UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 29 1987

PESTICIDES AND TOXIC SUB

MEMORANDUM

SUBJECT: An Epidemiological Study of Workers Exposed to 4-Chloro-o-Toluidine (a Chlordimeform metabolite

TO: Jan Auerbach, Chief
Special Review Branch
Registration Division (TS-767C)

Thru: Anne Barton, Deputy Director
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The following memorandum is intended to summarize available information concerning epidemiological evidence of bladder carcinogenicity in humans resulting from exposure to 5-chloro-o-toluidine, a chemical used in dye and pesticide manufacture and a human metabolite of chlordimeform. This memorandum also contains preliminary conclusions based on the limited available data pertaining to this study and a list of issues regarding the epidemiological study which warrant further investigation.

Notice of the apparent association of human bladder cancer with 5-COT was submitted by American Hoechst under §8(e) of TSCA and jointly by Ciba-Giegy and Nor-Am under §6(a)2 of FIFRA. In the submissions to OTS and OPP, it was noted that a total of 8 cases of bladder tumors were observed in a group of 139 workers exposed for at least 12 months in a Hoechst plant in West Germany prior to 1970. Less than one case would have been expected, according to Hoechst. Although a total of 1338 workers were exposed for more than one year during the lifetime of the plant from 1929 to the present, the vital status of only 252 workers was known and, of this group, 117 were exposed before substantial changes in the manufacturing process occurred in 1970. All cases of bladder cancer were observed in the cohort exposed before 1970, which is consistent with the long latency period generally observed for bladder cancer associated with dye exposure. Hoechst concluded "it appears to be reasonable to assume a cause-effect relationship between 5-COT and the observed bladder carcinomas." Their study has been accepted by the journal "International Archives of Toxicology" and is scheduled to be published in June. At the request of OTS, Dr. Heinz Trebitz and Dr. Fritz Schuckman of American Hoechst met with OTS, CAG, OPPE, and OPP representatives

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on April 29, 1987 to discuss the study. They verbally presented additional information not contained in the submissions to OTS and OPP. They stated that their investigations of the manufacturing process did not find exposure to known human carcinogens associated with the dye industry, such as benzidine or beta-napthylamine. In fact, the exposure history of the individuals in the plant was characterized by exposure to a very small number of chemicals, primarily methyl aniline, 5-COT and 6-COT. They estimated that about 80% of the exposure was to 5-COT. High levels of exposure to these few chemicals frequently occurred prior to 1970 with cyanosis and hematuria evident about 25% of the time in the summer months. Hoechst investigations of worker exposure to 6-COT and methyl aniline in other plants, in concert with animal oncogenicity data, led Hoechst to rule out these other chemicals as likely etiological agents in the observed bladder cancers.

On May 12, 1987 a group of individuals with expertise in epidemiology met to discuss the study. The group consisted of Elizabeth Margosches, OTS, Cheryl Siegel Scott, OTS, Jerome Blondell, OPP, Jim Cogliano, CAG and myself. Our review of all currently available information confirms that the magnitude of the observed bladder risk that appears to exist among workers exposed to 5-chloro-o-toluidine is unlikely to be explained by other causes of bladder cancer, e.g., smoking or exposure to other chemicals. However, the data are inadequate at this point for EPA to formally classify 5-COT as a human carcinogen. The epidemiological data are also inadequate to attempt to quantify human risk which would be associated with a particular 5-COT level and will likely remain so. Eventually, a determination can be made as to whether the data constitutes "limited", "sufficient" or "inadequate" evidence of human carcinogenicity and a weight of evidence determination considering all animal, human and structure-activity information can be made. In the meanwhile, it is recommended that an attempt be made to obtain additional information which might aid in this determination. It is noted that Nor-Am and Ciba-Geigy, the U.S. registrants of chlordimeform, have offered to cooperate with the Agency in obtaining additional information pertaining to this study. In addition, a commission of the West German government will meet in June to consider reclassifying 5-COT to the status of "known human oncogen" and additional information relevant to the epidemiological study will likely come out of that deliberation. OTS has contacted the West German Embassy to obtain a copy of the transcript as soon as it is available.

The following are among the areas in which additional information would be useful for assessing the strength of the human evidence for carcinogenicity;

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1. A precise definition is needed of the cohort used in the study. This should include the age structure of the cohort and the distribution of durations of exposure. The person-year structure of the cohort would also be helpful.

2. Were cohort comparisons made of job types or other subclassifications within the plant?

3. Were cohort comparisons made with other chemical factories in West Germany? We understand baseline rates have been developed for a group of German chemical companies.

4. How did the manufacturing process change in 1970?

5. What information is available regarding exposure to other chemicals in the plant?

6. What information is available regarding the cigarette and alcohol use history of the confirmed cases of bladder cancer? What information is available regarding work history, outside of the 5-COT plant, for these individuals? How do these histories differ from those of other members of the cohort?

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