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May 2, 2003

John H. Lichten
Dean for Administration and Finance
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1208 and Federalwide Assurance -FWA 2642

Dear Mr. Lichten:

The Office for Human Research Protections (OHRP) has reviewed your reports of September 27, 2002 and April 16, 2003 regarding human subject research conducted at the Harvard School of Public Health (HSPH). These reports contained information about the following research projects:

Research Project: Petrochemical Exposure and Reproductive Outcomes

Principal Investigator: Dr. David C. Christiani

HHS Project Number: R01 OH 03027

HSPH Project Number: 9203PETR

Research Project: Lead, Endocrine Disruption and Reproductive Outcomes

Principal Investigator: Dr. Xiping Xu

HHS Project Number: R01 ES08337

HSPH Project Number: 9602LEAD

Research Project: Rotating Shift Work and Reproductive Outcomes

Principal Investigator: Dr. Xiping Xu

HHS Project Number: R01 HD32505

HSPH Project Number: 9401ROTA

Research Project: Molecular Epidemiology of Preterm Birth: Environmental and Genetic Interactions

Principal Investigator: Dr. Xiping Xu
HSPS Project Number: 9804MOLE

Research Project: Molecular Genetic Epidemiologic Study on Obesity in China
Principal Investigator: Dr. Xiping Xu
HSPH Project Number: 9611MOLE

Research Project: Genetics of Hypertension and its Intermediate Phenotypes
Principal Investigator: Dr. Xiping Xu
HSPS Project Number: 9902GENE
HHS Project Number: R01 HL64109

Research Project: Longitudinal Investigation of Respiratory Disease in Chinese Textile Workers
Principal Investigator: Dr. David C. Christiani
HHS Project Number: OH02421
HSPH Project Number: 8701LUNG

Research Project: Genetic Susceptibility to the Effects of Aromatic Solvents on Reproductive Health
Principal Investigator: Dr. Xiping Xu
HSPH Project Number: 9707GENE

Research Project: Biomarkers for Human Reproductive Epidemiology
Principal Investigator: Dr. Xiping Xu
HHS Project Number: P01 ES06198
HSPH Project Number: 9810BIOM

Research Project: Genetic Epidemiology of Complex Traits Using Twins
Principal Investigator: Dr. Xiping Xu
HSPH Project Number: 9711GENE

Research Project: The Genetics of Airway Responsiveness and Lung Function
Principal Investigator: Dr. Xiping Xu
HHS Project Number: 1R01 HL56371
HSPH Project Number: 9912GENE

Research Project: The Genetics of Nicotine Addiction Vulnerability
Principal Investigator: Dr. Xiping Xu
HHS Project Number: 1R01 DA12905
HSPH Project Number: 9902GEN1

Research Project: Organophosphate Pesticide Exposure and Reproductive Toxicity
Principal Investigator: Dr. Xiping Xu
HSPH Project Number: 9605ORGA

In its July 24, 2002 letter, OHRP expressed the following unresolved concerns and questions:

(1) OHRP expressed concern about an abstract published by Dr. Xu and others at the American Society of Human Genetics 48th Annual Meeting, October 27-31, 1998, entitled “A novel and large-scale population genetics study of human phenotypic variation.” OHRP acknowledges HSPH’s statement that the language in the abstract was “vaguely written and conducive to confusion” and that the research was not conducted.

(2) OHRP expressed concern that HSPH did not appear to have written IRB policies and procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5): the procedures for ensuring prompt reporting to OHRP of any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB. OHRP acknowledges that the HSPH written IRB procedures now clearly address these activities. OHRP finds that this corrective action adequately addresses the above concern and is appropriate under the HSPH FWA.

(3) OHRP expressed concern that the informed consent document for the study “Organophosphate pesticide exposure and reproductive toxicity” may have failed to include information about genetic testing of subjects’ blood. HSPH acknowledged that the informed consent document for this study did not include these procedures, and that the study has not been renewed. OHRP acknowledges that HSPH has been planning, in cooperation with colleagues in China, to conduct real-time consent monitoring of the two projects that Dr. Xu plans to resume when OHRP’s investigation is complete. In addition, HSPH has established a standing oversight committee to guide Dr. Xu’s work at HSPH. The HSPH IRB also now pays closer attention to comparing the procedures listed on the protocol applications with those described in the consent document, and the IRB stresses to investigators in its training module that informed consent documents must include all procedures affecting human participants. OHRP finds that these corrective actions adequately address the above concern and are appropriate under the HSPH FWA.

(4) OHRP noted that the HSPH IRB found, upon initial review, that the project # R01 HL64109 “Genetics of Hypertension and its Intermediate Phenotypes” involved no more than minimal risk. HHS regulations at 45 CFR 46.102(i) define minimal risk as meaning that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. OHRP expressed concern that some of

the interventions in the protocol exceeded the level of minimal risk as defined by the regulations. OHRP acknowledges that the HSPH IRB has reassessed the risk level of this protocol and determined that the risk levels of these procedures are more than minimal but not likely to exceed moderate risk. OHRP finds that this response adequately addresses the above concern and is appropriate under the HSPH FWA. OHRP also acknowledges that Dr. Xu has decided not to continue the hypertension study.

(5) OHRP acknowledges that additional concerns and allegations regarding research conducted by Dr. Xu in China contained in a June 3, 2002 letter from the complainant have been investigated by an external auditor and that corrective actions are being implemented by HSPH to address the findings of the external auditor. OHRP notes that these findings are largely similar to findings that OHRP had previously made regarding other studies. OHRP finds that the corrective actions already taken and those described in the audit report adequately address these findings and are appropriate under the HSPH FWA.

(6) OHRP received a letter on June 19, 2002 regarding additional concerns and allegations from an anonymous complainant in China. The letter alleged that Dr. Xu directed Chinese researchers and employees to forge informed consent documents for several studies. OHRP requested that HSPH investigate this serious allegation and report to OHRP its findings regarding the possible forging and back-dating of informed consent documents. OHRP acknowledges that HSPH has extensively investigated these allegations and can find no evidence to substantiate the allegations. As a result, OHRP finds that the allegations of forged informed consent documents cannot be substantiated.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borrer, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Sarah Putney, HSPH
Dr. Troyen A. Brennan, Chair, IRB, HSPH

Dr. David Christiani, HSPH

Dr. Xiping Xu, HSPH

Commissioner, FDA

Dr. David Lepad, FDA

Dr. Bernard Schwetz, OHRP

Dr. Melody H. Lin, OHRP

Dr. Michael A. Carome, OHRP

Ms. Shirley Hicks, OHRP

Mr. George Gasparis, OHRP

Ms. Yvonne Higgins, OHRP

Ms. Patricia El-Hinnawy, OHRP

Ms. Melinda Hill, OHRP