SUMMARY SHEET

PROJECT TITLE: **Pooled Analysis of Petroleum Case Control Studies**

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KEY OBJECTIVE OF THE PROJECT:

This project will estimate dose response relationships for specific LH cancers and leukaemia subtypes with respect to benzene exposure. Three nested case control studies will be pooled to estimate dose response relationships. Before pooling the studies, all exposure estimates will be reviewed to rationalise any potential differences and to develop common estimates when warranted. Likewise, all cases will be reviewed with respect to FAB and WHO schemes, and common classification methods will be employed to classify LH cancer subtypes. Flexible dose response modelling procedures will be supplemented with standard logistic regression analyses as well as graphical techniques for displaying the data. A primary focus will be to develop measures of uncertainty for exposure and disease classifications for each study subject. This will allow focused sensitivity analyses using the best justified information to develop dose response relationships and no-effect or low-effect levels from the pooled data. Results will be interpreted according to established causal criteria, including the consistency of results within the pooled population and among other benzene exposed populations.

ESTIMATED COST: 618,000€

PROPOSED STARTING DATE: December 1, 2005

PROPOSED END DATE: June 30, 2007

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I) INTRODUCTION/BACKGROUND

Benzene is a well-known leukemogen, yet there remain a number of questions regarding its dose response relationship, especially for specific leukemia subtypes. Studies with relatively high levels of benzene exposure have served as a basis for risk assessment and regulatory rule making (Paxton et al 1994, Schnatter et al 1996a, Crump 1994, Hayes et al., 1997). Yet, the relevance of these exposure scenarios to current occupational and environmental exposure is open to question. The Pliofilm exposures were higher than current occupational exposures and benzene was experienced with relatively few other co-exposures. Today, trace amounts of benzene are present in gasoline, and petroleum workers can be exposed to benzene in the presence of other hydrocarbons. This exposure scenario is more germane to the public's benzene exposure patterns (e.g. even lower exposure, in the presence of many other hydrocarbons). As such, studies that characterize dose response relationships for these lower exposure scenarios may be useful to benzene risk assessment.

Three nested case control studies on benzene have been conducted in petroleum workers (Schnatter et al, 1996b; Rushton and Romaniuk, 1997, Glass et al., 2003). These studies have used the same over-arching methods to estimate benzene exposure and analyze the effect of benzene on leukemia risk. (Armstrong et al, 1995, Lewis et al., 1997, Glass et al, 2000). The present proposal is to perform a pooled analysis of these three case control studies to further clarify dose response relationships, particularly for specific leukemia subtypes.

In a previous report on the feasibility of conducting a pooled analysis for these studies (EMBSI et al., 2002), we concluded that a pooled analysis was feasible and recommended a stepped approach for conducting such an analysis. Since that time, CONCAWE has assumed responsibility for such an analysis and commissioned an independent examination of whether such an analysis was feasible. Hence, a team from IOM and IRAS recently evaluated the consistency and quality of the data in these studies and discussed aspects important for the possible pooling of the studies (IOM and IRAS, 2005).

Like our own analysis, the IOM/IRAS report found no intrinsic barrier to pooling the data, and recommended some consideration be given to extending follow-up (to case-sets available subsequent to the cut-off dates of the original studies). Other recommendations regarding validation of exposure "k-factors", setting up a panel of haematology experts, and use of refined data analysis strategies were also made. We have closely examined the IOM report and have taken many of their recommendations on board in this study proposal.

The main advantage of a pooled analysis is to improve power and allow a more systematic examination of factors important in characterizing the dose response relationship between benzene and leukemia. Each single study was able to provide limited information on items such as: (a) the dose response relationship for specific leukemia subtypes, (b) the relevance of benzene exposure timing on the risk, if any, (c) the relevance, if any, of specific jobs, tasks, and or locations on any benzene-specific risk, etc. When pooling data across studies, it is possible, in the absence of marked heterogeneity, to examine such issues in a more robust way.

II) AIMS AND OBJECTIVES

The primary objectives of this research are as follows:

- Estimate the exposure-response relationship for benzene and leukemia in petroleum workers.
- Estimate exposure-response for specific leukemia subtypes (e.g. ANLL, CLL, etc.) and benzene using consistent disease classification methods.
- Evaluate the influence of the following factors on benzene risk: study, industry sector, site type, job, lag/latency, type of diagnosis (e.g. mortality/incidence), era and specific exposure metrics such as cumulative exposure, exposure intensity, and, if feasible, exposure peaks and intermittency.

- Formally evaluate the robustness of results to uncertainties in the data through sensitivity analyses that account for data quality.

A secondary objective of this research will be to estimate the exposure response relationship between benzene and other LH cancers (non-Hodgkin lymphoma and multiple myeloma). This secondary objective applies to the IOL and Health Watch studies, since exposure estimates were not developed for these diseases in the IP study.

III) SCOPE

We have considered various recommendations made by the IOM/IRAS team to enhance a subsequent pooled analysis of these studies. After carefully considering the points made, as well as reconsidering our own previous recommendations, we believe that the following scope of effort is justified in a pooled analysis of the three studies:

Employ updated statistical methods to analyze the case control data. These methods will include more graphical displays of the data, as well as standard categorical and continuous analyses. In addition, dose response modelling will consider non-parametric models which employ smoothing spline functions to allow a flexible representation of dose response.

Compare, rationalize and change, if necessary, workplace estimates of exposure. This will be accomplished by comparing similar work history entries across studies. For similar work history entries it will be determined if any potential differences in workplace exposure estimates are justified due to study-specific exposure scenarios. If the differences are not justified, a new workplace exposure estimate will be assigned to the work history entry, using new base estimates and/or modifying (k) factors (see section 5B). It is anticipated that since more exposure data was available for the later studies, some changes in workplace exposure estimates are warranted, especially for earlier studies. In addition, common measures of peak and intermittent exposure will be investigated and put forward, if feasible.

Standardize the use of diagnosis data to classify (and re-classify, if necessary) leukemia subtype diagnoses. Since the pooled analysis will have greater power to examine leukemia subtypes, it is important that identical methods be used to classify disease. A review of all material used to establish the diagnosis will be made for all cases. If needed, diagnoses will be changed based on this review. A hierarchal scheme will be used to determine any uncertainty associated with the basis for each diagnosis. LH cancer classifications will be made according to the traditional FAB scheme (Bennet et al 1976) as well as the more recent WHO scheme (Harris et al 1994). In addition, cases resulting in fatal outcomes will be analyzed separately from those resulting in morbidity only.

Employ sensitivity analysis methods to address uncertainties in exposure and/or disease assessment. The highest quality information will be proffered a greater influence on the interpretation of results. Sensitivity analyses are becoming well accepted in the epidemiologic literature as an informed way to assess the impact of uncertainty in the data (Greenland, 1999).

While not part of the scope herein, Appendix 1 summarizes the scope, time and cost increases associated with including additional cases that have occurred since each case control study was published.

IV) DATA AVAILABILITY/ACCESS

Each data set is available to the respective original PI. In addition, EMBSI possesses a copy of the IP data set, which was used in previous analyses for the EU existing substances risk assessment submission. However in order to gain access to all necessary data and supporting materials, there are specific practical steps necessary for each study, described below. Once we receive written confirmation

of the intent to fund this analysis, each PI will initiate appropriate steps to gain approval for using each dataset.

Imperial Oil Limited (IOL) (Schnatter et al, 1996b).

The original IOL case control study was approved as a follow-up study to the original cohort study. However, since the approval was for a single study, a new protocol for the pooled analysis will need to be sent to Statistics Canada for approval. As part of this process, we will seek approval to use data subsequently obtained in a cohort update match to the Canadian Cancer Registry. This will allow analyses by leukemia subtype in the pooled analysis. Use of data from the CCR will be coordinated by Statistics Canada and will involve approval from each provincial registrar. Imperial Oil Limited will also need to formally approve the use of this data; it is anticipated that this will proceed smoothly.

There are some minor housekeeping issues that need to be addressed that will assure that specific workplace exposure estimates can be linked to specific base estimates for each study subject in the records housed at EMBSI. These will be addressed prior to the initiation of the pooled analysis.

