Supporting Statement

GENETIC STUDIES IN A COHORT OF U.S. RADIOLOGIC TECHNOLOGISTS

Submitted by

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A. JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

The Radiation Epidemiology Branch (REB), Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI), of the National Institutes of Health (NIH) is authorized under the Public Health Service Act, Section 411, [42 USC 285a] to collect information to generate hypotheses concerning environmental and host determinants of cancer (Attachment 1). It is the mandate of the REB to conduct a broad-based research program to identify, understand, and quantify the risk of cancer in populations exposed to medical, occupational, or environmental radiation. Overall, the REB mission is threefold: to characterize the carcinogenic effects of radiation; to improve our understanding of molecular mechanisms; and to address issues of public concern. The primary aim of the proposed collection is to substantially increase knowledge of the possible modifying role of genetic variation on cancer risks associated with protracted low- to moderate-dose radiation exposure.

This petition is for renewal with revision of a previously approved collection (OMB No. 0925-0405; expires 02/28/2007), formerly known as 'GENERIC CLEARANCE TO COLLECT MEDICAL OUTCOME AND RISK FACTOR DATA FROM A COHORT OF RADIOLOGIC TECHNOLOGISTS'. With this submission, the NIH, Office of Communications and Public Liaison, seeks to obtain OMB's approval to collect blood samples and cancer risk factor data in this ongoing cohort study of U.S. Radiologic Technologists (USRT) to assess genetic and molecular risk factors for cancer and to evaluate possible modifying effects of genetic variation on radiation carcinogenesis.

Researchers at the National Cancer Institute and the University of Minnesota have followed this nationwide cohort of 146,000 radiologic technologists since 1982 (Boice 1992 [2]; Doody 1998 [5]; Mohan 2003 [13]; Sigurdson 2003 [18]). This is one of the largest cohorts of medical radiation workers studied to date (Yoshinaga 2003 [27]), and the only one with substantial numbers of women, extensive covariate data, both incident and death outcomes, and estimated occupational radiation doses. More than 110,000 technologists completed at least one of three comprehensive questionnaire surveys administered over the last 20 years and 18,400 are deceased. The First Survey (OMB No. 0925-0405, expiration 9/30/1999) was mailed during 1984-1989 to 132,454 known living radiologic technologists, out of a total cohort of 146,022 technologists certified for at least two years by the American Registry of Radiologic Technologists between 1926-1980, of whom 90,305 (68%) responded (Boice 1992) [2]. The Second Survey (OMB No. 0925-0405, expiration 9/30/1999) was mailed during 1993-1998 to 126,628 known living technologists, of whom 90,972 (72%) responded (Sigurdson 2003) [18]. Both surveys included detailed questions about employment as a radiologic technologist, family history of cancer, reproductive history, height, weight, other cancer risk factors (such as alcohol and tobacco use), history of personal diagnostic and therapeutic medical radiation procedures, and information on cancer and other health outcomes. A third follow-up of this cohort was recently completed under the previously approved GENERIC CLEARANCE TO COLLECT MEDICAL OUTCOME AND RISK FACTOR DATA FROM A COHORT OF RADIOLOGIC TECHNOLOGISTS (OMB No. 0925-0405, expiration 2/28/2007). During 2003-2005, the Third Survey was mailed or administered by telephone to 101,694 living cohort members who had completed at least one of the two prior surveys; 73,838

technologists (73%) responded. The questionnaire elicited information on medical outcomes to assess radiation-related risks, detailed employment data to refine the occupational radiation dose estimates, and behavioral and residential histories for estimating lifetime ultraviolet (UV) radiation exposure for studies of melanoma and non-melanoma skin cancer.

