DEPARTMENT OF HEALTH & HUMAN SERVICES

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March 28, 2002

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

Dear Mr. Lichten:

The Office for Human Research Protections (OHRP), has reviewed your reports of July 26, August 15, and September 13, 2001 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. 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. Dr. Xiping Xu
HSPS Project Number: 9804MOLE

Research Project: Molecular Genetic Epidemiologic Study on Obesity in China
Principal Investigator: Dr. 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

Based upon its review, OHRP makes the following determinations regarding the above-mentioned research projects and HSPH's system for protecting human subjects:

A. OHRP Determinations Regarding General Human Subjects Protections at HSPH

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(b) require the Institutional Review Board (IRB) to ensure that additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects. OHRP finds that HSPH IRB records failed to document the consideration of such safeguards for the above-referenced projects, which appear to have involved vulnerable individuals, such as economically or educationally disadvantaged persons.

Corrective Actions: OHRP acknowledges that HSPH has implemented numerous corrective actions to respond to this and other OHRP concerns. HSPH is instituting a Quality Improvement Plan (QIP) which includes new worksheets for guiding the HSPH IRB discussion and recording the findings for various vulnerable subject populations, and has hired a new administrator. OHRP also acknowledges that the minutes have been reformatted to make specific citations to the regulatory bases for the IRB's findings, and has scheduled several workshops to educate HSPH IRB members and investigators about research involving vulnerable populations. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH MPA.

(2) HHS regulations at 45 CFR 46.116 require that the information that is given to subjects be in language understandable to the subjects. OHRP finds that many of the informed consent documents approved by the HSPH IRB for the above-referenced protocols included complex language that would not be understandable to all subjects, particularly for rural Chinese subjects.

Corrective Actions: OHRP acknowledges that the QIP worksheets should help ensure that such matters are considered and documented at HSPH IRB meetings. The HSPH IRB has also instituted a new standard for most informed consent documents which requires a computer-assisted determination that the reading level is at 5th or 6th grade before consent document approval. OHRP also acknowledges that HSPH is implementing procedures for informed consent for non-English speakers and persons who are illiterate. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH MPA.

(3) Continuing review of research by the IRB must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse

events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

OHRP finds that continuing review of research by the HSPH IRB regularly failed to be substantive and meaningful, and that continuing review for the above-referenced research, up until some time in 2000, was inadequate. It appears that annual report forms often did not require investigators to inform the IRB of withdrawal or complaints from subjects, recent relevant literature, or a copy of the current informed consent document. Even when the annual report form required the inclusion of the current informed consent documents, there is no indication that all the IRB members received these documents. Furthermore, it appears that the continuing applications (until 2000) were not individually reviewed and approved.

Corrective Actions: OHRP acknowledges that during 2000, the HSPH IRB began conducting and documenting more meaningful continuing review. In addition, the IRB has initiated a primary reviewer system for continuing review and protocol amendments, has revised the continuing review report forms, and has created new worksheets for continuing review. OHRP also acknowledges that the above-referenced studies that are still ongoing, and several which have ceased interventions, have been re-reviewed by the HSPH IRB. OHRP acknowledges that Dr. Xu was directed to suspend all human subjects interventions in his active studies pending the outcome of an internal audit. Please provide OHRP with a copy of the report from the internal audit when it is available. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH MPA.

(4) HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. OHRP finds that the HSPH IRB failed to meet this requirement for the IRB meetings noted in the December 9, 1999 report (March 5, 1992 and January 14, 1999) and the March 18, 1993 meeting of the IRB.

Corrective Actions: OHRP acknowledges that the HSPH IRB conducted a re-review of any

research projects reviewed at the above-referenced IRB meetings. OHRP also notes that since 1993 it has been the practice of the IRB chair to count a quorum before starting each meeting, which is verified by one other member, and is recorded by the administrative staff. OHRP finds that these corrective actions adequately address the finding and are appropriate under the HSPH MPA.

(5) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB. OHRP finds that the HSPH IRB did not always review the entire grant application for each of the above-referenced research projects.

Corrective Actions: OHRP acknowledges that since February 2000, the HSPH IRB adopted a primary reviewer system so that the Chair and the primary reviewer, as well as other members as needed, review the grant and the IRB application. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the HSPH MPA.

(6) HHS regulations at 45 CFR 46.116(a)(8) require that the informed consent documents reviewed and approved by the IRB include, among other things, the following:

> A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

OHRP finds that most of the informed consent documents approved by the HSPH IRB for the above-reference projects included language that was inadequate in this regard. For example, some documents stated that "...by not participating you will not affect your routine medical care" or "[m]y refusal to participate will not prejudice my future treatment or medical benefits at my current health care facility." There could be loss of other benefits besides "routine medical care," as well as other penalties unrelated to medical care access.