Institute of Petroleum (Rushton and Romaniuk, 1997)

The IP study data are held at the Institute of Occupational Health at the University of Birmingham and include both paper records such as site information, work histories and diagnostic data, and one computer. A catalogue of the information held on this computer (designated machine A) exists and it was verified by the IOM/IRAS team that this corresponded to the files stored on the computer. These files include the databases of work histories and exposure estimates and much other relevant information.

Analyses for the original case-control study were carried out on another computer (designated machine B) which was not transferred to Birmingham, although a catalogue also exists of the contents. A copy of the catalogued datasets required for analysis is held at EMBSI. Although the IOM/IRAS team were unable to examine any statistical programs or output from the original study, EBMSI used their datasets to confirm the original results as part of the previous quality review. The fields in these data sets would allow comparison of base estimates, k-factors, and resulting workplace exposure estimates by work history entry.

Ready access to all these data and information will be required for our proposed study and negotiations for temporary transfer of the material are underway with the Energy Institute (formerly the IP) and Birmingham University.

The use of the data for the cohort and case-control study was obtained from the Office of National Statistics. Approval will be sought from them for this re-analysis.

AIP Health Watch (Glass et al, 2003)

The Health Watch database is owned by the Australian Institute of Petroleum and housed at Monash University. The various Australian State and Territory Cancer Registries and the Australian Institute for Health and Welfare (AIHW) will need to approve use of this data in a pooled analysis.

The study data contains the subject study number, details of the job history, applicable base estimates, smoking and drinking status, the ICD9 code for the cancer if they are a case and the case set number for each control. There is sufficient information to allow calculation of an estimate of the exposure to benzene in ppm for each job and hence the cumulative exposure in ppm years. The data are de-identified and can be sent offsite in this form subject to ethical approval.

The forms and queries generating the cumulative exposure and intensity of exposure are in the database. Changes to the values ascribed to the base estimates can easily be made in the appropriate table, (e.g. background exposure attributed to office workers). A data dictionary and “do files” are available.

The AIP are willing to allow participation in the study but have not provided formal written agreement as yet. Ethical approval must be sought from the Monash University Ethical committee to release de-identified data for statistical analysis elsewhere and also from the State and Territory Cancer Registries.

V) PROGRAM OF WORK

In this section, we will describe an overall program of work, which will be made more specific in the formulation of the detailed protocol (which is step 1 of the pooled analysis). The key features of the studies that are to be included in the pooled analysis are described in Table 1.

Table 1. Comparison of key study design features.

Subject/Cohort/Study Characteristic	**IOL**	**IP**	**AIP (Heath Watch)**
Design	Retrospective	Retrospective	Prospective
Employment period for entry	1 yr	1 yr	5 yr
Source	HR records	HR records	Records and interview
Study employment period	1964-1983	1951-1975	1980-1995
Exposure era covered	1909-1983	1909-1993	1941-2000
Follow-up published data	12/83	12/92	6/00
Follow-up (full data)	12/94	12/98	6/00
Industry sectors			
- Refineries	No	No	Yes
- Distribution/marine	Yes	Yes	Yes
- Airports	Yes	Yes	Yes
- On & offshore production	No	No	Yes
Total (LH)	29	91	79
All leukemia	16	91	33
- ANLL	5	34	11
- CLL	?	31	11
- ALL	?	7	2
- CML	?	11	6
NHL	8	0	31
Multiple Myeloma	7	0	15
Cumulative exposure	Yes	Yes	Yes
Highest intensity job	Yes	Yes	Yes
Peak	None used in analysis, some surrogates defined	12 categories based on job title & freq/intensity/duration	high day exposure - - CB/BTX exposures
Time course analyses	simple drop last n years n=5,10, 20	simple drop last n years n=5,10, 20	Thorough – considered various time windows

The pooled population consists of 140 cases of leukaemia, 39 cases of NHL, and 22 cases of multiple myeloma. The 140 cases of leukaemia compares very favourably with other populations used as the basis of benzene regulations. Specifically, there are nearly nine times the number of cases compared to the Pliofilm population.

A) OUTCOME DATA

1) Methods used for current classification

Each study used a slightly different method to define cases. The IOL study used underlying cause of death codes specific to leukemia, multiple myeloma and non-Hodgkin lymphoma. All death certificates were coded by Statistics Canada. Further information was collected from the Canadian Cancer Registry on these cases including: ICD-9 diagnostic code, ICDO (morphology) code, ICDO (topography) code, other morphologic classifications, whether the source of notification was from a medical certificate, the method of diagnosis (i.e. autopsy, histology, cytology, radiology, clinical, or death certificate only), and whether the cancer was the first, second, etc. reported cancer. This data was not available for the previously published case control study, but is available now.

The IP study collected information from two sources to identify leukemia cases: death certificates and cancer registrations. Both underlying and contributory causes were used to identify leukemias from the death certificate. Contributory causes of death were used to provide some cancer incidence information. Of the 88 cases identified from death certificates, 75 (85%) were the underlying cause of death, including all acute leukemias. In contrast, 11 of the 13 cases identified as a contributory cause of death were chronic leukemias. This is not surprising, given that CLL can be a mild, chronic disease with very high survival. 43% of the 91 cases have histopathology data from hospital pathology departments. The majority of the cases (88) were identified primarily from death certificates, although a cancer registration was also received for 56 (90%) of the 62 deaths occurring after 1971 (the effective date for the cancer registration database). A comparison of diagnoses between the cancer registry data and the death certificate showed that the death certificate actually contained more specific information. Discrepancies in the diagnoses from these two sources were found for 12 cases. Histology reports were received for nine of the 12, and in all cases confirmed the death certificate diagnosis.

The Health Watch study used ICD9 codes for leukemia, multiple myeloma and non-Hodgkin lymphoma. For a case to be included in the study, it needed to be confirmed by a pathology report, cancer registration, a letter from a medical practitioner or a death certificate. For the 33 leukemias, just over half were based on histology reports.

2) Procedures to ensure consistent classifications across study

Various sources of information regarding the diagnoses for all cases were used in each original study. This includes hospital records, histopathology reports, information from cancer registries, etc. Since the publication of the original studies, more information is available for some of the cases in each study, particularly the IOL study. All previous and new information pertaining to the diagnoses of cases across studies will be assembled. Accounting for all of the assembled information, diagnostic entities will be defined in two ways. The first method allows comparison with many previous studies in the literature. This method will be based on the International Classification of Diseases, version 9 (i.e. ICD-9), supplemented by the French-American-British (FAB) criteria for AML. The second method allows comparison with anticipated future studies that will use the REAL and ICD-10 schemes (see below).

For the first method, a hierarchy will be established for the information that was used as a basis for the diagnosis. Each leukaemia and other LH cancer will then be scored against the specific hierarchal classification. Diagnoses based on higher hierarchal categories will be associated with greater certainty. In addition, diagnoses that are consistent across more than one source of information (e.g. morphologic information agrees with clinical notes and the death certificate diagnosis) will be associated with higher certainty. Subsequently, cases with higher certainty scores will be used in sensitivity analyses for leukemia subtype-specific risk analyses. Richard D. Irons, a board-certified clinical pathologist and toxicologist, will lead the establishment of the hierarchy and will aid in the classification of each case against the criteria established.

In 1994, the International Lymphoma Study Group proposed a new scheme (called the Revised European and American Classification of Lymphoid Neoplasms, or REAL) to classify LH cancers (Harris et al, 1994). This scheme was motivated by the observation that essentially the same disease could often present as a leukemia or lymphoma. The new scheme was based on better understanding of etiologic and prognostic factors important with the advent of new techniques used to diagnose and treat these tumours. The REAL scheme is based on the presumed cell of origin and has three major groupings: B-

cell lymphomas/leukemias, T-cell lymphomas/leukemias, and Hodgkin disease (Ottenseimer, 2001). The WHO classification, which is based on the REAL scheme, covers not only lymphoid tumours, but extends to myeloid, mast cell, and histiocytic/dendritic cell malignancies (Cogliatti and Schmid, 2002). In this scheme, traditional hierarchal criteria (e.g. headed by morphology and followed by immunohistochemistry and genetics) no longer apply. Instead, the relative impact of morphology, phenotypic, genotypic and clinical data varies among different diseases. Our proposed classification based on the REAL/WHO classification will consider the information that is present (or implied) in the records. For example, although a death certificate is often considered the lowest certainty source in common hierarchal schemes, the death certificate may imply that cytogenetic analyses were performed (e.g. specific translocations can be mentioned). In certain leukaemia or LH subtypes, the presence of such cytogenetic information is regarded as the primary information on which to base a diagnosis. Such cases would receive a greater certainty score, consistent with REAL/WHO diagnostic paradigms. Based on the existing diagnostic information used in each case, the relative uncertainty associated with the most likely WHO diagnosis will be estimated. While one would expect more residual uncertainty regarding the WHO/REAL scheme, it is not a foregone conclusion that this will be the case.

