



December 17, 2014

Mr. Aaron Y. Yeow
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Sent via email to: Yeow.aaron@Epa.gov

Re: Comments on the Revised External Review Draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide- Use of the Mikoczy et. al. Cohort Study (2011)

Dear Mr. Yeow:

The Ethylene Oxide Panel (Panel) of the American Chemistry Council (ACC) appreciates the opportunity to submit the following comments on the study of Swedish sterilant workers prepared by Mikoczy et. al.¹ At the November 18-20, 2014 meeting of the Chemical Assessment Advisory Committee (CAAC) held to review the draft IRIS assessment of ethylene oxide (EO), particular attention was paid to a cohort study of Swedish sterilant workers by Mikoczy et al. This study, in part, focused on very low EO cumulative exposure levels (e.g., median 0.13 ppm-years). The draft IRIS assessment gave little weight to this study in comparison to the NIOSH study.

Several CAAC members, however, expressed the opinion that this study showed a strong relationship between EO and breast cancer, including an exposure response trend as observed in the internal analyses. In the internal analyses, the incidence rate ratios (IRR) for each of the cumulative exposure categories (0.14-0.21 and greater than or equal to 0.22 ppm-years) were statistically greater than the baseline comparison group 0-0.13 ppm-years (IRRs = 2.76, 3.55, respectively). One CAAC member considered the pattern to be supralinear in the low dose that then leveled out.

The results of the external analyses, showing very low incidence rates of breast cancer in the baseline comparison group (SIR = 0.52; 95%CI: 0.25-0.96) and incidence rates comparable to the general Swedish population in the other two groups (1.06, 1.12, respectively) received

¹ Mikoczy, Zoli; Tinnerberg, Hakan; Bjork, Jonas; and Albin, Maria. Cancer Incidence and Mortality in Swedish Sterilant Workers Exposed to Ethylene Oxide: Updated Cohort Study Findings 1972–2006. International Journal of Environmental Research and Public Health- June 2011.



minimal attention, as did the deficit of breast cancer cases in the total population (41 observed, 51 expected SIR= 0.81; 95%CI: 0.58-1.09). In fact, one CAAC member recommended ignoring external analyses.

Internal analyses comparing workers with higher exposure to workers with lower or no exposure in the same facility are intended to create greater homogeneity among the groups compared, such that the only meaningful difference among them is the exposure. Unfortunately, this does not always work as intended. The lowest or no exposure group may differ from the other groups in ways other than exposure that may be related to the disease of interest, such that confounding may still be present. Several panel members attributed the different results between the external and internal analyses to the “healthy worker effect” (HWE).

Extreme differences in the results of external and internal analyses indicate that confounding but not the HWE has occurred in the Mikoczy study. A statistically significant deficit of breast cancer, SIR of 0.52, in the baseline group and normal rates in the other groups ensures a doubling or more of *relative* risks in internal analyses. To attribute the low breast cancer rates in the baseline group to the HWE is not plausible for several reasons:

- 1) HWE has been shown to be related to non-cancer causes, not cancer causes which impacts employability and fitness for work (Choi, 1992)²
- 2) A 15 year induction period for latency in the external analysis of the Mikoczy study did not meaningfully change the results, and the HWE is known to diminish with longer follow up (McMichael, 1976³ and Choi, 1992).
- 3) Since null parity, low parity and older age at first birth are positively related to breast cancer, working women going back to 1972, as in the Mikoczy study, would be more likely to have fewer children and, therefore, would not be expected to be “healthier” in regard to breast cancer (Schottenfeld and Fraumeni, 1996)⁴.

The findings of Grindley et al. (1999)⁵ further indicate that HWE is not a plausible explanation. This study was funded by the U.S. National Cancer Institute (NCI) and included co-authors from NCI (Mustafa Dosemeci and Sheila Hoar Zahm). In this study, cancer rates among employed Swedish women were compared to women “not gainfully employed”. Employed women did not have lower risks for cancers of the reproductive organs including breast cancer. The breast cancer SIR was 1.09 (95%CI: 1.07-1.11) for those employed in both 1960 and 1970 compared to those unemployed. The authors concluded, “These results show no general HWE for cancer incidence among employed Swedish women.”

² Choi BCK. 1992. Definition, sources, magnitude, effect modifiers, and strategies of reduction of the healthy worker effect. J Occup Med 34:979–988.

³ McMichael AJ. 1976. Standardized mortality ratios and the “healthy worker effect”: scratching beneath the surface. J Occup Med 18:165–168.

⁴ Schottenfeld D, Fraumeni JF Jr. 1996. Cancer epidemiology and prevention, 2nd ed. New York: Oxford University Press.

⁵ Gridley, Gloria; Nyren, Olaf; Dosemeci, Mustafa; Moradi, Tahereh; Adami, Hans-Olav; Carroll, Leslie; and Zahm, Shelia Hoar. 1999. Is There a Healthy Worker Effect for Cancer Incidence Among Women in Sweden?. American Journal of Industrial Medicine 36:193–199.



The uncertainty around the results of the Mikoczy study cannot be explained by the HWE. There remains some unexplained confounding. Two possible sources of bias include:

- 1) missing cumulative exposure data for 151 study subjects that included 10 cancers, and
- 2) large differences in duration of employment in the three exposure categories (3.6, 8.3 and 11.5 years, respectively) and the association between length of employment, risk factors for breast cancer and cumulative exposure. The major uncertainty around the baseline group in this study renders the results questionable and difficult to interpret.

Furthermore, this study is not consistent with the NIOSH breast cancer incidence study which had a median cumulative exposure of 6 ppm-years and reported only “suggestive” evidence of breast cancer risk at their highest cumulative exposure levels, not at the low levels indicated in the Mikoczy study.

If you have any questions or require additional information please feel free to contact me by phone (202-249-6714) or by email at bill_gulledge@americanchemistry.com.

Sincerely,

Bill Gulledge
Senior Director, Chemical Products and Technology Division
Manager, Ethylene Oxide Panel

