Guy H. Johnson, Ph.D.
Johnson Nutrition Solutions LLC
3801 28th Street, W.
Minneapolis, Minnesota 55416

RE: Petition for a Qualified Health Claim for Magnesium and Reduced Risk of High Blood Pressure (Hypertension) (Docket No. FDA-2016-Q-3770)

Dear Dr. Johnson:

This letter responds to the qualified health claim petition you submitted to the Food and Drug Administration (FDA or we) on behalf of The Center for Magnesium Education and Research, LLC on October 4, 2016. The petition was submitted in accordance with the July 10, 2003 Task Force Final Report on the Consumer Health Information for Better Nutrition Initiative and consistent with the January 2009, Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims.[1] The petition requested that the agency review a qualified health claim characterizing the relationship between the consumption of magnesium and a reduced risk of high blood pressure (hypertension).

The petition proposed the following model claim to be used on the labels or in the labeling of conventional foods and dietary supplements containing magnesium:

> "Supportive but inconclusive scientific evidence suggests that diets with adequate magnesium may reduce the risk of high blood pressure (hypertension), a condition associated with many factors."

[1] See FDA, "Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements. July 10, 2003. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-interim-procedures-qualified-health-claims-labeling-conventional-human-food-and. See FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final," January 2009 ("guidance on scientific evaluation of health claims") [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims]

The petitioner noted that the claim would apply to conventional foods and dietary supplements that contain at least 20 percent of the Daily Value (DV)[2] of magnesium per reference amount customarily consumed (RACC), thus qualifying as being a "high" source of this nutrient as defined in Title 21 Code of Federal Regulations CFR 101.54(b). The petition also proposed that foods and dietary supplements that bear the claim would comply with all of the general requirements for health claims as provided for in 21 CFR 101.14, except that tree nuts, which are high in magnesium, would be exempt from the total fat disqualifying level as defined in 21 CFR 101.14(a)(4).

FDA filed the petition for comprehensive review on November 18, 2016 (Docket number FDA-2016-Q-3770) and posted it on the Regulations.gov website with a 60-day comment period, consistent with FDA's guidance for procedures on qualified health claims. FDA received three comments regarding the petition, all of which expressed general support for the qualified health claim. However, the comments did not include additional information or further evidence for our consideration. We considered these comments in our evaluation of the petition.

This letter sets forth the results of FDA's scientific review of the evidence for the requested qualified health claim requested in the petition. As explained in this letter, FDA has determined that the current evidence supports a qualified health claim concerning the relationship between magnesium and a reduced risk of high blood pressure (hypertension) in conventional foods and dietary supplements. This letter also discusses the factors that FDA intends to consider in the exercise of its enforcement discretion for the use of a qualified health claim, on both conventional foods and dietary supplements, with respect to the consumption of magnesium and a reduced risk of high blood pressure (hypertension).

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition.[3] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.[4]

---

[2] 20% DV of magnesium per RACC for adults and children greater than 4 years of age corresponds to 84 mg (21 CFR 101.9(c)(8)(iv).

[3] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

[4] See FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final," January 2009 ("guidance on scientific evaluation of health claims") [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims] (accessed April 6, 2021).

FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[5] The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[6]

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[7] review articles,[8] and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[9] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.[10] If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

---

[5] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of this letter except when quoting or paraphrasing a regulation that uses the longer term.

[6] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See *supra,* note 4.

[7] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[8] Review articles summarize the findings of individual studies.

[9] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

[10] Although FDA does not generally use meta-analyses in its health claim evaluations for the reasons discussed in the text, the agency will include a meta-analysis in its scientific evaluation if the meta-analysis was conducted with pooled data from all the publicly available studies from which scientific conclusions can be drawn (based on the criteria in FDA's guidance on scientific evaluation of health claims) and the statistical analyses were properly conducted. See *supra*, note 4.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (National Research Council, 2011, Spilker, 1991). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low-quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[11] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[12] and the overall consistency[13] of the total body of evidence.[14] Based on the totality of the scientific evidence, FDA determines whether

---

[11] See *supra*, note 4.
[12] Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, 1990).
[13] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B., The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300); See also Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) [http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."
[14] See *supra*, note 4.

such evidence is credible to support a qualified health claim for the substance/disease relationship, and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of a food, regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified magnesium as the substance that is the subject of the proposed qualified health claim. Magnesium is an essential nutrient for humans and is ubiquitous in foods, although the magnesium content of individual foods varies substantially (IOM 1997). Magnesium is found in significant amounts in a variety of nuts, grains, vegetables, and dietary supplements. Accordingly, FDA concludes that magnesium, the substance identified in the petition, is a component of food and meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition proposes a qualified health claim about reducing the risk of high blood pressure, denoting this as hypertension. Hypertension is a disease in which blood flows through blood vessels or arteries at higher than normal pressures. Hypertension is diagnosed when systolic blood pressure is ≥130 mmHg or diastolic blood pressure is ≥80 mmHg when measured on more than one occasion.[15] Elevated blood pressure occurs when systolic blood pressure is between 120-129 mmHg and diastolic blood pressure is less than 80 mmHg.[16] Blood pressure is the force of blood pushing against the walls of the arteries and blood vessels as the heart pumps blood. Hypertension, also called high blood pressure, is when this force against the artery walls is too high.[17] Elevated blood pressure (higher than normal), but not yet in the hypertensive range, increases the risk of developing hypertension in the future. Elevated blood pressure is a risk factor for hypertension, meaning that it is also a state of health leading to hypertension. Therefore, elevated blood pressure is considered to be a health-related condition. In addition, elevated blood pressure and hypertension are risk factors for other diseases, such as chronic kidney disease and cardiovascular disease (diseases of the heart and circulatory system, including coronary heart disease and stroke).[18] Thus, hypertension is a state of health leading to cardiovascular disease (CVD) and other diseases, as well as a disease in its own right. Because hypertension and elevated blood pressure are both states of health leading to CVD and other diseases, they are also "health-related conditions" as defined in 21 CFR 101.14(a)(5). Therefore, the agency concludes that the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

---

[15] See NHLBI, "High Blood Pressure" [https://www.nhlbi.nih.gov/health-topics/high-blood-pressure] (accessed January 11, 2021

[16] See supra note 15

[17] See supra note 15

[18] See supra note 15.

C. Safety Review

Under 21 CFR 101.14(b)(3)(i), if the substance that is the subject of the health claim is to be consumed at other than decreased dietary levels, the substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in 21 CFR 170.3(o) to the food and must retain that attribute when consumed at levels that are necessary to justify a claim. The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify the claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act (the Act) (21 CFR 101.14(b)(3)(ii)).

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the substance, which is either a food or an ingredient that is the source of the substance, is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (21 CFR 101.70(f)). Dietary ingredients[19] in dietary supplements are not subject to the food additive provisions of the Act (see section 201(s)(6) of the Act (21 U.S.C. § 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. § 342). The applicable adulteration provisions of the Act require, for example, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. § 342(f)(1)(A))). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. § 342(f)(1)(D))). Dietary ingredients that were not marketed in the United States before October 15, 1994, are also subject to the new dietary ingredient requirements in section 413 of the Act (21 U.S.C. § 350b) and the corresponding adulteration provision in section 402(f)(1)(B) of the Act (21 U.S.C. § 342(f)(1)(B)).

Magnesium in Conventional Foods

The petitioner noted that several forms of magnesium have GRAS status, including: magnesium carbonate (21 CFR 184.1425), magnesium chloride (21 CFR 184.1426), magnesium hydroxide (21 CFR 184.1428), magnesium oxide (21 CFR 184.1431), magnesium phosphate (21 CFR 184.1434), magnesium stearate (21 CFR 184.1440) and magnesium sulfate (21 CFR 184.1443). In accordance with 21 CFR 184.1(b)(1), each of these ingredients may be used in food with no limitation other than current good manufacturing practice, which includes their use at levels not to exceed current good manufacturing practice.

[19] The term "dietary ingredient" is defined in section 201(ff)(1) of the Act (21 U.S.C. 321(ff)(1)) and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing the total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients.

The petitioner noted that magnesium is an essential nutrient that is a safe and necessary component of the food supply. Magnesium is naturally found in a variety of foods, such as tree nuts, seeds, bananas, legumes, fiber rich whole grains, certain dairy products, chard, green peas, and spinach. Thus, magnesium has a long history of being consumed from many food sources in the United States.

