

Technical Annex to the CONCAWE Request for Proposal:

Benzene Low Exposure Case-Control Studies ---- Data Consistency Review

Goal of Review

To characterize the data used in four major studies of leukemia in oil distribution and refinery workers with respect to aspects important for the outcome of the studies of interest. **Introduction**

Four cohort studies of oil distribution and refinery workers have reported on mortality patterns. These are the Institute of Petroleum (IP) study in the United Kingdom (Rushton 1993a, Rushton 1993b), the American Petroleum Institute (API) study in the United States (Wong 1993), the Canadian study (IOL, Schnatter et al. 1996) and the Australian Institute of Petroleum's (AIP) Health Watch study (Bisby et al 1993, Gun et al. 2000). The Health Watch study also reported cancer incidence. These studies are based on workers in the petroleum industry, where daily exposures are generally well below 5 ppm, and for whom potential exposure is from a mixture of volatile organic compounds.

In all these cohorts, nested case-control studies have been carried out (Rushton and Rumaniuk 1997a; Wong et al., 1999; Schnatter et al., 1996; Gray et al, 2001). Two studies (Rushton 1997a and Gray 2001) reported on both deceased and incident cases. Main characteristics of the case-control studies and the cohorts they were nested in are provided in Table 1.

Because all four nested case-control studies used slightly different methods and procedures, it is important to document the studies' similarities and differences prior to combining the data for a pooled analysis. Differences that are important to recognize include case definition and ascertainment, exposure assessment, selection and information biases, and confounding.

There is some consensus on the association of benzene exposure and acute myeloid leukemia (AML), and on the level of exposure to benzene where the effect manifests itself. However, there are no firm conclusions on the effect of benzene on other types of leukemia.

Nested case-control studies are conducted to allow for more efficient assessment of the effect of exposure and confounders. Several separate publications report on procedures used for exposure assessment (Lewis 1997 for IP, Smith 1993 for the API study, Armstrong 1996 for the Canadian study, Glass 2001a,b for Health Watch).

Of additional interest is the comparison of diagnosis of leukemia from death certificates, cancer registration and histological reports in the UK by Rushton (1997b). Differential ascertainment by these different sources may affect the overall conclusions of each study.

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 acute myeloid leukemia (AML). Results for other leukemia subtypes and the exposure levels associated with these risks are not consistent among the studies. The purpose of the data consistency review is to elucidate the reasons for the inconsistencies.

It can be difficult to draw strong conclusions based on studies of leukemia subtypes, because of the studies' limited power due to small numbers 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 cases and the smallest only 29. 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, data collection procedures (especially for obtaining work history data), quantitative exposure assessment, and the analytical methods used. Describing and comparing these study elements among the four studies may help explain differences in their findings.

Describing the studies and determining the quality of the various elements of the studies will also allow for an informed decision concerning the possible pooling of the data. Data quality regarding the following aspects of the case control studies will be defined by the reviewer prior to beginning the systematic review of the specific studies. The Scientific Advisory Board will approve these quality criteria in a timely manner before the actual review.

The five main aspects of the case control studies the investigator should focus on include:

- 1) Cohort identification and documentation of the methodology of the cohort assembly, including completeness of cohort identification, inclusion and exclusion criteria, 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 processing and data analysis, including methods and models used, adjustment of confounders, potential confounders not adjusted for.

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 lists some important questions to consider during the data quality 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 meant to be responded to point-by-point. The purpose of both Table 1 and Table 2 is to allow potential investigators to better understand the scope of the RFP before deciding to respond. The reviewer chosen may also use this list to assist them in developing criteria for determining data quality at the beginning of this review. Investigators should include a detailed budget and timeline in their response to this RFP.

Literature

Armstrong TW, Pearlman ED, Schnatter AR, Bowes SM 3rd, Murray N, Nicolich MJ. Retrospective benzene and total hydrocarbon exposure assessment for a petroleum marketing and distribution epidemiology study. *Am Ind Hyg Assoc J* 1996;57:333-334.

Bisby JA. Health Watch, the Australian Institute of Petroleum Health Surveillance Program, 9th report. Department of Public Health and Community Medicine, University of Melbourne, 1993.

