Supporting Statement B

Longitudinal Investigation of Fertility and the Environment – NICHD

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B. 1. Respondent Universe and Sampling Methods

Respondent Universe

A prospective cohort study design comprising couples interested in becoming pregnant in two well-defined geographic areas is underway to capture longitudinal collection of data on lifestyle factors and menstrual cycle characteristics over the time period in which couples are attempting pregnancy. This approach permits empirical evaluation of accession and drop out biases. Couples are being recruited prior to conception (i.e., preconception enrollment) to assess a *spectrum* of sensitive reproductive and developmental outcomes that can only be ascertained in this manner (e.g., time required for conception, and early pregnancy loss as measured by human chorionic gonadotropin hormone (hCG)). This allows us to capture most postimplantation pregnancies and losses long before clinical recognition (Wilcox et al., 1988) to assess exposures at critical windows such as before, at or shortly after conception that are capable of disrupting human development, while at the same time establishing a temporal ordering between exposure and outcome (Chapin et al., 2004).

Measuring the time required for couples to conceive has the added advantage of providing a valid estimate of incident infertility or the absence of conception after 12+ months of regular intercourse without the use of contraception, especially given the absence of *incident* data in the United States. The National Survey of Family Growth has done an excellent job measuring the prevalence of impaired fecundity and infertility for some subgroups of the population and report increasing rates for the more recent U.S. birth cohorts and subgroups such as women aged 20-24 years and non-whites (Stephen

and Chandra, 1998). Some authors interpret this to be consistent with an environmental etiology.

The study cohort has been recruited by two contractors - RTI International and Texas A&M University System (TAMU) School of Rural Public Health – who have sampled licensed fish holders or likely anglers as designated by marketing research. In each geographic site, state fish consumption advisories exist to advise the public about ways to minimize exposures associated with eating fish (www.mde.state.md.us/assets/document/fish/advisory_summary.pdf; www.michigan.gov/documents/FishAdvisory03_67354_7.pdf; www.tdh.state.tx.us/bfds/ssd/pdf/FishAdvisoryBooklet2004.pdf).

We are targeting anglers as they have been reported to consume more fish than non-anglers, thereby, enhancing the likelihood of a range in exposure for persistent compounds that have bioaccumulated and magnified with the aquatic ecosystems. The sampling strategy is purposefully designed to include couples from medically underserved and/or socioeconomically disadvantaged geographic areas, given concerns about environmental injustice (i.e., poorer individuals are more likely to reside closer to environmental hazards than wealthier individuals) (Sexton 1997). The limited body of evidence to date stems largely from convenient samples of white women from middle class backgrounds (Axmon et al., 2000; Buck et al. 2004). Based upon existing prospective pregnancy studies with preconception enrollment, we anticipated that between of 0.8 to 4.0% of women of reproductive age will be planning pregnancies at

any point in time (Buck et al., 2004). However, our realized experience to date suggests that this figure is <1.0%, similar to that reported for two other population based studies in Denmark and France (Bonde et al., 1998; Slama et al., 2006). Population-based research involving women of reproductive age in Pittsburgh as directed by Dr. Anne Sweeney (PI for TAMUS site) reported that 5% of women were planning to become pregnant (Sweeney et al., 1989) similar to NSFG estimates (Abma et al., 1997). Recruitment strategies and enrollment targets are rooted in the idea that approximately 120 women of reproductive age will need to be approached to enroll one woman who is planning to become pregnant. Telephone screening has been used to identify eligible couples (i.e., women aged 18 to 40 years and men aged 18+ who are planning a pregnancy).

Sampling Methods

A population-based approach is being attempted to identify and recruit couples planning pregnancies in three geographic U.S. sites. Each research site has targeted anglers or individuals with fishing interests of who are of reproductive age and residing near contaminated water bodies. Most anglers and/or their families consume at least some of the fish that they catch, placing them at higher risk of exposure to the study chemicals of interest (Belton et al., 1986), especially minority anglers (West, 1992).