The large number of women with estimates of cumulative radiation dose to specific organs (e.g. breast) (Simon 2006; see Figure 7 and Table 9) [22] offers a rare opportunity to study effects of low-dose radiation exposure on breast and thyroid cancers, the two most sensitive organ sites for radiation carcinogenesis in women. The overall study objectives are to: (1) quantify radiation dose-response for cancers of the breast, thyroid, and other radiation-related cancers; (2) assess cancer risks associated with genotypic, phenotypic, or other biologically measurable factors; and (3) determine if genetic variation modifies radiation-related cancer risks. We are not aware of any study population in which both quantified radiation doses and biospecimens are available for individuals with protracted low-dose radiation exposures. Incorporation of assessment of the role of genetic polymorphisms and molecular variants in DNA repair and other important genetic pathways that may be functionally important in radiation carcinogenesis would provide initial results on the possible role of genetic factors in the cancer-radiation relationship. Because large numbers of women are exposed to ubiquitous low-dose radiation from occupational, medical, and environmental sources, the presence of radiation-sensitive genetic variants that influence the risk of breast and other cancers would have important public health implications.

2. Purposes and Use of the Information

This is an epidemiological research study. The results will be used to further our understanding of cancer risks following protracted low-dose radiation exposure and the possible modifying effects of genetic variation on radiation-related cancer risks. This will be accomplished using cohort, case-cohort, and case-control study designs, depending upon the hypothesis of interest. Analyses of the Third Survey data are currently underway and findings will address an important gap in the scientific understanding of radiation dose-rate effects, i.e., whether cumulative exposures of the same magnitude have the same health effects when received in a single or a few doses over a very short period of time (as in the atomic bomb or therapeutic exposures) or in many small doses over a protracted period of time (as in medical or nuclear occupational settings).

Renewal of the previously approved clearance with revision is requested to administer a follow-on Genetic Studies Questionnaire (GQ) (Attachment 2) and collect blood samples from 10,000 previous questionnaire responders during the three-year period beginning on February 28, 2007. The GQ was the second of three surveys (i.e. Third Survey, Genetic Studies Questionnaire, and Fourth Survey) for which generic clearance was originally requested in 2003. Owing largely to budgetary cuts, but also to technical and logistical difficulties encountered in conducting the Third Survey, we were not able to complete the Genetic Studies Questionnaire and Fourth Survey during the original three-year period. The GQ will collect information on the following cancer risk factors to allow for adjustment in analyses of genetic variation, radiation and cancer: family history of breast and ovarian cancer in first-degree relatives (including a census of blood-related sisters and biological daughters, type of cancer, age at diagnosis);

reproductive and gynecologic histories in women (pregnancy outcomes, lactation history, menopause status, age at menopause, surgery); personal medical radiation exposure (frequencies of film x-rays, special procedures, CT scans, therapeutic x-rays by time period); and chemotherapy (ever, year first, reason for treatment). The survey will be in optical-read format for computerized data capture. A blood collection kit will be mailed along with the GQ, and technologists will be asked to take the kit to a phlebotomist to have a single tube of blood drawn and to return it to the study laboratory by pre-paid Federal Express overnight delivery. Copies of the genetic studies brochure, advance letter, questionnaire and blood collection kit cover letter, general instructions for study participants, health care provider blood collection letter, blood sample collection and shipping instructions, blood kit follow-up letter, script for 1st motivator telephone call, motivator postcard, script for 2nd motivator telephone call, final motivator letter, subject medical validation request letter, and physician or hospital medical validation request letter are provided in Attachment 3. Copies of the blood collection consent form and HIPPA authorization for medical record release are provided in Attachment 4.

3. Use of Information Technology and Burden Reduction

The information to be collected directly from cohort members will be in media that can be optically scanned by computer. Every effort has been made to minimize the length of the questionnaire and to format it in a manner that would optimize clarity and minimize the burden on the respondent. Responses for most questions involve checking a box or inserting a number; only two questions allow for limited write-in responses. Skip patterns reduce burden by allowing subjects to skip over questions that are not

applicable. The use of optical scanning information technology will lead to lower error rates by avoiding transcribed answers and potential distortion of information.