Corrective Action: OHRP acknowledges that the HSPH IRB has modified the sample consent form to include the required language and has included instructions making mandatory text which is consistent with the regulations, unless waived by the IRB. In addition, HSPH reports that the IRB is more rigorously reviewing the informed consent document under the guidance of the new administrator. It is OHRP's understanding that informed consent documents for any research that may continue in the future will have appropriate changes made prior to resumption of subject recruitment. OHRP also acknowledges plans to address this issue in mandatory seminars, as well as in workshops, and has develop an informed consent checklist to guide review of these documents. OHRP finds that these corrective actions adequately address the finding and are appropriate under the HSPH MPA.

B. OHRP Determinations Regarding the Above-Referenced Protocols

(7) OHRP finds that the informed consent documents reviewed and approved by the HSPH IRB for many of these projects failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116 (a):

(a) Section 46.116(a)(1):

(i) An explanation of the purposes of the research. The informed consent document for project # 9611MOLE stated that "...the purpose of the study is to...design and, eventually, develop novel therapeutics for the treatment of the disease [obesity]." However, there was no design phase of the protocol. The purpose, according to the protocol, was to "test the linkage relationship between candidate DNA markers and obesity." A subject might have read this and thought they might eventually get a therapy for their obesity, even though the form says they will probably receive no benefit.

(ii) A description of the procedures to be followed, and identification of any procedures which are experimental.

– The 1993 grant application calls for project # R01 OH 03027 for daily task diaries for men and personal air exposure samples to estimate exposures to toxins. These research activities were not outlined in the informed consent document.

– The original protocol for project # R01 ES08337 stated "the informed consent form will state that subjects are free to omit specific procedures ... from the study at any time...." This was not mentioned in the informed consent document.

– An early version of protocol # R01 HD32505 proposed to randomize the women to different shift schedules. Later, the study was changed to include a day shift controls (women who were already working day shift.) This change did not appear to be reflected in any subsequent revised informed consent document.

– The proposal for protocol # R01 HD32505 stated that information on the women's reproductive health will be "independently obtained from the family planning offices in each mill" and information on the subject's medication "...will be independently obtained from their physicians." These procedures were not described in the informed consent document.

– The grant application to the March of Dimes for project #

9804MOLE stated that clinical data on subjects and their babies would be obtained from their medical records. This was not mentioned in the informed consent document.

– The questionnaire for project # 9611MOLE was not mentioned in the informed consent document.

– The protocol for project # R01 HL64109 stated that "[t]o prevent blood pressure fluctuations, participants will receive an infusion of D5W and [will be] monitored for 30 minutes post-cessation of the AngII infusion." This procedure is not mentioned in the informed consent document or the grant application.

– In answering the Genetic Research Supplemental Questions for project # R01 HL64109, the principal investigator stated that "[s]ubjects ... may have their sample removed at any time." This possibility was not mentioned in the informed consent document.

– In a June 9, 1997 letter to the IRB regarding project # 9707GENE the principal investigator noted that "[i]ndividuals will be given results of the genetic testing should they request it. We will keep this information confidential...." In a July 23, 1997 letter to the IRB chair, the principal investigator stated "[w]e will not share any of the test results with study participants." There were no changes in the informed consent document to reflect this change in policy; the original consent form implied that participants could get test results ("Data will be released only upon your written request.")

– The final informed consent document for project # 9711GENE did not described the lung function testing procedures (spirometry).

– The investigators for project # 9711GENE changed the protocol to include a fasting blood sample with an overnight stay; this was never added to the informed consent document for this study.

– The protocol for project # 1R01 HL56371 stated that "subjects...may have their samples removed at any time;" this option was not described in the informed consent document.

– The informed consent document for the data collection for project # 1R01 HL56371 did not have an adequate description of the skin test procedure. The document simply stated "We will test your skin (using

forearms) to test 12 different local allergens to see if your skin reacts."

– The document for project # 1R01 DA12905 did not ask permission to contact family members for participation.

– In September 2000, the investigators requested a change to the informed consent for project # 1R01 DA12905, to add "you will receive the results of a free medical exam which will include EKG, blood lipids, blood glucose, ultrasound...as well as blood pressure." There was no consent to conduct these tests.

– The hospital was to provide information about the prenatal care, delivery, and outcomes to the researchers for project # R01 ES08337.

