Review of: Dolan, David G: *A Cohort Study of the Effects of Pentachlorophenol on Male Reproductive Function*

Reviewer: Thomas B. Starr, Ph.D.
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This study was conducted to assess the potential impacts of occupational exposure to pentachlorophenol on male reproductive function as characterized indirectly by fertility (i.e., live births to workers' wives) and the sex ratio (proportion of male births). The investigator employed an indirect standardization methodology for fertility assessment that was developed and refined by Dr. Richard J. Levine and his colleagues at CIIT in the early 1980's. This methodology compares workers' post-exposure reproductive experience with their pre-exposure reproductive experience and that of unexposed workers from the same plant.

Exposure status was determined from three information sources: an employee health information database maintained by the company, self-reporting on a questionnaire administered during a face-to-face interview, and presence of chloracne, as indicated in plant medical records or as self-reported. Workers were considered exposed if they 1) had worked a minimum of three days (cumulatively) in plant departments that produced chlorophenols or chlorophenoxy herbicides; 2) were maintenance workers who were listed on the plant chloracne registry; or 3) were workers noted to have chloracne on plant medical records but had not worked exclusively in the production of PCBs and benzene. Nearly 800 such potentially exposed workers were identified.

Approximately 1700 workers were identified who met exclusionary criteria qualifying them as unexposed. Of these, about 750 had an unknown vital status, and time constraints precluded any ascertainment. A "stratified random sample" of 765 of the approximately 950 unexposed workers whose vital status was known was selected for comparison purposes. The sample was "designed to minimize the imbalance" on potential confounders "while providing a sufficient oversample of (older age) strata." Details of the sampling procedure were not provided.

Reproductive histories of workers were ascertained by interview (blinded as to exposure status) and confirmed by interviews with spouses and, where possible, birth certificates. A master worker raw data file containing information on a total of 835 plant workers was prepared. It is not clear why the number of workers included in the raw data file is only about ½ of the roughly 1500 workers noted above. Exposure status was further refined to restrict attention to "ever exposed" or "exposed only" to pentachlorophenol (Department 236), and only once- married male workers without sexual partners outside marriage and whose spouse had never been pregnant by a man other than her worker husband were considered further (there were only 34 female workers identified). There were about 60 (~ 40%) more ever-exposed than only-exposed (~ 160) workers.

Four analyses were performed: comparisons of ever-exposed workers with unexposed workers using 1) birth certificate data or 2) worker recall regarding births, and only-exposed with unexposed using 3) birth certificate data or 4) worker recall. It appears that only one worker's experience did not have complete supporting birth certificate data. Thus, had the birth certificate

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group simply been supplemented by this additional worker's recalled experience, I suspect it would have made very small, if any, differences in the results.

No workers of age less than 25 at the time of examination were included. There was, however, a significant difference between the age distributions of the exposed and unexposed groups: there was a far higher percentage of unexposed than exposed workers in the 25-44 age groups, and slightly greater percentage of exposed than unexposed workers in the 75+ categories.

Author's Conclusions re Fertility

The author concludes that "for all parities, workers ever or only exposed to penta suffered impaired fertility as manifested by significantly lower SFRs than unexposed workers." A similar conclusion was drawn with regard to the subgroup of workers with chloracne. While these conclusions are tempered by the admission that results of analyses that were limited to parity 1+ experience failed to confirm the differences, I believe that the conclusions are far too strong, and indeed, are unwarranted. I believe that there is no significant evidence of reduced fertility in any of the exposed groups. What has been shown is that the fertility of unexposed and pre-exposed married workers is greater than is predicted by the US national birth rates.

As outlined below, I suspect that the differences observed in this study are due almost entirely to a "marital status artifact" induced by the differential in age distributions of the reproductive experience of unexposed and pre-exposed versus post-exposed workers. This distributional imbalance can cause significant problems in any assessment based on indirect standardization methods due to uncontrolled confounding by various factors that covary with age and reproductive ability.

The largest such factor is related to the baseline national birth rates, which are not specific to marital status, but rather, include unmarried reproductive experience, and are in fact strongly influenced by unmarried reproductive experience at the younger ages, particularly for the zero parity class. Social stigma associated with unmarried pregnancies and births induce far lower birth rates among unmarried than married women. Thus, the baseline rates, which include both unmarried and married experience, are unrepresentative of purely married experience, i.e., they are biased low for all age categories. The extent of this bias is age-dependent and most severe in the zero parity class at the younger ages. Restriction of the study to married reproductive experience, which is desirable because the unmarried reproductive experience of workers is almost certain to be very poorly characterized, actually introduces a bias toward high SFRs, especially at younger ages. We have previously called this bias a "marital status artifact", and we have also strongly recommended that all indirect standardization methods of fertility analysis employ marital status-specific birth rates when available, or restrict attention to parity 1+ experience.

While restriction to parity 1+ classes omits women of primary infertility, as noted by the author, I think this is a moot point. It would be virtually impossible to determine if the fertility of such women were further reduced by their husbands' exposures: SFRs for unexposed and exposed workers would both be very near zero and highly unstable. Little, if anything, could or should be

concluded with indirect standardization methodology in such a case.

Author's Conclusions re Sex Ratio

The author calls attention to apparent differences in the sex ratio for births among the various worker groups. There is no obvious effect of exposure on sex ratio. A possibly noteworthy finding is that the ratio may be low among unexposed workers post-employment. This is certainly not an *a priori* expectation, and I would not be inclined to make much of it without additional confirmation.

Summary

The study was generally well-conducted. Considerable care was taken to recognize and minimize, where possible, various potential sources of bias, e.g., as might be introduced by interviewer knowledge of exposure status. My principal concerns lie with the overly strong conclusions of the author regarding findings that, at least in my opinion, are far more likely due to "marital status artifact" or chance.