Nationally representative data from the 2015-2016 National Health and Nutrition Examination Survey indicated that the mean magnesium intake from foods and beverages, excluding dietary supplements, was 289 mg/day (SE= 5.0) for all individuals age 2 and over. For adults 19 years of age and older, the Recommended Dietary Allowance for magnesium intake is 400-420 mg/day for men and 310-320 mg/day for women. The DV for magnesium is 420 mg for adults and children greater than 4 years of age, 400 mg for pregnant and lactating women, and 80 mg for children 1-3 years of age. Therefore, FDA believes that the proposed qualified health claim would be unlikely to result in a mean dietary intake of magnesium from foods and beverages that would exceed the DV of 420 mg for adults and children greater than 4 years of age.

There are no reports of magnesium producing a toxic effect when consumed as a naturally occurring substance in food. Therefore, a Tolerable Upper Intake Level (UL) based on dietary magnesium obtained from conventional foods has not been established by the National Academies of Sciences, Engineering, and Medicine (NASEM) (formerly the Institute of Medicine (IOM)) (IOM, 1997).

Based on the data and information that FDA considered, FDA concludes that the consumption of magnesium in conventional foods, at levels necessary to justify the qualified health claims described in section IV, has been demonstrated to FDA's satisfaction to be safe and lawful under section 21 CFR 101.14(b)(3)(ii).

Magnesium in Dietary Supplements
As a dietary supplement, magnesium is available in a variety of forms, including magnesium oxide, magnesium citrate, magnesium chloride, magnesium aspartate, and magnesium glycinate. The different forms of magnesium have varying rates of absorption. The Supplement Facts label on dietary supplement products declares the amount of elemental magnesium in a serving of the product, not the amount in the entire magnesium-containing compound.

Magnesium is commercially available as a single-ingredient dietary supplement, in products where it is combined with other specific nutrients (such as vitamin B6 and vitamin E), or as an ingredient in multivitamin/multimineral dietary supplements. Many of the single-ingredient magnesium dietary supplements contain between 200 mg and 400 mg of elemental magnesium, while the amount present in multivitamin/multimineral supplements is typically 100 mg or less of elemental magnesium.

However, magnesium can cause adverse effects, including osmotic diarrhea, nausea, and abdominal cramping, when ingested from sources other than conventional foods. The Institute of Medicine (IOM) noted that adverse effects from excess magnesium intake in humans have been observed with intakes from pharmacological sources such as antacids (IOM, 1997).

Because all reports of adverse effects from magnesium are based dietary supplement intake in addition to food sources, the IOM has established **Tolerable Upper-Level Intakes (**Uls) for magnesium that apply only to supplemental magnesium, such as magnesium derived from dietary supplements or medications.

Using diarrhea as the clinically defined critical endpoint, the IOM identified the lowest-observed-adverse-effect-level (LOAEL) of magnesium intake as 360 mg (15 mmol)/day of magnesium from nonfood sources. The IOM established 350 mg (14.6 mmol)/day of magnesium as the UL for adults and adolescents greater than 8 years of age, as well as for pregnant and lactating women, by dividing a LOAEL of 360 mg by an uncertainty factor (UF) of approximately 1.0. This UF was chosen because the occurrence of osmotic diarrhea is apparent to an individual; is considered to be a mild and reversible condition; and is not a symptom that is masked until serious consequences develop. The IOM established a UL for children (who are also assumed to be susceptible to the osmotic effects of nonfood sources of magnesium) at a magnesium intake of 5 mg/kg/day (0.2 mmol/kg/day). Adjusting this value on the basis of body weight, the UL for children 1-3 years of age is 65 mg (2.7 mmol) of supplementary magnesium, and the UL for children 4-8 years of age is 110 mg (4.6 mmol) of supplementary magnesium. Based on the data and information that FDA considered, FDA concludes that the use of magnesium in dietary supplements, at levels necessary to justify the qualified health claims described in section IV – i.e., at levels that are "high" as defined in 21 CFR 101.54(b), but no greater than 350 mg/day (the UL) from dietary supplements – is safe and lawful under 21 CFR 101.14(b)(3)(ii). Therefore, FDA concludes that the petitioner has demonstrated to FDA's satisfaction that magnesium in conventional foods and dietary supplements, as long as it does not exceed 350 mg/day in dietary supplements when used according to their labeling, to be safe and lawful.

II. The Agency's Consideration of a Qualified Health Claim

The evidence included in the petition was for reducing the risk of high blood pressure (hypertension). FDA and NIH have identified diastolic blood pressure (DBP) and systolic blood pressure (SBP) as surrogate endpoints for predicting risk of hypertension.[20] Because either elevated SBP (≥ 130mm Hg) or DBP (≥ 80 mm Hg) can be used to diagnose hypertension, the reduction of either can be considered beneficial in reducing the risk of hypertension.[21] FDA has also identified Mean Arterial Pressure (MAP) as a surrogate endpoint for predicting risk of hypertension.[22] MAP is the average arterial pressure throughout one cardiac cycle, systole, and

[20] FDA-NIH Biomarker Working Group. BEST (Biomarkers, Endpoints, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Validated Surrogate Endpoint. 2017 Sep. [https://www.ncbi.nlm.nih.gov/books/NBK453484/] (accessed June 30, 2021). see supra, note 4 Section III.C]. See also Rasnake CM, Trumbo PR, Heinonen TM. Surrogate endpoints and emerging surrogate endpoints for risk reduction of cardiovascular disease. Nutr Rev 2008;66(2):76-81. See also Desai M, Stockbridge N, Temple R. Blood pressure as an example of a biomarker that functions as a surrogate. AAPS J 2006;8(1):E146-152.

[21] See NHLBI, "High Blood Pressure" [https://www.nhlbi.nih.gov/health-topics/high-blood-pressure] (accessed January 11, 2021).

[22] See "Memorandum to the File (Docket No. FDA-2016-Q-3770): Mean Arterial Pressure as a Surrogate Endpoint (November 9, 2021).

diastole.[23] For the purposes of this review, the agency evaluated only studies that measured SBP, DBP, or MAP. FDA evaluated the totality of the evidence for intake of magnesium, which the petition describes as the substance that is the subject of the claim and reducing the risk of high blood pressure (hypertension) through lowering SBP, DBP, MAP incidence of hypertension.

The petition cited 164 of publications as evidence to substantiate the relationship for the proposed claim. These publications consisted of: 20 review articles; 1 book and 1 book chapter; 6 meta-analysis; 2 abstracts; 1 *in vitro* study; 1 animal study; 1 article written in a foreign language without a complete English translation; 12 publications that did not evaluate the substance and disease relationship; and 120 publications that evaluated the relationship between magnesium intake lowering blood pressure or hypertension risk. The 120 publications described 75 intervention studies and 42 observational studies. The comments to the petition cited 6 additional publications that were not already included in the petition. References cited in comments during the public comment period included 3 government documents and 3 publications did not evaluate the substance and disease relationship. FDA also identified 10 relevant intervention studies and 1 relevant observational study through a literature search for studies evaluating the relationship between magnesium intake and risk of hypertension.

A. Assessment of Review Articles, Meta-Analysis, Book Chapters and Government Reports

Although useful for background information, review articles, meta-analyses, book chapters, letters, and government reports do not contain sufficient information on the individual studies which they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors, such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement). Similarly, the lack of detailed information on studies summarized in review articles, meta-analyses, book chapters, and government reports prevent the agency from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles, meta-analyses, book chapter, and government reports supplied by the comments and in the petition do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship.

B. Assessment of Intervention Studies

FDA evaluated 85 intervention studies described in 88 publications that were designed to investigate the relationship between magnesium intake and risk of hypertension. Of the 85 intervention studies, conclusions could not be drawn from 47 studies for the reasons discussed below.[24]

---

[23] MAP = DBP + 1/3(SBP – DBP)

[24] This section contains a general discussion of major flaws in the reports of intervention studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.

In four studies[25] magnesium was given to subjects intravenously or intramuscularly rather than by the oral route. The biological effects of magnesium when ingested cannot be determined from studies that use another route of administration without additional studies evaluating the effect of the difference in route of administration. FDA does not have data demonstrating that giving magnesium intravenously does not alter its biological effects by bypassing the chemical alterations that occur during digestion, absorption, and first-pass metabolism following oral administration. FDA does not consider studies that administer magnesium intravenously relevant for determining risk reduction of hypertension from consumption of magnesium.

