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B Analysis of Exposure

Enrolled subjects' concurrent and previous medical history will be carefully evaluated for evidence of relevant infections or exposure to hematotoxic drugs or agents using a written checklist. Subjects' and controls' previous exposure to benzene will be classified according to duration of exposure, concentration of exposure, and exposure variability and intermittency. The SMCDCP has an extensive database of benzene exposure from 1980 to the present that will be used for initial exposure characterization. Precise exposure definition is critical to this study's success and concurrent sampling will be used extensively to arrive at final exposure concentrations for various work assignments and tasks over a subject's career. These criteria will be further defined subsequent to the conduct of feasibility analyses for exposure assessment. Exposure assessment will be conducted blindly – i.e. without revealing whether a subject is a case or control. For the case subset comparisons, the "outcome of interest" will not only be benzene or confounding exposure, but clinical features of the disease (i.e. blood counts, phenotypic characteristics of the underlying bone marrow lesion, and clonal cytogenetic abnormalities). Available previous clinical laboratory data will be included as part of clinical history but will not be reported as study data.

EXPOSURE ASSESSMENT STATEGY AND EXPOSURE MONITORING

26.1 Exposure Assessment Approaches.

A Introduction

The tiered approach discussed in this document provides a means of meeting the exposure assessment needs of the family of planned epidemiology studies; different levels of exposure assessment information are needed for different phases and aspects of the various studies. Each tier builds upon the information and data used in prior levels. The tiers outlined below are directed toward the disease progression study and other case-control aspects, but also form a base for the molecular epidemiology study. See Figure 26.1 (following) for an overview of the exposure assessment process. In this section, we provide information the exposure assessment approaches for:

1. Ordinal range exposure to benzene
2. Quantitative assessment of work history benzene exposures
3. Pattern of benzene exposure assessment
4. Potential confounding exposures

A fourth tier (detailed personal and biological exposure monitoring) is discussed in the Molecular Epidemiology protocol. These tiers are not intended to be rigidly sequential. In many cases, especially during initial facility reviews, information for several of the anticipated assessment levels will often be assembled, in order to minimize repeat site visits.

For the disease progression study, the initial assessment goal is to sort study subjects (cases and controls) into one of three categories: likely unexposed, uncertain, and exposed. For the exposed subjects, they will

subsequently be assigned to ordinal benzene exposure categories (as discussed below). Then, follow up assessment (tier 2) will be used to clarify the uncertain exposure category and to further quantitate the work history exposures for the benzene-exposed subjects. Tier 3 will be used to determine the exposure concentration-time patterns of the benzene-exposed subjects.

B Tier 1. Ordinal Range Exposures to Benzene

This provides the first stage of the assessment strategy, and will be used as a component of the exposure assessments for all of the study exposure assessment aspects. The main goal for the Tier 1 assessment stage is to assign benzene exposed subjects to ordinal ranges, for each major segment of their work history. The ranges for the categories, such as 0 to 1 ppm, 1 to 10 ppm, 10

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to 50 ppm, and > 50 ppm, will be set following further evaluation of the Shanghai industries' exposure data. Aspects discussed in this section include:
• Study enrollment questionnaires and initial work histories
• Shanghai Municipal Centre for Disease Control and Prevention (SMCDCP) monitoring database queries and data summaries
• Assessment of exposure to chemicals other than benzene
• Facility reviews and workplace record use
• Exposure classification process
• Data time trends

Study enrollment questionnaires will be used to initiate the work history information for this tier and subsequent tiers of the exposure assessment. Subjects will be entering the study from a broad range of employment, industries and job categories in the Shanghai area. The Shanghai Municipal Centre for Disease Control and Prevention (SMCDCP) database will be queried for information about benzene and other exposures for each subject's work location (if employed in an industry covered) in order to classify study personnel according to factory type and occupation. Factories or jobs not matching on "known benzene exposure" criteria from the database query will be set aside for further review and assignment. We expect this initial categorization to be efficient and effective with regard to benzene exposure due to the long-standing interest in and regulatory definition of "benzene poisoning" as a compensable disease.
For other chemical exposures, the intent at this stage is simply to record the identity of other major chemical exposures for the subject. The SMCDCP database may have a lower information yield for chemicals other than benzene since many other chemicals do not have disease registries and the long standing regulatory requirements such as are established for benzene poisoning.
Work history information collection will start with recruitment of the subject. An interview will be conducted to determine the subject's employment history, and as much as possible of the job positions held. The main objective of the initial work history interview is to establish the type of industry, the work location, and to the extent possible, main jobs held. We do not expect to use interviews to gather worker's self reported exposures, as these are known to be often unreliable (118) and better information sources, such the CDC database and factory records, will be available. The hospital staff who recruits study subjects will conduct this initial interview. A standardized interview data recording form and instruction in its use will be provided. The exposure assessment staff may complete follow-up interviews using a more detailed questionnaire, following their review of the initial interview results. Follow-up will also be completed the initial interviews that were classified as having no significant occupational exposure (e.g., administrative office only jobs). If a subject is incorrectly assigned in a 10% sample, the classification process will be reviewed and modified. Sequential sampling methods will be applied to assure that no more that 1% of the remaining "unexposed" subjects are incorrectly assigned.
For many subjects, workplace records (rather than follow-up interviews) will be the primary and preferred source for details about their work history. As a general rule, most workers in Shanghai tended to stay with the same work location for a career. This work history stability

