Status Report: CC/DP Exposure Assessment

Report Summary

Multiple lines of exposure assessment project work are progressing to assemble the supporting information for the qualitative and quantitative aspects of the study. The qualitative assessments are now progressing in pace with the subject accrual, for substances of concern, including benzene. The semi-quantitative and quantitative exposure assessment (EA) goals for benzene include more detailed data assembly, and the time lines on these not unexpectedly lag accrual. Although lagging accrual, these are in control for completion when needed for detailed benzene EA in Q3 2006. Details on the following aspects of the CC/DP EA project follow:

- Study Goals
- Status (Figure 1)
- Study design summary (Figure 2)
- Overall timeline (Figure 3)
- Main CC/DP EA Processes, responsibilities and timing (Table 1)
- Pilot test for the EA Matrix (Sector Analysis)
- Plan Forward

The faculty members and graduate students assigned to the SHS projects, as well as the Fudan/JCML exposure assessment team members must be credited for the achievements to date, and for the successes continued work on the plan forward will assure.

Study Goals

The exposure assessment strategy was originally developed for the disease progression (DP) study, but in 2H 2001 the Science Review Panel suggested that it also be applied to the CC study. A main goal of the DP study is to evaluate if the earlier disease states (e.g., benzene poisoning or aplastic anemia) are pre-requisites for subsequent development of benzene-related leukemia. The CC study has somewhat different goals, with a main aspect evaluating whether other study exposures or explanatory variables (e.g., viral status) are associated with certain diseases (e.g., NHL). To this end, the benzene assessment is akin to a positive control by which an expected association of high level exposure with AML provides some verification of the overall exposure assessment integrity. Ordinal range assessments (no, low, medium, high exposure or with ranges such as <0.4, 0.4 to < 4, 4 to 40 and > 40 mg/m3) as planned for in the protocol support these study goals.

Status

Figure 1 provides a summary of the CC/DP subjects accrued, questionnaire collection/data entry, and completion of the various EA stages. The goal for the benzene-exposed assessment progress is based on the prior to study start expected prevalence of 10% in the study subjects. Exposures other than benzene were assigned to 2631 subjects. Prevalence for the other exposures

was not projected prior to study start. The progress continues to meet expectations of the lead team, given that developments in a few original expectations (as discussed below) required additional staffing and additional efforts for information to supplement the IPHS database.

Study Design Summary

The SHS studies have several different designs and the exposure assessment approaches differ, with the Molecular Epidemiology studies designed for extensive quantitative exposure data. The ME studies select factories for inclusion based on good records and participation in current personal exposure monitoring. The protocol for the Disease Progression study anticipated significant difficulty in reaching the fully quantitative benzene assessments for the great diversity of the subjects' work histories. Thus, the protocol for the DP exposure assessment included:

- Screening decision on ever/never exposed to benzene
- Screening decision on ever/never exposed to other substances
- Ordinal (no, low, medium , high) for the ever exposed (benzene and other) subjects
- Ranges for the benzene exposed (such as <0.4, 0.1 to < 4, 4 to 10 and > 40 mg/m3)
- Quantitative by work history segment and pattern of exposure for benzene

Figure 2 illustrates the general process and decision flow for the CC/DP EA. Figure 3 illustrates the stepwise exposure assessment information building process, where the details assembled at the lower tiers determine the feasibility of and approach for additional investigations to support the higher tier assessments. Additionally, the process involves developing qualitative and quantitative exposure assessment skills in the broad study team as the work progresses.

The study subjects recruited as cases and controls from the participating hospitals come from diverse work experiences, ages, and locations around and remote from Shanghai. The upper level investigations, when they are feasible, require more time to complete. In recent discussion with SRP members on the exposure assessment, the ordinal range tier meets their maximum expectations of feasibility for the major fraction of the subjects in such a general population based case control study. The next higher tier for quantitative benzene assessment remains a goal for a fraction of the subject, but the yield may be too low and may have too much potential for misclassification for the tier to assuredly provide data for meaningful analyses.

Overall Timeline

See Figure 4. Note that the path for the quantitative benzene assessment becomes time critical around Q2 2006. This is the time when the investigation lines converge to a consistency check and assembly of the final CC/DP EA

matrix. Following that assembly, the assignment of final benzene exposure will be completed in a few weeks of focused effort.