Nine studies did not include a control group.[26] Without a control group, it cannot be determined if the changes in blood pressure (SBP, DBP, or MAP) were due to magnesium intake or uncontrolled extraneous factors (U.S. Food and Drug Administration, January 2009). Thus, scientific conclusions could not be drawn from these studies.

Eight[27] studies provided magnesium in combination with other vitamin and mineral supplements that were not controlled; therefore, it was not possible to determine the independent effects of magnesium on blood pressure or risk of hypertension. Therefore, scientific conclusions about the effect of magnesium on hypertension could not be drawn from these studies.

Two studies (Plum-Wirell et al., 1994, Toprak et al., 2017) used magnesium supplements in combination with other dietary advice that could lead to changes in the amount of sodium and potassium in the diet. These studies did not adequately control for or provide information on sodium intake in the diet. Since sodium intake also influences blood pressure, the independent effects of magnesium intake on blood pressure could not be determined (National Academies of Sciences et al., 2019). Hence, scientific conclusions could not be drawn from these studies.

For one parallel study (Mortazavi et al., 2013), the baseline blood pressure values were very different between the magnesium and control group. When baseline values are statistically different between groups in a parallel study, a statistical analysis that included an adjustment for baseline, or calculations of change from baseline should be conducted. Since this study did not properly adjust for baseline values we cannot determine if differences at the end of the study were due to the intervention or to differences at the beginning of the study. Therefore, it was not possible to compare the results between the two groups. Thus, scientific conclusions about a relationship between magnesium intake and reduced risk of hypertension could not be drawn from this study.

[25] Vickovic et al., 2016;Altman et al., 2002;Kosucu et al., 2020;Kim et al., 2015
[26] Cohen et al., 1984;Banjanin and Belojevic, 2018;Haga, 1992;Katz et al., 1999;Motoyama et al., 1989;Rylander and Arnaud, 2004;Sebekova et al., 1992;Taylor et al., 1988;Yokota et al., 2004
[27] Wary et al., 1999;Geleijnse et al., 1994;Sacks et al., 1995;Wu et al., 2006;Zhou et al., 2016;Vongpatanasin et al., 2016;Farvid et al., 2004;Kim et al., 2018

Fifteen studies were conducted in subjects with hypomagnesaemia (serum magnesium concentrations less than 0.75 mmol/L).[28] Results of these studies are not relevant to the general U.S. population (Institute of Medicine (IOM), 1997, U.S. Food and Drug Administration, January 2009). A response to magnesium supplementation in these studies may be due to the correction of suboptimal magnesium status or a magnesium deficiency for which health claims are not intended.

Seven studies did not conduct statistical analysis between the control and treatment group.[29] Statistical analysis of the substance/disease relationship is a critical factor because it provides the comparison between subjects consuming magnesium and those not consuming magnesium (i.e., control) to determine whether there is a reduction in blood pressure or risk of hypertension (U.S. Food and Drug Administration, January 2009). Hence, scientific conclusions could not be drawn from these studies.

Kisters et al., (1993) was a parallel study in which 69 German subjects consumed a placebo (n=32) (mean age 47.9 years) or 500 mg/day elemental magnesium as magnesium hydrogen aspartate (n=37) (mean age 49.8 years) in addition to an energy restricted (< 1,200 kcals) and low cholesterol diet (<90 mg/day) for 4 weeks. This study had several quality issues (Kisters et al., 1993). For example, the study was not randomized and information on study blinding was not reported. Also, adequate descriptions were not provided for the composition of the background diet (e.g. data on sodium and potassium intake) and study compliance. Additionally, the study measured biomarkers (SBP or DBP) instead of clinical outcomes. Therefore, this study is so deficient in methodological quality that it is considered to be low-quality design, and, as a result we could not draw scientific conclusions about a relationship between magnesium intake and reduction in blood pressure or risk of hypertension (U.S. Food and Drug Administration, January 2009).

Based on the rationale discussed above, scientific conclusions could be drawn from 38 intervention studies that evaluated the relationship between magnesium intake or risk of hypertension. Those studies are discussed below.

For the purposes of this review, studies that measured blood pressure were sorted into two categories 1) subjects with normal blood pressure or elevated blood pressure (SBP ≤ 129 mm Hg or DBP < 80 mm Hg) and 2) subjects with hypertension (SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg).[30] Because the mechanisms by which magnesium may reduce blood pressure in

[28] Barragan-Rodriguez et al., 2008;Guerrero-Romero and Rodriguez-Moran, 2009;Guerrero-Romero et al., 2004; Guerrero-Romero and Rodriguez-Moran, 2011;Lutsey et al., 2018;Rodriguez-Hernandez et al., 2010;Rodriguez-Moran and Guerrero-Romero, 2014;Rodriguez-Moran et al., 2018;Rodriguez-Moran and Guerrero-Romero, 2003;Rodriguez-Ramirez et al., 2017;Simental-Mendia et al., 2014;Simental-Mendia et al., 2012;Zemel et al., 1990;de Araujo et al., 2020;Sibai et al., 1989

[29] Dyckner and Wester, 1983;Hattori et al., 1988;Henderson et al., 1986;Reyes et al., 1984;Shafique et al., 1993;Sur and Maftei, 2006;Sanjuliani et al., 1996

[30] See NHLBI, "High Blood Pressure" [https://www.nhlbi.nih.gov/health-topics/high-blood-pressure] (accessed January 11, 2021).

normotensive and hypertensive subjects are the same, studies in hypertensive subjects were included in this review (Romani, 2013). Also, the amount of magnesium discussed in this letter is expressed in weight of elemental calcium rather than weight of magnesium compounds (e.g., magnesium citrate, magnesium hydroxide).

Studies that added magnesium supplements to the diets in subjects with normal or elevated blood pressure (SBP ≤ 129 mmHg or DBP < 80 mmHg)

Bullarbo et al., (2018) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 176 pregnant Swedish women (mean age 28 years) consumed a placebo (control) (n=93) or 400 mg/day elemental magnesium as magnesium citrate supplement (n=83) in addition to their usual diets. The study was designed to evaluate if magnesium supplementation would prevent an increase in blood pressure during pregnancy. Subjects in 12 to 14 weeks of pregnancy were enrolled and continued until delivery (Bullarbo et al., 2018). There was no significant difference in the increase in SBP or DBP between the control group and the magnesium group.

Kass and Poeira (2015) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 13 American subjects were assigned to an acute intervention (1 week) or chronic intervention (4 weeks). The two studies ran parallel to each other and subjects consumed a corn flour placebo (control) or 300 mg/day elemental magnesium as magnesium citrate. Subjects also performed a timed trial on bicycle (40 km timed trial) and bench press at 80% 1 RM (repetition maximum). Blood pressure was measured at rest before and after the bench press (recovery). The study measured blood pressure across two consecutive days at each time point. The results reported for DBP in the text of the paper and in the accompanying tables and abstract do not match each other for both the acute and chronic phases of the study (Kass and Poeira, 2015). Therefore, it was not possible to compare the results for DBP between the two experimental groups. For these reasons, scientific conclusions about a relationship between magnesium intake and reduction in blood pressure or risk of hypertension could not be drawn from this study for DBP. For day 1, there was no significant difference in resting SBP between the control and magnesium groups for both the chronic and acute intervention. For day 2, resting SBP was not significantly different between the control and the magnesium group in the chronic intervention. However, resting SBP was significantly lower ($P<0.05$) in the magnesium group compared to the control on day 2 of the acute intervention. Post SBP was significantly lower ($P<0.05$) on day 1 the chronic intervention, but not the acute intervention. Post SBP was also significantly lower ($P<0.05$) on day 2 for both the chronic and acute interventions.

Cosaro et al., (2014) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 16 Italian men (mean age 26 years) consumed a placebo twice a day (control) or 184 mg elemental magnesium as magnesium pidolate powder twice a day (368 mg/day total) for 8 weeks each period. There was no significant difference in SBP or DBP between the control group and the magnesium group (Cosaro et al., 2014).

