HUMAN SUBJECT CONSIDERATIONS IN ENVIRONMENTAL RESEARCH: THE UNIVERSITY OF MICHIGAN DIOXIN EXPOSURE STUDY

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Introduction and Background

In recent years there has been an increase in studies of environmental exposures and potential consequences of such exposures on human health. Investigators have sought to measure and quantify environmental pollutants inside and outside of private residences, including contaminants in soil, water, air, and house dust. While some studies attempt to relate measured exposures to individual human health outcomes and so it is obvious that the research involves human subjects, many environmental studies are solely intended as exposure studies and do not assess individual health outcomes. In these cases it may be less apparent to investigators that they may be engaged in human research. Most human research studies involve potential risks to subjects that fall into one of the following three domains: 1) physical risk; 2) psychological risk; 3) and risk to reputation. A less common and possibly underrecognized category is financial risk to subjects. Certain types of environmental investigations may create substantial financial risk for study participants (e.g., loss of property value or inability to sell property, or responsibility for clean up costs). An additional complication is that many environmental studies investigate chemicals for which little is known about human health effects, and/or there may be no environmental regulations (e.g., what is a "high" level?). This paper is meant to be an exploration of some of these issues as illustrated by the University of Michigan Dioxin Exposure Study (UMDES). The ultimate goal is to enhance the understanding of research risks, and the protection of human participants in future environmental research studies.

The University of Michigan Dioxin Exposure Study

The UMDES is designed to assess exposures to dioxins, furans and coplanar polychlorinated biphenyls (PCBs), describe the pattern of serum dioxin, furan and PCBs (collectively 'dioxins' or 'dioxin-like compounds') levels among adults, and to understand factors that explain variation in serum dioxin levels. The study was undertaken in response to concerns among the population of Midland and Saginaw Counties in Michigan that dioxin-like compounds from the Dow Chemical Company facilities in Midland have contaminated areas of the City of Midland and sediments in the Tittabawassee River flood plain. There is concern that residents' body burdens of dioxins may be elevated because of environmental contamination (i.e., soil and house dust). To address these concerns the study was designed to measure the serum levels of dioxins in a random sample of the population in the region and to estimate each individual's past exposure to various factors that are believed to contribute to the body burden of dioxin-like compounds. By measuring factors that reflect potential exposure to dioxins, furans and co-planar PCBs through air, water, soil, food intake, occupations, and various recreational activities, the study can identify factors that correlate with (and explain variation in) serum congener levels. A central goal of the study is to determine which factors explain variation in serum congener levels, and to quantify how much variation each factor explains. A key element of the study design is measurement of the 29 congeners of dioxins, furans, and co-planar PCBs for

which there are consensus toxicity equivalency factors (TEFs)[1], in serum, and in house dust and soil from the residence of each study participant. The UMDES is an exposure pathway study. The study does not address potential adverse health effects of exposures to dioxin-like chemicals. Full details on the study design, field and laboratory methods, and study findings are posted on the study website: www.umdioxin.org.

Since the UMDES involves interviews and obtaining blood samples from subjects, there was never any question that the study was human research that required oversight of an Institutional Review Board (IRB). However, the risks related to the interview are minimal (there are no questions that are embarrassing such as sexual activities, or seeking information about illegal behavior such as drug abuse), as are the risks related to drawing blood (i.e., standard phlebotomy from healthy subjects). The complicated issues arose from sampling and analyses of house dust and soil from the yard, activities that involve no physical, psychological or reputational risks to subjects.

In the State of Michigan environmental regulations govern the identification, management, and clean-up of soil with 'elevated' levels of dioxins. The Michigan Department of Environmental Quality (MDEQ) currently has a combined residential standard for total dioxins, furans and PCBs in soil of 90 parts per trillion (ppt) total toxic equivalency (TEQ). (The United States Environmental Protection Agency (USEPA) has a Superfund policy guideline of 1,000 ppt total TEQ.) In contrast, we are not aware of any government regulations pertaining to dioxins in house dust in private residences.

MDEQ considers any residential property with soil at or above the combined standard of 90 ppt to be a "facility" (as in 'hazardous waste facility') for the purposes of state regulations. Briefly, if a property owner has knowledge that his property is a "facility", and he caused the contamination, there are a number of regulatory requirements he must comply with to address the contamination. If he did not cause the contamination, but it migrated onto his property, he has no obligation to notify the MDEQ or clean it up (which is the circumstance that probably applies to most or all subjects in the UMDES). However, in either case he may not move the contaminated soil in such a manner that it would spread or exacerbate the contamination. There may also be additional due care obligations. In the future the MDEQ could lower the soil standard, thus triggering the designation as a "facility" for properties that had previously not been labeled as such. If the property owner does not learn results of soil analyses, then he would not know whether his property is a "facility" under state regulations now or in the future. Regardless of whether the property is or is not a "facility", there are other risks and burdens of knowing levels of dioxin in soil and/or house dust. Knowledge of levels of dioxins, furans and PCBs in soil or house dust could potentially have negative consequences on the value of the property. At the time of sale of the property the owner may be obligated to divulge knowledge of these results to potential buyers. Knowledge of the soil and/or house dust analyses could also have negative consequences for landlords or other types of property owners if, for example, tenants or other residents on the property want the owner to take remedial actions. Again, if the property owner does not know results of analyses of soil or house dust, then he would have no information to divulge to buyers or others with an interest in the property.