4. Efforts to Identify Duplication and Use of Similar Information

Genetic and molecular studies of radiogenic cancers (such as breast, thyroid, melanoma skin, and non-melanoma skin cancer) will contribute to better understanding of radiation carcinogenesis. We previously reported increased risks for cancers of the breast (Doody 2006) [7], thyroid (Zabel 2006) [29], melanoma (Freedman 2004) [8], and basal cell carcinoma (Yoshinaga 2004) [28] in this cohort that were consistent with a radiation etiology. Single and double strand breaks in DNA are generated when cells are exposed to ionizing radiation. Miss-repaired or un-repaired double strand breaks lead to cell killing, mutation induction, chromosomal translocations and cancer. Genes involved in double strand break repair in mammalian cells are part of the homologous recombination, non-homologous end-joining, and cell cycle checkpoint control pathways. Many of these genes harbor polymorphic variants and several have been shown to result in reduced DNA repair capacity and/or increased cancer risk. Initially, we have been evaluating the main effects of polymorphic gene variants. The dose assessment, which is nearly completed, in combination with additional cases and a large comparison group selected on the basis of dose, will allow us to assess dose-related cancer risks and the combined effects of radiation and genetic susceptibility (gene-radiation interaction).

It is well-recognized that women who are exposed to moderate- to high-dose radiation, especially at young ages, are at substantially increased risk for breast cancer, and that risk increases linearly with increasing dose (UNSCEAR 2000) [25]. Using

ranked estimates of cumulative badge dose available to date, we reported a 1.5-fold breast cancer risk (95% CI, 1.0-2.2) for U.S. radiologic technologists in the highest exposure category relative to the lowest (Doody 2006) [7]. Because the direct and indirect damaging effects of external radiation include oxidized bases and DNA single and double strand breaks, we are investigating candidate variants in genes that are either involved in base excision repair, interact with the BRCA1 gene, or regulate cell growth. Subtle functional deficiencies in highly conserved DNA repair or growth regulatory processes resulting from germ-line genetic variation have been proposed as possible mechanisms for increased genetic susceptibility to breast cancer. In a case-control study of 859 breast cancer cases and 1083 age-matched controls within the USRT cohort, we initially assayed and analyzed single nucleotide polymorphisms (SNPs) in DNA double strand break repair (Stredrick 2005 [23]; Bhatti submitted) [1], oncogenes (Hauptmann 2003) [9], cell cycle (Mateus Pereira 2004) [12], BRCA-1 interacting genes (Rutter 2003) [17], apoptosis, oxidative stress, inflammatory cytokines, vitamin D biosynthesis, and estrogen metabolism genes. Because ionizing radiation causes base damage to DNA and because several base excision repair (BER) genes had been characterized, we initially evaluated promising SNPs within the BER pathway (Sigurdson 2004) [19] or that functionally interrogated several BER genes; using Comet functional assays, we observed a continuum of endogenous DNA damage that was highest in cancer cases, lower in controls, and lowest in long-lived individuals with no personal or family history of cancer (Sigurdson 2005) [20]. Our preliminary studies suggest a number of possible variants that interact with radiation in breast cancer, although the statistical power to detect such interactions is currently limited. Ongoing blood sample collection from additional breast

cancer cases (~900 to date) identified from the Third Survey conducted in 2003-2005 (OMB No. 0925-0405, expiration 2/28/2007) and from the proposed comparison group of 10,000 subjects randomly selected by dose to over-sample high dose subjects will increase statistical power to detect possible gene-radiation interactions.

