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CASE-CONTROL STUDIES OF ACUTE NON-LYMPHOCYTIC LEUKEMIA AND NON-HODGKIN'S LYMPHOMA IN SHANGHAI

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1.0 INTRODUCTION

In 1979-1981 the Institute of Occupational Medicine, Chinese Academy of Preventive Medicine (CAPM), carried out a national survey in China, in which more than 500,000 workers were identified to have been exposed to benzene (Yin and Li, 1986; Yin et al., 1987a). The 95% range of benzene concentrations at workplaces was 0.06-844.74 mg/m^3 (0.02-266 ppm). Subsequently, 28,460 of these exposed workers from a variety of industries in 12 cities and 28,257 unexposed workers from the same cities were included in a historical cohort study (the "CAPM" study). The results were reported in a number of publications (Yin and Li, 1986; Yin et al., 1987b; Yin et al., 1989). A total of 25 leukemia deaths and 5 incidence cases were reported among the exposed workers, while 4 deaths among the unexposed workers were attributed to leukemia. The standardized incidence ratio (SIR) of leukemia for the exposed workers in comparison to the unexposed workers was 5.74 ($p < 0.01$). No exposure-response analysis was performed, but the authors reported actual benzene measurements from locations where leukemia deaths and cases were observed (Yin and Li, 1986; Yin et al., 1987b; Yin et al., 1989). Exposure levels reported were as high as 5,508 mg/m^3 or 1,732 ppm. In 1988, Li and Yin published a case-control study of leukemia and benzene exposure in four cities in China (Li et al., 1988). The reported relative risk was 3.4. No benzene exposure levels were available in the case-control study.

Since 1987, the US National Cancer Institute (NCI) has collaborated with CAPM in expanding and updating the Chinese benzene study. The previous study was expanded to include 74,828 benzene-exposed workers and 35,805 unexposed workers who were employed for any length of time between 1972 and 1987 at 712 factories in 12 cities (the "CAPM-NCI" study). The general methods and resources of the expanded study were described by Yin et al. (1994). In a second paper, an historical benzene exposure assessment to characterize benzene exposure profiles of the cohort members was outlined (Dosemeci et al., 1994).

Based on comparisons between the exposed and unexposed workers, increased mortality risk ratios (RR) were reported for a variety of cancers (Yin et al., 1996). Some exposure-response analyses in terms of cumulative exposure (ppm-years) for selected disease categories were reported by Hayes et al. (1996). In one of the latest papers derived from the CAPM-NCI study, Hayes et al. (1997) reported dose-related incidence of hematologic neoplasms. For leukemia, the RR was 2.5 (95% CI: 1.2-5.1). For acute non-lymphocytic leukemia (ANLL), the RR was 3.0 (95% CI: 1.0-8.9). The RR for non-Hodgkin's lymphoma (NHL) was 3.0 (95% CI: 0.9-10.5). The trend between ANLL and cumulative exposure was close to, but did not achieve, statistical significance ($p = 0.06$). For NHL, the highest risk (RR = 7.8) was observed among "chemical" workers, which included "organic, insecticide, and benzene production workers."

Although the Chinese benzene study was one of the largest studies in terms of number of exposed workers, some results were based on comparisons to small numbers of cases for disease categories of interest in the unexposed group. For example, there were only 4 ANLL cases and 3 NHL cases among the unexposed workers. In the Chinese

benzene study, results depended not only on the number of deaths in the exposed group but also on the number of deaths in the unexposed group. The small number of deaths in the unexposed group rendered the results unreliable.

Exposures to industrial chemicals in addition to benzene among the exposed workers in the CAPM-NCI study represented a serious problem of concomitant exposures. The exposed workers were employed in a variety of industries. In the CAPM study, 64% of the exposed workers were painters or paint production workers (Yin et al., 1987b). Painters are exposed to a variety of organic solvents, which may or may not consist of benzene. In terms of exposures, only 5% were exposed to benzene only (Yin et al., 1987a). In addition to painters, the benzene-exposed group included, for example, agricultural chemical workers, wood and furniture workers, printing workers, pharmaceutical workers, rubber and plastic workers, metallurgy workers, fabricated metal workers, electrical equipment workers, transportation equipment workers, and precision machinery workers. These workers might have been exposed to a variety of both chemical and physical agents, some of which are known carcinogens. For example, agricultural chemical workers are exposed to arsenic compounds, wood and furniture workers to wood dust, printing workers to printing inks, and electrical equipment workers to ionizing radiation or electromagnetic filed.

On the other hand, the unexposed workers were selected from a number of factories, *"in which there was no known exposure to benzene or other occupational carcinogens* [emphasis added]" (Yin et al., 1987b). Thus, according to the authors, the control workers were exposed to neither benzene nor any other occupational carcinogens, whereas the exposed workers were exposed to not only benzene but also possibly to other occupational carcinogens. Thus, by design, a comparison between the benzene-exposed workers and control workers would not be limited to the effects of benzene, but would also reflect the effects of other occupational carcinogens. Therefore, the study was not designed properly to address the effects of benzene only (Wong, 2000).

The potential problem of concomitant exposures in the CAPM-NCI study complicated the interpretation of results in relation to benzene exposure. For example, an excess of NHL was found in workers exposed to benzene and insecticides in addition to other chemicals (agricultural chemical workers). The NHL finding was consistent with insecticide exposure (as reported in numerous studies of farmers and agricultural chemical workers), but not consistent with benzene exposure (Wong, 1998, Wong and Raabe, 2000).

