P : F D I B D!

A A ,[1] J D ,[2] J E ,J ,[3] J CK ,[4] B JL ,[5,6] B O ,[7]
C M [8,9] G F D
D B

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relations between nutrient exposure and biological/clinical indicators of adequacy (typically to prevent de ciency), excess, or reduction of chronic disease risk (3, 4). A similar construct is lacking for developing evidence-based recommendations for safe and e ective intakes of bioactives that have broader e ects promoting health, rather than primarily preventing de ciency or decreasing chronic disease risk. The Framework in this article addresses this gap by providing a process based on quality evidence from systematic evidence reviews fully vetted by quali ed experts, which can lead to recommended quanti ed intakes from food of speci c dietary bioactive compounds with identi ed health bene ts.

Quantifying intake recommendations for bioactives differs from doing this for nutrients with established DRIs, which typically are well de ned chemically, with well-characterized metabolic roles in speci c health outcomes. In contrast, most bioactives are chemically complex and diverse, and their role or e ects on health can be partially met at times by other very similar chemical constituents, making their individual contributions to speci c health outcomes or status often di cult to ascertain. Some bioactives can be rapidly converted into other active or nonactive constituents through the processes of digestion, absorption, and metabolism. Therefore causal inference associating a quanti ed intake of a bioactive with a bene t to normal structure/function or disease risk reduction can be more complex than that which occurs with nutrients.

This Framework provides a step-by-step approach to quantify bioactive intake recommendations in food forms when the quality of evidence for bene t is determined to be

(species) and physical form (matrix) must be relevant to those consumed in food forms.

This Framework builds on the 2017 FNB report *G*
P
C

have broad reach. However, if evidence is not relevant to the general population, then the subpopulation of interest should be speci ed at the onset of the process to ensure recommendations are developed within the context of the speci ed subpopulation. This is consistent with the 2017 FNB guiding

1.1 Characterize a single bioactive or group of bioactive compound(s).
1.2 Ensure that sufficient food composition data are available to enable the translation of quantified intakes into dietary choices.
1.3. Determine that intake of the bioactive is quantified by a reliable intake exposure or a validated biomarker of intake.

2.1 Quantify what a relatively high level of dietary exposure is for the bioactive.
2.2 Document its history of safe consumption within the population.
2.3 Ascertain bioactive quantity with no known adverse health effects.

3.1 Select a health outcome associated with the bioactive & relevant population.
3.2 Identify specific physiologic or biochemical measures recognized as indicators.
3.3 Characterize through systematic evidence review, relationships between quantified intakes of the bioactive(s) with health outcomes in the target population.

are unavailable, standard toxicological testing should be used to quantify safe levels, particularly if it appears that bene ts accrue when consumed at levels above historical safe use. [Note that Step 2 is inappropriate for documenting

C d c i g he e ide ce e ie .

C . A systematic evidence review of the association between a bioactive and a health outcome is necessary (not simply a general or narrative expert review). The evidence review should be published in a peer-reviewed publication and completed by experts in systematic reviews using current standards of practice in the eld and experts in the bioactive–disease outcome relationship. An example of an approach to conducting nutrition systematic reviews is available from the USDA NESR website (23). The review methodology should be appropriate for evaluating nutrition ndings because the body of evidence generally di ers from placebo-controlled medical or clinical treatment research. Evidence reviewed should focus on human studies representing the population for which the recommendations are intended and can include separate subgroups or a separate review if results could di er by subgroup (e.g., building muscle strength in athletes separately from maintaining lean body mass in sedentary adults).

If the recommendation is intended for the general population, evidence should be based on research conducted in generally healthy people by excluding research designed to treat or reduce symptoms in persons with relevant medical conditions. For example, studies of subjects with diseases known to a ect cognitive function (such as multi-infarct dementia and Alzheimer disease) are excluded when evaluating maintenance of normal cognitive function in older adults, and studies of persons with type 2 diabetes are excluded when evaluating maintenance of normal blood glucose after a meal, but not those with elevated glycated hemoglobin at levels deemed prediabetic. Inclusion and exclusion criteria for population, intervention, control, and outcome (PICO) de ne the scope of the nal recommendation.

