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April 25, 2011

VIA UPS OVERNIGHT
Jon Leibowitz, Chairman
Federal Trade Commission
600 Pennsylvania Ave., N.W.
Washington, D.C. 20580

Re: **Petition for Rulemaking to Adopt Statutory and First Amendment Limits on FTC Orders Concerning Health Benefit Claims and Enact Regulations to Implement *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999)**

Dear Chairman Leibowitz:

Please find enclosed two hardcopies of the petition for rulemaking filed on behalf of Petitioners the Alliance for Natural Health USA, Durk Pearson, and Sandy Shaw. Petitioners file the enclosed petition pursuant to 16 C.F.R. § 1.9, 1.21, and 1.25 of Section 18 of the Federal Trade Commission Act, 15 U.S.C. § 57(a)(1)(B). Please do not hesitate to contact us with any questions concerning this filing.

Sincerely,

Jonathan W. Emord
Andrea G. Ferrenz
Peter A. Arhangelsky
Christopher K. Niederhauser

Before the

FEDERAL TRADE COMMISSION

Washington, D.C. 20580

In Re: Petition for Rulemaking to Adopt Statutory and First Amendment Limits on FTC Orders Concerning Health Benefit Claims and Enact Regulations to Implement *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999)	**Docket No. _____**

PETITION FOR RULEMAKING

BY

THE ALLIANCE FOR NATURAL HEALTH USA

AND

DURK PEARSON AND SANDY SHAW

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PETITION FOR RULEMAKING

The Alliance for Natural Health-USA and Durk Pearson and Sandy Shaw ("Petitioners"), by counsel and pursuant to 16 C.F.R. §§ 1.9, 1.21, and 1.25 and Section 18 of the Federal Trade Commission Act ("FTCA"), 15 U.S.C. § 57(a)(1)(B), hereby petition the Federal Trade Commission ("FTC" or "Commission") to recognize and enforce statutory and First Amendment limits on FTC Orders concerning health benefit claims and to enact regulations implementing *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999) and its progeny.

SUMMARY OF ARGUMENT

Recently the FTC altered the content of language used in its Consent Orders to specify two new requirements applicable to the advertisers in question and (by dint of the chilling effect stemming from those Orders) to all advertisers similarly situated, selling essentially equivalent products with essentially the same claims. Thus far, the Orders imposing the two new requirements have applied to advertising concerning the effects of dietary supplements: (1) on

enhancing immune system function with claims FTC views as expressing or implying reduction in the risk of colds and flu (*FTC v. Iovate Health Sciences*, No. 10-CV-587 (W.D.N.Y. 2010)); *In re Nestle Healthcare Nutrition, Inc.*, FTC Docket No. C-4312 (Jan. 18, 2011); *In re The Dannon Company, Inc.*, FTC Docket No. C-4313 (Feb. 4, 2011)); (2) on weight loss (*Iovate Health Sciences*, No. 10-CV-587 (W.D.N.Y 2010); and (3) on temporary relief of irregularity and improved digestive transit time (*In re The Dannon Company, Inc.*, FTC Docket No. C-4313 (Feb. 4, 2011). Based on those Orders, it appears that FTC intends to rely on the same two requirements in future consent orders affecting the aforementioned speech categories as well as other, as yet specified, speech categories.

The alterations in question involve the FTC: (1) using as a proxy for determining the sufficiency of advertising substantiation reference to FDA's prohibition on health claims, barring claims that a dietary supplement treats, cures, prevents, or mitigates disease until approved by FDA under its Nutrition Labeling and Education Act "significant scientific agreement" health claim review standard, 21 U.S.C. § 343(r)(5)(d), and (2) requiring two well-designed clinical trials substantiating the claim at the time of first advertising to avoid a charge of deceptive advertising or a finding of Order violation.

In particular, the consent order language compelling compliance with FDA's prior restraint on nutrient-disease risk reduction claims and on disease treatment claims reads as follows:

> It is ordered that respondent, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any covered product, in or affecting commerce, *shall not represent*, in any manner, expressly or by implication, including through the use of a product name, endorsement, depiction, or illustration, *that such product prevents or reduces the risk [or likelihood] of [upper respiratory tract, getting a cold or the flu] unless the representation is specifically permitted in labeling for such product*

> *by regulations promulgated by the Food and Drug Administration pursuant to the Nutrition Labeling and Education Act of 1990.*

See In Re Nestle, FTC Docket No. C-4312, Order at Part I (emphasis added); *In re Dannon Company*, FTC Docket No. C-4313, Order at Part I; *see also FTC v. Iovate Health Sciences*, Case No. 10-CV-587 (W.D.N.Y), Stipulated Final Judgment and Order for Permanent Injunction at Part I (prohibiting immunity claims unless "such product is subject to a final OTC drug monograph promulgated by the [FDA] for such use, and conforms to the conditions of such use; remains covered by a tentative final OTC drug monograph for such use, and adopts the conditions of such use; or is the subject of a new drug application for such use approved by FDA, and conforms to the conditions of such use"). Throughout this petition we will refer to this requirement of equating the absence of prior FDA health claim approval with deceptive advertising as the "FDA Prior Restraint Requirement."

The consent order language requiring two well-designed clinical trials in substantiation for immunity claims that FTC regards as expressing or implying prevention or treatment of colds and flu; for weight loss claims; for temporary relief of irregularity and improved digestive transit time claims; and for attentiveness claims reads as follows:

> It is ... ordered that respondent, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of [product] in or affecting commerce, shall not represent, in any manner, expressly or by implication, including through the use of a product name, endorsement, depiction, or illustration, that [product] [has a particular health benefit], unless the representation is non-misleading ... *providing, however*, that nothing in this Part II shall prohibit respondent from representing that such benefit can be achieved ... if such claim is non-misleading and respondent possesses and relies upon competent and reliable scientific evidence that substantiates that the representation is true. *For purposes of this Part II, competent and reliable scientific evidence shall consist of at least two adequate and well-controlled human clinical studies of [product], or of an essentially equivalent product, conducted by different researchers, independently of each other, that conform to acceptable designs and protocols and whose results, when considered in light of*

> *the entire body of relevant and reliable scientific evidence, are sufficient to substantiate that the representation is true.* Respondent shall have the burden of proving that a product satisfies the definition of essentially equivalent product.

See In Re Nestle, FTC Docket No. C-4312, Order at Part II (emphasis added); *In re Dannon Company*, FTC Docket No. C-4313, Order at Part II; *see also FTC v. Iovate Health Sciences*, Case No. 10-CV-587 (W.D.N.Y), Stipulated Final Judgment and Order for Permanent Injunction at Part II. Throughout this petition we will refer to the requirement of two well-designed clinical trials as the "Two Clinical Trial Requirement."

As explained in detail below, the FDA Prior Restraint Requirement is being imposed by FTC without requisite statutory authority. There is no authority under the FTCA for the Commission to impose a prior restraint on advertising representations; rather, the Act limits FTC authority to post-publication review of advertising. *See* 15 U.S.C. §§ 52, 55. The FDA Prior Restraint Compliance Requirement is also being imposed in violation of controlling precedent holding that the FDA may not encumber the right of a party to communicate potentially, but not inherently, misleading nutrient-disease risk reduction claims *even if* FDA does not authorize the claims under the Nutrition Labeling and Education Act [Pub. L. No. 101-535, 104 Stat 2353] ("NLEA") and, more particularly, under its statutory "significant scientific agreement" schema. *See Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999) ("*Pearson I*"); *Whitaker v. Thompson*, 248 F.Supp. 2d 1 (D.D.C. 2002) ("*Whitaker I*"); *Pearson v. Shalala*, 130 F.Supp. 2d 105, 112-13, 118-19 (D.D.C. 2001) ("*Pearson II*"); *Pearson v. Thompson*, 141 F.Supp. 2d 105, 112 (D.D.C. 2001) ("*Pearson III*"); *Alliance for Natural Health U.S. v. Sebelius*, 714 F.Supp. 2d 48 (D.D.C. 2010). It is thus the case that claims not approved by FDA under the NLEA are nevertheless constitutionally required to be allowed by the agency under *Pearson I* and its progeny.

The FTC lacks jurisdiction to enforce the provisions of the Food Drug and Cosmetic Act. Only the FDA has that jurisdiction. FTC may not lawfully compel parties to remove from their labels, labeling, and advertising nutrient-disease claims by enforcing the FDA Prior Restraint Requirement through its Orders. The FTC is limited in its jurisdiction to determining whether such claims constitute false and deceptive advertising, apart from whether they comply with the FDA Prior Restraint Requirement or the FDCA generally. FTC's extension of its jurisdiction beyond the bounds of its enabling statute is *ultra vires* action in violation of the FTCA and the jurisdictional limits on agency authority. *See, e.g., FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125-26 (2000).

The Petitioners ask FTC to eliminate the FDA Prior Restraint Requirement from all present orders and discontinue use of the FDA Prior Restraint Requirement in all future Orders, including Consent Orders. If FTC does not, then FTC, when defining the prior restraint as a proxy for a finding of violation of the FTCA and FTC's implementing regulations, must simultaneously implement the constitutional mandate in *Pearson v. Shalala I* and its progeny by specifying claim qualifications that will cure misleadingness or, if there are none, by presenting empirical evidence establishing the absence of such qualifications. *See Whitaker v. Thompson*, 248 F.Supp. 2d at 9-10. Under that mandate, the burden of proof lies on the government agency responsible for limiting future speech to establish that there is no less speech restrictive alternative such as a claim qualification that would avoid misleadingness. *Alliance for Natural Health U.S.*, 714 F.Supp. 2d at 61-62.

As explained in detail below, the Two Clinical Trial Requirement causes qualified claims of an association between a nutrient and a health benefit effect that can be communicated truthfully with claim qualifications to be disallowed until two well-designed clinical trials on the

product are obtained. It thus categorically excludes qualified claims based on evidence other than two clinical trials when such claims qualified to reveal the inconclusiveness of scientific support are an accepted less speech restrictive alternative to outright suppression and to onerous imposition of restrictions that burden speech. *Pearson I*, 164 F.3d at 655-58; *Alliance for Natural Health U.S.*, 714 F.Supp. 2d at 60-62. Thus in the immediate case it has the effect of censoring prospective speech that may be true but it also has a chilling effect on all similarly situated who sell essentially equivalent products with essentially the same claims. *See Multimedia Holdings Corp. v. Circuit Court of Florida, St. Johns County*, 544 U.S. 1301, 1304 (2005); *Virginia v. Am. Booksellers Ass'n, Inc.*, 484 U.S. 383, 393 (1988); *Laird v. Tatum*, 408 U.S. 1, 12-13 (1972) (stating that "constitutional violations may arise from the deterrent, or 'chilling' effect of governmental regulations that fall short of a direct prohibition against the exercise of First Amendment rights").

For the reasons provided in detail below the Petitioners respectfully request that the FTC remove from all current Orders and refrain from including in all future Orders, including Consent Orders, the FDA Prior Restraint Compliance Requirement and the Two Clinical Trial Requirement. The Petitioners also respectfully request that the FTC implement the constitutional mandate of *Pearson v. Shalala I* and its progeny in all future Orders, including Consent Orders, by refraining from imposing any limit on future speech of an accused party if the agency can identify a qualification for a claim that avoids misleadingness or, if not, present empirical evidence to prove the claim incapable of being rendered non-misleading through qualification. That is FTC's minimum constitutional burden under *Pearson v. Shalala I* and its progeny. *Pearson*, 164 F.3d at 659-60 ("we are skeptical that the government could demonstrate with empirical evidence that disclaimers similar to the ones we suggested above would bewilder

consumers and fail to correct for deceptiveness"); *Whitaker v. Thompson*, 248 F.supp. 2d 1, 4-5 (D.D.C. 2002) ("*Whitaker I*") ("the FDA must demonstrate with empirical evidence that disclaimers similar to those suggested would bewilder consumers and fail to correct for deceptiveness"); *Pearson v. Shalala*, 130 F.Supp. 2d 105, 115 (D.D.C. 2001) ("*Pearson II*") (same); *Pearson v. Thompson*, 141 F.Supp. 2d 105, 111-12 (D.D.C. 2001) ("*Pearson III*") (same); *Alliance for Natural Health U.S. v. Sebelius*, 714 F.Supp. 2d 48, 60 (D.D.C. 2010) (same).

The FTC's reliance on Consent Orders rather than formal rulemaking to establish these new criteria does not eliminate the need for constitutional compliance because the agency's enabling statute and the First Amendment, unlike the Administrative Procedure Act, apply to whether, in the first instance, the FTC has a power to act. Moreover, the FTC may not constitutionally "fence-in" violators in a manner that imposes a prior restraint on future constitutionally protected speech. As explained more fully below, FTC lacks the power to act in the ways it has chosen because its enabling statute includes no jurisdiction to enforce the Food Drug and Cosmetic Act and its actions are prohibited by the First Amendment.

BACKGROUND

A. Interests of the Petitioners:

The **Alliance for Natural Health USA** (formerly the American Association for Health Freedom and, before that, the American Preventative Medical Association, a plaintiff in *Pearson I*, certain of its progeny, and in *ANH USA v. Sebelius*) ("ANH USA")) is a Virginia nonprofit corporation, founded in 1992. ANH USA is a membership-based organization with more than 400 members consisting of consumers; healthcare practitioners; food, and dietary supplement

company members; and 150,000 advocate members. A key focus for ANH USA is the protection and promotion of access to information in the market on the actual and potential benefits of health foods and dietary supplements. By educating the general public and ANH USA members about the actual and potential benefits of a healthy diet and lifestyle that includes supplements, ANH USA strives to arm consumers with the information necessary for them to make informed market selections and to take personal responsibility for their health, thereby promoting disease prevention, reducing the extent of medical intervention required, and reducing the public cost of healthcare in the United States. Among ANH USA's dietary supplement company members are companies that would sell dietary supplements with qualified advertising claims of immune system enhancement; qualified advertising claims of weight loss; and qualified advertising claims of relief from irregularity but engage in self-censorship because they neither have FDA health claims approval for the claims nor possess two well-designed clinical trials in support of them.

In particular, ANH USA board members, comprised of eleven representatives of the natural health (consumer, industry, and professional) community, are deprived of the ability to satisfy the ANH USA mandate: to facilitate the free flow of credible scientific information to educate consumers about the actual and potential benefits of supplements so that they may take more personal responsibility for their health and well-being. The result is that all ANH USA members suffer from the loss of truthful health claims that ANH USA supplement company members would make but for the chilling effect stemming from the FTC Prior Restraint Requirement and the Two Clinical Trial Requirement.

Durk Pearson and Sandy Shaw design dietary supplement formulations, including products that affect the immune system, contribute to satiety and weight maintenance, and

improve digestive function. They license those products to companies that, in turn, sell them, depending on the ability to make truthful claims in the market based on qualifications of the evidence to avoid misleadingness. FTC's requirements have a chilling effect on Pearson and Shaw who have ordered their licensees not to communicate to the public on labels, in labeling, or in advertising any claim of association between the products they sell and immune system enhancement, weight loss, and relief of temporary irregularity for fear that the FTC will deem the claims deceptive advertising in light of the FDA Prior Restraint Requirement and the Two Clinical Trial Requirement. In particular, they do not possess two well-designed clinical trials to support the qualified claims and they do not possess FDA approval for any of the truthful qualified claims concerning immune system enhancement, weight loss, and relief of temporary irregularity that they would like to make.

For example, Pearson and Shaw have a prune juice product. In connection with the promotion and sale of the product they would like to include the advertisement text cited herein.[1] Although they possess scientific evidence concerning the benefit of fiber to reduce the symptoms of chronic constipation and the claim is one accepted generally as true, they do not possess two

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[1] Petioners Pearson and Shaw intend to market their prune juice product with the following claims in advertisements:

Durk Pearson & Sandy Shaw's FLUSH

> The prune juice that flushes your regulation problems down the toilet.
>
> Don't put up with a poorly functioning regulatory system—Get regular with a morning constitutional with FLUSH.
>
> FLUSH prune juice helps relieve chronic constipation. See your doctor first to ensure your regulation problem is not more serious than a need to increase your dietary fiber. Use one to four 8 ounce glasses per day as needed to help FLUSH your regulation problem.

well-designed clinical trials substantiating the claim nor do they have FDA approval for the claim. Consequently, they fear that if the content is communicated in advertising, it will place them at risk of adverse FTC action.

B. The FTC's New Policies Concerning Claim Substantiation:

The FTC and FDA have collaborated in regulating products since 1954. Under a Memorandum of Understanding between the two agencies, Working Agreement between FTC and Food and Drug Administration, 4 Trade Reg. Rep. (CCH) ¶ 9,850.01 (1971) ("Memorandum of Understanding"), FTC "has primary responsibility with respect to the regulation of the truth or falsity of all advertising (other than labeling) of foods, drugs, devices, and cosmetics" and the FDA "has primary responsibility for preventing misbranding of foods, drugs, devices, and cosmetics shipped in interstate commerce." The FTC's standard for substantiating advertisements has long been whether an advertiser possesses "competent and reliable scientific evidence;" heretofore the FTC has consistently rejected a "fixed formula" to define "competent and reliable scientific evidence." *See* FTC Enforcement Policy Statement (May 1994) ("[t]here is no fixed formula for the number or type of studies required or for more specific parameters like sample size and study duration")[2]; *see also FTC v. National Urological Group, Inc.*, 645 F.Supp. 2d 1167, 1186 (N.D. Ga. 2008) ("Obviously, this definition is context specific and permits different variations on 'competent and reliable scientific evidence' depending on what pertinent professionals would require for the particular claim made").

FTC has, on some occasions, stipulated that two clinical trials would suffice as "competent and reliable scientific evidence." *See FTC v. California Pacific Research, Inc.*, No. CV-N-88-602BRT (D.Nev. 1991) (unpublished), 1991 WL 208470, *1; *Sterling Drug, Inc. v.*

[2] *Available at*, http://www.ftc.gov/bcp/policystmt/ad-food.shtm.

FTC, 741 F.2d 1146, 1156 (9th Cir. 1984). However, the FTC never before set a minimum threshold of two studies as requisite to the making of future health benefit claims. FTC has explained that:

> The benefits of a flexible approach are especially significant when the information relates to consumer health. Advertising and labeling can be extremely effective tools to educate consumers about diet-disease relationships, to increase their awareness of diseases, to inform them of different treatment options, and to empower them to manage better their own health. The ability to present information in advertising and labeling can also provide a strong incentive to competitors to develop new products and to improve existing products, giving consumers more and better choices.

See Comment of the Staff of Bureau of Economics, the Bureau of Consumer Protection, and the Office of Policy Planning of the Federal Trade Commission in the Matter of Request for Comment on First Amendment Issues, FDA Docket No. 02N-0209 (Sept. 13, 2002), at 22.

In August 2009, the FTC sued Lane Labs-USA, a supplier of dietary supplements alleged to have violated a 2000 FTC Consent Order. *See FTC v. Lane Labs-USA, Inc.*, No. 00-cv-3174 (D.N.J. 2009) (unpublished), 2009 WL 2496532, *overruled by*, 624 F.3d 575 (3d Cir. 2010). Asked to interpret whether Lane Labs violated the consent decree, the Federal District Court for the District of New Jersey determined that FTC did not meet its heavy burden to prove that Lane Labs lacked "competent and reliable" scientific evidence to support its advertisements. *Id.* at *9-10. The FTC publicly stated that the Court's decision in *Lane Labs* stemmed from an overbroad definition of "competent and reliable scientific evidence" included in the Consent Decree. The Commission publicly stated that it would narrow consent orders in response to *Lane Labs.*

Director of FTC's Bureau of Consumer Protection, David Vladeck, speaking before the National Advertising Division in New York on October 5, 2009, stated:

> [S]ome federal courts seem to have had difficulty, in certain situations, applying the standard injunction that prohibits particular kinds of claims unless the defendant "possesses and relies upon competent and reliable scientific evidence

> that substantiations the representation." As a result, we will be crafting more precise language in future orders. In addition to achieving greater precision, we will also seek orders that harmonize with laws and regulations administered by sister agencies. A third goal will be to address those situations where a given piece of research, though it may have been conducted according to established protocols, achieved results inconsistent with the weight of scientific evidence in the relevant field.

See Remarks of David Vladeck, National Advertising Division Annual Conference, New York, NY (Oct. 5, 2009) at 3. [3]

Speaking before the Council for Responsible Nutrition, on October 22, 2009, Mr. Vladeck reiterated that FTC will heighten scrutiny of dietary supplement and health products and collaborate with FDA in taking enforcement action against those making health benefit claims. *See* Remarks by David C. Vladeck, Council for Responsible Nutrition Annual Symposium for the Dietary Supplement Industry, Rancho Palos Verdes, CA (Oct. 22, 2009).[4] Discussing the *Lane Labs* decision, Mr. Vladeck explained:

> Our experience in bringing enforcement and contempt actions in federal courts suggests that we need to take steps to make our standard injunctive language that prohibits particular kinds of claims unless the defendant "possesses and relies upon competent and reliable scientific evidence that substantiates the representation" more exact. For instance, you may be aware of the recent decision in the *Lane Labs* case, where a district court judge denied the FTC's motion to find the defendants in contempt of a prior FTC order requiring them to have "competent and reliable scientific evidence" substantiating the health claims. The Commission is disappointed with the results and intends to appeal.
>
> We will be looking for more precise injunctive language in future orders that will provide clearer guidance to defendants and courts alike as to the amount and type of scientific evidence that will be required in future advertising.

Id. at 11-12.

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[3] *Available at*, http://www.foodpolitics.com/wp-content/uploads/NAD-Vladeck-Speech-10-5-09.pdf.

[4] *Available at*, http://www.ftc.gov/speeches/vladeck/091022vladeckcrnspeech.pdf.

FTC initiated enforcement proceedings against four major companies marketing health benefit claims in the summer of 2010. *See In re Nestlé HealthCare Nutrition, Inc.*, FTC File No. 092-3087 (filed July 2010); *In re The Dannon Company, Inc.*, FTC File No. 0823158 (filed December 2010); *In re POM Wonderful LLC and Roll International Corp.*, FTC Docket No. 9344 (filed September 2010); *Federal Trade Commission v. Iovate Health Sciences USA, Inc.*, FTC File No. 072 3187 (filed July 2010). The FTC's orders included the FDA Prior Restraint Requirement and the Two Clinical Trial Requirement. *See In re Nestlé HealthCare Nutrition, Inc.*, FTC File No. 092-3087 (Jan. 18, 2011); *In re The Dannon Company, Inc.*, FTC File No. 0823158 (Feb. 4, 2011); *Iovate Health Sciences*, No. 10-CV-587 (W.D.N.Y 2010).