We regard the direct participation of clinical experts in the characterization of diagnostic uncertainty using two schemas as novel, and a key strength of the proposal.

B) EXPOSURE DATA

Estimates of benzene exposure were made for all individuals in each of the three studies using the same general model. This generated exposure intensity estimates for benzene expressed as parts per million (ppm) for each job. The job's intensity was multiplied by the years for which the job was held, the job exposures were summed over the individual's career and this generated cumulative exposure in ppm-years for each person. All exposure estimates were carried out blind as to case/control status. The following general model was used to develop workplace exposure estimates (WE's):

$WE = BE * K_W * K_M * K_T * K_E$, where BE was a base estimate of exposure, and K's were modifiers based on differences in the workplace(W), materials(M), tasks(T), and/or environment(E).

A WE was developed for each line of work history amongst all study subjects, and was measured in parts per million. Each line of work history generally consisted of a job, unit, location (site), and applicable dates.

1) Development of consistent rankings of uncertainty for the exposure estimates.

Each original study attempted to derive an estimate associated with the uncertainty involved in the exposure estimation process. The approaches had similar goals but involved somewhat different criteria. Thus, it is necessary to define a mutually agreed procedure and rules for assignment resulting in common measures of uncertainty that are not study-specific. To do so, we plan to examine the uncertainties and the relative weighting for each uncertainty category in the entire exposure estimation process, as follows:

- Work history will likely have the greatest effect on uncertainty. We will examine work history with respect to its completeness as well as its specificity.
- How well the site is characterized. Site characterization will assess how well the products handled, operations present, and site-wide exposure control technology are documented for the particular site.
- How well the jobs are characterized, including the task frequency and job-specific work practices in place
- The certainty of the products/material characterization, specifically the benzene content
- The precision of the BE's, examining the number of samples on which they are based, the variability of the underlying data as well as the absolute magnitude.

- The variability of the K-factors and how many K-factors were necessary.
- The applicability of the estimate to the work history entry. This can be thought of as residual uncertainty unaccounted for by BE * K_i-model.

We will then aggregate uncertainty by individual, considering all of the uncertainties in exposure estimation over the entire work history. From this, we will allocate an uncertainty score that encompasses all sources of data used to characterize the individual's benzene exposure estimates. The higher certainty WEs for a given job category will be given more weight in the rationalization process. This rationalisation process may provide more insight on the validity of the WEs thus the uncertainty scores may be revised.
The resolved certainty scores will also be used to categorize the exposure assessments for sensitivity analyses.

2) Comparability of background exposure between studies

Higher background exposures were attributed in the Health Watch study compared to the other studies. A common basis is needed.

Initially, the exposure assessment team (EA) will produce a list of all work history lines amongst all subjects in the three studies. The list will be initially sorted by whether a background exposure was assigned to the specific work history line. For all work history lines assigned to a background exposure, we will simply verify that a background exposure is/was appropriate, and consider whether a site background exposure (i.e. at a site where benzene was present) is applicable, or whether a true background exposure is applicable. We will assign a common value to similar sites for similar eras across the three studies.

3) Rationalization of differences across studies

For all remaining work history lines, we will seek to categorize the lines into equivalent entries across studies. An obvious equivalent entry involves the term "route salesman" in the IOL study, and the term "tanker driver" in the other two studies. Thus, thousands of original work history lines may be reduced to hundreds of "work history categories".

Work history categories will be further examined by era. For example, if top loading was used at one site through 1970, and bottom loading was then subsequently used, terminal operators working before 1970 versus 1970 and after would merit unique "era-specific work history categories".

Next, the EA team will examine the WE's in the era-specific work history categories by study. For some work history entries, appreciable differences in workplace exposure estimates will be identified. The absolute magnitude of the differences will vary with the WE, we will establish /a priori/ criteria for "appreciable differences". For these differences, the original base estimate and K factors will be scrutinized. If the difference can be justified due to a study-specific scenario (e.g. fewer loads due to longer distances traveled), the original BE and K factor(s) will be used. If the difference is due to the fact that it is based on fewer data, a change to the better-justified workplace exposure estimate will be made. The certainty scores discussed above will be used to guide this revision process. Of course, these revisions will be made by the exposure assessors who will be unaware of whether the work history belongs to a case or a control.

Because the studies cover different sectors of the industry, not all WEs can be compared between the studies. However, it is probable that the ranking of exposures within one study is correct. After the revisions have been made, the overall changes to each study will be compared and if the WE's have been revised up or down consistently between the studies, changes of a similar magnitude will be considered for the remaining non-comparable WEs.

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For purposes of study analyses, both the original and revised estimates of exposure will be retained in the database. The revised estimates of exposure will be used in the initial dose response analyses on the pooled population. However, retaining the original estimates will allow sensitivity analyses that estimate the impact of the revised exposure estimates on the study findings.

4) Development of common methods of peak exposures

The three studies used different methods to estimate the impact of peak and intermittent exposures. The IOL study did not identify peak exposures to benzene other than by assigning a code for jobs with "high day" exposure that would be well above the average for that job. This study did not use this metric in the statistical analyses, however. The IP study classified exposures qualitatively into 12 categories according to the likelihood whether exposure took place in intermittent peaks, defined by: frequency (daily, weekly, monthly), intensity (1-3 ppm, >3 ppm), and duration (1-15 minutes, 15-60 minutes) (Lewis et al. 1997). The AIP study identified subjects with a likelihood of high exposures qualitatively, those handing 70-100% benzene products or feedstock. The study also made a quantitative estimate by identifying those who had high exposure days, for example when handling concentrated benzene or BTX or drum fillers not using local exhaust ventilation and estimating how many days per year were experienced at that higher exposure. In a separate analysis, the exposure contributed by occasional accidental or historic exposures (not thought to be included in the BE data set) was added to the cumulative exposure and the risk associated with this added exposure was estimated. (Glass et al 2005)

Based on the our understanding of current uptake, distribution and metabolism models for benzene, 15 minute peak exposures are not biologically relevant. They are also almost impossible to assign to an individual with any certainty, particularly in an historic study.

We consider that some qualitative metrics of peak exposure based on objective empirical data can be assigned without requiring a significant investment of time and effort. Examples of qualitative peak measures would be identifying jobs with exposure to products containing more than 20% benzene (similar to one approach in the AIP study), or identifying jobs in which exposure was above a chosen threshold concentration and was experienced in an episodic manner such as those workers assigned to occasional rail car loading. Another example being considered would be flagging those workers with a greater than 50% chance of exposure greater than 5ppm based on the statistical distribution of the data underlying the BEs.

Peak metrics will be examined separately as well as simultaneously with cumulative exposure. Model fit and the magnitude of risk will be compared between peak and cumulative metrics in order to provide insight on the relative strength of association. We also intend to examine the risk for peak-exposed individuals after adjusting for cumulative exposure. We consider that the peak metrics used in the 3 studies can be reworked relatively easily to the proposed peak metrics.

We would value the opportunity to discuss the approach to peak estimations with the SAB after providing further details in the protocol.

C) STATISTICAL ANALYSIS

1) Overview of Statistical Techniques

Statistical analyses will be employed to estimate the dose response relationship between benzene and leukemia as well as leukemia subtypes. The statistical analysis will use commonly employed strategies such as logistic regression as well as graphical approaches to enhance the presentation of results. These analyses will be used to compare results with the original studies, and as screening analyses in the present study. In addition, more flexible techniques that employ smoothing spline functions to represent dose response relationships will be used.