Thyroid carcinogenesis is hypothesized to result from mutational events combined with growth stimulation (Williams, 1995) [26], a hypothesis consistent with the marked inverse association between radiation dose-response and age at first exposure. The evidence for dose-related increased thyroid cancer risk after radiation exposure (both therapeutic and environmental) at young ages is strong and consistent with linearity (Thompson 1994 [24]; Ron 1995 [16]; UNSCEAR 2000 [25]), but thyroid cancer is rare even for persons with substantial radiation exposure at young ages. It is likely that there may be individual variation in susceptibility linked to genetic background, including single nucleotide polymorphisms (SNPs) that may moderate risk. To our knowledge, there are no published studies examining the role of SNPs in DNA repair pathways and thyroid tumors; however, a small study using a functional DNA repair assay found slower repair kinetics in thyroid cancer cases vs. controls (Leprat 1998) [10] and we found higher DNA damage in thyroid cancer cases than in controls using the Comet assay (Sigurdson 2005) [20]. Investigation of repair pathways using SNPs could help to establish a mechanism by which thyroid tumors develop, particularly after environmental radiation exposures. The primary mechanism of DNA damage from ionizing radiation is thought to be double-strand breaks which, if imperfectly repaired, may contribute to the induction of neoplasms; however, this is not known with certainty and is one of the gaps in knowledge that we intend to address. A recent study revealed elevated thyroid nodule

risks associated with two polymorphisms in the RET pathway among subjects exposed as children to radioactive iodine from atomic weapons tests in Kazakhstan (Sigurdson, submitted) [21]. We are currently assessing thyroid cancer risk with these same SNPs in a case-control study of 167 cases and 491 controls within the USRT cohort. We found suggestive evidence for an increased risk of thyroid cancer associated with a non-synonymous polymorphism in the *RET* gene that was more pronounced among women diagnosed at younger ages (Lönn 2007) [11]. Given the rarity of the radiogenic papillary thyroid tumors of interest, it will be necessary to pool cases from several different studies to fully assess gene and gene-radiation relationships for this rare form of cancer. To this end, we are now assembling an international Thyroid Cancer Association Consortium similar to the Breast Cancer Association Consortium (BCAC 2006) [3].

Ultraviolet radiation exposure plays the most important role in melanoma and non-melanoma skin cancer occurrence, but many aspects of the complex UV-skin cancer relationship are not fully understood. Ionizing radiation has been associated primarily with basal cell carcinoma and with melanoma in a few studies. The systematic ascertainment of non-melanoma skin cancer is difficult because these cancers are not reportable to cancer registries. Several thousand cases of non-melanoma skin cancer (6,000 basal cell and 1,200 squamous cell) and 1,200 cases of melanoma were identified by our second or third surveys, which will provide a unique opportunity to study genetic susceptibility to radiation (gene-radiation interaction), as well as the interaction between ultraviolet and ionizing radiation in skin cancer occurrence. Among the candidate genes to be studied are the series of DNA repair genes in relation to ultraviolet and ionizing radiation exposures, and genes involved in the Patched (PTCH) and related pathways.

The interaction between radiation and PTCH is of special interest as this gene has been associated with basal cell carcinoma (and medulloblastoma) in patients with germ-line mutations (called "Gorlin" syndrome), who are extremely prone to radiogenic cancer.

5. Impact on Small businesses or Other Small Entities

No small businesses will be involved in this study

6. Consequences of Collecting the Information Less Frequently

The genetic studies questionnaire will collect detailed information on family history of breast and ovarian cancers in first-degree relatives, reproductive and gynecologic histories in women, personal medical radiation exposure, and chemotherapy from a sample of 10,000 (out of ~100,000) cohort members who are known to be alive and having completed at least one of three prior surveys (OMB No. 0925-0405, expiration 9/30/1999; reinstated in 2003, expiration 2/28/2007). Data on these factors will be collected only one time during the 3-year period and are essential to control for possible confounding in the relationships between genetic make-up, radiation, and cancer. The consequence of not collecting these data is that NCI will not be able to appropriately assess cancer risks associated with genotypic, phenotypic, or other biologically measurable factors and to determine if genetic variation modifies radiation-related cancer risks.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

There are no special circumstances that require collection to be conducted in a manner inconsistent with Guidelines in 5 CFR 1320.5.

8. Comments in Response to the *Federal Register* Notice and Efforts to Consult Outside Agency

In compliance with 5 CFR 1320.8(d), a notice of proposed data collection was published in the Federal Register on December 29, 2006 (Volume 71, Number 250, page 78445-78446) (Attachment 5). Comments were solicited on the proposed information collection. No public comments were received.

