Supporting Statement A for:

A multi-center international hospital-based case-control study of lymphoma in Asia (AsiaLymph) (NCI)

March 2, 2012

Submitted by:

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This is a request for an emergency clearance of the "AsiaLymph Study" on the grounds that this is essential to the mission of National Cancer Institute (NCI) and that NCI cannot reasonably comply with the normal clearance procedures and this would likely prevent or substantially disrupt the collection of information (5CFR 1320.13). In addition, prevention of the study would cause public harm through the loss of critically needed information to understand and reduce the cancer burden from lymphoid malignancies in the Asian population, the incidence of which has risen in recent decades. The planned start date for AsiaLymph is March 5, 2012.

A.   JUSTIFICATION

A.1   <u>Circumstances Making the Collection of Information Necessary</u>

Under Section 411 of the Public Health Service Act (42 USC *§* 285a), the Division of

Cancer Epidemiology and Genetics (DCEG) of the National Cancer Institute (NCI) is authorized

to collect information to generate and test hypotheses concerning environmental and host

determinants of cancer. The mission of the DCEG is to conduct "multidisciplinary research to

discover the genetic and environmental determinants of cancer and new approaches to cancer

prevention. The Division's research impacts public health policy in the United States and around

the world." More specifically, the mission of the Occupational and Environmental

Epidemiology Branch is to "conduct studies in the United States and abroad to identify and

evaluate environmental and workplace exposures that may be associated with cancer risk." The

AsiaLymph study will test hypotheses regarding the association of specific environmental,

occupational, viral, and other exposures and lymphoid malignancies.

Incidence rates of certain lymphomas have increased in the United States and in many

other parts of the world. The contribution of environmental, occupational, and genetic factors to

the cause of lymphoma has generated a series of novel findings from epidemiological studies

conducted in the United States that have attempted to explain this increase. However, none of the

chemical associations have been conclusively established and the identification of the key,

functional alleles in gene regions associated with risk of NHL requires further elucidation.

Further, the ability to follow-up, confirm, and extend these observations in the United States is limited by the low prevalence and limited range of several important chemical and viral exposures and the high to complete linkage disequilibrium among key candidate genetic loci in Western populations. To optimize the ability to build on and clarify these findings, it is necessary to investigate populations that differ from those in the West in both exposure patterns and underlying genetic structure. A multidisciplinary case-control study of lymphoma in Asia, where lymphoma rates have also risen, provides an opportunity to replicate and extend recent and novel observations made in studies in the West in a population that is distinctly different with regard to patterns of key risk factors, including range of exposures, prevalence of exposures, correlations between exposures, and variation in gene regions of particular interest. It will also improve the ability to understand the causes of certain types of rare lymphoma tumors in the United States that occur at much higher rates in Asia. As such, AsiaLymph will confirm and extend previous findings and yield novel insights into the causes of lymphoma in both Asia and in the United States.

Research suggests that organochlorines (OCs), trichloroethylene (TCE), and benzene may be associated with risk of lymphoma and that benzene and TCE have immunotoxic properties (Stewart 2009; Lan et al. 2004; Lan 2009), that genetic variation in certain loci involved in immunologic regulation (e.g., *TNF/LTA*, *IL10*, and *IL4*) may contribute to risk of lymphoma, and that interactions between these chemicals and genes may exist (Lan et al. 2004; Colt et al. 2009; Wang et al. 2007). However, none of these chemical or genetic associations have been conclusively established, and the underlying biologic plausibility, including identification of critical functional alleles in genetic studies, requires further elucidation. At the same time, there is a growing appreciation of the critical need for high quality pathology review

in etiologic studies of lymphoma, as evidence is increasing that some risk factors may be highly specific to one or more subtypes of lymphoma and therefore the subtypes need to be very accurately characterized (Morton et al. 2008).

