July 25, 2012

California Biomonitoring Science Guidance Panel

Re: Variability discussion at July 26, 2012 meeting

We commend the Biomonitoring California staff for recognizing the need to deal with the issue of intra-individual variability as an important issue for interpreting biomonitoring results and for communicating results to participants. This memorandum conveys some thoughts based upon our research and scientific journal publications that we hope will be useful to the CA Biomonitoring staff and the Science Guidance Panel (SGP).

As noted in the meeting materials for the SGP meeting of July 26, 2012, recent studies that have collected repeat samples of urine voids over an extended time period (Preau et al., 2011; Li et al., 2009; Ye et al., 2011; Teeguarden et al., 2010), for the first time, show that intra-individual variability can be quite high for some compounds due to a short half-life in the body and infrequent exposure events. Our recent review paper (Aylward et al., 2012) on this topic highlights the available data and the precautions that should be taken when interpreting concentrations of chemicals in spot urine voids or single blood samples for chemicals that have a short half-life of elimination from the body relative to the intervals between exposure events.

The draft communication materials being considered by the CA Biomonitoring Program provide a good start for communicating results to participants. For compounds with short half-lives, it would be useful to provide some context as to how much variability might be expected for an individual, reasons for such variability, and language about the limitations of measurements of the concentration of a chemical in a spot sample for assessing an individual's longer term average levels or exposure rates. Examples of ways to address these issues are provided below.

Degree of Variability

- For any compound for which published data exists on intra-individual variability (see Aylward et al., 2012, for a review of available sources), some indication on the extent of variability could be provided (e.g., "Concentrations of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), a metabolite of di(2-ethylhexyl) phthalate (DEHP), have been found to vary by a factor of 100-1000 within an individual within a day and across a week").

- When such data do not exist, a pharmacokinetic model could be used to provide some predictions of variability resulting from infrequent exposures. One such tool is provided along with this memo (Urinary Excretion model – Summit.xls). Summit Toxicology scientists developed this tool for a course that was given at last year's annual meeting of the International Society of Exposure Sciences. This model enables visualizing of potential urinary biomarker concentration variations under user-defined scenarios for exposure timing, chemical-specific characteristics, and urine void and sampling timing. We encourage California Environmental Protection Agency scientists and the SGP to explore the utility and applicability of this model. In particular, this tool can be useful for estimating intra-individual variability for specific chemicals where half-life is known or estimated and some estimates of frequency of exposure can be made. The results of this modeling could be used to make similar statements to those above (e.g., "Concentrations of Chemical X are expected to vary by a factor of Y-Z within an individual within a day and across a week based on what is known about how fast Chemical X is cleared from the body and based on how often people are expected to be exposed to chemical X").

Reasons for Variability

There are numerous factors that contribute to intra-individual variability (e.g., half-life of elimination, frequency of exposure, timing of urine void in relation to exposure events, urine void volume, creatinine excretion rates, etc.). Aylward et al., (2012) provides a review of each of these issues. Recognizing that it is appropriate for the current draft communication materials to be presented at a fairly high level, a detailed discussion of the factors contributing to variability would not match the current level of detail in the draft communication materials. However, we recommend that the CA Biomonitoring Program consider developing web-based communication materials to provide a more detailed discussion and a link could be provided (or offered in print format) for those participants wishing more information.

Generic Language on Variability

More generic language could also be provided to help volunteers appreciate that if their measured levels are at the high end of the range, a different (subsequent) urine void may indicate much lower levels. Conversely, someone with very low measured levels may have higher levels in a different void. Based on scientific research and analysis of the factors related to variability of biomarker concentrations, such language might include the following:

- Chemical X is very rapidly eliminated from the body. As a result, concentrations of chemical X measured in urine (or blood) may vary by a large amount. That is, shortly after an exposure event, the concentration of chemical X may be very high in urine. However, after a few more hours, the concentration of chemical X may not be detectable. As a result, the concentration of chemical X measured in the sample you provided is an indication of the concentration of chemical X only at a

specific moment in time. Depending upon the amount of exposure and the time between exposures and sample collection, large differences in concentrations of chemical X will occur. Therefore, if your levels of chemical X are found to be at the high end of the range, it may only mean that your urine (or blood) sample was obtained shortly after you were exposed to chemical X. Or it may mean that you actually have experienced a greater degree of exposure. Similarly, if very low, your sample might have been collected quite a while after your last exposure to chemical X, or, again, it may mean that you actually experienced a low degree of exposure. In order to obtain a more accurate measure of the longer term average concentration of chemical X, researchers would have to collect numerous samples over an extended period of time. "Because of this variability, the concentrations of Chemical X in any individual at any point in time are difficult to interpret for an individual. However, collection of such data across the population helps researchers evaluate and understand the overall exposure profile in the public."

We hope these comments are helpful to the CA Biomonitoring Program staff and the SGP. Please feel free to contact either of us if you would like additional information about our paper (Aylward et al., 2012), our comments, or the modeling tool provided.

Respectfully,

Sean Hays
Summit Toxicology, LLP
165 Valley Rd.
Lyons, CO 80540
(303)747-0722

Lesa Aylward
Summit Toxicology, LLP
6343 Carolyn Drive
Falls Church, VA 22044
(703)349-3515

References

Aylward LL, Kirman CR, Adgate JL, McKenzie LM, Hays SM. Interpreting variability in population biomonitoring data: Role of elimination kinetics. J Expo Sci Environ Epidemiol. 2012 Jul;22(4):398-408. doi:10.1038/jes.2012.35