(b) Section 46.116(a)(2): A description of the reasonably foreseeable risks and discomforts.

(i) It appears that there could have been a risk to employment status of subjects enrolled in project # R01 OH03027 if workplace exposure to toxic substances was found and reported to officials. This was not mentioned in the informed consent document.

(ii) The informed consent document for the new hire cohort for project # OH02421 failed to adequately describe the risks of the methacholine challenge tests.

(iii) The final informed consent document approved by the IRB in 1998 for project # 9711GENE did not list the risks or discomforts of bone density measurement (X-rays) or the lung function test (spirometry).

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the research. The informed consent document for project # OH02421 did not mention possible benefits or lack thereof.

(d) Section 46.116(a)(7): An explanation of whom to contact for answers to questions about research subjects' rights (should include someone other than the investigator), and whom to contact in the event of a research-related injury to the subject. The informed consent document for project # 1R01 HL56371 included no contact in China listed for questions regarding subjects' rights.

Corrective Action: OHRP acknowledges that the HSPH IRB has developed an informed

consent checklist to assist it in reviewing informed consent documents. In addition, informed consent documents for any research that may continue in the future will have appropriate changes made prior to resumption of subject recruitment. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH MPA.

(8) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the following protocol changes were implemented without IRB approval:

(a) In the 1993 grant application for project # R01 OH03027, the 7-day-per-month approach to urine collection for hCG was changed to daily collection until pregnancy is confirmed.

(b) In their annual report to IRB on January 29, 1998 for project # R01 OH03027, the investigators reported they had exceeded the enrollment limit set by the IRB and requested an extension after the fact.

(c) An early version of protocol # R01 HD32505 proposed to randomize the women to different shift schedules. Later, the study was changed to include a day shift controls (women who were already working day shift.) Upon continuing review, this addition was not specifically pointed out to the IRB as a change in the protocol.

(d) Inclusion of a new hire cohort for project # OH02421 was approved by the IRB in January of 1996. However, the informed consent document for the new hire cohort was apparently not presented to the IRB until 1/14/2000. On 1/12/96, the investigators proposed to include 400 additional subjects for project # OH02421– new hires. The Annual/Continuing Review form did not point out that the new hires would be undergoing many more tests than the previous cohort. The previous cohort received 2 spirometry tests; the new hires received 11 spirometry tests over 3 years, skin allergy tests, and 2 methacholine challenges, additions that added significantly to the risks and discomforts of the protocol.

(e) The investigators for project # 9711GENE changed the protocol to include a fasting blood sample with an overnight stay prior to obtaining approval from the HSPH IRB.

(f) The HSPH IRB initially approved project # 9711GENE for participants six years of age or older. At a later date the investigators changed the age range to between the ages of 15 and 70 years. This change was not submitted to the HSPH IRB for review and approval.

(g) The principle investigator changed the site (from Anqing 4th Hospital to Heqiu County Hospital) for R01DA12905 prior to obtaining review and approval by the HSPH IRB.

Corrective Actions: OHRP acknowledges that the HSPH IRB has reminded Drs. Xu and Christiani that any change in a study protocol must be approved by the IRB before being implemented, and has reprimanded them for this omission. HSPH has stated its intention to select an outside auditor with expertise in human subjects research to conduct a thorough audit of all of Dr. Xu's active studies that have not been audited in connection with the response letter. OHRP acknowledges that the IRB is also reminding all researchers of their obligation to submit changes to the IRB before implementation, through clarified and comprehensive instructions in the IRB application, in the approval letter sent to investigators, and through enhanced information on the IRB website. OHRP also acknowledges the HSPH IRB new policy that requires an investigator who requests an amendment to submit an updated version of the protocol. OHRP finds that these corrective actions are appropriate under the HSPH MPA.

Question: HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) require that the IRB have written policies and procedures for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review. Given the breadth and seriousness of Dr. Xu's violations, has HSPH considered implementing a plan to monitor his research records on an ongoing basis to verify that he is conducting the research in accord with the IRB-approved protocols?

(9) OHRP finds that when reviewing these protocol applications, the HSPH IRB often lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, OHRP notes the following:

(a) For project # R01 ES08337 a letter was sent to all eligible women inviting them to participate; this letter was not reviewed and approved by the HSPH IRB.

(b) Protocol # R01 HD32505 included a plan under which "all the potential eligible women will be sent a letter by STIBFH inviting them to participate..." OHRP finds that the letter was not reviewed and approved by the HSPH IRB.