Main CC/DP EA Processes

The main stages of the CC/DP process, with responsibilities and progress dates are shown in Table 1. One currently open decision hinges on whether or not broad collaboration with IPHS on the database develops. Such access was part of the original study design and expectations. The alternative of relying on the currently available extracted portions of the database will impact (to a difficult to evaluate extent) the quantitative benzene assessments. However, the assembly of the EA matrix calls on information from several lines of investigation as shown in Figure 5.

Note that the EA processes include periodic reviews and recycles of the completed assessments, due to the expectation that the capabilities and data available will evolve over the project [illegible] the assessments [illegible] the project will likely not be complete until [illegible] and recycles are part of our current collaboration, and will expand in [illegible] detail as the information resources complete and capabilities develop. [illegible] largely to this iterative recycle, the majority of the benzene exposure assessments are preliminary until that last review, planned for 2H 2006.

Pilot Test for EA Matrix (Sector Analysis)

Testing of the SA approach (completed in May 05), mainly for the shoe industry and secondarily for the rubber industry, involved:

- Sorting available IPHS data into industries
- Sorting the data into sectors within an industry
- Adding task categories (not an IPHS data field) based on sample location descriptions
- Qualitatively evaluating the frequency-concentration distributions of the sector, task, time data
- Calculating preliminary summary statistics for the identified sector, task and time categories
- Assigning exposure to the JCML subjects (n=17) via the SA based on the subject's questionnaire information on industry, job, task and time period.

See Table 2 for a summary of the preliminary statistical analysis results. There are statistical treatment considerations that will be reviewed with SRP members or personnel with expertise with exposure data analysis. This work is planned in Q3 05. The pilot evaluation yielded additional insights that triggered several research efforts currently underway. These are largely covered in the following Plan Forward section. Additional coding to reduce heterogeneity in the data sets and analyses are planned before using these data for final assessment of benzene exposures. Timing of completion of such analyses is linked to whether or not further cooperative research with IPHS/CDC on the database proves possible. This IPHS/CDC agreement is particularly valuable since the database lacks the contextual information on the facility and sampling that might be

improved upon with IPHS collaboration and access to at least selected original written reports. Further work on the currently available extracts of the IPHS database does not seem productive if full access and collaboration with IPHS progresses.

Plan Forward

- Continued interactive planning with Fudan lead team on investigative directions, EA reviews, team development: 2H05
- Access to IPHS database expanded - assure all relevant data available and IPHS partnership in DATA REVIEW: Go/No Go Q3 05
  - ✓ If Go - Quality checks on IPHS sector data completed: Q4 05-Q2 06
  - ✓ If No Go - Not Applicable
- Industry Sector "History Reports" to be completed - history and trends for the sector: Current, complete by Q3 06
- [illegible] translated and integrated: Q3 06
- [illegible]
- On site first round CRP review of [illegible] results: Proposed Q3 05
- EA matrix for the sector completed and applied to CC/DP work histories: Q3-Q4 06

It is expected that ALL PHASES will be done in conjunction with appropriate Fudan EA Team members.