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Conditional logistic regression analysis will be used to account for the matching factors. Since the studies were not uniform in the number of controls selected, the variable matching option will be employed in conditional logistic regression models. Within logistic regression models, both categorical and continuous representation of exposure variables will be used. The advantages of using categorical representations are that no assumptions are implied regarding the shape of the dose response curve, and results are readily presentable. The two main disadvantages are that a certain amount of information is lost by categorizing, and the selection of cutpoints can influence the results obtained. Sensitivity analyses as to the choice of cutpoints can address the latter objection to some degree. The main advantage in using continuous measures of dose response is that all of the data is used. However, in ordinary logistic regression, the use of a continuous exposure variable assumes that the resulting dose response relationship is exponential. This assumption can often be violated in real data.

The preferred analytic approach will be to employ flexible dose response modelling via the use of smoothing spline functions. This technique calls for the specification of "knots" which are somewhat analogous to cutpoints. While ordinary logistic regression with categorical independent variables assume constant risk within a category (or between knots), spline functions avoid this simplifying assumption (Rothman and Greenland, 1998). Dose response relationships between knots can vary through specification of a power function. We anticipate that quadratic and/or cubic splines will allow sufficient flexibility in dose response modelling exercises. Quadratic splines allow successive parabolic representations of risk between knots, while cubic splines allow more flexibility regarding the shape of the dose response function. The choice of the number of knots in spline regression is somewhat arbitrary, and we plan to examine models with different numbers of knots to determine the sensitivity of this parameter on the dose response. When addition of another knot has little effect on the dose response and/or model fit, we would not introduce this additional knot. We will thus seek the parsimonious yet representative model regarding the number of knots.

2) Factors that may Influence Dose Response Relationships

A primary advantage of this pooled analysis will be a more structured and informative analysis of factors that may influence dose response relationships. While each study examined some of these factors individually, a more informative analysis based on larger numbers of cases and controls will be possible in this study. In particular, a larger number of cases and controls will allow examination of these factors by specific LH cancer subtypes.

a) LH cancer subtypes

Existing literature shows that a consistent dose response relationship is found between higher benzene exposures and AML, but not other LH cancer subtypes. Models will be constructed for all leukemias, leukaemia subtypes, NHL, and multiple myeloma. We expect that the ANLL and CLL (FAB designations) will have sufficient cases for statistical analysis. We will not perform analyses when the number of cases falls below 5. We will perform analyses for subtypes with at least 10 cases. For subtypes containing between 5 and 10 cases, we will explore whether regression models exhibit adequate stability to be included in final results. To the extent possible, LH cancer subtypes will be further examined by factors below if there are a sufficient number of cases present.

b) Time course

Existing literature suggests that in situations where benzene has caused excess leukaemia, it may do so in a relatively brief period of 5 to 15 years. Exposure experienced greater than 15 years ago may portend little, if any, excess risk. We will explore various time windows (i.e. we will simultaneously consider effects of latency and lag) to assess whether excess risk of LH cancer subtypes is manifested in similar time windows.

c) Workplace factors

While quantitative estimates of benzene exposure are the focus of this proposal, we intend to examine simpler workplace indices to examine whether there are dose response relationships. These include type

of worksite (e.g. refinery, large terminal, marine, etc.), job type (terminal operator, maintenance, gauger, etc.), and, as stated above, whether benzene exposure is experienced intermittently versus continuously.

d) Exposure metrics

Models will be constructed for different benzene exposure metrics, including cumulative exposure, average exposure intensity, maximum exposure intensity, and peak/intermittent exposure. For cumulative exposure, the effect of revisions to the exposure assessment, described in the previous section, will also be examined.

e) Study

Study-specific results (using analogous cutpoints, knots and smoothing spline functions) will be examined and potential study-specific heterogeneity will be examined for different LH cancer subtypes.

f) Information Quality

A primary aim of the pooled analysis will be to examine the sensitivity of results with respect to information quality. To this end, disease and exposure metrics will carry with them measure of certainty. We will seek to base interpretations and conclusions based on information of the highest quality (see next section).

3) Statistical Analysis Strategy

While a more detailed description of the statistical analysis will be contained in the study protocol, a general strategy is given here and in the next section. Our strategy will be to start statistical analyses that are fairly simple (e.g. graphical results, standard logistic regression) and proceed to those that are more complex (e.g. smoothing spline functions). In parallel, a strategy which starts with all of the data and examines key potential modifiers (e.g. study, time-course, exposure metric, site-type, etc.) will be employed. Sensitivity analyses will be employed relatively late in the process, and will test whether well-validated models are borne out by the more certain (with respect to exposure and disease classification) data. If not, we will focus on the more certain data provided it is based on a reasonable fraction of all data. An overriding strategy in all of our analyses will be internal consistency. That is, we will focus on results that are representative of the data, and will strive to discount results based only small subsets that are not fairly consistent seen within the analyses performed. Standard goodness of fit tests will be run, and the Akaike's information criterion will be calculated and used to guide model selection (Harrell, 2001) from a statistical viewpoint. Residual distributions will also be examined to guard against over (or under) dispersion. Final models will be selected based on fit, internal consistency, biological plausibility, and parsimony considerations.

Our overall strategy will be to start with the pooled data and examine it for marked heterogeneity. If found, we will seek to identify the sources of heterogeneity and evaluate its impact on the interpretation of results.

D) RATIONALE FOR INTERPRETING RESULTS

We expect the precision of this pooled analysis to be greater than that which could be obtained by examining the results of the three subject studies. This is due to both the larger numbers involved and the greater consistency in methods that will be used. By having the three original PI's intimately involved in this exercise, any nuances in any one of the studies is also more likely to be identified.

However, there are remaining uncertainties that cannot be addressed through aggregating cases/controls or standardizing methods. Clearly, distant exposure estimates are less certain than recent estimates, and incomplete work histories cannot be improved upon in a pooled analysis. Early diagnoses, or those

derived from only a death certificate, are likely to be more uncertain than those backed up by morphologic confirmation.

We believe that these uncertainties can be quantitatively assessed through the use of sensitivity analyses. Sensitivity analyses will be used to derive dose response relationships using all cases and controls, and also the cases and controls that are characterized by less uncertainty (e.g. in diagnoses, in exposure, and in both diagnosis and exposure). Where results differ markedly, we would rely more heavily on the results derived from the subjects with less uncertainty, while also recognizing potential losses in precision and representativeness of the study populations. In addition, marked variability identified via sensitivity analyses could suggest a more cautious interpretation, or reliance on measures that do not display such variability. Sensitivity analyses may also suggest that pertinent results only apply to a segment of the population, for example, if sensitivity analyses reveal that only early years of study are responsible for a finding, it would be misleading to interpret the finding as being representative of current day workers.

VI) ETHICAL AND PRIVACY ISSUES

The proposed combined analysis will provide more power to answer the questions originally set out in each of the main studies. Thus the proposal does not seek to use the existing data for a new purpose. Indeed it could be argued that it is simply a continuation of the individual studies. We do not therefore see that it is necessary to seek consent from the existing subjects or next-of-kin. The recruitment of new subjects is not part of this proposal. If new subjects are later added to the study, we recognize that new ethics approvals will be required.

We do however recognize that the ethics and privacy landscape of research has changed over the years of these studies. To this end we will:

1. Seek approval for the combined study proposal from the relevant ethical committees detailed under each study in Section IV.
2. Send only de-identified data to EMBSI for statistical analysis. Cases and controls will only be identified by their study number. Identification data on the individuals will remain with the original study records.
3. De-identify the information obtained about the case's diagnoses, doctor's letters etc, by removing the name of the individual and that of their treating medical practitioner from any material sent to the haematologist.
4. Report only grouped data with cell sizes of greater than 4 so that individuals cannot be identified in subsequent reports and papers.

VII) PROJECT MANAGEMENT/MILESTONES

Upon acceptance of this proposal, CONCAWE would draw up a contract with ExxonMobil Biomedical Sciences, Inc. (EMBSI) for the exercise. EMBSI will execute all necessary subcontracts (viz, with Monash University, Imperial College, University of Colorado, and McMaster's University). CONCAWE will be responsible for coordinating all funding and all reporting to other trade associations, including, but not limited to: API, CPPI, EI, AIP, and CEFIC/APA.

CONCAWE will be provided with brief progress reports every four months during the duration of the project. A draft report of the results will be provided to CONCAWE at the end of month 16 (see time scales and milestones below). Following collation of all comments it is proposed to have a joint meeting with the technical committee and the Scientific Advisory Board to discuss these comments. Following this, a detailed final report will be provided, considering all comments. It is understood that the PI is under no obligation to address each comment in the report, although all feedback is welcome and encouraged.