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will enhance the role of facility records for work history and exposure history development. However, in cases

where records are unavailable or are inadequate (for example, small or closed employment sites), follow-up interviews will be the main information source. The work history records for this project will be coded with regard to the source(s) of the information for the work history (for example, subject interviews, other interviews, written records, combinations of sources.) For small sites, closed sites, or for non-industrial employment, techniques discussed in the following retrospective assessment section will be used. These include read-across to most similar jobs, or collecting current information and adjusting to represent important changes in exposure potential. Following assembly of the work history, the exposure assessment staff will construct the subject's exposure history. The first objective will be to classify the subject as a) likely exposed to chemicals, which may or may not include benzene b) unexposed to chemicals above non-occupational background or c) requires further investigation to adequately classify the subject's exposure potential. This classification will be completed by a combination of professional knowledge and information from the SMCDCP database. Going back in time (beyond approximately 1987 and the start of the database) will require much further investigation of written sampling records and facility information. See section 26.8 Retrospective Exposure Assessment Approaches for further discussion.

For the "exposed" subjects, the initial exposure characterization for the subject's work history will be completed to the extent possible based on the SMCDCP database for current and recent past work locations and job assignments. Measured exposure data in the database were largely obtained using the SMCDCP traditional short-term breathing zone samples that were taken at specified work locations. Part of the exposure assessment development will be relating these to personal exposure. Observations during prior visits to factories in Shanghai indicated that in many cases, the factory workstations represented a point in a "well mixed chamber" due to the influence of ventilation or a multitude of similar sources in the general vicinity.

One of the objectives of facility visits and additional monitoring (concurrent using both personal monitoring and traditional short-term breathing zone measurements) is establish how the available data represents the subjects' exposure. This additional monitoring will generally cover workers in the same job assignment as held by the subject whose exposure history is being developed. To translate the short-term breathing zone measurements into personal full shift exposure estimates, a "task-time weighted average" approach will be applied (119), in conjunction with an exposure zone approach (120). See Section 25.7 for further discussion of statistical analysis of the exposure data. The exposure data (full shift personal samples, short-term breathing zone samples, and possibly partial shift task-specific personal samples) will also be used for probability distribution analysis using standard (121) or via Monte Carlo simulation methods (122). See Section D. Tier 3. Assessing the Pattern of Exposure (below) for further discussion.

For other chemicals identified as present and involving occupational uses in the workplace, only their presence will be noted. At present, for the disease progression studies, there is no plan to quantitatively evaluate the extent of other exposures.

This ordinal ranking process for benzene will be used as a starting point for the exposure assessments supporting the studies. The ordinal ranking will also be part of the historic exposure

estimating process. However, how far back retrospective assessment can be confidently accomplished requires further investigation. The extent and nature of workplace design changes, work practice changes, changes in materials used, and work hour changes are a few examples of factors to resolve during the field phases of the exposure assessment project.

C Tier 2. Quantitative Assessment of Work History Exposures

Individual job-location exposure records existed for the factories evaluated in the study feasibility investigation. Additionally, the SMCDCP has regulatory authority for access to factories and for conduct of exposure measurements. Also, the work histories reviewed were relatively uncomplicated (few job changes), and this job history simplicity is expected as the norm. This combination of exposure data and simple work histories is expected to support individualized benzene exposure histories. These individual exposure histories will support additional epidemiologic analyses than can be conducted with the ordinal category data. Steps in assembly of information to develop the individual subject's work history-based quantitative benzene exposure assessments include:

