L. TAYLOR

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

JUN 29 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Summary Report of Epidemiological Assessment of Fertility in Male Workers Exposed to Ordram (Molinate) at the Stauffer Chemical Company (MRID # 426658-03)

TO: Kathryn Davis, Product Manager 52
Accelerated Reregistration Branch
Special Review and Reregistration Division (H-7508-C)

FROM: Ruth H. Allen, Ph.D., M.P.H. Ruth H. Allen 6-27-98
Environmental Scientist (Health)
Special Review and Registration Section
Occupational and Residential Exposure Branch (H-7509-C)

THRU: Steve Knott, Section Head (Acting) Steven Knott
Special Review and Registration Section
Occupational and Residential Exposure Branch (H-7509-C)

Larry Dorsey, Chief
Occupational and Residential Exposure Branch
Health Effects Division (H-7509-C)

I. Introduction

This memorandum updates a previous review on molinate, completed in 8/91. The present document is a clearly written summary of the previous lengthy and detailed epidemiological report, and contains no new data and no new analysis. The original material was complex and difficult to follow because of the complexity of the design, and varied exposure patterns for different workers. Results and problems with the previous study are included as attachment A and not repeated here.

II. Conclusions

The summary report is clear and useful. It delineates several important problems with the original study. It concludes, on p. 17, that no exposure related effects are demonstrated. Because of study omissions and design problems detailed below, the validity of this conclusion is questionable. The evidence presented does not fully support the conclusion in the report. The possibility still exists that at higher levels of human exposure, and for older

workers (higher parity in present wife) molinate alters fertility in male workers. Carefully designed and executed longitudinal studies of highly exposed and unexposed workers would be helpful to support the no effects conclusion.

III. Detailed Considerations

The "no effects" conclusion can be questioned because:

a. Table 1 indicates relatively low study participation rates, as low as 49% and typically in the mid-60% range, and omits workers who were absent sick. Highly exposed workers could be absent sick more often, thus there could be a healthy worker effect operating in the data.

b. The summary of "current" exposure on p. 20 shows wide variability in exposure, even within the production group. Averaging data for low and highly exposure workers can bias results toward the null.

c. Paired comparisons are included to handle inter-person variability, but as shown in Table 2, the number of participants in both occasions is only about one third of the total pairs analyzed.

d. The plant with the highest range, and highest total exposure values, contributed the lowest number of total samples and samples for pairing. Averaging across plants yields higher numbers for statistical analyses, but masks biologically important information about effects for those at the high end of the exposure.

e. For results in Tables 3 and 4, inter-plant variability, normal seasonal intra-person variability, and the wide range of exposures reported among plants could mask any subtle season effects related to chemical exposure.

f. The text on p. 12 correctly notes that technical factors, sperm volume and days of abstinence can and did have a significant effect on outcomes. The author of the summary correctly notes the study shortcomings, e.g., complexity in the form of the analysis, that the approach chosen does not seem to be the most valid, and that this leads to results that are "difficult to interpret."

g. In the fertility analysis, Table 9, the inclusion of all women, married and single, and women of all ages may bias the expected values to the low end, and this could bias the observed to expected ratio in the direction of false negative results. Moreover, it is clear that age distribution of the exposed men may be uneven, suggesting a younger workforce, where the healthy worker effect operates, and where sicker individuals leave the worker force and are not available to be studied, even though their illness may be related to prior cumulative chemical exposure. There is no discussion of individuals lost to follow-up, or of work related illness outcomes.

h. In the season of birth data, Table 10, the highest exposure group shows the lowest number of births for both season categories. This observation supports concern for reproductive health in the most highly exposed workers.

i. The meaning of confidence intervals is unclear on p. 13, and, the reference to sample size needed to detect a lung cancer risk in a retrospective cohort is irrelevant because reproductive alterations do not have the latency period of lung cancer. It is the high end exposure that could produce the adverse reproductive outcomes of concern here. If sample size is a problem for population based studies, then molecular epidemiology and biomonitoring with a longitudinal study design would be more important.

