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OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Clarifying comments in response to the 18-20 November public peer review meeting of the augmented SAB CAAC reviewing EPA's draft ethylene oxide carcinogenicity assessment

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TO: Aaron Yeow, EPA Science Advisory Board

As a follow-up to the 18-20 November public peer review meeting, this memorandum provides some clarifying comments to the augmented SAB CAAC panel reviewing EPA's draft ethylene oxide carcinogenicity assessment. Clarifying comments are provided on four separate issues below. If the panel has any questions about these comments or any other issues pertaining to the assessment, we would be happy to provide additional information.

1. "ppm-day" units in the NIOSH study

   EPA understands the "ppm-day" cumulative exposure unit in the NIOSH study to correspond to an 8-hour time-weighted average (TWA) exposure level multiplied by duration of exposure as reflected by *calendar days* (i.e., 365 calendar days/year, as opposed to 240 occupational days/year) of employment in a given job. EPA bases its understanding on footnote "‖" of Table 6 (page 794) of Stayner et al. (1993), which shows that the cumulative exposure for 45 years at the OSHA standard (8-hour TWA) of 1 ppm is calculated as (45 ppm-years) * (365 days/year) for input to the rate ratio equation. EPA also confirmed with Dr. Steenland that "ppm-years" were in terms of 365 days/year.

   Thus, to convert to lifetime continuous environmental exposures, EPA first converts the occupational cumulative exposures to ppm-years by dividing the ppm-days by 365 days/year. Next, EPA converts the 8-hour TWA exposures to continuous exposure over the course of a year by multiplying by (10 m^3/20 m^3) to account for the different volumes breathed by workers over an 8-hour shift and the general population over a 24-hour day and by (240 days/365 days) to account for the days worked by the workers in a year, consistent with EPA practice when using occupational data. The "years" are then accounted for in the life-table analysis (see Appendix E and the EXCEL spreadsheet provided as supplemental information on 14 November 2014; note that in the life-table analyses the conversions are in reverse because the starting point is the environmental exposure, here 0.0114 ppm).

2. Exposure metrics used in the NIOSH study

As the consideration of exposure metrics other than cumulative exposure was discussed at the public meeting, EPA notes that the NIOSH investigators explored metrics other than cumulative exposure in their Cox regression modeling, specifically, duration of exposure, average exposure, and maximum exposure, as mentioned briefly on pages 4-5, 4-30, and 4-51 of the draft assessment and as described on page 790 of Stayner et al. (1993). These metrics were tried for the Cox model “with no lag or different lags”, according to page 3 of Steenland et al. (2004). While Stayner et al. (1993) reported statistically significant positive Cox regression coefficients with cumulative exposure for lymphoid and all lymphohematopoietic cancers, they observed that the coefficients for duration of exposure and for average and maximum exposure were “weakly positive or negative”. In the follow-up study of the NIOSH cohort, Steenland et al. (2004) considered the same four exposure metrics and reported that “models using duration of exposure, peak [i.e., maximum][1] exposure, and average exposure did not predict [lympho]hematopoietic cancer as well as models using cumulative exposure” (page 5). Steenland et al. (2004) report the same finding that the exposure metrics of duration of exposure, peak exposure, and average exposure were not as predictive as cumulative exposure in the paragraph on lymphoid cancers. Similarly, Steenland et al. (2003) considered the same four exposure metrics in the breast cancer incidence study and observed that the Cox regression “model using duration of exposure (with a 15 year lag) fit slightly better than the model using cumulative exposure” and that the “[m]odels using peak [i.e., maximum] or average exposure did not fit as well” (page 535). In summary, the NIOSH investigators considered four exposure metrics – cumulative exposure, duration of exposure, maximum 8-hour TWA exposure, and average exposure – and their results indicate that Cox regression models using cumulative exposure generally outperformed Cox models using the other metrics in predicting cancer risk.

3. Mean versus median exposures for the categorical groups

The panel seemed to be of the view that EPA should use median, rather than mean, cumulative exposures to represent the categorical groups in the linear regressions of the categorical results. We recognize that the median might be a useful central tendency description of the exposures in the categorical groups and that, because the median exposures are lower than the means, using the medians would yield a higher, more “conservative” unit risk estimate in the face of uncertainty in representing the categorical exposures. Nonetheless, it is our understanding that, at least for the specific case in which the relative risk, or rate ratio in this case, is a linear function of cumulative exposure, the mean is the better representation of exposure for the purposes of reflecting

1 “Peak” and “maximum” exposures are used in the different papers, but both terms refer to the highest 8-hour TWA exposure experienced by a worker over his or her work history.

risk. This is illustrated in the simplified example below:

> Assume that the relative risk (rate ratio) is a linear function of cumulative exposure; i.e., RR = 1 + $\Sigma\beta x_i$, where the x_i are the individual cumulative exposures.
> Assume also that the linear coefficient (β) is 1 per ppm-year.
>
> Assume for a group of 10 people that 9 have cumulative exposures of 0.1 ppm-years and 1 has a cumulative exposure of 1 ppm-year.
>
> Then, if you sum the individual extra relative risk estimates of the 10 people, you get:
> $\Sigma\beta x_i$ = 9 * (0.1 ppm-years * 1 per ppm-year) + 1*(1 ppm-year * 1 per ppm-year) = 1.9; or RR = 1 + $\Sigma\beta x_i$ = 2.9.
>
> Similarly, if you use the group mean of 0.19 ppm-years, you get an extra relative risk for the group of:
> $\Sigma\beta x_{mean}$ = 10 * (0.19 ppm-years * 1 per ppm-year) = 1.9, or RR = 2.9.
>
> However, if you use the group median of 0.1 ppm-years, you get an extra relative risk for the group of:
> $\Sigma\beta x_{median}$ = 10 * (0.1 ppm-years * 1 per ppm-year) = 1.0, or RR = 2.0,
> which, unlike for the mean exposure, does <u>not</u> replicate the sum of the individual extra relative risks.