1) Work history initial development. This has been discussed in Section B above. For cases and controls, current factory and current job information will be obtained from an initial questionnaire. The SMCDCP database will then be queried for an initial profile of the factory and exposure potential. From the SMCDCP system, a

classification into exposure categories will be completed. Note that for subjects classified as not exposed to benzene, based on information from the database, no further work on the exposure history will be routinely completed. Again, a statistical sample will be further evaluated as a quality assurance process.
2) Work history completion. For subjects for whom a complete and detailed work history is needed, factory records and interviews will be used to expand the initial work history. Interviews may be used for coworkers or supervisors in the facility, as well as for the study subject. Again, the record will be coded with regard to the information source. For each job held by the subject, the nature of the work performed and the frequency/duration of work with benzene-containing materials and/or in benzene-contaminated areas will be established. This information on the tasks will be used with task-specific exposure data in a task-time weighted average model to develop an estimate of the associated job exposure. Details on short duration, high exposure activities (possibly infrequent) will be sought, as will be the information on the more routine tasks. If sufficient data (air concentration, task duration, and task frequency/intermittence) are available, a probability distribution of the estimated task exposure will be developed.
3) Exposure monitoring records. The SMCDCP database will be queried regarding exposure data for the relevant jobs and factory according to the information gathered in steps 1 and 2. At present, it seems that the SMCDCP database is structured so that each year's monitoring data are in a separate file. One early objective is to consolidate the records so that multi-year summaries and analyses of the data may be more easily and rapidly completed. This may require migration of the database to different software. Additional exposure monitoring records from factories will be assembled, entered into the database (coded appropriately to track its origin and descriptors) and summarized to supplement the existing SMCDCP records. This will be essential for more historic job exposure estimates. The data will be subject to the time-trend and statistical analyses

(Section 26.7). The data assembly will be structured to provide long-term average exposure estimates, variability of exposure information (See Section D. Assessing the Pattern of Exposure discussion below) and specific job activity related exposure data. The job-activity exposure data are particularly of value in exposure reconstruction when the frequency or duration of the activity may have differed, or was performed by someone in another job category.
If data are sparse for a given facility, use of data from other factories within the industry segment will be considered, if several conditions are met. Some of those factors to be considered include: the similarity of: physical structure, layout, equipment, controls (enclosure, ventilation, other), work assignments, materials used and material composition. The decision on application of data from other facilities will be made by personnel who have visited the facilities or who have other substantive rationale on which to establish the similarity.
Initial site characterization efforts will focus on the work areas relevant to the subject. This should cover the work locations where all the initially known potential exposure activities (even if infrequent) occur. A walk-through inspection and screening level measurements for benzene (see Section 26.4) will be completed. The objective of this review is to identify the locations from the area monitoring database that are relevant to the subject, and identify any significant gaps in coverage. The gaps will be resolved via additional, new monitoring.
4) New monitoring. SMCDCP network and/or SMU personnel will compete additional monitoring to develop exposure profiles for facilities where further data are needed to characterize current exposure or to support estimation of past exposure. Note that the SMCDCP has regulatory authority to undertake the monitoring. The surveys will be either targeted to specific tasks/activities and/or randomly completed for the job assignments relevant to the subject's work history. Targeted surveys will provide data for specific data gaps. The random data will support developing statistical projections of long-term average exposures, and statistical estimates of exposure variability.
5) Dermal exposure potential. We will evaluate the potential for dermal contact and its relative importance compared to inhalation exposure. We will use a "range finding" table (too be developed) that provides estimates (from conservative modeling) of the absorbed dose resulting from: assumed ranges of a) extent and frequency of skin contact and b) the potential benzene-content of the materials used. Its use will depend on the ability to estimate the potential dermal contact pattern and to understand the materials contacted for the subject being assessed. Initially, these may be rather rough, uncertain and conservative assumptions. They can be used to decide, based on the estimated inhalation potential, whether or not further consideration of the dermal contribution is merited. If so, efforts to better quantitate (e.g., via better characterization of contact and materials or refined modeling) the dermal exposure will be considered. However, without use of unusual control measures or routine use of reliable respiratory protection, we expect elevated dermal exposure will also involve substantial inhalation exposure. If further dermal assessment is undertaken, the benzene content of the materials contacted becomes an important parameter to elucidate.

6) Reconstruction and monitoring. Reconstructing certain exposure scenarios will be undertaken, if necessary to fill key data gaps. Then, measurement will provide data for historic exposure assessments. Personnel involved in the reconstructed work should be

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protected from overexposure according to current good operating practices. See Section 26.8 (Retrospective Exposure Assessment Approaches) for further discussion.
Details on monitoring methods are provided in Sections 26.5 and 26.7.