(c) The protocol for project # 9611MOLE stated that "[f]amilies...will be contacted through a letter...." OHRP finds that the HSPH IRB did not review or approve such a letter.

(d) The HSPH IRB did not review and approve the questionnaires for project # R01 HL64109 prior to their use in the research.

(e) At the July 13, 2000 meeting, the HSPH IRB raised concerns regarding new

Chinese regulations to report genetic research to Chinese officials and the impact of these regulations on subject privacy and confidentiality. They requested more information from the principal investigator. HSPH's September 13, 2001 report stated that the request was not received by the principal investigator until June 2001, and he did not reply until July of 2001. Although the HSPH IRB did not receive these materials addressing serious concerns of the IRB until much later, the protocol was approved anyway on April 5, 1999.

(f) The 6/11/99 and 6/15/00 Annual/Continuing Review form for project # 9707GENE stated that there were no findings to date. However, the investigators indicated findings and publications from this research in a NCERQA Grant Annual Report Summary dated November 15, 1999.

(g) The HSPH IRB failed to review the questionnaires for project # 1R01 DA12905 (initial screening survey, FTND, RTQ, information on smoking, family history, other substance use, family information.)

(h) At its July 13, 2000 meeting, the HSPH IRB reviewed the changes to the informed consent document regarding the National Institute on Drug Abuse's (NIDA's) requirement to share data and to create cell lines from blood for project # 1R01 DA12905. The investigator submitted a new, additional consent form without any change to the protocol. The HSPH IRB had concerns regarding reporting requirements to the Chinese government, vis a vis reporting rules implemented by the People's Republic of China (PRC) in 1998. The HSPH IRB was concerned that China required reporting of names of subjects– "[t]he necessity to report names would create potential danger for research subjects." The committee requested more information regarding whether or not the government would receive information on individual participants. This issue was not resolved until July of 2001, one year after the HSPH IRB reviewed and approved these changes.

(i) In September 2000, the investigators requested a change to the informed consent for project # 1R01 DA12905, to add "you will receive the results of a free medical exam which will include EKG, blood lipids, blood glucose, ultrasound...as well as blood pressure." Your September 13, 2001 report to OHRP notes that these tests were always part of the study design. However, they were not described in the IRB-approved protocol.

Corrective Actions: OHRP acknowledges that Dr. Xu has been reminded that all such materials must be submitted to the HSPH IRB for review and approval prior to their distribution, and reprimanded for his omission. In addition, the IRB has revised the instructions for initial and continuing review application, and reminded investigators through its website and Operations Manual, that a complete set of study materials must be submitted to the IRB. The

IRB is also planning to cover this requirement at the mandatory IRB Basics seminar. The IRB has modified its Operations Manual to clearly convey that findings and publications must be reported to the IRB as part of the continuing review process, and has revised the continuing review application materials to more clearly remind investigators that such findings must be reported to the IRB at continuing review. OHRP also acknowledges that protocol materials for these projects which may continue in the future will be reviewed and approved by the IRB before implementation. (ii) The hospital was to provide information about the prenatal care, delivery, and outcomes to the researchers for project # R01 ES08337. OHRP finds that these corrective actions are appropriate under the HSPH MPA.

Action 1– Required: By May 10, 2002, please provide OHRP with additional corrective action plans to ensure that the HSPH IRB does not act on protocols in absence of adequate information.

(10) HHS regulations at 45 CRF 46.103(b) and 46.109(a) require that research involving human subjects be reviewed and approved by an IRB. HHS regulations at 46.111(a)(4) require that the IRB determine that informed consent will be sought from each prospective subject in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116.

(a) In a document labeled "Final Report," several studies were mentioned besides the prospective study involving the petrochemical workers being followed for pregnancy. This included several studies for which publications were provided. There were also termination and drop-out questionnaires for the study(s). OHRP finds that these activities were human subjects research and were conducted without prior review and approval by the HSPH IRB.

(b) The supplement proposal for protocol # R01 HD32505 stated that the project would "utilize...serum samples already being collected as part of a large prospective NIH study entitled "Rotating Shift Work and Reproductive Outcomes." The collection of blood was never approved for the "Rotating Shift Work and Reproductive Outcomes" project by the HSPH IRB. The proposal also stated that the investigators had already done preliminary genotype analysis, before the supplement was reviewed and approved by the HSPH IRB. The HSPH IRB did not require any changes in the consent form that would have indicated that blood was being drawn or that the study would perform genetic analysis of that blood.