The linear regression model assumes that risk is linear with cumulative exposure. Even though we have lost the ability to distinguish the lowest from the highest exposures within a categorical group, we expect the response (risk of cancer mortality) to reflect the linear exposure-response relationship with cumulative exposure that we are assuming across the categorical groups.

If the panel recommends that EPA should use the median cumulative exposures to represent the categorical groups in the linear regressions of the categorical results, it would be helpful if the rationale is included to inform us if we are misinterpreting the suitability of the mean cumulative exposure for predicting risk when risk is a linear function of cumulative exposure.

4. Presentation of unit risk estimates

Some panel members wanted to compare the lymphoid cancer unit risk estimate from the linear regression of categorical results with the unit risk estimates from the Cox regression with log cumulative exposure and the two-piece spline models and expressed frustration that not all of the unit risk estimates were provided in the Tables, noting that they would expect the unit risk estimates from the latter models to be higher but could not know how much. We regret that the draft was not clear enough for the panel to quantitatively compare these models.

For the panel's convenience, all of the unit risk estimates for Tables 4-5 and 4-13 have been filled in in Tables later in this memorandum.

While we are supplying the unit risk estimates in this memorandum, it was our intention in listing all the major models in the Tables with their EC_{01}s and LEC_{01}s that these models could be compared quantitatively using the EC_{01} and LEC_{01} values, hence providing transparency about the model results. Unit risk estimates for all the models can be readily derived by calculating $0.01/LEC_{01}$. In addition, these models can be compared directly by comparing the LEC_{01}s, the relative value of which, in inverse, is the same as the relative value of two given unit risk estimates. This is illustrated in the following example (in which all the models include a 15-year lag):

> From Table 4-5 of the draft assessment, the LEC_{01} from the Cox regression model with log cumulative exposure is 8.98×10^{-5} ppm, which yields a unit risk estimate of $0.01/(8.98 \times 10^{-5}$ ppm) = 111 per ppm.
>
> Likewise, the LEC_{01} from the low-exposure spline from the two-piece log-linear spline model with the knot at 100 ppm × days is 2.91×10^{-4} ppm, which yields a unit risk estimate of $0.01/(2.91 \times 10^{-4}$ ppm) = 34.4 per ppm.
>
> The unit risk estimates from these models are *127* times and *39* times, respectively, the unit risk estimate of 0.877 per ppm from the linear regression of the categorical results.
>
> Alternatively, these same ratios can be calculated directly from the LEC_{01}s, where the LEC_{01} from the linear regression of the categorical results is 1.14×10^{-2} ppm:
> $(1.14 \times 10^{-2}$ ppm)/(8.98×10^{-5} ppm) = *127*
> $(1.14 \times 10^{-2}$ ppm)/(2.91×10^{-4} ppm) = *39*

We understand that it is useful for those evaluating the models to see how the model results compare, such as by comparing the resultant unit risk estimates or their reciprical correlates, the LEC_{01} values. We welcome the panel's advice as to whether it might be misleading to present all the unit risk estimates without regard to whether the model being described was judged to have a reasonable fit or provide a credible low-exposure response. Our thought was that the LEC_{01} values would allow quantitative comparison of a value directly related to the unit risk estimate without implying that all of the models were reasonable for the purpose of deriving unit risk estimates.

Table 4-5 (augmented). EC_{01}, LEC_{01}, and unit risk estimates for lymphoid cancer

Model	Mortality			Incidence		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Cox regression model, log cumulative exposure, 15-yr lag	0.00441	0.000428	20.8	0.000288	0.0000898	111
low-exposure log-linear spline from 2-piece spline model with maximum likelihood (knot at 100 ppm × days), cumulative exposure, 15-yr lag	0.000982	0.000545	18.3	0.000525	0.000291	34.4
Alternative low-exposure log-linear spline (knot at 1,600 ppm × days), cumulative exposure, 15-yr lag	0.0203	0.0109	0.917	0.0108	0.00583	1.72
Linear regression of categorical results, cumulative exposure, 15-yr lag	0.0564	0.0252	0.397	0.0254	0.0114	**0.877**

Table 4-13 (augmented). EC_{01}, LEC_{01}, and unit risk estimates for breast cancer incidence in females—invasive and in situ

Model	With interviews			Full cohort		
	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)	EC_{01} (ppm)	LEC_{01} (ppm)	Unit risk (per ppm)
Cox regression, cumulative exposure, 15-yr lag	0.135	0.0788	0.127	0.237	0.115	0.0870
Cox regression, log cumulative exposure, 15-yr lag	0.0000765	0.0000422	237	0.000124	0.0000529	189
Linear regression of categorical results, excluding highest exposure quintile; cumulative exposure, 15-yr lag	0.0257	0.0118	0.847	0.0503	0.0188	0.532
Low-exposure log-linear spline, cumulative exposure, 15-yr lag	0.0166	0.00991	1.01	--		
Linear model with continuous cumulative exposure, 15-yr lag	0.0437	0.0224	0.446	--		
Low-exposure linear spline, cumulative exposure, 15-yr lag	0.0112	0.00576	**1.74**	--		

Stayner, L; Steenland, K; Greife, A; Hornung, R; Hayes, RB; Nowlin, S; Morawetz, J; Ringenburg, V; Elliot, L; Halperin, W. (1993). Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. Am J Epidemiol 138: 787-798.

Steenland, K; Stayner, L; Deddens, J. (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med 61: 2-7.

Steenland, K; Whelan, E; Deddens, J; Stayner, L; Ward, E. (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control 14: 531-539.