Evaluation of Differences between Strata Coworker Models

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Introduction

ORAUT-RPRT-0053 provides a statistical approach for the evaluation of potential stratification in coworker models. The concept employs a two-tiered evaluation where the stratified distributions are first compared on a year-by-year basis (or other selected monitoring interval) to determine if any of the individual distributions are significantly different. Significance in this case is evaluated using a Monte Carlo permutation test or a Peto-Prentice test at the 0.05 significance level. If a significant difference is observed in any of the modeled time intervals, then a test of practical significance is employed. This test compares the slopes of the chronic intake models over the time periods where a statistically significant difference in the modeled distributions was observed. One of the objections raised by Sanford Cohen & Associates (SC&A) to the use of these test statistics is that they are, in certain cases, capable of only detecting large differences in geometric means between datasets. This is particularly true in the situation where there are small sample sizes and the distributions have large standard deviations.

The National Institute for Occupational Safety and Health's (NIOSH) standard practice is to use the 95th percentile value of the distribution of all monitored workers to estimate doses for all unmonitored workers with a potential to be highly exposed[1]. If a stratum within the all monitored workers distribution can be identified, the worker's dose would be represented by the lognormal distribution that defines that stratum. Given this, it is of interest to compare the differences between using the probability of causation (PC) outcomes for the 95th percentile value and the lognormal distribution for the stratified subset.

Preliminary Evaluation

As discussed during the April 7, 2014, Advisory Board on Radiation and Worker Health's Work Group on Special Exposure Cohort (SEC) Issues meeting[2], unmonitored workers who are judged to have been highly exposed would receive the 95th percentile of the all monitored workers coworker model. This value would be used as a constant to calculate the dose for the period of time covered by the coworker model. If there are sufficient data available to develop a stratified subset of the full model, the lognormal distribution of the stratified model would be used to calculate doses, rather than the 95th percentile. In this white paper, NIOSH explores the relationship between the PC generated for a stratified model and the use of the 95th percentile as a constant for the full model.

During the April 7th Work Group meeting, NIOSH proposed to outline a possible strategy that could be used to make such a comparison. As part of this effort, NIOSH first evaluated the relationship that exists between the PC generated using either a distribution or a constant. That is, NIOSH determined the amount of increase in the geometric mean of a lognormal distribution required to produce a PC in

[1] For purposes of this discussion, a highly exposed worker would be one who routinely conducted work that had the possibility of generating airborne radioactivity.
[2] See pages 33-59 of the meeting transcripts: <http://www.cdc.gov/niosh/ocas/pdfs/abrwh/2014/wgtr040714.pdf>

NIOSH-Interactive Radio Epidemiological Program (IREP) that is equivalent to the input of the 95th percentile of the distribution as a constant. There are, of course, a number of factors that contribute to the overall uncertainty of the PC calculation that will likely affect the outcome of such a comparison. These include: 1) the type of the exposure (alpha, beta, gamma or neutron); 2) whether the exposure is chronic or acute; 3) the age at exposure and the time period between exposure and the development of a cancer; 4) the relative uncertainties associated with the full and stratified distributions; 5) the cancer model being applied to the case; and 6) gender.

Because there is substantial uncertainty associated with the radiation effectiveness associated with alpha exposure, this exposure type was chosen for the initial evaluation. The rationale behind this choice was that those parameters that tend to increase the overall uncertainty of the input dose will also tend to maximize the effect of the overall uncertainty in the PC outcome. This would have the effect of maximizing the 99th percentile of the outcome of the calculation for a given dose input. The age at exposure and age at diagnosis for this analysis was fixed at 27 and 68 years for solid cancers and 33 and 49 years for leukemia. These were the median values observed for these cancers in the previous analysis of practically significant dose.