It is expected that results will also be submitted to peer reviewed journals and presented at scientific conferences. We will again welcome comments and feedback on these articles.

PROPOSED MILESTONES:
Awarding of contract (12/05)
a) DETAILED PROTOCOL + 2 months (2/06)
b) ETHICAL APPROVALS IN PLACE +3 months (3/06)
c) MEETING WITH TECHNICAL COMMITTEE + 3 months (3/06)
d) MEETING WITH SAB + 3 months (3/06)
e) Progress reports: every 4 months (7/06, 11/06, 3/07)
f) PRELIMINARY REPORT +16 months (4/07)
g) Opportunity for comment
h) MEETING WITH SAB +17 months (5/07)
i) FINAL REPORT +18 months (6/07)
j) Publication(s) prepared for peer reviewed literature (9/07)
k) Presentation(s) at scientific conferences (within one year of final report)

VIII) PERSONNEL

Co- Principal Investigator(s): A. R. Schnatter, D. C. Glass, L. Rushton
Exposure Assessment Team: D. C. Glass (lead), T. W. Armstrong, E. Pearlman, S. Lewis, L. Rushton, D. Verma, C. Gray
Leukemia Subtype Classification: R. D. Irons (lead), J. Ryder, M. Sim, A. R. Schnatter
Epidemiologic/Statistical Analysis: A. R. Schnatter (lead), M. Nicolich, L. Rushton, M. Sim

The personnel involved in this proposal are extremely well-qualified to undertake this project. All three original principal investigators are leading this collaborative pooled analysis. These three individuals are close to their own study's data and the investigators shared their expertise in the subsequent studies. There is therefore a history of collaboration between the PIs and they retain a keen interest in benzene/occupational health. Dr. Schnatter has recently authored a review of epidemiologic studies of benzene and leukemia subtypes, was the primary author of industry's submission of the EU existing substances risk characterization on benzene, and has served on EPA, WHO, and other advisory boards regarding benzene. Dr Rushton has recently moved to Imperial College after 6 years at the MRC Institute for Environment and Health. In addition to carrying out occupational related research in the silica and printing industries and the UK armed services, she has been involved in an assessment of the potential risks to the health of the population of benzene in the environment and has an active research programme in systematic review and meta-analysis, including a large industry meta-analysis of chemical workers. Dr. Glass has recently taken over responsibility for the Health Watch cohort, has authored the Health Watch case control study, and has given numerous presentations on the subject (IP conference, Utrecht conference, Munich conference etc.). She is also a member of the ACGIH TLV committee, which considers appropriate threshold limit values for chemical substances.

Dr. Irons is a board certified clinical laboratory scientist and toxicologist and is leading a large collaborative study on benzene exposure in Shanghai China. As part of this project, he is co-founder of JCML – The Joint Clinical and Molecular Laboratory (joint between University of Colorado and Fudan University). He is diagnosing upwards of 50 LH cases per month with independent verification using the WHO scheme as part of this multi-year project. Dr. Ryder is a board-certified hematopathologist, who is also involved in the Shanghai benzene study. He has published on a variety of topics, including the classification of lymphoid neoplasms according to the WHO classification.

Dr's Lewis and Armstrong were the main exposure assessors for the IP and IOL study, respectively, and advised Dr Glass over the AIP exposure assessment and their assistance is critical to the success of this project. Eileen Pearlman assisted Dr. Armstrong in the IOL study and Dr. Lewis in the IP study. Associate Professor Malcolm Sim is head of the Occupational and Environmental Epidemiology Unit at Monash University and has extensive clinical and epidemiologic experience in several studies including

Healthwise, the Australian Aluminum industry cohort, the Australian Gulf War Veterans Study, Arsenic in drinking water. He has recently been appointed study director for the Heath Watch cohort study.

Dr. Nicolich is an experienced biostatistician who has been involved in several publications regarding benzene, particulate matter, ozone, asphalt, and other several other substances. He has extensive experience in applying spline functions, logistic regression, and other modelling techniques to the epidemiologic data. Dr. Nicolich has authored over 200 publications and is adept in the use of regression diagnostics and analysis of statistical fit to arrive at parsimonious dose response models.

Dr. David Verma is the head of the Occupational Health/Environmental Medicine Unit at McMaster University and has recently completed a comprehensive examination of benzene exposures from Canadian service stations and small distribution terminals. His work was not available when the first IOL study was conducted and there is a high probability that this new work may improve the precision of exposure estimates, especially form the Canadian (IOL) study. He was an advisor to the IOM/IRAS data quality review regarding these studies. Professor Chris Gray is Health of Occupational Hygiene at Deakin University and chairs the Academic Board. He was a co-author of the Health Watch case control study and is well known and respected member of the occupational hygiene community in the UK and Australia.

IX) BUDGET

The total number of days of effort for each person involved in this proposal is as follows:

Person	No. Days
A. R. Schnatter	123
D. Glass	85.5
L. Rushton	51.5
T. Armstrong	42
M. Nicolich	37
Systems Analyst	20.5
M. Sim	19
S. Lewis/E. Pearlman	18.5
R. Irons	15
D. Verma	12.5
C. Gray	10.5
J. Rider	8.5

The approximate costs of this project include time and travel as detailed below. We would also recommend setting aside a contingency fund, not included in the estimates below. All costs are in €

Task	TOTAL (€)
Protocol	22599
Disease Re-classification Assemble past info Collate/classify info Develop classification scheme Review info for classifying/classify cases Develop scheme for assigning uncertainty Enter/review classified info..QA etc	77031

Exposure Re-classification Assemble past info Assign like work histories Investigate assumptions behind estimates BE's/K's/etc) Resolve/rationalize intensity estimates Preliminary data review Review info for peaks Assemble necessary info for peaks Assign qualitative peaks Assign quantitative peaks Develop scheme for assigning uncertainty Assign uncertainty scores Apply scaling if justified Enter/review classified info…QA etc.	156087
Statistical Analysis Frequencies/ QA Data polishing Analyses by study, site type, era, time course, etc. Prelim. data review, graphical analyses Logistic regression modelling Smoothing spline function analyses Sensitivity analyses on disease Sensitivity analyses on exposure Overall sensitivity analyses/ data quality assessment	168885
Report writing/review Preliminary report Review/revisions Final draft report SAB/TC presentations Final report Publication(s)	91692
Administration/other	61398
Travel	40338
TOTAL	618030

X) REFERENCES

Armstrong TW, Pearlman ED, Schnatter RA, Bowes SM, Murray N, Nicolich MJ (1996). Retrospective benzene and total hydrocarbon exposure assessment for a petroleum marketing and distribution worker epidemiology study. American Industrial Hygiene Association Journal 57:333-343.

Bennett JM, Catovsky D, Daniel MT et al. (1976). Proposals for the classification of the acute leukaemias: French-American-British Cooperative Group, Br J Haematol 33:451-458.

Cogliatti SB, Schmid U (2002). Who is *WHO* and what was *REAL*?, Swiss Med Wkly 132:607-617.

Crump K (1994). Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates, J Toxicol Environ Health 42:219-242.

Glass DC, Gray CN, Jolley DJ, Gibbons C, Sim MR, Fritschi L, Adams GG, Bisby JA, Manuell R (2003). Leukaemia risk associated with low level benzene exposure, Epidemiology 14:569-577.

Glass DC, Adams GG, Manuell RW, Bisby JA (2000). Retrospective exposure assessment for benzene in the Australian Petroleum Industry. Annals of Occupational Hygiene 44(4):301-320.

Glass DC, Gray CN, Jolley DJ, Gibbons C, Sim MR (2005). Health Watch Exposure Estimates: Do they underestimate benzene exposure? Chemico-Biological Interactions 155-154:23-32.

Greenland S (1999). Useful methods for sensitivity analysis of observational studies, Biometrics 55(3):990-991.

Harrell FE (2001). Regression Modelling Strategies Springer, New York, NY.

Harris NL, Jaffe ES, Stein H, Banks PM, Chan JKC, Cleary ML, et al. (1994). A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group, Blood 84:1361-1392.

Hayes RB, Yin SN, Dosemeci M, Li GL, Wacholder S, Travis LB, Li CY, Rothman N, Hoover RN, Linet MS (1997). Benzene and the dose-related incidence of hematologic neoplasms in China, J Natl Cancer Inst 89:1065-1071.