Bullarbo et al., (2013) was a moderate quality randomized, double-blind, placebo-controlled parallel study in which 59 Swedish pregnant women (mean age 28 years) consumed a placebo (control) (n=30) or 300 mg/day elemental magnesium as magnesium citrate (n=29) in addition to their usual diets. The study was designed to evaluate if magnesium supplementation would

prevent an increase in blood pressure during pregnancy (Bullarbo et al., 2013). Subjects received a placebo or magnesium supplement from pregnancy week 25 until delivery. The study reported that there was no significant difference in SBP between the control group and the magnesium group at week 37, but the mean data and change in SBP were not reported. However, mean DBP and change in DBP were significantly lower (P=0.031 and P=0.022) in the magnesium group compared to the placebo group at week 37, but there was no significant difference between the two groups at weeks 32 or 35.

Kass et al., (2013) was a moderate quality randomized, not blinded, placebo-controlled, parallel study in which 16 British men (mean age 20 years) consumed a control (n=8) or 90.5 mg of elemental magnesium as magnesium oxide twice a day (181 mg/day total) (n=8) in addition to their usual diets for 14 days. Blood pressure was measured at both groups before (resting) subjects completed a 30-minute cycle at maximal capacity (Kass et al., 2013). Immediately following the 30-minute cycle subjects completed 3 x 5 second maximal isometric bench press contractions. Blood pressure was also measured after completing the three isometric contractions (post exercise) and again after a 5-minute seated recovery period (recovery). Resting, post exercise and recovery SBP were all significantly lower in the magnesium group compared to the control group (P<0.05).

Doyle et al., (1999) was a moderate quality randomized, double blind, placebo-controlled, cross-over study in which 26 Irish women (mean age 23 years) consumed a placebo (control) or 124 mg elemental magnesium as magnesium hydroxide twice a day (247 mg/day total) in addition to their usual diet for 28 days each period. There was no significant difference in SBP or DBP between the two periods (Doyle et al., 1999).

Sacks et al., (1998)[31] was a high quality randomized, double-blind, placebo-controlled, parallel study in which 153 American women (mean age 39 years) consumed a placebo (control) (n=103) or 168 mg of elemental magnesium as magnesium lactate twice a day (336 mg/day total) (n=50) in addition to their usual diets for 16 weeks. There was no significant difference in 24-hour ambulatory[32] SBP or DBP between the control group and the magnesium supplement group (Sacks et al., 1998).

Studies in subjects with cardiovascular disease (CVD)

Baker et al., (2009) was a moderate quality randomized, double-blind parallel study in which 50 Finish subjects[33] with a newly implanted cardioverter defibrillators consumed a placebo (control) (n=26) (mean age 61 years) or 252 mg elemental magnesium as magnesium L-lactate twice a day (504 mg/day total) (n=24) (mean age 68 years) in addition to their usual diets for 24 weeks. SBP was significantly lower (P=0.04) in the magnesium group compared to the control group at 12 weeks, but not at 24 weeks. DBP was not significantly different between the two groups at 12 or

[31] This study also had a potassium chloride group (n=49), calcium carbonate group (n=53), and a group that received potassium chloride, calcium carbonate and magnesium lactate combined (n=45). We could not draw conclusions from these comparisons in this study because they did not evaluate the substance and disease relationship and/or the independent effects of magnesium could not be determined.

[32] Ambulatory blood pressure monitoring measure blood pressure at regular intervals usually over a continuous period.

[33] 50 subjects completed 12 weeks (n=26 placebo, n= 24 magnesium), 44 subjects completed 24 weeks (n=25 placebo, n=19 magnesium)

24 weeks (Baker et al., 2009). In subjects with a document history of hypertension, SBP was significantly lower (P<0.02) in the magnesium group compared to the control group. However, there was no significant difference in SBP at 24 weeks. There was no significant difference in DBP between the two groups in subjects with a history of hypertension at 12 or 24 weeks.

Bashir et al., (1993) was a moderate quality randomized, double blind, placebo controlled cross-over study in which 21 British subjects (mean age 63 years) with congestive heart failure secondary to coronary artery disease consumed a placebo (control) or 379 mg/day elemental magnesium as magnesium chloride in addition to their usual diet for 6 week each period. There was no significant difference in SBP or DBP between the two periods (Bashir et al., 1993). However, MAP was significantly lower (P=0.028) in the magnesium period compared to the control period.

Studies that added magnesium supplements to the diets of subjects with hypertension (SBP ≥ 130 mmHg or DBP ≥ 80 mmHg)

Cunha et al., (2017) was a moderate quality randomized, double-blind, placebo-controlled parallel study in which 35 British women treated with hydrochlorothiazide [34] consumed a placebo (control) (n=18) (mean age 57 years) or 300 mg elemental magnesium as magnesium chelate twice a day (600 mg/day total) (n=17) (mean age 54 years) in addition to their usual diets for 6 months. There was no significant difference in 24-hour ambulatory SBP or DBP between the control group and the magnesium group (Cunha et al., 2017).

Joris et al., (2016) was a high quality randomized, double-blind, placebo-controlled parallel study in which 52 overweight or obese Dutch subjects (mean age 62 years) consumed a starch placebo (control) (n=25) or 116.7 mg mg/day elemental magnesium as magnesium citrate three times a day (350 mg/day total) (n=26) in addition to their usual diet for 12 weeks. There was no significant difference in 24-hour ambulatory SBP or DBP between the control group or the magnesium groups (Joris et al., 2016).

Mooren et al., (2011) was a moderate quality randomized, double-blind, placebo-controlled parallel study in which 47 insulin resistant obese German subjects (age range 30 to 70 years) consumed a placebo (control) (n=22) or 365 mg/day elemental magnesium as magnesium-aspartate-hydrochloride (n=25) in addition to their usual diet for 6 months. There was no significant difference in SBP or DBP between the control group and the magnesium group (Mooren et al., 2011).

Barbagallo et al., (2010) was a moderate quality controlled parallel study in which 60 Italian subjects (mean age 71.1 years) with type 2 diabetes consumed their usual diet (control) n=30 or 184 mg elemental magnesium as magnesium pidolate twice a day (368 mg/day total) (n=30) plus their usual diet for one month. There was no significant difference in SBP or DBP between the control group and the magnesium group (Barbagallo et al., 2010).

[34] Hydrochlorothiazide is a diuretic used to treat high blood pressure.

Hatzistavri et al., (2009) was a moderate quality not blinded, controlled parallel study in which 48 Greek subjects matched for age and sex[35] were provided standard recommendations for lifestyle changes[36] (control) (n=24) (mean age 46.9 years) or 300 mg twice a day elemental magnesium (600 mg/day total) as magnesium pidolate plus standard recommendations for lifestyle changes (n=24) (mean age 45.3 years) for 12 weeks. Overall 24-hour ambulatory SBP and DBP were significantly lower in the magnesium group compared to the control group ($P<0.001$) (Hatzistavri et al., 2009). Daytime and nighttime ambulatory SBP were also significantly ($P=0.002$, $P<0.05$ respectively) lower in the magnesium group compared to the control group. Similar reduction in daytime and nighttime DBP were also reported ($P <0.001$). MAP for overall 24-hour, daytime and nighttime were also significantly lower in the magnesium group compared to the control group ($P<0.001$, $P<0.001$, and $P<0.01$ respectively).

Lee et al., (2009) was a high quality randomized, double-blind, placebo-controlled, parallel study in which 121 overweight or obese Korean subjects consumed a placebo (control) (n=72) (mean age 40.5 years) or 300 mg/day elemental magnesium as magnesium oxide (n=69) (mean age 39.6 years) in addition to their usual diet for 12 weeks. There was no significant difference in SBP or DBP between the two groups in all subjects (Lee et al., 2009). However, in subjects with SBP >140 mm Hg the mean change in SBP was significantly lower ($P=0.016$) in the magnesium group (n=8) compared to the control group (n=16). The mean change in DBP in subjects with DBP 80-90 mm Hg was also significantly lower ($P=0.043$) in the magnesium group (n=27) compared to the control group (n=29). The results reported for the mean change in DBP for subjects > 90 mm Hg in the text of the paper and in the accompanying graph were contradictory. Therefore, it was not possible to compare the results between the two groups for DBP in subjects with DBP > 90 mm Hg.

