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Subject: Subject 8EHQ-0502-15135A and 8 EHQ-0605-1513B: Response to EPA Toxicological Evaluation and Epidemiological Evaluation (EPA letter Dtd. November 22, 2005)

Ladies and Gentlemen:

BASF Corporation has reviewed the copies of the evaluations by Drs. Woo and Beaubier provided in the letter dated November 22, 2005.

Our experts have provided the following comments:

Response to EPA Toxicological Evaluation:

The EPA toxicological evaluation indicated that it was puzzling how BASF could ignore mentioning this chemical (referring to ethylene dichloride).

As a component of our investigation of cancer occurrences among bentazon unit employees, we reviewed toxicological profiles of the substances used in the unit and listed in our TSCA submissions including the profile for ethylene dichloride (EDC). We additionally reviewed industrial hygiene records for the unit and occupational medical records to identify acute exposure incidents during the 8 years of operation from 1979 to 1987.

Specifically, with respect to EDC, we were aware of its potential human carcinogenicity based on positive tumor responses in oral gavage studies conducted in rats and mice and took this into consideration when evaluating our findings.

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Our review of industrial hygiene records had identified 222 full-shift personal air samples for EDC among study subjects. These were examined in relation to job assignment, in part, as a check on our classification of jobs into those involving high and low potential direct contact with process chemicals. The ACGIH TLV-TWA for EDC was 10 ppm (40 mg/m³) during the period of unit operation. Of the 222 personal full-shift samples for EDC, 90% were below 1 ppm TWA. Twelve samples showed EDC concentrations above 2 ppm, 2 of which also exceeded 10 ppm TWA. There were 5 acute exposure incidents involving EDC during the 8 years of unit operation, all of which related to either skin or eye contact with EDC. There was no indication of any systemic responses to EDC in these incidents and there have been no subsequent diagnoses of cancer among the five individuals.

Response to EPA Epidemiological Evaluation:

The EPA epidemiological evaluation states that the cancer incidence results were based on an "informal compilation of statistics from self-reports" and further states: "Therefore without a formal historical prospective cohort or case control epidemiologic study, there is a reasonable likelihood some incident cases were missed in the follow-ups and thus the real incidence rates are likely even higher than the significant ones reported." The evaluation also indicates that cancer incidence rates for South Louisiana are high compared to national rates and that the interpretation of the company does not consider the healthy worker effect. Finally, the evaluation states that 3 of 20 cancer cases among employees assigned to the unit during the first year of operation were identified through company examinations.

Our 2001 investigation was initiated in response to employee and management concerns regarding a perceived cancer cluster. The study was not performed as informally as implied by comments contained in the EPA evaluation of our two submissions. The BASF Medical Department followed Centers for Disease Control guidelines for investigating disease clusters including meeting with employees on multiple occasions and gathering basic data about the initial group of cases identified by employees. Based on results of a medical review (i.e., personal interviews and review of medical records) of the reported cancer cases, we undertook a preliminary assessment of observed and expected occurrences of cancer.



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This followed a retrospective cohort study design and was based, in part, on having previously established a cohort of production and maintenance personnel who had worked in the unit for 3 or more months. The assignments of production personnel were verified by review of unit census lists and employee work histories. In addition, we reviewed medical records (annual examinations included building assignments) and available maintenance records of all employees on site during the years of operation to identify service personnel who may have spent 3+ months in the unit during its years of operation. A few additions to the cohort were made based on personal interviews to clarify time spent in the unit. It is unlikely that employees with long-term assignments in the unit were missed.