Access to state fish license registries for research purposes varies, as does the type of data included in those registries. This necessitates flexibility with regard to defining the target population and recruitment strategy at each site (see Table 1). The Texas site is

using the Texas Parks and Wildlife Department's angler database to recruit participants from ten counties along the Gulf Coast. Access to Michigan's angler registry is restricted by law (Michigan Public Act No. 442 of 1976, as amended, 15.243, Section(1)(a); as such, RTI International recruited study participants by using a commercially available marketing database (InfoUSA®) to sample from four counties in Michigan. To ensure a diverse study population, each site has oversampled individuals of a racial or ethnic minority. Oversampling has been operationalized in a manner consistent with other government-sponsored projects such as the Current Population Survey and the National Medical Expenditure Survey (Cohen et al., 1987; Singh et al., 1994). [Please note that the requested OMB extension for which this application is being submitted requires only continued recruitment in Texas. The Michigan site has completed recruitment.]

Table 1. Recruitment Strategy and Expected Response Rates by Research Site

Research Site	**Michigan**	**Texas**
Target Area	4 counties	10 counties
Recruitment Strategy	InfoUSA® identify people with fishing interests	State fishing license registry
Initial Contact Approach	Bulk mailing with telephone follow-up	Bulk mailing with telephone follow-up
Size Target Population	234,182 individuals	188,601 individuals
# Couples Enrolled/ # Completing	104/72	396/317
Response	Actual = 69%	To date, 80%

NOTE: The Michigan site has completed all data collection. This extension pertains only to the Texas site.

B. 2. Procedures for the Collection of Information

The absence of a sampling framework for couples of reproductive age planning pregnancies complicates the ability to truly define the target population. Fish license registries in Texas have been merged with InfoUSA® to weight selection by age to maximize sampling individuals or reproductive age in the event of missing registry data. RTI statisticians assessed the capture of InfoUSA® households in relation to 2000 U.S. Census data and finds comparable listing for the four Michigan counties, i.e., 173,347 and 172,522, respectively.

Two competitively chosen research sites were selected for the recruitment of 500 couples for up to 12 months as they try to conceive to become pregnant (most will become pregnant within the first three months) and through pregnancy for couples achieving a clinical pregnancy (a minimum of 400 couples are expected to complete the entire study protocol). Anglers comprise the target population, given their potential for exposure to persistent environmental chemicals. The study's primary environmental exposures are listed in Section A.2. and Attachment5.a.. Study outcomes include time-to-pregnancy, infertility (the absence of pregnancy following 12 months of trying), pregnancy loss, gestation, and birth size. Three data collection instruments have been designed to capture covariate data: a 25-minute baseline interview; 2-minute daily journal while attempting pregnancy; and a 5-minute monthly journal for pregnant women. An illustration of data collection activities is provided in Attachment 1.a. along with all data collection instruments and related information in Attachments 1.b.-1.o. Couples can elect to complete journals either online or via postage paid postcards as discussed in Supporting Statement A.3. Research sites have been ensuring the completeness of reporting. The

DCC has developed a web-based data management system that ensures the collection of internally consistent and complete information with appropriate consideration of missing data. Highly trained research nurses are instructing couples in the use of commercially available home fertility monitors to aid them in timing intercourse to enhance the probability of pregnancy and digital pregnancy test kits to identify postimplantation pregnancies and pregnancy losses. Blood and urine samples are being collected at baseline from both partners of the couple for measurement of the environmental exposures including cotinine and phytoestrogens. Two semen samples are being collected from male partners as a global measure of male fecundity and to quantify contaminants in seminal fluid. Two saliva samples are being obtained from female partners to measure cortisol levels as a marker of stress. This will allow us to evaluate whether or not stress modifies the relation between environmental exposures and human reproduction and development. Illustrations of the at home specimen collection kits, fertility monitors and pregnancy test kits are included in Attachment 4.d..

The Longitudinal Investigation of Fertility and the Environment protocol incorporates a number of quality control measures. Nurses and interviewing staff have received extensive training regarding study equipment and procedures. Nurses are, in turn, training participants in the use of fertility monitors and home pregnancy test kits. Computer assisted interviewing software incorporate consistency checks and the DCC will perform periodic checks for missing and inconsistent data. Problems, if identified, are being referred to the research sites for resolution.

