Memorandum

To: IHF Chromium Chemicals Health and Environmental Committee

CC:

From: Marianne C. Kaschak

Date: July 3, 2001

Re: Cohort Mortality Study of Four Chromate Production Facilities – INTERIM REPORT

See Attached

JUL 2

Cohort Mortality Study of Four Chromate Production Facilities, 1958 - 1998: INTERIM REPORT

Applied Epidemiology, Inc.
July 1, 2001

Following is a brief summary of project tasks accomplished as of June 30, 2001. The focus of our efforts over the past months has been on two major tasks: establishment of the final job exposure matrices for each facility; and refining and verifying the analytical tools to conduct standardized mortality ratio (SMR) analyses using time-dependent individual exposure estimates. Completion of both tasks was complicated by the departure of our data manager and exposure assessment expert, Bob Austin. Bob kindly scheduled his leaving to coincide with the completion of this study, but with the delays encountered in obtaining all necessary study data from some facilities, he could no longer postpone his departure. We are fortunate to have been able to recruit earlier this year, before Bob left, two very talented data manager/analysts, Annie Skillings and Rachel Gross. Annie and Rachel have made remarkable progress coming up to speed with the study, the study data and our analytical tools, so that any delays resulting from the transition have been minimal.

Data Acquisition

As reported in January, data acquisition was officially completed for all four participating plants, with the exception of some gaps and corrections. As of June 15, 2000, all expected corrections, verifications, and answers to data-related questions have been received.

The preliminary SMR analyses presented last fall had been derived using United States mortality rates as the referent group. For Germany, mortality rates had to be constructed from census data, and converted into a format and grouped according the specific cause of death categories used in the United States (and Texas and North Carolina) mortality rate files. All German mortality rate data have been acquired and have been prepared for the final analyses, including full rates for Germany overall and lung cancer rates for North Rhein Westfalen (the state in which both Bayer plants were located).

Data Editing and Database Construction

All cohort data received by AEI to date have been edited and entered into our ProQuest database management system. No further edits, changes or corrections are anticipated. Individual plant modules (standardized overall for the study) are being maintained so that plant-specific analyses may be conducted, or that individual plant data may be separately archived or returned to the companies (with data that we are prohibited by law to share, such as cause of death data, removed).

Exposure Data / Job Exposure Matrix (JEM)

Construction of the job exposure matrices (JEMs) recently has been completed for each facility. As reported in the previous interim report, each job had been mapped to specific work areas, thus linking work histories for each employee to specific exposure measurements made within discrete areas and calendar periods (the axes of the matrix). However, it was noted in the previous report that there were a number of issues to resolve before being able to conduct mortality analyses by exposure categories. Specifically, the following were noted:

1. For periods identified or identifiable as upset conditions/accidents, multiple repeated measurements need to be summarized so that exposure estimation includes but does not overweight these incidents (similar for periods identified during rebricking kilns or other scheduled maintenance);

2. JEM cells with sparse or no exposure data will need to be filled with imputed values using a number of available approaches such as aggregation, interpolation, etc.; and

3. Harmonization of measurements using different measurement techniques (e.g., Bayer urinary chromium measures include both creatinine-adjusted and non creatinine-adjusted values).

The following represent the approaches taken to address each of the issues, respectively:

1. Multiple measures surrounding upset or other unusual conditions were reduced to the single highest measurement recorded such that the upset condition would be represented in the data as a real potential exposure, but that such an occurrence would not dominate the exposure estimation for that area or time period. Most values removed from calculations were recorded within a few days following the peaks.

2. Sparse (or no) data in specific JEM cells is a common problem, with several alternative approaches suggested in the literature. For this project, the research team developed a running average algorithm. For the first year of the JEM, data for each year/work area cell are added to the data for the following year and a geometric mean is computed based on the two years of data. For the second year and all subsequent years, data for each year/work area cell are added to the previous year and the successive year and a geometric mean is computed based on three years of data, provided that each year/work area cell contained a minimum of three exposure values. For year/work area cells with fewer than three exposure values, the algorithm looked for the nearest cell with at least three measurements and added the data from these "anchor" cells (i.e., cells with at least three measurements) to the data in between the anchor cells and generated a geometric mean. This approach to imputation fills sparse or vacant cells, based on the nearest years' information. The effect of this approach is to reduce the variability (often considered "noise") over time, as well as fill gaps and reduce the reliance upon small numbers of observations occurring in any year/work area cell.

Before applying this algorithm for filling gaps and sparse cells, and based on extensive descriptive analyses of exposure measurements by work area and over time, we determined that several work areas defined had relatively or very low exposures. Comparing these areas, we were able to detect no differences or patterns between areas, other than apparently random variability. Therefore, we decided to combine the exposure data from these areas, resulting in more stable, but still low, exposure estimates. These low-exposure areas also differed considerably from all other areas with more substantial exposure or with some discernable trend over time. The remaining areas, as well as the combined low-exposure area were then processed by the gap-filling algorithms to produce the final JEMs for each plant.

3. The harmonization of urinary with air data proved to be a study in itself. Personal air data were very sparse for the German plants and urine samples were never taken at the U.S. plants. After reviewing the published medical literature on urinalysis vs. air monitoring data, including alternatives for standardizing urinalyses using specific gravity or creatinine adjustments, we conducted extensive statistical analyses on the data available to us (from Bayer) for the years where both air and urine data were available. These analyses included crude ecologic comparisons of all urine samples and all air samples for years in which both existed as well as ecologic comparisons matching air and urine data by exposure area and year and by exposure area within the same month and year. Additional analyses compared air and urine samples for study subjects matching on year. There were very few air and urine samples taken within the same month for the same study subject. A consistent relationship between air and urine did not emerge from these analyses, perhaps due to the lack of matched samples. We elected to convert air data for the U.S. plants to urine, rather than converting urine data for the German plants to air, both for a pragmatic reason (more urine data are available than personal air data) and a theoretical purpose (urine data are presumably a better measure of exposure to study subjects). We used exposure equivalents for carcinogenic substances (EKA) published by the Deutsche Forschungsgemeinschaft[1] to calculate a conversion factor to transform air data for the U.S. plants to urinary samples. This conversion factor was roughly equivalent to the ratio of the urine means to personal air means when the air and urine samples were matched on exposure area and month. Clearly, much more work is needed to clarify the relationship between air and urinary measures of chromium, especially in light of the recently published intentions of ACGIH to establish a biological exposure index (BEI) for chromium.

Next Steps

Final SMR analyses are underway, including the use of both national (United States and Germany) and local (Texas, North Carolina and North Rhein Westfalen) reference rates for each plant, respectively. SMR analyses using time-dependent cumulative exposure estimates and other

[1] World Health Organization (1996): Biological Monitoring of Chemical Exposure in the Workplace, Vol. 1, p. 102.

conventional cohort analyses using procedures such as Cox proportional hazards models or Poisson regression will begin shortly.

The draft final report has been begun, with major sections of the background (literature review), methods, and preliminary results in place. It is expected that the analyses will be completed within the next two months, and that a complete draft of the final report will be available for preliminary review and comment by October 1, 2001. We would propose that if the IHF members are present at the ICDA meeting in Corpus Christi in late October, a special session for discussion of the draft final report would be helpful, at which time we would expect to have our expert reviewers' comments as well. Provided that this schedule is reasonable, the final report could be submitted by December 1, 2001 and a first manuscript for publication submitted by the end of the year. It is our expectation that we would prepare and submit abstracts based on the report for possible presentation at one or more international occupational health meetings in 2002.