j. The strengths and weaknesses, on p. 16 are helpful. The second weakness is of the greatest concern from a regulatory epidemiology viewpoint.

cc Mark Dow, OREB/HED
Karen Whitby, CCB/HED
Linda Taylor, ToxII/HED
Ernie Dobbins, ARB/SRRD
Paul Parsons, SRB/SRRD
OREB chron. file
OREB Chemical file

Unsigned copy of signed memo-From disc dated 11-14-91

MEMORANDUM

SUBJECT: Review of Epidemiologic Assessment of Fertility in Male Workers Exposed to Molinate (Ordram) at the Stauffer Chemical Company (MRID # 415892-01 and -02)

TO: Laurence Chitlick, Senior Scientist
Science and Analysis Coordination Branch
Health Effects Division (H-7509-C)

FROM: Ruth H. Allen, Ph.D., M.P.H.
Environmental Scientist (Health)
Special Review and Registration Section
Occupational and Residential Exposure Branch (H-7509-C)

THRU: Curt Lunchick, Section Head
Special Review and Registration Section
Occupational and Residential Exposure Branch (H-7509-C)

Chuck Trichilo, Ph.D., Chief
Occupational and Residential Exposure Branch
Health Effects Division (H-7509-C)

I. Introduction

A review was requested by SACB on 24 July 1991 for reproductive epidemiology studies concerning molinate, also called (Ordram). This chemical is a selective herbicide, registered by ICI Americas, Inc., and used to control watergrass in rice. The purpose of the review is to state the level of concern or likelihood, given the evidence, that molinate may be a significant cause of infertility in a study population of male workers at three facilities.

The only report being reviewed is Vol. 3 (# 415892-01), because Vol. 4 (# 415892-02) is a duplicate of the North Little Rock, Arkansas findings contained in Vol. 3.

The study title is "Epidemiologic Assessment of Fertility in Male Workers Exposed to Ordram at the Stauffer Chemical Company." The authors are Donald R. Taves, M.D., Ph.D., M.P.H., Abraham T.K. Cockett, M.D., Christopher Cox, Ph.D., University of Rochester, and Jane McCusker, M.D., Dr. Ph.H. of University of Massachusetts.

The study is dated April 20, 1984, and it was transmitted to EPA on 8/7/90 by ICI Americas, Inc. Company Agent Becky Sherman. No claim of confidentiality is made for any information contained in the study, but the document and information are proprietary property of ICI Americas, Inc.

The study involves men at facilities in California (n=62), Alabama (n=77), and Arkansas (n= 77). One to three sperm samples were collected from men at the beginning of the shift, during the chemical plant production cycle (exposed), and during the non-production cycle (unexposed). These cycles were separated by three months, enough time for a complete cycle of sperm regeneration.

Sperm counts vary within and between men for reasons other than chemical exposure. Therefore, each man was used as his own control. This reduced variability by 25%. Sperm counts are known to be higher in the spring, and quite variable. For example, one man had a count ten times the average, and a few men had very low sperm counts. Therefore, sperm motility and morphology were also examined, but not reported in detail in the report.

There are a number of gaps in the reports of study methods and findings. These are discussed under detailed consideration below. Consultation with Dr. Sherry Selivan, ORD's Reproductive Epidemiologist confirmed that the study contains significant omissions and numerous points of confusion.

II. Conclusions

1. This study is presented as a negative study, but it contains data that suggest a human reproduction effect in male workers. For example, although the numbers are small for wife's parity (birth number) 3 and 4 in Table III, there are fewer than expected sons and daughters at medium and high doses. This finding is not discussed by the authors, who combine sites and exposure categories in confusing ways. For example, low exposure equals a dose of 0-1 mg, medium equals 1-20 mg, and high is 20 to 1500 mg.

I would recommend a stratified analysis, on total number of years of molinate (Ordram) exposure, at a minimum.