Lewis SJ, Bell GM, Cordingley N et al. (1997). Retrospective estimation of exposure to benzene in a leukaemia case-control study of petroleum marketing and distribution workers in the United Kingdom, Occup Environ Med 54:167-175.

Miller BG, Fransman W, Heederik D, Hurley JF, Kromhout H, Fitzsimons E (2003). A review of the data quality and comparability of case-control studies of low-level exposure to benzene in the petroleum institute, Institute of Occupational Medicine (IOM) Research Report TM/05/04.

Ottenseimer C (2001). The classification of lymphomas and leukemias, Chemico-Biological Interactions 135-136:653-664.

Paxton MB, Chinchilli VM, Brett SM, Rodricks JV (1994). Leukemia risk associated with benzene exposure in the pliofilm cohort. II. risk estimates, Risk Anal 14:155-157.

Rothman KJ, and Greenland S (1998) Modern Epidemiology Lippincott-Raven, Philadelphia, PA

Rushton L, Romaniuk H (1997). A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom, Occup Environ Med 54:152-166.

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Schnatter AR, Gray CN, Rushton L, Glass DC, Armstrong TW (2002). Comparability and feasibility of enhanced analyses of petroleum industry benzene case-control studies, ExxonMobil Biomedical Sciences, Inc. (EMBSI) Report 2005EMBSI 2454.

Schnatter AR, Bird MG, Nicolich MJ (1996a). Determination of leukemogenic benzene exposure concentrations: refined analyses of the pliofilm cohort, Risk Anal 16:833-840.

Schnatter AR, Armstrong TW, Nicolich MJ, Thompson FS, Katz AM, Huebner WW, Pearlman ED (1996b) Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers, Occup Environ Med, 53:773-781.

Appendix

Incorporation of New Leukaemia Cases

There are 140 cases of leukaemia in the pooled study. Since the original case-control studies were carried out, additional cases of leukaemia have occurred. There are now an additional 25 cases from IOL, 41 from IP and 16 from AIP for leukaemia i.e. 82 new leukaemia cases. There is thus the potential for extending the pooled analysis to include these cases, which would bring the total to 222 cases. . Some advantages and disadvantages of doing this are given below:

Advantages	Disadvantages
More power for cell types	Power gain relatively less for ANLL
More power for subgroup/sensitivity analyses	increased time and cost
Improved time course analysis	Logistical problems in obtaining data
Improved scientific integrity	Data may be less certain
	Loss of corporate memory

There would be an increase in the power of the pooled study for leukaemia, particularly for analyses by leukaemia subtype and for subgroup and sensitivity analyses. It would lead to improved time course analysis. However, it should be noted that the distribution of leukaemia subtypes that are now occurring seem to be different from that of the original studies. Based on preliminary data from the AIP study, a higher proportion of the leukemias will be chronic leukemias particularly chronic lymphatic leukaemia. This may be due to the fact that CLL is a disease of the elderly and the cohorts are rapidly aging. The increase in power will thus be less for the acute leukemias. There are also important resource implications, particularly time and cost, see below, although some of the work could be carried out in parallel with the activities outlined in V(A) and (B) of our main proposal.

Methods for obtaining the data

There are a number of steps common to each study in order to acquire the data for new cases and their controls. These are:
Obtain the necessary ethical approval
Identify cases and select controls
Obtain work histories and confounding information for each case and control
Obtain data for exposure assessment (site histories, exposure control factors, etc.)
Develop new base and modifying factors if appropriate
Allocate base estimates and modifying factors to each line of work history.
Include study subjects in rationalization processes (i.e. common exposure estimates and disease classification).

The processes for carrying out these six steps vary between the three case-control studies, as do the time and resources required for each step. This is partly due to differences between the three countries in requirements regarding ethical issues and the processes for obtaining death and cancer incidence information. Separate flow charts for the three studies are given in Figures 1-3 to illustrate some of these differences.

The IOL study requires collaboration with Statistics Canada and IOL to identify site and work history data before steps 4-6 can be carried out (see Figure 1). In the IP study, collaboration with the Institute of Occupational Health at the University of Birmingham, where the original cohort data are held, is required to identify cases and controls. As shown in Figure 2, obtaining work histories will be complex as there are 4 oil companies involved and most of the records are archived in a variety of locations and of variable format including hard copy and microfilm. Information for terminals not already obtained for the original case-control study will have to be searched for in historical records. For the AIP study, step 1, obtaining ethical approval, is a complex and lengthy procedure, although the other steps are relatively straight forward.

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Timescales and Resources for Obtaining the Data

Overall, obtaining the data for new leukemia cases and their controls will take a minimum of 1 year. The estimated elapsed time for completion (in months) for the six basic steps for each study is given in Figure 4. As can be seen, the time for each step to be completed varies between the three studies. The tasks required for pooling the existing data would also have to be carried out for the new data, i.e. disease and exposure reclassification, and the statistical analyses would need to include the impact of adding the new cases. In addition, the report writing and interpretation will need to address the inclusion of new cases (with respect to differences in cell type distributions, potential differences in uncertainty estimates, etc.). We estimate that these additional processes will add a further 6-9 months to the total time, assuming excellent cooperation from all participating companies.

In addition to input from the Principal Investigators and others from three studies already involved in the pooling of the existing data, the IP study would require a full time research assistant for 1 year and collaboration with the University of Birmingham. The IOL study would require input from hygienists and other personnel from IOL. AIP will require input from a data manager/research assistant in order to aid in data processing, filing, and preserving the anonymity of cases and controls during the exposure assessment process.

Budget Estimate for Including New Cases and Controls

The estimated budget to include new leukaemia cases and controls for the three populations is 492,000 euros. The bulk of this estimate is from the IP study. There are several reasons that the IP study results in a higher estimated budget for updating cases, including the following: (a) there are a larger number of cases, (b) there has been a study handoff, requiring involvement of an additional institution (Birmingham University), (c) the study handoff requires more coordination and administration, (d) some companies requested original records back, (e) necessary involvement of four different companies with turnover of personnel since the original study, (f) uncertain status of original records, particularly work history records from one company, (g) the presence of microfiche records for one company, (h) the original personnel involved in exposure estimating are not available, requiring increased travel costs from other resources. Thus the estimated cost for including the IP population is 288,000 euros. The IOL update is estimated as 134,000 euros, while the AIP update is estimated at 70,000 euros.

A further breakdown of costs (euros) involved is as follows:

Ethics reviews/approval	37,000
Case identification	39,000
Work history assembly	134,000
Assemble EA data	112,000
Assemble data for BE's, K's	19,000
Apply BE's K's	43,000
Aggregate with other cases	7,000
Additional analyses	7,000
Coordination	75,000
Travel	19,000

These costs include additional time for the present investigators, plus estimated time for the following new investigators: Tom Sorahan (Univ. Birmingham), Lorrie Thompson (formerly IOL, retired), research assistant (IP study), data manager (AIP).

A summary of different possibilities is provided below

Scenario	Leukaemia cases (IOL/IP/AIP)	Comment	Cost (euro's)
Original proposal	140 (16/91/33)	Lowest unit cost, highest unit value	618,000
Add IOL	165(41/91/33)	IOL and IP would have similar follow-up dates (1994)	752,000
Add IOL + AIP	181(41/91/49)	Ibid.	822,000
Add IOL,AIP,IP	222 (41/132/49)	Most difficult logistically	1,120,000

Other lymphohaematopoietic cancers

In addition to additional cases of leukaemia, there is an opportunity for including other lymphohematopoietic cancers, such as multiple myeloma and non-Hodgkin's lymphoma (NHL) in the IP study. Some of these tumours would be classified along with CLL in the new WHO scheme. This would provide an opportunity to explore the relationship between exposure to benzene and these diseases. The exact numbers of cases of the diseases are currently unknown but, general estimates (based on expected incidence ratios) are given. For NHL, in addition to the 8 cases in IOL and 31 cases in HW, it is estimated that an additional 20 and 14 cases would have occurred in the IOL and AIP studies respectively. In addition 132 cases are estimated for the IP study (there are no NHL cases in the IP case control study). Thus there would be an additional 166 cases in addition to the 39 for which exposure estimates have been made. These would need to be matched to 664 controls for 830 new study subjects. For MM, in addition to the 7 cases in IOL, and 15 cases in HW, it is estimated that an additional 8 cases occurred in each study. In addition, 45 cases are estimated in the IP study. Thus, an additional 61 cases and 245 controls, or 306 study subjects could be included. This would result in an additional 1136 study subjects. Data collection, exposure assessment and analysis would thus be time consuming and costly.