The results of the CAPM-NCI study also demonstrated the lack of comparability between the exposed and unexposed workers. When compared to the unexposed workers, the exposed workers were reported to have increased risks in a variety of diseases. More specifically, increased mortality risks among exposed male workers when compared to unexposed male workers were reported for many specific cancer sites which have not been demonstrated to be related to benzene exposure in other studies; including lung cancer, liver cancer, stomach cancer, intestinal cancer, esophageal cancer, and nasopharyngeal cancer. For example, no study has ever demonstrated an association

between benzene exposure and nasopharyngeal cancer. These observations raised potential concerns regarding the comparability of the unexposed workers, potential under-ascertainment of cancer among the unexposed workers, and confounding exposures (or other risk factors) in the exposed group (Yin et al., 1989).

One of the areas of uncertainty in the Chinese benzene study involved the exposure estimates. Comparing the assumptions used in the development of estimates and the exposure estimates themselves to actual data reported identified a number of inconsistencies and/or inadequacy of exposure categories. For example, the actual average exposure of spray painters (full-day exposure) at a factory in Shanghai in 1965-1969 was 331 mg/m^3 (104 ppm), whereas the estimate developed by Dosemeci et al. (1994) for spray painters in the same time period was 22.1 ppm. There are other similar examples. It appeared that the exposure estimates were consistently lower than the actual exposure data. One of the major problems was that an extremely large number of industries and occupations were included in the cohort study, and, as a result, it was necessary to use broad exposure categories and to generalize individual workers' exposures. Dosemeci et al. (1994) recognized that little confidence could be attached to the estimates: only 2% of the estimates for the time interval 1949-1959 and only 6% of the estimates prior to 1975 were rated in the "high confidence" category by Dosemeci et al. Exposure-response analyses based on these exposure estimates should be interpreted with extreme caution. A detailed critique of the exposure assessment developed by Dosemeci et al. has been published by Wong (1999).

Both CAPM and NCI have made substantial efforts in studying the relation between benzene exposure and malignancies. Unfortunately, because of the problems discussed above, the results of the CAPM-NCI study are difficult to interpret. Nevertheless, because of the large number of Chinese workers who are or have been exposed to relatively high levels of benzene (compared to, for example, levels at refineries in the US), China represents a unique opportunity for investigating the carcinogenic effects of benzene.

In this proposal, we will outline an epidemiologic investigation to assess the relation between exposure to benzene and the risk of developing acute non-lymphocytic leukemia (ANLL) or non-Hodgkin's lymphoma (NHL) in China. More specifically, the investigation will consist of hospital-based case-control studies of male and female patients diagnosed with ANLL or NHL in Shanghai.

2.0 PROPOSED OUTLINE OF INVESTIGATION

2.1 Objectives

The primary objectives of the proposed hospital-based case-control studies of ANLL and NHL in Shanghai are as follows:

1. To determine the risk of developing ANLL or NHL (and major subtypes) among workers exposed to benzene in Shanghai.

2. To quantify the exposure-response relations between exposure to benzene and ANLL or NHL among these workers.

3. To determine other occupational risk factors (i.e., occupational exposures other than benzene, such as ionizing radiation, heavy metals and pesticides) and non-occupational risk factors (e.g., medications such as chloramphenicol) of ANLL or NHL among these workers.

2.2 Reasons for choosing Shanghai

Shanghai is the largest city in China, with a population of 13 to 14 million. A wide variety of industries are located within the metropolitan area, and benzene has been and still is used in many industries in Shanghai, making Shanghai well-suited for an industrial investigation. The reasons for choosing Shanghai as the location for our investigation are summarized below.

1. Shanghai was the largest data contributor in the CAPM-NCI cohort study.

2. It is one of the four sites of the CAPM case-control study.

3. It is the site of the CAPM-NCI clinical investigation.

4. Shanghai has a large population (13-14 million), which translates into a relatively large number of ANLL and NHL patients diagnosed each year.

5. Many high-quality medical establishments (universities, hospitals, and a long-standing regional tumor registry) are located in Shanghai.

6. There are many well-qualified investigators in Shanghai who are experienced in collaborating with both US and European investigators.

7. A wide variety of industries are located in the Shanghai metropolitan area. Occupational exposures in addition to benzene (e.g., heavy metals) have been liked to the development of leukemia in several previous studies in Shanghai (Lin et al., 1987 and 1991).

8. Benzene has been and still is used in a variety of different industries, resulting in a wide range of benzene exposure levels.

9. Issues related to industrial health in the entire metropolitan area are under the jurisdiction of the Shanghai Municipal Center for Disease Prevention and Control (CDPC).

10. Documented employment histories from employers of study subjects can be obtained through the Shanghai Municipal CDPC.

11. Measurements of benzene exposure at workplaces will also be available through the Shanghai Municipal CDPC, although the pre-1970 data are limited.

12. Unlike women in western countries, a large proportion of Chinese women are employed in a variety of manufacturing industries and exposed to industrial chemicals including benzene. Therefore, the proposed study will be one of the few studies dealing with industrial exposures in female workers.

2.3 Overall study design

We propose using the hospital-based case-control study design. In this section we will present an overview of the study design, and will provide additional details in subsequent sections. The case-control study design is used, since an historical cohort study requires detailed age-gender-year-specific rates for ANLL and NHL, which are not available for the general population in Shanghai. Newly diagnosed adult cases of ANLL and NHL will be identified at participating hospitals in Shanghai. The diagnoses will be confirmed in a parallel investigation, which is described in a separate protocol. Matched controls will be selected from other patients at the same hospitals.

