examined the effectiveness of complete soil abatement (e.g. excavation and replacement) combined with stabilization of exterior lead paint (to prevent further accumulation of lead in soil) on soil lead levels. (EPA Baltimore 1993; Farrell, et al. 1998). The results did not provide evidence that soil abatement and exterior lead paint stabilization had a significant impact on children's blood lead (PbB) levels (Farrell, et al. 1998). However, the abated yards were found to have lower soil lead levels at baseline than had been anticipated; the intervention could still have a positive impact on individuals exposed to residential soil with higher lead levels. In the sludge study, 7/9 yards had baseline levels of soil lead that were more than twice as high as the average in the original EPA study. (Farell, et al. 1998; Farfel, et al. 2005). Thus, the results of the previous research were not necessarily generalizable to this population; the high soil lead levels, combined with the high cumulative lead exposure of individuals living in Baltimore, suggested that remediating the contaminated soil might be effective in reducing soil lead hazards.

With respect to parameters relating to issues of priority – urgency, magnitude, and severity, the sludge study fared well. There is a small window of opportunity for reducing children's exposure to lead; the effects of lead exposure are often irreversible, even with the use of treatments to remove lead from the body (Stehouwer and Macneal 1999; Guilarte 2008). At the time of the study, poisoning and cognitive impairment due to lead exposure were significant public health problems in Baltimore, yet funding for screening and primary prevention efforts was declining (Silbergeld 1997; Needleman 1998; MD DEP 2000).[20] The costs associated with the putative "gold standard" - complete soil lead abatement – made it highly unlikely that this method would be implemented in the future. A less expensive method for reducing the risk associated with soil lead exposure could have a significant and more immediate impact on the problem.

Moreover, despite the fact that leaded gasoline and lead paint had been banned for nearly twenty years, significant sources of lead remained in the urban environment, necessitating the development of more targeted public health interventions to reduce exposures. Interior lead paint abatement alone was no longer adequate to address the risks associated with exposure to lead. In fact, contrary to conventional wisdom that lead paint was the primary source of lead exposure, much of the scientific work had shown that lead in household dust represented the main source of exposure (Mielke and Reagan 1998). The lead in household dust could come from both pulverized lead paint *and* lead in soil (Mielke and Reagan 1998). Some claimed that soil lead represented a public health hazard equal to, if not greater than, lead paint in terms of its contribution to lead in household dust (Mielke and Reagan 1998).

The parameter that poses the biggest challenge to the scientific and ethical justification of the sludge study is the choice of endpoints. The ultimate outcome of interest is reduction in children's PbB levels; a method that reduced lead levels in soil but

[20] Throughout the 1990s, the prevalence of elevated PbB levels (≥ 10 μg/dL) among children screened in Baltimore was over 20% - nearly twice that of any other city or county in Maryland (Silbergeld 1997; MD 2000).

failed to reduce PbB levels [in children] would fail to achieve the goals of primary prevention. However, the sludge study only looked at soil lead levels; PbB levels were not measured (Farfel, et al. 2005).

The researchers argued that measuring PbB levels in the context of this pilot study was not feasible or scientifically sound.[21] Many of the participants were adults, and PbB levels are not usually a helpful indicator of exposure in this population.[22] Additionally, measuring PbB levels would have required other extensive measurements to control for confounding, and even then any data generated may have been little more than "noise." Finally, the researchers may not have been able to secure funding for the study if they were required to include this host of additional measurements.

However, measuring changes in the lead content of household dust – in addition to soil lead levels may have been an appropriate alternative (to measuring PbB levels). If one exposure pathway for lead was through household dust, and a reduction in soil lead levels decreased household dust levels, there would be increased evidential support for the hypothesis that reduction in soil lead levels reduced children's PbB levels. The researchers had much experience in measuring and collecting data on household dust levels (EPA 1997),[23] and in this study they had sampled lead levels in outdoor dust, suggesting that data on dust lead levels was potentially quite useful (Farfel, et al. 2005).

In light of these considerations, was the uncertainty targeted by the sludge study sufficient to justify the research? Those defending the research claimed, "The purpose of

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[21] I thank Peter Lees for much helpful and insightful discussion on these issues.

[22] PbB levels in adults are not usually reflective of recent exposure (e.g. from soil lead in the yard). An adult's PbB levels can be influenced by his or her bone-lead level, which is a measure of cumulative (lifetime) lead exposure. I thank Sue Moodie for helpful discussion on this issue.

[23] A previous project undertaken by many of the same researchers involved in the sludge study used measurements of household dust and lead content in order to examine the effectiveness of different methods of lead paint abatement.

the KKI study was to assess by *how muc*h and *how efficiently* the [intervention] could help reduce lead dust in soil around homes and *it ultimately proved highly effective in this regard*." (emphasis added, KKI 2008). Moreover, they argued that the research was in "direct response to those communities that were most heavily impacted by lead poisoning" and that this was an attempt to provide the community with "a means to reduce one source of lead exposure" (KKI 2008). These efforts were important insofar as government agencies and property owners had "generally decided the cost of soil replacement is prohibitive in all but the most grossly contaminated cases" (KKI 2008). These statements reflect the ways in which the research on this intervention addressed the urgency, magnitude, and severity of the public health problems.

The sludge study also addressed two of the parameters in the category of scientific concerns – comparative effectiveness and generalizability of the study. First, the researchers were investigating an intervention that was designed to have a larger impact on soil lead hazards than alternative interventions being developed at the time (e.g., raised boxes for planting vegetables). Second, the population targeted by the study was exposed to higher soil lead levels than those in previous research. Therefore, even though the prior research had failed to find a reduction in PbB levels from soil abatement, the current study population could plausibly benefit from this intervention. When measured against these parameters, as well as those addressing issues of priority, the sludge study appears justified by the underlying uncertainty.