Using the above parameters, the NIOSH-IREP program was used to compute the value of the increase in geometric mean that produces the same 99th percentile PC result as the input of the 95th percentile of the lognormal distribution associated with the full model. This evaluation was done for all the 33 cancers models in NIOSH-IREP. The distribution for all monitored workers was assumed to have a geometric mean (GM) of 1 and a geometric standard deviation (GSD) of 3. As indicated in Table 1 on page 6, the 95th percentile of this distribution is equal to 6.09. This represents the value that would be used for unmonitored workers who were judged to be highly exposed. The last two columns of Table 1 provide the parameters of a lognormal distribution that produces the same 99th percentile PC result as that of using the constant equal to the 95th percentile of the full model. As can be seen the results vary by cancer model, with the lowest geometric mean (2.07) associated with the cancer model for urinary organs, excluding the bladder.

If the GSDs of the all monitored worker and stratified subset models are the same, the geometric mean of the stratified model would have to be at least two times higher than the geometric mean of the full model for the stratified model to produce a more claimant favorable outcome. In other words, a stratified model would need to have a GM of 2.07 with a corresponding GSD of 3.0 to produce the same PC result as the input of the 95th percentile value of 6.09 as a constant. This is based on the urinary organ cancer model which, as indicated in Table 1, required the lowest multiplier. All other cancers would need to have an even larger increase in the geometric mean to equal the PC value produced by the 95th percentile as a constant.

The above evaluations were conducted assuming a GSD of 3.0 for both the full distribution and the stratified subset. Preliminary analysis of this relationship using increased GSDs of 4 and 5 for both the full and subset distributions indicate that the factor of two is still a reasonable approximation. When the stratified model has an increase in GSD over the full distribution, the difference in GM for the stratified model is reduced. Although it has not yet been fully evaluated, observation of a few stratified distributions indicates that the GSD tends to increase when the stratified subset has a lower GM than the full distribution. The converse of this also appears to be true. That is, the GSD for stratified models tends to be lower as the GM increases over that of the full model. This relationship requires further evaluation.

Example Evaluation

The concepts outlined above were applied to the example coworker models that were provided in Figures A-1 and A-3 of Attachment A to ORAUT-RPRT-0053, which are reproduced in Figure 1 of this document. As can be seen in Figure 1 on page 8, the full distribution that includes all monitored workers has a GM of 0.7509 and a GSD of 4.055, while the stratified subset has GM of 0.9306 and a GSD of 3.753. Even though the geometric mean for the stratified subset is almost 24 percent greater than that of the full distribution, it is likely that statistical testing would find that there is no significant difference between these two distributions. While it might be tempting to decide that it would be claimant favorable to stratify these distributions (even though they might fail the significance test) it is worth evaluating what effect this might have when applied to a PC calculation.

As described previously, the 95th percentile of the full distribution will be applied to those unmonitored workers who are judged to have been highly exposed. In this case, the 95th percentile of the distribution for all monitored workers is $0.7509 \times (4.055^{1.645}) = 7.51$. This value is used is to account for the fact that the full distribution may be comprised of several distributions and the most highly exposed unmonitored workers could fall into the upper tail of the all worker distribution. In this way, there is less than a 5% chance that the unmonitored workers exposure is greater than the value used in his or her dose reconstruction. Once a stratified model is produced, the distribution is considered representative of the stratified subset of workers and the GM of the dose associated with the bioassay value, along with its associated GSD, will be used to generate the NIOSH-IREP output.

To evaluate whether the stratified subset would produce a greater PC value than the 95th percentile of the distribution of data for all monitored workers, each scenario was run through the NIOSH-IREP calculation using the same default values as those used to establish the results provided in Table 1. That is, the worker was considered to have been: 1) male, first exposed when 27 years old; 2) chronically exposed to alpha activity; 3) diagnosed when 68 years old; and 4) developed cancer of a urinary organ other than the bladder. The urinary organ was chosen because previous testing indicated that this cancer model produced the most claimant favorable result. Although the input to NIOSH-IREP requires values in units of dose, the bioassay values observed were used as NIOSH-IREP inputs for this exercise. This

is acceptable because this analysis is only interested in the relative PC outcomes between the two models. Thus, the first NIOSH-IREP run used 7.51 as the input term, while the second run used the full lognormal distribution with a GM of 0.9306 and a GSD of 3.753. At the 99th percentile, the NIOSH-IREP output results were 12.2% for the stratified subset and 20.0% for the 95th percentile of the all monitored workers distribution.

