See corresponding article on page 159.

Relying on biomarkers for intake assessment in nutrition

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Nutritional science relies on accurate dietary assessment. In observational studies of nutrition and health as well as dietary intervention, it is essential that dietary intakes are determined with sufficient accuracy to allow correct classification or compliance assessment. Although dietary instruments based on recalls, interviews, diaries, and questionnaires have been refined extensively in the past decades, they are inevitably confounded by subjectivity (1). Moreover, calculations of the intake of food-derived compounds, nutrients as well as nonnutrients, are additionally biased by variable compositions of most foods, as tabulated in food-composition databases (2). Biomarkers based on analyses of diet-derived compounds in body fluids are an attractive alternative; however, biomarkers also come with flaws. Analytic cost is an important factor and analytic reliability is a sine qua non. Modern high-sensitivity, multitarget analytics have already opened a new era promising hundreds of simultaneous high-accuracy measurements at a price only a few times higher than previous single-target analytics (3). The validity of a biomarker for intake estimates also depends on how representative an analytic sample is for average exposures, the kinetics of the analyte in the body, and how variable the biomarker is within and between individuals (4). There are comparatively few data on these issues, and the article by Sun et al. (5) in this issue of the Journal provides a large amount of new information and guidance to the community with regard to biomarkers measured in urine. The study compares repeated measurements of common electrolytes, nutrients, phenolics, and contaminants in 3 large cohorts of American health professionals to outline the effects of repetition number, sampling intervals, and anthropometric and nutritional variables. None of these covariates have a major impact, which means that the variabilities measured are highly consistent between the studies.

The metric used, intraclass correlation coefficient (ICC), relates the intraindividual variation to the total variation for each biomarker. This metric is closely related to the practical usefulness of the biomarker in nutritional epidemiology. If it is low it means that most variation in the cohorts cannot be assigned to the individual, including the person's diet, lifestyle, genetics, or metabolism. This may happen if noise is the major factor affecting variability, either because extrinsic factors (e.g., episodes of pollution) affect the biomarker in a random fashion or because the individuals in the cohort are so similar that variations within and between individuals are the same. The majority of the ICCs are actually well above the level previously termed "fair," as a rule of thumb (6), and reliability measurements in the study by Sun et al. (5) actually confirm the previous empirical ICC threshold. This result is expected from a large number of recent studies in metabolomics that indicate short excretion half-lives of most food-derived compounds (7). The overall message to the community is therefore that three 24-h urine samples collected with intervals of $\geq$1 mo will provide reliable estimates of average individual exposures for the majority of compounds in a urine sample. This could have major impact on future planning of large cohort studies and trials. It could also affect ongoing studies to make sure that protocols are updated so that three 24-h urine samples are collected.

The lower ICC determinations observed for some compounds are particularly important to understand. Four intriguing examples are sodium, urea, catechin, and phthalates. These findings could be seen as a possible consequence of the similarity of the cohorts used by Sun et al.; however, for sodium, similar low ICCs have been published by many others. For urea, as for total nitrogen, it is also well known that a reliable estimation of nitrogen excretion should incorporate at least 5–8 samples (8). Sodium and urea seem to be broadly representative of Western diets, and their low ICCs are likely due to as-yet-undefined physiologic variation affecting most individuals. The low ICC for catechin is puzzling because its epimer, epicatechin, has a much higher ICC. Provided that analytic error can be ruled out, the result could be caused by sporadic high catechin amounts in some common foods or by highly uniform exposures across the cohort. Amounts that are $\geq$10 times higher than in most other foods are observed for certain berries, beans, and for high-quality cocoa powder and chocolate (www.foodB.ca). Epicatechin has a similar distribution; however, the amount found in tea is much higher than for catechin, which possibly explains a more common habitual source of intake and consequently explains a high ICC. This would indicate that compounds in urine derived from less common foods or spices would generally present with low ICCs in three 24-h urine samples, even if they were quite valid biomarkers. Three samples would just not suffice to cover such compounds or foods, meaning that similar to the number of items covered in a dietary instrument, the number of 24-h urine samples would represent coverage of diet. The phthalates seem to be a very good example of markers that are affected by a multitude of extrinsic factors beyond diet. Diet is thought to be the major contributor to phthalates in urine (9);

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First published online December 21, 2016; doi: 10.3945/ajcn.116.148320.

 Am J Clin Nutr 2017;105:8–9. Printed in USA.

however, amounts in foods vary considerably, so that even a highly uniform diet may be flawed, with variable amounts present in many food items (10). Average exposures may therefore be more highly related to variables leading to fluctuating contamination with phthalates in the manufacture of many common foods, including food packaging, than to intraindividual food preferences.

Several aspects of quality, reliability, validity, and usefulness of biomarkers are likely to be central research themes in the coming years if a transition from subjective to objective assessment of dietary intakes gradually takes place. The number of samples collected will still be the single factor determining the level of detail observable by biomarkers, but the observation that two to three 24-h urine samples are already providing considerable coverage of the average intakes of many food-derived compounds is likely to bring about additional impetus to such a transition.

The author had no conflicts of interest in relation to the topic.

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