FTC's new Consent Order language and the public pronouncements of its agents to the industry engender a chilling effect on commercial speech. Advertisers similarly situated with the defendants in the above-referenced Consent Orders, who sell essentially equivalent products with essentially the same claims, perceive that they may not continue to do so without risk of adverse FTC enforcement unless they first satisfy the FDA Prior Restraint Requirement and the Two Clinical Trial Requirement.

LEGAL ARGUMENT

A. FTC Lacks Jurisdiction to Enforce the Federal Food Drug and Cosmetic Act

The FTC regulates food advertising in accordance with its statutory authority under Section 5 of the Federal Trade Commission Act ("FTCA"), 15 U.S.C. §45, to prevent unfair methods of competition and unfair or deceptive acts or practices in or affecting commerce, and under Sections 12 and 15 of the FTCA, 15 U.S.C. §§ 52, 55, which prohibit the dissemination of"any false advertisement" that is likely to induce the purchase of food. Moreover, the FTC is authorized to prescribe "interpretive rules and general statements of policy with respect to unfair or deceptive acts or practices in or affecting commerce" and "rules which define with specificity

acts or practices which are unfair or deceptive acts or practices affecting commerce." *Id.* at § 57a(a)(1). Although FTC may regulate advertising claims, it has no authority to compel compliance with the FDCA, enforce the FDCA, or use as a proxy for determining the sufficiency of advertising substantiation reference to FDA's prohibition on health claims on labels and in labeling, barring claims that a dietary supplement treats, cures, prevents, or mitigates disease unless approved by FDA under its Nutrition Labeling and Education Act "significant scientific agreement" health claim review standard, 21 U.S.C. § 343(r)(5)(d). The FTC's FDA Prior Restraint Requirement exceeds the authority vested in FTC by the Federal Trade Commission Act. The FTC may not act without specific Congressional authorization and it has no authorization from Congress to enforce the NLEA. *See, e.g., La. Pub. Serv. Commn. v. FCC*, 476 U.S. 355, 374 (1986) ("an agency literally has no power to act . . . unless and until Congress confers power upon it."); *Adams Fruit Co., Inc. v. Barrett*, 494 U.S. 638, 650 (1990) (stating that "[a]lthough agency determinations within the scope of delegated authority are entitled to deference, it is fundamental 'that an agency may not bootstrap itself into an area in which it has no jurisdiction'") (quoting *Fed. Mar. Commn. v. Seatrain Lines, Inc.*, 411 U.S. 726, 745 (1973)); *Am. Library Assn. v. FCC*, 406 F. 3d 689, 702 (D.C. Cir. 2005) (an agency does not possess plenary authority to act within a given area simply because Congress has endowed it with some authority to act in that area); *In re Keim*, 212 B.R. 493, 499 (Bkrtcy. D. Md. 1997) ("[a]n act of a governmental agency is *ultra vires* if it is beyond the express or implied powers conferred by statute"). Accordingly, "[a]gency action taken without statutory authorization, or which frustrates the congressional policy which underlies a statute, is invalid." *Yankton Sioux Tribe v. Kempthorne*, 442 F. Supp. 2d 774, 784 (D.S.D. 2006).

The FTC simply has no authority to enforce the FDCA through FTC consent orders (an *ultra vires* activity). The FTCA does not provide authority to compel compliance with the FDCA, or institute enforcement proceedings for failure to comply with FDA regulations. *See Food and Drug Administration v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125-26 (2000). The Supreme Court has held that executive branch administrative agencies are limited to the jurisdiction conveyed in their enabling statutes. *Id.* In *Brown & Williamson*, the Supreme Court addressed the FDA's attempt to regulate tobacco products, a category of goods excluded from FDA's jurisdiction in the FDCA. *Id.* at 134-43. "Regardless of how serious the problem an administrative agency seeks to address ... it may not exercise its authority in a manner that is inconsistent with the administrative structure that Congress enacted into law." *Id.* at 125-126 (holding that "we believe that Congress has clearly precluded the FDA from asserting jurisdiction to regulate tobacco products. Such authority is inconsistent with the intent that Congress has expressed in the FDCA's overall regulatory scheme..."). FDA could not regulate tobacco products, which were already regulated by the Bureau of Alcohol, Tobacco, Firearms and Explosives. As in *Brown & Williamson*, so too here, the FTC cannot unilaterally extend its jurisdiction beyond the express language of the FTCA to enforce provisions of the NLEA precisely because Congress has given that jurisdiction exclusively to the FDA.

Under Section 5 of the FTCA the FTC is only authorized to regulate and prevent deceptive acts or practices in food advertising. *See Peters v. Hobby*, 349 U.S. 331, 345 (1955) ("[a]gencies, whether created by statute or executive order, must of course be free to give reasonable scope to the terms conferring their authority. But are not free to ignore plain limitations on that authority"); *Marquette Cement Mfg. Co. v. FTC*, 147 F.2d 589, 594 (7th Cir. 1945) (the jurisdiction and authority of administrative agencies is confined solely to that which

Congress bestows, and there are no limitations upon this congressional power other than the Constitution). That authority under the FTCA permits FTC to regulate false and deceptive claims once published and does not incorporate FDA's prior restraint on nutrient-disease relationship labeling claims contained in the NLEA, 21 USC 343(r)(5)(d) or in FDA's implementing regulations in 21 C.F.R. § 101.14. *Pediamed Pharm., Inc. v. Breckenridge Pharm., Inc.*, 419 F. Supp. 2d 715, 727 (D. Md. 2006) (explaining that only the FDA is entitled to enforce the FDCA, including adulteration, mislabeling, and new drug applications); *Eli Lilly and Co. v. Roussel Corp.*, 23 F. Supp. 2d 460, 476 (D.N.J. 1998) ("[o]nly the federal government, by way of either the FDA or the Department of Justice, has exclusive jurisdiction to enforce violation of the FDCA").

By requiring advertisers to comply with the NLEA prior restraint on nutrient-disease claims, 21 USC 343(r)(5)(d), as a condition precedent to deeming the claims when in advertising not deceptive, the FTC has exceeded its statutory grant of authority and has invaded a province vested in a sister agency, the FDA. If the *sine qua non* for FTC claim substantiation is in this instance compliance with FDA laws, then FTC can enforce its Order only by interpreting and applying the FDCA in an FTC proceeding. Those actions are *ultra vires* for the FTC.

In addition, even if FTC possessed requisite authority to enforce the FDCA, the FTC's Prior Restraint Compliance Requirement violates controlling constitutional precedent limiting FDA's ability to prevent a party from communicating potentially, but not inherently, misleading nutrient-disease risk reduction claims even if the FDA disallows the claims under the NLEA standard for health claim approval, 21 U.S.C. § 343(r)(5)(d) as implemented by 21 CFR 101.14. By imposing the FDA Prior Restraint Requirement on future advertising claims via its consent orders, the FTC necessarily subjects itself to the constitutional limits on prior restraint in

Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999) ("*Pearson I*"); *Whitaker v. Thompson*, 248 F.Supp. 2d 1 (D.D.C. 2002) ("*Whitaker I*"); *Pearson v. Shalala*, 130 F.Supp. 2d 105, 112-13, 118-19 (D.D.C. 2001) ("*Pearson II*"); *Pearson v. Thompson*, 141 F.Supp. 2d 105, 112 (D.D.C. 2001) ("*Pearson III*"); *Alliance for Natural Health U.S. v. Sebelius*, 714 F.Supp. 2d 48 (D.D.C. 2010).

In *Pearson I* our Court of Appeals held that FDA could deem a claim unapproved under the NLEA "significant scientific agreement" standard but would still be required to permit the unapproved claim to enter the market unless the agency could prove with empirical evidence that no qualification of the claim would suffice to eliminate misleadingness. *See Pearson I*, 164 F.3d at 657-58.

The FDA Prior Restraint Requirement expressly requires that the defendants obtain FDA approval for claims under the NLEA schema (which is the health claims approval process in 21 USC 343(r)(5)(d)). The pertinent language reads that the defendant "*shall not represent*, in any manner, expressly or by implication, including through the use of a product name, endorsement, depiction, or illustration, *that such product prevents or reduces the risk [or likelihood] of [upper respiratory tract infection, getting a cold or the flu] unless the representation is specifically permitted in labeling for such product by regulations promulgated by the Food and Drug Administration pursuant to the Nutrition Labeling and Education Act of 1990.*" The requirement imposed by FTC does not mention, let alone apply, the constitutional mandate in *Pearson I*. That mandate *requires* that claims not approved under the NLEA statutory prior restraint regime be evaluated to determine whether claim qualifications would suffice to eliminate misleadingness. The federal government is obliged to allow claims backed by credible but inconclusive evidence to enter the marketplace and to rely on claim qualification as a less speech

restrictive alternative to prohibition unless the government can prove with empirical evidence that no claim qualification will suffice to eliminate misleadingness. *Pearson I*, 164 F.3d at 658-60; *Whitaker I*, 248 F.Supp. 2d at 4-5; *ANH USA*, 714 F.Supp. 2d at 58-60. Thus, FTC violates that constitutional stricture because its FDA Prior Restraint Requirement is imposed to prohibit future speech concerning a nutrient-disease relationship without undertaking the required *Pearson I* analysis to determine whether there exists any qualified claim that would suffice to eliminate misleadingness or, if not, proving that to be so before demanding that the party comply with the prior restraint. The burden of proof is on the government, i.e., the government must prove that no claim qualification will suffice; the speaker is not required to offer claim qualifications in anticipation of a potential act of suppression by the state. *ANH USA*, 714 F.Supp. 2d at 61-62. Thus, the FDA Prior Restraint Requirement imposed by FTC in its Consent Orders violates the First Amendment and must immediately be removed from all existing consent orders and must not be imposed in any future ones.

Under the NLEA health claim schema, the FDA has no discretion to approve or deny a claim that is, at worst, only potentially misleading and falls short of FDA's "significant scientific agreement" standard. *See Whitaker v. Thompson*, 248 F.Supp. 2d at 9-10. Thus, under the FDA Prior Restraint Requirement, the FTC is condemning prospectively a whole class of claims constitutionally required to be permitted under *Pearson I* and its progeny because they are not approvable under the NLEA schema (but can be rendered nonmisleading through the addition of a claim qualification).

The *Pearson I* decision and its progeny are First Amendment commercial speech cases. The FTC is bound by constitutional doctrine when it implements a claim-approval schema of its own, including when using the NLEA prior restraint on health claims as a proxy for advertising

substantiation. Because the FTC's FDA Prior Restraint Compliance Requirement requires FDA pre-approval under Section 343(r)(5)(D) without providing room for approval of claims expressly not approved under the NLEA, the FTC's approach violates the *Pearson I* doctrine by imposing an unconstitutional prior restraint on constitutionally protected commercial speech.

The *Pearson I* Court differentiated between "potentially" misleading claims (which cannot be subject to prior restraint) and "inherently" misleading claims (which can be), thus applying the four-part test as established in *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of New York*, 447 U.S. 557 (1980) in the context of health claims. *Id.* at 655 (*citing In Re R.M.J.*, 455 U.S. 191 (1982)) (states may not place an absolute prohibition on potentially misleading information if the information also may be presented in a way that is not deceptive). The Court also held that the preferred remedy for potentially misleading advertising information is "more disclosure, rather than less," *Id.* at 657 (*citing Bates v. State Bar of Arizona*, 433 U.S. 350, 376 (1977)) and that the Supreme Court has repeatedly pointed to "disclaimers as constitutionally preferable to outright suppression." *Id.* (*citing Peel v. Attorney Registration and Disciplinary Comm'n of Illinois*, 496 U.S. 91 at 110 (1990); *In Re R.M.J.*, 455 U.S. at 206, n.20; *Shapero v. Kentucky Bar Association*, 486 U.S. 466, 478 (1988)).

In *Alliance for Natural Health U.S.* the United States District Court for the District of Columbia reaffirmed that:

> The government has the burden of showing that the regulations on speech that it seeks to impose are not more extensive than is necessary to serve the interests it attempts to advance. If the Government can achieve its interests in a manner that does not restrict commercial speech, or that restricts less speech, the Government must do so... For this reason, the Court in *Pearson I* concluded that when government chooses a policy of suppression over disclosure—at least here there is no showing that disclosure would not suffice to cure misleadingness—the government disregards a far less restrictive means.

ANH USA, 714 F.Supp. 2d at 61-62. As held in *Pearson I* and *Whitaker I*, and reaffirmed in *ANH USA*, the *government* bears the burden to show that "disclaimers would bewilder consumers and fail to correct for deceptiveness." *See ANH USA*, 714 F.Supp. 2d at 62; *Pearson I*, 164 F.3d at 659-60; *Whitaker I*, 248 F.Supp. 2d at 11.

B. The FTC's Two Clinical Trial Requirement Violates the First Amendment Standard in *Pearson v. Shalala I.*

The FTC's Two Clinical Trial Requirement similarly fails under the First Amendment and, in particular, the *Pearson I* doctrine. The Two Clinical Trial Requirement causes future advertising that could be communicated in a non-deceptive way by revealing the limited nature of supportive evidence, i.e., its inconclusiveness, to be prohibited based on an arbitrary two clinical trial requirement. Thus, the universe of truthful advertising is delimited not by proof of deception but by the creation of an arbitrary barrier making the minimum price for the right to advertise about immune system enhancement, weight loss, temporary relief of irregularity and improved digestive transit time, and attentiveness the possession of two well designed clinical trials. FTC thus categorically excludes truthful qualified claims that reveal the existence of the association between a nutrient and one of those physiological effects to be supported by credible but inconclusive evidence. The Two Clinical Trial Requirement has the effect of censoring prospective speech protected under the First Amendment. *See Pearson I*, 164 F.3d at 655-58; *ANH USA*, 714 F.Supp. 2d at 60-62.

The federal courts have explained that a blanket ban on health benefit claims is permissible only under the narrowest of circumstances. The federal government may only impose an outright ban on a health claim when it can prove that no qualification of the claim will suffice to eliminate misleadingness. *Pearson I*, 164 F.3d at 660, n.10. The District Court of the District of Columbia, applying the original *Pearson I* decision in *Pearson II*, held "the mere

absence of significant affirmative evidence in support of a particular claim ... does not translate into negative evidence against it." *Pearson II*, 130 F. Supp. 2d at 115.

FTC's Two Clinical Trial Requirement, defining the type and number of studies that must be present before commercial speech in the categories thus far defined may lawfully be communicated in advertising, produces a chilling effect that causes all those similarly situated who are selling substantially similar products with substantially similar claims to engage in self-censorship, eliminating from their advertising lexicon all manner of truthful, qualified claims concerning immune system enhancement, weight loss, temporary relief of irregularity and improved digestive transit time, and attentiveness. *See Pearson I*, 164 F.3d at 659-60. In *Pearson I* and its progeny, the courts have repeatedly held that when there is "credible evidence" but inconclusive scientific evidence to support a claim, a claim may not be banned but must be allowed with qualifications unless proof exists that no qualification will not suffice to cure misleadingness. *Pearson*, 164 F.3d at 659. If credible evidence exists, a disclaimer is appropriate and constitutionally mandated. The *Pearson* Court was skeptical that "the government could demonstrate with empirical evidence that disclaimers similar to the ones [the Court] suggested ... ["The evidence in support of this claim is inconclusive" or "The FDA does not approve this claim"] would bewilder consumers and fail to correct for deceptiveness." *Id.* at 659-660. The FTC's Two Clinical Trial Requirement thus increases burdens on protected speech because it eliminates a class of health claims supported by credible but inconclusive science, including science short of two human clinical trials.

The FTC unconstitutionally shifts its burden onto advertisers to prove that disclaimers will cure misleadingness. That burden belongs to the governmental entity imposing the speech limitation. Summarizing its recent Consent Order in the Dannon Matter, the FTC explained:

> Respondent may decide to make an advertising claim characterizing limited scientific evidence supporting the relationship between a covered product and a reduced likelihood of [disease]. However, if the net impression of that advertising is that the covered product reduces the likelihood of getting [the disease], and not merely that there is limited scientific evidence supporting the claim, the advertisement would be covered [by the Consent Order]. The Commission notes that its experience and research show that it is very difficult to adequately qualify a disease risk-reduction claim in advertising to indicate that the science supporting the claimed effect is limited. In other words, reasonable consumers may interpret an advertisement to mean that the product will reduce the likelihood of getting [the disease], even if respondent includes language indicating that the science supporting the effect is limited in some way. **However, if respondent possesses reliable empirical testing demonstrating that the net impression of an advertisement making a qualified claim for a covered product does not convey that it will reduce the likelihood of getting [the disease], then that claim would be covered under [the Consent Order].**

See In re The Dannon Company, Inc., FTC File No. 0823158, Analysis of Proposed Consent Order to Aid Public Comment (Dec. 15, 2010).[5] The FTC's conclusion, when applied not to advertising already in the market but as a prior restraint on prospective advertising in one of the categories defined in the Consent Orders above, violates the constitutional requirement of *Pearson I*, *Whitaker I*, and *Alliance for Natural Health*. *See Pearson I*, 164 F.3d at 659-60; *Whitaker I*, 248 F.Supp. 2d at 7; *ANH USA*, 714 F.Supp. 2d at 63. It is not the prospective advertiser that must bear the burden of proof, it is the government. Apposite precedent in the prior restraint context (such as exists when Consent Orders restrict the right to engage in future advertising) places the burden firmly on the government to prove that less speech-restrictive measures, such as claim qualifications, cannot cure misleadingness as a condition precedent to imposition of the commercial speech restriction. *See Pearson I*, 164 F.3d at 659 ("[a]lthough the government may have more leeway in choosing suppression over disclosure as a response to the problem of consumer confusion where the product affects health, *it must still meet its burden of justifying a restriction on speech*") (emphasis added); *Whitaker I*, 248 F.Supp. 2d at 7 ("both

[5] *Available at*, http://www.ftc.gov/os/caselist/0823158/101215dannonanal.pdf.

Pearson I and *Pearson II* established a very heavy burden which Defendants must satisfy if they wish to totally suppress a particular health claim"); *ANH USA*, 714 F.Supp. at 61 ("[t]he government has the burden of showing that the regulations on speech that it seeks to impose are not more extensive than is necessary to serve the interests it attempts to advance"); *Edenfield v. Fane*, 507 U.S. 761, 770-71 (1993) (governments' obligation to "demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree" "is not satisfied by mere speculation or conjecture").

Finally, the FTC's Two Clinical Trial Requirement conflicts with principles of evidence-based nutrition. FTC's new policy reflects an evidentiary threshold commonly reserved for drug products or evidence-based medicine (EBM). *See* Andrew Shao, PhD and Douglas Mackay, ND, *A Commentary on the Nutrient-Chronic Disease Relationship and the New Paradigm of Evidence-Based Nutrition*, Natural Medicine Journal 2010; 2(12):10-18 (Exhibit 1). The use of human clinical trials to demonstrate nutrient-disease reduction relationships is often impractical or impossible. *Id.* at 10-11; Jeffrey Blumberg, et al., *Evidence-based criteria in the nutritional context*, Nutrition Reviews 2010; 68(8):478-484 (Exhibit 2); Robert P. Heaney, MD, Connie M. Weaver, PhD, and Jeffrey Blumberg, PhD, *EBN (Evidence-Based Nutrition) Ver. 2.0*, Nutrition Today 2011; 46(1):22-26 (Exhibit 3). "Several nutrition researchers have, in recent years, raised concerns over what is perceived to be the misapplication of drug-based trials to assess nutrition questions, without taking into account the totality of the evidence or the complexities and nuances of nutrition." Shao, *supra*, at 11. The difficulties applying clinical intervention studies to the nutrition context lead experts to conclude that "[r]ecommendations, whether they be public health-based or practitioner-patient-based, should be developed from the totality of the available evidence, not on a single study or study design." *Id.* at 12.

Substantial differences between drugs and nutrients limit the effectiveness of clinical trials in the nutrition context. Dr. Shao, Senior Vice President of Scientific & Regulatory Affairs at the Council for Responsible Nutrition, explains:

> Drugs tend generally to have single, targeted effects; drugs are not homeostatically controlled by the body and can easily be contrasted with a true "placebo" group; drugs can act within a relatively short therapeutic window of time, often with large effect sizes. In contrast, nutrients tend to work in complex systems in concert with other nutrients and affect multiple cells and organs; nutrients are homeostatically controlled, and thus the body's baseline nutrient "status" affects the response to a nutrient intervention; a nutrient intervention group cannot be contrasted with a true placebo group (i.e., "zero" exposure group); and with respect to chronic disease prevention, nutrient effect sizes tend to be small and may take decades to manifest. Finally the very absence (or inadequacy) of a given nutrient produces disease, which is a fundamental difference compared to drugs.

Shao, *supra*, at 11.

Dr. Blumberg, head of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts, concurs and explains:

> [C]ertain features of [Evidence-Based Medicine] seem ill-suited to the nutrition context. Some of the differences between the evaluation of drugs and nutrients cited previously are as follows: (i) medical interventions are designed to cure a disease *not* produced by their absence, while nutrients prevent dysfunction that would result from inadequate intake; (ii) it is usually not plausible to summon clinical equipoise for basic nutrient effects, thus creating ethical impediments to many trials; (iii) drug effects are generally intended to be large and with limited scope of action, while nutrient effects are typically polyvalent in scope and, in effect size, are typically within the "noise" range of biological variability; (iv) drug effects tend to be monotonic, with response varying in proportion to dose, while nutrient effects are often of a sigmoid character, with useful response occurring only across a portion of the intake ranges; (v) drug effects can be tested against a nonexposed (placebo) contrast group, whereas it is impossible and/or unethical to attempt a zero intake group for nutrients; and (vi) therapeutic drugs are intended to be efficacious within a relatively short term while the impact of nutrients on the reduction of risk of chronic disease may require decades to demonstrate—a difference with significant implications for the feasibility of conducting pertinent [randomized clinical trials].

Blumberg, *supra*, at 480 (concluding "it is unlikely that [randomized clinical trial] evidence could feasibly or appropriately be produced with respect to the role of a nutrient for many

nonindex-disease endpoints"). For example, where low intake is the hypothesis for causation, clinical trials would present "nearly insuperable ethical barriers because the investigative team has to be prepared to put subjects in harm's way" by, for instance, lowering or maintaining low levels of nutrient intake. *See* Heaney, et al, *supra*, at 23.[6]

Accordingly, scientists question "whether we need as much proof of efficacy for a nutrient policy decision as we do for approval of powerful, expensive, and potentially dangerous pharmaceutical agents." *Id.* at 24. Nutrients, by contrast, can often be consumed with low risk of toxicity and are available at low cost. The standards that govern scientific data should be relative to the risks presented by the nutrient, but also reflect the limitations of clinical trials in the nutrient context. *Id.* at 22, 24 (noting that the field of nutrition has "seemingly swallowed [evidence-based medicine] whole without either asking how well it might fit, or adapting it to the unique features of the nutrition context").