Walker et al., (2002) was a moderate quality randomized, double-blind, placebo-controlled, parallel study in which 36 British subjects consumed a 1) cellulose placebo (control) (n=10) (mean age 49.1 years) or 2) 600 mg/day elemental magnesium as magnesium amino acid chelate (n=9) (mean age 53.2 years) or 3) 500 mg/day of Hawthorne extract (control) (n=7) (mean age 53.3 years) or 4) 600 mg/day elemental magnesium as amino acid chelate plus 500 mg /day Hawthorne extract (n=10) (mean age 48.8 years) in addition to their usual diets for 10 weeks. Blood pressure was measured at rest, after 5 minutes on an exercise bicycle, and after a 5-minute computer stress test. There was no significant difference in SBP or DBP between the cellulose control group and the magnesium group at rest, after exercise, or a computer stress test (Walker et al., 2002). There was also no significant difference in SBP or DBP between the Hawthorne extract control and the magnesium plus Hawthorne extract group at rest, after exercise, or a computer stress test.

---

[35] The study did not randomize but used an alternative to randomization called "minimization." See Altman et al. (2001) ("Minimization is an acceptable alternative to random assignment."). Minimization tries to balance intervention groups for specific factors. In Hatzistavri et al., 2009 the participants were matched for age and sex.

[36] Participants were given standard recommendations for lifestyle changes in accordance to guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).

de Valk et al., (1998) was a moderate quality randomized, double-blind, placebo controlled, parallel study in which 50 Dutch subjects with type 2 diabetes consumed a placebo (control) (n=25) (mean age 62 years) or 360 mg/day elemental magnesium as magnesium aspartate hydrochloride (n=25) (mean age 63 years) in addition to their usual diet for 3 months. There was no significant difference in SBP or DBP between the control group and the magnesium group (de Valk et al., 1998).

Kawano et al., (1998) was a moderate quality randomized, not blinded, controlled, cross-over study in which 60 Japanese subjects (mean age 58.1 years) consumed their usual diet (control) or 240 mg magnesium as magnesium oxide twice a day (480 mg/day total) in addition to their usual diet for 8 weeks each period. SBP and DBP were significantly lower during the magnesium period compared to the control period when measured in the office ($P<0.01$ and $P<0.05$ respectively), at home ($P<0.05$) and during the day ($P<0.05$) (Kawano et al., 1998). Ambulatory (24-hour) SBP and DBP were also significantly lower ($P<0.05$ and $P<0.05$ respectively) in the magnesium period compared to the control period. However, there was no significant difference in SBP or DBP between the two periods when measured at night.

Itoh et al., (1997) was a moderate quality randomized, double-blind, placebo controlled, parallel study in which 33 Japanese subjects consumed a placebo (n=10) (mean age 66 years) or elemental magnesium (548 mg/day men and 411 mg/day women) as magnesium hydroxide (n=23) (mean age 64 years) in addition to their usual diets for 4 weeks. SBP was significantly lower after 2 weeks ($P<0.01$) and 4 weeks ($P<0.05$) in the magnesium group compared to the control group (Itoh et al., 1997). However, DBP was not significantly different between the two groups at 2 or 4 weeks.

Borrello et al., (1996) was a high quality randomized, double-blind, placebo controlled parallel study in which 83 Italian subjects consumed a placebo (control) (n=41) (mean age 49 years) or 241 mg magnesium as magnesium oxide (n=42) (mean age 51 years) in addition to their usual diet for 12 weeks. SBP was significantly lower ($P<0.01$) in the magnesium group compared to control group when measured in the office at 12 weeks, but not at 4 or 8 weeks (Borrello et al., 1996). However, there was no significant difference in office DBP between the two groups at any time point. Ambulatory (24-hour) SBP and DBP were not significantly different during the daytime or nighttime at 12 weeks.

Eriksson et al., (1995) was a moderate quality randomized, double-blind, cross-over study in which 56 Finish subjects (mean age 43 years) with diabetes [insulin-dependent diabetes mellitus (type 1 diabetes) (n=29), non-insulin dependent diabetes mellitus (type 2) (n=27)] consumed: no active treatment (control 1); 2 g/day ascorbic acid (control 2); or 300 mg twice a day elemental magnesium (600 mg/day total) in addition to their usual diets for 90 days each period. In subjects with type 1 diabetes (n=29) SBP and DBP were significantly lower ($P<0.05$) during the magnesium period compared to the no active treatment period and the ascorbic acid control period (Eriksson and Kohvakka, 1995). In subjects with type 2 diabetes (n=27) there was no significant difference in SBP or DBP between the magnesium period and the no active treatment or ascorbic acid control periods.

Purvis et al., (1994) was a moderate quality randomized, double-blind, placebo controlled, cross-over study in which 28 American subjects (age range 28 to 84 years) with type 2 diabetes consumed a placebo or 384 mg/day elemental magnesium as magnesium chloride in addition to their usual diet for 6 weeks each period. SBP was significantly lower ($P<0.006$) in the magnesium period compared to the control period (Purvis et al., 1994). However, there was no significant difference in DBP between the two periods.

Wirell et al., (1994) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 39 Swedish subjects (mean age 35.4 years) treated with beta-blockers consumed a placebo or 121.6 mg three times a day elemental magnesium as magnesium aspartate hydrochloride (365 mg/day total) in addition to their usual diets for 8 weeks each period. There was no significant difference in the change for supine (lying) or standing SBP or DBP for all subjects combined (Wirell et al., 1994). However, supine and standing SBP was significantly ($P=0.005$ and $P=0.028$) lower in subjects when magnesium was given after the placebo period. There was no significant difference in standing or supine DBP when magnesium was given after the placebo period. When magnesium was given before the placebo there was no significant difference in SBP or DBP between the two periods.

Witteman et al., (1994) was a high-quality randomized, double-blind, placebo controlled parallel study in which 91 Dutch women (mean age 57 years) consumed 4 packets of a matched placebo with meals (control) (n=44) or 485 mg/d elemental magnesium as magnesium aspartate hydrochloride (four packets with meals) (n=47) in addition to their usual diets for 6 months. There was no significant difference in SBP when measured at 3 months or at 6 months. DBP was also not significantly different between the two groups at 3 months (Witteman et al., 1994). However, DBP was significantly lower ($P=0.003$) in the magnesium group compared to the control group at 6 months.

Widman et al., (1993) was a moderate quality randomized, double-blind, placebo controlled, cross-over study in which 16 Swedish subjects (mean age 50 years) consumed: 1.5 placebo tablets (control 1); 3 placebo tablets (control 2); 4 placebo tablets (control 3); 1.5 tablets providing 360 mg/day elemental magnesium;3 tablets providing 720 mg/day elemental magnesium; or 4 tablets providing 960 mg/day elemental magnesium, in addition to their usual diets for 3 weeks each period. The elemental magnesium was provided as magnesium hydroxide (Widman et al., 1993). There was no significant difference in SBP and DBP between the 360 mg/day and 760 mg/day magnesium periods when compared to their respective control periods (controls 1 and 2). However, SBP and DBP were significantly lower ($P=0.0051$ and $P=0075$ respectively) in the 960 mg/day magnesium period when compared to the control period 3.

Wirell et al., (1993) was a moderate quality randomized, double-blind, placebo controlled, cross-over study in which 36 Swedish subjects (mean age 46 years) treated with thiazides consumed a placebo or 121.6 mg three times a day elemental magnesium as magnesium aspartate hydrochloride (365 mg/day total) in addition to their usual diets for 8 weeks each period. There was no significant difference in supine (lying down) or standing SBP or DBP between the two treatment periods (Wirell et al., 1993). There was also no significant difference in MAP between the two treatment periods.

Ferrara et al., (1992)[37] was a moderate quality randomized, double-blind, placebo controlled, parallel study in which 14 Italian subjects consumed a placebo three times a day (n=7) (control) (mean age 47 years) or 120 mg/d magnesium as magnesium pidolate three times a day (360 mg/day total) (n=7) (mean age 48 years) in addition to their usual diet for 6 months. Supine (lying down) SBP was significantly lower ($P<0.01$) in the magnesium group compared to the control group (Ferrara et al., 1992). However, there was no significant difference in supine DBP between the two groups. Standing SBP and DBP were significantly lower in magnesium group compared to the control group.