D Tier 3. Pattern of Exposure Assessment

There is a mechanistic rationale to explore the possible differences in risk related to patterns of exposure other than long term average exposures (e.g., cumulative exposure as ppm-years). Certain (to be determined) concentration-time-intermittence patterns' contribution to risk may be disproportional compared to their contribution to the long-term average concentration and that risk. Benzene has been shown to produce cell cycle dependent hematotoxicity in experimental animals. The biological significance of different patterns of intermittent exposure may be related to hematopoietic compartment cell cycle times. Therefore, episodic and elevated shift duration exposures separated by several days or more may lead to episodic patterns of proliferation and subsequent increased potential for toxicity. These altered commitment and response states may be more prone to errors in cell replication than would be produced by a similar dose resulting from more uniform daily exposure patterns. Thus, the main goal in Tier 3 is to establish patterns involving substantially elevated exposures that are separated on the time scale of several days or more, rather than emphasizing variability within a day. The resulting data will be used in the epidemiologic analyses to evaluate if any of the patterns show increased risk. The pattern of exposure approach will require extensive field data collection, often via interviews of factory personnel. Monitoring data will be used to help establish the intensity and variability of the exposures. From the variability (e.g., geometric standard deviation) or the probability distribution, the percentage of time above selected cut points can be statistically estimated. That is, provided the data can be fit (with standard statistical criteria) to a log-normal or other well-characterized mathematical distribution. As an alternative, bootstrap or Monte-Carlo methods may be used125-127 with the raw data's probability distribution. Ranges will be used to classify intermittence, for example:
1) exposed daily, steady state (low GSD), with an average concentration of X PPM.
2) exposed daily, intermittent or highly variable (high GSD) at X PPM, where X represents the average concentration from the available monitoring data. Estimates of the probability of exposures above the arithmetic mean (or other specified cut points) will be developed if sufficient data are available to develop the distribution model. From these data, a probability of exposure above a selected cut point would be expected to follow a random rather than a periodic pattern.
3) exposed less than daily but more often than once per week for T minutes or hours at X PPM. Estimates of the probability distribution of exposures above the arithmetic mean will be developed if sufficient data are available to develop the estimates.
4) exposed less than once per week, approximately Z times per year, for T minutes or hours per exposure event. Estimates of the probability distribution of exposures above the arithmetic mean will be developed if sufficient data are available for their development.

26.2 Blinding

Blinding (intentionally keeping the exposure assessment staff from knowing the subject's case/control status) reduces the likelihood of biasing the extent of effort and the assigned results

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in the exposure assessment. In these studies, blinding will be maintained when necessary and where possible. For the Disease Progression study, blinding as to disease status should be maintained. However, once the initial stratification into exposed, unexposed, or uncertain has been done, access to the “exposed” or uncertain subjects may be needed to clarify work history and lifestyle/hobby aspects through subject interviews. At that time, blinding could be compromised. We think that this is not an overwhelming issue, compared to the benefits

of improving the work history and consequently the exposure information. Nevertheless, steps will be taken to minimize compromising blinding, and/or understand and control for possible bias if blinding is compromised. The exposure assessment staff will be briefed with regard to the potential biases if blinding is compromised. The staff will be instructed not to intentionally seek to learn the subject's case/control status. The work history information form will have a block for the exposure assessor to indicate if they learned or have strong suspicion of the subject's status. This code may be used in the epidemiology analyses as a "confounding" variable. Another approach will be to complete follow-up interviews for a sample of subjects who have complete, records derived work histories, and where the follow-up interview indicates blinding was compromised. Then, a comparison may be made on the differences in exposure assessment from the two variations on the work history. The third (but not favored) alternative would be to have another exposure assessment team member complete the exposure assessment. However, our preference will be to have the staff member most knowledgeable about the facility, exposure data, tasks, and other exposure information complete the assessment, even if possibly aware of the subject's status.
The Molecular Epidemiology study (Protocol II) is prospective, so blinding of the exposure assessment staff is not a factor.

26.3 Exposure Assessment Air Sampling and Analytical Procedures

Passive Sampling Organic Vapor Monitoring. Passive organic vapor monitors (POVM) will be the primary collection method for new surveys of air concentrations. These will be used for both full-shift breathing zone samples, and for monitoring during key tasks to establish their contribution to total exposure. For these studies, we expect to select and use primarily 3M 3500 or SKC 575-001 devices. However, 3M 3520 devices will be used where high exposures (e. g. over 50 PPM) are anticipated since these devices have higher capacity and a backup section to evaluate if overloading occurred. Unique location and job identification codes will be used for tracking the samples and data in the project. Each sample collected will have a field data record in the study database. See Figure 26.2 (following page) for an example of a field data recording form that will be modified to meet the Shanghai study needs. Computerized forms will be used to the extent possible to minimize both data transfer time burdens and potential transcription errors. Surveys will also employ more traditional Chinese exposure measurement techniques (i.e., short-term breathing zone monitoring using charcoal tubes and a calibrated air sampling pump) in order to establish analytical and survey equivalence.
Laboratory analysis will follow the procedure outlined in NIOSH Method 4000: “Toluene by diffusive sampling.” The file is available at: http://www.cdc.gov/niosh/nmam/pdfs/4000.pdf. This laboratory method is also applicable (and is widely used) for benzene. Passive organic vapor monitors have been used in previous studies in China (123), and have been used by and analyzed at the SMCDCP laboratory. Additional information on laboratory procedures for