There is not a scientific consensus, therefore, that strict reliance on clinical trials is appropriate in evidence-based nutrition. Because clinical trials are rarely, if ever, designed to demonstrate nutrient disease-*reduction* relationships, a two clinical trial requirement forecloses claims that can be supported by the totality of the scientific record without need for well-

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[6] Dr. Blumberg further explains that clinical trials are rarely effective in nutrition because the goals of an intervention trial are inapposite:

> [Evidence-based nutrition] thus departs from the situation of [evidence-based medicine], where, for most interventions, the use of a no-intake control group is usually quite appropriate. In EBM, the hypothesis is that *adding* an intervention ameliorates a disease, whereas in EBN it is that *reducing* the intake of a nutrient causes (or increases the risk of) disease. This distinction is critical. No one proposes in EBM that a disease is caused by the absence of its remedy; wherease for nutrients the hypothesis is precisely that malfunction is caused by deficiency. A hypothesis about disease causation can rarely, if ever, be directly tested in humans using the [randomized clinical trial] design.

Blumberg, *supra*, at 480.

designed clinical trials. The FTC's requirement of two clinical trials conflicts with scientific principles uniquely applicable in the nutrition science context and serves to bar nearly all nutrition claims.[7]

In sum, FTC's Two Clinical Trial Requirement violates the First Amendment by imposing a prior restraint on the right to engage in commercial speech in the absence of two well designed clinical trials and unconstitutionally shifts the burden of proof to advertisers.

C. The FTC Cannot Violate the Constitution in Consent Orders

The FTC's "fencing-in" authority does not excuse agency violations of the First Amendment. The FTC has authority to "fence-in" violators, but that authority has generally been limited to product categories and methods of advertising. *Telebrands Corp. v. FTC*, 457 F.3d 354, 357 (4th Cir. 2006) ("'[f]encing-in' relief refers to provisions in a final FTC order that are broader than the conduct that is declared unlawful. Fencing-in remedies are designed to prevent future unlawful conduct"). In *Telebrands*, the Court discussed FTC's fencing-in

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[7] The Department of Agriculture's Dietary Guidelines have never been supported by multiple clinical trials. *See* Roger Clemens, *Dietary Guidelines May Produce Unintended Health Consequences*, Food, Medicine & Health (Exhibit 4); Joanne Slavin, *Dissecting the Dietary Guidelines*, Food Technology (2011) (Exhibit 5). The Guidelines are "based on evidence that consuming ... foods within the context of an overall healthy eating pattern is associated with a health benefit..." *See* Dietary Guidelines for Americans, 2010 (Jan. 31, 2011), at Ch. 4, *available at*, http://tinyurl.com/6k55bl6. Again, "making strict recommendations for optimal dietary practices is difficult to support with evidence-based nutrition science." Slavin, *supra*, at 40, 46 ("the scientific support for these recommendations is more historical than evidence-based"). "Intervention studies, where diets following the Dietary Guidelines are fed long-term to human volunteers, do not exist." *Id.* at 46 (noting that, "[g]enerally, adherence to the Dietary Guidelines is measured in epidemiological studies by determining a healthy eating index (HEI), a measurement of adherence to the diet recommendations of the Dietary Guidelines"). What is good for the goose must likewise be good for the gander. The federal government has never subjected itself to a two-clinical trial requirement when promulgating dietary guidelines which are intended to impact on consumer purchasing decisions. *See* USDA Press Release, *USDA and HHS Announce New Dietary Guidelines to Help Americans Make Healthier Food Choices and Confront Obesity Epidemic* (Jan. 31, 2011), *at*, http://tinyurl.com/4kpafy5.

authority at length. *Id.* A reasonable relationship must exist between the violation and the FTC's remedy. But fencing-in authority has never been interpreted to grant FTC power to render more onerous the substantiation requirements for prospective claims, only alter the scope of the order. The FTC lacks authority *ab initio* to insert unconstitutional language in its consent orders. *See* 5 U.S.C. § 706(2)(B) (agency action is unauthorized if "contrary to constitutional right, power, privilege, or immunity").

Broad categorical restrictions, like those attempted in the recent agreements, have been struck down by the courts in previous FTC cases. In *Beneficial Corp. v. FTC,* 542 F.2d 611 (3rd Cir. 1976), *cert. denied,* 430 U.S. 983, 97 S.Ct. 1679, 52 L.Ed.2d 377 (1977), the Third Circuit reviewed an FTC order that forced a company "to abandon entirely its copyrighted and heavily promoted phrase ('Instant Tax Refund')." *Id.* at 618. While the court upheld FTC's finding that prior use of "Instant Tax Refund" in advertising was deceptive, it would not enforce the order to prohibit use of the term or other similar words in future advertising because the order went farther than was necessary to eliminate the deception. *Id.* at 620. Violations of the FTCA do not lift the constitutional limitations on prior restraint affecting future speech in FTC consent orders. *See U. S. v. Reader's Digest Ass'n, Inc.*, 464 F.Supp. 1037, 1051 (D.C. Del. 1978).

Rather, federal courts have consistently held that the doctrine of prior restraint and First Amendment protections are directly applicable to FTC consent orders and limit the expansion of FTC advertising regulation. *See, e.g., Standard Oil C. of California v. F.T.C.*, 577 F.2d 653, 662 (9th Cir. 1978) ("first amendment considerations dictate that the Commission exercise restraint in formulating remedial orders which may amount to a prior restraint on protected commercial speech"); *Sears, Roebuck and Co. v. F.T.C.*, 76 F2d 385, 399 n.31 (9th Cir. 1982); *Beneficial Corp*, 542 F.2d at 611; *F.T.C. v. Simeon Management Corp.*, 532 F.2d 708, 713 (1976)

("[a]lthough commercial advertising may be subject to regulation serving an important public interest, it is not beyond the protection of the first amendment... [S]afeguards would be inadequate if courts were required under section 53(a) to enjoin advertising because FTC claimed it was false, without first making an independent determination of the sufficiency of that claim"). The First Amendment limits explained in cases concerning nutrient-disease relationship claims are applicable to all instances of federal government imposition of prior restraints, not solely to those arising under the FDA's enforcement of its enabling statute, but also to the FDA Prior Restraint Requirement and the Two Clinical Trial Requirement imposed in FTC Consent Orders. The First Amendment limitations on prior restraint are global protections that guard against restrictions of protected commercial speech, which includes speech not only provable to a conclusive degree but also speech that is backed by credible but inconclusive scientific evidence.

D. The FTC's New Policies Chill Protected Speech

1. The FTC's New Policies Apply to the Industry As a Whole

The FDA Prior Restraint Requirement and the Two Clinical Trial Requirement for health benefit advertising announced in the Iovate, Dannon, and Nestlé consent orders apply to all similarly situated advertisers who sell substantially the same kind of products and make substantially the same kind of claims. The FTC has been vocal in communicating the restrictions to the industry through its agents. Although those agents disclaim that their views are those of the agency, they are the very individuals responsible for creating and enforcing the new requirements. *See* Dan Schiff, *FTC's Pending Claims Substantiation Changes Will Weigh on Small Firms*, The Tan Sheet at 9, Mar. 1, 2010. Richard Cleland, Assistant Director of the Division of Advertising Practices, has explained that "FTC plans to promulgate the revised

standard initially through consent orders and eventually revise its advertising guide for the supplement industry." *Id.*

The FTC's use of consent orders to express policy qualifies as an industry-wide rule. The APA defines a "rule" as

> the whole or part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency.

5 U.S.C. § 551(4). Courts recognize the applicability of FTC consent orders on the entire market. *See Watson v. Philip Morris Companies, Inc.*, 420 F.3d 852, 859 (8th Cir. 2005) ("[b]ringing a single case against one cigarette company would have the effect of bringing the whole industry into compliance and would do so much more quickly than would a formal rulemaking process"). Interpreting *Watson*, the United States District Court for the District of New Mexico explained that "[t]he FTC's enforcement mechanisms through consent orders is no less effective and coercive than direct enforcement through a formal regulation." *See Mulford v. Altria Group, Inc.*, 506 F.Supp.2d 733, 762 (D.N.M. 2007); *see also Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 513 & n.7 (1992) (stating that FTC has "long regulated unfair and deceptive advertising practices in the cigarette industry," and citing a number of FTC opinions in support of this proposition, implicitly recognizing that FTC opinions and orders are a form of FTC regulation). "The legal and regulatory effect of the consent orders is evidenced by the FTC's own description of its consent orders as 'regulatory activity.'" *Mulford*, 506 F.Supp. 2d at 762 (stating further that "[t]he history of FTC involvement in cigarette advertising demonstrates that the FTC used consent orders such as these to regulate the cigarette industry, make general rules, and express FTC policies for the industry in lieu of formal rulemaking").

Although the *Watson* decision, relied upon in *Mulford*, has been overruled by the Supreme Court on another issue, whether an informal industry agreement between the FTC and the cigarette industry constituted a delegation of FTC authority thus making it a federal contractor, the Court's observation that FTC uses consent orders as binding regulatory policy is good law. S*ee Watson v. Philip Morris Companies, Inc.*, 551 U.S. 142, 156, 127 S.Ct. 2301 (2007) (*Watson II*). In fact, the Supreme Court in *Watson II*, cited the FTC's regulatory activity, including the use of consent orders recognized in *Watson*, as binding regulation for the cigarette industry. *See Watson II*, 551 U.S. at 154-155 (accepting as true facts listed in Phillip Morris brief). Thus, the proposition in *Mulford* that interpretations and commentary in FTC consent orders bind advertisers is the law.[8]

The content of consent orders demonstrating the FTC's thinking or interpretation of substantiation requirements is significant evidence that the consent orders with Nestle, Iovate, and Dannon constitute an agency rule under the APA standard. *See* 5 U.S.C. § 551(4). The FTC and the courts are fully aware of the coercive nature of FTC consent orders on the market and intend those advertisers similarly situated who sell substantially the same products and make substantially the same claims to take heed and avoid doing so. FTC relies on the regulatory power of those actions time after time as evidenced in the string consent orders used to regulate

[8] In addition, several state courts have also acknowledged the coercive and rule like nature of consent orders published by the FTC. *See Azar v. Prudential Ins. Co. of America,* 68 P.3d 909, 929 (2003) (suggesting that agency can "expressly permit" action in interpretations where it "specifically addressed" and authorized action); *see also Price v. Philip Morris, Inc.,* 219 Ill.2d 182, 848 N.E.2d 1, 46, 53-54 (2005) (holding that FTC's informal regulatory activity of cigarette advertising, including use of consent orders, fell within Illinois Consumer Fraud Act's exemption provision exempting actions or transactions "specifically authorized by laws administered by" a state or federal regulatory body).

the cigarette industry. *See e.g., Mulford,* 506 F.Supp.2d at 762; *Cipollone*, 505 U.S. at 513 & n. 7, 112 S.Ct. 2608; *Watson I*, 420 F.3d at 859-60; *Watson II*, 551 U.S. at 154-155.

Industry members cannot afford to disregard FTC's FDA Prior Restraint Requirement or its Two Clinical Trial Requirement in relevant consent orders. FTC consistently refrained from specifying precise quantitative requirements for advertising substantiation of health claims, stating instead that the FTC has discretion to determine on a case-by-case basis what evidence is required to meet the standard. *See, supra*, FTC, Dietary Supplements: An Advertising Guide for Industry (April 2011) ("[t]here are no fixed formula for the number or type of studies required..."). An affirmative statement in a consent order requiring FDA prior approval under the NLEA or two clinical trials represents to industry that FTC believes FDA prior approval along with two clinical trials are requisite to avoid a charge of deceptive advertising for the type of health claim addressed above in the cited consent orders. Indeed, when interpreting text, even Courts generally give a word or phrase the same meaning when it is repeated in other sections of that text. *See Sierra Club v. Seaboard Farms Inc.*, 387 F.3d 1167 (10th Cir. 2004); *Sorenson v. Sec'y of the Treasury*, 475 U.S. 851, 860 (1986). It is logical for industry to do the same.

2. The Fear of Enforcement under FTC's New Policies Chills Protected Speech

Because the FTC's consent orders apply across the industry, the FTC's FDA Prior Restraint Requirement and Two Clinical Trial Requirement have created an environment of fear for companies promoting the health benefits of products substantially the same as those in the Consent Orders with substantially similar claims. Courts recognize that a history of prosecution can give rise to an actionable belief on the part of the advertisers that similar prosecution could be their fate in the future. *See Lopez v. Candaele*, 630 F.3d 775, 786-87 (9th Cir. 2010) (speaker need not be the direct target of government enforcement to have standing; a "history of past

enforcement against parties similarly situated to the plaintiffs cuts in favor of a conclusion that a threat is specific and credible"). Therefore, the FTC's new policies create a real fear within the dietary supplement industry that similarly situated advertisers will be required to meet the FTC's new standards for advertising substantiation without the constitutionally mandated protections articulated in *Pearson v. Shalala I*, 164 F.3d at 655-58.

The FTC polices health benefit claims with unbridled discretion to launch costly, time consuming investigations of companies without being required to produce any evidence that targeted advertising claims cannot be remedied with adequate qualifications. That power to investigate anyone in the market without the requirement to meet any kind of burden before instituting the investigation has a chilling effect on important beneficial speech. The threat of FTC enforcement action stemming from its consent orders constitutes a prior restraint that chills speech. *See Multimedia Holdings Corp. v. Circuit Court of Florida, St. Johns County*, 544 U.S. 1301, 1304 (2005) ("A threat of prosecution or criminal contempt against a specific publication raises special First Amendment concerns, for it may chill protected speech much like an injunction against speech by putting that party at an added risk of liability"); *Virginia v. Am. Booksellers Ass'n, Inc.*, 484 U.S. 383, 393 (1988), ("self-censorship . . . can be realized even without an actual prosecution"); *Rangra v. Brown*, 566 F.3d 515, 519 (5th Cir.2009) ("*A credible threat of present or future prosecution is an injury sufficient to confer standing, even if there is no history of past enforcement*").

The Supreme Court does not require formal action from an agency restricting the speech of an individual or company to find a prior restraint, "informal procedures undertaken by officials and designed to chill expression can constitute a prior restraint" of themselves. *Multimedia Holdings*, 544 U.S. at 1306) (citing *Bantam Books, Inc. v. Sullivan*, 372 U.S. 58

(1963)). "Any system of prior restraints of expression comes to [the] Court bearing a heavy presumption against its constitutional validity." *Bantam Books, Inc. v. Sullivan*, 372 U.S. 58, 70 (1963). The presumption against prior restraints was designed to prevent self censorship arising from fear of prospective regulatory action against a speaker. *See City of Lakewood v. Plain Dealer Publishing Co.*, 486 U.S. 750, 757-58 (1988); *see also* Blasi, *Toward a Theory of Prior Restraint: The Central Linkage*, 66 Minn.L.Rev. 11 (1981); Emerson, *The Doctrine of Prior Restraint*, 20 Law & Contemp.Probs. 648 (1955).

In *Lakewood*, the Supreme Court explained the danger that exists to First Amendment rights when a prior restraint is created by the threat of prosecution when an agency has unbridled discretion to act against individuals or companies,

> Self-censorship is immune to an "as applied" challenge, for it derives from the individual's own actions, not an abuse of government power. It is not difficult to visualize a newspaper that relies to a substantial degree on single issue sales feeling significant pressure to endorse the incumbent mayor in an upcoming election, or to refrain from criticizing him, in order to receive a favorable and speedy disposition on its permit application. Only standards limiting the licensor's discretion will eliminate this danger by adding an element of certainty fatal to self-censorship.

City of Lakewood v. Plain Dealer Publishing Co., 486 U.S. 750, 757-58. Thus, it is unnecessary that an agency actually abuses the power it has, it is enough that the power exists. *See id.* (quoting *Thornhill v. Alabama*, 310 U.S. 88, 97 (1940)) ("Proof of an abuse of power in the particular case has never been deemed a requisite for attack on the constitutionality of a statute purporting to license the dissemination of ideas. . . . It is not merely the sporadic abuse of power by the censor but the pervasive threat inherent in its very existence that constitutes the danger to freedom of discussion").

The potential for unlawful application of the FTC's new FDA Prior Restraint and Two Clinical Trial Requirements thus has the effect of chilling protected health benefit claims in

advertising—those claims that are not FDA approved and are without two human clinical trials substantiating them in the categories thus far identified in the above-referenced FTC consent orders. The new policies limit even traditional, well-recognized health benefit claims in advertising supported by abundant scientific evidence, but without two human clinical trials, such as Pearson and Shaw's desired claim for their prune juice product relieving symptoms of chronic constipation.

CONCLUSION

For the foregoing reasons, to bring the FTC's Consent Orders concerning health benefit claims in advertising within the confines of the First Amendment, the petitioners hereby request that FTC remove from all Consent Orders issued to date and avoid inclusion in all future Consent Orders and other Orders of the FTC the FDA Prior Restraint and the Two Clinical Trial Requirements. The petitioners also request that FTC enact regulations implementing *Pearson v. Shalala I*, 164 F.3d 650 (D.C. Cir. 1999) and its progeny by avoiding the imposition of any restriction on the future right to make a claim of health benefit without first establishing with empirical evidence that claim qualifications will not suffice to cure for misleadingness.

Petitioners request that the Commission act expeditiously in its response to this petition. *See Elrod v. Burns*, 427 U.S. 373 (1976) ("[t]he loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury"); *Washington Free Community v. Wilson*, 426 F.2d 1213, 1218 (D.C. Cir. 1969) ("Speakers...cannot be made to wait for years before being able to speak with a measure of security").

Respectfully submitted,

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EXHIBIT 1

NATURAL MEDICINE JOURNAL

A Commentary on the Nutrient-Chronic Disease Relationship and the New Paradigm of Evidence-Based Nutrition

By Andrew Shao, PhD, and Douglas Mackay, ND

Abstract

Understanding the role of nutrition in the prevention of long-latency chronic disease is one of the greatest challenges facing the health sciences field today. The scientific community lacks consensus around how to appropriately generate and/or evaluate the available nutrition data to inform treatment recommendations and public policy decisions. Evidence-based medicine (EBM) is a well-established research paradigm for the evaluation of drug effects. Currently, EBM is arguably being misapplied in order to establish the relationship between nutrients and human health. Nutrients and other bioactive food components are not drugs, and several distinguishing characteristics are overlooked in the design and/or interpretation of nutrition research. Unlike drugs, nutrients work in complex networks, are homeostatically controlled, and cannot be contrasted to a true placebo group. The beneficial effects of nutrients are small and can take decades to manifest. A new paradigm of evidence-based nutrition (EBN) needs to be established that sets criteria and guidelines for how to best study the effects of nutrients in humans. EBN must consider the complex nuances of nutrients and bioactive food components to better inform the design and interpretation of nutrition research. Practitioners, researchers, and policy makers will be better served by a nutrition-centered framework suited to assess the totality of the available evidence and inform treatment and policy decisions. Several recommendations for guidelines and criteria that could help define the EBN research paradigm are discussed.

Introduction

There is general agreement within the nutrition science and practitioner communities that one's diet, nutritional status, and lifestyle can substantially predispose one to (or protect against) many chronic diseases and other conditions, including heart disease, diabetes, and cardiovascular disease. For decades, the US government has invested, and continues to invest, enormous resources to support programs such as the Dietary Guidelines for Americans[1] and the Institute of Medicine's (IOM) Dietary Reference Intakes[2] to develop recommendations for diet and nutrient intake levels that will, among other things, reduce chronic disease risk within the population. The nutrient-chronic disease relationship is also addressed by the Food and Drug Administration (FDA) when it reviews Health Claim and Qualified Health Claim petitions,[3] both of which are viewed as broad public health statements. But many questions unique to nutrition still remain when it comes to evaluating the evidence on which these and other recommendations are based. Although a research paradigm for the evaluation of drug effects—evidence-based medicine (EBM)—has been well established for years,[1] the amount, level, and scope of scientific evidence, and the interpretation needed to support nutrition recommendations, continue to be of intense debate.[4–6] Obtaining this evidence has proved to be challenging due to resource and feasibility limitations. Consensus does not yet exist about how to appropriately generate and/or evaluate the available data to inform clinical and/or public policy decision making. These and other important issues are currently being debated by scientists from government (FDA, NIH, USDA), academia, and industry, as well as among practitioners.

Evidence-Based Medicine Vs. Evidence-Based Nutrition

Unlike pharmaceuticals, which have long been studied under the principles of EBM, nutrition and chronic disease research is in a relative state of infancy. Nutrition researchers have yet to

* A PubMed search for "evidence-based medicine" resulted in 41,096 publications; the same search for "evidence-based nutrition" resulted in 37 publications. http://www.ncbi.nlm.nih.gov/sites/entrez. Accessed August 10, 2010.

establish clear criteria and guidelines for how best to study the effects of nutrients in humans, and subsequently how to evaluate those findings—in other words, what constitutes evidence-based nutrition (EBN). In the absence of such guidelines, the long-established principles of EBM and its strong reliance on randomized, controlled trials (RCTs) have been applied to fill this void (Figure 1). Within this paradigm, expert opinion is given the least weight, while practitioners' clinical experiences are not even considered part of the evidence base.

The traditional RCT is viewed in the EBM hierarchy as the gold standard for research on cause-and-effect relationships, and its design has been more suited to assess the efficacy and safety of drugs, not nutrients. When designed, executed, and analyzed properly, the results of RCTs can be persuasive and provide a high level of certainty. Such certainty, one could argue, is necessary when assessing the effects of expensive, potent, and potentially dangerous drug therapies. This cost-benefit-risk equation, while appropriate for drugs, is substantially different for nutrients. Several nutrition researchers have, in recent years, raised concerns over what is perceived to be the misapplication of drug-based trials to assess nutrition questions, without taking into account the totality of the evidence or the complexities and nuances of nutrition.[5–8] Drugs tend generally to have single, targeted effects; drugs are not homeostatically controlled by the body and can easily be contrasted with a true "placebo" group; drugs can act within a relatively short therapeutic window of time, often with large effect sizes. In contrast, nutrients tend to work in complex systems in concert with other nutrients and affect multiple cells and organs; nutrients are homeostatically controlled, and thus the body's baseline nutrient "status" affects the response to a nutrient intervention; a nutrient intervention group cannot be contrasted with a true placebo group (ie, "zero" exposure group); and with respect to chronic disease prevention, nutrient effect sizes tend to be small and may take decades to manifest. Finally, the very absence (or inadequacy) of a given nutrient produces disease, which is a fundamental difference compared to drugs (summarized in Table 1).