Still, the sludge study should not be judged to address an ethically and scientifically sound uncertainty unless the researchers can address two key concerns – risks of exposure to the sludge itself and the choice of endpoints. First, the researchers must provide an independent evaluation and valid justification for the “safety” of the biosolids compost amendments, rather than just stating that the product is “EPA-approved.” This requires acknowledgement of the risks associated with the use of the sludge and possibly additional precautions, such as independent testing of the biosolids compost for metals and pathogens.

The researchers did in fact conduct their own tests to determine the levels of six metals, including lead, in the biosolids compost that was applied to the study sites. The concentrations of all metals were well below the limits set by the EPA, but the researchers did not provide justification as to their reliance on these standards as limits. This is particularly important insofar as the NRC was in the process of reviewing, and ultimately recommending, changes to the EPA’s risk-assessment process upon which these standards were based. The researchers acknowledged the NRC’s work but did not provide any explication about what effect, if any, these recommendations would have for the lead concentration standards they cited in arguing that the sludge was “safe.” Additionally, no mention was made of independent testing of the biosolids compost for pathogen levels, which is a significant source of concern in terms of the adverse health effects resulting from exposure to the sludge. A more thorough discussion of the uncertainties concerning the possible health effects associated with exposure to the sludge would have better met the requirements of the background knowledge parameter.

Second, in order to demonstrate that the study was sufficiently responsive to the public health problem of interest, the researchers need to establish that measurement of PbB levels or household dust lead levels for use as an endpoint would *not* (1) accurately reflect the outcomes of interest (e.g. adding too much “noise” to the data) or (2) be prohibitively difficult or expensive to perform. Given that a reduction in soil lead levels is only one part of the pathway to reducing soil lead hazards, and that the ultimate aim of this research is to reduce children's PbB levels, it should be made explicit how this pilot study is situated with respect to a broader research agenda for the research group or other institutions.

If the researchers can satisfactorily address these two concerns, then the sludge study should be considered to have passed the first stage in evaluation; that is, it addresses a scientifically and ethically sound uncertainty. This determination should only be made after a systematic assessment of the nature and scope of the relevant uncertainty has been undertaken. In this section, I have provided an illustration of how such an assessment might be conducted using the framework I developed in Section IV.

VI. Conclusion

Public health intervention research provides a foundation for the development and implementation of policies targeting public health problems. Given the complexity of public health problems, such research must be designed to address uncertainties arising not only from gaps in scientific knowledge but also from factors related to economic, social, institutional, and political conditions. This presents unique challenges for any approach to determining the permissibility of public health intervention research.

In this paper, I present a practical approach to the analysis of public health intervention research that begins with a characterization of the nature and scope of the uncertainty. Agnosticism and conflict represent distinct types of uncertainty, and a public health intervention study should be designed to resolve the type of uncertainty present.

Similarly, public health intervention research must be responsive to the parameters governing the scope of uncertainty, including, but not limited to, background knowledge; comparative effectiveness; generalizability of existing research; the urgency, magnitude, and severity of the problem; and the choice of endpoints.

As I have shown in my analysis of the sludge study, it is necessary for a public health intervention study to respond to uncertainties that are scientifically and ethically sound in order to constitute permissible research. A better understanding of the nature and scope of the uncertainty enables us to make a more informed judgment in this matter

Of course, determining whether scientifically and ethically sound uncertainty obtains is not sufficient to ensure that public health intervention research is permissible. Among other concerns, issues of informed consent, risk-benefit profiles, and subject selection must be adequately addressed. Again, public health intervention research may pose unique challenges for any proposed response to these concerns. For example, public health interventions often address problems that affect a particular community. Here, securing individual informed consent is not enough; researchers must engage the community in the design and conduct of the research.[24]

However, a more systematic understanding of the uncertainty assumed to justify the research is necessary prior to addressing these issues. Public health intervention research that fails to target an ethically and scientifically sound uncertainty precludes questions concerning issues such as community engagement or potential risks and benefits. That is, it would not be permissible to offer individuals or communities enrollment in such research, regardless of the potential benefits or the stringency of the informed consent procedures.

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[24] I thank Sue Moodie for helpful discussion on this issue.

As such, my approach can augment existing frameworks used to determine the ethical permissibility of public health research.[25] Insofar as these frameworks require uncertainty as a necessary condition for [public health intervention] research involving human subjects, the guidelines offered in this paper provide a more robust method of characterizing uncertainty. A better understanding of the nature and scope of the uncertainty enables public health intervention research to better target the public health problem of interest, which has implications for issues such as risk-benefit profiles.[26]

The preliminary account of uncertainty offered in this paper represents an important effort to examine the epistemic aspects and ethical implications of uncertainty in public health intervention research. I have outlined ways in which the uncertainty characterization influences the ethical permissibility of the study, and the sludge study serves as an example of how these guidelines might be operationalized. Still, my analysis of the sludge study and uncertainty in public health intervention research remains incomplete. Additional work is needed to better understand (1) the ways in which economic and political factors should influence the uncertainty characterization, and thus the permissibility, of public health intervention research and (2) the relationship between public health intervention research, advocacy, and practice. My hope is that these issues will receive increased attention among those interested in the ethics of public health intervention research.

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[25] For a review and critique of some of the dominant frameworks, see London (2007a).

[26] For example, public health intervention research that targets a more precisely defined uncertainty may minimize unnecessary risks by eliminating aspects of a proposed protocol that are not necessary for addressing the research question. Similarly, to the extent that the research addresses the relevant scope of uncertainty, [potential] benefits to subjects may increase (e.g., focusing on the effectiveness of interventions in reducing the risks associated with an exposure in a manner that is feasible, reliable, and sustainable).

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