Lymphoma in Asia

Although NHL rates historically have been lower in Asia than in the West, there is evidence that rates have been rising in recent decades in Asia from some of the best cancer registries in this region located in Shanghai and Singapore (Jin et al. 1999; Chia et al. 2001). For example, in Shanghai between 1972-3 and 1993-4, NHL rates rose 33% in males and 66% in females, while there was a small drop in incidence rates for leukemia in both sexes. Overall, there was an 11% and 13% decline in the incidence rates of all cancers for males and females, respectively, during this time period (Jin et al. 1999). The distribution of NHL histologic subtypes also differs in Asians and Caucasians. Although diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype in both Asians and Caucasians, rates of follicular lymphoma are substantially lower in Asians, whereas rates of T-cell lymphomas, particularly nasal type Natural Killer T (NK/T) cell lymphomas, are substantially higher in Asians (Au and Lo 2005; Ng et al. 1986; Gross et al. 2008; Kadin et al. 1983). As a consequence, this study provides a unique opportunity to replicate and extend key findings observed in Caucasians for histologies with characteristics shared by both populations as well as to rigorously study the epidemiology of those tumors that appear to be more common in Asia than in Western populations. See the protocol for a complete discussion of the background and rationale to study environmental exposures to industrial emissions, genetic susceptibility, viral exposures, early life exposures, ultraviolet (UV) radiation exposures, and other risk factors for lymphoma overall and specifically for populations in Asia (**Attachment 1)**.

Organochlorines, Trichloroethylene (TCE), and Benzene

Organochlorine compounds (OCs) include several classes of chemicals including dioxin, polychlorinated biphenyls (PCBs), and pentachlorophenols (PCPs). OCs were first introduced in the 1940's, are relatively long-lasting, and have been widely used as insulators and pesticides. OCs have been suggested to be associated with a number of health concerns, including thyroid, metabolic, and reproductive disorders, in addition to several cancers, although results have been inconsistent (Toft et al. 2004; Langer 2010; Longnecker et. al. 1997; Gallagher et al. 2010; Purdue et al. 2009). There are several advantages to studying OCs and lymphoma in Asia including much higher plasma levels and a wider range of several OCs (e.g., DDE, the major DDT metabolite) than in the West and the weaker overall correlation pattern between certain compounds. This opportunity will provide us with a unique opportunity to assess chemical-specific OC associations with NHL, which will complement previous and ongoing efforts to study these associations in the West.

TCE, a chlorinated solvent used in several industries primarily for metal degreasing, is one of the most important ground water contaminants in the United States. Despite the cohort and case-control studies carried out to date, a connection between TCE and lymphoma has still not been established. It is currently rated by International Agency for Research on Cancer (IARC http://www.iarc.fr/) as a probable carcinogen (Group 2A). Due to the extensive use of TCE in Asia, a higher proportion of the population is exposed, and there is a wide range of exposure levels. Whereas less than 1% of women in the NCI-SEER case-control study were ever exposed to TCE, approximately 7% of women in the Shanghai Women's Health Study have been exposed, with half of these exposures continuing beyond 1990. A case-control study of lymphoma in Asia will take advantage of the higher prevalence of exposure and the opportunity

to link to extensive TCE databases in Asia (e.g., Shanghai CDC database; Guangdong Poison Control Center database). AsiaLymph will also benefit from the use of refined questionnaire workplace modules developed by DCEG investigators to capture chlorinated solvent exposures.

Benzene is a ubiquitous occupational and environmental contaminant worldwide, and is used for many applications including pesticides, detergents, and dyes, as well as in the rubber manufacturing process. Although an established leukemogen, there is substantial controversy about its lymphomagenic potential. Both cohort and case-control studies have been somewhat inconsistent (Orsi et al. 2010; Vlaanderen et al. 2010; Cocco et al. 2010, Alexander et al. 2010). Although DCEG has studied hematopoietic malignancies in a large cohort of Chinese workers with detailed benzene exposure data spanning a 50-year period (OMB No. 0925-0454, expiration date 4/31/2008), the number of NHL cases is limited (i.e., there are ~ 20 benzene-exposed cases with a high probability of being NHL). Because the follow-up period was 1972-1999, almost half of the exposed cases have no specific molecular or histologic information and only nine cases have pathology material for re-review. AsiaLymph will complement the NCI-China CDC benzene cohort study, as the case-control investigation would have substantial power to detect an association between occupational exposure to benzene with confirmed cases of lymphoma (e.g., we expect ~180 NHL cases with a high probability of exposure to benzene, assuming a prevalence of 3% among controls and an OR of 2.0), would be able to analyze benzene effects on lymphoma by subtype, and would take advantage of the extensive benzene databases we have accumulated on workplace exposures in China.