2. The study has other shortcomings which prevent meaningful interpretation. These are highlighted below.

A) There is inadequate discussion of study methods, e.g., whether these workers were exposed to any other chemicals, and for how long, or how these workers were recruited, or how specimens were preserved prior to sperm morphology and motility analyses.

B) Exposure measures are confusing. The authors use an index of hours exposed at the worksite x ORDRAM air concentration at the end of the 3 mo. production cycle. There is no discussion of

what variation exists in exposure throughout the production cycle. This is confounded by seasonal variations that affect sperm counts, and seasonal variations in the production cycle between plants.

C) Worker exposure varies at different plants and is relatively low, compared to reported past exposures a few years earlier. There is no discussion of the changes in industrial hygiene practices that brought on the lower levels of exposure.

D) The California site is described as a dusty environment, and maintenance workers are assumed to have the same exposure as production workers. However, maintenance workers were exposed at a different season of the year. Because of the statistical procedures used in the analysis, e.g., subtracting spring and fall values, this produced negative exposure numbers where exposures actually are positive. This is very confusing to follow in the analysis.

E) There is no discussion of the "healthy worker" effect as a potential bias, e.g., men experiencing adverse reproductive effects may have preferentially left the Ordram workforce, and thus be unrepresented in the study population.

F) There is inadequate discussion of the cases of azoospermia in the study population. There should be a careful discussion of their total work history and clinical test results, as well as, other confounding factors, such as excess drug or alcohol use.

Detailed Consideration

1. In order to understand the epidemiology findings, it is helpful to provide background on what is known so far.

The present human study was triggered by concerns raised in previous animals studies. Molinate has a very low NOEL in animals and has been associated with adverse, anti-fertility effects on reproduction, including testicular degeneration, abnormal spermatozoa, and lower sperm count with decreased motility and abnormal morphology.

Animal metabolism studies show the slowest rate of disappearance of the compound is in blood and blood rich tissue. Histology and histopathology of the testes (Russell et al, 1990) confirm that testicular capillaries are not fenestrated (having one or more openings or pores) and that lymphatic fluids percolate thru cells of the interstitium (supporting tissue around the undeveloped reproductive cells).

Spermatogenesis is an energy intensive process that happens in blood rich tissue. There are numerous mitoses (cell divisions) to produce a large population of cells that subsequently undergo meiosis (reduction division to produce cells with half the chromosomes). While stems cells are very resistent to insults to

the testes, proliferative cells and differentiating spermatogonia show higher mitotic rates and are therefore more susceptible to chemical agents that affect spermatogenesis.

Therefore, adverse reproduction effects may be reversible for a time as indicated by initial animal study findings, but not so with longer or repeated periods of exposure, such as in an occupational setting. This means that it is biologically plausible for workers exposed to molinate to become infertile eventually, even if they show few effects initially after a short three month period of exposure.

From the chemistry of molinate, there is the suggestion of the formation of an isocynate by removal of a thio group, or formation of an acylating agent which could adversely impact terminal amino groups and therefore inactivate protein enzymes. Many functional proteins are secreted by Sertoli cells in the testes, e.g., inhibin to inhibit FSH secretion via feedback to anterior pituitary, and androgen binding protein (ABP) a carrier for androgen. And so any chemical that interferes with protein chemistry in the testes, could produce adverse reproductive effects, both directly on reproductive cells, and indirectly by altering blood or functional protein enzyme activity.

2. Given that time required for more exhaustive review is limited, and given the confusing nature of exposure patterns and statistical analyses presented in this study, more detailed review is deferred, pending consultation with the team being assembled to consider the inclusion of molinate in special review.

Summary

This study is suggestive of human male reproduction problems that would preclude accelerated reregistration, and would favor the initiation of special review.

Moreover, because of the methods problems mentioned above, the results of this single epidemiology study are not definitive enough to support immediate suspension, or other emergency regulatory action by the Agency.

Reference

Russel, Lionel D., et al. 1990. Histological and Histopathological Evaluation of the Testes Cache River Press, Clearwater, Fla.

cc: Chemical File: Molinate
Larry Dorsey (H7509C)