Figure 1. June 2005 CC/DP EA Status

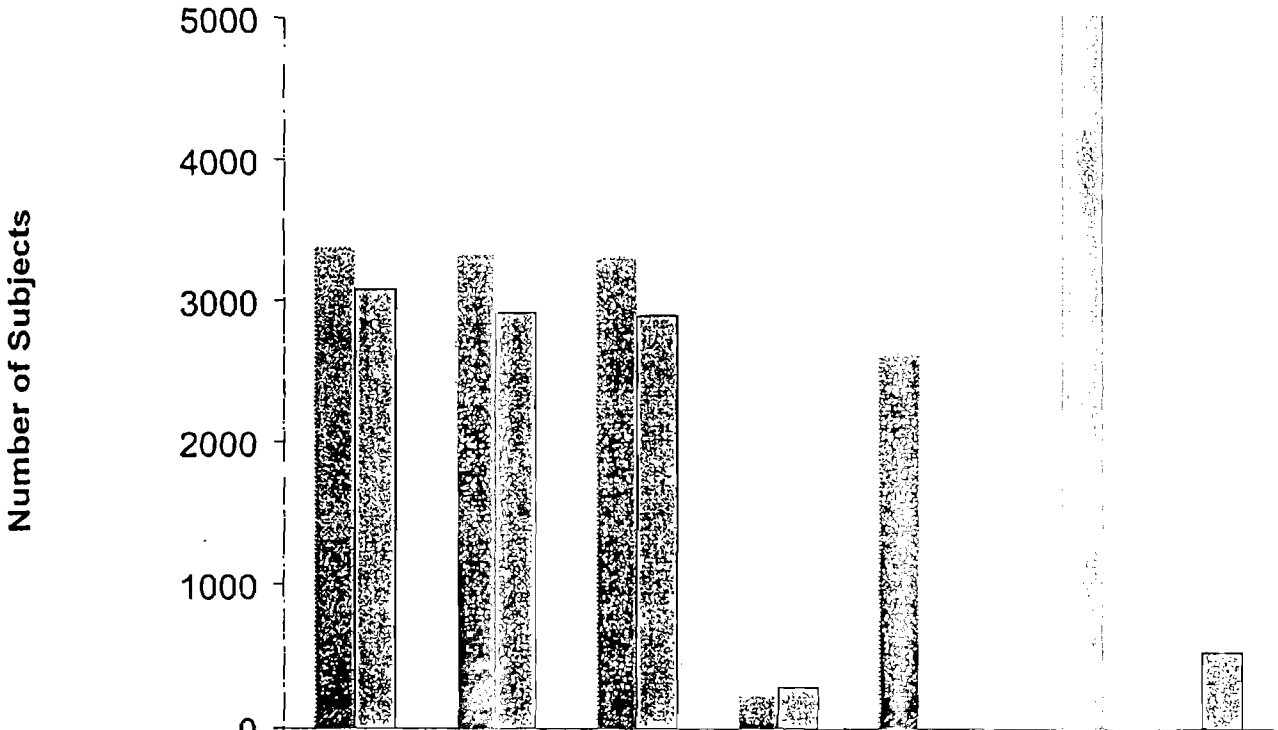

Figure 2. CC/DP Exposure Assessment