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WASHINGTON, D.C. 20460

OFFICE OF

PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

9/13/1996

MEMORANDUM

SUBJECT: Review of Two Atrazine Epidemiology Studies

TO: Kathryn Boyle
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Health Effects Division (7505C)

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Please find below, the OREB review of:

DP Barcode: D226645

Pesticide Chemical Code: 080803

EPA Reg. No.: various

EPA MRID No.: 440086-01, 440086-02

I. Introduction

Ciba-Geigy has submitted two epidemiologic studies of plant workers exposed to atrazine. The first study is "A Follow-up Study of Workers at the Ciba-Geigy St. Gabriel Plant" by Elizabeth Delzell, Ilene Brill, and Colleen Beall, completed April 8, 1996 (MRID no. 440086-01). A number of earlier reviews have been completed for earlier versions of this study:

1. Ciba-Geigy Triazine Herbicide Mortality Study (HED Project No.

- 0-224). Memorandum from Jerome Blondell to Lois Rossi, January 22, 1990.
2. Letter from Dr. Aaron Blair, National Cancer Institute to Jerome Blondell, January 29, 1990.
 3. Review of Retrospective Triazine Mortality Studies (DP barcode 189027). Memorandum from Jerome Blondell to Walt Waldrop, July 15, 1994.
 4. OREB Epidemiology Review and Recommendations for the Special Review of Atrazine (DP Barcode 215496). Memorandum from Ruth Allen to Joe Bailey, July 11, 1996.

The second epidemiology study submitted is "Atrazine: an Epidemiological Study at the Schweizerhalle Plant" by R. Gass and G. A. Stalder completed on January 15, 1993 (MRID No. 440086-02).

II. Conclusion and Recommendation

OREB concludes that neither of the epidemiologic studies reviewed here add significant new information concerning adverse health effects of atrazine. A non-significant elevation in non-Hodgkin's lymphoma continues to be observed at the Louisiana plant among workers exposed to triazines, including atrazine. By itself this study, does not support a conclusion of increased cancer from exposure to triazines. However, this study could be considered supportive, but only supportive and not definitive, if evidence of an association between non-Hodgkin's lymphoma and triazine exposure was available from other studies. Follow-up by the National Cancer Institute in four states looked specifically to determine whether earlier associations in individuals studies could be attributed to atrazine when adjustment was made for exposures to other pesticides. They concluded that "detailed analyses suggested that there was little or no increase in the risk of NHL attributable to the agricultural use of atrazine". The Occupational and Residential Exposure Branch concurs with this finding.

OREB has no specific recommendation on these two studies.

III. Detailed Considerations

1. St. Gabriel mortality and cancer incidence study.

The most recent version of the mortality study at the St. Gabriel plant in Louisiana includes a larger number of workers and a longer period of follow-up. The current study adds 731 subjects, 13,011 person-years of follow-up and 39 deaths to their previous report. This represents a doubling of person-years and a four-fold increase in the number of deaths available for study. Subjects had

to have worked at least six months prior to 1993 to be included in the study. Subjects had to have some exposure to triazines or their precursors to be included in the study. The final updated cohort included 2,203 workers. Vital status was ascertained on 99% of all subjects and the average period of follow-up was 10.8 years.

Mortality rates for each race and gender subgroup were compared with expected rates corresponding to the US or Louisiana general population. Cancer incidence was compared to expected number of cases based on the Surveillance, Epidemiology and End Results (SEER) program for 1986-1990, covering a major portion of the nation. Age-specific incidence rates for Louisiana are not available for the time period under study. Appropriate statistical techniques were used to analyze both mortality and cancer incidence.

As reported in earlier studies, plant workers had lower than expected numbers of deaths. The overall Standardized Mortality Ratio (SMR: age and sex adjusted ratio of observed to expected deaths multiplied by 100) for these workers was 70 (95% confidence interval 52-91) indicating 30% fewer deaths than expected. As discussed in the earlier reviews, this was partly due to a healthy worker effect and partly due to the relatively young age of the cohort (87% of the person-years of follow-up was accounted for by persons under 45 years of age).

The plant worker's cancer mortality rate was similar to the U.S. population (SMR = 110 based on 13 cases with a 95% confidence interval (CI) 59-188). Among the 13 deaths were 5 due to lung cancer, 4 lymphopoietic cancer (leukemia or lymphoma), 2 stomach cancers, one breast cancer, and one kidney cancer. The lymphopoietic cancers included 3 observed non-Hodgkin's lymphoma (NHL) cases compared to 0.6 expected. However, examination of the medical records revealed that one of these cases had a diagnosis of poorly differentiated nasopharyngeal cancer. Judging from the way the authors have presented this information, they seem unsure whether the medical record can be accepted as the definitive diagnosis, probably because there was insufficient pathological diagnostic information to support the medical record.

A total of 28 cases of nonfatal cancer were observed in the worker cohort which equaled the number of cases expected based on SEER data. Standardized Incident Ratios (SIR) were recorded for specific cancers occurring in 3 or more cases: lung cancer (SIR = 204, 95% CI 75-444); prostate cancer (SIR = 245, 95% CI 79-572); and lymphopoietic cancer (SIR = 142, 95% CI 46-331).

Dr. Allen in her earlier review (item 4 listed above) concluded that multiple exposure to different pesticides (i.e., atrazine, 2,4-D and organophosphates) may have been a factor resulting in increased cancer risk. However, it is also possible that 2,4-D and organophosphates alone were responsible for the

observed associations. The authors seem to support this view in their discussion, stating "In our judgment, these data provide little evidence that atrazine is associated with non-Hodgkin's lymphoma among white men".

2. Schweizerhalle Plant study of health disorders (MRID #440086-02)

In this study, performed in a German plant, 154 workers were selected from about 350 exposed employees who had been at the plant since 1979. Why all workers were not included or whether temporary or part-time workers were excluded is not explained. Each of the 154 exposed workers were matched with one non-exposed workers at the same plant who met the following criteria: year of birth plus/minus one year; year of entry into plant plus/minus one year; same or neighboring nationality; and, if there was more than one potential match, the closest body index (height divided by weight). Apparently all workers were supposed to receive a yearly medical examination which included some blood tests, blood pressure, and vital capacity measurements. The number of cases and controls that did not receive yearly examination or complete testing is not reported. Actual exposure levels to atrazine in the plant are not reported. The absence of a discussion of non-response and the completeness of the collected data are serious defects for an epidemiologic survey of this type.

Testing at entry into the plant showed very similar results for cases and controls. During their time at the plant both groups had similar rates of smoking, alcohol consumption, and physical activity. Over the course of observation, blood tests (e.g., blood sedimentation, leukocyte count), blood pressure, and vital capacity were not significantly different in cases and controls. Analysis by years of exposure did show occasional differences, but given the large number of statistical tests, they may well be due to chance. No dose-response relationships were identified.

Illness and accidents were also evenly distributed between cases and controls. One exception to this finding was a higher prevalence of gastritis among cases (12%) than controls (2%). The occurrence of gastritis did not increase with years worked at the plant. Gastritis can be due to a wide variety of causes and no biologically plausible connection with atrazine has been proposed. Other factors (e.g., job stress) are more likely to account for the association with gastritis than atrazine exposure.

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RDI: ActSecHd:FDGriffith:9/11/96:ActBrSrSci:SHummell:9/13/96:
ACTBrCh:EZager:9/13/96

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