Genetic Susceptibility and Viral Exposures

Lymphomas show significant familial aggregation in the population indicating that genes are likely to play a role in susceptibility. A large-scale evaluation of genes associated with lymphoma in Asian populations that parallels efforts being conducted in Caucasian populations (e.g., currently a genome-wide association study (GWAS)) would be particularly informative because of Asian population genetic differences in patterns of linkage disequilibrium (LD) and local haplotype structure (Lan et al. 2007). Further, the study of Asian populations also would allow for identification of novel susceptibility genes.

Several aspects of lymphoma epidemiology in Asia support the importance of studying potential infectious etiologies for these tumors including the higher incidence of certain types of T-cell lymphomas than in Western countries that are known or likely to be virally-related and the higher prevalence of exposure to certain viruses such as Hepatitis B (Aoki et al. 2008; Aozasa et al. 2008; Du et al. 2009; Kadin et al. 1983). For example, the profound excess incidence of nasal NK/T-cell lymphoma, a uniformly Epstein Barr Virus (EBV)-positive tumor, suggests the existence of important co-factors related to host control of EBV that may be unique to Asian populations (Kadin et al. 1983). This study will screen all collected tumor samples by EBV-encoded RNA (EBER) *in situ* hybridization to identify the EBV-positive lymphomas. Risk factors including demographic, environmental, and genetic characteristics for NK/T-cell lymphoma and for other EBV-positive lymphomas will be compared and contrasted to the risk factors for EBV-negative lymphomas in case-case and case-control comparisons.

We will also be collecting an unprecedented number of these tumors for molecular pathologic analysis with uniform processing and histologic interpretation. Results from this study, as well as other studies, could lead to the identification of candidate lymphoma genes

causally involved in NK lymphoma tumor initiation and/or progression. These tumors will be analyzed for evidence of oncogenic viral infections that could explain the excess incidence.

Finally, chronic hepatic inflammation caused by hepatitis B (HBV) or hepatitis C viral (HCV) infection has been implicated as a potential risk factor for NHL. The evidence for HCV infection is somewhat more suggestive, although the associated histologic sub-types have not been consistent between studies (Dal and Franceschi 2006). Evidence for HBV is more mixed, with both null (Anderson et al. 2008) and positive associations (Chen et al. 2008; Engels et al. 2010). A NHL study in East Asia, with its relatively high prevalence of HBV infection in particular (Du et al. 2009), provides a valuable opportunity to examine potential important etiologic associations. With centralized pathologic review with extensive immunophenotyping, we will have greater precision for examining the associated subtypes and the magnitude of association for each infection. Risk factor analyses for viral-positive cases as well as for histologies with high attributable risk will provide important additional insight into the role of these viruses in lymphomagenesis.

A multidisciplinary case-control study of lymphoma in Asia is timely because it will provide an opportunity to replicate and extend recent and novel observations made in studies among Caucasians in a population that is distinctly different with regard to patterns of key risk factors. Refer to **Attachment 1** (p. 3-10) for a complete discussion of background, rationale and references. This study involves some of the leading lymphoma clinicians and pathologists in Asia and represents the culmination of a seven year effort to launch (**Attachment 2**). If this study is not conducted, it will result in the loss of an extraordinary opportunity to learn about the etiology of this important tumor in one of the largest populations in the world and to confirm

many leads identified from previous studies conducted in the United States and elsewhere in the West.