Pro[illegible] Overview

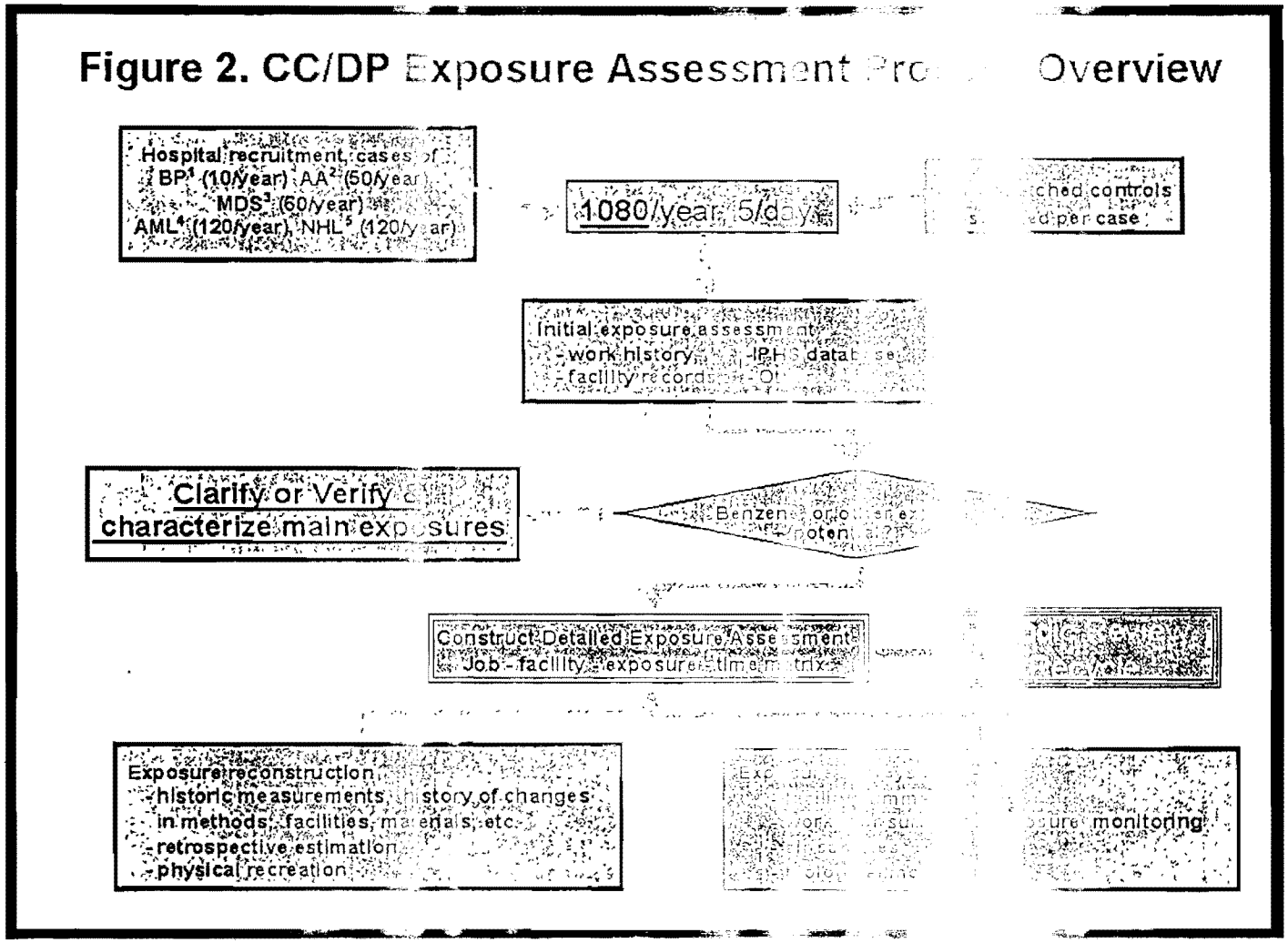

Figure 3. Case Control Studies Tiered EA Design:

