Importance of Meta-analyses for Evaluating Carcinogens

http://dx.doi.org/10.1289/ehp.1104755

Camargo et al. (2011) published the most complete meta-analysis on asbestos and ovarian cancer, concluding that "Our study supports the IARC [International Agency for Research on Cancer] conclusion that exposure to asbestos is associated with increased risk of ovarian cancer." Imagine if it had not!

The IARC Monograph Working Group met in 2009 (Straif et al. 2009), but the working group, which included four authors of the Carmargo et al. (2011) paper, apparently did not make use of a formal meta-analysis of all available studies to evaluate the evidence. Although the *IARC Monographs* staff have occasionally conducted meta-analyses prior to a monograph (e.g., Guha et al. 2009), formal meta-analyses are not prepared routinely for the evaluations. However, such meta-analyses can be considered when they are publicly available and, as stated in the "Preamble to the *IARC Monographs*," "ad-hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting" (IARC 2012).

Although meta-analyses have been widely used in social sciences and medical research for decades, it is only recently that they have become more widely used in epidemiology (Greenland and O'Rourke 2008), and they were not widely used at the time that the *IARC Monograph* procedures were first developed. As Greenland and O'Rourke (2008) comment,

> Epidemiologic studies of specific topics have tended to be fewer [than is the case in social science or medicine], and the epidemiologic community appears to be more hospitable to tentative, limited inferences based on narrative reviews. Nonetheless, to neglect quantitative aspects of review would be akin to presenting a study and supplying only a narrative discussion of the raw data, with no attempt to group and compare subject outcomes.

Having participated in several Monograph Working Groups, we know that informal meta-analyses are performed by members of the working groups (at least by ourselves) because this is one of the standard ways to quantitatively summarize the evidence. Meta-analyses can be challenging and controversial depending on assumptions, particularly for studies on occupational and environmental exposures that frequently are not easy to quantify. Certainly meta-analyses cannot be done for all agents evaluated by IARC, and results of meta-analyses have to be critically interpreted in a manner similar to that of all other data.

Even without using formal procedures for a quantitative summary of the epidemiological evidence, IARC Working Groups reach conclusions that are seldom seriously challenged, particularly for Group 1 carcinogens. This is probably because IARC Working Groups tend to express the consensus in the scientific world. When they occasionally have made controversial decisions, for example the 1997 dioxin evaluation reclassifying TCDD from a Group 2B (possible) carcinogen to Group 1, they seem to have been proven right by later research. IARC has revised procedures for the *Monographs* evaluations, incorporating the systematic inclusion of biological knowledge into the criteria for the classifications, and has also updated the whole process for other items, such as conflict of interest and the prodecure for the selection of participants. These changes have strengthened the validity and acceptance of these evaluations. Given the international importance of the *IARC Monographs,* it seems advisable to use all the tools available for summarizing the scientific evidence, one of which is meta-analysis. The meta-analysis by Camargo et al. (2011) clearly demonstrates this regarding both the overall meta-estimate that is not negligible (standardized mortality ratio of around 1.8) and the discussion of the heterogeneity of the findings between studies that can be formally examined in a meta-analysis. If we had been members of that Working Group, we would certainly have preferred to have this meta-analysis on hand before doing the evaluation.

The authors declare they have no actual or potential competing financial interests.

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Editor's note: In accordance with journal policy, Camargo et al. were asked whether they wanted to respond to this letter, but they chose not to do so.

Relationship of Creatinine and Nutrition with Arsenic Metabolism

http://dx.doi.org/10.1289/ehp.1104807

Basu et al. (2011) reported the associations of both dietary and blood nutrient measures, as well as urinary creatinine (uCr), with arsenic (As) methylation capacity, as assessed by the proportions of urinary inorganic, monomethyl, and dimethyl As metabolites. One finding was that uCr was the strongest predictor of As methylation; participants with higher uCr concentrations had a higher percentage of total urinary As as dimethylarsinic acid (DMA) compared to those with lower uCr. This is consistent with what we have previously reported in Bangladeshi adults and children (Gamble et al. 2005; Ahsan et al. 2007; Hall et al. 2009), and is an interesting and potentially very important observation. Approximately 40% of *S*-adenosylmethionine (SAM)-derived methyl groups are devoted to the biosynthesis of creatine, the precursor of creatinine (Brosnan et al. 2011; Mudd and Poole 1975). At high levels of As exposure (500–1,000 μg/L), based on one-carbon kinetics (Schalinske and Steele 1989), we estimated that methylation of 80% of a daily dose of inorganic As (InAs) to DMA would require approximately 50 μmol SAM, thus consuming approximately 2–4% of the SAM normally turning over in a well-nourished adult per day. Low dietary creatine intake associated with low-protein or vegetarian diets places an increased demand for SAM for creatine biosynthesis (Brosnan 2011). This could potentially reduce the availability of SAM for As methylation, providing a plausible mechanism underlying this highly reproducible observation. This assumes that uCr reflects, to some extent, dietary creatine intake, as we have observed (Gamble M, unpublished data). Conversely, dietary creatine intake and/or creatine supplementation down-regulates endogenous creatine biosynthesis,

potentially sparing SAM for methylation of other substrates such as As. We are currently testing this hypothesis in a randomized controlled trial of creatine supplementation. In addition, as Basu et al. (2011) noted, and as we have previously reported (Gamble and Liu 2005), one implication of the observed association between uCr and As methylation capacity is that urinary As should not be expressed per gram creatinine to correct for urine concentration. Rather, uCr should be included as a covariate in regression models.