The preliminary assessment utilized a person years approach to evaluate observed and expected incident cases and focused on the time period of active employment. This was done because of the completeness of information for cohort members during active company employment. At completion of the follow-up study, employees in the cohort had collectively participated in over 1,550 occupational medical examinations or an average of 6.2 examinations per employee. These examinations included a health history, spirometry, clinical laboratory testing, and a physical examination by a physician. Additionally, interviews by a health professional were conducted for individuals who had transferred to other sites or had not had a recent examination. Medical referrals as a result of the physician examinations contributed to detection of 8 cancer cases in the cohort. Of the 20 cancer cases detected among men assigned to the unit throughout 1979, referrals for further evaluation occurred in 5 and not 3 of the cases. Calculation of the expected number of cancer cases using age-, gender-, and race-specific South Louisiana cancer incidence rates included only person years of observation for which follow-up was complete.

Based on results of the preliminary study and in consultation with employees, the Medical Department undertook to contact all former employees and provide them with a summary of the preliminary study and to address any questions they had about the study. In addition, each employee for whom, a forwarding address was available was contacted by a health professional to obtain an updated health history. Mailing of notification letters was attempted for 141 left and retired employees. No current address could be verified for 8 former employees. Among the remaining 133 employees, interviews were completed for 120 (114 personal interviews and 6 spouse interviews). There was only one refusal in 120 interviews. Overall cancer incidence follow-up was completed for 89% of the study population. Mortality follow-up was complete for 97% of the cohort members and the overall mortality experience was less than that for the general U.S. population and comparable to that observed among other site employees.



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Healthy worker selection would be expected to impact mortality results during the first 10-15 years of follow-up, but should be diminished in populations followed for longer periods of time as ours was. Furthermore, our study should not be subject to ongoing healthy worker selection since we followed employees after they had left active employment. With respect to cancer incidence, the differential impacts of initial selection versus active medical surveillance may be difficult to assess. However, for prostate cancer, a large-scale randomized clinical trial involving a screened and unscreened population reported a five-fold higher prostate cancer incidence over a 4-year period in the screened population (van der Crujisen-Koeter et al., 2003). Thus, the contribution of enhanced detection of some types of cancer through screening can easily outweigh an impact of initial selection of healthy individuals.

Our updated cancer incidence information (active plus left and retired employees) was analyzed as described in the second submission to the EPA. Person years were again accumulated only up to the date of last follow-up for each subject and standardized incidence ratios (SIRs) were calculated. In these analyses, comparisons were reported based on comparable data for the South Louisiana general population. However, we had also computed expected numbers of cases using age- and race-specific cancer incidence rates from National Cancer Institute SEER data (all SEER registries combined) for the years 1992-2002 [Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Databases: Incidence – SEER 13 Regs Public-Use, Nov 2004 Sub for Expanded Races (1992-2002) and Incidence – SEER 13 Regs excluding AK Public-Use, Nov 204 Sub for Hispanics (1992-2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission]. Our findings were that the expected number of total cancer and prostate cancer cases adjusted for age and race was 23.8 and 6.7 cases, respectively and hence were higher when based on SEER rather than available South Louisiana cancer incidence rates. Thus, given the specific age and race structure of our study population, the SIRs would have been lower had we presented results using SEER rates instead of rates for South Louisiana.

In comparing the cancer experience reported by employees to that of established registries, it is at least equally plausible that individuals could over report as under report cancers. It is unlikely that a physician would report a cancer to a tumor registry without the patient being aware of the diagnosis. The external comparison rates (i.e., Louisiana Tumor Registry) used in our analyses were for invasive cancers. Given the nature of our study, we did not request permission to review histopathology records of the individual cases and therefore presumed all cases to be invasive for analysis purposes.



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Reference:

van der Crujisen-Koeter IW, van der Kwast TH, Schröder FH. Interval carcinomas in the European Randomized Study of Screening for Prostate Cancer (ERSPC)-Rotterdam. *J Natl Cancer Inst* 2003; 95: 1462-6.

Please note that this letter does not contain confidential business information. Any further technical questions should be addressed directly to our Corporate Epidemiologist, Gerald Ott, Ph.D., at Rockaway, NJ (Telephone: 973-895-8023).

Sincerely,

A handwritten signature in cursive script that reads "Sree Jasti".

Sree L. Jasti, Ph.D.
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