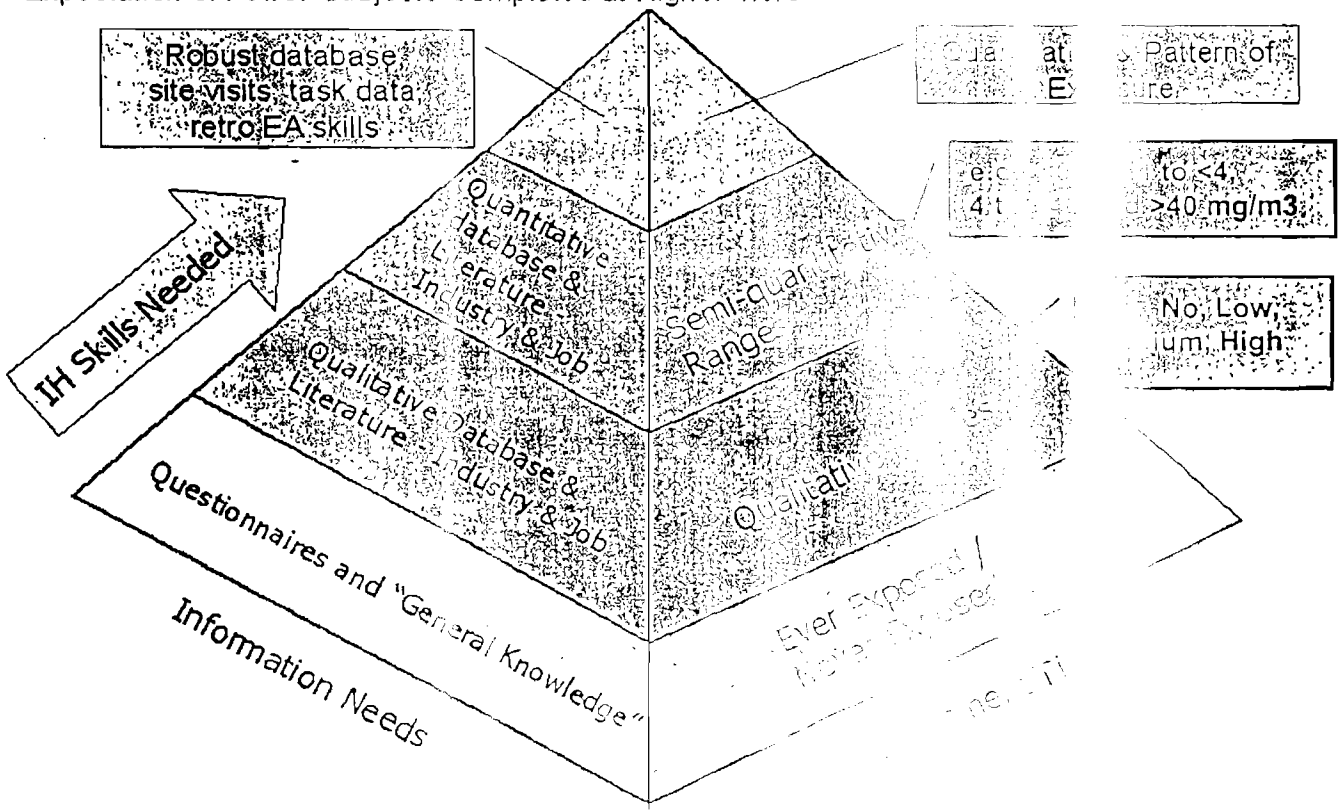

Figure 4. Study Timeline

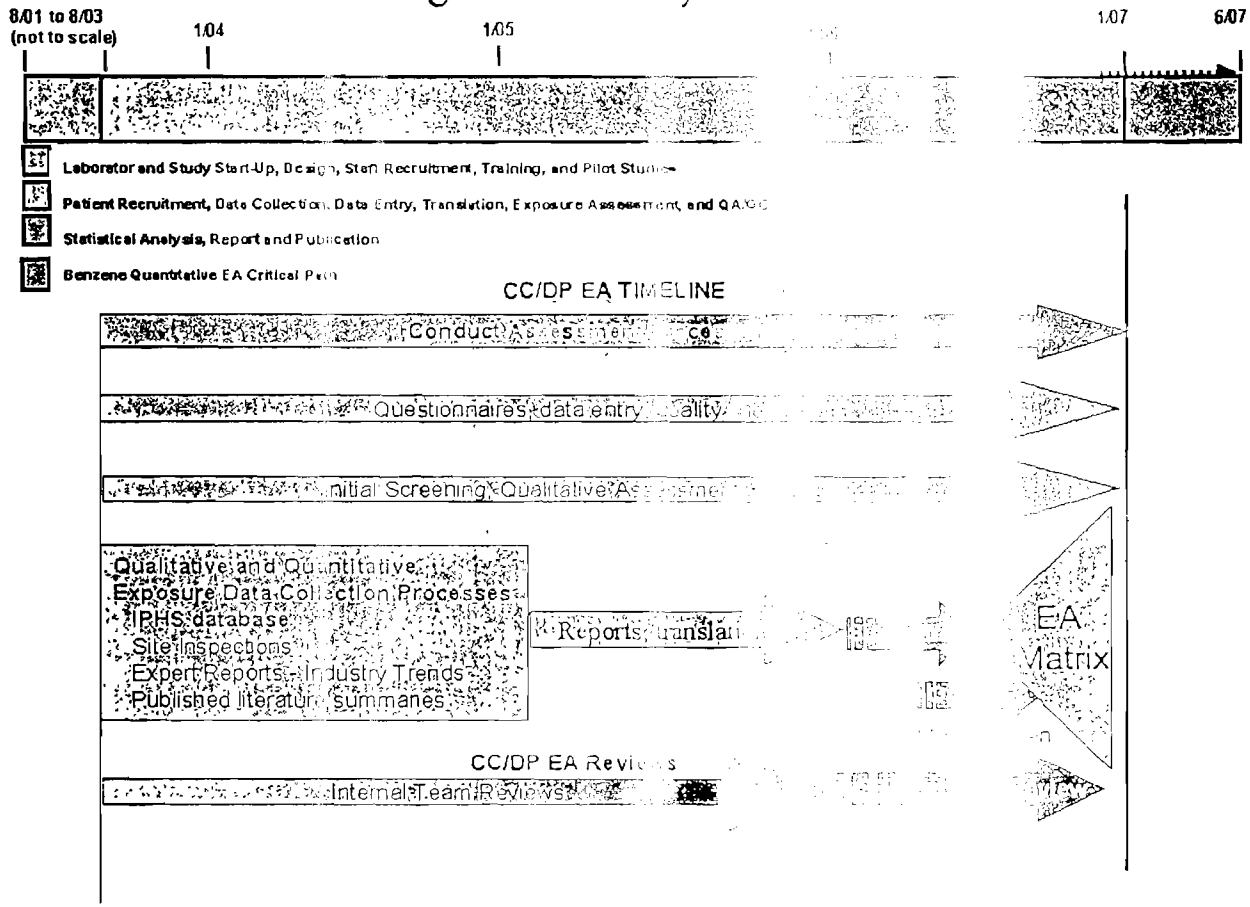

Figure 5. Additional Details - CC/DP Exposure Assessment
for PROBABLE "BENZENE" EXPOSED
Multiple Lines of Investigation and Information