Glass DC, Adams GG, Manuell RW, Bisby JA. Retrospective exposure assessment for benzene in the Australian petroleum industry. *Ann Occup Hyg* 2001a;44:301-320.

Glass DC, Gray CN. Estimating mean exposures from censored data: exposure to benzene in the Australian petroleum industry. *Ann Occup Hyg* 2001b;45:275-282.

Glass DC, Gray CN, et al. Leukemia risk associated with low-level benzene exposure. *Epidemiology*, 2003;14:569-577.

Glass DC, Gray CN, et al. Validation of exposure estimation for benzene in the Australian petroleum industry. *Toxicol Indust Health*. 2002;17:113-127.

Gray C. Lympho-haematopoietic cancer and exposure to benzene in the Australian petroleum industry. Technical Report and Appendices. Monash University and Deakin University, June 2001.

Gun R, Pilotto L, Ryan P, Griffith E, Pratt N, Ewing S, Dimitri H, Phillips S, McDermot B. Health Watch, the Australian Institute of Petroleum Health Surveillance Program, Eleventh Report. Department of Public Health, Adelaide University, South Australia 2000.

Lewis S, Bell GM, Cordingley N, Pearlman ED, Rushton L. Retrospective estimation of exposure to benzene in a leukemia case-control study of petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med* 1997;54:167-175.

Rushton L. Further follow up of mortality in a United Kingdom oil distribution center cohort. *Br J Ind Med* 1993a;50:561-9.

Rushton L. A 39 year follow up of the United Kingdom oil refinery and distribution centre studies: results for kidney cancer and leukemia. *Environ Health Perspect* 1993b;101(suppl 6):77-84.

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

Rushton L, Romaniuk H. Comparison of the diagnosis of leukemia from death certificates, cancer registration and histological reports – implications for occupational case-control studies. *Br J Cancer* 1997b;75:1694-1698.

Schnatter AR, Katz AM, Nicolich MJ, Theriault G. A retrospective mortality study among Canadian petroleum marketing and distribution workers. *Environ Health Perspect* 1993;101(suppl 6):85-99.

Schnatter AR, Armstrong TW, Nicolich MJ, Thompson FS, Katz AM, Huebner WW, Pearlman ED. Lymphohematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occup Environ Med* 1996;53:773-81.

Smith TJ, Hammond SK, Hallock M et al. Health Effects of gasoline exposure. I Exposure assessment for US distribution workers. *Environ Health Perspect* 1993;101(suppl 6) 13-21.

Wong O, Harris F, Smith TJ, Health effects of gasoline exposure: II Mortality patterns of distribution workers in the United States. *Environ Health Perspect* 1993;101(suppl 6): 63-76.

Wong O, Trent L, Harris F. Nested case-control study of leukemia, multiple myeloma, and kidney cancer in a cohort of petroleum workers exposed to gasoline. *Occup Environ Med* 1999;56:217-221.

Table 1. **Study characteristics**

	IP (Rushton et al)	API (Wong et al)	IOL (Schnatter et al)	AIP (Gray et al)
Case source cohort study: industry segments	UK oil distribution center workers	US Land based and marine distribution workers, potentially exposed to gasoline	Operating segments of a petroleum company	Marketing, distribution, upstream refining
Number of sites	Oil distribution centers from 3 UK companies	30 record location centers	89	235
Cohort size	23 306	18 135	34 597	17525
Inclusions/exclusions	> 1 yr empl 0101 1950-3112 1975	1 yr empl between 1946 and 1985	1) All active empl and annuitants 0101 1964 2) all new regular empl hired 0101 1964 – 3112 1983	Being employed in Australian Petroleum industry at 1980 or later for at least 5 years.
Follow up period	0101 1950 -3112 1975	0101 1947 – 3112 1989	0101 1964 – 3112 1983	0101 1980 – 3112 1998 (mortality) 3112 1996 (incidence)
% Deceased	16.8 %	26.3 %	11 %	5%
Case Definition	Cohort members who died before 010193 and had mention of leukemia, or had cancer registration of leukemia	Land based and marine distribution workers	In cohort, died in follow period from leukemia and ever worked in marketing, distribution, marine or pipeline segments	Men in Health Watch cohort. No definition of cohort given
# Cases (type)	91 (decedent &	35 (decedent)	29 (decedent)	79 (decedent &