In your September 13, 2001 report to OHRP, HSPH stated that "[b]ecause the supplement was never funded, no women ever were enrolled." However, a recent publication of Dr. Xu clearly indicated that the research was carried out (Ronnenberg, et al "Anemia Deficiencies of Folate and Vitamin B-6 are Common and Vary with Season in Chinese Women of Childbearing Age." Journal of Nutrition, 130: 2703-2710, 2000). This publication stated "supported in part by grant 1R01HD/OH32505"

and "[t]he current assessment of nutritional status was conducted in conjunction with an on-going prospective study of the effects of rotating shift work on reproductive outcomes among female textile workers in Anquing, China....**For the present study, eligible subjects were the 563 women enrolled in the shift work study** between August 1996 and December 1998 [emphasis added]."

(c) The research referenced in the article "Microsomal Epoxide Hydrolase Polymorphism and Risk of Spontaneous Abortion," (*Epidemiology*, 1998; 9: 540-544) was conducted by Beijing Medical University in Anqing, with Dr. Xu as consultant.

(d) The data for project # 1R01 HL56371 was collected under Brigham and Women's Hospital protocol #94-6932-01 "Molecular Epidemiology Study on Asthma," funded, in part, by Millennium Pharmaceuticals. Protocol #94-6932-01 was reviewed and approved by the Brigham & Women's Hospital IRB in September of 1995, but not by the HSPH IRB. HL56371 was not reviewed by HSPH until 3 years after the application was submitted in October of 1996.

(e) The grant proposal for project # 1R01 DA12905 mentioned a pilot study having been conducted. OHRP finds that Dr. Xu was a collaborator on at least one of these studies, which was never reviewed and approved by the HSPH IRB.

OHRP notes that institutions whose employees or agents obtain, receive, or possess private information that is individually identifiable (either directly or indirectly through coding systems) for research purposes (e.g., obtaining private information from medical records in an individually identifiable form) are considered to be engaged in human subjects research, unless the employee acts as a consultant on research, obtains "coded" data for analysis at the consultant's institution, and a written agreement unequivocally prohibits release of identifying codes to the consultant (see "Engagement of Institutions in Research" memo, http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm).

Corrective Actions: OHRP acknowledges that the HSPH IRB has reprimanded Dr. Xu for his omission and is educating all investigators and key research staff of the proper treatment of consulting projects through its new Operations Manual and at the mandatory IRB Basics seminar. In addition, in a memo containing the HSPH MPA, the HSPH Dean reminded all faculty and researchers of their obligations to the IRB and that the terms of the MPA apply to all HSPH research that uses humans, human tissue, or other data gathered from human subjects. OHRP finds that these corrective actions are appropriate under the HSPH MPA.

Action 2– Required: By May 10, 2002 please provide OHRP with a plan for the HSPH IRB to review the above-referenced research projects that were not reviewed and approved by the HSPH IRB. In your report to OHRP, please provide a description of the informed consent

process used to inform the subjects involved in these activities. The HSPH IRB should also consider the need to recontact subjects to inform them that they were in research without proper review and approval and, perhaps without proper informed consent.

(11) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) require that each institution "engaged" in human subjects research provide OPRR with a satisfactory Assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b). (Please see OHRP guidance at http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm)

An institution becomes "engaged" in human subjects research when its employees or agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes [45 CFR 46.102(d),(f)].

OHRP finds that an (a) Beijing Medical University or Anhui Medical University were engaged in human subject research under project # R01 ES08337 and (b) neither site obtained and OHRP-approved Single Project Assurance (SPA) for this research.

Corrective Action: OHRP acknowledges HSPH's statement that HSPH now understands that it is responsible for ensuring that each performance site obtains an OHRP-approved Assurance prior to its involvement with human subjects, and that the lack of a request from OHRP does not negate this responsibility.

(12) HHS regulations at 45 CFR 46.111(a) state that in order to approve research the IRB shall determine that the following requirements, among others, are satisfied: (a) risks to subjects are minimized; and (b) risks to subjects are reasonable in relation to anticipated benefits; and (c) selection of subjects is equitable.

(a) OHRP notes that (i) the IRB-approved protocol for project # R01 HL64109 stipulated that treated hypertension was an exclusion criterion; and (ii) the protocol and informed consent document stated that subjects would receive medical referrals or recommendations for lowering hypertension. However, it is not clear that such referrals would result in treatment of subjects since the principal investigator noted in the grant application that "...drug therapy [for hypertension] is typically inaccessible and generally unaffordable in Anqing...." He also noted that "...only 3% [of Chinese with hypertension] are effectively controlling it." Access to adequate health care appears to be particularly problematic for rural Chinese. The subject population is a rural one; the principal investigator noted that the study will focus "...on six of the most geographically isolated...townships of Yuexi...."