Gullestad et al., (1992) was a moderate quality randomized, double-blind, placebo-controlled, parallel study in which 49 Norwegian subjects (mean age 57 years) with chronic alcoholism consumed a placebo (control) (n=25) or 120 mg three times a day (360 mg/day total) elemental magnesium as magnesium lactate citrate (n=24) in addition to their usual diet for 6 weeks. There was no significant difference in SBP or DBP between the control group and the magnesium group (Gullestad et al., 1992).

Paolisso et al., (1992) was a high-quality randomized, double-blind placebo controlled parallel study in which 18 Italian subjects (mean age 64 years) treated with hydrochlorothiazide consumed a placebo (control) (n=9) or 379 mg/day elemental magnesium as magnesium pidolate (n=9) in addition to a normal weight maintaining diet for 8 weeks. SBP was significantly lower ($P<0.04$) in the magnesium group compared to the control group (Paolisso et al., 1992). DBP was also significantly lower ($P<0.05$) in the magnesium group compared to the control group.

TOHP study group (1992)[38] (Trials of Hypertension Prevention) was a moderate quality randomized, double blind, placebo controlled parallel study in which 461 American subjects (mean age 43 years) consumed a placebo (control) (n=234) or 180 mg twice a day elemental magnesium as magnesium diglycine (360 mg/day total) (n=227) in addition to their usual diet for 6 months. There was no significant difference in SBP or DBP between the control group and the magnesium group. There was also no significant difference in incidence of hypertension between the control group and the magnesium group.

Lind et al., (1991) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 71 Swedish subjects consumed a placebo (n=22) (mean age 62 years) or 122 mg elemental magnesium as magnesium lactate or magnesium citrate three times a day (360 mg/day total) (n=49) (mean age 60 years) in addition to their usual diets for 6 months. There was no significant difference in SBP or DBP between the two groups when measured supine (lying down) or standing (Lind et al., 1991).

Daly et al., (1990) was a high-quality randomized, double-blind, placebo-controlled parallel study in which 38 American subjects consumed a placebo (n=19) (mean age 61 years) or 250 mg elemental magnesium twice a day as magnesium oxide (500 mg/day total) (n=19) (mean age 57

[37] SBP and DBP were also measured after a cold pressor test, tilt test, and handgrip test in this study. Since these tests do not represent real-world conditions, scientific conclusions about the relationship between magnesium consumption and blood pressure or risk of hypertension could not be drawn from them.

[38] The results of the Trials of Hypertension Prevention study (TOHP Study Group, 1992) were also discussed in Whelton et al., 1995;Whelton et al., 1997;Yamamoto et al., 1995.

years) in addition to their usual diet for 12 weeks. SBP was significantly lower (P=0.004) in the magnesium group compared to the control group (Daly et al., 1990). However, there were no significant differences in DBP and MAP between the two groups. The slopes of individual linear regression lines for decrease in SBP, DBP and MAP were significantly greater in the magnesium group (P=0.007, P=0.02, P=0.015).

Patki et al., (1990)[39] was a high-quality randomized, double-blind, placebo controlled cross-over study in which 37 Indian subjects (mean age 49.9 years) consumed 1,170 mg/day potassium twice a day (2,340 mg/day total) (control) or 240 mg/day elemental magnesium as magnesium chloride twice a day (480 mg/day total) plus 1,170 mg/day potassium twice a day (2,340 mg/day total) potassium in addition to their usual diets for 8-weeks each period. There was no significant difference in SBP or DBP between the potassium (control) group and potassium plus magnesium group (Patki et al., 1990).

Lumme and Jounela, (1989) was a moderate quality randomized, double-blind, placebo-controlled cross-over study in which 11 Finish subjects (32-68 years) treated with hydrochlorothiazide consumed 500 mg of potassium as potassium chloride twice a day (1 g/day total (control) or 205 mg elemental magnesium as magnesium hydroxide twice a day (410 mg/day total) plus 1 g/day potassium for 8 weeks each period in addition to their usual diet. There was no significant difference in SBP or DBP between the two periods (Lumme and Jounela, 1989).

Nowson and Morgan, (1989) was high quality randomized, double-blind, placebo controlled parallel study in which 25 Australian subjects (mean age 62.7 years) consumed a placebo (control) (n=13) or 240 mg/day elemental magnesium as magnesium aspartate (n=12) in addition to their usual moderately low sodium diet for 8 weeks. There was no significant difference in SBP or DBP between the control group and the magnesium group when measured erect or supine (Nowson and Morgan, 1989).

Olhaberry et al., (1987) was a high-quality randomized, double-blind placebo controlled, parallel study in which 14 Uruguayan women (mean age 46 years) consumed a placebo (control) (n=7) or 127.6 mg three times a day elemental magnesium as magnesium chloride (383 mg/day total) (n=7) in addition to a daily diet with 1,610 mg to 2,300 mg/day of sodium for four weeks. There was no significant difference in SBP or DBP between the control group and the magnesium group when measured erect or supine (Olhaberry et al., 1987).

Cappuccio et al., (1985) was a high-quality randomized, double-blind, placebo controlled, cross-over study in which 17 British subjects (51.7 years) consumed a placebo or 122 mg of elemental magnesium as magnesium aspartate hydrochloride three times a day (365 mg/day total) in addition to their usual diets for one month each period. There was no significant difference in SBP or DBP between the two groups when measured supine (lying down) or standing (Cappuccio et al., 1985).

[39] This study also had a placebo group. However, we could not draw conclusions from the comparison between the potassium and placebo because it did not evaluate the substance and disease relationship. Also, conclusions could not be drawn from the comparison between the placebo group and the magnesium and potassium group because the independent effects of magnesium could not be determined.

Studies in subjects with CVD

Kohvakka et al., (1989) was a moderate quality randomized, double-blind, controlled cross-over study in which 10 Finish subjects (mean age 64 years) with heart failure treated with hydrochlorothiazide consumed 527.5 mg potassium as potassium chloride twice a day (1, 055 mg/day total) or 206.5 mg elemental magnesium as magnesium hydroxide twice a day (413 mg/day total) plus 1,055 mg/day potassium in addition to their usual diets for 6 weeks each period. There was no significant difference in SBP or DBP between the two periods (Kohvakka et al., 1989).

C. Assessment of the Relevant Observational Studies

FDA reviewed 43 observational studies the evaluated the effect of magnesium intake on risk of hypertension or blood pressure. For reasons discussed below, conclusions could not be drawn from 43 of the observational studies.[40]

Ten[41] observational studies estimated magnesium intake from magnesium containing foods. In observational studies that calculate nutrient intake from conventional foods, measures of magnesium intake are based on recorded dietary intake methods such as food frequency questionnaires, diet recalls, or diet records, in which the type and amount of foods consumed are estimated. A common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied as a result of poor memory, over- or underestimation of portion sizes, and recall bias (Flegal, 1999). Furthermore, the nutrient content of foods can vary (e.g., due to soil composition, food processing and cooking procedures, or storage conditions such as duration or temperature). Thus, FDA cannot ascertain an accurate amount for magnesium consumed based on reports of dietary intake of foods (U.S. Food and Drug Administration, January 2009).

Ten[42] observational studies did not assess magnesium intake from single-nutrient supplement sources. These studies collected information on a combination of vitamin and mineral supplements plus dietary intake data. The agency will consider findings from observational studies that examined a supplement containing only magnesium. Such studies do not present the same degree of difficulty in ascertaining the nutrient intake as studies involving foods or multi-nutrient dietary supplements containing other substances that may have a possible role in reducing the risk of hypertension. Rather, observational studies assessing the role of single supplements of magnesium are more reliable than those involving foods or multi-nutrient dietary supplements because they are based on a specific nutrient supplement and can therefore provide a more accurate measure of magnesium intake. Thus, FDA cannot ascertain an accurate amount for magnesium consumed based on reports of dietary intake of a combination of foods containing magnesium and magnesium supplements.

---

[40] This section contains a general discussion of major flaws in the reports of observational studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.