	incident)			incident)
#Controls/Case	4	5	4	5
Matching criteria	Company, age alive at case ident. data	Alive at time of death case, company, date of birth +-2 yrs, sex	Decade of birth, alive at cases death, frequency matched	Year of birth, alive at case dx
Leukemia subtypes analysed	ALL, CLL, AML, CML	AML, multiple myeloma	Leukemia, NHL, multiple myeloma.	NHL, MM, CLL, CML, ALL, AML
Source of work history	Personnel records and pension fund, medical records interviews	Hard copy personnel/work history records	Hard copy personnel records	Computerized company job history and interview of case or proxy
Exposure period covered	1909 -1993	?	1909-1983	1940ies –1998
Basis for exposure estimates	Benzene measurements, benzene content in petroleum (3%)	Total hydrocarbons, benzene is estimated 1.6 %.		Task were linked to exposure data and literature data and extrapolated
Exposure measures	Ppm, ppm-years, peaks, skin	For gasoline: duration of exposure, cumulative exposure, frequency peak exposure, time first exposure	ppm (8h TWA) benzene and total hydrocarbons, ppm-years, mean ppm, maximum intensity, dermal exposure potential	PPM, duration, cumulative dose, grouped in quintiles
Lagging	5-10 yrs		5-10-15 yrs	5,10,15 years
Analysis method		Logistic regression		several
Confounders adjusted for				

Table 2:

Data Element	Question/Concern
Data Acquisition and Extraction from Source Files	Errors; Check (10%?) sample
Cohort	Uneven participation over different jobs or areas within and across studies Selection bias Loss to follow-up Open enrollment (Cole) Effect of different entry criteria on censoring Calendar years of entry to the cohort, average/median years of follow-up, corroboration of full ascertainment of all eligible members
Cases	Does case definition vary across studies? Under-ascertainment of non-fatal cases in studies using only mortality Were cases pathologically verified? Cancer registry completeness Validity of death certificate data, especially regarding leukemia subtype diagnosis Longitudinal consistency of diagnosis Differences in disease staging in study cases vs. comparison population cases (possibly indicating increased screening in oil distribution/refinery workers vs. the general population) Impact of active vs. passive surveillance Specificity of diagnosis on death certificates vs. cancer registry Sources for active identification of cases What if benzene exposed cases are all included and non-exposed cases are missing? Impact of incidence vs. mortality Comparison of relative incidence of leukemia subtypes (in comparison population?)
Controls	Control selection, matching criteria, technique for selecting

Work history	Are there differences in data sources for cases and controls? Interviewer bias? Recall bias in those interviewed about work history ? Is the proportion of proxy interviews the same in cases and controls? Is there varying completeness/ quality of computerized or hard copy work history records within studies? Any potential missclassification?
Exposure assessment	Are there differences in categorization of jobs/tasks across studies? Distribution of cumulative dose within and across studies Impact of different type of exposure measurements across studies How were exposures quantified across studies? Validity of techniques used in exposure assessment - Issues regarding read-across between sites, time periods, products (% benzene), and even countries. Applied justification criteria should be retrieved. - Are there indications that homogeneity was checked and confirmed for exposure data sets collected for a given job class? - What was the data availability per site, were there data for each site included in the studies – or better, for what proportion of included study sites were there measured data? - How were local circumstances, such as average wind speed, characterised? - How were exposure data registered and presented? [cfr. NVVA brochure for data registration in NL]. Were survey reports available? - How were data below the detection limit treated? What were the detection limits?
Analysis	Effect of limitations of internal comparisons Are there differences in confounders adjusted for across studies? Are there additional potential confounders that were not adjusted for? Completeness of confounder information (especially smoking) within each study? Differences in measurements of confounders across studies?

Analysis strategy for cases with non-specific leukemia diagnosis (eg, acute leukemia, lymphoid leukemia)

Was the analysis appropriate for the type of matching used

Was the specificity of information available, and/or the use of such information in the analysis model sufficient to prevent residual confounding.