(b) At their February 18, 1999 meeting, the HSPH IRB noted in their review of protocol #HL56371 that "US standards of care would require that these people be

> treated." The HSPH IRB was concerned about the safety of subjects during the clinical procedures, and therefore tabled the application. When reviewing the protocol again in April of 1999, there were still concerns regarding not treating the hypertension, but the HSPH IRB approved the protocol anyway.

As the Belmont Report notes:

> ...it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that **such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.** (Emphasis added)

Based upon the above observations, OHRP finds that the HSPH IRB failed to adequately consider whether or not (a) the subjects would benefit from this research, either in the short term or the long term; (b) the risks to which they are subjected might outweigh the benefits; and (c) that the subject selection was equitable.

Action 3– Required: By May 10, 2002, please provide OHRP with a satisfactory corrective action plan to address the above finding.

(13) HHS regulations at 45 CFR 46.117(a) require that, unless appropriately waived by the IRB, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject, or the subject's legally authorized representative. As noted by the principal investigator, the subject population for project # R01 HL64109 was largely illiterate. OHRP finds that consent was not documented in writing for the Chinese textile workers for project # OH02421 (only oral consent). Furthermore, OHRP finds that the HSPH IRB failed to find and document that oral consent was appropriate under the regulations. OHRP notes that under 45 CFR 46.117(b) when oral consent is used, there shall be a witness to the oral presentation and the IRB shall approve a written summary of what is to be said to the subject.

Action 4– Required: By May 10, 2002, please provide OHRP with a satisfactory corrective action to respond to the above finding.

(14) OHRP finds that the procedures for enrolling subjects for project # OH02421 failed to minimize the possibility of coercion or undue influence as required by HHS regulations at 45

CFR 46.116. In specific, OHRP notes that all the informed consent documents stated "[y]our cooperation is needed for the successful undertaking of this study." This could be coercive, especially for workers.

Corrective Action: OHRP acknowledges that HSPH has revised its consent form instructions and its model consent form to include mandatory language on the voluntary nature of participation. OHRP also acknowledges HSPH's plans to educate investigators and key research staff about the appropriate content at the mandatory IRB Basics seminar and has scheduled a workshop at which consent forms will be discussed. HSPH also plans to pilot a monitoring program to monitor the informed consent process which would include international sites. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH MPA.

(15) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP finds that the HSPH IRB failed to document the required findings when it reviewed project # 9711GENE, which involved children.

Corrective Actions: OHRP acknowledges that the HSPH IRB has instituted new procedures for documenting its review of research involving children and now require the use of a worksheet to guide the HSPH IRB discussion of such issues and the recording of findings related to Subpart D. OHRP finds that these corrective actions adequately address the finding and are appropriate under the HSPH MPA.

(16) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for the initial or continuing review of certain minimal risk research and for reveiw of minor changes to previously approved research. OHRP finds that the HSPH IRB employed expedited procedures for initial review of research and changes that exceed the limitation. In addition, OHRP finds that HSPH IRB members were not advised of (a) initial or continuing review approvals of research protocols, or (b) approvals of minor changes in research protocols as required by HHS regulations at 45 CFR 46.110(c). In specific, OHRP notes the following:

> (a) An amendment to the protocol for project # 1R01 DA12905 in August 2000 requested an in-depth interview with 20 subjects, smokers and non-smokers. The request was approved by the IRB chair. There are no records indicating that this approval was reported to the HSPH IRB. This change involved a new cohort and new interview instrument and thus appears to have exceeded the limit of a minor change.
>
> (b) The HSPH IRB had concerns regarding project # 1R01 HL56371 and tabled the proposal until they could get more information for the principal investigator. The HSPH IRB chair apparently approved the protocol after receiving a response from the principal investigator regarding the IRB concerns. The HSPH IRB never met again to discuss and approve this protocol. OHRP finds that the HSPH IRB chair

inappropriately approved this research under an expedited review procedure. Furthermore, there appears to be no evidence that this expedited review by the chair was ever reported to the HSPH IRB, as required by HHS regulations at 45 CFR 46.110(c).

Corrective actions: OHRP acknowledges that these studies were re-reviewed by the convened HSPH IRB on July 20, 2001. OHRP finds that these corrective actions are appropriate under the HSPH MPA.

Action 5– Required: Please provide OHRP with plans for additional corrective actions to ensure that this oversight does not occur in other studies reviewed by the HSPH IRB.

