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MEMORANDUM

SUBJECT: OREB Epidemiology Review and Recommendations for the Special Review of Atrazine [Chemical #080803, Case #838836, (in three parts)]

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7-9-96

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THROUGH: Bart Suhre, Acting Section Chief
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7-11-96

Introduction

This review covers the following three items submitted by Ciba-Geigy in response to the Special Review PD 1 on Atrazine.

1. Submission # S487183 "An Evaluation of Epidemiologic Studies, of Exposure to Triazines and Cancer in Humans" by Elizabeth Delzell, Sc.D. and Nalini Sathiakumar, M.D., March 10, 1995 (Volume 26 of 54), pp. 1-51.
2. Submission # S487200 "Mortality Among Workers at Two Triazine Herbicide Manufacturing Plants" by Nalini Sathiakumar, Elizabeth

Delzell, Sc. D. and Philip Cole, M.D., March 16, 1995 (Volume 27 of 54), pp. 1-31.

3. Submission # S487201 "Response to EPA Review of Retrospective Triazine Mortality Studies" by C. Breckenridge March 22, 1995, (Volume 28 of 54), pp. 1-25.

For simplicity, here after I refer to item 1 as "the literature evaluation." Item 1 is an unpublished triazine exposure and cancer epidemiology literature review prepared for the company under contract to the Department of Epidemiology, School of Public Health, University of Alabama at Birmingham.

Item 2 will be referred to as the "worker mortality study." Item 2 compares cancer mortality for two Ciba-Geigy occupational cohorts exposed to pesticides, including triazines and DDT, from 1960 on, at the McIntosh, Alabama Plant, and from 1970 on, at St Gabriel, Louisiana Plant.

Item 3 is here called the "company response" (Ciba-Geigy responding to EPA's review) by Clement International Company. Item 3 contains the response of the original authors of the worker mortality study (Dezell, et al., 1995) and the views of two experts hired by Ciba-Geigy, Drs. Checkoway and Neuberger.

Conclusions and Recommendations

1. Potential Hazards of the Triazines

The worker mortality study (Item 2), and the literature evaluation (Item 1) indicate that for the populations studied, the excess human cancer, here measured as an increased rate of non-Hodgkins lymphoma (NHL), would be 20%, and from 40% to 170% for increased exposure based on the Nebraska studies of, farmers who applied atrazine more than 20 days per year. This trend has public health significance.

Exploratory statistical studies in Illinois support a finding of increased breast cancer associated with places where triazine herbicides are heavily used. Various groups, including scientists, other leaders and the public, support further research to untangle the potential environmental causes of these cancers. The current reports (Items 1, 2, and 3) are insufficient and further research is advisable.

2. Unresolved Issues

a. The literature review (Item 1) and other materials presented (Items 2 and 3) do not fully address all of the relevant currently published literature. Another more complete literature review is advised.

3. Further Research Needed

a. The suggestive pattern of higher breast cancer rates in Illinois is an example of one area that might be fruitfully studies.

b. Such a follow-up study on the Illinois evidence would be feasible with joint support from EPA and NCI.

Detailed Considerations

This section summarizes the key issues using a Q's and A's format. I include points of agreement and disagreement, and other information to support the conclusions and recommendations above.

1. What are the study strengths, and do they validate the study conclusions?

a. The worker mortality study was conducted according to standard, well-accepted epidemiology methods, according to Dr. Checkoway, a University of Washington, Department of Environmental Health expert hired by Ciba-Geigy.

b. The worker mortality study pooled results from two previous published studies to increase statistical power to detect a difference.

2. What are the study limitations, and do they invalidate the study conclusions?

a. There is missing death certificate data, especially for African American workers. This is a potentially important omission that would lead to an underestimation of the true risk. Given the EPA efforts to implement the recent Presidential Executive Order on environmental justice, this topic would warrant follow-up.

Even if the exclusion of people of unknown race (n = 69) and of women (n = 169) is because of low sample size, available information should be included, given recently published findings of triazines as endocrine disrupters (Davis and Bradlow et al., October, 1995 Scientific American). Triazines were shown in the test system to be an inducers of estrogen metabolic pathways (C16 hydroxyestrone) that are also associated with cell proliferation and excess breast cancer in humans.

b. Because the work force was young and relatively healthy (healthy worker effect, shown by SMR's <100 for non-cancer deaths), and cancer is predominantly a disease of late age, with peak incidence at ages 50 to 85 (Doll, Fraumeni, and Muir, 1994 Trends in Cancer Incidence and Mortality), as yet there are a relatively small numbers of deaths.

More years of follow-up would be necessary to see the full experience of the cohort. Also, the survival rates for NHL after diagnosis are high (5 year survival: whites 50%, and blacks 45%) so mortality is not the optimal endpoint to study this cancer, especially if the true association is weak.