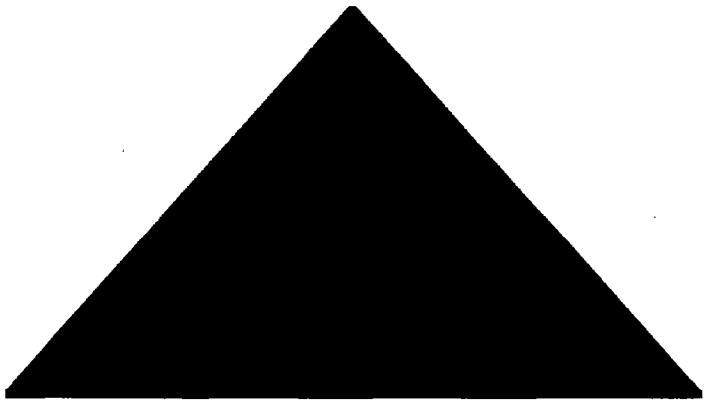

Figure 1. Pyramid describing the hierarchy of evidence-based medicine, the cornerstone of which is its strong reliance on the randomized, controlled trial as the "gold standard" of evidence.

Table 1. Contrast Between Drugs

Parameter	Drugs	Nutrients
Essentiality	None	Essential
Inadequacy results in disease	No	Yes
Homeostatically controlled by the body	No	Yes
True placebo group	Yes	No
Targets	Single organ/tissue	All cells/tissues
Systematic function	Isolated	Complex networks
Baseline "status" affects response to intervention	No	Yes
Effect size	Large	Small
Side effects	Large	Small
Nature of effect	Therapeutic	Preventive

These nuances, while seemingly apparent, have been largely overlooked in the design and/or interpretation of some of the most resource-intensive, high-profile RCTs conducted in recent years. The results of these recently published trials[9–13] by EBM criteria has led to conclusions that there is no evidence to support the supplemental nutrient-chronic disease relationship. But given the clear, yet under-appreciated differences between drugs and nutrients, one must ask a series of important questions regarding study design, the questions intended to be addressed, and the questions that were actually addressed and whether broad conclusions can be drawn from these studies to serve as the basis for recommendations (or lack thereof). If blind application of EBM to nutrition questions is inappropriate, the scientific paradigm within which nutrients should be evaluated needs to be defined.

The Women's Health Initiative (WHI) trial[13] is a glaring example of the difficulties researchers face when conducting large-scale, long-term RCTs examining the effect of supplemental nutrients on chronic disease risk, even when adequate resources are readily available. While well intentioned, the trial (which included multiple arms: calcium and vitamin D supplementation; low-fat diet; hormone replacement therapy) suffered from a host of logistical limitations, including poor compliance, extensive use of supplemental nutrients in the placebo arm (due to ethical constraints), and other administrative difficulties associated with multicenter trials. Because the investigators found themselves caught in an ethical dilemma (WHI was initiated when awareness of the bone-protecting benefits of calcium was just becoming widespread), they could not prevent the use of calcium supplements by the placebo group. The result was a median calcium intake in the placebo group of nearly 1,100 mg/day. Thus, the hypothesis ostensibly tested in the WHI trial was not "low vs. high calcium intake" but "high vs. higher calcium intake." The erroneous message sent

from this multimillion dollar ($625 million), NIH-sponsored trial was that calcium and vitamin D supplementation is not useful for maintaining bone health in post-menopausal women, which is counter to the overwhelming majority of evidence. This has prompted some to question the value of large and expensive RCTs: "The results of the WHI add further evidence that clear answers to questions about the long-term effects of diet on risks of cancers and other major diseases may not be obtainable by large randomized intervention trials, no matter how much money is spent conducting them."[14] Despite this assertion, regard for the principles of EBM and the RCT as the unquestioned gold standard have resulted in the misuse of the WHI trial as part of the evidence base supporting calcium and vitamin D's effect on fracture risk. In a recent meta-analysis,[16] the WHI study, as a large RCT, was automatically assigned the most weight by far among the 17 studies included in the analysis. This resulted in a skewed effect on fracture risk toward the null (although the combined effects of the other, smaller trials included in the analysis still resulted in a statistically significant [17] combined 12% reduction in fracture risk). Systematic reviews and meta-analyses should be interpreted judiciously and should not be considered on their own as high-level evidence because they are statistically assisted interpretations of primary evidence that carry their own set of limitations and biases.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)[11] is an example of a high-profile RCT whose results have been largely misinterpreted and miscommunicated. The investigators terminated the study early, concluding there was no beneficial effect of selenium and vitamin E supplementation on prostate cancer risk. The form of selenium used in SELECT (selenomethionine) is different from the yeast-based selenium product used in a previous trial, which suggested through a secondary analysis that supplemental selenium could lower the risk of prostate cancer.[16] The decision to utilize an alternate form of selenium was apparently driven by the need to use standardized and highly stable material that would maintain consistency throughout the length of a multiyear trial. This could not be achieved with yeast-based selenium, hence the decision to use selenomethionine. This is a common dilemma encountered by nutrition researchers investigating bioactive compounds derived from natural sources, such as fish oil, bovine colostrum, and probiotics, and yet illustrates another way the traditional RCT model does not account for the subtle nuances of nutrition interventions. Furthermore, the subjects enrolled in the study by Clark et al had relatively low baseline serum selenium levels (suggesting they were inadequate or insufficient), whereas the majority of men enrolled in SELECT were relatively replete in selenium. Finally, the men enrolled in SELECT had extremely low risk for prostate cancer—only 1 death due to prostate cancer occurred in the entire cohort, making it more difficult to detect an effect of the intervention. These seemingly minor limitations may have had a major impact on the outcome, an issue that has been inadequately communicated to practitioners and the public.

A more recent example of inappropriate application of EBM to nutrition research comes from the recent study of the effect of antioxidant supplementation on preeclampsia.[17] Investigators randomized more than 10,000 women to receive 1,000 mg vitamin C and 400 IU vitamin E daily or placebo between the 9th and 16th weeks of pregnancy and concluded there was no effect of antioxidants on preeclampsia. Analysis of the findings reveals that the majority of the women enrolled in the study (80%) were using multivitamins, which could have affected their baseline nutritional status and, therefore, their response to the supplemental vitamin C and E. Furthermore, vitamin C and E status was not assessed at baseline or during the study, so one cannot know whether these women were truly in need of supplementation. Finally, the premise of the study is that oxidative stress may induce preeclampsia. However, oxidative stress was neither measured at baseline nor during the study, so the "oxidative stress status" of these women was not known; if they were not oxidatively stressed in the first place, it follows that the antioxidant supplements would fail to have an effect. These critical nutritional nuances were overlooked by the investigators and the publishing journal as well. Clinicians should not take the results from this RCT at face value and abandon antioxidant supplementation among this target population, but instead should determine what level of confidence they have that the data from this trial are transferable to the individual patients sitting in their offices.

This "blind faith" in RCTs without consideration of study limitations and quality should be of greater concern than it currently is. A well-designed RCT eliminates variables such as comorbid conditions, concomitant interventions, and assumes individual variability in treatment response will be randomly allocated if the trial is large enough. Conversely, a clinician must carefully consider these same variables when deciding if a particular treatment is suited for an individual patient. From the clinician's perspective, an RCT may be the best way to determine if a treatment works; however, it reveals little about which individuals will benefit. EBM applies a hierarchy of evidence (with the RCT as the "gold" standard) to guide clinical judgment rather than using clinical judgment as a guide to evidence that is relevant to an individual patient.[18] Recommendations, whether they be public health-based or practitioner-patient-based, should be developed from the totality of the available evidence, not on a single study or study design.

Prevention Vs. Treatment

Perhaps one of the most important, but often ignored, differences between the research paradigms for drugs and nutrients is the cost and logistical complexities associated with conducting RCTs. Not taking into account the preclinical research needed for drug development (which is substantially resource intensive, due in part to the number of candidate drugs that do not

* Presentation at CRN's Day of Science, May 8, 2008. "NCCAM research initiatives focused on prevention" by Josh Berman, MD, PhD, National Center for Complementary and Alternative Medicine, NIH.

make it to the market), human trials involving nutrients are far more costly than those for drugs. Drugs are most often studied in a therapeutic context (ie, to treat, cure, or mitigate a disease or condition), while nutrients are studied with a focus on health promotion or disease risk reduction. These are fundamentally different approaches that have tremendous implications on cost and feasibility. In the context of a RCT, studying treatment of a disease or condition (when all subjects have the disease at baseline) is far less costly than studying the prevention or risk reduction of the disease (when no subjects have the disease or condition at baseline). The subtle effect of nutrients and small effect sizes mean far more subjects are needed to demonstrate statistical significance. It is estimated that the net cost in terms of subjects, duration, and total dollars for chronic disease risk reduction trials exceeds that for therapeutic trials by more than 10-fold (Table 2).* Furthermore, chronic diseases can take decades to develop, so demonstrating a statistically significant and clinically relevant reduction in risk with any intervention requires very long-term trials. It is also important to note that unlike the pharmaceutical industry that funds, designs, and controls its own research, the food and dietary supplement industries must rely almost exclusively on government and/or academically funded studies. This is due largely to the inability or lack of means (legally or financially) for food and dietary supplement firms to develop, maintain, and defend intellectual property. As a result, these firms have little or no exclusivity on the use of research to support marketing efforts. Thus, the profit margins and, ultimately, research and development budgets of food and dietary supplement firms tend to be much smaller than their pharmaceutical counterparts.

The case of beta-carotene is an excellent example of inappropriate application of a therapeutic study design to address a prevention question. Decades ago, observational studies suggested that diets and/or serum high in beta-carotene were associated with a lower risk of certain cancers, including lung cancer. This lead to RCTs published in the mid-1990s (the famous "Finnish trials"[19,20]) in which lifelong smokers or asbestos workers were supplemented with high doses of antioxidants, such as beta-carotene. The results at the time were shocking: compared to placebo, supplementation with beta-carotene significantly *increased* the risk of lung cancer in these smokers and asbestos workers. To this day, some people misuse this example is misused to demonstrate that the results of a RCT invalidated earlier epidemiological data. Some clinicians guided by EBM conclude that beta-carotene presents a similar risk of increased lung cancer to *all* patients, including those who do not smoke or have asbestos exposure, and discontinued its use altogether. Indeed, in its evidence-based review system guidance document, FDA touts this example as one that justifies the EBM approach to data evaluation, stating that the results of RCTs "trump" those of observational studies.[3] Ignored is the fact that the RCTs in smokers and asbestos workers asked and answered questions different from those of the earlier epidemiological studies. Assessing the effect of lifelong exposure to a modest amount of a nutrient in the context of the whole diet in a general population that is healthy at baseline is completely different from administering a high dose of a single, purified, and isolated nutrient to a very specific population (eg, lifelong smokers) that is not healthy at baseline (because lung cancer was likely well on its way). In the latter case, beta-carotene was studied as a therapeutic drug, not a nutrient. Asking the question of whether beta-carotene can behave like a drug is certainly worthwhile, sometimes necessary. But the design and interpretation of such a study should be vastly different from one that studies a nutritive effect. A quote from a recent editorial on nutrition and cancer summarizes the well intended, but misguided, beta-carotene trials: "By analogy, when keys are missing, it is common to look for them under the lamppost where there is light rather than in the murky location where the keys were more likely dropped."[21]

Table 2. Cost Comparison Between Therapeutic and Risk Reduction RCTs*

	Therapeutic (drug) trial	**Risk reduction (nutrient) trial**
Those with disease at baseline	100%	0
Placebo administration	20% cured (80% still have disease)	20% acquire disease (80% do not acquire disease)
Intervention administration—if 25% effective	¼ of 80% (20%) cured; 60% still have disease	¼ of 20% (5%) do not acquire disease; 15% acquire disease
Desired statistical power	a = 0.05, power = 0.8	a = 0.05, power = 0.8
Subjects required per group	64	714
Cost ($)	1.3 million	>15 million

* Based on presentation at CRN's Day of Science, May 8, 2008. "NCCAM research initiatives focused on prevention" by Josh Berman, MD, PhD, National Center for Complementary and Alternative Medicine, NIH.

The Double Standard

A number of public health recommendations urge Americans to increase the consumption of fruits and vegetables in the diet, including the Dietary Guidelines for Americans[1] and several FDA-approved health claims.[22–24] But the evidence on which these recommendations are based consists almost entirely of observational studies in various forms, not the "gold standard" RCT. With a few exceptions, such as the DASH trial,[25] there are almost no RCTs that demonstrate chronic disease risk reduction from fruit and vegetable intake, and researchers still cannot definitively conclude that it is the presence of fruits and vegetables in the diet or displacement of other foods that is respon-

sible for the observed effects. Yet few would debate that fruit and vegetable consumption is important for health and can lower one's risk of chronic disease. The apparent double-standard—when a strong recommendation arises from what is perceived as "poor quality" data—is more likely due to some of the practical constraints already mentioned than a lowering of scientific standard. RCTs involving whole foods or diets are extremely difficult to conduct—perhaps even more so than nutrient-based trials, but for some of the same reasons (eg, ethical issues, no true placebo group, compliance). The key for policy and regulatory scientists has been the *consistency* of the relationships demonstrated in food-based epidemiological studies. Despite the apparent incongruent findings of 2 recent, large prospective studies showing no relation between fruit and vegetable intake and cancer outcomes,[26,27] the totality of the evidence continues to be in support of a beneficial effect with respect to chronic disease when assessed. As with the case of smoking (there are no RCTs that show smoking causes lung cancer, but the cause-and-effect relationship is well accepted due to the consistency of observational data), the association of fruit and vegetable consumption with positive health outcomes has been very consistent.

In 2006 NIH held a state-of-the-science conference on multivitamins and chronic disease prevention.[28] Despite a lengthy list of observational studies suggesting the use of multivitamins is associated with a variety of health benefits including lower chronic disease risk, the expert panel concluded that it could not recommend for or against the use of multivitamins for reduction of chronic disease risk. This conclusion was inevitable in light of the fact that the panel used a strictly EBM approach, excluding all observational data and relying solely on RCTs (achieved after excluding all but 63 of the over 11,200 possible reports in the literature). As scientists, we can only wonder what the conclusions would have been if the panel had been tasked with addressing fruits and vegetables. And if these same panelists were your physicians, they may not advise you to cease smoking because of the lack of RCT data demonstrating that smoking causes lung cancer.

Related to the feasibility and ethical constraints of conducting RCTs, consider the following scenario: Consumption of a nutrient or bioactive or group of these during pregnancy (ie, exposure in utero) is linked to reduction of adult chronic disease risk in the offspring. Such a nutrient-disease relationship could never be "validated" in a RCT because of ethical, resource, and other logistical constraints. This presents a challenge when attempting to base public health or patient recommendations on a sound evidence base. However, the absence of this kind of experimental data should not be an excuse for indecision or inaction. Despite its many limitations, EBM has become the de facto standard for developing guidelines and criteria for medical training, clinical practice, reimbursement decisions, and public policy. EBM's emphasis on reductionist science, research methodology, and statistical power and concurrent de-emphasis of epidemiological evidence, expert opinion, and clinical experience have left many clinicians wondering: Are we letting the tail wag the dog?[18]

Testing Single, Isolated Nutrients

In January of 2009, FDA released a final guidance explaining the agency's evidence-based review system for the evaluation of health claims, in which it states clearly that RCTs "trump" observational studies, demonstrating its adherence to EBM principles.[3] Given the difficulties associated with conducting these studies on single, isolated nutrients, industry may need to reconsider single-nutrient health claims altogether. In hindsight, it seems farfetched to have hypothesized that supplementation with a single nutrient can reduce the risk of chronic diseases like cardiovascular disease and cancer. Certainly, this is not an approach taken by integrative medical practitioners. And while the question still remains to be answered—whether certain single nutrients, when provided in supplemental quantities, can on their own reduce chronic disease risk—the research to date suggests this to be a tall order. One obvious reason is that nutrients do not function in isolation. Rather, they function in vast, complex networks (eg, the antioxidant network, the methylation pathway). In addition, today's medical landscape is dominated by multi-organ, multifactorial, long-latency degenerative and chronic diseases that result, in part, from a complex interplay of genetics, diet, lifestyle, inactivity, stress, and environmental toxins. Studies involving supplementation with single nutrients do not take this complexity into account. There are a few exceptions, such as vitamins D and E and long-chain omega-3 fatty acids; supplementation with these alone has been shown to have beneficial effects on chronic disease risk, immune function, and inflammation. The body's response to supplemental nutrients depends on its baseline status—the lower the status (or more inadequate) the greater the response. Americans are known to have low status or inadequate intakes of all three of the aforementioned nutrients,[29-36]which may explain why many supplementation studies have demonstrated positive effects. Interestingly, and unlike single-agent, single-target drug trials, in all of these examples the benefits appear to be through multiple mechanisms, which is another difference between measuring drug vs. nutrient efficacy. Nevertheless, NIH funding of large-scale, long-term RCTs that at present appear to be needed to inform nutrition policy decisions is likely to stall or even decline. This is mainly due to the null results of some recent high-profile trials. Those large-scale trials that are now being funded by NIH, such as the Age-Related Eye Disease Study-2 (AREDS 2)[37,38] and the Vitamin D and Omega-3 Trial (VITAL)[39] tend to involve multiple nutrients.

"Bioactives"

A challenge for the dietary supplement and functional food industries, amidst the backdrop of EBM as the currently accepted research paradigm, is resolving the quandary of how "bioactives" are to be studied. Also referred to as "nutraceuticals" or "functional ingredients," these substances are neither drugs nor essential nutrients (although they may be considered "conditionally essential" for some patient populations). They are, however, prevalent in the food supply, in dietary supple-

ments and functional foods, and they do have purported health benefits. An important question regarding assessment of their effects on health and chronic disease risk is whether well-known substances such as flavonols, carotenoids, isoflavones, anthocyanidins, and so on, should be studied like drugs or like nutrients (Figure 2). The answer largely depends on how the body views bioactive substances and how these substances behave in the body (ie, whether or not they are homeostatically controlled). Little is known about aspects of the body's metabolism and regulation of bioactives, but we do know that in many cases humans have been exposed to them through the diet for millennia and that we have evolved to physiologically depend on some dietary bioactive compounds to function in our environment. Examples include emerging evidence showing the long-chain polyunsaturated fatty acid, DHA, being utilized as a chemical messenger that signals resolution of inflammation[40] and how the carotenoids lutein and zeaxanthin from green leafy vegetables protect the eyes from oxidative stress and the high-energy photons of blue light.[41] It is suggested that bioactives behave more as nutrients than drugs, and hence may require a different research paradigm to assess their impact on health.

Importance Of Biomarkers

The single greatest barrier to researching the role of nutrition in health promotion and chronic disease prevention is the paucity of biomarkers validated as surrogates for disease and wellness endpoints. A surrogate endpoint is a biomarker that, if modified, directly modifies the risk of the endpoint itself. Having the ability to rely on surrogate endpoints dramatically improves the feasibility of human trials, both in terms of duration and total cost. As far as health claims are concerned, FDA has denied several in part because the studies submitted in support of the petitions relied on non-validated biomarkers as surrogate endpoints for disease.[42–44] In the absence of validated biomarkers as surrogates for disease, study outcomes must assess the disease endpoint(s) directly, rendering assessment of the effects of nutrients or food components on disease risk extremely lengthy and costly. To date, FDA has relied on advice from authoritative bodies, such as IOM or NIH, as to which biomarkers are validated surrogate endpoints. The current accepted list is disappointingly brief and has changed little in the past decade

Figure 2. Essential nutrients vs. "bioactives"

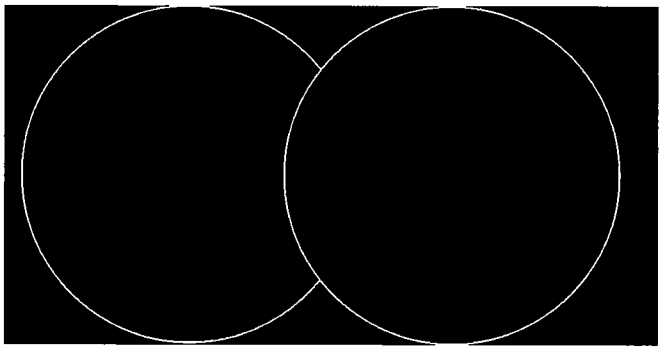

Table 3. *Biomarkers That Are Recognized (and Not Recognized) by FDA as Surrogate Endpoints for Chronic Disease*

Chronic disease	**Surrogate endpoint—Recognized**
Cardiovascular disease	LDL-C
	Blood pressure
Colon cancer	Polyps
Osteoporosis	Bone mineral density, fracture
Diabetes	Blood sugar/insulin resistance
Dementia	Cognitive decline
	Surrogate endpoint—Not recognized
Cardiovascular disease	Serum homocysteine, triglycerides, HDL-C
	Inflammatory factors, CRP, etc.
Osteoarthritis	Cartilage deterioration, joint-space narrowing
Macular degeneration	Macular pigment optical density
Prostate cancer	Prostate specific antigen
Various chronic diseases	Single nucleotide polymorphisms (SNPs), other "omics"

(Table 3). FDA recognizes this deficiency and, in 2009, funded an IOM expert committee to examine this issue and develop a scientific framework on which validation of biomarkers should be based. The committee report, released in May 2010,[45] stresses 3 steps for biomarker evaluation, including analytical validation, qualification, and utilization. The recommendations for biomarker validation make it abundantly clear that the process will be both time- and resource-intensive. It may not be sufficient for FDA to simply apply the framework to the scientific literature to determine which biomarker candidates can be validated as new surrogate endpoints for disease, since much more research is clearly needed to establish existing biomarkers as legitimate candidates. The IOM report is a positive step in the right direction, but it will be years before a significant number of new surrogate endpoints are added to FDA's "recognized" list.