(17) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, the approval period must begin on the date the protocol was reviewed by the convened IRB, not on the date the IRB Chair or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that the investigator continued to conduct research on project # 1R01 DA12905 even though the protocol had not received continuing review and approval at least once per year.

If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. (Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. OHRP and IRBs must address on a case-by-case basis those rare instances where failure to enroll would seriously jeopardize the safety or well-being of an individual **prospective** subject.)

Corrective Actions: OHRP acknowledges that the HSPH IRB has sent a written reprimand to Dr. Xu and a clear explanation as to how a lapse of approval affects the operation of a study. OHRP finds that these corrective actions are appropriate under the HSPH MPA.

Action 6– Required: By May 10, 2002, please provide OHRP with additional plans for corrective actions to ensure that other investigators do not conduct research past the date of approval.

(18) OHRP finds that the HSPH IRB approved project # 1R01 DA12905 contingent upon

substantive modifications or clarifications that were directly relevant to the IRB determinations required under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB. At its February 18, 1999 meeting, the HSPH IRB had questions regarding recruitment and procedures to have samples destroyed at the request of a subject. The protocol was "approved pending modification" and was not resubmitted to the HSPH IRB. It is not clear if the approval by the chair of the modifications was ever reported to the HSPH IRB.

OHRP recommends the following guidelines in such cases: (a) When the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

Corrective Actions: OHRP acknowledges that this protocol was re-reviewed at the HSPH IRB's July 20, 2001 meeting. OHRP also acknowledges that the HSPH IRB is promulgating standards for processing applications that require additional information, clarification or modifications. In conjunction with these standards, the IRB plans to establish a database to help identify protocols that require such clarification and will remind the investigators to provide this clarification. OHRP acknowledges HSPH's statement that approval of any such research must be delayed pending subsequent review by the IRB. In addition, the HSPH IRB is instituting a new file system to ensure that all documents for a particular protocol are in one file. These corrective actions adequately address the above finding and are appropriate under the HSPH MPA.

C. OHRP Concerns and Questions Regarding Specific Research Protocols

(19) HHS regulations at 45 CFR 46.111(a)(7) require that, in order to approve research, the IRB shall determine that, among other things, when appropriate, there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. OHRP is concerned that for the "Organophosphate pesticide exposure and reproductive toxicity" study, the HSPH IRB failed to satisfy this requirement because the IRB approved the research on 5/16/96 even though the IRB had "grave doubts about whether [research] information would be kept confidential." Please respond.

(20) OHRP is concerned that the informed consent document for the study referenced in (19) may have failed to include information about genetic testing of subjects' blood, and may not have minimized the possibility of undue influence, in contravention of HHS regulations at 45 CFR 46.116. In specific, the informed consent document stated "the findings of this study are

important to your health and that of your fellow workers....” but the study was not designed to benefit the subjects. Please respond.

(21) Beijing Medical University provided OHRP with a list of subjects for project # R01HL64109 and their enrollment dates and a copy of each informed consent document (with subject’s names redacted.) After review of these documents, OHRP has the following concerns:

> (a) It appears that several subjects may have been enrolled and undergone study interventions prior to signing informed consent documents. The following subjects appeared to have signed informed consent documents at least 1 day after being enrolled in the research: HS0051, HS0054, HS0055, HS0203, HS0052, HS0053, HS0170, HS0204, HS0205, HS0206, HS0207, HS0208, HS0220, HS0221, HS0223, HS0238.
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> (b) OHRP is concerned that the handwriting for the dates next to the subject’s signatures appear to be identical. For example, most of the subject signature dates on the six informed consent documents signed on 2-26-2001 have an identical style. OHRP is concerned that it appears that subjects did not date the informed consent documents themselves, even those subjects who could write (as evidenced by their signature), or that the documents may have been back-dated.

Please respond in detail.

(22) Brigham and Women’s Hospital provided OHRP with a copy of each informed consent document (with subject’s names redacted) for the protocol “Molecular Genetic Epidemiologic Study on Asthma.” After review of these documents, OHRP is concerned that the handwriting for the dates next to the subject’s signatures appear to be identical. Furthermore, OHRP is concerned that subjects did not date the informed consent documents themselves, even those subjects who could write (as evidenced by their signature), or that the documents may have been back-dated. Please respond.

(23) In a December 20, 2000 article in the Washington Post, Dr. Xu was quoted as saying that for these studies an arrangement was made between the local hospitals and the Anhui Medical University. Dr. Xu gave local hospitals a budget and estimated costs for recruiting and examining subjects, and the clinics in turn used incentives like free exams and discounted health care to attract subjects and hopefully retain their business. OHRP is concerned that there is no apparent evidence that the HSPH IRB ever reviewed and approved the use of such incentives. Please respond in detail.