A questionnaire will be administered in person to both cases and controls to solicit information on occupational and medical histories and certain lifestyle information. Detailed employment and exposure histories of both cases and controls will be sought from the Shanghai Municipal CDPC and the subjects' places of employment. An individual quantitative benzene exposure assessment will be developed for each study participant. Since the number of study subjects is relatively small, exposure profiles can be individualized. This individualized approach will minimize the inaccuracy inherent in the generalized approach that was necessary in the large multi-city CAPM-NCI cohort study, which relied heavily on invalid or inconsistent modeling and overly broad exposure categories. In our proposed case-control studies, the number of exposed subjects will be much smaller, and an individualized exposure assessment approach becomes both feasible and practical. Both matched and stratified analyses will be performed to identify occupational as well as non-occupational risk factors of ANLL and NHL and to determine the exposure-response relations between benzene and ANLL or NHL.

2.4 Potential benefits of the case-control studies of ANLL and NHL

In addition to the general advancement of science, we must be able to justify the proposed investigation in terms of potential benefits to the individual patients and workers, whether they are in the current investigation or in the community at large. The 1975 Declaration of Helsinki in its guidelines for biomedical research stated: "Every biomedical research project involving human subjects should be preceded by a careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concerns for the interest of the subject must always prevail over the interests of science and society." Similarly, the Nuremberg Code also affirmed the right of individuals to be given full disclosure of potential risks and benefits of biomedical investigations. We will discuss potential "risks" of participation in the case-control studies later in this protocol. Below we will summarize potential benefits of the investigations.

1. The study may identify workplaces in Shanghai with potentially unacceptable levels of benzene exposure (for example, above the current national occupational benzene standard in China). These workplaces will be reported to the appropriate Chinese authorities (such as the Shanghai Municipal CDPC) that are responsible for enforcing or implementing corrective actions, so that such levels of benzene exposure can be avoided in the future.

2. The study will provide much needed data on benzene threshold or other occupational risk factors of ANLL or NHL in China. For example, in a previous study in China exposure to heavy metals has been linked to an increased risk of leukemia, although the finding was not conclusive because of the small numbers involved. If our case-control study of ANLL confirms this preliminary result, appropriate regulatory decisions based on our findings will likely prevent further exposure among study participants and other workers. This is a benefit to future and possibly current workers exposed to benzene and other industrial chemicals.

3. The study may identify new non-occupational risk factors such as family histories of cancer or medications (including traditional Chinese medicines). The findings will be used to identify high-risk groups to facilitate early detection as well as prevention.

In reference to No. 2 above, a discussion of the potential use of the study results in regulatory decisions in China was held in October in Shanghai with Professor Liang You-Xin at Fudan University Medical Center. Professor Liang is a professor of occupational medicine at Fudan University Medical Center, and he is also the Chief of the Subcommittee of Standard Setting for Occupational Health, National Committee of Health Standard Setting in China. Professor Liang specifically pointed out that the current occupational benzene standard in China was based on outdated data, and new data on benzene are needed as the basis of a new standard so that workers can be adequately protected. At the October meeting Professor Liang indicated that he would communicate

to his committee of our studies. A letter from Professor Liang expressing the interests in and benefits of our proposed case-control studies is attached (Attachment 1).

In reference to No. 3 above, the identification of non-occupational risk factors is important in that high-risk groups can be identified early. Thus, workers and individuals in the community (including controls participating in the current investigation) will potentially benefit from the findings of the study.

On the other hand, it must be pointed out specifically that participation in the current case-control studies of ANLL and NHL will not result in any direct benefits to individual patients already diagnosed with ANLL or NHL. The case-control investigation is designed to assess risk factors in ANLL or NHL patients (thus aiming at the prevention of exposure to such risk factors in the future). The investigation, however, does not involve in any evaluation of treatments of the diseases. This lack of immediate benefits to the participants already diagnosed with ANLL or NHL needs to be pointed out to potential study subjects at the time of interview before the consent form is signed, even if it may discourage some patients from participating in the investigation.

2.5 Identification of ANLL/NHL cases and matched controls

ANLL and NHL cases will be identified at hospitals that treat cancer patients in Shanghai (see below). Since all cancer cases diagnosed in Shanghai are reported to the Shanghai Tumor Registry maintained by the Shanghai Cancer Institute, the Shanghai Tumor Registry will be another data source for ANLL and NHL cases. Other supplemental sources will include member hematologists of the Shanghai Hematology Association. The selection of participating hospitals or other health care facilities will be determined by Fudan University Medical Center. Tentatively, the following 15 hospitals in Shanghai have been identified:

- Hua Shan Hospital (affiliated with Fudan University Medical Center),
- Zhong Shan Hospital (affiliated with Fudan University Medical Center),
- Cancer Hospital (affiliated with Fudan University Medical Center),
- Jin Shan Hospital (affiliated with Fudan University Medical Center),
- Rui Jin Hospital (affiliated with Shanghai Second Medical University),
- Ren Ji Hospital (affiliated with Shanghai Second Medical University),
- Shanghai Ninth Hospital (affiliated with Shanghai Second Medical University),
- Xin Hua Hospital (affiliated with Shanghai Second Medical University).
- Shanghai First Hospital (Municipal Hospital),
- Shanghai Sixth Hospital (Shanghai Health Bureau),
- Chang Zheng Hospital (affiliated with Second Military Medical University),
- Chang Hai Hospital (affiliated with Second Military Medical University),
- Railway Central Hospital (affiliated with Tongji University),
- Gan Quan Hospital (affiliated with Tongji University), and
- Shu Guan Hospital (affiliated with Shanghai Institute of Traditional Medicine).

Both male and female patients will be eligible for participation in the case-control studies. Only newly diagnosed patients of ANLL and NHL more than 18 years of age will be considered. Eligible cases will be enrolled on a prospective basis and will become potential study subjects in the proposed case-control studies as well as in the parallel disease progression investigation. After a brief description of the purpose and nature of the investigation has been presented, eligible cases will be asked to answer a questionnaire. In addition to the original preliminary diagnoses made at the admission hospitals, eligible cases will be asked to undergo additional detailed diagnostic procedures, which may not be directly related to their treatments. These additional diagnostic procedures will be part of the parallel investigation of disease progress investigation. Both the technical and ethical issues related to these additional diagnostic procedures and the corresponding risks and benefits will be addressed separately in the protocol of the disease progression investigation.