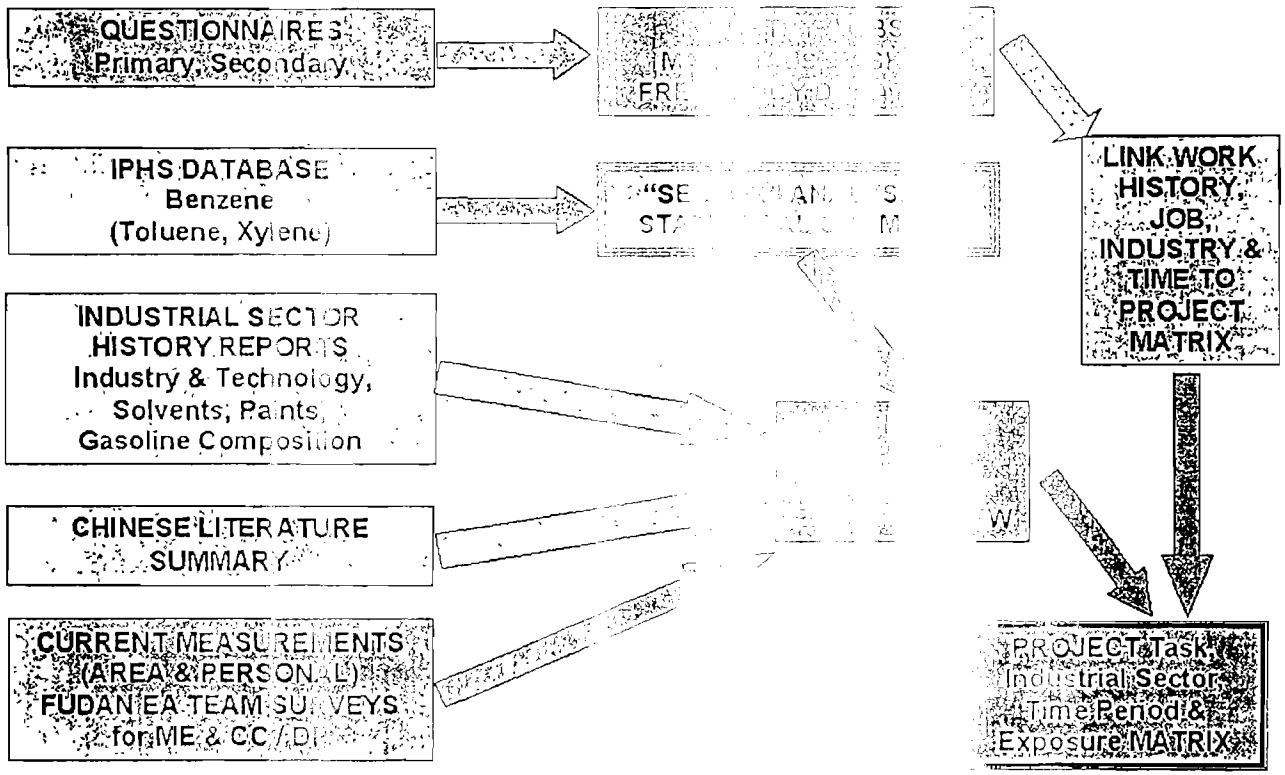

Table 1. Exposure Assessment Processes & Responsibilities for CC/DP Study

STEP	WHO	WHEN	NOTE
Questionnaires – primary and secondary	Questionn... Admin Staff	On-going	
Industry/job/materials/task/frequency/duration (key data for EA and follow-up planning)	QA/data ... EAT	On-going	
Industry codes assigned (to group work histories for consistency and follow-up planning)	EAT	On-going	
Translations of key information to English	External ... rces	On-going	
Task descriptions (essential to link to IPHS area descriptions)	EAC	On-going	
Task coding (to group work histories for consistency and follow-up planning)	EAC	4Q 05'	
Link work history/task/industry/time to reference data via EA matrix	EAC/EM...	06'	
Access to IPHS data base	PIs	ASAP	Pre-requisite
Data extraction	IPHS/Fu... EAT	On-going	
Industry coding (code system as for the work histories)	IPHS/Fu...	Existing/verification	
Key Tasks and time periods summaries	EAC	3Q 05'	
Time/task coding	EAC	4Q 05'	
Translation	External ... s	4Q 05'	
Statistical analysis of IPHS data	EMSSI	1Q 06'	
Chinese literature searching/gathering (qualitative insights, quantitative information to supplement IPHS database)	Fudan E...	3Q 05'	
Literature summary	Fudan E...	3Q 05'	
Industry coding	Fudan E...	3Q 05'	
Translation	External ... rces	3-4Q 05'	
Exposure assessment by time/sampling objective	EAC/E...	4Q 05'	

Current site EA	IPHS/Fu	On-going	
Preliminary EA of CC/DP cases to plan follow-up actions and set investigation objectives, including site ea goals	EAC	On-going	
Industry and task coding of the current data to facilitate is use including comparisons to IPHS data	EAC	4Q 05'	
Translation	Externa	On-going	
Expert reports – summary of industry, technology, time **variations**	EAC, a (IPHS)	4Q 05'	
Translation	Externa	4Q 05'	
Consistency check	EMBSI	2Q 06'	
Project time/industry/task exposure matrix	EMBSI/	2Q 06'	
Final exposure assessment	EMBSI	2 – 4 Q 06'	
External EA review	Fudan EA experts	4Q 06'	
Final report	EMBSI	1Q 07'	

EAT = Exposure Assessment Team. Responsible for initial scre and for field ation work, including investigation of workplaces for current exposure sampling and for subject work history. The EAT is under the direction of the EAC

EAC = Exposure Assessment Committee. Comprised of s nior pe nel, curr nt Liang and Dr. Jin of Fudan and Dr. Fang, retired from IPHS. Lead team member from EA serves e cretary.

TABLE 2. Preliminary Statistical Summaries of Job Category and Time Data Blocks for Shoe Industry Exposures in mg/m3

Job A General shoe making (not otherwise specified)

	1970s & prior	1980s	1990s+
Mean	57.3	29.7	89.1
Median	25.0	1.0	27.4
Minimum	0.3	0.3	0.3
Maximum	600.0	1376.7	760.0
Count	52	315	78

Job B Shoe application

		1990s
Mean	2	41.4
Median	9	6.7
Minimum	0.	0.3
Maximum	1	1323.5
Count	7	179

* 2 outliers censored

Job F Assembling shoes

	1970s & prior	1980s	1990s
Mean	150.2	22.5	40.1
Median	67.5	1.6	6.0
Minimum	0.3	0.3	0.3
Maximum	900.0	1199.3	598.5
Count	38	455	63

Job F [illegible] applications,

1980s and on only

Mean	3
Median	3.
Minimum	0.
Maximum	2
Count	3

Job C Glue mixing
1980s Only Available

Mean	191.5
Median	3.4
Minimum	0.3
Maximum	6964.5
Count	153

Rubber cements (code 3-

All ex

Mean	5
Media	4.
Minim	0
Max	7
Cou	1