A.2   **Purpose and Use of the Information**

The purpose of the study is to evaluate the etiology of lymphoma in Asia. The main focus of the study is on chemical exposures, viral exposures, and genetic susceptibility, with central pathology review to characterize effects by histologic subtype. Specific study goals are as follows:

1) Investigate the role of environmental exposure to organochlorines and occupational exposure to trichloroethylene, benzene, and other chemical solvents as well as to other potential occupational exposures;

2) Investigate the role of family history, high-prior candidate genetic variants (e.g., *TNF/LTA* locus) and emerging findings from genome-wide association studies of lymphoma in Caucasians, and use state-of-the-art genomics to study genetic variants that may be unique to risk of lymphoma in Asia;

3) Investigate the etiologic role of Epstein Bar (EBV), Hepatitis B (HBV) and Hepatitis C (HCV) viruses; evaluate potential novel viral agents in T-cell lymphoma; carry out studies to understand pathogenetic mechanisms of Natural Killer T (NK/T) cell lymphoma;

4) Study other potential determinants of lymphoma including early childhood exposures including crowding and animal exposures, medical conditions, ultraviolet radiation exposure, and other lifestyle factors;

5) Determine the influence of risk factors for lymphoma overall and by histologic subtype determined by central pathology review.

The study methods include a core questionnaire that is administered by trained interviewers on risk factors (**Attachment 3**). In addition, depending upon the occupational history obtained, the computer-assisted personal interview (CAPI) will bring up one or more occupational assessment modules which consist of questions that are targeted to capture additional information regarding chemical exposures (**Attachments 4 and 5**). A blood and buccal cell sample will be collected from each subject to measure chemical and viral exposures

and genetic factors. Samples of tumor tissue will be collected from pathology blocks from cases after clinical diagnostic tests are completed and used for confirmatory tests, viral studies, and molecular diagnostic tests to be conducted by the study pathology center.

The study will be the largest molecular epidemiology study of lymphoma ever carried out anywhere in the world and the results and information from this study will be used in a number of different ways including to:

- Contribute substantial scientific contributions to the literature concerning the etiology of lymphoma in Asia and world-wide focusing on the risk factors being studied;

- Confirm previous occupational, environmental, viral, genetic and other hypotheses identified in epidemiologic studies conducted among in the West;

- Assist senior leadership of DCEG to determine how best to allocate resources to study lymphoma in the future and;

- Contribute to a better understanding of the etiology of lymphoma world-wide and thus may eventually help to understand the reason for the increase in the incidence of this cancer in Asia and elsewhere and identify approaches that can be used for its prevention.

A.3   <u>Use of Improved Information Technology and Burden Reduction</u>

AsiaLymph will employ cutting edge methodologies to efficiently collect detailed information about occupational exposures using a new software tool (OccIDEAS) that is integrated into the computer assisted personal interview (CAPI), which has never been used in a previous study of lymphoma. Further, each interviewer will use a touch-tablet (Lenovo X 220) to administer the questionnaire. Together, these are expected to reduce the time required to administer the questionnaire to an average of 60-75 minutes.

A discussion with the NCI Privacy Act Coordinator will determine whether a Privacy Impact Assessment (PIA) is needed and if so, then the application and review will be undertaken.

A.4 **Efforts to Identify Duplication and Use of Similar Information**

There are no other sources of similar information that has been collected that will yield

that same results as this effort in Asia. First, almost every epidemiologic study of lymphoma has

been conducted among primarily Caucasians in Western countries and no large scale multi-

center study of lymphoma has ever been conducted in Asia. Secondly, no large-scale study

epidemiologic study of lymphoma in any population has ever conducted central

immunophenotyping and pathology review, which is critical to understand risk factors for

specific subtypes of lymphoma. Third, this will be the largest multidisciplinary study of

lymphoma ever conducted anywhere in the world. As such, it will have better statistical power

than any previous study to evaluate risk factors for histological subtypes, all collected and

characterized using the same uniform methods.

A.5 **Impact on Small Businesses or Other Small Entities**

There is no impact on small businesses or other small entities.

A.6 **Consequences of Collecting the Information Less Frequently**

Patients are asked to participate once for the interview and biological specimen

collection.

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

The study fully complies with the Guidelines.

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

NCI received approval from OMB to publish an Emergency <u>Federal</u> <u>Register</u> notice

which occurred on February 17, 2012 (77 FR 9665). This allowed a 15-day comment period

prior to submitting this information collection. Additionally, a 60-day Federal Register was

published on February 24, 2012 (77 FR 11136) soliciting additional comments from the public.