It is anticipated that some eligible ANLL or NHL patients may not wish to undergo the additional diagnostic procedures that are not directly relevant to their treatments, but are willing to participate in the case-control studies, which will require the patients to respond to a questionnaire only and will not involve any additional medical procedures. These patients will be included in the case-control studies of ANLL and NHL. The inclusion of these patients will not only maximize the sample sizes of the case-control studies but will also provide a basis for comparing patients who undergo additional diagnostic procedures and patients who do not.

Controls will be selected from other patients at the same hospitals or health care facilities as the cases. Patients with other lymphohematopoietic cancers (Ninth Revision of the International Classification of Disease, ICD9 200-208) or nonmalignant diseases of the blood and blood-forming organs (ICD9 280-289) will be excluded from the selection of controls. Matching variables will include gender, age (within 5 years) and date of admission. The actual selection procedure will be as follows. After a case has been identified, the next two patients admitted to the same hospital and satisfying the matching criteria (identified from the admission log at the hospital) will be selected. If a selected potential control refuses to participate in the study, the next eligible patient on the admission log will be used as a replacement.

It is estimated that the study will consist of approximately 500 ANLL patients, 500 NHL patients and 2,000 controls. This sample size would allow us to detect a risk in ANLL or NHL as small as three-fold. (In the CAPM-NCI study, the relative risks of ANLL and NHL were both approximately 3-fold.) As indicated above, the study subjects will be enrolled on a prospective basis, and, based on *previous* figures in Shanghai, it is estimated that it will take approximately 4 years to reach the required study size. It should be pointed out that diagnoses of patients in the case-control studies will be confirmed according to the criteria set forth in the parallel disease progression investigation, which may have an impact on the number of eligible ANLL and NHL patients.

2.6 Questionnaire

Demographic data, certain lifestyle information, medical histories and employment histories will be obtained from medical records and through the use of a questionnaire. A preliminary questionnaire (in Chinese) was developed and tested in a sample of ANLL and other patients at the Hua Shan Hospital during a feasibility trip to Shanghai in 1998 by Otto Wong and Fu Hua. Information solicited through the questionnaire can be grouped in the following categories:

- Demographic,
- Occupational history,
- Medical history, and
- Lifestyle (primarily questions concerning cigarette smoking).

During the pilot test, a number of problems were identified and subsequently modifications were suggested. In particular, questions on family and medical histories as well as lifestyle (cigarette smoking) will be more restricted and more specific. The questionnaire has been revised accordingly. Additional changes have been made under the guidance of Dr. Xu Zongliang, Professor of Bioethics at Fudan University. A final version of the questionnaire is now available for review. We anticipate that the questionnaire will be administered in person by a trained interviewer (a medical graduate) at the hospitals and will take approximately 30 minutes to complete.

2.7 Informed consent

As stated above, additional diagnostic procedures will not be a prerequisite for participating in the case-control studies of ANLL or NHL. The proposed case-control studies do not require administrating additional diagnostic tests or any other "physically invasive" procedures to study participants, withholding therapies, or prolonging exposures of any study participants. As such, the case-control studies of ANLL and NHL will not place study participants at any risk of physical harm. However, the investigation does ask for certain personal information, and therefore involves ethical issues relating to communication, informed consent and data confidentiality.

In a health investigation, the first step in communicating with potential study subjects is the informed consent, which follows from a consideration of the principle of "autonomy," i.e., the respect for human dignity, individual rights and freedom – one of the most fundamental requirements of a democratic society. Furthermore, in the present investigation, we should also be sensitive to the cultural differences in the perception of autonomy among the Chinese people. Below we will discuss issues involving informed consent, and will address communication of study results later in this protocol.

In our questionnaire, we will ask questions regarding study subjects' occupational and medical histories and certain aspects of their lifestyle (i.e., smoking). Some questions will cover personal and family disease histories. We will restrict the diseases to cancers and blood disorders only, since these diseases have been linked to an increased risk of

leukemia in some previous studies. However, we will not probe into any "delicate" areas. In particular, we will not seek information on potentially "embarrassing" diseases such as sexually transmitted diseases (STD) or any diseases that Chinese are sensitive to (e.g., reproductive disorders, abortions, impotence, or hepatitis).

The first part of the informed consent process involves the interviewers' presentation of a full disclosure of information regarding the investigation to potential study subjects. We fully recognize that the study subjects should understand clearly the nature and purpose of the investigation, the possible risks and benefits, data confidentiality, and his or her right to withdraw from the study at any time.

A short description of the nature and purpose of the investigation (in non-technical language) will be developed and this standard description will be used by interviewers to explain to potential participants. The potential risks and benefits of the investigation as well as procedures taken to ensure data confidentiality will also be explained to the participants. The nature of the questions and the estimated time required to complete the questionnaire will also be provided.

Consent will be solicited without any misrepresentation, duress, cajolery or bribes. Although we plan to reimburse participants for the patients' inconvenience or loss of time (no out-of-pocket expenses are anticipated), we are mindful of the possibility or impression that an excessive reimbursement may be viewed as or actually turn into a bribe or undue inducement. That is, excessive financial incentive may induce individuals to participate in the investigation against their better judgment.