[41] Bo et al., 2006;Choi and Bae, 2013;Hajjar et al., 2001;Ideno and Kubena, 1989;Kim and Choi, 2013;Kesteloot and Joossens, 1988;Witteman et al., 1989;Van Leer et al., 1995;Ferre et al., 2010;Beydoun et al., 2008

[42] Ascherio et al., 1992;Ford et al., 2007;Song et al., 2006;Song et al., 2005;Stamler et al., 2003;McGarvey et al., 1991;McKeown et al., 2008;He et al., 2006;Papanikolaou et al., 2014;Joffres et al., 1987

Sixteen[43] observational studies measured blood levels (serum or erythrocyte) as a biomarker of magnesium intake. Blood levels of magnesium are not reliable surrogate measures of dietary or supplemental magnesium intake. Blood magnesium levels are tightly controlled, do not correlate well with total body magnesium, and have not been validated as a reliable indicator of body magnesium status (Institute of Medicine (IOM), 1997, Workinger et al., 2018). Changes in blood levels can be altered by many factors other than dietary intake of magnesium such as the variability in the amount of magnesium excreted by the kidneys and albumin levels (Workinger et al., 2018). Since blood levels of magnesium are not a reliable surrogate measure of dietary or supplemental magnesium intake, scientific conclusions cannot be drawn from studies that used blood levels of magnesium as a biomarker of intake.

Five[44] observational studies measured urinary magnesium as a biomarker of magnesium intake. Urinary magnesium is not a reliable surrogate measure of dietary or supplemental intake. Urinary magnesium does not correlate well with magnesium intake due to the large amount of magnesium that is excreted in the kidney (Workinger et al., 2018). Since urinary magnesium levels are not a reliable surrogate measure of dietary or supplemental magnesium intake, scientific conclusions cannot be drawn from studies that used urine magnesium as a biomarker of intake.

One observational study (Panhwar et al., 2014) measured magnesium in scalp hair as a biomarker of magnesium intake. FDA could not identify any studies that correlated hair magnesium with intake and thus we were unable to determine if magnesium in scalp hair is a reliable surrogate measure of dietary or supplemental intake. Therefore, scientific conclusion cannot be drawn from studies that used hair magnesium as a biomarker of intake.

One ecological study (Yang and Chiu, 1999) used levels of magnesium in municipal drinking water as an indicator of magnesium exposure to evaluate the relationship between magnesium exposure and hypertension death. However, this observational study did not control for sodium and potassium intake, body weight, or smoking, all of which are known to affect blood pressure (National Academies of Sciences et al., 2019, U.S. Food and Drug Administration, January 2009). Therefore, no scientific conclusions about the association between magnesium intake and blood pressure or hypertension risk could be drawn from this study.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the number of studies and number of subjects per group, whether the body of scientific evidence supports a health claim relationship for the U.S. population or a target subgroup, whether study

[43] Huang et al., 2012;Rotter et al., 2015;Rodriguez-Ramirez et al., 2015;Rasic-Milutinovic et al., 2012;Peacock et al., 2010;Ma et al., 1995;Syedmoradi et al., 2011;Sudhakar et al., 1999;Liao et al., 1998;Lutsey et al., 2014;Khan et al., 2010;Johnson et al., 1987;Peacock et al., 1999;Guerrero-Romero and Rodriguez-Moran, 2013;Rooney et al., 2019

[44] Chidambaram et al., 2014;He et al., 1991;Kesteloot et al., 2011;Liu et al., 2001;Yamori et al., 1992

results supporting the proposed claim have been replicated,[45] and the overall consistency[46] of the total body of evidence.[47] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

As discussed in Section II, the totality of scientific evidence about a possible relationship between magnesium intake and risk of high blood pressure (hypertension) includes 40 publications reporting on 38 intervention studies from which scientific conclusions can be drawn. All 38 intervention studies provided elemental magnesium in the form of single-nutrient dietary supplements, and the agency did not identify any studies in conventional foods that evaluated the independent effects of magnesium on reduced risk of hypertension. FDA concludes it is appropriate to evaluate the strength of the scientific evidence for both conventional foods and dietary supplements that contain magnesium. Studies that provided magnesium as a dietary supplement were designed to evaluate the independent effects of magnesium on reduced risk of hypertension, and any potential independent effects demonstrated in single-nutrient dietary supplements with magnesium would be expected to occur in conventional foods containing magnesium. For this reason, FDA considered the effects demonstrated in studies with single-nutrient dietary supplements to support an independent role for magnesium (a food component) and reduced risk of high blood pressure (hypertension) in both conventional foods and dietary supplements that contain magnesium. Of these 38 intervention studies, nine of these studies were conducted in subjects with normal blood pressure or elevated blood pressure (SBP ≤ 129 mm Hg or DBP < 80 mm Hg), and 29 studies were conducted in subjects with hypertension (SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg). Of the 38 studies that looked at the relationship between blood pressure and intake of elemental magnesium from dietary supplements, only 18 showed a statistically significant benefit. The duration of these moderate to high quality studies showing a benefit ranged from 1 week to 6 months, and the dose of elemental magnesium ranged from 181 mg/day to 960 mg/day. The remaining 20 intervention studies that showed no benefit were also moderate to high quality studies. The duration of these studies ranged from 1 month to 6 months, with elemental magnesium intake ranging from 240 mg/day to 720 mg/day. One moderate quality study (the Trial of Hypertension Prevention) also measured incidence of hypertension in addition to blood pressure and did not find a significant benefit for magnesium intake (n=227) on risk of hypertension.

Based on the findings of these 38 intervention studies, FDA concludes there is some credible evidence suggesting a relationship between the intake of elemental magnesium from conventional foods and dietary supplements and reduced risk of high blood pressure (hypertension). However, this evidence is inconclusive because the results of the studies are inconsistent. The findings of the minority of intervention studies that found a statistically significant lowering of blood pressure from intake of elemental magnesium are undermined by the larger body of evidence that found no effect on blood pressure. Study results were

[45] See *supra*, note 12.
[46] See *supra*, note 13.
[47] See *supra*, note 4.

inconsistent in both subjects with normal or elevated SBP or DBP or in studies conducted in subjects with hypertension. Results were also inconsistent in studies conducted in subjects with preexisting CVD (including coronary artery disease and other forms of coronary heart disease). In addition, results were inconsistent across the whole range of magnesium intakes and forms of magnesium studied (181 mg/day to 960 g/day), age of study participants (mean ages 20 to 71 years, study durations (2 weeks to 6 months) and sample sizes (7 to 227 subjects consuming magnesium)). Consistency of the findings among similar and different study designs is important for evaluating causation and the strength of the evidence. Lack of consistency among studies evaluating the same substance-disease relationship weakens the strength of the evidence. Therefore, FDA concludes that while there is some credible evidence suggesting that combined intake of elemental magnesium from conventional foods and dietary supplements may reduce the risk of hypertension by lowering blood pressure, this evidence is inconclusive and inconsistent.

IV. General Requirements for Health Claims and Enforcement Discretion Factors

A qualified health claim about reducing the risk of high blood pressure (hypertension) on the label or in the labeling of conventional foods and dietary supplements containing magnesium is required to meet all applicable statutory and regulatory requirements under the Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. In addition, enforcement discretion factors specific to qualified health claims describing how consuming magnesium may reduce the risk of high blood pressure (hypertension) are discussed below.

A. Qualifying Level of Magnesium to Achieve the Claimed Effect

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for "high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (21 CFR 101.14(d)(2)(vii)). FDA has defined "high" in 21 CFR 101.54(b), which provides that a food is "high" in a nutrient if it contains 20 percent or more of the DV for the nutrient. Thus, based on the current DV for magnesium in 21 CFR 101.9(c)(8)(iv), which is 420 mg, conventional foods or dietary supplements that provide 84 mg or more magnesium per day would meet the are "high" definition. Therefore, for a conventional food or dietary supplement to be eligible to bear the claim, it must contain at least 84 mg of magnesium per Reference Amount Customarily Consumed (RACC).

B. Level of Magnesium Intake From Dietary Supplements When Used as Labeled

For a substance to be eligible for a health claim, its use at the levels necessary to justify a claim must be demonstrated to be safe and lawful (21 CFR 101.14(b)(3)(ii)). In Section I.C of this letter ("Safety Review"), we discussed that magnesium can cause adverse effects when ingested from sources other than conventional foods and that a Tolerable Upper Level Intake for magnesium was determined to be 350 mg per day for supplemental magnesium. As noted in the Safety Review, we concluded that the use of magnesium in dietary supplements, at levels necessary to justify the qualified health claims described in section IV.A (i.e., at levels that are

"high" as defined in 21 CFR 101.54(b)), but no greater than 350 mg/day (the UL) from dietary supplements is safe and lawful under 21 CFR 101.14(b)(3)(ii). Thus, we intend to consider, as a factor in the exercise of our enforcement discretion, that dietary supplements bearing the claim do not provide more than 350 mg magnesium combined when used according to their labeling.