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SUGGESTED NOMINATIONS for Science Advisory Board

We suggest that CONCAWE convene a Science Advisory Board for this project. We suggest that the following individuals may merit consideration from CONCAWE:

John Cherry (Exposure Assessment)
Dick Heederick (Exposure Assessment)
Charles Poole (Epidemiologic Analysis)
Richard Larson (Haematology)
Fintan Hurley (Statistical Analysis)
Brian Miller (Statistical Analysis)

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BIOGRAPHIES

THOMAS W. ARMSTRONG

Tom Armstrong received his B.S. in Chemistry from Drexel University in 1974 and an M.S. in Environmental Health, also from Drexel University in 1978. He expects to complete requirements for his Ph.D. in Environmental Engineering at Drexel University in September, 2005. He has been active in the American Industrial Hygiene Association Exposure Assessment Strategies Committee, and its modeling and statistics subcommittees. He has also served as lead investigator on a quantitative exposure assessment for a petroleum marketing and distribution workers epidemiology study and provided supporting advice on the techniques developed to other studies. He completed a critical review of the literature on worker exposure, public exposure, and ambient air levels of benzene around service stations and fuel distribution terminals, which was used in discussions of air contaminant regulations with Environment Canada. He has also prepared a number of technical reports, including: Exposure Assessment for Polycyclic Aromatic Compounds; Industrial Hygiene Sampling Data Interpretation; A Review of Environmental Tobacco Smoke and Health Implications for the Workplace. Ongoing activities involve statistics of monitoring data, predicting modeling of exposure (especially for occupational and consumer applications), stochastic approaches to exposure analysis, and quantitative risk assessment for Legionella.

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DEBORAH C. GLASS

Deborah Glass has an MA in Natural Sciences from Cambridge University, a Post-Graduate Certificate of Education from Leicester University, an MSc in Occupational Safety and Hygiene from Aston University (all in the UK) and a PhD from Deakin University Australia. In addition, she has professional qualifications including the British Examining Board in Occupational Hygiene Certificate and Diploma.
She was appointed as a consultant Occupational Hygienist at the Institute of Occupational Health, University of Birmingham and for 4 years carried out most of the occupational hygiene consultancy service offered by this Institute. In 1989 she became a lecturer in occupational hygiene, carrying out teaching, research and consultancy. In 1995, she joined the Department of Public Health and Community Medicine at Melbourne University to carry out retrospective benzene exposure assessments for a case-control study nested in the Health Watch cohort. She was appointed a Research Fellow in 1998, at Monash University Department of Epidemiology and Preventive Medicine and became Senior Research Fellow in 2005. Research projects include: care of the Health Watch Cohort, occupational exposure assessments for a prostate cancer study and a childhood ALL study; non-occupational BTEX exposure in the general community in Melbourne; exposure assessment for the Australian Gulf War Veterans Study. She was a member of the Scientific Advisory Committee for the DVA sponsored SHOAMP Health Study. She has presented many times at occupational hygiene and epidemiological conferences authored or co-authored over 50 reports and peer reviewed publications and regularly reviews papers.

She has served on organizational and scientific committees for AIOH, ISEE, EPICOH and Exposure Assessment Conferences. Since 2002, she has been a Senior Lecturer at Deakin University Faculty of Chemical and Biological Sciences acting as Unit Chair for the Post Graduate Certificate and Diploma courses in Occupational Hygiene.

She is a member of the Australian Institute of Occupational Hygienists (AIOH), and sits on Council and chairs the Education subcommittee; a member of the British Occupational Hygiene Society (BOHS) and the American Conference of Governmental Industrial Hygienists (ACGIH), and is an applicant member of the ACGIH TLV standards setting committee.

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CHRISTOPHER N. GRAY

Chris Gray has a Bachelors degree in Chemistry (Lancaster, UK), a Masters degree in Pollution Control (Leeds, UK) and Ph.D. in the Occupational Hygiene of Welding (Bradford, UK). He is also a Certified Industrial Hygienist of the ABIH. He is Professor of Occupational Hygiene and Industrial Toxicology at Deakin University Australia. He has worked in the chemical industry, in a government environmental health department and in academe. While working at the Institute of Occupational Health (Birmingham, UK, 1982 – 89) he carried out the exposure assessment for various research projects including: a multi centre cohort study of cancer among welders (International Agency for Research on Cancer); a cohort study of neurobehavioral effects of solvents among painters (Health and Safety Executive, UK), and a case control study of renal disease (Health and Safety Executive). He also helped to develop a protocol for the study of the neurobehavioral effects of organic Solvents on behalf of the World Health Organization. Other research over this period involved dermatitis related to pine resins. Since moving to Deakin University, Australia, in 1989, Chris has been involved in the research on the health effects of synthetic mineral fibers, and fume and gas emissions from electric arc welding. He has been involved with the Health Watch case control study since its inception and carried out work related to the methodological issues in the estimation of benzene exposure of personnel in the Australian petroleum industry. Chris has over 110 publications including approximately 40 in refereed journals.

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RICHARD D. IRONS

Richard Irons is Professor and Director of the Sino-US Joint Clinical and Molecular Laboratory at Fudan University in Shanghai, China. He is Professor of Toxicology in the School of Pharmacy and Professor of Pathology in the School of Medicine at the University of Colorado Health Sciences Center in Denver, Colorado, USA and is Professor of Pathology at Fudan University. Dr. Irons holds degrees from the University of the Pacific, the University of California San Francisco and the University of Rochester School of Medicine. He is board-certified in toxicology and clinical laboratory sciences and is a former member of the board of directors of the American Board of Toxicology. He is a former leader of the Carcinogenesis and Primary Prevention Program of the University of Colorado Comprehensive Cancer Center, has served as chairman of the Toxicology Study Section of the National Institutes of Health and as a member of the Toxicology Information Program of the National Academy of Sciences. He has been a consultant to a number of governmental organizations and agencies including The U.S. Environmental Protection Agency, the U.S. Food and Drug Administration, California Department of Health Services, NATO, and the governments of the United States, Canada, Great Britain and China. For the past 25 years Dr. Irons research has focused on understanding the pathogenesis, causes and mechanisms of leukemia and lymphoma. He has authored or co-authored over 150 articles, abstracts, and book chapters on subjects ranging from occupational carcinogenesis, hematotoxicity, immunotoxicity, and virology. Dr. Irons is currently Principal Investigator on two international projects to study 1) the differential diagnosis, pathogenesis and mechanisms of leukemia and lymphoma in Shanghai, China and 2) the health effects associated with benzene exposure. This project represents a formal collaboration between the UCHSC and Fudan University and is sponsored by the Benzene Health Research Consortium.

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MARK J. NICOLICH

Mark Nicolich received his Ph.D. in Statistics from Rutgers University in New Brunswick, NJ in 1974, and his thesis topic was non-linear urban air pollution models. He also holds a Masters of Science in Statistics from Rutgers, and a Masters of Science in Engineering Science and a Bachelor of Mechanical Engineering from Rensselaer Polytechnic Institute, Troy, NY. Dr. Nicolich was tenured at Rider University in Trenton, NJ, and held an Associate Professorship at University of Medicine and Dentistry of New Jersey. He has been a Statistician at ExxonMobil Biomedical Sciences, Inc. since 1979.

His areas of interest are model building and fitting, interpretation of data, and general application of basic statistics including multivariate analysis, experimental design, and time series analysis. Dr Nicolich is well versed in current statistical techniques such as general additive models, mixed effects models, Bayesian analysis techniques, and robust methods. His applications and research are in the areas of the life sciences with specific experience in epidemiology and environmental health models. He is currently active in the model building and evaluation of the various areas particulate matter (PM) research, modeling responses to benzene exposure, low dose extrapolation modeling, and the initiative to reduce the number of animals used in laboratory testing.