The issue of payment in the current investigation is further complicated by the disparity of wages and costs of living between the US and China. For example, an average Chinese worker makes approximately US$300 a month. Therefore, any reasonable amount (or even a token) from the American perspective will most likely be a relatively significant sum according to the Chinese standard. However, it would be inappropriate to set the amount of reimbursement based on wages or cost of living in China. We have decided to pay Chinese study subjects for their participation in the case-control investigation the same amount that we would pay in a similar study conducted in the US. We propose reimbursing each participant in the case-control studies (ANLL or NHL patients and controls) ¥250 (approximately US$30).

If, after receiving the above information concerning the investigation, the patient agrees to participate in the study, he or she will be asked to sign a consent form. Two slightly different consent forms will be used separately by the cases and controls. In the version for the cases, it is stated that ANLL or NHL might be related to benzene exposure, whereas in the one for controls the diseases are not related to benzene exposure. Draft consent forms for the case-control studies of ANLL and NHL are presented in Attachment 2. This draft consent form will be translated into Chinese. After the draft consent forms have been approved by the Institutional Review Board at Applied Health Sciences and the Ethics Committee at Fudan University Medical Center, they will be tested in a small pilot group of patients in Shanghai.

An interview manual will be developed, and training sessions will be held in Shanghai prior to the actual enrollment of study subjects into the case-control studies of ANLL and NHL. Sensitivity will be emphasized throughout the training sessions.

2.8 Exposure assessment

An industrial hygienist at Fudan University Medical Center will review the occupational history recorded in the questionnaire and, based on a predetermined list of occupations with potential benzene exposures, will assess whether the occupations reported in the questionnaire entailed potential exposures to benzene. For study subjects (cases and controls) identified to have worked at factories with potential benzene exposures, copies of employment records will be obtained from the employers through the Shanghai Municipal CDPC. The job titles and job locations of the workers will be abstracted from employment records.

In China each factory can be identified by a unique "danwei haoma" or work-unit number (WUN). For each factory, an archive is kept at the regional CDPC. The archive includes a basic description of the primary processes at the factory, major raw materials and products, and the number of workers. Measurements of workplace exposures are also maintained at regional CDPC. Records of measurements are organized by WUN and maintained in electronic databases. These records provide information on date and location of sampling, chemicals sampled, and concentrations.

The linkage between study subjects' exposures and Shanghai Municipal CDPC's database of workplace exposure measurements will be through the use of WUN. In the case-control studies, reports of measurements of exposures to benzene and/or other chemicals at the factories where the study subjects worked as well as other relevant documents (such as raw materials used, work practice and engineering controls) will be obtained from the employers and from Shanghai CDPC.

Exposure estimates specific to job title, job location or department, factory and calendar year will be developed by a senior industrial hygienist in conjunction with the industrial hygienist at Fudan University Medical Center and the Shanghai Municipal CDPC. Based on employment histories and exposure estimates, an individualized exposure profile will be developed for each exposed study subject in the case-control studies of ANLL and NHL. These individual exposure profiles will be used in the epidemiologic analyses.

The actual detailed exposure assessment procedure will be developed as part of the investigation itself. The exposure assessment team of the case-control studies of ANLL and NHL will consist of industrial hygienists, environmental scientists and epidemiologists from Applied Health Sciences, Fudan University Medical University and Shanghai Municipal CDPC.

2.9 Epidemiologic analyses

Both stratified analyses (the Mantel-Haenszel χ^2 procedure) and multivariate analyses (logistic regression) will be used in assessing the relation between exposure to benzene and the risk of developing ANLL or NHL. Exposure variables will include type of industry, type of occupation, length of exposure, time period of exposure, cumulative exposure, truncated exposure, peak exposure, and short-term exposure. These analyses will determine whether there is an increased risk of ANLL or NHL among workers exposed to benzene in Shanghai. If there is an increased risk, the exposure-response analysis will determine the level of exposure associated with the increased risk.

Similar analyses will be conducted to assess the relations between other concomitant occupational exposures to other chemicals and the risk of developing ANLL or NHL. Personal or lifestyle factors (such as family histories, the use of certain medications, and cigarette smoking) will also be investigated. Confounding factors will be controlled for in the analyses of occupational exposures to benzene and/or other chemicals.

2.10 Data management and data confidentiality

In dealing with data security and data confidentiality in the case-control studies of ANLL and NHL, we will rely on the universally accepted principles of (1) identification blocking in data storage and transfer, and (2) limiting data access to selected team members.

Hard copies of completed questionnaires and employment records will be stored in locked cabinets in secured offices at Fudan University Medical Center. Computerized information derived from the questionnaires and employment records will be stored in an electronic database, which will be protected by passwords. Each study participant will be assigned a study identification (SID) number. The list of SID numbers corresponding to participants' names will be kept separate from the electronic database. Access to the list will require special approval from one of the two principal investigators. Study subjects will be identified by SID numbers only in both data transfer and data storage (i.e., the electronic database). Only a limited number of authorized project team members at Applied Health Sciences or Fudan University Medical Center will have access to the electronic database. Since personal identifiers (such as names) are not part of any data transfer or the electronic database, even in the unanticipated event of breach of data security, the information will not be linked to any particular individual.

Furthermore, we will limit data access to selected team members who are directly involved in the case-control studies of ANLL and NHL, and will maintain only the data that are directly relevant to the case-control studies of ANLL and NHL. For example, in the supporting diagnostic database, extensive detailed clinical data are kept on individual ANLL and NHL patients. In the case-control studies of ANLL and NHL, we require only the final diagnoses (including subtypes) of the patients and we will not include any unnecessary clinical data in our database. In the parallel investigation of disease

progression, in addition to ANLL and NHL cases, patients diagnosed with benzene poisoning (BP), aplastic anemia (AA) or myelodisplastic syndromes (MDS) will also be studied. The BP, AA and MDS patients are not directly relevant to the research questions in the case-control studies of ANLL and NHL, and as such it is not only unnecessary but also inappropriate for us to have access to the data of BP, AA or MDS patients. Similarly, control subjects in our case-control studies of ANLL and NHL are not part of the disease progression investigation, and in fact have not consented to participation in the disease progression investigation. Therefore, information on control subjects will be maintained in the database in the case-control studies only.