Therefore, the worker mortality study finding of "no convincing evidence of a causal relationship between triazine exposure and specific forms of cancer, including NHL, or mortality from other diseases" should be interpreted with caution. A better conclusion (see p18 of 25 by Checkoway) would be that there is some evidence that warrents further study.

c. Disease latency ranges from 5 to 30+ years, so the short time follow-up (16-19 years) is insufficient to additional observed cancer deaths. Of the 2683 exposure, the breakdown is: definite (n = 251), (n = 149), probable, intermittent (n = 283), or (n = 1,267) and possible intermittent (n = 967) exposure.

Of the worker mortality study population, at follow-up in 1986, 96% were presumed living, 86 (3%) had died, and 38 (1%) were lost to follow-up.

Given that an additional ten years of follow-up is now **possible**, and within the decision timeframe on reregistration of atrazine, then additional follow-up might be prudent. In this worker mortality study, of the definite and probable exposure category total of 2,683 men, 740 (28%) are listed as Black and 1,943 (72%) are listed as White.

d. There is insufficient statistical power to detect a 1.5 fold increase for either all cancers or site-specific cancers, according to the Clement International EPA sponsored reviewers.

e. Accuracy and quality control of computations, rounding errors, statistical significance, typographical errors and other errors of omission are mentioned in the Clement International review.

f. Appropriateness of various statistical tests, choice of confidence intervals are also questioned. The worker mortality study authors append information for statistical tables to show that their approach of using standardized mortality ratios (SMR's) as a measure of association is basically sound.

g. A key drawback in this study, as in many retrospective studies of this type, is the lack of quantitative data on triazine exposure. This is an important gap because personal hygiene practices are as important as job titles and work areas in the determination of internal dose. Also, comparable doses may have different health outcomes for persons with differing genetic susceptibility, prior disease, or current lifestyle stressors, e.g. drug, alcohol, and tobacco use, nutrition, none of which were adequately measured.

3. How do cohort mortality rates compare with cancer mortality rates for the state and elsewhere?

Appropriate comparison groups were used including, cancer mortality rates for AL and LA for 1960 through 1986, and national cancer mortality rates for non-cancer deaths for 1962-1986. Of note are the elevated SMR's or more than expected deaths for all lymphatic and hematopoietic tissue cancer (LHT) (5 deaths observed/2.6 expected, SMR = 192, Confidence Intervals (CI) = 62 - 447) and for non-Hodgkins lymphoma (NHL) (3 deaths observed/0.78 expected, SMR = 385, CI 79 - 1,124).

4. What is the strength of the experimental animal and human evidence for triazine and DDT carcinogenicity?

International Agency for Cancer Research (IARC) ranked the triazines as Group 2B, possible human carcinogens.

5. What key aspects of chronic disease etiology are not covered at all in the present analysis? Several key items are omitted in

the present work. They are: triazines as endocrine disrupters, non-occupational exposure via drinking contaminated ground water, non-cancer end-points such as chemical sensitivity, and differential genetic susceptibility. Information on these omitted topics would be helpful in the PD 2/3 evaluation process.

6. What other literature is relevant to evaluate the health effects of triazines?

a. Endocrine Disruption. Statistical errors are not as critical for interpreting the results of the worker mortality study as the total omission of any review or discussion of hormone metabolism and endocrine disruption. Endocrine disruption has been shown to happen in human breast tissue and human breast cancer cells in culture with atrazine exposure [see Bradlow et al., 1995, Telang et al., 1995]. This research was the subject of a recent workshop on hormones and hormone metabolism sponsored by the Cancer Etiology Working Group of the National Action Plan for Breast Cancer.

Moreover, in Science, June 7, 1996 Arnold and others in Dr. John McLachlan's lab at Tulane University published a report on markedly increased estrogen response with exposure to two pesticides in combination. Estrogen responses have been associated with cell proliferation and breast cancer.

b. Geographic Cancer Studies. Also, National Cancer Institute mid-west cancer study in Eastern Nebraska, Zahm et al., (1988b) reported that the use of atrazine was associated with a slight excess risk (40%) (Relative Risk of 1.4, CI = 0.8 - 2.2) and that the risk increased to 2.7 (170% excess risk) with increasing duration of use. This finding is important because it suggests a dose response relationship for human use of atrazine and excess mortality is farmers.

Zahm et al., (1993a) in the Scan. J. Work and Environ. Health. noted that in a pooled analysis from three of the four NHL NCI studies, the combined relative risk (RR) for atrazine was 1.4 (CI = 1.1 - 1.8), and it was 1.2 (CI = 0.9 - 1.7) after adjustment for the use of 2,4-dichlorophenoxyacetic acid and organophosphate insecticides.

This means that multiple exposure to different chemicals increased human cancer risk by as much as 150 %. This estimate

represents the range between the highest risk of RR 2.7, a 170% excess, compared to the lowest risk RR = 1.2, a 20% excess risk. The risk assessment process does not yet handle multiple exposure well. Epidemiology provides useful insights for this multiple exposure problem.

c. Future Data Review. An electronic literature search for the last few years on triazine exposure and epidemiology yielded 163 pages of abstracts. Therefore, a full literature review would be useful.

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