Dr Nicolich has approximately 50 publications in the peer-reviewed literature and a large number of refereed and invited conference presentations that reflect the application of statistics to the physical and biological sciences. He is part of the evaluation and testing group for the EPA Benchmark Dose Program and a reviewer for Environmental Health Perspectives chiefly for statistical modeling papers.

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LESLEY RUSHTON

Lesley Rushton is a medical statistician and epidemiologist with a degree in Mathematics from Oxford University and an MSc in Statistics from Sussex University. She holds a PhD in methodological aspects of epidemiological studies gained at the Institute of Cancer Research, London and was awarded an OBE for service to occupational health in 2004. She has worked in several UK academic institutions including the Universities of Greenwich and Nottingham. Since 1998 she has been working at the Medical Research Council Institute for Environment and Health in Leicester, where she leads a core research group providing epidemiological and statistical skills, and developing multidisciplinary research programmes into occupational and environmental causes of ill health. She will shortly be transferring her research to Imperial College, London.

Lesley has specialised in health studies in various industries, including a long involvement with the petrochemical industry carrying out research into mortality and cancer incidence, and case-control studies. Other recent occupational research includes studies of lung cancer and silicosis in the silica sand industry and dermatitis in the printing industry. She has also carried out several studies in the area of indoor and out door air pollution, particularly in relation to children's health. An on-going project is investigating the incidence of pesticide related ill health reported in the primary health care sector. Systematic review and meta-analysis methodology is a particular interest with on-going projects on cross-design synthesis, in particular of epidemiological and toxicological studies, and a systematic review and meta-analysis of the large number of epidemiological studies of mortality and cancer incidence in chemical industry workers. Membership of UK government committees includes the Committee on Toxicity (current) and the Industrial Injuries Advisory Council (10 years).

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JOHN RYDER

John Ryder is an Associate Professor and Director of Hematopathology in the Department of Pathology at the University of Colorado Health Sciences Center, Denver Colorado, USA. He is also Section Head of Clinical Hematology in the Division of Pathology and Laboratory Medicine at UCHSC. He holds degrees from Harvard University and the University of Colorado Health Sciences Center. Dr. Ryder completed internship and residency programs in pathology at the University of Colorado and a fellowship in hematopathology at the University of Cleveland. Dr. Ryder has published a variety of peer reviewed publications on a variety of topics including the classification of lymphoid neoplasms according to the WHO criteria, gating strategies for immunophenotyping of leukemia and lymphoma, myeloid/NK cell neoplasms, and ex vivo mobilization of CD34-positive progenitor cells from bone marrow and peripheral blood. He is currently a co-investigator on the Shanghai Health Project.

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8/10/05

A. ROBERT SCHNATTER

Rob Schnatter has a B.S. degree in Biology and an M.S. in Biostatistics from Rutgers University and the University of Pittsburgh, respectively. He also holds a Dr.PH degree in Epidemiology from Columbia University. Following his work at the National Center for Health Statistics, he spent six years at Union Carbide as Corporate Biostatistician. During this time, he organized worker health surveillance systems and investigated health effects in several product lines. He authored papers on carbon products workers, brain cancer in petrochemical workers, and health surveillance findings in chemical workers.

In 1987, Rob joined Exxon Biomedical Sciences, Inc. Occupational Health and Epidemiology Division as a Senior Epidemiologist, where he initially established a company-wide mortality surveillance system. He later became Section Head of the Epidemiology section, while authoring studies on Imperial Oil workers, reproductive health surveillance in laboratory workers, benzene risk assessments and the use of epidemiologic data in risk assessment. During this time, he was the primary author of an extensive benzene risk assessment which served as industry input to the EU existing substances program. He also authored reports for CONCAWE on benzene air quality standards.

More recently, Rob has assumed the role of Senior Scientific Advisor for ExxonMobil Biomedical Sciences and is a co-investigator for a large industry-funded study on benzene health effects in Shanghai, China. He is a visiting Senior Scientist at the Joint Clinical Molecular Laboratory (JCML) at Fudan University. He has served on several government advisory panels considering health risks from benzene exposure. He is a previous chairman of the American Industrial Health Council's Epidemiology Subcommittee, is active in a number of professional societies, trade associations, and serves as a frequent journal reviewer for occupational epidemiology studies. He is currently on the Environmental Protection Agency's Environmental Health Committee's Science Advisory Board and is an external advisor to the U.S. National Death Index.

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MALCOLM SIM

Malcolm Sim is an occupational physician who is Head of the Centre for Occupational and Environmental Health in the Department of Epidemiology & Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences at Monash University in Melbourne Australia. He has a medical degree from the University of Melbourne, an MSc London School of Hygiene and Tropical Medicine, a Graduate Diploma in Occupational Hygiene from Deakin University, and a PhD from Monash University. In 1993 he spent a post-doctoral year in occupational epidemiology at the National Institute for Occupational Safety and Health (NIOSH) in the USA. He has Fellowships from the Faculties of Occupational Medicine and Public Health Medicine of the Royal Australasian College of Physicians and the Faculty of Occupational Medicine of the Royal College of Physicians, London.

Since returning to Australia from the USA in 1994, he has developed an active research program in occupational and environmental epidemiology, currently comprising about 20 research staff, with several studies investigating risk factors for occupational and environmental disease, occupational disease surveillance, exposure assessment in epidemiological studies and veteran health research. He is the Principal Investigator for the Healthwise cohort study of cancer, death and respiratory morbidity in aluminium industry workers, the Health Watch cohort study of petroleum industry workers and the Australian Gulf War Veterans' Health study. He is a regular reviewer of research grants and papers for international and national scientific journals and grant bodies.

Malcolm is an Associate Editor of the international journal, *Occupational and Environmental Medicine*, a member of the Scientific Committee for Occupational Epidemiology of the International Commission of Occupational Health and a member of the Human Research Ethics Committee of the Cancer Council Victoria. He was also the Chair of the Organising Committee for the 17th International Symposium on Epidemiology in Occupational Health, which was held in Melbourne, Australia in October 2004. He has been a member of the Scientific Task Group on Inorganic Arsenic for the International Program on Chemical Safety (IPCS), and is undertaking an international survey of the use of human data in chemical assessments, part of the Human Data Initiative of IPCS. He sits on Research Advisory Committees for the National Centre for Environmental Toxicology, the National Centre for Occupational Contact Dermatitis and the Australian Centre for Posttraumatic Mental Health. He has had several roles in the Royal Australasian College of Physicians, which awarded him a College Medal for Outstanding Service in 2003.

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DAVID K. VERMA

Dave Verma is a Professor in Family Medicine and Acting Director of the Program in Occupational Health and Environmental Medicine at McMaster University in Canada. He is also the founding Director of the Occupational and Environmental Health Laboratory, which has been accredited by the American Industrial Hygiene Association (AIHA) since 1981. Dave was born in India and obtained his B.Sc., M.Sc. and Ph.D. degrees in Engineering from University of Wales in UK. His professional certifications include: P.Eng (ONT); CCM (UK); CIH (USA) and ROH (CAN). Dave has many years of experience in occupational hygiene and occupational and environmental health, working with industry, government and the university. Prior to coming to McMaster in 1978, Dave worked as an Occupational/Industrial Hygienist with the provincial governments of Ontario, Saskatchewan and Alberta for 8 years and for several years within the mining industry in the UK and India. He is now involved in research, education and provision of services. Dave's research interests include: dust and fibres, PAHs, diesel exhaust, mining environments, benzene and hydrocarbons, metalworking fluids, Construction Industry, air pollution, sampling and analysis and hygiene aspects of epidemiological studies. He has received 48 research grants and contracts and has over 115 publications (papers and technical/research reports) of which 83 are in peer-reviewed journals. Dave has served as President, Committee Member, Chief Examiner and Editorial Board Member of national and International Hygiene Associations/Journals. He has received several scholarships including the 1966-69 University of Wales Postgraduate Research Scholarship and several awards including the 1988 AIHA's E.J. Baier Technical Achievement Award (as a member of the Laboratory Accreditation Committee), 1996 Hugh Nelson Award of Excellence in Occupational Hygiene, 1997 OSH Canada's Award of Excellence, 1999 ACGIH's Meritorious Achievement Award and 2001 AIHA's Donald E. Cummings Memorial Award for outstanding contribution to the knowledge and practice of occupational and environmental hygiene. In 2004, Dave was elected a Fellow of the AIHA.

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