Financial support for this study is derived from the Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute. This study is being conducted in collaboration with researchers in the Division of Environmental Health Sciences, School of Public Health, University of Minnesota (Bruce H. Alexander, PhD, Principal Investigator; telephone 612-625-7934, email balex@umn.edu, 1998 to present). Permission was obtained from Jerry B. Reid, PhD, Executive Director of the American Registry of Radiologic Technologists (telephone 612-687-0048, email www.arrt.org, 1995 to present) to contact study subjects identified from Registry records. Both of the above-mentioned individuals provide regular on-going consultation with respect to the availability of data, clarity of instructions and reporting format, and data elements recorded.

9. Explanation of Any Payment or Gift to Respondents

In an earlier randomized trial of the use of financial incentives, we found that inclusion of a monetary incentive as small as a $1.00 bill with the second follow-up mail questionnaire (OMB No. 0925-0405, expiration 9/30/1999) significantly improved questionnaire response (Doody 2003); the $2.00 bill, likely because of its' novelty, was especially effective. For this genetic studies component, we plan to include a $2.00 bill with the GQ and blood collection kit as a "small token of our appreciation" to encourage participation.

10. Assurance of Confidentiality Provided to Respondents

This study is supported by Contract NO1-CP-31018 with the University of Minnesota, entitled "U.S. Radiologic Technologists Cohort: New Strategies for Follow-Up and Detailed Study of Radiation". Research involving human subjects conducted by the University of Minnesota is covered under Assurance of Compliance number FWA00000312. This study has been reviewed and approved annually by Institutional Review Boards at the National Cancer Institute (protocol number OH97-C-NO53) and The University of Minnesota (protocols 8005M02489 and 9312M07534) (Attachment 6).

The University of Minnesota will print and optically scan all data collection forms. University staff are cognizant of the sensitive nature of the data on the basic cohort of radiologic technologists, obtained from the American Registry of Radiologic Technologists (ARRT) and have proven their ability to provide secure and confidential management of the data for this population over more than 25 years.

After updating subject addresses based on certification renewals with the American Registry of Radiologic Technologists and other tracing resources, the

University will print and mail out the GQ and blood collection kits. All completed forms will be returned directly to the University, to be opened, edited, and batched for optical scanning. All data scanned from the forms will be stored in computer files without personal identifiers. Hardcopy scanned questionnaires will be stored by the individuals' study ID number. No data forms will be indexed by name, social security number, ARRT registration number, or any other personal identifier. All hardcopy questionnaires will be stored in secure locked rooms. Only authorized project staff will have access to these areas.

Medical records obtained to validate cancer diagnoses, State cancer registry records, and death certificates, which will also contain subjects' personal identifying information, will be stored in locked file cabinets at the University of Minnesota or RTI International (support services contractor to NCI). Data from these records will be linked to the respondent by person-specific study identification number only.

All study records are kept in locked files in locked study offices. Electronic data are stored on password-protected computers. Access to the study offices and computer files is strictly limited to study staff. Access to data is limited to only those data files needed by the staff members to perform their duties. Data are stored by ID number only in separate files from study identifiers (e.g. participant names). Data tapes containing no subject personal identifiers will be delivered to NCI periodically and will be accessible only to a limited number of individuals from the Radiation Epidemiology Branch, NCI and Information Management Services, Inc. (IMS) (computing support services contractor to NCI) directly involved in the study and who are responsible for analyzing the data.

Blood samples are assigned a unique blood sample ID number (BSI) that is used as the study identifier at the biorepository (SAIC at Frederick Cancer Research and Development Center, Frederick, MD). Samples are shipped with only the BSI number and not the participant name or Study ID. The linkage between the BSI number and the participant's Study ID or name is maintained only at the University of Minnesota and is not provided to the biorepository or to researchers analyzing the data or samples. The genetic study laboratory results are submitted to the NCI and analyzed with the assistance of IMS, where no identifying data are maintained. Genetic study results are never sent to the University of Minnesota, thus, cannot be linked with specific individuals.

