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June 8, 2015

Mr. Thomas Carpenter
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US EPA Science Advisory Board, MC 1400R
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RE: Comments on SAB draft report reviewing the EPA's *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide* – Use of the Mikoczy et al (2011) Cohort Study

Dear Mr. Carpenter:

My name is Gary Marsh. I am Professor of Biostatistics, Epidemiology and Clinical & Translational Science, and Director of the Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. Since 1978, I have designed and conducted more than 50 occupational epidemiology studies of potential health effects from workplace exposures, including man-made mineral fibers, formaldehyde, acrylamide, acrylonitrile, arsenic, chloroprene, tungsten carbide with cobalt binder, petrochemicals, aromatic amines and pharmaceuticals. I am a Fellow of the American College of Epidemiology and have more than 200 publications in the areas of occupational/environmental epidemiology, biostatistics, statistical computing and health services evaluation.

I was asked by the Ethylene Oxide (EO) Panel of the American Chemistry Council to share with you my evaluation and critique of the study of Swedish sterilant workers published by Mikoczy et al. in 2011, in which the authors reported a positive exposure-response relationship with EO and breast cancer incidence based on internal cohort analyses. It is my understanding that at the November 18-20, 2014 meeting of the Chemical Assessment Advisory Committee (CAAC), held to review the draft IRIS assessment of EO, particular attention was paid to the Mikoczy et al. study and the authors' conclusion of a positive exposure-response relationship with EO and breast cancer. I also understand that several CAAC members expressed strong support of this conclusion.

I submit that the data presented in the Mikoczy et al. study do not support the conclusion of a positive exposure-response relationship with EO and breast cancer. This opinion is based on three major findings in the Mikoczy et al. study that I describe below.

Finding 1: No evidence of elevated breast cancer incidence or mortality based on external comparisons

The external comparisons made by Mikoczy et al. were based on the general Swedish population in the regional area of Scania County. Such local rates are usually considered the most valid comparison as they can help adjust for social, cultural, and economic factors related to diseases such as breast cancer. Further, the external comparisons were based on a sufficiently large number of observed breast cancer cases or deaths to produce stable risk estimates overall and in the subcategories examined.

Mikoczy et al. found that the number of breast cancer cases observed during 1972-2006 was considerably less than the number of cases expected based on the external comparisons of sterilant workers with local Swedish population. Specifically, 19% and 14% deficits in breast cancer cases were observed, respectively, for the full cohort of 2,171 workers using no induction latency period (41 cases observed, 50.9 cases expected, Standardized Incidence Ratio (SIR)=0.81, 95%CI=0.58-1.09) and the subgroup of 2,046 workers with a minimum induction latency period of 15 years (33 cases observed, 38.54 cases expected, SIR=0.86, 95%CI=0.59-1.20). Second, a 9% deficit in breast cancer cases was observed among the 2,077 workers at risk in the updated 1991-2006 follow-up of the original cohort (36 cases observed, 39.4 cases expected, SIR=0.91, 95%CI=0.64-1.27). Third, Mikoczy et al. observed essentially null findings for breast cancer incidence in each of the three cumulative EO exposure groups used in both external and internal comparisons (i.e., a statistically significant 48% deficit in breast cancer cases in the baseline category (0-0.13 ppm years, 10 observed cases, SIR=0.52, 95%CI=0.25-0.96), and slight, not statistically significant 6% and 12% elevations in breast cancer cases in the second and third cumulative EO exposure categories (0.14-0.21 ppm-years, SIR=1.06, 95%CI=0.58-1.78, and ≥ 0.22 ppm-years, SIR=1.12, 95% CI=0.65-1.79, respectively,)). While data were not shown in tables, Mikoczy et al. also reported that none of the corresponding breast cancer mortality risk estimates (SMRs) were statistically significantly elevated.

My interpretation of Finding 1: If EO is associated with breast cancer incidence or mortality, one would expect to see large, statistically significant elevations in risk, not deficits or slight excesses, among workers followed for longer periods of time or exposed to higher levels of EO.

Finding 2: No evidence of elevated breast cancer incidence risk based on internal comparisons

Mikoczy et al. used Poisson regression analysis stratified by gender, age and calendar period to generate breast cancer incidence rate ratios (IRRs) for the two highest categories of cumulative EO exposure (0.14-0.21, and ≥ 0.22 ppm-years) relative to the baseline EO exposure category (0-0.14 ppm-years). This analysis yielded IRRs for the second and third cumulative EO exposure categories that were statistically significantly greater than the baseline category (IRR=2.76, 95%CI=1.20-6.33 and IRR=3.55, 95%CI=1.58-7.93, respectively). This was the key finding in the Mikoczy et al. study that led to the authors' spurious conclusion of a positive exposure-response relationship with EO and breast cancer. This finding also led to my main criticism of this cohort analysis.

Such internal analyses comparing workers with higher exposure to workers with lower or no exposure in the same facility are intended to enhance the homogeneity of the groups being compared, such that

exposure is the only meaningful difference among them. Unfortunately, as in the Mikoczy et al. study, internal comparisons do not always work as intended and can lead to seriously distorted risk estimates for higher exposure categories and inappropriate conclusions regarding exposure-response.

