Request for Proposal
Benzene- Low Exposure Case-Control Studies--- Data Consistency Review

Background

Long-term exposure to high concentrations of benzene is generally believed to be a cause of acute myeloid leukemia (AML). Benzene's etiologic role with other forms of leukemia and other lympho-hematopoietic cancers is not well-established, nor are its low dose effects on AML. Because of the potential for benzene exposure during petroleum refining and bulk product distribution, the petroleum industry has had a keen interest in the health of its employees who work in these areas. Daily potential exposure to hydrocarbons among these workers is generally well below 5 ppm, and is usually in the form of a mixture of volatile organic compounds which may include benzene.

Many cohort studies have been conducted among these workers. Four have included nested case-control studies: (Rushton and Rumaniuk 1997a; Wong et al., 1999; Schnatter et al., 1996; Gray et al, 2001). Three of the studies have comparable findings while the fourth suggests a benzene leukemogenic effect at levels much lower than the others. Because all four nested case-control studies used slightly different methods and procedures, comparing the results is not straightforward and the reason for the different results is not clear. As such, CONCAWE is interested in better understanding how the four studies were conducted and in a later phase determining whether their results can be pooled to help overcome limitations inherent in each study. Differences that are important to recognize include case definition and ascertainment, exposure assessment, selection and information biases, and confounding.

Objectives of the Study

CONCAWE is seeking an investigator or investigative team to evaluate data consistency and quality in the four major case-control studies of leukemia in oil distribution and refinery workers noted above. Note that any pooled analysis that may be possible is not part of this RFP and no costs for such an activity should be included as part of your bid.

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Data Consistency Review

Results for the association of benzene exposure and various leukemia subtypes are not consistent among the four studies of interest. The only consistent results indicate an increased risk for acute non-lymphocytic leukemia (ANLL) and the similar but slightly smaller subcategory AML. The primary purpose of the data consistency review is to elucidate the reasons for the inconsistencies by characterizing the similarities and differences among the four case-control studies.

It can be difficult to draw strong conclusions based on studies of leukemia subtypes, because of the studies' limited power due to a small number of cases, even when the cohorts are of substantial size. All four studies are affected by problems of sample size, as the largest study utilizes only 91 lympho-hematopoietic cancer cases and the smallest only 29. This is the reason CONCAWE is interested in determining the feasibility of combining study data into a single analysis. The results of the consistency review described here will be important for this later decision.

Other major factors that may affect consistency among the studies are differences in identification of the original cohort, ascertainment of cases and controls, exposure measures, job-exposure matrix creation, data collection procedures (especially for obtaining work history data), quantitative exposure assessment, and the analytical methods used. As such, your proposal should describe how you will characterize and compare these factors.

Another aspect of this review concerns data quality per se. It is possible that data extraction and transcription errors occurred and these may have created spuroius findings. CONCAWE is interested in having a sample for the cases' and controls' data files verified against the original records as part of this project.

The investigator is encouraged to use information from available reviews and audits of the four studies to assist in quickly identifying issues and questions during the normal course of the systematic review. Table 2 in the appended Technical Annex lists some important questions to consider during the data consistency review. However, this list is not exhaustive, nor are all issues equally important. This list is a starting point for the reviewer to begin the systematic review and it is not necessarily meant to be responded to point-by-point. The purpose of both Tables 1 and 2 is to allow potential investigators to better understand the scope of the RFP before deciding to respond. RFP respondents may chose to use this list to assist them in developing criteria for assessing data consistency/quality.

Availability of Data Records and Original Principal Investigators

[the content of this entire section needs to be confirmed] CONCAWE has made preliminary contact with the four study principal investigators and their sponsoring organizations. All have agreed to support this project and make themselves and their data available to the investigator. Please note the Data Location column in the table below as this may affect the cost estimate in your bid.