Publication of study results will be of an aggregate and statistical nature only. Individuals will not be identified or identifiable in any report from the study. All contractor personnel working on this project and who have access to subject identifying information have received training in protecting the confidentiality of study subjects

As this is a prospective cohort study, there are no current plans to dispose of the information obtained. The data will be stored indefinitely unless a decision is reached not to conduct any further follow-up of this study population. Should that decision be made at a future date, all items containing personal identifiers will be destroyed through shredding, degaussing, or incineration at the direction of the NCI Project Officer.

It has been determined that the Privacy Act will apply to this collection (Attachment 7). The data collection is covered by NIH Systems of Record 09-25-0200 , "Clinical, Epidemiologic, and Biometric Studies of the National Institutes of Health (NIH), HHS/NIH/OD" (Attachment 7) because the information will be retrieved and maintained by personal identifiers, and data analysis will involve critical parameters

relevant to the targeted audiences (e.g., family history of cancer, gynecologic and reproductive histories, medical irradiation, chemotherapy, participant names, age, race, gender, home address, telephone number).

11. Justification for Sensitive Questions

Some of the questions that will be asked may be considered sensitive, including family history of cancer, gynecologic and reproductive history, and history of medical irradiation or chemotherapy. Data on medical irradiation and chemotherapy are necessary to assess risks of cancer and other conditions associated with occupational radiation exposure. Data on other factors (family history of cancer, gynecologic and reproductive histories) are needed because these factors are strongly related to an individual's risk of cancer and/or other health conditions, and may confound the risks associated with genetic make-up and/or radiation. This valuable cohort of radiologic technologists continues to be followed and is anticipated to be followed indefinitely for incidence and mortality from cancer and other conditions Subjects will be advised in the study brochure (Attachment 3A) and advance letter (Attachment 3B) sent prior to any interviews or mail questionnaires, that their participation is completely voluntary and that they may refuse to respond to any or all questions without penalty. Verbal consent will be obtained during any telephone interview; completion and return of any mail questionnaires implies consent. Written consent will be obtained for collection and use of biospecimens (Attachment 4A) and medical records (Attachment 4B). Confidentiality measures are discussed in Section A10.

12. Estimates of Hour Burden Including Annualized Hourly Costs

Table 1 displays the respondent and burden estimate for the proposed collection. Eligible sub-cohort members are a subset of U.S. radiologic technologists who willingly participated in earlier investigations to quantify the carcinogenic risks of protracted low- to moderate-dose occupational radiation exposures.

Table 1. RESPONDENT AND BURDEN ESTIMATE (OMB No. 0925-0405)						
Type of Respondent	Number of Respondents (3 yr)	Frequency of Response	Total Respondents (3 yr)	Average Hours Per Response	Total Hours (3 yr)	Annual Hour Burden
Genetic Studies Risk Factor Survey and Blood Collection						
Sub-Cohort	10,000	1	10,000	1.66666	16,666	5,553
Medical Validation						
Hospitals/ Physicians	2,700	1	2,700	0.08333	225	75
TOTAL	**12,700**		**12,700**		**16,891**	**5,628**

Based on 2005 Department of Labor wage rates (http://www.bls.gov/oes/current/oes2920), and allowing for an increase of 5% per year, we assumed an average hourly rate of $24.92 for radiologic technologists and $24.22 for physician office personnel. The total estimated cost to respondents over three years is $420,738; thus, the estimated annual burden cost is a maximum of $140,246 (Table 2). There will be no direct costs to the respondents other than their time to complete the questionnaires, provide a blood sample, or to retrieve medical validation information.