Since for most people their home is their largest single financial investment, the potential financial risk to study participants can be large. Faced with such potential risk, many subjects might have chosen to decline to participate in the UMDES. A reduced rate of participation of eligible subjects might have introduced bias, and might have reduced the validity and generalizability of the results. In addition to standard confidentiality practices governing human research, the UMDES sought to mitigate the financial risk to subjects via two mechanisms. First, after providing a description of the potential risks to subjects, they were offered the option to receive or not to receive results of analyses of soil and/or house dust (and, they could change their decision). As noted above, if subjects do not receive the results, then they have no knowledge and they have no reporting obligations. Also, the investigators, as third parties, have no requirement to report results to government agencies or other parties, and in fact, cannot do so under standard confidentiality practices governing human research. Second, the investigators obtained a Certificate of Confidentiality (CoC) from the National Institutes of Health (NIH). With the CoC third parties cannot

force researchers to disclose information that may identify subjects, even by a court subpoena, although subjects are free to disclose their personal results if they so choose. The CoC is intended to enhance research that has great social value, but which may involve undue risk to individual study participants if their information is disclosed. A full description of the CoC program is available at the following web site: http://grants.nih.gov/grants/policy/coc/. All consent documents and a copy of the UMDES CoC are posted on the study web site: www.umdioxin.org. It should also be mentioned that subjects solicited to be in the UMDES were offered an incentive totaling $100 if they participated in all four phases of the research (interview, blood sampling, soil sampling, house dust sampling).

How successful were these steps in convincing potential subjects to participate in the research? While the UMDES was not designed as an experiment to test this hypothesis directly, the observed results suggest that the study was very successful in convincing eligible subjects to allow soil and house dust samples to be collected and analyzed. Overall, despite a high 'subject burden', and potential financial risk, more than 90% of subjects who were eligible to have soil and/or house dust sampled agreed to do so (over 700 subjects in each instance – see Table 1). Furthermore, it would appear that the option to not receive results (with the added protection of the CoC) was a critical element of the recruitment process, since approximately one third of subjects elected to not receive results of soil and/or house dust analyses, while, in contrast, 95% of subjects elected to receive results of their serum analyses (see Table 2).

Table 1. Cooperation rates for interview, serum, dust, and soil sampling, UMDES, 2005-2006.

Study area	Cooperation rate			
	Interview	Serum	Dust	Soil
Flood plain	83.7%	83.9%	91.0%	91.3%
Non-flood plain	82.4%	73.7%	90.9%	93.2%
Control (Jackson & Calhoun counties)	82.2%	78.4%	93.8%	91.9%
Overall	82.9%	79.6%	91.7%	92.0%

Table 2. Rates of choosing to receive results of analyses of serum, dust, and soil, UMDES, 2005-2006.

Study area	Rate of Choosing to Receive Results		
	Serum	Dust	Soil
Flood plain	95%	65%	61%
Non-flood plain	97%	74%	71%
Control (Jackson & Calhoun counties)	93%	62%	59%
Overall	95%	67%	63%

Discussion and Conclusions

Exposures in the environment, including the home environment, are a growing concern. Public health agencies, academic investigators and others have engaged in a variety of studies to better understand exposure pathways for various toxins, and, hopefully, to reduce exposures and possible associated health risks. There is great public interest in these questions, and considerable controversy. In the process of attempting to address such questions, investigators have an obligation to protect human subjects and to minimize the risks of the research, while at the same time addressing questions that have great social importance. These are often competing interests that can be difficult to reconcile. This paper has attempted to illustrate some of these issues, and how they can be addressed, via the example of one study, the UMDES. There are a number of other questions that have not been addressed in this paper. For example:

- Environmental exposure studies may be conducted by investigators who traditionally have not been involved directly in human research (e.g., engineers, chemists), and therefore they may be less likely to recognize potential risks to human subjects and/or that the research may require oversight by an IRB. In addition to a possible lack

of awareness on the part of investigators, IRBs may have less experience with addressing the type of risk generated by environmental exposure studies.

-The definition of "human subject" under the Common Rule (the federal regulations adopted by more than a dozen federal agencies for the protection of human participants in research studies) is imprecise. A human subject is defined under the Common Rule as a "living individual" about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. (*See* 45 C.F.R. § 46.102(f), or http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102.) Property is not a living individual. But what if a researcher collects a soil sample from a public area adjacent to a person's property? An "intervention" is defined to include a "manipulation . . . of the subject's environment . . . performed for research purposes." Does the researcher's soil sampling constitute an intervention?

-How and to what extent does the Common Rule, and associated IRB practice, address risk generally and financial risk more specifically? To approve a proposed research study, an IRB must find, among other things, that risks to subjects are minimized and are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result. (*See* 45 C.F.R. § 46.111(a), or http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.111.) Under what circumstances can the potential benefits to society of environmental research outweigh the very real risks to individuals whose future financial security is at risk? Notably, the term "financial risk" is mentioned only once in the Common Rule, in an unrelated context. Yet the Office for Human Research Protections, the agency that enforces the Common Rule in federally supported studies, clearly recognizes that financial risk must be addressed in at least some instances. For example, research proposals may not be approved through an "expedited review" mechanism where identification of individual subjects may put them at risk of financial harm, unless procedures can be implemented to ensure that risks of disclosure are minimized.

-A key part of the mission of public health agencies is to protect the public's health. When a public health agency investigates potential public health risks, such as environmental contamination in soil, what is the proper balance between confidentiality of individual subjects and reduction of financial risk to subjects versus the public's right to know?

-What are a researcher's legal and ethical obligations not only to current but also to potential future residents? To the extent the Common Rule does not currently address these concerns, should federal laws or regulations be amended to do so? What are the potential implications for future environmental and other traditionally unregulated research?

These and other issues will be addressed in a future paper.

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