Not addressed in the IOM report is the need for biomarkers of health or wellness. A primary goal of nutrition is health maintenance and promotion, yet no validated biomarkers of health exist. In the search for new biomarkers of health and wellness, investigators are turning to the classical principles of homeostasis, proposing that the term "health" be defined as the ability to adapt to internal and external stimuli or stresses.[46] New models are being developed that take into account the complexity and balance of homeostatic mechanisms. These models are based on dynamic processes (systemic inflammation) instead of single endpoints (such as serum LDL-C). A broader and likely more predictive indication of health status may be

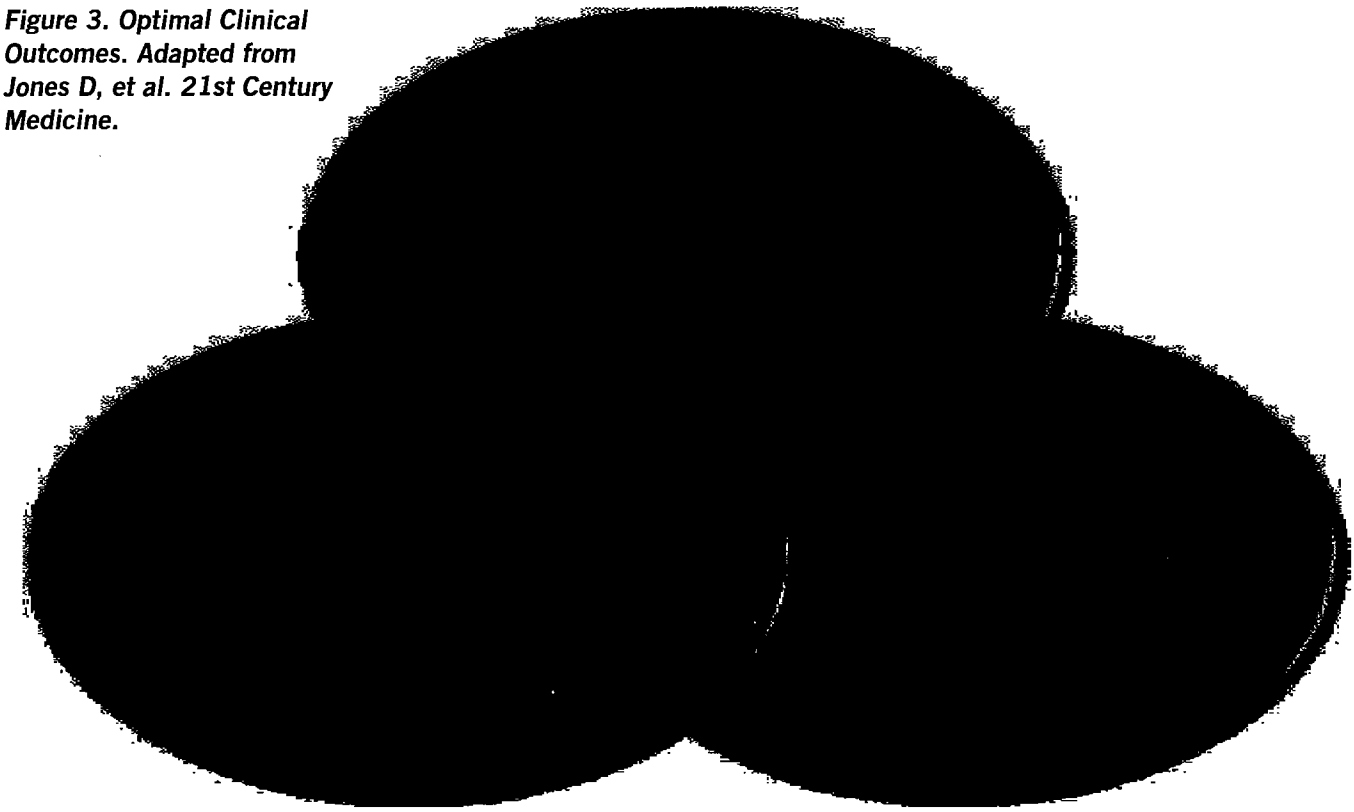

Figure 3. Optimal Clinical Outcomes. Adapted from Jones D, et al. 21st Century Medicine.

obtained by measuring the ability of individuals to adapt to a stress (ie, maintain homeostasis). Physiologic challenges such as the oral glucose and lipid tolerance tests, organ function tests, exercise stress, and psychological-stress tests could be incorporated more in nutrition research to better assess a given intervention's effect on health.

Recommendations

There is no question that the RCT is an important component of the evidence base, whether dealing with medicine or nutrition. No other approach can establish causality, in the latter case, between supplemental nutrients or other food components and chronic disease risk. However, the RCT in its current form is ill-suited to assess the effects of nutrients on chronic disease risk and must be modified if it is to serve as an effective tool for EBN. We need not go as far as to recommend that large RCTs on nutrition and chronic disease be abandoned,[47] but a paradigm shift is necessary.

Expectations among nutrition and policy scientists, industry, and practitioners must be redefined. The complex but important nuances of nutrition science need to be incorporated into the design and interpretation of the evidence base (ie, we must move from EBM to EBN).

- Applying the "reductionist" approach of targeting single, isolated nutrients is no longer appropriate. Nutrients (and perhaps bioactives) interact with each other in vast and complex networks (eg, optimizing calcium's bone-protective effect also requires adequate or optimal vitamin D and protein, and perhaps vitamin K and magnesium as well; B vitamins function together in the one-carbon metabolism pathway; antioxidants are known to recycle each other in a network). Studying one isolated nutrient, without understanding the contextual biology of the nutrient and its interactions and underlying status of the patient or population, will surely be met with failure.
- A paradigm for assessing the effects of "bioactives" is needed. Whether these are studied as nutrients or drugs must be established to properly inform future regulatory and policy decisions.
- The limitations of the RCT, whether ethical, logistical, or cost-related, clearly render this approach unfeasible and at times worthless under certain circumstances. However, these limitations cannot preclude totally decision making. It is critical to assess the totality of the available evidence in order to make informed decisions for patients and public health, even in the face of suboptimal evidence.
- In most cases of the nutrient-health and disease relationship, the optimal evidence base is not achievable, due to the host of aforementioned limitations and other constraints. However, the absence of optimal evidence should not completely preclude decision making. The important cost-risk-benefit equation is vastly different for nutrients vs. drugs. The low cost, low risk, and modest benefit of nutrients suggests that decisions might still be made in the face of sub-optimal evidence or lesser certainty. Indeed, nutrition science is an ever-evolving continuum (in both directions) that rarely,

if ever reaches 100% certainty, with most of the evidence falling somewhere between "uncertain" and "probable."

- RCTs are still necessary to inform the evidence base, when and where possible. It is important to recognize their limitations and still be willing to take action when RCTs are not feasible, but that is not license to lower the standard of scientific rigor for nutrition science. In general, RCTs involving nutrients should incorporate greater utilization of biomarkers, including those of nutrient exposure/status, both at baseline and throughout intervention, and where applicable, those of surrogate disease and wellness endpoints. Although not discussed in this paper, incorporation of nutrigenomic, proteomic, and metabolomic analyses in the design of RCTs is critical. These may not only serve as surrogates for important phenotypic or clinical endpoints, but also can help define groups of responders and non-responders to a given intervention (both in terms of efficacy and harm). The multisystem characteristic of nutrient effects calls for measurement of multiple outcomes in RCTs. For example, a nutrition intervention, even one involving a single nutrient, might lower blood pressure, affect visual function, decrease biomarkers of inflammation, and enhance insulin sensitivity, among other beneficial effects. Individually, these outcomes, due to inherent biological and individual variability and subtle effect sizes, might tend to be nonsignificant (both clinically and statistically). However, if assessed in the aggregate they might well present an overall "global" benefit. Ideally, such analyses would be incorporated a priori, with the research approach to assess some composite or "global index" of all of the appropriate endpoints (ie, whether a given intake of a nutrient(s) provides a total body health benefit).
- Clinicians should avoid the current trend toward being reduced to technicians who deliver EBM-based algorithms and guidelines. Best practice should include a reliance on clinical experience, evaluation of the best available and most relevant evidence, and the therapeutic relationship between the doctor and patient (Figure 3).

About the Authors

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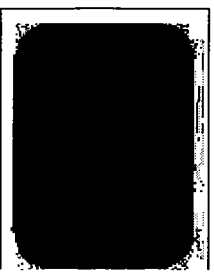

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EXHIBIT 2

Evidence-based criteria in the nutritional context

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During the last decade, approaches to evidence-based medicine, with its heavy reliance on the randomized clinical trial (RCT), have been adapted to nutrition science and policy. However, there are distinct differences between the evidence that can be obtained for the testing of drugs using RCTs and those needed for the development of nutrient requirements or dietary guidelines. Although RCTs present one approach toward understanding the efficacy of nutrient interventions, the innate complexities of nutrient actions and interactions cannot always be adequately addressed through any single research design. Because of the limitations inherent in RCTs, particularly of nutrients, it is suggested that nutrient policy decisions will have to be made using the totality of the available evidence. This may mean action at a level of certainty that is different from what would be needed in the evaluation of drug efficacy. Similarly, it is judged that the level of confidence needed in defining nutrient requirements or dietary recommendations to prevent disease can be different from that needed to make recommendations to treat disease. In brief, advancing evidence-based nutrition will depend upon research approaches that include RCTs but go beyond them. Also necessary to this advance is the assessing, in future human studies, of covariates such as biomarkers of exposure and response, and the archiving of samples for future evaluation by emerging technologies.

INTRODUCTION

In a Medline search of article titles, the term "evidence-based" occurred less than 100 times in articles published in 1995. Since then, citations have risen steadily to nearly 7,900 in 2009 alone. This level of occurrence provides ample documentation of a substantial shift in both awareness and vocabulary in the community of scientists and policymakers involved with the clinical sciences. Evidence-based medicine (EBM) was established for the evaluation of medical interventions. It provides a hierarchy of research designs, with the results of randomized, placebo-controlled trials (RCTs) considered the highest level of evidence.[1,2] EBM and its underlying concepts and

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The authors have worked in nutritional science, policy, and practice throughout most of their professional careers, serving, for example, on the US Dietary Guidelines Committee and various advisory panels of the Institute of Medicine concerned with dietary reference intakes. Several have chaired National Institutes of Health study sections and have been recipients of major nutrition awards of the American Society for Nutrition and the United States Department of Agriculture.

Key words: benefit, evidence-based, nutritional policy, randomized clinical trials, risk

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methods were soon directly extended to the field of clinical nutritional science as evidence-based nutrition (EBN). Beginning with the 1997 Dietary Reference Intakes,[3] the Institute of Medicine explicitly sought to provide the evidence base for its recommendations. A similar approach was used in developing the DHHS Dietary Guidelines for Americans, beginning with the 2005 edition.[4] Similarly, the U.S. Food and Drug Administration has put forth a set of evidence criteria for nutrient-related health claims[5,6] and professional associations such as the American Dietetic Association[7] have promulgated EBN guidelines for their own policies and publications. A popular approach has been the use of evidence-based systematic reviews and meta-analyses; their application to nutrition questions has been recently reviewed.[8–11] Adherence to EBN guidelines is increasingly required by peer-reviewed nutrition journals.

While multiple research approaches in nutrition science afford evidence of nutrient effects, there often appears to be an almost exclusive reliance on the RCT as the only type of evidence worthy of such consideration (e.g., references[12–16]). However, certain features of EBM seem ill-suited to the nutrition context.[17–19] Some of the differences between the evaluation of drugs and nutrients cited previously[18] are as follows: (i) medical interventions are designed to cure a disease *not* produced by their absence, while nutrients prevent dysfunction that would result from their inadequate intake; (ii) it is usually not plausible to summon clinical equipoise for basic nutrient effects, thus creating ethical impediments to many trials; (iii) drug effects are generally intended to be large and with limited scope of action, while nutrient effects are typically polyvalent in scope and, in effect size, are typically within the "noise" range of biological variability; (iv) drug effects tend to be monotonic, with response varying in proportion to dose, while nutrient effects are often of a sigmoid character, with useful response occurring only across a portion of the intake range; (v) drug effects can be tested against a nonexposed (placebo) contrast group, whereas it is impossible and/or unethical to attempt a zero intake group for nutrients; and (vi) therapeutic drugs are intended to be efficacious within a relatively short term while the impact of nutrients on the reduction of risk of chronic disease may require decades to demonstrate – a difference with significant implications for the feasibility of conducting pertinent RCTs.

Nevertheless, it is indisputable that the RCT, in one of its variant forms, is the clinical study design that best permits strong causal inference concerning the relationship between an administered agent (whether drug or nutrient) and any specific outcome. Both drug indications and health claims for nutrients that are backed by one or more well-conducted RCTs are appropriately considered to have a more persuasive evidence base than corresponding claims based primarily upon observational data.[20] However, it is also generally understood, if not often acknowledged, that it can be difficult to implement RCTs correctly. For certain types of questions, such as those concerning epigenetic effects (which seem increasingly likely for several nutrients), RCTs would often be precluded on both ethical and feasibility grounds. Or, when trying to assess the potential benefits of conditionally essential nutrients (e.g., α-lipoic acid and ubiquinone, which are synthesized in vivo) and putatively nonessential nutrients (e.g., carotenoids and flavonoids, which are nearly ubiquitous dietary constituents), the problem of providing this evidence through RCTs becomes even more challenging. Additionally, a poorly executed RCT may have no more (or even less) inferential power than a cohort study.[21,22]

For all these reasons, it seemed useful to suggest some ways to advance the current approach to EBN, ways which better reflect the unique features of nutrients and dietary patterns, and which also recognize the need to deal with uncertainty in situations in which evidence from RCTs might never be obtained. The perspective that follows constitutes a summary of the deliberations on these issues that took place at an invitational workshop convened in Omaha, Nebraska, September 3–4, 2008, by Tufts and Creighton Universities. In approaching this issue here, a few key questions are asked and an attempt is made to define the evidence needed to support nutritional policy decisions. Instances of some of the details, as well as brief allusions to the background science, are included in the Supporting Information available online.

PROOF OF WHAT BENEFIT?

By definition, an essential nutrient is a substance that an organism needs for optimal function and which must be obtained from the environment because it cannot be adequately synthesized in vivo. That nutrients produce benefits is a truism enshrined in the Dietary Reference Intakes of the Institute of Medicine,[23] and in the intake recommendations of most nations of the world. Contrariwise, inadequate intakes produce dysfunction or disease. Hence, the association of inadequate intake with disease is not so much a matter of proof as of definition. A substance would not be an essential nutrient if low intake were not harmful; i.e., a null hypothesis analogous to that for a drug ("nutrient ***X*** confers no health benefit") is not tenable for most nutrients. Instead the questions clinical nutrition scientists must ask are: (i) What is the full spectrum of dysfunctions or diseases produced by low intake of a nutrient? and (ii) How high an intake is required to ensure optimal physiological function or reduced risk for disease across *all* body systems and endpoints?

Among the many advances of modern nutritional science are (i) the recognition of long-latency deficiency diseases and (ii) the understanding that nutrients often act through several distinct mechanisms within the organism.[24] Thus, inadequate intake of a single nutrient can result in multiple dysfunctions, some of which may be quite slow to manifest. Further, there often is not a sharp transition between health and disease, but a multidimensional continuum, with different organ systems in the same individual exhibiting varying sensitivities, and with individuals varying among themselves in sensitivity. The Recommended Dietary Allowances (RDAs) are designed to account for interindividual differences in requirements[3] but, as implemented, they largely focus on single organ system endpoints, and do not usually deal with the multiplicity of a nutrient's effects throughout the body. Typically, policy-making bodies have tended to adopt the default position of defining the intake requirement mainly for prevention of the disease for which there is the clearest evidence or at least a clear consensus, i.e., the "index" disease.

This approach raises questions regarding the adequacy of such recommendations, since prevention of the nonindex diseases may require more than the intake needed to prevent the index disease. For example, the intake of dietary folate necessary to reduce the risk of neural tube birth defects is greater than that necessary to prevent macrocytic anemia,[25] and the amount of vitamin D required to reduce the risk of falls and hip fracture in the elderly is greater than that required to prevent rickets or osteomalacia.[3]

For several nutrients, RCTs have been conducted with nonindex diseases as the outcome measure, but they have most often failed to show a significant effect on the occurrence of the selected disease endpoint (e.g., references[26–31]). Such RCTs are often flawed, not so much in their conduct as in their design; for example, they do not provide a sufficiently low intake of the nutrient for the control group[26,27] or they do not ensure adequate intake of other essential nutrients needed for the test nutrient to manifest its own proper effect.[32–34] It is worth noting that, in this latter respect, such nutrient RCTs emulate drug RCTs, which usually strive to eliminate all confounding variables and effect modifiers, rather than to optimize them.

ARE RANDOMIZED CONTROLLED TRIALS AVAILABLE TO TEST NUTRIENT EFFECTS?

In order to conduct a RCT that adequately tests the efficacy of a nutrient for a specific chronic disease, it will usually be important to ensure an adequate contrast in intake between the intervention and the control groups. The control intake is an approximate analog of the placebo control in drug RCTs. However, since sufficiently low intakes are associated with significant disease in some body systems, doing so can lead to serious ethical problems, particularly if the disease outcome is serious and/or irreversible, e.g., preeclampsia, hip fracture, neural tube defect, or myocardial infarction. In contrast to observational studies, which typically assess nutrient exposures ranging from low to high, most RCTs of nutrient effects have employed a control group receiving an intake typical of the population, oftentimes near the RDA, and certainly above the thresholds for many deficiency states, while the intervention group receives even more. This approach transforms the hypothesis ostensibly being tested to one of "more is better". Such trials are ethical and feasible, but they often do not test the hypothesis that low intake of nutrient ***A*** causes (or increases the risk of) disease ***X***. This is not to question the value of asking such secondary questions, but simply to stress that they are different questions.

EBN thus departs from the situation of EBM, where, for most interventions, the use of a no-intake control group is usually quite appropriate. In EBM, the hypothesis is that *adding* an intervention ameliorates a disease, whereas in EBN it is that *reducing* the intake of a nutrient causes (or increases the risk of) disease. This distinction is critical. No one proposes in EBM that a disease is caused by the absence of its remedy; whereas for nutrients the hypothesis is precisely that malfunction is caused by deficiency. A hypothesis about disease causation can rarely, if ever, be directly tested in humans using the RCT design. This is because in the RCT the disease/dysfunction occurs in at least some of the study participants, and the investigators must ensure that this will happen. Instead where EBN must operate is with respect to two related, but different questions: (i) In addition to disease ***X***, does the inadequate intake of nutrient ***A*** also contribute to other diseases? and (ii) At what level of intake of nutrient ***A*** is risk of *all* related disease minimized or all related functions optimized?

In brief, it is unlikely that RCT evidence could feasibly or appropriately be produced with respect to the role of a nutrient for many nonindex-disease endpoints. Therefore, the majority of the evidence with respect to nutrients and nonindex diseases will continue, of necessity, to be derived from observational studies. That does not mean that action must be suspended. Over 30 years ago, Hill[35] described guidelines to assess causation under such circumstances (see Supporting Information).

HOW MUCH CERTAINTY IS NECESSARY?

RCTs, if well designed and well executed, provide a high level of certainty that a specific intervention can reliably be counted on to produce a specific effect in a selected

population. As a society, we have determined that a high level of certainty is required for the evaluation of efficacy for therapeutic drugs. Such a standard is justified by the usually high cost of such medical treatment, by the risk that therapeutic decisions based on inadequate evidence would shift treatment away from possibly more efficacious therapies, and from the need to balance benefit against the risks that accompany pharmacotherapy. These same concerns are substantially less pressing for nutrients. Nutrients are orders of magnitude less expensive than drugs and often exhibit a broader margin between efficacy and toxicity. Is the same high level of certainty required regarding the nutrient intake recommendations to *prevent* disease as is needed for drugs used to *treat* disease?

There is no simple answer to this question. Nevertheless, it seems clear that requiring RCT-level evidence to answer questions for which the RCT may not be an available study design will surely impede the application of nutrition research to public health issues. Moreover, to fail to act in the absence of conclusive RCT evidence increases the risk of forgoing benefits that might have been achieved with little risk and at low cost. This is not to suggest that the standards of what constitutes proof ought to be relaxed for nutrients, but to propose instead that nutrient-related decisions could be made at a level of certainty somewhat below that required for drugs. Under such circumstances, confidence in the correctness of a decision would necessarily be lower.

Figures 1 and 2 present these considerations graphically, where confidence in the correctness of a certain recommendation (vertical axis) is the dependent variable, expressed as a function of the following: i) the level of certainty (or strength of the evidence) relating a given intake to any specific effect; and ii) the benefit-to-risk ratio that follows from acting. "Acting" here means specifying an intake level as a recommendation for the general public (or approving a drug for a given indication). In EBN, the strength of the evidence, ranging from high to low, might be quantified in an ordinal fashion, such as "established", "probable", "likely", and "unclear." Here, "unclear" means simply no ability to decide one way or the other, i.e., the null position.

As Figure 1 shows, confidence in the correctness of a decision to act rises as a function of both certainty and benefit : risk, reaching its maximum only when the levels of both certainty and benefit : risk are high. This would be typical of the drug decision context (Figure 2A). By contrast, Figure 2B depicts what would seem to be appropriate for nutrients, for which a lower level of certainty would be acceptable; i.e., the confidence needed to act would be less than that needed for drugs.

As inspection of Figure 2B shows, the intersection of the cut-point plane with the three-dimensional surface is

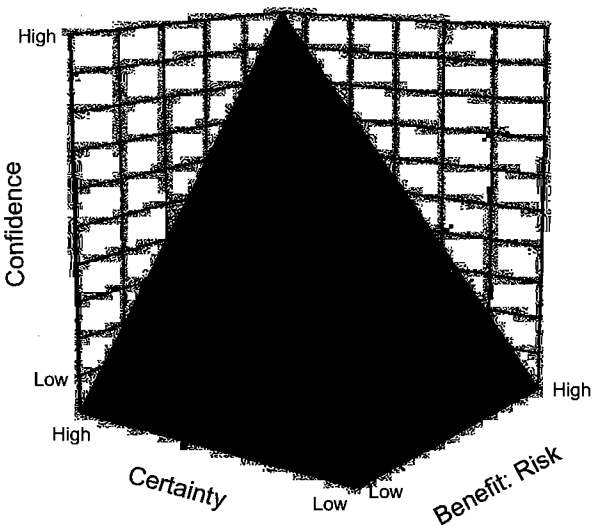

Figure 1 **Three-dimensional plot depicting the relation between *confidence* that a decision to act or to implement a nutrient recommendation is the correct thing to do (the vertical axis), and the degree of *certainty* about efficacy (*strength* of the evidence) of the nutrient (left horizontal-plane axis), and the ratio of *benefit to risk* of the change in intake (right horizontal-plane axis).** The surface represented by the grid illustrates a confidence outcome, incorporating the full range of inputs of efficacy and benefit : risk. (Copyright Robert P. Heaney, 2010. Used with permission.)

a curved line. This line itself is a reflection of an inverse relation between certainty and benefit : risk for any given degree of confidence in the correctness of an action. Thus, for nutrients with high benefit : risk, less certainty might be adequate to permit action, whereas for nutrients with less potential benefit (or more potential risk), a higher certainty of efficacy would be needed.