One concerning aspect of the study by Basu et al. (2011) is the handling of blood samples used for nutrient measurements. As noted by Basu et al. and in a previous publication on these same participants (Chung et al. 2006), the blood samples were stored in an ice chest in the field for up to 24 hr before processing. This 24-hr delay can be problematic for some nutrients, especially folate, which is extremely sensitive to oxidative degradation (Drammeh et al. 2008). Basu et al. (2011) reported that in univariate analyses, they observed higher urinary percentages of InAs in individuals with higher serum folate concentrations. This finding is contrary to our previous findings that folate facilitates As methylation (Gamble et al. 2005, 2006, 2007; Hall et al. 2007, 2009). This discrepancy might be explained by differences in sample processing.

Basu et al. (2011) also reported associations between dietary intake of several nutrients (assessed using a modified 24-hr recall) and As methylation capacity. One of the most critical and widely discussed issues in nutritional epidemiology is the method used to adjust for total energy intake (TEI) (Willett et al. 1997). The main reasons to adjust for TEI are to *a*) adjust for potential confounding by TEI, *b*) remove extraneous variation in nutrient intakes that is due only to their correlation with TEI, and *c*) simulate a dietary intervention. What is often most relevant is diet composition, or nutrient intake in relation to TEI (Willett et al. 1997). Several methods are available to adjust for TEI, and the best approach can vary depending on the nutrient and question of interest. Basu et al. (2011) adjusted for TEI by dividing each nutrient intake by TEI (nutrient density method). While this approach is appealing because of its simplicity, in reality it can create a complex variable (Willett and Stampfer 1998). For example, when TEI is related to the outcome of interest, the use of nutrient densities can actually induce confounding in the opposite direction. Although we cannot determine from Basu et al.'s article whether TEI measured by the 24-hr recall was associated with As methylation, in theory, an association seems plausible. Also, because their statistical analysis tested for associations between multiple nutrients and urinary As metabolites, it is best to acknowledge that some of the statistically significant associations might be due to chance alone.

The authors declare that they have no actual or potential competing financial interests.

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Relationship of Creatinine and Nutrition with Arsenic Metabolism: Smith et al. Respond

http://dx.doi.org/10.1289/ehp.1104807R

We thank Hall and Gamble for their interest in our findings. In our article (Basu et al. 2011), we cited their earlier results concerning urinary dimethylarsinic acid (DMA) and creatinine concentrations, noting that in 2005 they reported a strong correlation between urinary creatinine and the percentage of DMA (DMA%) (Gamble et al. 2005). We also noted rather similar findings from another group working in Bangladesh (Nermell et al. 2008), so together with our findings in India, there are three separate studies that have reported this association (Basu et al. 2011; Gamble et al 2005; Nermell et al 2008). Our results highlight the strength of the relationship between urinary creatinine and urinary DMA%, which was stronger than the relationship between DMA% and any of the 19 dietary factors and 16 blood micronutrients that we investigated.

Gamble and Hall state that they had previously reported (Gamble and Liu 2005) that one implication of the observed association between urinary creatinine and arsenic methylation was that urinary As should not be expressed as per gram creatinine to correct for urine concentrations. This is not quite what they said, although they did point out risks in expressing urinary arsenic per gram of creatinine. However, in that letter (Gamble and Liu 2005) and again in this one, they state that urinary creatinine should be included as a covariate in regression models. We do not agree with this recommendation. Steinmaus et al. (2009) reported a spurious relationship between low-level arsenic concentrations and diabetes in the United States after including urinary creatinine in a regression model. They noted that urinary creatinine concentrations may change as a consequence of diabetes, which is known to affect renal function, and that it is not appropriate to adjust for a factor that is a consequence of the disease being studied.

We also do not agree with Gamble and Hall's criticism of our blood sample handling, which they appear to have raised because our folate findings were different from theirs (e.g., Gamble et al. 2005). For our study (Basu et al. 2011), blood samples were collected in remote villages, and on occasion they had to be stored on ice for up to 24 hr. Gamble and Hall state that "this 24-hr delay can be problematic for some nutrients, especially folate, which is extremely sensitive to oxidative degradation." In support of this statement they cite Drammeh et al. (2008), who found reductions in serum folate concentrations