In the process of conducting the systematic review, bioactive intakes from observational studies reported qualitatively as categories from low to high (e.g., quartiles rather than speci c quantities) need to be converted to speci c quantities of intake by obtaining that information from the original research investigators. A meta-analysis or pooled study can help determine the amounts (grams per day) of bioactive intake related to the e ect. The systematic evidence review of avan-3-ols and cardiometabolic health by Raman et al. (11) illustrates how to conduct a review for the intended purpose of assessing quanti ed intake levels of a bioactive with a measurable health outcome.

C . In addition to quantifying the amount of bioactive intake associated with the health bene t, the evidence should be graded to re ect con dence in the estimated e ect of the relationship. Credible up-to-date methods in the eld of systematic evidence review practices include but are not limited to GRADE, which rates the quality of evidence based on study design factors, and “risk of bias, imprecisions, inconsistency, indirectness, and magnitude of e ect” (21). Other examples include the Agency for Healthcare Research on Quality (commonly referred to a AHRQ) review methodology and the USDA NESR process.

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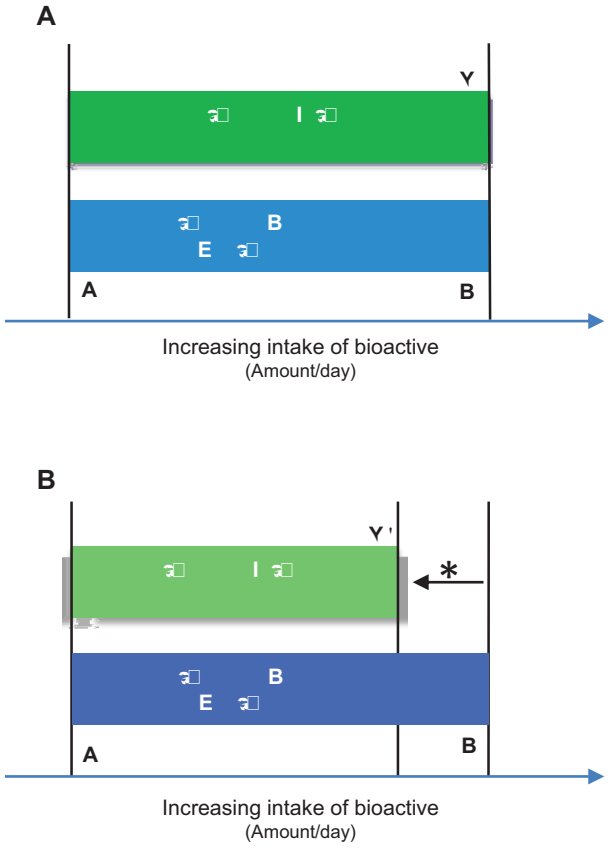

A = Lowest intake level with efficacy evidence
B = Highest intake level with efficacy evidence
X = Lowest level of intake recommended
Y = Highest level of intake recommended; an amount that is efficacious with no known safety issues

FIG E 2 Establishing the recommended intake range for a bioactive. (A) E□cacy intake range *a e a e*: the recommended intake range (X to Y) IS SET EQUAL TO the range of demonstrated e□cacy (A to B) when this range is) equal to or less than high historical use (e.g., 90th percentile intake) in relevant populations and forms, and) below intake levels with known

19. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scienti c Opinion on the substantiation of a health claim related to cocoa avanols and maintenance of normal endothelium-dependent vasodilation pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA J 2012;10(7):2809.
20. Food and Drug Administration (FDA). Guidance for industry: evidence-based review system for the scienti c evaluation of health claims [Internet]. 2009 [cited January 2021]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scienti c-evaluation-health-claims.
21. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, Debeer H, et al. GRADE guidelines: 1. Introduction – GRADE evidence pro les and summary of nding tables. J Clin Epidemiol 2011;64(4):383–94.
22. Balsham H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64(4):401–6.
23. United States Department of Agriculture. Nutrition Evidence Systematic Review (NESR). Methodology overview [Internet]. [cited January 2021]. Available from: https://nesr.usda.gov/methodology-overview.
24. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. Updated October 2013[cited January 2021]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html.
25. Stamler R. Implications of the INTERSALT Study. Hypertension 1991;17(1 Suppl):I16–20.
26. Guyatt G, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A,