Importantly, these figures are simply illustrative; their use here is not intended to propose a rigid, mathematical approach that could be applied robotically to such questions. The purpose is simply to illustrate a potential willingness to act for low-risk interventions with probable benefit and at a level of certainty below what would be needed for approval of medical interventions.

WHAT FEATURES AFFECT CERTAINTY?

It is interesting to note that while regulatory agencies from around the world rely on RCTs, there is a high degree of discordance regarding how different jurisdictions evaluate the strength of the evidence produced by the same studies for the substantiation of health claims for nutrients and foods. Thus, in advancing approaches

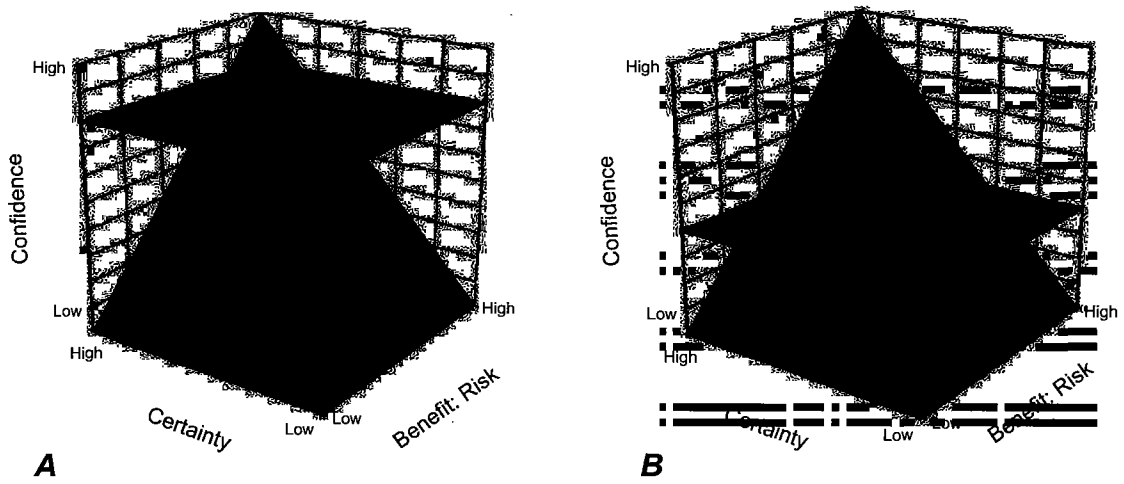

Figure 2 **The decision plot for the relationship of Figure 1, as implemented for drugs (*A*) and for nutrients (*B*). Any value above the cut-plane would permit action.** Notice that a high benefit : risk ratio would permit action at a lower level of evidential certainty and vice versa. (Copyright Robert P. Heaney, 2010. Used with permission.)

Table 1 **Factors affecting the level of certainty of evidence provided by various study designs.**

Study type	Factors
Randomized controlled trial	Control group (or period) with sufficiently low intake
	Accuracy of intake assessment
	Minimal losses of sampling units
	Replication
	Adherence/compliance
	Optimization/control of conutrient intakes
	Effect size (e.g., relative risk >2.0 [or <0.5])
Cohort design	Low intake control group
	Intake estimate validation
	Correct temporal sequence
	Dose-response relationship
	Replication/multiplicity of studies
	Low between-subject variance
	Biological plausibility
	Adequate control for conutrient intake
	Adequate control for other confounding factors
	Effect size (e.g., relative risk >2.0 [or <0.5])
Case-control design	Low intake control group
	Contrast groups randomly derived from population
	Biological plausibility
	Adequate control for conutrient intakes
	Effect size (e.g., odds ratio >2.0 [or <0.5])

to EBN, it will be useful to set forth some of the factors that we judge will affect the level of *certainty* (evidential strength) that various study designs offer (Table 1), as well as the factors that affect the level of *confidence* in a decision that may flow from any given degree of certainty (i.e., high benefit : risk ratio; important consequences of possible Type II error; low deployment cost; low opportunity cost; multiplicity of lines of supporting evidence).

Additionally, certainty can be enhanced by ancillary measurements. Discussion of these features is further developed in the Supporting Information.

As listed in Table 1, an RCT gains or loses certainty depending upon whether or not the following apply: i) there is an adequate contrast in intake between the intervention and control group; ii) it has been replicated; iii) it suffered only minimal losses of sampling units; iv) it measured and controlled adequately for conutrient intakes;

and (v) its estimate of effect size is large. While not all of those factors are absolutely necessary, each contributes a degree of certainty in its own right. These features are developed at greater length in the Supporting Information.

As RCT-based evidence may not be available ethically or feasibly to answer many nutrient-related questions, it is important to attend to the factors needed to support action when evidential certainty is less than perfect. The factors affecting confidence, as listed above, represent a start at this effort. Perhaps the most compelling concern regarding this issue is the fact that benefits may be forgone when action is deferred, i.e., the consequence of the type II error when the conclusion from available evidence is "not proven". Offsetting that risk are the costs associated with action when the true effect is actually negligible or null. Therefore, low deployment cost and low opportunity cost should be important considerations. Any change in nutritional policy creates work for both industry and regulators, efforts that have a cost and that may displace other action that might have been more productive. There is no single or simple correct answer to these questions about cost, but it is worthwhile to stress that they must be factored into the decision matrix on a case-by-case basis.

CONCLUSION

Inadequate intakes of nutrients result in a variety of dysfunctions and diseases. The full spectrum of those untoward effects is unknown. Because deliberately reducing intake to deficient levels in humans is ethically impermissible, the RCT will often not be available as a means of elucidating many potential nutrient-disease relationships. The general principles of EBN can provide a sufficient foundation for establishing nutrient requirements and dietary guidelines in the absence of RCTs for every nutrient and food group. Sackett et al.,[36] among the intellectual fathers of EBM, stressed nearly 15 years ago that EBM was "not restricted to randomized trials and meta-analyses", a counsel that has been shunted aside in recent years. A general approach to acting in the absence of ultimate certainty should include a broader consideration of other research strategies along with revised estimates of the certainty level of the evidence and the confidence needed to act in support of public health. In such judgments, it will be important to assess the balance between the potential harm of making any given recommendation and the potential harm of not making it. Additionally, a key challenge will be to find appropriate educational strategies to convey varying levels of strength of evidence for a given recommendation.

Acknowledgments

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Amplification on certain of the points discussed in the paper "Evidence-Based Criteria in the Nutritional Context", by Blumberg et al. [*Nutr Rev* 2010;68(8):478–484].

Figure S1. Plateau diagrams illustrating the difference in measurable response for studies in which the low intake contrast group falls above or below the plateau intake. As Fig. A1*A* depicts, at least one of the contrast intakes must be below the response plateau if a measurable effect is to be produced. With both intakes at an above the threshold of the plateau (i.e, A1***B***), response would be expected to be minimal or absent entirely. (Copyright Robert P. Heaney, 2008. Used with permission.)

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Evidence-based criteria in the nutritional context: Appendix

This Appendix amplifies on certain of the points discussed in the paper "Evidence-Based Criteria in the Nutritional Context", by Blumberg et al. (Nutr Rev 2010;68:478-84).

Similar Systems

It is worth noting also that the approach to certainty we propose closely parallels the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system criteria[S1] developed for medical interventions, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, which also include these issues within their evaluation scheme.[S2] In GRADE, degree of certainty is termed "quality of evidence" and is ranked as "high", "moderate", "low", and "very low". These terms correspond to our designations of level of certainty: "established", "probable", "likely", and "unclear."

The American Institute for Cancer Research and World Cancer Research Fund use similar criteria for clarifying risk as "convincing," "probable," "limited-suggestive," and "substantial effect unlikely".[S3] In GRADE, evidence is considered of high quality if it is judged that further research is unlikely to change the estimate of an effect, while it is judged to be of low quality if it is deemed that further research is likely to have an appreciable impact on that estimate. While the same distinctions apply to our proposed certainty scale, we judge that the term "quality" in GRADE is not apposite, inasmuch as an animal or cell biologic study may be of very high quality and still have little persuasive force with respect to a recommendation for humans. Hence, the term "certainty" (or "strength") appears better suited to this application as it is not pejorative and speaks directly to the decision context. We note also that GRADE (and other

similar systems) relate largely if not exclusively to the certainty axis in Figures 1–2 of the comparison paper, with little or no direct consideration of benefit or risk.

For observational studies (see STROBE[S2]), factors affecting the persuasiveness of the evidence listed in Table 1 of the companion paper include the familiar criteria of replication (particularly in different populations and with different investigational approaches), the correct temporal sequence (exposure prior to outcome), the expected dose response relationship of intake and risk, biological plausibility (e.g., animal and/or cell biologic studies defining the mechanism and predicting the clinical effect), and effect size.[S4,S5]

Factors Affecting Certainty of the Evidence

The importance of a low intake control group relates to the "plateau" or "sigmoid" character of the dose response curve, and has been described elsewhere.[S6,S7] A trial such as that illustrated in Figure S1***B*** (i.e., contrast groups with both intakes at or above the plateau threshold) demonstrates nothing except that supra-threshold intakes confer little or no additional benefit. Nor does such an RCT establish the location of the plateau threshold itself or answer the question about efficacy relative to sub-threshold intakes. In the field of calcium nutrition, several RCTs have unfortunately followed the pattern of Figure S1***B***, notably the Women's Health Initiative[S8] and the Calcium for Preeclampsia Prevention[S9] trials, both with high control group intakes and both producing predictably inconclusive results.

Other factors can be equally important. More than minimal losses of sampling units jeopardize the randomization of a RCT[S10] and seriously degrade its degree of persuasiveness. This is a widely ignored problem and cannot usually be countered by over-recruiting subjects. Further, failure to take into consideration nutrient-nutrient interactions can lead to negative or even paradoxical results. Thus, in the field of bone biology, neither calcium nor vitamin D will exert

much of an effect on bone if each is evaluated without attention to the intake of the other.[S11–S13] Similarly, at low calcium and vitamin D intakes, protein can have a negative effect on bone status,[S14] but at high calcium and vitamin D intakes, protein has a positive effect.[S15–S17] Not optimizing protein intake in these studies may thus blunt or obscure calcium and vitamin D effects. Similarly complex interactions occur between many B vitamins and also between nutrients within the antioxidant defense network. Such interactions markedly limit the practical value of studies of single nutrient interventions that fail to control for (or ensure adequate intakes of) covariate nutrients in the diet (and/or concomitant drug therapy).

Factors Affecting Confidence in a Decision

We do not suggest that high intakes of certain nutrients (or the foods that contain them) always present only trivial risks. For example, vitamin A toxicity can be a serious problem in its own right, and oily fish may be a source not only of omega-3 fatty acids, but also of environmental toxins, such as mercury. In any event, these consequences, while not negligible, will usually not be of the same character or magnitude as the result of approving a potentially dangerous drug for treatment of disease without strong evidence of efficacy.

Desired Evidential Components of Studies of Nutrients

In addition to the study features listed in Table 2 in the companion paper, it may also be important to emphasize the type of data that, if accumulated in a well-designed nutrient study, could improve both the level of certainty of its conclusions and contribute to a future meta-analytic exploration of differences between studies (see below). As noted previously, nutrient effects are often subtle and multi-systemic, often falling within the noise range of biological or analytical variability. [It is important to recall that small effects are not unimportant at a population level.[S7,S18]] Measurement and reporting of key covariates should, by adjusting for

their presence, clarify the true nutrient effect and enhance understanding of the biology of the nutrient concerned.

Biological profiling. Drug RCTs routinely measure indices of hepatic, renal, bone marrow, and other functions before and during treatment with an investigational agent. Analogous measurements should become routine in nutrient studies. Certain classes of covariates, if measured and reported, would generally help to clarify study outcomes (anthropomorphic, socioeconomic, educational, and demographic data). Recommended collateral measurements to be reported in studies of nutrient effects include the following: ethnicity; biomarkers of intake/exposure; tobacco, alcohol, and drug usage; physical activity level; biomarkers of response; baseline intakes of both the nutrient tested and all related co-nutrients, including related energy or biomarker data; changes in intake of other nutrients during study; and multiple endpoints. The following list identifies certain specimens that ideally should be obtained and archived to permit possible subsequent analysis in light of yet-to-be-discovered biological relationships: samples for DNA; serum/plasma for proteomics; fasting plus postprandial serum/plasma for metabolomics; urine; other tissue samples as may be applicable; archiving of primary data. Many of the classes of covariates listed above are straightforward and require no comment except to note that they are sometimes missing in reports of nutrient studies.

Biomarkers. Biomarkers – both of exposure and of response – would seem to be critically important to advancing the application of EBN. For most nutrients, it is not the actual intake itself that is important, but the nutrient concentration achieved in the target tissues. Intake biomarkers, where available, are essential to assessing both compliance with the intervention and inter-individual variations in the bioavailability and metabolism of the nutrient, and thus facilitate explanation for observed variations in response. Similarly, systematic reviews and

meta-analyses of nutrient interventions must consider the relative bioequivalence of the different bioactive forms of the same nutrient in RCTs evaluating such nutrients, which, unfortunately, many have failed to do.[S12,S19]

In contrast, changes in biomarkers of response (or intermediary measures of pathogenesis or disease) are proxies for the health benefit at issue. They may substitute for actual disease endpoints, help to clarify the mechanism of an effect, and/or reinforce a conclusion because of concordance between the biomarker and other endpoint data. Examples include clinical measures such as blood pressure, bone mineral density, and cognitive performance, and/or biochemical measures such as mediators of inflammation, insulin resistance, and oxidative stress.

Polymorphisms. One of the reasons for gathering this additional information is that, while humans have very similar genetic codes, they have great variation in the ultimate result of gene expression, the phenotype. Some of the variation between individuals is due to the approximately 50,000 single nucleotide polymorphisms (SNPs) that each of us harbors.[S20–S22] In total, more than one-fifth of these SNPs occur in more than 1% of the population.[S21] And some common SNPs occur in from 5% to more than 50% of the population. For example, the dietary requirement for choline is dependent on whether or not the individual has SNPs in genes for choline or folate metabolism.[S23,S24] The methyl-tetrahydrate folate reductase (MTHFR) gene has a common SNP that results in reduced enzymatic activity, and individuals homozygous for this allele have elevated plasma homocysteine concentrations unless they ingest high amounts of folate.[S25] The gene for PPAR-α has a SNP that has been associated with alterations in total cholesterol, LDL-associated cholesterol, and apo-B concentrations,[S26] and this SNP alters response to dietary n-6 polyunsaturated fatty acid (PUFA) intake. In persons with the variant allele, increased n-6 PUFA intake is associated with a marked reduction in triacylglycerol

concentration.[S26] Clearly, such allelic variation defines responder and non-responder groups, which, if not recognized or factored into study design, could easily result in null effect conclusions. It needs to be recognized that the occurrence of SNPs affecting the metabolism of most conditionally essential nutrients and phytochemicals has yet to be characterized. For all such reasons, clinical studies in nutrition need to collect DNA for possible future SNP analyses.

These understandings have been achieved only recently, and to date most nutrition studies seem to have assumed that all people have average dietary requirements and average responses to nutrients. If nutrition studies could better identify potential biological responders and differentiate them from potential non-responders, the sensitivity to detect differences between groups could be greatly increased. Modern genomics, when built into the study design, can help to explain some of the individual variation in response and hence in requirement for nutrients.

In the near future metabolomic platforms will permit simultaneous analyses of thousands of small metabolites in plasma or urine at a cost equivalent to obtaining a cholesterol analysis today,[S27] thereby permitting more complete characterization of individual metabolic variations in response to a nutrient. Though the analytical and informatics capacity to effectively use metabolomics are a few years away, nutrition studies would be wise to bank plasma or urine samples for future analyses.

Global outcome measures. Multiple endpoint measurements[S7] are a frequently overlooked but potentially helpful feature of well-designed nutrient studies and flow naturally out of the multi-system character of nutrient effects. For example, an intervention (whether involving a single nutrient or a set of nutrients) might lower blood pressure, maintain visual function, decrease biomarkers of inflammation, improve nerve conduction velocity, and enhance insulin responsiveness, among other effects. If most or all of these changes were within the range of

usual biological variability, they would, individually, rarely be statistically significant, whereas in the aggregate they might well be. Ideally, such analyses should not be *post hoc,* and the research approach should employ a single hypothesis for some composite or global measure of all of the appropriate endpoints. To reflect the multi-system action of nutrients, the *a priori* research question should be whether a given intake of a nutrient(s) provides a *total body* health benefit. A global index, as the design endpoint, not only corresponds to that more general question, but also compensates for the inherent heterogeneity of nutrient response, both between systems within individuals, and between individuals within populations.[S28] It is important to stress that a specific global index must be carefully constructed. Too enthusiastic inclusion of dubious elements will defeat the purpose, as a diabetes trial using a global score recently demonstrated.[S29]

Meta-analyses. One of the factors recognized as strengthening the body of evidence is replication (cited above). Here we note that multiple studies are important for another reason as well. Studies with differing design features can provide insight into variability in biological response. An over-reliance on meta-analysis restricted to RCTs, without factoring in the physiologic reasons for heterogeneity, can result in misleading conclusions that lack coherence with the totality of available information derived from all research approaches.[S27,S30,S31] Meta-analysis is most commonly thought of as *synthetic*, i.e., a means of aggregating different studies to obtain a better estimate of the overall effect. Perhaps of greater interest is the *analytic* potential of meta-analysis, i.e., the delineation of why studies differ in the magnitude and direction of nutrient effects. In order to enable this analytic function, the lists of covariates and specimens in the section above on biological profiling could be of crucial importance, since such measurements

may serve to provide the data necessary for understanding some portion of the biological variability in nutrient response.

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Figure Legend

Figure S1. Plateau diagrams illustrating the difference in measurable response for studies in which the low intake contrast group falls above or below the plateau intake. As Fig. A1***A*** depicts, at least one of the contrast intakes must be below the response plateau if a measurable effect is to be produced. With both intakes at an above the threshold of the plateau (i.e, A1***B***), response would be expected to be minimal or absent entirely.

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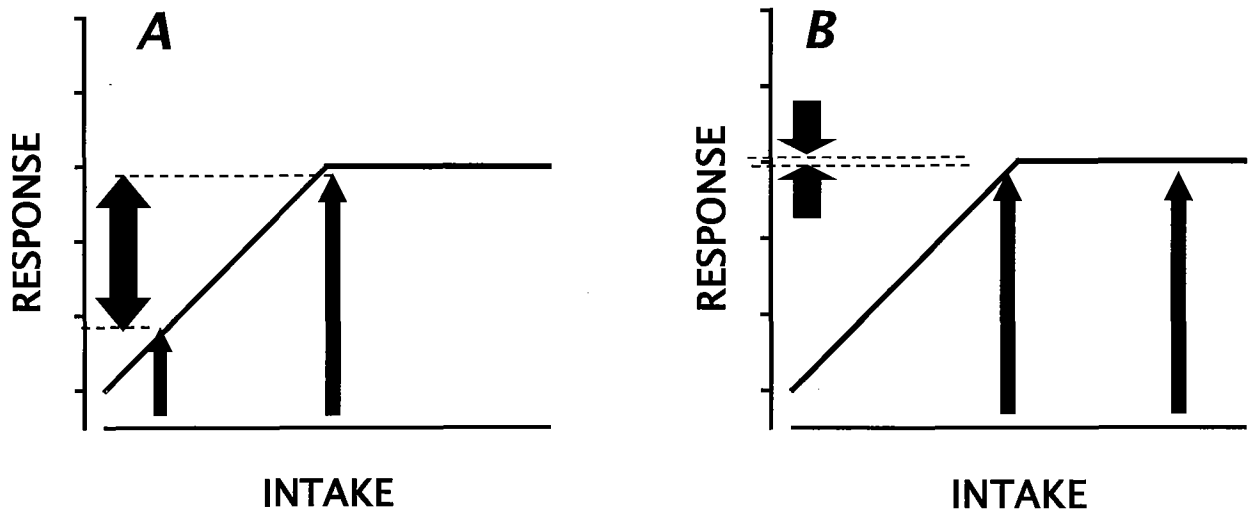

Fig. S1

EXHIBIT 3

EBN (Evidence-Based Nutrition) Ver. 2.0

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The criteria used in evidence-based medicine provide a poor fit for decisions concerning nutrient intake recommendations. For many nutrient-disease relationships, level 1 evidence cannot be ethically obtained. The challenge is to design an approach that will allow responsible development of national policy in the absence of randomized clinical trials. A decision strategy based not on proving benefit but on estimating harm is proposed. We note that not changing a recommendation is itself a recommendation. Nutr Today. 2011;46(1):22–26

Over the past 15 years, the term "evidence-based" has spread like a wildfire through the field of clinical science. Once confined mainly to the criminal courts, the term is now used to characterize budget decisions, treatment approvals, and nutrient intake recommendations. It is clear that we all want to represent to our various publics that our proclamations and recommendations are based in evidence. Indeed, who would want to represent otherwise?

The term "evidence based" entered the clinical sciences as evidence-based medicine (EBM), stimulated in large part by the fact of wide disparities in the uses of certain interventions or medications and by the need of managed care groups and third-party payors to establish standards about what should be done or what might be reimbursed. How effective this effort may have been is arguable, but the need to attempt something of the sort seemed obvious. It was not that decisions in the pre-EBM era were not based on evidence; rather, "How good was the evidence?" "How sure could we be that a particular intervention made an appreciable difference, or didn't do more harm than good?"