In addition to its own research questions on disease progression of ANLL cases, the disease progression study will also be responsible for providing detailed diagnostic information on ANLL and NHL cases to the case-control studies. However, some of the ANLL patients may not wish to participate in the disease progression study and none of the NHL patients will be part of the disease progression study. To limit data access and to maintain data security, the following three separate databases will be developed:

1. Database of ANLL and NHL cases and matched controls in the case-control investigation.

2. Database of detailed clinical information on disease progression of ANLL, MDS, and BP cases in the disease progression investigation.

3. Database of diagnostic information on ANLL and NHL cases (for both studies) and other patients. This database functions strictly as a vehicle for the transfer of diagnostic information from the diagnostic laboratory in the disease progression investigation to the case-control studies.

These three databases will be kept separately, and the accessibility of each database will be limited to project members of the appropriate investigations only. Thus, only the diagnostic data of ANLL cases will be shared in both the disease progression study and the ANLL case-control study. As such, we suggest that SAS be used as the database software program, since SAS is compatible to both the disease progression study and the case-control study.

With respect to NHL cases, the laboratory in the disease progression study will be responsible for providing the diagnostic information only, and no analysis of the NHL patients will be performed in the disease progression study.

To maintain personal confidentiality, findings of the case-control investigation will be presented in terms of statistics only. In particular, individuals' personal identifications will not be revealed in any report or publication. Records and data in the study will not be transferred to any other party. The questionnaires and employment records will be destroyed one year after the project is completed and results published. During this one-year period, the records will remain in the sole custody of the principal investigators at Applied Health Sciences and Fudan University Medical Center.

2.11 Reporting structure

Based on current discussions, we anticipate that there will be a Scientific Committee and an Ethics Advisory Panel. The Scientific Committee will consist of scientists with experience in occupational epidemiology and/or benzene research. The Ethics Advisory Panel will consist of international experts in bioethics.

We will report study progress to both the Scientific Committee and the Ethics Advisory Panel on a semi-annual basis. In addition, any unanticipated events will be reported immediately. Furthermore, any modifications to the protocol will be submitted to both the Scientific Committee and the Ethics Advisory Panel for review and approval.

2.12 Interim Monitoring of Progress and Results

As stated above, for the results to be statistically meaningful we need approximately 500 ANLL and 500 NHL patients. Based on *previous* figures in Shanghai, it will take approximately 4 years to reach the required sample sizes. However, it may be possible that we reach the required sample sizes in a shorter time, as a result of population growth, more complete reporting, or more accurate diagnosis.

The number of patients enrolled in the case-control studies will be closely monitored and reported to the Scientific Committee and the Ethics Advisory Board on an annual basis. If we reach the required sample sizes in less than the estimated 4 years, we will revise the proposed schedule and begin immediately with the proposed analyses. The study results will then be communicated to the sponsors, appropriate regulatory and/or health agencies in China and the US, relevant employers and unions in Shanghai as outlined below in Section 2.13.

2.13 Communication of study results

Study results will be reported at scientific conferences and in the form of scientific publications. In particular, we will present our studies at two international scientific conferences. Scientific papers derived from the studies will be submitted to both peer-reviewed English-language and Chinese-language journals in epidemiology or occupational medicine. Draft presentations and manuscripts will be provided to the sponsors for comment in advance. Applied Health Sciences and Fudan University Medical Center will carefully consider each and every comment from the sponsors. However, it must be emphasized that the preparation of presentations and manuscripts is the sole responsibility of Applied Health Sciences and Fudan University Medical Center and that Applied Health Sciences and Fudan University Medical Center will have the complete control of the content of the presentations and manuscripts.

In addition to scientific publications, study results will also be communicated to the appropriate regulatory and/or health agencies in China (e.g., the Shanghai Municipal CDPC) and the US (e.g., US NCI, EPA, OSHA and NIOSH). Study results will also be communicated to relevant employers and unions (or any other worker populations) in

Shanghai. The communication will be publicized and carried out jointly by Fudan University Medical Center and Shanghai Municipal CDPC.

Although we have outlined above a broad process of communication of study results, it is not possible to develop at this time a detailed plan of action. The latter will require the identification of the appropriate government agencies and other interested parties in China as well as the most efficient means of communication with these parties. We intent to identify these interested parties through our project activities and interactions with various Chinese agencies during the course of our investigation in China. In summary, at this time we recognize the importance of a communication plan and we are committed to its development and implementation. A detailed communication plan will be developed as an integral part of the proposed investigation.

3.0 INSTITUTIONAL REVIEWS AND THE RESERCH TEAM

3.1 Institutional Reviews

The study protocol and all related documents (including the questionnaire and consent form) will be submitted to the respective Institutional Review Board (IRB) at Applied Health Sciences and the Ethics Committee at Fudan University Medical Center for review. The Chair of the IRB at Applied Health Sciences is Dr. Donald Whorton, who is an occupational physician licensed to practice medicine in California, a former faculty member of the University of California at Berkeley, a Fellow of the American College of Epidemiology, and a Member of the Institute of Medicine at the National Academy of Science. Over the years the IRB at Applied Health Sciences, under the leadership of Dr. Whorton, has reviewed and approved numerous applications to various federal and state agencies for health data, including the National Center for Health Statistics' National Death Index (NDI) and health departments of almost all 50 states.