Summary and Conclusions

Because of large uncertainties associated with coworker model distributions, it is not possible to statistically detect small differences between geometric means of a coworker model based on all monitored workers and one based on an identified subset (strata) of data from the full model. This white paper has explored an alternative method of evaluating the significance of differences between coworker models that was not based on statistical considerations, but based on the probability of causation outcome. For heavily exposed, unmonitored workers it was determined that fairly large differences in geometric means between the stratified subset and the all monitored worker distributions were required to produce PC results that exceeded those produced using the 95th percentile of the all monitored worker distribution.

Under the test parameters used in this analysis, it was found that this difference was approximately a factor of two when the GSDs of the distributions being compared were the same. Although attempts were made to ensure that the comparisons made were conservative (e.g., the magnitude of the differences required was minimized), further analysis is required to evaluate the concepts explored in this white paper more fully. Nonetheless, it does appear that the inability to statistically detect small or even somewhat large (i.e., a factor of 2) differences in geometric means between distributions may be mitigated by NIOSH's claimant favorable practice of using the 95th percentile of the all monitored workers distribution. Unless a statistically significant difference is detected using the methods outlined in ORUAT-RPRT-0053, it might be more claimant favorable to continue to use the 95th percentile of the all monitored workers distribution as a constant to represent exposures to unmonitored workers who may have been highly exposed. If a statistically significant difference is detected, the subset should be stratified, regardless of the effect on the outcome of a dose reconstruction.

Table 1

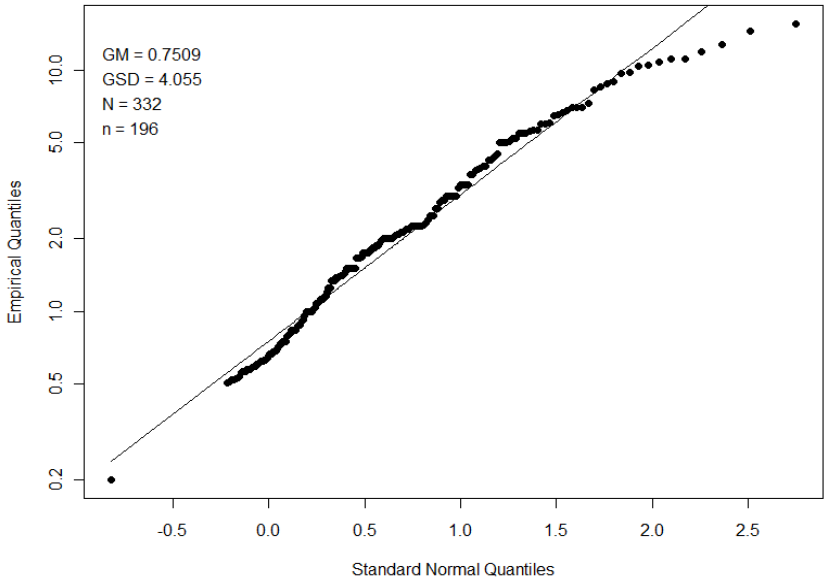
Parameters of the Lognormal dose distribution for a Stratified Model that are needed to get the same PC result in IREP, as the PC result obtained by using the constant dose equal to the 95th percentile of the Full Model (continued on next page).