To address such questions, EBM adopted a hierarchy of evidence, placing the experimental design above all observational designs. The principal experimental designs include controlled feeding studies, physiological studies, and double-blind, placebo-controlled, randomized clinical trials (RCTs), with basic research and expert opinion at the bottom of the hierarchy of persuasiveness. The dominance of the RCT was due to the fact that, given the multitude of factors that may influence an outcome, the experimental design is the only one that permits strong causal inference, allowing one to say with a specified degree of confidence that a given intervention causes a certain effect in a selected population. Other study types, able at best to control only weakly for confounding factors, can never have that same persuasive force. Nevertheless, it is worth recalling that Sackett,[1] one of the intellectual fathers of EBM, commented many years ago that there would be situations in which RCT data would not likely be available and that such absence should not paralyze the decision context.[1] To some extent, this conclusion has been lost sight of in subsequent years. This is especially true in the field of nutrition, which, as evidence-based nutrition (EBN), has seemingly swallowed EBM whole without either asking how well it might fit, or adapting it to the unique features of the nutrition context. Several efforts at better systematizing the process have recently been published,[2–5] but without providing assurances that they can be effectively implemented. Indeed, at least one of them,[2] by including a biologically flawed study as one of its examples, gives hints of the practical difficulty of doing so.

Several of the critical differences between medical interventions and nutrients have been explored in depth elsewhere,[6–10] as have the consequences of those differences for the kind of evidence that can be produced and the often ignored limitations of RCTs themselves. They need not be further reviewed here. However, 2 of those differences are of such force that, alone, they call for a different approach to decision-making concerning nutrients (which we term "EBN Ver. 2.0").

How can there be this contrast between the evaluation of medical interventions and nutrient intake

recommendations? It might seem, on the surface, that the underlying hypothesis behind testing a medical intervention and a nutrient intake recommendation would be fundamentally the same, that is, "intervention A (whether nutrient or drug) ameliorates condition B." Although we hope that the medical intervention will work, we have what ethicists term "equipoise" and are prepared to accept the fact that it may not. That is because, for the drug at least, we do not suppose that the disease is caused by the drug's absence.

It is fundamentally different with nutrients. All nutrients are necessary for health, and low intake of any nutrient will compromise physiological function in some way or other (and express itself as some form of "disease"). The actual hypothesis, therefore, is one of disease causation: "low intake of nutrient A causes, or contributes to, disease B." That is the ultimate rationale for the cognate, secondary hypothesis that increased intake of nutrient A will ameliorate the burden of disease B. The reason for the amelioration (if it actually occurs) is that we are correcting a deficiency that is the cause of the dysfunction we are treating or preventing.

So what we are reduced to testing is the hypothesis that low intake is causative. Using RCTs to do that can create nearly insuperable ethical barriers because the investigative team has to be prepared to put subjects in harm's way. It does not matter that the hypothesis may be incorrect for a specific nutrient-disease relationship, that is, that nutrient A may have no actual relationship to disease B. Rather, simply because of the fact that A is a nutrient, we know that low intake causes some disease, if not specifically disease B.

The resulting ethical dilemma is illustrated nicely in the Calcium and Preeclampsia Prevention (CPEP) Trial sponsored by the National Heart, Lung, and Blood Institute.[9] It simply would not have been acceptable for a major federal research agency to mount a trial in pregnant women for which a control group was assigned to an intake of calcium generally understood to be inadequate. As a consequence, the control group in CPEP received a calcium intake that averaged above the current recommendations for pregnancy, whereas the treated group received 1000 mg/d more. Clearly, this was not a test of causation, but instead, a test of the hypothesis that more is better.

This dilemma arose because of a second, prominent feature of nutrients, that is, the sigmoid character of response to varying intakes (Figure). Such response curves are typical of many biological systems and probably, to some extent, true also for response to pharmacologic agents. Recognizing the existence and relevance of such a response curve is critical. The reason is that, in a properly designed RCT, 1 of the 2 contrast groups must have an intake at the low end of the curve, and the other at or above the high end. This does not create a problem for drugs because the low end is the placebo-controlled group, and the high end is a dose that, in phases 1 and 2 trials, was found to be sufficient to elicit the desired response. But for nutrients, it is a constantly vexing problem. The observational data leading to investigation of a particular nutrient-disease relationship will commonly have included individuals with intakes at the lower end of the curve, but investigators would usually be unwilling (or not permitted) deliberately to place individuals there for purposes of an RCT or a feeding study, as was the case for the CPEP Trial.

In addition, there is a commonly occurring, healthy volunteer effect in recruitment for studies of this sort, which tends to push the intake of the control group to levels atypical for the population. As a result, an attempt to study a population "as it now exists" will often be

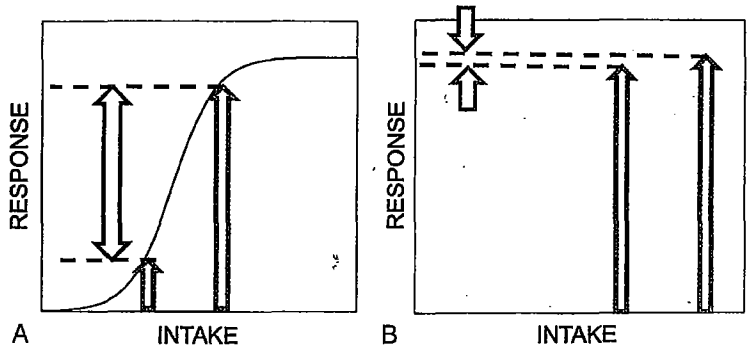

Figure. Sigmoid plots depicting the relationship between nutrient intake and indicator response. Both panels show the contrast in response to similar differences in intakes. In A, with the intakes straddling the ascending limb of the response curve, the response would be both highly detectable and biologically significant. By contrast, in B, with intakes mostly above the inflection point of the curve, the response is neither easily detectable nor meaningful if detected. The situation presented in B is what occurred in WHI[10] and CPEP Trial for calcium[9] and graphically demonstrates why those trials were inconclusive. (Copyright Robert P. Heaney, 2010. Used with permission.)

frustrated. This was clearly the case with the calcium and vitamin D arm of the Women's Health Initiative (WHI).[10] In the design phase, the investigators, relying on National Health and Nutrition Examination Survey data, anticipated a median calcium intake for the control group around 600 mg/d.[11] When the trial was fully enrolled, it turned out that the control group had a median intake of about 1100 mg/d. That intake was actually above the then-recommended level for the age of most of the women enrolled. Thus, all that WHI could show was that, like CPEP, giving more calcium than the recommended amount conferred little appreciable additional benefit. But neither with CPEP nor with WHI did these trials actually test the hypothesis that low calcium intake increased the risk of (or was the cause of) their preeclampsia or osteoporotic fractures. And the reason, as the Figure makes obvious, is that there was, in fact, no low calcium intake group for either study.

Incidentally, the sigmoid response to nutrients must be taken into consideration, also, in the preparation of systematic reviews. Most such reviews, for calcium and vitamin D at least, have failed to use such biological (as contrasted with methodological) criteria in the selection of studies to be reviewed and evaluated. Thus, many such reviews of calcium, for example, have included the WHI trial and found it to be "negative." (Actually, technically, it was a null trial, not negative.) But, as just noted, that conclusion is quite incorrect. In brief, WHI, as implemented, was simply not informative about the question concerned and should not have been included at all. Also, many systematic reviews tend to downgrade controlled feeding studies despite their being inferentially equivalent to RCTs. It is likely that most reviews of nutrients will come to erroneous conclusions if they are not performed by individuals who are content experts in the relevant biology.

This need for content expertise is forcefully illustrated by 2 systematic reviews of vitamin D effects, using the hallowed Cochrane approach.[12,13] Both included studies that failed to use vitamin D at all, but instead used related compounds with very different pharmacologic profiles and no nutritional relevance whatsoever. Yet, both did not hesitate to conclude that they were able to find no appreciable effect of "vitamin D" for the end points concerned. Thus, systematic reviews, on which we have been taught we can rely for unbiased analysis, although correct in concept, can easily produce flawed results. The reason is that they often analyze intrinsically flawed or inappropriately selected studies.

Systematic reviews aside, the ethical (and other) problems attendant upon RCTs mean that policymakers must face the fact that there will be important nutritional policy questions for which we will never have adequate level 1 evidence, as Sackett et al[1] had originally recognized and as Willett[14] has recently forcefully argued. Are we, therefore, to stay high-centered in the status quo? Are we precluded from making further recommendations that would be based of necessity largely on observational data?

An argument commonly cited against proceeding without definitive proof is the issue of postmenopausal estrogen replacement therapy. It had been recognized for many years that premenopausal women seemed to be protected from coronary artery disease and that that protection extended beyond menopause if the woman received estrogen replacement. A large body of observational studies was consistent with this experience. Then, when the results of the WHI trial were published,[15] the data were represented as showing the opposite. But the common perception of what WHI showed in this regard is simply incorrect.

The hypothesis of estrogen protection against coronary artery disease was tested in 2 groups, one in women with a uterus (who received estrogen plus a synthetic progestogen) and one in those without (who received estrogen alone). The former group showed not only the oft-cited lack of protection but an actual increase in risk. However, the estrogen-only group, by contrast, experienced the predicted decrease in coronary artery disease risk. Presumably, it was the progestogen that was responsible for the difference. In any case for estrogen alone, the results of the RCT were entirely concordant with the results of observational studies, not contradictory as often represented. A second publication from WHI[16] showed, in addition, that for both groups of women there was protection in the first 10 to 15 years following menopause—precisely the period when estrogen replacement is usually prescribed, once again largely concordant with the observational data. Why the RCT data are so often misinterpreted or misrepresented is uncertain, but it is important here to note simply that this claimed instance of reversal of the conventional wisdom simply falls apart in the light of the actual data. This is not an isolated problem. Similar misinterpretations of seemingly definitive RCTs of other nutrients (such as vitamin E) have been described elsewhere.[17]

So, is it prudent to proceed without definitive proof? In answering this question, we stress that we do not suggest that the standards of proof should be relaxed for nutrients. Rather, we question whether we need as much proof of efficacy for a nutrient policy decision as we do for approval of powerful, expensive, and potentially dangerous pharmaceutical agents.

We suggest that a solution to this quandary can best be sought by shifting the decision context from one of irrefutable proof to one of probable harm. There are 2 ways harm can result from a nutrient policy decision,

which will need to be evaluated nutrient-by-nutrient. First, in the absence of conclusive proof, there is the harm that may flow from making an intake recommendation about a certain benefit when the relationship postulated is actually nonexistent. (In the jargon of clinical research, a type I error.) Countering that is the harm that results from failing to make a recommendation that would actually be beneficial when the relationship concerned is real but still not conclusively proven (ie, a form of the type II error).

It is hard to point to an instance of harm from a type I error for nutrients, perhaps because current nutrient intake recommendations (once termed "minimum daily requirements") tend still, in practice, to be located toward the low end of the primitive (and often current) intake range. Examples of the second kind of harm come more readily to mind, such as the damage done by the 24-year delay (1974–1998) in mandating folate fortification of cereal grain products in the United States. This has been calculated[7] to have resulted in at least 6000 infants with preventable neural tube defects—a devastating outcome that, at least for those 6000-plus babies and their families, was unnecessary and, we submit, indefensible.

There are 3 levels at which this calculus of benefit versus harm is operative: (1) What do I choose for my own intake? (2) What do I recommend to patients or clients who come seeking my professional advice? And (3) what should policymakers recommend for the bulk of the population who, usually without individual consideration, will nevertheless be affected by a policy decision? We recognize that EBN operates mainly at this third level, and it is there that we focus the following recommendation.

Consider any given nutritional question, for example, "What is the serum 25(OH)D level during pregnancy that minimizes the risk of low-birth-weight newborns?" For such a question, there may be at most one, or perhaps no level 1 studies. When that is the case, policymakers should evaluate whether 1 or more RCTs could feasibly be performed; that is, could a control group be found that had a vitamin D status comparable to the low end of the range that now prevails in the population, and, if found, could supplementation ethically or feasibly be withheld or withdrawn through the course of such a study? If the answer to that question is no or probably not, then policymakers should evaluate the preponderance of the now available evidence and come to a tentative decision with respect to what might seem to be a desirable intake/status level. That weighing of the evidence should, manifestly, include not only the anticipated benefit but also possible harm both from changing and not changing the intake recommendation (including opportunity cost). A decision to change, based on the available evidence, is arguably a better recommendation than the one it would replace. As always, the revised recommendation would itself be subject to change as more complete evidence becomes available.

To sum up, it is both appropriate and necessary to make recommendations in the absence of definitive proof, particularly when it is recognized that not changing an existing recommendation is itself a recommendation. That fact cannot be sidestepped. With nutrients, the question is always not "whether" but "how much?"

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EXHIBIT 4

by Roger Clemens

Dietary Guidelines May Produce Unintended Health Consequences

The 2010 U.S. Dept. of Agriculture Dietary Guidelines are now public. This 445-page document has many implications for the food industry, national nutrition policy, and consumers. Aside from the obvious major action items that surround the primary issue (obesity), the modeling exercises by the Dietary Guidelines Advisory Committee revealed many possible unintentional consequences. In the absence of monitoring the American population with respect to nutrients of concern, compliance with the guidelines could pose additional public health challenges.

Within the Nutrient Adequacy section, the report notes several food groups and dietary components that are underconsumed and may be low enough to be of concern. These include vegetables, fruits, whole grains, milk and milk products, and oils. Despite the recommendations presented in the 2005 Dietary Guidelines, scientific evidence indicates that Americans still do not consume adequate amounts of these products. For example, among adults over the age of 50, 75% to 90% do not meet the recommended intake of 2.5–3 cup equivalents of dairy products daily.

Even more compelling are the whole grain consumption data, which indicate that more than 95% of the population fails to meet minimum requirements. Consistent with these observations is consumption of dietary fiber; an even greater percentage of the population fails to meet the fundamental requirement of 14 g/1,000 calories. Milk products, which contain high quality protein, calcium, potassium, vitamin D, and vitamin A, are not consumed at recommended levels. Evidence indicates that at-risk populations, such as growing children, consume only about 25% of the recommended amount of milk.

Similarly, even the intake of meat, poultry, fish, eggs, soy products, nuts, and seeds is below recommended amounts among many females. These foods are nutrient-rich in protein, heart- and brain-friendly fatty acids, vitamins, and other important nutrients.

As one would expect, the consequences of such underconsumption also represent a shortfall of numerous nutrients, including vitamins A, C, D, E, K, and choline, as well as calcium, magnesium, potassium, and dietary fiber. One could attribute the low levels of vitamins A and C, and the other fat-soluble vitamins to low intake of vegetables and fruit. Of course, low intake of vitamin D and calcium may also reflect, in part, insufficient milk intake, while a poor vitamin D status may also be a sign of insufficient exposure to sunlight.

Considering the dietary goal of limiting saturated fatty acid intake to 7% of total calories, and assuming dietary stearic acid is neutral relative to cardiovascular risk, as well as limiting dietary cholesterol to less than 200 mg (particularly among those at risk of heart disease and type 2 diabetes), one of the shortfall nutrients is choline. Eggs (~125 mg/fresh egg with yolk) are a primary source of dietary choline. If eggs are restricted to four per week (to minimize saturated fat and cholesterol), the daily intake of choline (~450-500 mg/day) may not be achieved. Inclusion of other choline sources, such as meat, poultry, and some starchy vegetables such as potatoes is critical. Hence, this is one of the unintended consequences that deserve further research.

The Dietary Guidelines also pose challenges in terms of the agricultural supply chain. A 2006 report from USDA's Economic Research Service (based on 2002 data) indicates that an additional 8.9 million acres of cropland are necessary to support the guidelines' vegetable intake recommendation, and about 4.1 million more acres are needed to produce the advised fruit consumption. Independent modeling suggests that by 2015 an additional 10.3 million acres of cropland will be necessary to meet vegetable production needs and an additional 4.7 million acres for fruit production. Thus, total harvestable cropland would need to increase by about 3%, or nearly 320 million acres, a level equivalent to 1997 acreage. Equally challenging is the production of fluid milk and milk products. The 2002 data suggest an increase of 107.7 billion pounds is needed, equivalent to a 66% increase in the number of dairy cows, feed grains, and grazing acreage. To meet 2015 expectations, a more appropriate increase is nearly 80%.

In the absence of monitoring the American population with respect to nutrients of concern, ***compliance with the guidelines could pose additional public health challenges.***

The term "aspirational" has been ascribed to the new dietary guidelines. This term is applicable to consumer compliance, food industry challenges, public health policy harmonization, and agricultural practices. It is, therefore, incumbent that all stakeholders, including nutrition educators, food scientists, dietitians and nutritionists, government agencies, farmers, environmental advocates, and public health policy makers, collaborate in developing a strategic plan for successfully implementing the new Dietary Guidelines and reducing the risk of unintended consequences. **FT**

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EXHIBIT 5

DISSECTING THE DIETARY GUIDELINES

Strict recommendations for an optimal diet are difficult to support with evidence-based nutrition science.

I was lucky enough to be appointed as a member of the 2010 Dietary Guidelines Advisory Committee and write this article from that perspective. In the past, I have always been on the outside looking in on the Dietary Guidelines process, wondering why bigger changes were never made and why it took five years to publish a little pamphlet with broad dietary guidelines. I now appreciate the amount of effort it takes to develop and support dietary guidelines and also appreciate the implications that dietary guidelines have on federal nutrition and feeding programs, food product developers, and consumers. I have concluded that making strict recommendations for optimal dietary practices is difficult to support with evidence-based nutrition science. Scientific insights are continually evolving, and weighing sometimes contradictory research results is a complex process.

Humans have survived on a wide range of diets, mostly reflecting access to food supply. During the time of Hippocrates, in the fifth century B.C., physicians supported the view that all edible substances contained aliment, the source of nourishment. In the 1770s, the French chemist Lavoisier described oxidation, fueled by food, launching the study of metabolism and nutrition (Harper, 1988). In 1827, Prout identified three components of food—carbohydrates, fats, and proteins—and suggested getting a balance of these. Over the next 100 years, amino acids, vitamins, minerals, fatty acids, and other essential components of foods were determined, and the study of nutrition science flourished.

Traditionally, nutrient recommendations were made to prevent deficiency diseases. In 1941, the National Academy of Sciences began issuing Recommended Dietary Allowances (RDAs), the quantity of nutrients a person needs to consume daily to ensure basic good health, proper growth, and reproductive success, and to prevent nutrient deficiency diseases. The current nutrition standards for the United States and Canada are the 2002 Dietary Reference Intakes (IOM, 2002). These standards include the RDA, but also Adequate Intakes (AI) for nutrients such as dietary fiber and choline and Tolerable Upper Level Intake (UL), estimates of intakes of nutrients that could cause potential harm. Nutritional deficiency diseases have been virtually eliminated in the U.S., thanks to the enrichment of refined grains with thiamin, riboflavin, and niacin and the consumption of fortified foods such as ready-to-eat breakfast cereals.

A second universally accepted dietary guideline is to maintain appropriate body weight by consuming only enough food to balance the amount of energy expended. This has become much more difficult as modern life has removed all needs for physical labor, and tasty foods are inexpensive and easily obtainable.

Eating to Stay Healthy

A paradigm shift occurred in 1977 when the Senate Select Committee on Nutrition and Human Needs proposed Dietary Goals for the United States (the McGovern Report). These goals were:

1) Increase carbohydrate intake to account for 55–60% of energy intake.

2) Reduce fat consumption to 30% of energy.

3) Modify the composition of dietary fat to provide equal proportions of saturated, monounsaturated, and polyunsaturated fatty acids.

4) Reduce cholesterol consumption to 300 mg/day.

5) Reduce sugar consumption by 40%. »»

BY JOANNE SLAVIN

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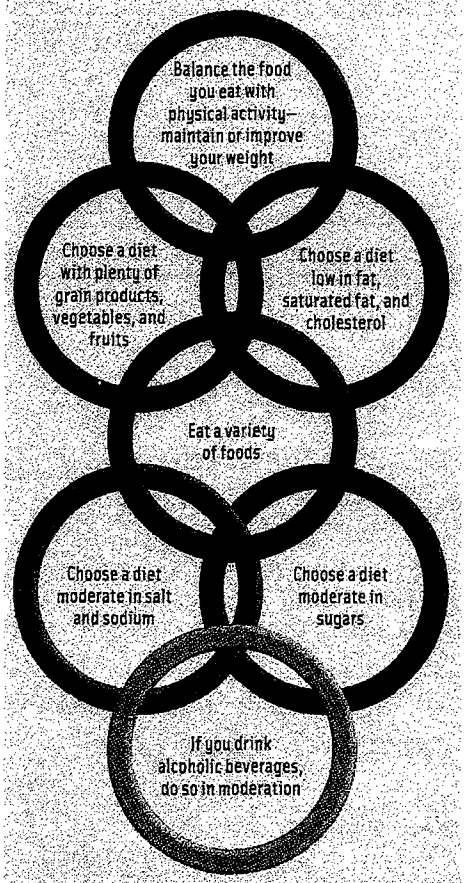

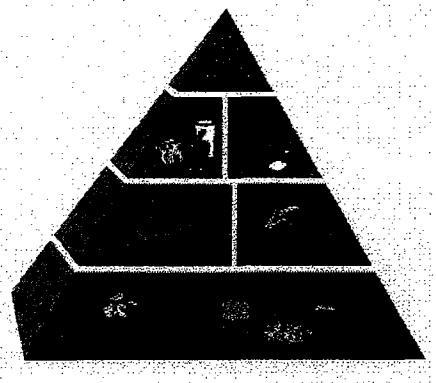

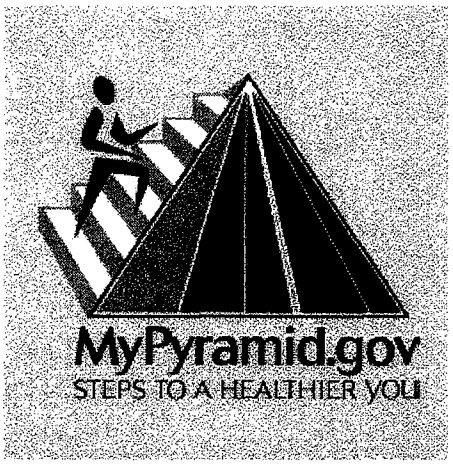

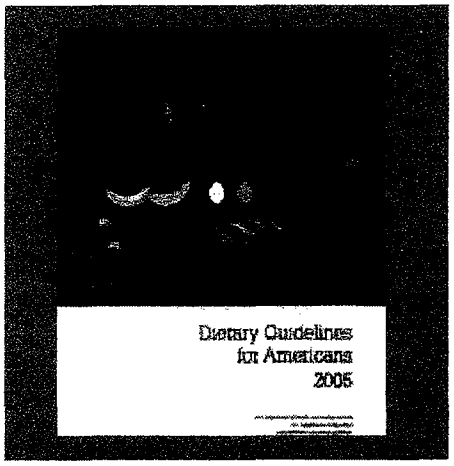

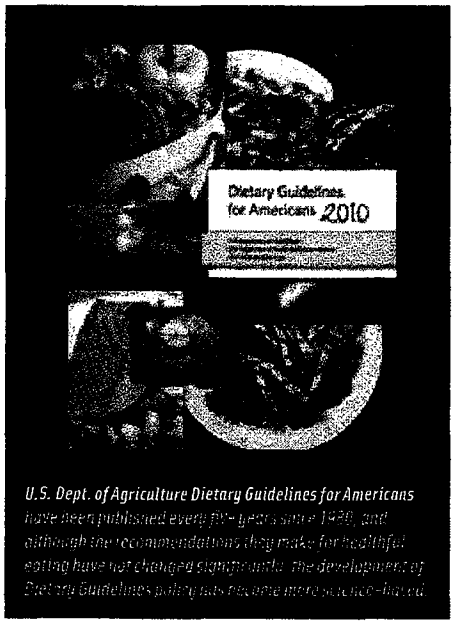

U.S. Dept. of Agriculture Dietary Guidelines for Americans have been published every five years since 1980, and although the recommendations they make for healthful eating have not changed dramatically, the development of Dietary Guidelines policy has become more science-based

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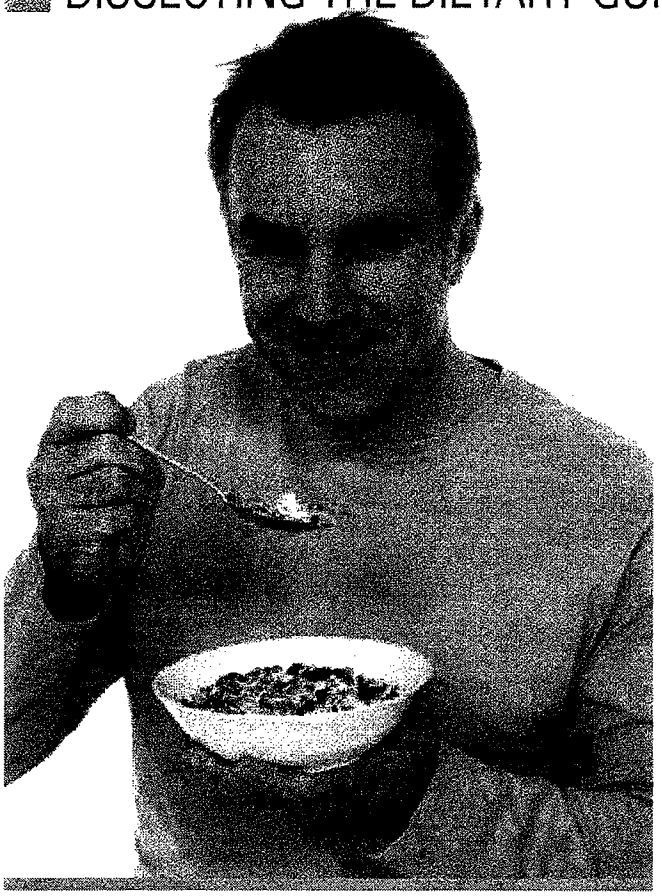
DISSECTING THE DIETARY GUIDELINES



***Determining the relationship** between any dietary components and health outcomes is difficult.* Photo copyright@istockphoto.com/JohnnyGreig

6) Reduce salt consumption to 3 g/day.