At Fudan University Medical Center, all projects involving human subjects have to be submitted to the Ethics Committee for review and approval. The Ethics Committee is currently chaired by Professor Yao Tai. Professor Yao is the former President of the Shanghai Medical University (now Fudan University Medical Center), the former Chair of the Department of Physiology at the university, and a member of the Chinese National Committee for Academic Degrees in Science. The Ethics Committee at Fudan University Medical Center, under the leadership of Professor Yao, has reviewed and approved numerous regional, national and international health and medical research projects involving human subjects.

3.2 Research team

A joint research agreement between Shanghai Medical University (now Fudan University Medical Center) and Applied Health Sciences has been signed, and a copy has been filed with the Office of International Exchange Programs at the university.

The Principal Investigators of the case-control studies of ANLL and NHL will be Professors Otto Wong and Fu Hua. Professor Wong has 28 years of experience in occupational research and has conducted more than 200 epidemiologic studies investigating occupational and environmental cancers. Professor Fu is the Deputy Dean of the School of Public Health, Fudan University Medical Center, and has full access to a variety of health data in Shanghai as well as the full cooperation of health agencies in Shanghai. Professors Wong and Fu will be supported by their staff at both Applied Health Sciences and Fudan University Medical Center (School of Public Health, Hematology Department and Pathology Department). The tentative list of Co-Investigators includes senior scientists in hematology, industrial hygiene, and occupational medicine. Biographical sketches of the Principal Investigators and Co-Investigators are provided below. Additional consultants in epidemiology, biostatistics, industrial hygiene, pathology, hematology, and occupational medicine may be added to the research team in the future.

Principal Investigators:

- Otto Wong, Sc.D., F.A.C.E.

    - Chief Epidemiologist, Applied Health Sciences, Inc., San Mateo, California
    - Adjunct Professor of Epidemiology, Tulane University Medical Center, New Orleans, Louisiana
    - Adjunct Professor of Community and Family Medicine, Chinese University of Hong Kong, Hong Kong
    - Visiting Professor of Occupational Epidemiology, Fudan University Medical Center, Shanghai, China
    - Visiting Professor of Epidemiology, NDMC School of Public Health, Taipei, Taiwan
    - Secretary and Executive Member, Scientific Committee on Respiratory Disorders, International Commission of Occupational Health
    - Fellow, American College of Epidemiology
    - Associate Editor, *Annals of Epidemiology*
    - Editorial Board Member, *Regulatory Pharmacology and Toxicology*
    - Editorial Board Member, *Occupational and Environmental Medicine*

- FU Hua, M.B., Ph.D.

    - Professor of Preventive Medicine and Epidemiology, Fudan University Medical Center, Shanghai, China
    - Deputy Dean, School of Public Health, Fudan University Medical Center, Shanghai, China
    - Senior Scientist, Applied Health Sciences, Inc., San Mateo, California
    - Visiting Scientist at the International Agency for Research on Cancer, Lyon, France (1993-1994)
    - Executive Member, Scientific Committee on Respiratory Disorders, International Commission of Occupational Health

Co-Investigators:

- LIN Guowei, M.D., M.Sc. (U. of Penn.)

    - Professor of Medicine, Fudan University Medical Center, Shanghai, China
    - Director, Center of Clinical Epidemiology, Fudan University Medical Center, Shanghai, China
    - Vice President, Shanghai Society of Hematology
    - Chairman, Chinese Clinical Epidemiology Association
    - Editor, *Chinese Journal of Hematology*
    - Editor, *Chinese Journal of Internal Medicine*

- Raymond Taetle, M.D.

    - Chief of Hematology, University of Arizona Medical Center, Tucson
    - Professor of Medicine, Pathology and Oncology, University of Arizona, Tucson, Arizona
    - Director, Bone Marrow Transplantation Laboratory, University of Arizona Medical Center, Tucson, Arizona
    - Author of chapter "Tumor Steam Cells" in Harrison's *Principles of Internal Medicine*
    - Editorial Board Member, *Journal of National Cancer Institute*

- Roy Rando, Sc.D., C.I.H.

    - Associate Professor of Environmental Health Sciences, Tulane University Medical Center, New Orleans, Louisiana
    - Adjunct Associate Professor of Environmental Medicine, Tulane Medical School, New Orleans, Louisiana
    - Certified Industrial Hygienist, American Board of Industrial Hygiene
    - Member, American Academy of Industrial Hygiene
    - Member, American Conference of Governmental Industrial Hygienists

- LU Wei, M.D., M.P.H. (Umea, Sweden)

    - Deputy Director General, Shanghai Municipal Center for Disease Prevention and Control
    - Chief Physician, Shanghai Municipal Center for Disease Prevention and Control

3.3 Estimated schedule

It is estimated that the proposed case-control studies of ANLL and NHL will take approximately 5 years to complete. Of the estimated 5 years, 4 will be devoted to enrollment of cases and controls. After we have completed the investigation, we plan to present the study results at two international conferences and submit manuscripts for publication in scientific peer-reviewed journals.

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Attachment 1

Letter from Professor Liang

School of Public Health,
Medical Center of Fudan University

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Tel: +86-021-64041900-2196 Ext, Fax: +86-021-64178160,
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2001/1/4

Dr. Otto Wong
Chief Epidemiologist
Applied Health Sciences, INC
181 Second Avenue, Suite 628
Post Office Box 2078
San Mateo, California 94401
USA

Dear Dr. Wong:

I am pleased to know that a proposed joint-project on health risk of benzene and its carcinogenicity is being worked-out between the Applied Health Sciences, Inc., USA and the Fudan University School of Public Health, China. As the Chairman of the National Technological Committee for Occupational Health Standards Setting, I am particularly interested in the part of epidemiological study of benzene exposure and its health effects assessment among workers exposed to benzene. The data obtained from the study will be extremely important and greatly helpful for the Chinese authorities in amending the adopted occupational exposure limit of benzene in workplace in China.