Many people were consulted on all aspects of this study including previously existing information, identification of study centers and hospitals, study design, and study methods over the last three years. This includes some of the world's leading lymphoma pathologists, clinicians, and epidemiologists, and occupational and environmental exposure assessment experts. These individuals are located in the United States, Europe, Australia, and Asia (**Attachment 2**). All issues were successfully resolved through these consultations.

A.9   Explanation of Any Payment or Gift to Respondent

We will give $22.50 to all study subjects who agree to participate for their time, effort, and invasive nature of the biological sample. The dollar amount was arrived at after consultation with clinicians and epidemiologists at each of the four study centers and hospital and considered a reasonable amount that is needed in order to obtain high participation rates. This amount of remuneration has been approved by the NCI Special Studies Institutional Review Board (SSIRB) and the NIH IRB (**Attachment 6A**).

A.10   Assurance of Confidentiality Provided to Respondents

Procedures have been developed to protect the security of all information collected from study subjects and approved by the NCI SSIRB and NIH IRB (**Attachment 6A**). All files sent from interviewers to the study coordinating center (Hong Kong University School of Public Health) by internet will be fully encrypted. All original questionnaire responses and other study documents with personal identifiers will be kept securely at the study coordinating center. All scanned medical records will have the subject name blocked out before scanning and be identified by only a subject ID number. All biological samples will be identified only by a subject ID and not have any personal identifiers, and these samples when sent from the NCI biorepository to laboratories for analysis will be characterized by identifier numbers only.

Biological sample analytic results will be sent to for addition to the study database. All personal

identifiers will be stripped from data analysis files prepared by the study coordinating center for

study investigators. Finally, no individual results will be presented in publications or other

reports. See **Attachment 1** for additional details.

The study and its informed consent forms (**Attachment 7**) were approved by the NCI

SSIRB and NIH IRB on July 5, 2011 (**Attachment 6A**); the IRB at Hong Kong University on

November 1, 2011 (**Attachment 6B**), which is the overall study coordinating center and the

study center for Hong Kong; Sichuan University Huaxi (West China) Hospital on December 9,

2011 (**Attachment 6C1,2**), which is the coordinating center for Chengdu; Tianjin Medical

University Cancer Institute and Hospital on November 24, 2011(**Attachment 6D1,2**), which is

the coordinating center for Tianjin; and Dalin Tsu-Chi General Hospital on February 20, 2012

(**Attachment 6E1,2**), which is the coordinating center for Taiwan.

The Privacy Act does not apply to an international population.

A.11 <u>Justification for Sensitive Questions</u>

Personally identifiable information (PII) will be collected. Most questions asked in the

study questionnaire (**Attachment 1**) are typically not considered sensitive. Some questions, such

as those about alcohol consumption, medical history, family history, reproductive health, and

family income may seem sensitive to some respondents. However, these are important factors to

evaluate as possible confounders and are known or suspected risk factors in and of themselves

for lymphoma and represent questions that are common to health studies. National ID numbers

are important to collect since they are often used as a way of identifying patients and their

medical records in hospital databases and are unique. Respondents are informed that their

responses will be kept secure and they have the right to skip any questions even if they consent to the interview as a whole (**Attachment 7**).

A.12   **Estimates of Annualized Burden Hours and Costs**

It is conservatively estimated that 3,100 patients will be screened to gain 2,200 patients per year for participation in the study. Controls will be drawn from patients seen at the same hospital for diseases/conditions that are unlikely to be associated with risk factors under study, such as injuries and selected diseases of the circulatory, digestive, genitourinary, and central nervous system (**Attachment 1**). The category of respondents is considered "Individuals."