The committee suggested that these goals could be met by increasing the consumption of fruits, vegetables, whole grains, poultry, fish, skim milk, and vegetable oils and by decreasing the consumption of whole milk, meat, eggs, butterfat, and foods high in sugar, salt, and fat.

Questions on the relationship between dietary exposure and disease outcome are challenging and contentious.

In 1980, Nutrition and Your Health: Dietary Guidelines for Americans was issued in response to the public's desire for authoritative, consistent guidelines on diet and health. Public Law 101-445, Section 3, requires publication of the Dietary Guidelines at least every five years. They represent federal nutrition policy established jointly by the U.S. Dept. of Agriculture (USDA) and the Dept. of Health and Human Services (HHS). They are designed to provide science-based advice for ages 2 and older to help prevent chronic diseases and promote health. They lay the foundation for federal nutrition programs and nutrition education programs and serve as a basis for research gaps and priorities. They are designed to ensure that messages and materials are consistent throughout the federal government and that government speaks with "one nutrition voice."

The overall recommendations of the Dietary Goals have been carried forward to the Dietary Guidelines. Since the first edition of the Dietary Guidelines in 1980, suggestions to decrease dietary fat, saturated fat, cholesterol, and salt have always been part of dietary guidance. Additionally, suggestions to increase starch, dietary fiber, whole grains, and plant foods have found their way into the guidelines in some fashion. Some fine-tuning has occurred over time, with recommendations to remove *trans* fats from the diet and specific recommendations for intake of whole grains.

Dietary recommendations have always been controversial. Alfred E. Harper, department chair at the University of Wisconsin-Madison during my graduate school years, spoke and wrote widely of the challenges of setting dietary guidance policy. In his paper, "Killer French Fries: The Misguided Drive to Improve the American Diet," he clearly describes our ways of learning about nutrient deficiencies and how such a model does not work for chronic diseases such as heart disease and cancer (Harper, 1988). He also points out misinformation in the early Dietary Guidelines reports. For example, fruits are listed as a source of "complex carbohydrates," when in reality they are mostly a source of sugar and often are poor sources of nutrients including vitamins and minerals. The high protein quality and quantity of animal products has been lost in our translation of dietary guidance for public health. As Harper suggests, clinical advice to change diet based on the need to lower serum cholesterol is much different than public health advice to suggest that all Americans should consume plant foods of low protein quality. He notes that "publications of this type from federal agencies carry considerable weight with the public. To the best of my knowledge, the guidelines were developed by the staffs of the two departments and have not been reviewed by professional nutrition organizations" (Harper, 1981). In 1983, a Federal Advisory Committee of nine nutrition scientists selected from outside the federal government was convened to review and make recommendations to HHS and USDA. Since that time, a Dietary Guidelines Advisory Committee (DGAC) has been appointed from outside the government to review the links between diet and risk for major chronic disease.

An Evidence-Based Approach

Although the recommendations of the Dietary Guidelines have not changed significantly since the 1980s, the development of the Dietary Guidelines policy has become more open and science-based. The 13-member DGAC is composed of scientists with a broad range of expertise needed to represent nutrition, physical activity, food behavior, and nutritional changes through the life cycle. The Advisory Committee meets publically to agree on questions to examine in order to set nutrition

policy. These meetings are open to the public; public comments are solicited throughout the process. The DGAC report is prepared and presented to the Secretaries of USDA and HHS, which occurred in June, 2010. At this point in the process, the Advisory Committee is dismissed and has no other input into the Dietary Guidelines. USDA and HHS write the policy document, and the Dietary Guidelines are released, which this year took place on Jan. 31.

The DGAC works in subcommittees to address questions of diet and disease risk. Subcommittees include energy balance, carbohydrates and protein, fats, nutrient adequacy, sodium and fluids, and food safety. I served as the chair of the carbohydrate and protein committee and also served as a member of the energy balance committee and the nutrient adequacy committee.

How exactly do the DGAC and the subcommittees go about addressing the agreed-upon questions on the relationships of diet to health outcomes? The Hierarchy of Evidence used for the 2010 Advisory Committee's evidence-based review process is shown in Figure 1. Strongest evidence is found in randomized controlled trials, preferably double-blinded. Of course, food studies suffer in this arena since it is difficult or impossible to conduct blind food treatments; subjects know they are consuming an apple or apple juice. These types of trials can work with nutrients, as nutrients can be added to food or drinks without the knowledge of the participants or investigators (double-blind). The next-strongest studies are prospective cohort studies, studies where a group or cohort of subjects are studied over time. Food frequency instruments are used to collect dietary information before any diagnosis of disease, making these studies more reliable than cross-sectional studies. No case-control studies, animal research, or in vitro studies are included in DGAC review, and typically cross-sectional studies are only included if no stronger prospective studies are available for review.

The body of evidence for each question is then examined, and in an evidence-based review, conclusions can be deemed strong, moderate, limited, or lacking data to support them. There may be strong evidence that there is no

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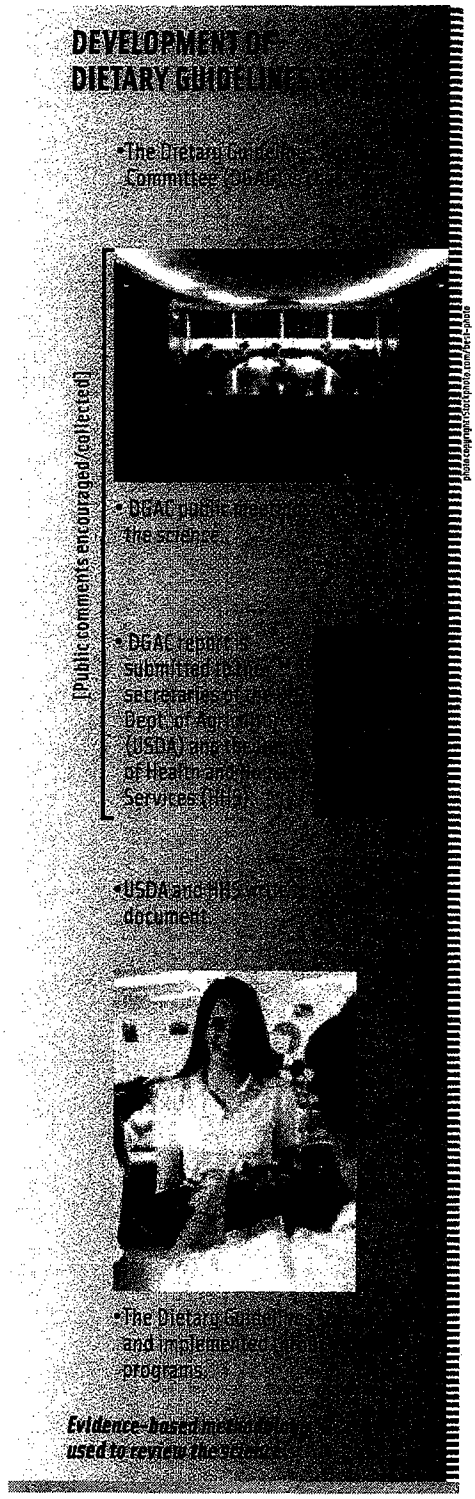

relationship. For example, there was strong evidence of no relationship between glycemic index and disease outcomes.

Agreeing on the strength of the relationship is difficult since, for each question, different types of studies have been published. For each question the 2010 Dietary Guidelines Advisory Committee addressed in the evidence-based report, the search criteria, inclusion and exclusion criteria for studies, the range of dates searched, and other information used in the review is all available on the USDA portal. The transparency used in an evidence-based approach is designed to minimize bias.

Questions on the relationship between dietary exposure and disease outcome are challenging and contentious. I will describe some of the challenges we faced for two topics, carbohydrates as an example of a macronutrient and fruits and vegetables as an example of a food group.

Carbohydrates

In the 2002 Institute of Medicine (IOM) report, *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids,* the IOM established a RDA for carbohydrate of 130 g/day for adults and children age 1 year and older. This value is based on the amount of sugars and starches required to provide the brain with an adequate supply of glucose. The IOM set an Acceptable Macronutrient Distribution Range (AMDR) for carbohydrate of 45–65% of total calories. The DRI committee concluded that evidence was insufficient to set a UL for carbohydrates. However, the panel suggested a maximal intake level of 25% or less of total calories from added sugars. This suggestion was based on dietary intake survey data showing that people with diets at or above this level of added sugars were more likely to have poorer intakes of important essential nutrients.

The amount of dietary carbohydrate that confers optimal health in humans is unknown (IOM, 2002). Adults should consume 45–65% of their total calories from carbohydrates, except for younger children who need a somewhat higher proportion of fat in their diets. Vegetables, fruits, whole grains, milk, and milk products are the major food sources of carbohydrates. Grains and certain vegetables including corn and potatoes are rich in starch, while sweet potatoes are mostly sucrose, not starch. Fruits and dark green vegetables contain little or no starch. Regular soft drinks, sugar/sweets, sweetened grains, and regular fruitades/drinks comprise 72% of the intake of added sugar (Marriott et al., 2010).

Marriott et al. examined the intake of added sugars and selected nutrients from 2003–2006 National Health and Nutrition Examination Survey (NHANES) data. Thirteen percent of the population had added sugars intake of more than 25% of calories. The predominant issue of concern for the authors was the overall high calorie and low quality of the U.S. diet, not added sugars.

Fruits and Vegetables

Historically, consumption of certain plant foods, fruits, vegetables, and legumes was thought to prevent or cure ailments ranging from headaches to heart disease (Steinmetz and Potter, 1996). Early medicine revolved around the prescription of specific foods for certain disorders. Many of these plant foods are also high in dietary fiber and phytoestrogens, so often the hypotheses were driven by fiber, carotenoids, phytoestrogens, or other plant chemicals. Of course, determining the relationship between any dietary component and health outcomes is difficult since diet is a complicated exposure; each day we eat a variety of foods and nutrients, and the ability to link any particular food or nutrient to a health or disease outcome is limited.

In epidemiologic studies, it is possible to count number of servings of fruits and vegetables consumed daily. Of course, fruits and vegetables consumed vary greatly in nutrient composition and calories per serving. The earliest definition of a fruit was "any plant used as food," and a vegetable was a "plant, as opposed to an animal or inanimate object" (Smith et al., 1995). In the 18th century, botanical definitions were standardized, and the definition of a fruit was based on its anatomy, whereas that of a vegetable was based on culinary usage. Generally, culinary custom dictates which plant foods are considered vegetables or fruits. A drawback of using culinary definition is the misclassification of botanical fruits such as squash, tomatoes, and mature beans, which, from a culinary perspective, are considered vegetables.

Within each category, other classifications can be used. For example, for vegetables, raw, cooked, canned, pickled,

leafy green, and legumes are often examined. Fruits and vegetables have also been described as part of a phytochemical group—for example, carotenoids, vitamin C, or folate (Smith et al., 1995).

Earlier reviews that included cross-sectional studies found stronger support for the consumption of fruits and vegetables and disease prevention. Steinmetz and Potter (1996) concluded that the scientific evidence regarding a role for vegetable and fruit consumption in cancer prevention is generally consistent and supportive of current dietary recommendations. Yet Hung et al. (2004), using data from the Nurses' Health and Health Professionals cohort studies, concluded that increased fruit and vegetable consumption was associated with a modest, although not statistically significant, reduction in the development of major chronic disease. Smith-Warner et al. (2001) examined data from eight prospective studies of breast cancer and intake of fruits and vegetables. No association was found for total fruits, total vegetables, or total fruits and vegetables. No additional benefit was found in comparisons of the highest and lowest deciles of intake. Additionally, no associations were observed for green leafy vegetables, eight botanical groups, and 17 specific fruits and vegetables. They conclude that fruit and vegetable consumption during adulthood is not significantly associated with reduced breast cancer risk.

More recent reviews of fruits, vegetables, and other diseases are also less positive on a role between intake of fruits and vegetables and disease protection. Dauchet et al. (2009) suggests that evidence that fruit and vegetable consumption reduces risk of cardiovascular disease remains scarce thus far. They agree that under rigorous controlled experimental conditions, fruit and vegetable consumption is associated with decreased blood pressure. Little experimental data exist that fruit and/or vegetable consumption affect blood lipids or other cardiovascular risk factors.

In a population-based cohort study in the Netherlands, higher consumption of fruit and vegetables, whether consumed raw or processed, was protective against coronary heart disease (CHD) incidence (Oude Griep et al., 2010). The risk of CHD incidence was 34% lower for participants with a high intake of total fruit and vegetables (>475 g/day) compared with participants with a low total fruit and vegetable consumption (<241 g/day).

A systematic review and meta-analysis of fruit and vegetable intake and incidence of type 2 diabetes included six studies, four of which provided separate information on the consumption of green leafy vegetables (Carter et al., 2010). No significant benefits on incidence of type 2 diabetes were found with increased consumption of vegetables, fruit, or fruit and vegetables combined. Hamidi et al. (2010) systematically reviewed observational and intervention studies that investigated the effects of fruit and vegetable intake on incidence of osteoporotic fractures, bone mineral density, and bone turnover markers in women age 45 years and older. They concluded that, based on limited evidence, the benefits of fruit and vegetable intake on bone health remain unclear. »»

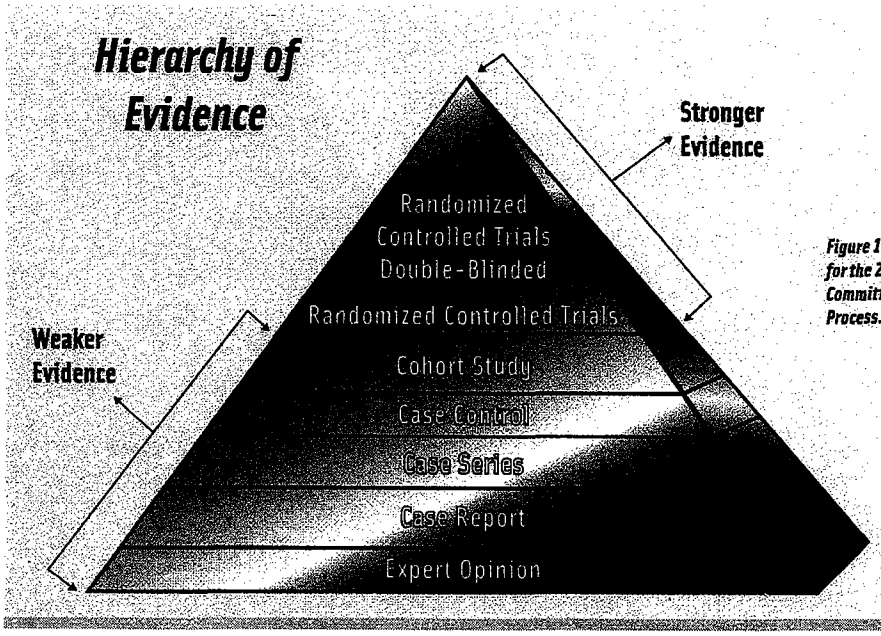

Figure 1. The Hierarchy of Evidence Used for the 2010 Dietary Guidelines Advisory Committee's Evidence-Based Review Process.

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Although dietary guidance encourages *consumption of fruits and vegetables, recent research has been less positive than earlier studies on the role between fruits and vegetables and disease prevention.*
Photo by Peggy Greb, courtesy of USDA's Agricultural Research Service

Fruits, vegetables, and legumes vary widely in nutrient content so should not be expected to have similar physiological effects. Although dietary guidance is supportive of a more vegetarian eating pattern, including increased servings of fruits and vegetables, the scientific support for these recommendations is more historical than evidence-based. Prospective cohort studies find weak support for the protectiveness of fruits and vegetables against chronic diseases. Additionally, few randomized controlled trials are published on the addition of fruits and vegetables to the diet and changes in biomarkers or health status. Nutrients in fruits and vegetables such as dietary fiber, vitamins, minerals, and phytochemicals are all biologically plausible as mechanisms whereby fruits and vegetables play a role in health.

Few people notice that fruits and vegetables, especially fresh, are not high in fiber. With the public health message to combat obesity with lower calorie intakes, foods devoid of protein, such as fruits, will need to be considered for their nutrient density. Articles similar to one by Weichselbaum (2008), suggesting that fruit makes us fat, as well as negative feelings about carbohydrates in general may temper enthusiasm for fruit consumption.

Challenges in Evaluating Diet and Disease Relationships

Inconsistencies in the DGAC report exist, often because of differences in inclusion criteria for studies. For example, limited evidence was found for a relationship between intake of sugar-sweetened beverages and body weight in adults in the carbohydrate chapter, where cross-sectional studies were excluded. In contrast, strong evidence was found between intake of sugar-sweetened beverages and body weight in children when cross-sectional studies were included in the review conducted in the energy balance committee.

Issues with contradictory evidence in the DGAC 2010 report were reviewed by Hite et al. (2010). They suggest that the report does not provide sufficient evidence to conclude that increases in whole grain and fiber and decreases in dietary saturated fat, salt, and animal protein will lead to positive health outcomes. They state that lack of supporting evidence limits the value of the proposed recommendations as guidance for consumers or as the basis for public health policy. They suggest that it is time to reexamine how U.S. dietary guidelines are created and ask whether the current process is still appropriate for our needs. Their support of lower carbohydrate intakes, a view shared by many of the public comments to the DGAC, is definitely an area needing more discussion for the 2015 Dietary Guidelines.

The Dietary Guidelines and Our Health

Does adherence to the Dietary Guidelines makes us healthier? This question is generally answered by cynical comments that no one adheres to the Dietary Guidelines anyway so it doesn't matter. Intervention studies, where diets following the Dietary Guidelines are fed long-term to human volunteers, do not exist. Generally, adherence to the Dietary Guidelines is measured in epidemiologic studies by determining a healthy eating index (HEI), a measure of adherence to the diet recommendations of the Dietary Guidelines. McCullough et al. (2000) found that the HEI was only weakly associated with risk of major chronic disease. Zemora et al. (2010) determined the relationship between weight gain among black and white young adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study (1985–2005). The authors created a 100 point Diet Quality Index. They concluded that their findings do not support the hypothesis that a diet consistent with the 2005 Dietary Guidelines benefits long-term weight maintenance in young adults in America. They suggest the need for attention to obesity prevention in future Dietary Guidelines.

In the 1973 Woody Allen movie *Sleeper,* a patient who has been cryogenically frozen and wakes up 200 years later asks for "charmed foods" including wheat germ, organic honey, and tiger's milk for breakfast. Why not deep fat, steak, cream pies, and hot fudge, asks the nurse. "Those foods were thought to be unhealthy" says the doctor, "precisely the opposite of what we know to be true." It is unlikely that the 2015 Dietary Guidelines will include the *Sleeper* dietary recommendations, but nutrition science demands that moderation and variety continue to be the guiding principles of nutrition advice.

Efforts to micromanage the diet by imposing strict dietary rules are difficult to support with evidence-based nutrition science. We eat foods, not nutrients, and cultural norms and traditions must be considered when determining dietary

guidance. Professor Harper's final advice is this: "A federally supported nutrition education program based on established knowledge that would help to teach people what sound nutrition practices are and more particularly what can, and what cannot, be expected from following such practices, would be of infinitely more value to the general public than a set of recommendations for nutrition treatment of chronic diseases based on fear of food and fear for health and proposed on the basis of highly selected information under the guise of dietary goals" (Harper, 1978). More than 30 years later, his advice rings just as true. **FT**

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