Sponsoring Organization	**Principal Investigator**	**Data Location**
AIP – Sponsor Contact	Glass	100+ different locations in Australia
API – Sponsor Contact	Otto Wong	1 location, Wash DC, USA
ExxonMobil	Rob Schnatter	1 location, New Jersey, USA
IP – Sponsor Contact	Leslie Rushton	1 location, London, UK

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Science Advisory Board

CONCAWE has set up, and will fund, an independent external Science Advisory Board (SAB) for this project. The SAB consists of experts in epidemiology, occupational exposure assessment, and hematology and should be viewed as a resource for the investigator. At a minimum, the investigator will submit their protocol, status reports and draft final report to the SAB for review and comment. The investigator's written responses to the SAB's comments will be submitted to CONCAWE.

Issues to Address in the Proposal

The RFP must include your plans for addressing the non-exhaustive list of issues shown below. Your plan should include how you intend on making the comparisons including:

- what data elements you will seek to review and
- what criteria you will use to determine such characteristics as data completeness, accuracy, potential bias, consistency, and other aspects of "quality".

The Technical Annex appended to this RFP should also be reviewed for issues germane to the project. You should also include relevant issues identified from your past experience in comparing study results.

1) Cohort identification and documentation of the methodology of the cohort assembly. Include completeness of cohort identification, inclusion and exclusion criteria, and data sources.

2) Ascertainment of cases and controls, including case definition, completeness of case identification, source of cases, incident vs. decedent cases, any potential selection bias.

3) Collection of work history data, including availability and use of computerized and/or hard-copy work history records, completeness of computerized/ hard-copy records, use of interview of case or proxy, recall bias due to interview, any other potential information bias.

4) Construction of job exposure matrices, including procedures, reliability and accuracy of assessing the exposures, any potential misclassification.

5) Data analysis, including methods and models used, adjustment of confounders, potential confounders not adjusted for.

6) Review of original investigator's quality assurance procedures, including those pertaining to epidemiologic and exposure-related data collection and disease coding, should be described. Also, include your plan for reviewing original records (e.g., proportion of original records to be reviewed, how records will be obtained, etc)

7) Given the nature of the key studies forming the basis of this project, CONCAWE believes a multidisciplinary team consisting of epidemiologists, industrial hygienists/exposure assessors, and perhaps experts in other disciplines maximize the chance for a successful project. Please describe how you will provide the expertise needed for this project. If a team approach is proposed, the principal investigator should be identified and letters of intent from all collaborators must be included. Please highlight the qualifications of the investigator/investigative team with regard to expertise in:
    - conducting occupational epidemiological studies,

- exposure assessment in industrial settings,
- creation of job-exposure matrices, and/or
- medical knowledge of lympho-hematopoietic cancers.

Curriculum Vitae for the key members of the investigative team should be included with the RFP.

Additional Requirements

1. The proposal should present a fixed price for performance of the study. A budget itemizing major study component costs broken down into direct and indirect costs should be included.
2. Procedures to ensure the confidentiality of individual study member information should be described.
3. The time frame for completing the study should be included and major milestones denoted. CONCAWE is interested in beginning the study immediately and completing it in 8 to 12 months, including delivery of the final report to CONCAWE.
4. Deliverables:
   - Study protocol (including any updates/modifications occurring during the course of the study)
   - Written response to SAB protocol comments
   - At least one interim written progress report
   - Draft technical report
   - Written response to SAB technical report comments
   - Final technical report (3 printed, 1 electronic)
   - Plan for disposition of materials collected or generated as part of this project.
5. One printed copy of your complete proposal, and one electronic copy (preferably in Microsoft Word, sent via email, CD-ROM, or 3.5" floppy disk) must be received by October 28, 2003.

Additional Information

CONCAWE encourages the publication of the project's findings in a scientific peer-reviewed journal. Bidders may wish to itemize any additional costs this may engender in their proposal budget.

Please note there is no provision for reimbursement of costs incurred by bidders in the preparation of bids responding to this solicitation. Also, CONCAWE reserves the right to reject any or all proposals without assignment of reasons for doing so.

All correspondence and questions should be directed to:

Jan Urbanus
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Telephone:
e-mail:

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