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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

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SUBJECT: Review of midwest cancer epidemiology studies related to triazines. HED Project No. INTRA-0141

TO: Henry Spencer
Toxicology Branch I
Health Effects Division (H7509C)

FROM: Jerome Blondell, Health Statistician
Special Review and Registration Section
Occupational and Residential Exposure Branch
Health Effects Division (H7509C)

Jerome Blondell

THRU: Curt Lunchick, Acting Chief
Special Review and Registration Section
Occupational and Residential Exposure Branch
Health Effects Division (H7509C)

Curt Lunchick

Charles L. Trichilo for
Charles L. Trichilo, Ph.D., Chief
Occupational and Residential Exposure Branch
Health Effects Division (H7509C)

I. Background

A review has been requested of the available cancer epidemiology studies concerning triazine herbicides used in the midwest. The purpose of the review is to state the level of concern or likelihood, given the evidence, that triazines are a significant cause of human cancer.

The following studies have been identified as the only available U.S. studies that specifically address the potential association between triazine exposure and cancer incidence or mortality:

1. Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni, Jr. JF. 1986. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *Journal of the American Medical Association* 256:1141-1147.
2. Brown LM, Blair A, Gibson R, Everett GD, Cantor KP, Schuman LM, Burmeister LF, Van Lier SF, Dick F. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Research* 50:6585-6591.

3. Hoar SK, Blair A, Holmes FF, Boysen C, Robel RJ. 1985. Herbicides and colon cancer (letter to the editor). *Lancet* 1 (8440):1277-1278.
4. Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Cantor KP, Blair A. 1988. A case-control study of non-Hodgkin's lymphoma and agricultural factors in Eastern Nebraska. *American Journal of Epidemiology* 128:901.
5. Cantor K, Everett G, Blair A, Gibson R, Schuman L, Isacson P. 1985. Farming and non-Hodgkins's lymphoma (Meeting Abstract). *American Journal of Epidemiology* 122:535-536.

A year ago, Ciba-Geigy submitted a study of mortality at a Triazine herbicide manufacturing plant in Louisiana. A copy of the review of this study is attached. The study by Cantor et al. (1985) has not yet been published in final form, but is currently being drafted and may be available in mid summer.

II. Conclusion

The study by Hoar et al. (1985) of colon cancer and the study by Brown et al. (1990) of leukemia did not find a significant association between cancer and triazine exposure. The Kansas study of Non-Hodgkin's lymphoma (NHL) by Hoar et al. (1986) found a significant association for triazines (odds ratio = 2.5, 95 % confidence interval 1.2-5.4) which was not studied in detail because the main focus of the study was phenoxy herbicide exposure. A follow-up study in Nebraska found a risk of 1.4 (confidence interval 0.8-2.2) which was not significant but did show evidence of increasing with duration of use (odds ratio with 16 or more years of use was 2.0). The study in Iowa and Minnesota by Cantor et al. (1985) found an elevated risk of small cell lymphocytic lymphoma associated with use of atrazine (odds ratio = 1.6, confidence interval not given) and cyanazine (odds ratio = 1.6, confidence interval not given). This last study, however, is only available in abstract form and insufficient detail is available to evaluate the apparent elevation in risk. The Louisiana plant study submitted by Ciba-Geigy previously reviewed found one NHL death and one NHL incident case which provide suggestive evidence of an association.

More detailed follow-up and/or analysis is needed in all four of the NHL studies (Kansas, Nebraska, Iowa and Minnesota, and Louisiana plant) to determine the strength and specificity of the associations found. While these studies suggest an association between triazine exposure and NHL, an association has not yet been established. Other explanations or confounding factors could account for the associations that have been seen.

III. Detailed Considerations

Epidemiologic studies of farmers conducted to date provide only preliminary information on the possible association between triazine exposure and cancer. A letter from the Environmental Epidemiology Branch of the National Cancer Institute NCI to Lancet describes an analysis of 57 colon cancer cases and 948 controls from Kansas where herbicides are widely applied (Hoar et al 1985). Four chemical groups of herbicides were analyzed for association with cancer, including phenoxy, uracil, triazines, and amides. No significant associations were found.

A detailed study of pesticide exposure and leukemia in Iowa and Minnesota examined exposure to chemical groups of herbicides and insecticides and specific pesticide chemicals (Brown et al. 1990). The risk of leukemia for men who had ever used triazines was 1.1 with a 95% confidence interval of 0.8 to 1.5. For the chemical atrazine, the risk or odds ratio for mixing, handling, or applying the pesticide was 1.0 (confidence interval 0.6-1.5). Similarly, for cyanazine the odds ratio for leukemia was 0.9 (confidence interval 0.5-1.6). Thus, there was no evidence in this study of an association between triazine use and leukemia.

The first key study of herbicide use and NHL, Hodgkin's disease (HD), soft-tissue sarcoma (STS) was conducted by NCI in Kansas and reported in the Journal of the American Medical Association in 1986. The primary purpose of this study was to determine whether agricultural use of pesticides, especially phenoxy herbicides, affect the risk of STS, HD and NHL. No association was found between herbicide use and HD or STS. Due to an association between herbicide use and NHL, a more detailed evaluation was made of the chemical groups farmers had used. Eight different herbicide groups were tested based on responses of study subjects or next-of-kin to a questionnaire. Five of the eight herbicide groups yielded statistically significant associations with NHL. For triazines the odds ratio was estimated as 2.5 with a confidence interval of 1.2 to 5.4. Further hierarchical analysis of triazines, after eliminating subjects exposed to phenoxy herbicides or uracils did not yield a significant association (odds ratio 2.2, confidence interval 0.4-9.1), however the sample size (3 cases and 11 controls) was very small. Because of the limited sample size and the focus on phenoxy herbicides, no detailed analysis of duration or frequency of triazine use was made to see if the association was specific or exhibited a dose-response trend with NHL. Thus the significant association that was observed may be due to some other pesticide or agriculturally related factor correlated with triazine use.

A follow-up study, identical in design to the Kansas study, was conducted in Eastern Nebraska (Zahm et al. 1988). Information on 2,4-D has been published but the information on atrazine and NHL is only available in abstract form. Risk from atrazine was

elevated though not significant with an odds ratio of 1.4 and a confidence interval of 0.8 to 2.2. However there was evidence of increased risk in those users with a longer duration of exposure. Those exposed for 16 years or more exhibited an odds ratio of 2.0.

The only other published study which examines the association between NHL and triazines is also only available as an abstract. This case-control study conducted in Iowa and Minnesota found elevated risks for atrazine (1.6) and cyanazine (1.6) and small cell lymphocytic lymphoma. Even higher elevated risks were found for glyphosate, 2,4,5-T, lindane and nicotine, however no confidence intervals were reported. Significant risks of NHL were reported for users of DDT and chloramben. Without adjustment for exposure to different groups of pesticides, little confidence can be placed in any one association.

One other study, previously reviewed (see review attached) examined mortality experience in a triazine herbicide manufacturing plant. Workers were exposed to triazines (principally atrazine, simazine, and propazine), their precursors, and for one brief period, to chlordimeform. No significant excess of deaths were reported for any disease category. However, there was one death due to NHL of a worker at age 31 who worked at the plant five years and one incident case of NHL (age unknown) who worked in the plant for 16 years. Due to the relatively short period of follow-up (maximum of 18 years) and small sample size, this study has very limited power to detect significant effects. The two cases of NHL are suggestive, however, and investigators plan to continue to follow the experience of this group of workers.

cc: Atrazine File
Marion Copley, Tox I Branch
Larry Dorsey, SACB
Correspondence
Circulation

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