(24) A journal article authored by, among others, Drs. Xu and Christiani entitled “Tofu Consumption and Blood Lead Levels in Young Chinese Adults” (American Journal of

Epidemiology, 2001; 153(12):1206-1212) stated that "[c]ouples were recruited at the time of marriage registration...." The research was supported by R01 ES08337 and R01 HD32505. In addition, a June 28, 2000 paper titled "Background Information on Three Harvard School of Public Health Epidemiological Studies Conducted in China" stated regarding protocol #R01 HD32505, "[w]omen who undergo the medical exam that is required before marriage in China are informed at the time of the exam about the study and asked to consider participating."

OHRP is concerned that these statements are in conflict with the recruiting practices outlined in all of Drs. Xu and Christiani's research protocols– that couples were recruited after obtaining permission to conceive a child. The process for marriage registration is quite different, and information about the couples at that time could possibly affect their ability to receive permission to marry or to conceive. In addition, OHRP is concerned that approaching women before they have obtained permission to marry or conceive might possibly coerce the women into enrolling with the thought that it might improve their chances for marriage or conception permission. Please respond. In your response, please verify whether or not all the subjects in all the reproductive studies conducted by these investigators in China were recruited *after* they had received permission to conceive.

(25) The January 10, 2002 China Daily contained an article by Xiong Lei that tells the story of a farmer in Toutuo, Anhui Province who was a participant in the HSPH genetic research study on asthma. The farmer told the reporter that he had blood taken from him on 2 separate occasions, November 1996 and March 1997, but was not asked to sign nor given an informed consent document. He stated that the researchers came later and asked him to sign a paper; he was not told what the paper said, and he could not read it without his glasses. The date on this informed consent document is apparently October of 1997. The farmer told the reporter that he did not know he was participating in the genetic study on asthma; he said he was willing to give blood so that he could get some treatment for his children's asthma. Was this subject enrolled in protocol #1R01 HL56371 or another HSPH study? Does HSPH have knowledge of other allegations of post-dated or post-signed informed consent documents for this or other studies? Please respond.

(26) Dr. Xu and others published an abstract at the American Society of Human Genetics 48th Annual Meeting, October 27-31, 1998. This abstract, titled "A novel and large-scale population genetics study of human phenotypic variation" does not seem to match any of the IRB-approved protocols for research by Dr. Xu in China. Please inform OHRP which protocol this abstract refers to. If this is not in the list of protocols at the beginning of this letter, please provide OHRP with a copy of the protocol, grant application, and minutes from the HSPH IRB meeting in which it was approved.

D. OHRP Concerns and Questions Regarding General Human Subjects Protections at HSPH

(27) OHRP is concerned that HSPH does 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(b)(4) and (5):

> (a) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
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> (b) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and Department or Agency head of (i) 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; and (ii) any suspension or termination of IRB approval.

Please respond.

(28) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP is concerned that the HSPH IRB may not have satisfied these requirements when reviewing by expedited review certain projects that propose waiver of informed consent (see, for example, protocol # 0106PATH, reported to the HSPH IRB 6/15/01). Please respond.

(29) On 6/15/01, the HSPH IRB reviewed and approved several studies in which the investigators only provided drafts of the documents they plan to use in the study (see, for example, protocols reviewed on 6-15-2001 involving overtime work and working conditions, as well as protocol # 9806ATRI). It is unclear whether or not the HSPH IRB made it clear to the investigators that no human subjects may be involved in research until the final version of the project documents had been reviewed and approved by the HSPH IRB, as required by HHS regulations at 45 CFR 46.118. Please clarify.

(30) Minutes of HSPH IRB meetings indicated that several projects were appropriate for waiver of documentation of informed consent "under standards set forth at 45 CFR 46.117(c)." OHRP notes that there are two different categories that may be made for such waivers, and recommends that the IRB make and document their findings on which specific category applies, 45 CFR 46.117(c)(1) or (c)(2). Please respond.

Please submit to OHRP your response to the above determinations, questions, and concerns no later than May 10, 2002. If upon further review of this matter you identify additional instances of non-compliance with the HHS regulations for protection of human subjects, please describe the corrective actions that have been or will be taken to address the noncompliance.

Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

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

cc: Ms. Angela Foss, HSPH
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Dr. Troyen A. Brennan, Chair, IRB, HSPH
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Mr. George Gasparis, OHRP
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