Specifically, in the Mikoczy et al. study, the greater than 2-fold *relative* excesses in breast cancer incidence risk in the two highest cumulative EO exposure categories in the internal analyses were ensured by the inordinately large, statistically significant 48% *deficit* in breast cancer incidence in the baseline category to which the higher exposure categories were compared. The inordinately low baseline SIR for breast cancer is especially puzzling given that regional rates were used in the external comparisons (which usually enhance the homogeneity of the external comparison groups) and that there was no apparent problem with under-ascertainment of breast cancer cases. Had the breast cancer SIR in the baseline category been a more reasonable value closer to 1.00 (as would be expected among workers with low or no EO exposure) the IRRs in the two highest cumulative exposure categories would have been only slightly elevated and unremarkable, as were the corresponding SIRs.

In the Mikoczy et al. study it appears that for reasons unknown at this time, the lowest or no exposure group differs from the highest two cumulative EO exposure groups on factors other than exposure. Even worse, these factors may be related to breast cancer, leading to uncontrolled negative confounding. It is possible that the low baseline SIR could be due, at least in part, to the missing cumulative EO exposure data for 151 workers that included 10 cancers, or to the large difference in duration of employment in the three EO 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.

It is also highly unlikely that the low baseline SIR is due to the healthy worker effect (HWE) (McMichael, 1976). First, the HWE has been shown to be limited to non-cancer outcomes, such as cardiovascular disease, which impact initial and continued employability (Choi, 1992). Second, the HWE is known to diminish over time and this was not evident in the external breast cancer incidence analysis using the 15-year induction latency period (McMichael, 1976, Choi, 1992). Third, null or low parity and older age at first birth are factors positively related to breast cancer. Thus, working women going back to as early as 1964, as in the Mikoczy et al. study, would be more likely to have fewer children and, therefore, be associated with a higher risk of breast cancer (Schottenfeld and Fraumeni, 1996). Finally, Grindley et al. (1999) provide direct evidence that the HWE is not a reasonable explanation for the low baseline SIR for breast cancer. In this NCI-funded study, employed Swedish women compared to women “not gainfully employed” did not have lower risks for cancers of the reproductive organs, including breast cancer, leading the authors to conclude that, “These results show no general HWE for cancer incidence among Swedish women.”

My interpretation of Finding 2: In effect, the uncertainties around the reasons for the inordinately low, statistically significant SIR for breast cancer in the baseline EO exposure category invalidate the results of the internal analysis reported by Mikoczy et al. An internal analysis based on a more realistic baseline breast cancer risk (SIR \approx 1.00) would not reveal evidence of an association between EO and breast cancer.

Finding 3: The EO exposure-response results in the Mikoczy et al. study are inconsistent with those of the NIOSH breast cancer incidence study

Cumulative EO exposure levels in the Mikoczy et al. study were very low relative to NIOSH breast cancer incidence study of 7,576 female sterilant workers exposed to EO (Steenland et al., 2003). For example, in the Mikoczy et al. study the median cumulative EO exposure values of workers in both the second and third cumulative EO exposure categories (0.17 and 0.39 ppm-years, respectively) fall well within the *lowest* non-baseline cumulative EO exposure category (>0 - <2.34 ppm-years) used in the NIOSH study (with no exposure lag as in Mikoczy et al.).

For this lowest non-baseline category of cumulative EO exposure, Steenland et al., using external comparisons, observed a 26% deficit in breast cancer cases (SIR=0.74, 95%CI=0.57-0.97) compared with slightly elevated SIRs of 1.06 and 1.12 reported by Mikoczy et al. for workers with similar levels of cumulative EO exposure. More importantly, in the NIOSH study, the internal analysis of the entire cohort also yielded a deficit in breast cancer cases in the lowest EO cumulative exposure category (Odds Ratio=0.98, 95%CI=0.69-1.38). This is a striking, qualitatively different result than the statistically significantly elevated IRRs of 2.76 and 3.55 reported by Mikoczy et al. for workers with similar levels of cumulative EO exposure. Further, the median cumulative EO exposure in the NIOSH study was about 8.0 ppm-years and the range of cumulative EO exposures in the highest two categories of cumulative EO exposure (no lag) were two orders of magnitude greater (17.4-45.0 and 45.0+ ppm-years, respectively) than those experienced by workers in the Mikoczy et al. study. Even at these considerably higher levels of EO exposure, Steenland et al. concluded only “suggestive” evidence of an elevated breast cancer risk.

My interpretation of Finding 3: The major inconsistency in the cumulative EO exposure-related findings between the Mikoczy et al. and NIOSH studies provides further evidence that the corresponding IRRs in the Mikoczy et al. study were inflated by the inordinately low, statistically significant reduced risk for breast cancer in the baseline category, leading to their spurious conclusion of a positive association between EO and breast cancer.

Overall Conclusions

Contrary to the authors’ suggestion, the data presented in the Mikoczy et al. study do not support the conclusion of a positive exposure-response relationship with EO and breast cancer. The EPA SAB evaluating the carcinogenicity of EO should weigh the findings of the Mikoczy et al. study accordingly.

Respectfully submitted,



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Page 5.

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