Power calculations affirm our ability to detect meaningful differences for each of our hypotheses (see Table 2). Our assumptions are based upon the empirical data from prospective pregnancy studies conducted to date (Buck et al., 2004) and exposure estimates from the CDC's Second National Report on Human Exposure to Environmental Chemical (2003) and the New York State Angler Cohort Study (Buck et al., 2003). Based on a sample size of 400 couples completing the entire study protocol, we anticipate that 320 (80%) couples will become pregnant of which 202 (63%) will have a live birth (92% term birth and 8% preterm birth). Power calculations are based on two-tailed tests with alpha = 0.05, and a mean PCB exposure of 4.0 ng/g serum.

Table 2. Summary of Estimated Statistical Power by Study Hypothesis

Study Outcome	Sample Size	Minimal Effect Size	Model*	Power (%)
Time-to-pregnancy	400	a hazard ratio of 2.5 per unit increase in PCB ng/g serum	Discrete Time Cox	88
Infertility	400	OR = 1.50	Logistic	90
Pregnancy Loss**	320	OR = 1.57	Logistic	85
Preterm delivery	202	OR=2.46	Logistic	80
Gestational age	202	$\geq$0.26 weeks reduction in gestation per unit increase in PCB	Linear Regression	89
Birth Weight	202	$\approx$73 gram reduction in birth weight per unit increase in PCB	Linear Regression	81

*Primary model, although others may be used.
**Power for early or human chorionic gonadotropin (hCG) detected pregnancies with home pregnancy test kits.

B. 3. Methods to Maximize Response Rates and Deal with Nonresponse

As shown in Table 2, we expect a minimum of an 80% completion rate, which is consistent with the response rates of other population-based prospective pregnancy studies with preconception enrollment (Bonde et al. 1998; Brown et al. 1997; Buck et al.,

2002; Ellish et al. 1996). Participants are receiving remuneration of $75 each for providing biological specimens, as described in detail in Section A.9, which is well within the range used in similar studies (Buck et al., 2004).

To enhance participation, introductory letters are being sent to potential study participants followed by a personalized telephone call within two weeks to elicit participation and establish eligibility. A public website is available (www.lifestudy.us) and individual research sites have developed promotional materials tailored to their target populations. Study sites have interviewers fluent in both English and Spanish. All study instruments have been translated into Spanish.

An exhaustive literature review of incentives for groups traditionally underrepresented in research identified several retention strategies that will be incorporated into the Longitudinal Investigation of Fertility and the Environment protocol. These include: 1) acquiring contact information for at least three contacts (friends or relatives of the participants) once a signed release is obtained by the participating couple (Areán et al., 2003; Boots Miller et al., 1998; Boys et al., 2003; Ribisl et al., 1996; Senturia et al., 1998); 2) including change of address cards in the daily journals or on the website (Napholz, 1998; Prinz et al., 2001; Ribisl et al., 1996; Senturia et al., 1998; 3) developing an electronic database of all information regarding contact with participants (e.g. when interviews and contacts were made, day and time of each to facilitate identification of a "best time" to reach study participants (Ribisl et al., 1996; Senturia et al., 1998; Shumaker et al., 2000); and 4) periodically sharing successful tracking techniques among

research sites (Senturia et al., 1998). In addition, each site will establish and maintain a trusting relationship with study participants by ensuring that: 1) they have a complete understanding of the study requirements (Marmor et al., 1991; Senturia et al., 1998); 2) there is a flexible interview and follow-up schedule (Areán et al., 2003; Janson et al., 2001; Marmor et al., 1991; Prinz et al., 2001; Ribisl et al., 1996; Senturia et al., 1998); 3) there is regular feedback about the study through a newsletter or website (Bender et al., 2003; Janson et al., 2001; Marmor et al., 1991; Prinz et al., 2001; Wilcox et al., 1995); 4) reminder cards or more personalized thank you notes or birthday cards are sent (Bender et al., 2003; Boots Miller et al., 1998; Boys et al., 2003; Dennis & Neese, 2000; Marmor et al., 1991; Napholz, 1998; Prinz et al., 2001; Senturia et al., 1998); and 5) there is continuity of contact by making every effort to have the same nurse/interviewer contact the couple over time (Boots Miller et al., 1998; Gilliss et al., 2001; Prinz et al., 2001; Senturia et al., 1998). Lastly, the DCC has devised a tracking mechanism to keep research sites informed about the status of complete, incomplete, pending, and missing data. As described in Section A.9., a quality control plan has been developed to ensure accuracy and reliability of data.