IREP Cancer Model	Gender	Age at Exposure	Age at Diagnosis	Full Model	Stratified Model	
				95th percentile of Lognormal (1,3)	GM	GSD
Female Genitalia, excl. ovary	Female	27	68	6.09	4.11	3
Non-melanoma skin-Squamous Cell	Male	27	68	6.09	3.05	3
Leukemia, excl. CLL	Male	27	68	6.09	2.62	3
Other respiratory	Male	27	68	6.09	2.53	3
Chronic Lymphocytic Leukemia	Male	27	68	6.09	2.51	3
Gallbladder	Male	27	68	6.09	2.48	3
All Male Genitalia	Male	27	68	6.09	2.46	3
Chronic Myeloid Leukemia	Male	33	49	6.09	2.46	3
Lymphoma & multiple myeloma	Male	27	68	6.09	2.45	3
Stomach	Male	27	68	6.09	2.45	3
Thyroid	Male	27	68	6.09	2.42	3
Malignant melanoma	Male	27	68	6.09	2.34	3
Non-melanoma skin-Basal Cell	Male	27	68	6.09	2.34	3
Nervous system	Male	27	68	6.09	2.31	3
Pancreas	Male	27	68	6.09	2.31	3
Rectum	Male	27	68	6.09	2.31	3
Acute Myeloid Leukemia	Male	33	49	6.09	2.29	3
Leukemia, excl. CLL	Male	33	49	6.09	2.26	3
Liver	Male	27	68	6.09	2.26	3
Esophagus	Male	27	68	6.09	2.22	3
Lung	Male	27	68	6.09	2.22	3
Ovary	Female	27	68	6.09	2.22	3
Oral Cavity and Pharynx	Male	27	68	6.09	2.21	3
Other and ill-defined sites	Male	27	68	6.09	2.16	3
Bladder	Male	27	68	6.09	2.15	3
Breast	Female	27	68	6.09	2.14	3
Connective tissue	Male	27	68	6.09	2.14	3
Eye	Male	27	68	6.09	2.14	3

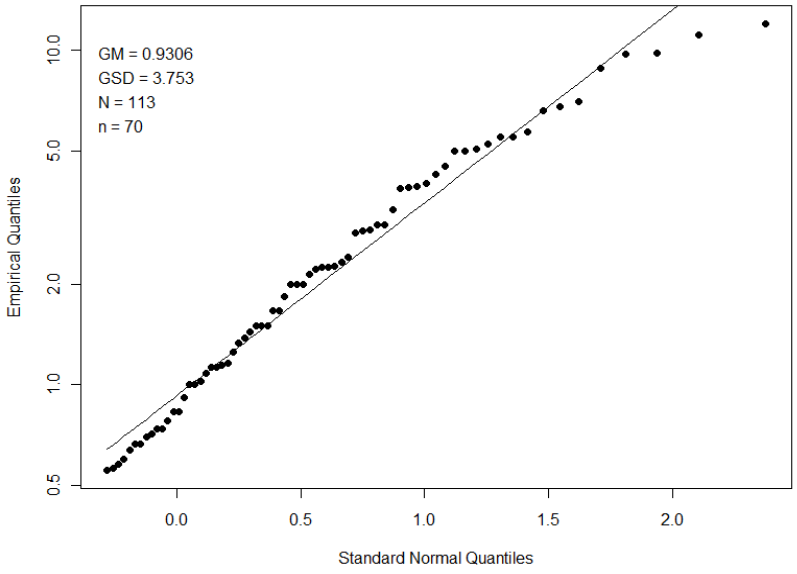
IREP Cancer Model	Gender	Age at Exposure	Age at Diagnosis	Full Model	Stratified Model	
				95th percentile of Lognormal (1,3)	GM	GSD
Acute Lymphocytic Leukemia	Male	33	49	6.09	2.12	3
Bone	Male	27	68	6.09	2.12	3
All digestive	Male	27	68	6.09	2.11	3
Colon	Male	27	68	6.09	2.11	3
Other endocrine glands	Male	27	68	6.09	2.11	3
Breast	Male	27	68	6.09	2.09	3
Urinary organs, excluding bladder	Male	27	68	6.09	2.07	3

Figure 1

Examples of a Full and Stratified Model



Distribution for All Monitored Workers



Distribution of a Stratified Subset