Table 2. ESTIMATES OF ANNUALIZED COST TO RESPONDENTS (OMB No. 0925-0405)					
Type of Respondent	Number of Respondents	Frequency of Response	Average Hours Per Response	Average Hourly Wage	Total Cost
Radiologic Technologists	3,333	1	1.66666	$24.92	138,430
Physician Office Personnel	900	1	0.08333	$24.22	1,816
TOTAL	4,233				$140,246

13. Estimate of Other Total Annual Cost Burden to Respondents or Record Keepers

No additional cost burden to respondents and record keepers is anticipated. No equipment or other technology is required for generating, maintaining, and disclosing or providing the information. There are no capital, operating or maintenance costs to report.

14. Annualized Cost to the Federal Government

Contract costs to conduct the genetic studies survey and collect blood samples, as described above, include $450,000 to the University of Minnesota, $200,000 to SAIC/Frederick, $75,000 to RTI International, $225,000 to the Core Genotyping Facility, NCI or other collaborating laboratories, and $150,000 to Information Management Services, Inc. over the three-year period for which OMB approval is being requested. The total cost for NCI intramural staff over three years is $100,000. These figures include the costs of study design, subject tracing, data collection, biospecimen collection and processing, laboratory and statistical analyses, and report writing. The total cost is therefore $1.2M and the annualized cost is $400,000.

15. Explanation for Program Changes or Adjustments

This is a renewal with revision of a previously approved collection of information with the total annual hours requested as Program change in OMB 83-I, Item 13, f.1. The number of hours requested is substantially lower than in the generic clearance requested three years ago because the current petition is for approval of only one of the three generic surveys originally envisioned (i.e. the Genetic Studies Questionnaire and blood collection). The first of the three previously anticipated surveys, the third follow-up of

the cohort (i.e. Third Survey), was completed during 2003-2005 (OMB No. 0925-0405, expiration 2/28/2007). It took much longer to design and administer the Third Survey than expected. To accurately estimate occupational ionizing radiation doses, it was necessary to ask difficult and detailed calendar-specific questions about frequency and intensity of radiologic procedures performed many years in the past, plus procedure-specific protection practices. The survey was lengthier than anticipated (20 pages vs. 4), obtaining in addition a complete history of medical outcomes, residential history (for UV radiation dosimetry), and selected cancer risk factors. To ensure that subjects would be able to understand the detailed employment questions and provide meaningful responses, we initially conducted a focus group with early workers from the Minneapolis-St. Paul area to gather information about practices and procedures before 1960. The information gathered, along with input from other sources, was used to refine the work history questions. Different pre-test versions of the questionnaire were sent to multiple groups of 9 subjects each. Based on follow-up interviews to obtain comments and reactions to the questionnaire and/or to find out reasons for non-participation, revisions were made to questions that were problematic. Before beginning, a final pre-test version was mailed to 300 subjects. Probably because of the number and complexity of the questions asked, after two mailings of the full-length questionnaire, follow-up with a reminder letter, a study newsletter, and a reminder postcard with a non-monetary (i.e. magnet with study logo) incentive, the response rate was only 60%. Design, printing and mailing of the newsletter, reminder postcard, and study magnet were all time- and cost-intensive efforts that were not previously anticipated. To increase the final response to 73%, it was further necessary to abbreviate the questionnaire to 8 pages and mail it a third time with a $1.00

bill as an incentive. These additional efforts delayed development of the Genetic Studies Questionnaire and Fourth Survey and drained resources that were already increasingly limited owing to broad programmatic budget cuts. As a consequence of major budget cuts, the Fourth Survey is on indefinite hold.

16. Plans for Tabulation and Publication and Project Time Schedule

A projected time schedule for the GQ and biospecimen collection described in Section A.6 is displayed in Table 2. All times are after initial OMB approval is received.

Table 2. PROJECT SCHEDULE

Blood Collection	**0-24 months**
Information Collection	**0-30 months**
Analysis and Manuscript Writing	**24-36 months**
Submit First Publication	**36 months**

17. Reason(s) Display of OMB Expiration Date is Inappropriate

There are no reasons to preclude display of the OMB expiration date on the questionnaire.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification statement.