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Dietary Biomarkers and the Unresolved Challenges

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Recently, increasing interest is being focused on the human diet and its relation to health and disease outcomes. The epidemiological tools traditionally used to assess this relation relies mainly on food frequency questionnaires and are subject to their limitations including memory bias of the respondents and their inability to identify or quantify certain diets or nutrients under investigation. Dietary biomarkers are, thus, presented as independent tools that are not affected by the above limitations. However, dietary biomarkers may suffer from other limitations related to their validity and that needs to be assessed.

Dietary biomarkers can be defined as any response, chemical or physical, that can be measured in a biological specimen and can reasonably reflect the diet of an individual or a population. Thus, a reasonable dose-dependent relation between dietary exposure and the level in the body is expected. Dietary biomarkers fall into two categories, i.e.

1. Recovery biomarkers, usually in urine including e.g. urinary sodium, urinary potassium, urinary nitrogen, and
2. Concentration biomarkers, usually in blood including plasma vitamin C and plasma carotenoids for fruits and vegetables.

Dietary biomarkers are validated in intervention and epidemiological studies. The intervention studies, in humans and animals, are mainly performed to provide data on the nature of metabolites, pharmacological properties (ADME: Absorption, Distribution, Metabolism, and Excretion), and dose-response relation under standardized conditions. Epidemiological studies, on the other hand, allow the assessment of reproducibility of the biomarker(s) in free-living populations. The reproducibility of a biomarker is a measure of the stability of the biomarker concentration over time. The reproducibility can be measured by the Intraclass Correlation Coefficient (ICC), which is defined as the ratio of between-persons variance to total variance. A high reproducibility is indicated by a high ICC, i.e. a small proportion of the total variation in the biomarker is due to within-person variations. The ICC ranges from 0 to 1 with an ICC $\geq$ 0.75 indicating excellent reliability and an ICC < 0.4 indicating poor reliability. Depending on the validity and application, dietary biomarkers can be used as biomarkers of dietary exposure, biomarkers of compliance, and/or biomarkers for validation of other dietary assessment methods.

During the last decade, we have been evaluating a group of alkylresorcinols and their metabolites as dietary biomarkers of wholegrain wheat and rye intake. Alkylresorcinols, 17-25 carbons in the alkyl tail, are present almost exclusively and concentrated in the outer layers, specifically the brans, of wheat and rye cereals. They are stable during food processing and are absorbed by humans and can be determined in blood plasma and in the form of two metabolites in urine [1]. The alkylresorcinols are metabolized, similar to tocopherols, by phase 1 enzymes (CYP 450) catalyzing omega-oxidation of the terminal methyl group followed by beta-oxidation and shortening of the alkyl tail to the metabolites dihydroxy phenyl propionic acid (DHPPA) and dihydroxy benzoic acid (DHBA), which are excreted in urine. Blood alkylresorcinols are mainly present in lipoproteins, particularly HDL, and red blood cell membranes. Alkylresorcinols showed two absorption maxima in human plasma, at 2.4-3.4 h and at 6.4-5.5 hours for the different homologues, and a model with two absorption compartments has been developed. The calculated elimination half-lives ranged 4.4-5.5 hours, increasing from C17:0 to C25:0 [2]. Reproducibility of plasma AR and correlation to intake is good in intervention studies and, thus, alkylresorcinols can successfully be used as biomarkers of compliance in studies involving wholegrain or bran-rich wheat and/or rye diets. As expected, the reproducibility is lower in epidemiological studies involving free-living people. For example, plasma alkylresorcinol concentrations measured 4 months apart in fasting plasma samples from 100 participants from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study showed moderate reproducibility in women (ICC = 0.55) and low reproducibility in men (ICC = 0.17) [3].

Other dietary biomarkers have been assessed although not as strictly as alkylresorcinols, for example, lycopene for tomatoes, odd-chain fatty acids C15:0 and C17:0 for milk and dairy products, and long-chain fatty acids C20:5 (EPA) and C22:6 (DHA) for fish lipids. These biomarkers were found to serve as useful indicators for the presence of their respective food sources in the diet and to correlate with questionnaire data. However, there is still a need to answer the question about the validity of these and other dietary biomarkers in large epidemiological studies. Unlike questionnaire-based methods, dietary biomarkers may be considered as *objective* measures not associated with measurement errors related to the participant's memory and motivation. On the other hand, they are *subjective* to body metabolism and interferences from hidden dietary sources and interacting nutrients which also may result in systematic and random errors. For example, several determinants may affect the metabolism and plasma concentration of alkylresorcinols e.g. age, sex, vitamin E and other substrates of CYP 450-4F2 (omega-hydroxylase), as well as Na, K, Ca, Mg, *etc.* [4]. A number of determinants related to genetic, demographic, and environmental factors are known to affect the metabolism and, thus, the validity of dietary biomarkers. The validity of currently suggested dietary biomarkers is challenged *inter alias* by issues related to specificity, seasonal variations, stability during food processing, and metabolic interferences and interactions with drugs

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and other food components. Until the issue of validity is resolved, dietary biomarkers should only be used as additional estimates of dietary intake to complement questionnaire data.

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