Aimed at protecting workers from peripheral hemopathy, such as leukopenia, the Maximum Allowable Concentration, MAC for benzene at workplaces has been documented at the level of 40mg/m^3 (~12 ppm) by the Ministry of Health, P. R. China since 1979. Actually, this value was set up without awareness of benzene as a leukemogen during early 1970s. At that time, the Chinese health authorities recognized that there was insufficient evidence to demonstrate that exposure to benzene below 16 ppm causes blood disorders and that a ceiling exposure limit (MAC) of 12 ppm provided a suitable margin of safety for such effects.

With the development of human health risk assessment and toxicological studies at molecular level, there are many reasons to reduce the current occupational exposure limit

for benzene in China. The success of your proposed study will be crucial to support our Committee's agenda in implementing such an important revision approach.

I am looking forward to working with you for our common goal of Occupational Health for All.

Please accept the assurances of my highest consideration.

Yours sincerely,

You-xin Liang, M.D.

Professor of Occupational Health and Industrial Toxicology,
Fudan University School of Public Health
Director, WHO Collaborating Center for Occupational Health, Shanghai
Chairman, National Technological Committee of Occupational Health Standards Setting,
Chinese Academy of Preventive Medicine

Attachment 2

Draft consent forms

Consent form for participants in the case-control studies of ANLL and NHL (version for cases)

I have been informed that Fudan University Medical Center (formerly the Shanghai Medical University), in collaboration with Applied Health Sciences, Inc., a health research organization in California, USA, is conducting an occupational health study of acute non-lymphocytic leukemia and non-Hodgkin's lymphoma. The purpose and general nature of the study have been explained to me. The purpose of the investigation is to determine both occupational and non-occupational risk factors of the two diseases. The study involves a comparison of occupational exposures and medical histories among the study subjects. In particular, benzene exposure (which has been associated with these two diseases in some previous studies) will be the major focus of the investigation. I understand that there will be no medical procedures required. The potential risks and benefits of the study have also been explained to me.

I agree to participate in the study, with the understanding that my participation will involve:

1. Being interviewed for approximately 30 minutes concerning information about my employment and medical histories as well as certain aspects of my lifestyle.

2. Having my employment records and medical records reviewed.

I understand that my participation is entirely voluntary and that my agreement or refusal to participate will not affect the treatments or health care that I will receive. I further understand that I may refuse to answer any question if I so choose, and/or I may withdraw my consent to participation at any time in the future without in any way affecting the health care that I receive. I understand that there are no special risks involved in being a participant, and that, even though I may not benefit from the results of the study directly, such results may benefit workers or individuals in the community who are exposed to potential risk factors of the two diseases.

I have been assured that the information collected on me will be treated in a confidential manner and that I will not be personally identified in the reporting of study results. I understand that the analysis will be statistical in nature. Up to 3,000 patients will be interviewed and the data concerning me will be combined with others in the analysis.

I have been assured that only research scientists at Fudan University Medical Center and Applied Health Sciences who are directly involved in the project will have access to the data, and that the data will not be transferred to any other party in the future. I understand that it is the intention of the investigators to destroy all questionnaires and employment records one year after the completion of the study.

It is my understanding that if I have questions regarding the study or its results in the future, I may contact Dr. XXX at Fudan University Medical Center (Tel: XXX, Address: XXX).

I acknowledge that I have received ¥250 for my participation in the study.

_____ _____

Participant's signature and date Interviewer's signature and date

(1 copy for participant and 1 copy for interviewer) (Draft 6/18/01)

Consent form for participants in the case-control studies of ANLL and NHL (version for controls)

I have been informed that Fudan University Medical Center (formerly the Shanghai Medical University), in collaboration with Applied Health Sciences, Inc., a health research organization in California, USA, is conducting an occupational health study. The purpose and general nature of the study have been explained to me. The purpose of the investigation is to determine both occupational and non-occupational risk factors of acute non-lymphocytic leukemia and non-Hodgkin's lymphoma, which are not the diseases that I have been diagnosed with. The study involves a comparison of occupational exposures and medical histories among the study subjects. I understand that there will be no medical procedures required. The potential risks and benefits of the study have also been explained to me.

I agree to participate in the study, with the understanding that my participation will involve:

1. Being interviewed for approximately 30 minutes concerning information about my employment and medical histories as well as certain aspects of my lifestyle.

2. Having my employment records and medical records reviewed.

I understand that my participation is entirely voluntary and that my agreement or refusal to participate will not affect the treatments or health care that I will receive. I further understand that I may refuse to answer any question if I so choose, and/or I may withdraw my consent to participation at any time in the future without in any way affecting the health care that I receive. I understand that there are no special risks involved in being a participant, and that, even though I may not benefit from the results of the study directly, such results may benefit workers or individuals in the community who are exposed to potential risk factors of the two diseases.

I have been assured that the information collected on me will be treated in a confidential manner and that I will not be personally identified in the reporting of study results. I understand that the analysis will be statistical in nature. Up to 3,000 patients will be interviewed and the data concerning me will be combined with others in the analysis.

I have been assured that only research scientists at Fudan University Medical Center and Applied Health Sciences who are directly involved in the project will have access to the data, and that the data will not be transferred to any other party in the future. I understand that it is the intention of the investigators to destroy all questionnaires and employment records one year after the completion of the study.

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I acknowledge that I have received ¥250 for my participation in the study.

Participant's signature and date

Interviewer's signature and date

(1 copy for participant and 1 copy for interviewer)

(Draft 6/18/01)