The estimated average time for a patient to complete the core questionnaire (75 minutes), the patient-specific computer-triggered occupational exposure assessment modules (15 minutes), and to collect the biospecimens (15 minutes) is estimated to be no more than one hour and 45 minutes (105 minutes) (**Attachments 3, 4, and 5**). Based on previous experience in other studies that use patient-specific computer-triggered occupational job modules, about 50% of the study subjects will not have any job module asked and the remaining 50% will have 1-3 job modules asked, and the overall estimated time burden is an average of 15 minutes. The time estimates for the core questionnaire and occupational job modules are based on pilot testing of 9 people as well as previous experience with similar questionnaires.

In addition to the patients, the study interviewers and the hospital pathologists will complete administrative forms related to the collection of the biospecimens (**Attachment 8 and 9**). The 19 pathologists will fill out the form in Attachment 8 for 1100 cases, for an average of 58 forms per pathologist. The 19 interviewers will fill out the forms in Attachment 9 for 2200 subjects (1100 cases and 1100 control patients) for an average of 116 set of forms per interviewer.

The annual burden for the respondents, the pathologists, and the interviewers is estimated to be 5,302 hours which amount to a total of 15,906 hours over a three-year data collection period (Table A.12-1).

Table A.12-1. Estimates of Annual Burden Hours					
Types of Respondents	**Instrument**	**Number of Respondents**	**Frequency of Response**	**Average Time per Response (Hours)**	**An Bu Ho**
Potential Study Subjects	Screening Questions	3,100	1	5/60	2
Consented Patients with Lymphoma	Questionnaire	1,100	1	105/60	1,
Consented Patient Controls	Questionnaire	1,100	1	105/60	1,
Study Pathologists	Pathology sample request and tracking form	19	58	5/60	9
Interviewers	Tracking forms	19	116	30/60	1,
Total					5,

Based on a median hourly wage rate of $10 for study subjects, $40 for pathologists, and $7 for interviewers, the annualized average cost is $52,474 which amounts to $157,422 over a three-year period (Table A.12-2).

Table A.12-2. Annualized Cost to Respondents				
Type of Respondent	**Instrument**	**Annual Burden Hours**	**Hourly Wage Rate**	**Respondent Cost**
Potential Study Subjects	Screening Questions	258	$10.00	$2,580.00
Consented Patients with lymphoma	Questionnaire	1,925	$10.00	$19,250.00
Consented Patient Controls	Questionnaire	1,925	$10.00	$19,250.00
Study Pathologists	Pathology sample request and tracking form	92	$40.00	$3,680.00
Interviewers	Tracking forms	1,102	$7.00	$7,714.00
Total		5,302		$52,474.00

A.13 Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers

There are no direct costs to the patients, pathologists or interviewers other than their time to participate in the study.

A.14 Annualized Costs to the Federal Government

This includes contractor costs, NCI staff time, and biological collection, biological transport, biological sample analysis and data analysis. This comes out to an annualized cost of is $909,200. The total costs to the Federal Government over the five-year period of data collection and analysis are estimated to be $4,546,000 (see Table A.14-1).

Table A.14-1. Annual Cost to the Federal Government

	5 YEAR TOTAL	ANNUAL AVERAGE
Contractor Costs	$2,400,000	$480,000
NCI Personnel Subtotal	$435,000	$87,000
Biologic sample collection and processing, and data analysis	$855,000	$171,000
Purchase of Computers for Interviewing and Data Management	$45,000	$9,000
Pathology Reagents	$495,000	$99,000
Travel Costs for NCI Staff for Study Management and Development	$316,000	$63,200
Total	$4,546,000	$909,200

A.15 Explanation for Program Changes and Adjustments

This is a new information collection.

A.16 Plans for Tabulation and Publication and Project Time Schedule

Full-scale data collection, cleaning and analyses will be followed by publication in peer-reviewed, scientific journals. Our project time schedule is given in Table A.16-1.