B. 4. Test of Procedures of Methods to be Undertaken

The NICHD undertook a series of preparatory tasks, including publishing literature reviews of methodologic relevance (Buck et al., 2004; Rockett et al., 2004). Site PIs have considerable expertise in conducting epidemiologic research on sensitive outcomes in relation to environmental exposures. Dr. Anne Sweeney (PI of the Texas site) has

successfully led two prospective pregnancy studies with preconception recruitment and Dr. Timothy Wilcosky (PI of the Michigan site) is an expert in biomarkers, as evidenced by his well-regarded textbook on the topic. Prior to coming to the NICHD, Dr. Germaine Buck Louis (NICHD) also conducted a prospective pregnancy study with preconception recruitment with funding from the ATSDR. This highly successful project enrolled mothers planning pregnancy with follow-up of infants through age two years, underscoring the willingness of families to participate in research on this important topic. Dr. Steven Schrader (NIOSH) has conducted numerous field based studies focusing on semen quality and has successfully utilized the methodologies included in this study ($\geq$80% response).

Research sites obtained IRB approval to pilot test aspects of the proposed Longitudinal Investigation of Fertility and the Environment protocol, particularly those pertaining to the use of the digital fertility monitor. None of these pilot tests included more than eight people. The results of the pilot work support the feasibility of using the monitor in population-based research and are consistent with the communication that we have had with two investigators currently in the field with studies that incorporate the use of the monitor to: 1) aid couples in conceiving (Dr. Cecilia Pyper, Oxford University) and 2) to assess prediction of cervical mucus (Dr. Joseph Stanford, University of Utah). No formal evaluation of the digital pregnancy test kits was undertaken, as their utility for field research is evidenced by their designation as an U.S. FDA class II medical device. A historical presentation of the development and use of home pregnancy test kits, which

were first developed investigators at the NICHD, is available at:

www.history.nih.gov/exhibits/thinblueline/timeline.html.

B. 5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

Intramural investigators at the NICHD have developed the analytic plan in collaboration with the PIs from the two research sites. In doing so, a number of experts in epidemiology, longitudinal data analysis, measurement error, and biomarkers have been contacted. A list of these individuals is presented in Table 3.

Recruitment and all aspects of data collection have been done by two government contractors: 1) RTI International in Michigan and 2) Texas A&M Rural School of Public Health in Texas. Intramural investigators at the NICHD will do the data analysis. A complete listing of these individuals is provided under the heading NICHD in Table 3.

Table 3. Individuals who have Provided Statistical/Methodological Consultation to the Longitudinal Investigation of Fertility and the Environment Study

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NICHD, DHHS	
Germaine M. Buck Louis, PhD MS (PI)	*301-496-6155*
Mark Klebanoff, MD MPH	301-496-5267
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Aiyi Liu, PhD	301-435-6953
Courtney D. Lynch, PhD MPH	301-435-6928
Leila Jackson, PhD MPH	301-435-6918
Oklahoma University Health Science Center *(consultants to TAMU)*	
Jennifer Peck, PhD	405-271-2229 ext 48053
B. Mitchell Peck, PhD	405-271-2114 ext 37082
RTI International	
Tim Wilcosky, PhD (PI)	*919-541-7367*
Jacquelyn Murphy	202-728-2077
Roy Whitmore, PhD	919-541-5809
Jennifer Staab, MPH	919-541-6125
Texas A & M University Health Science Center (TAMU)	
Anne Sweeney, PhD MS (PI)	*979-458-0068*
Li Zhu, PhD	979-458-0079
Ruzong Fan, PhD	979-845-3156
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Cecilia Pyper, MD	01865 75971
University of Utah	
Joseph B. Stanford, MD MSPH	801-587-3331

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