TABLE A.16-1. PROJECT SCHEDULE FOR PHASE III	
Component	**Time after OMB approval**
Data collection	1 day to 36 months after approval
Data editing	1 week to 40 months after approval
Data analysis	40 to 60 months after approval
Publication	42 to 60 months after approval

Since lymphoma comprises a group of related yet heterogeneous diseases, each characterized by the malignant transformation of lymphoid cells but with distinctive

morphologic, immunophenotypic, genetic, and clinical features, we will analyze risks by lymphoma subtype as well as larger subgroups. For analyses by subtype, odds ratios (ORs) and 95% confidence intervals (CIs) will be derived for each risk factor from polytomous unconditional logistic regression models adjusting for matching variables. P values for the linear trend will be computed for continuous variables and using ordinal variables. To evaluate heterogeneity among lymphoma subtypes, we will use 2 statistical approaches. First, we will conduct a homogeneity test in the polytomous model, testing the null hypothesis that the regression coefficient for each risk factor was the same for all subtypes. Values of P less than .05 will be considered to provide evidence of heterogeneity. The test for homogeneity has the greatest power to detect risk differences when the risks for the subtypes all vary slightly from one another. Second, we will analyze all possible case-case pairwise comparisons using dichotomous logistic regression models (Morton et al. 2008). We will compute test the null hypothesis that the particular risk factor does not discriminate between the 2 disease groups modeled. To account for the pairwise analysis, we will apply a Bonferroni correction. In contrast to the test for homogeneity, the pairwise analysis has the greatest power to detect risk differences when the risk for one disease group is distinct from the other(s). For risk factors with more than 2 categories, we will use the ordinal variable for the homogeneity test and pairwise analysis. Analyses will also be conducted for larger lymphoma subgroups including NHL and B-cell lymphomas using unconditional logistic regression models in order to utilize all controls, adjusting for the matching factors. Analyses will also be conducted for the entire study population using conditional logistic regression models.

For genetic analyses, standard methods will be used to test the effect of each SNP. We will also use a new powerful and flexible subset-based approach to the combined analysis of

heterogeneous traits, which is an approach that agnostically explores subsets of the traits to identify the strongest association signal and then evaluates the significance of the detected association using efficient adjustment for multiple correlated tests involved (N. Chatterjee, Chief DCEG Biostatistics Branch, personal communication). Data obtained from the study will be analyzed using the STATA and SAS package of statistical programs. Data will be cross-classified by age and sex, but analyses by sex-specific groups will also be performed.

Initial analyses will be conducted for lifestyle risk factors, occupational exposures, environmental exposures, viral exposures, and genetic main effects. Exploratory gene-environment interaction analyses will also be conducted. We will also conduct genetic pathway analysis to evaluate whether the set of genes in a well-defined pathway (e.g., Th1/Th2 pathway) are associated with the disease risk. This type of analysis is particularly helpful in situations when the pathway is enriched with multiple SNPs with small effects. All models will be adjusted for sex, age, study center, and date of enrollment (the control matching factors) and education. Additional potential confounders will be selected based on initial analyses of the study data set and through identification of well-established risk factors in the literature. Essentially the entire study population will be comprised of Han Chinese so race-specific analyses will not be conducted. Analyses by sex-specific groups will be performed. Adjustments for potential confounding factors will depend upon the exposures under consideration.

Separate questionnaire-based publications will include the relationship between lymphoma and occupational exposure to trichloroethylene, occupational exposure to benzene, occupational exposure to chemical solvents, occupational exposure to formaldehyde, farming, residential proximity to traffic, residential proximity to incinerators, animal exposures, indoor air pollution from heating and cooking, family history, medical conditions, childhood crowding,

early childhood exposures, UV exposure, physical activity, alcohol use, tobacco use, selected

dietary factors (e.g., green tea, soybean products), hair dye use, reproductive history, and

socioeconomic status. As indicated in **Attachment 1**, there is support in the literature for a

relationship between each of these types of exposures and lymphoma. Further, descriptive

papers on the distribution of lymphoma subtypes will be published. In addition, chemical and

molecular laboratory analyses of the collected biological samples including pathology samples

will result in separate publications on the relationship between lymphoma and organochlorine

plasma levels, exposure to Hepatitis A, B, and C, Epstein Barr Virus, and genetic susceptibility

using cutting-edge technology at the NCI. Additional publications will be produced on potential

gene- and viral-chemical interactions.

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

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

questionnaires.

A.18   **Exceptions to Certification for Paperwork Reduction Act Submissions**

There are no exceptions to the certification statement.