C. Low Sodium Enforcement Discretion Factor for High Blood Pressure (Hypertension)-related Health Claims

Given the scientific evidence that diets high in sodium are associated with a high prevalence of hypertension or high blood pressure,[48] FDA has required that foods meet the "low sodium" criterion defined by 21 CFR 101.64(b)(4) in authorized health claims regarding high blood pressure (see authorized health claim in 21 CFR 101.74(c)(2)(ii)). Sodium attracts water, and a high-sodium diet draws water into the bloodstream, which can increase the volume of blood and subsequently your blood pressure. High blood pressure or hypertension is a condition that makes the heart work too hard, and the high force of the blood flow can harm arteries and organs (such as the heart, kidneys, brain, and eyes). Uncontrolled high blood pressure can raise the risk of heart attack, heart failure, stroke, kidney disease, and blindness, and diets higher in sodium can increase these risks. In addition, scientific evidence shows that reducing sodium intake reduces that risk, as well as the risk of developing CVD (National Academies of Sciences et al., 2019), and the *2020 Dietary Guidelines for Americans* also notes that healthy eating patterns should limit intake of sodium (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2020-2025).

"Low Sodium", as defined by 101.61(b)(4), means a food contains less than 140 mg of sodium per RACC. If the food has a RACC of 30 g or 2 tablespoons or less, the food must contain less than 140 mg of sodium per 50 g. We note that nuts, a food that can be high in magnesium content, have a RACC of 30 g, and therefore to meet the "low sodium" criterion in 21 CFR 101.61(b)(4), would need to contain less than 140 mg of sodium per 50 g. In addition, we note that foods that the petitioner identified as high in magnesium (i.e., leafy greens like spinach and chard) would likely meet the "low sodium" criterion. Therefore, FDA intends to consider, as part of the agency's exercise of enforcement discretion, that conventional foods must meet the "low sodium" criterion to be eligible to bear the magnesium and high blood pressure (hypertension) qualified health claim.

D. Disqualifying Nutrient Levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)), a food may not bear a health claim if that food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in § 101.14(a)(4), unless FDA establishes an alternative level. Section 101.14(e)(3) applies to all health claims regardless of types of diseases and health-related conditions. The disqualifying nutrient levels vary for individual foods, meal products,

[48] The Nutrition Labeling Act of 1990 required the agency to issue regulations to implement section 403(r) of the Act (21 U.S.C. 343(r)), and as part of that rulemaking process, determine, among other things, whether claims respecting 10 topic areas (including sodium and hypertension) met the requirements of section 403(r)(3) of the Act (21 U.S.C. 343(r)(3)). As part of this mandate, FDA conducted a comprehensive review of the scientific data regarding the relationship between sodium and high blood pressure and concluded there was significant scientific agreement among qualified experts that diets low in sodium may help lower blood pressure in many people (56 FR 60825 (Nov. 27, 1991); 58 FR 2820 (Jan. 6, 1993)).

and main dishes. Disqualifying total fat levels for individual foods are 13.0 g per RACC per label serving size, and for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying saturated fat levels for individual foods are 4.0 g per RACC per label serving size, and for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying cholesterol levels for individual foods are 60 mg per RACC per label serving size, and for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g. Disqualifying sodium levels for individual foods are above 480 mg per RACC per label serving size, and for foods with a RACC of 30 g or less or 2 tablespoons or less, per 50 g.

The general requirements for health claims also provide for FDA to authorize a health claim for a food despite the fact that a nutrient in the food exceeds the disqualifying level, if FDA finds that such a claim will assist consumers in maintaining healthy dietary practices (21 CFR 101.14(e)(3)). In such cases, a disclosure statement that complies with 21 CFR 101.13(h), highlighting the nutrient that exceeds the disqualifying level, would apply.

With the exception of tree nuts, FDA intends to consider, as a factor in the exercise of its enforcement that conventional foods labeled with a magnesium and high blood pressure (hypertension) qualified health claim meet the disqualifying levels for "total fat", "saturated fat", "cholesterol", or "sodium" level as described in 21 CFR 101.14(a). As discussed below, we intend to provide enforcement discretion from the disqualifying nutrient level for "total fat" for tree nuts since FDA believes that an appropriately worded qualified health claim about consumption of magnesium from tree nuts could assist consumers in maintaining healthy dietary practices.

"Total fat" Disqualifying Level for Tree Nuts

The petitioner specifically requested that FDA not apply the total fat disqualifying level for tree nuts. The petition noted that tree nuts, such as almonds and cashews, that contain approximately 20 percent of the DV for magnesium per one ounce serving, would exceed the total fat disqualifying nutrient level as defined in 21 CFR 101.14(a)(4). FDA believes that an appropriately worded qualified health claim about consumption of magnesium from tree nuts could assist consumers in maintaining healthy dietary practices, given that nuts in general are nutrient dense foods that can serve as protein sources and contribute to a healthy U.S.-style eating pattern, as well as the Healthy Vegetarian Dietary Pattern. The *Dietary Guidelines for Americans, 2020-2025* note that unsalted nuts are a nutrient-dense food. Nuts are included in the protein group, which is one of the core elements that make up a healthy dietary pattern (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2020-2025). FDA has previously exercised enforcement discretion for foods that did not meet the total fat disqualifying level where qualified health claims could assist consumers in maintaining healthy dietary practices, particularly in instances of consumption of tree nuts as part of a healthy dietary pattern. For example, in 2003, FDA issued a letter of enforcement discretion for a qualified health claim about the consumption of peanuts and certain tree nuts and reduced risk of heart disease (FDA-2002-P-0131). As part of FDA's exercise of enforcement discretion for this

qualified claim, FDA explained that although the nuts cited in the petition (including almonds, hazelnuts, pecans, pistachio nuts, and walnuts) exceeded the total fat disqualifying levels for health claims in 21 CFR 101.14(a)(4), the agency believed that an appropriately qualified claim about consumption of most nuts would assist consumers in maintaining healthy dietary practices, provided that the label bears a disclosure statement that complies with 21 CFR 101.13(h) (i.e., "See nutrition information for fat content.").

In 2004, FDA issued a letter of enforcement discretion for a qualified health claim for the consumption of walnuts and reduced risk of CHD, even though walnuts exceeded the total fat disqualifying level in 21 CFR 101.14(a)(4) (FDA-2002-P-0128). The fat content of walnuts (32.6 g total fat/50 g) exceeds the health claim disqualifying level (FoodData Central). In this enforcement discretion letter, FDA explained that walnuts have a good ratio of unsaturated fat and may contain other potentially beneficial substances such as dietary fiber and phytosterols. In 2017, FDA issued a letter for enforcement discretion for a qualified health claim on macadamia nuts and CHD (FDA-2015-Q-4850) even though macadamia nuts exceed the total fat disqualifying level.

According to the FoodData Central, the total fat content of raw macadamia nuts is 37.9 g total fat/50 g, which exceeds the health claim disqualifying level. FDA noted in the 2017 enforcement discretion letter that because macadamia nuts have a favorable ratio of unsaturated fat to saturated fat (5:1) and contain other potentially beneficial substances such as dietary fiber and phytosterols, a qualified health claim about macadamia nuts and reduced risk of CHD might assist consumers in maintaining healthy dietary practices.

Therefore, given that tree nuts are a nutrient dense food that can contribute to a healthy dietary pattern, and consistent with our exercise of enforcement discretion for other qualified health claims regarding consumption of tree nuts, FDA intends to exercise enforcement discretion for tree nuts that bear the qualified health claim and exceed the disqualifying levels for total fat set forth in 21 CFR 101.14(a)(4), provided that the label bears the disclosure statement, "See nutrition information for total fat content" that complies with 21 CFR 101.13(h).

We expect, with the exception of tree nuts, that any foods that bear the qualified health claim would not exceed the total fat disqualifying level as described in 21 CFR 101.14(a)(4).

E. 10 Percent Minimum Nutrient Content Requirement

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the DV of certain nutrients per RACC (21 CFR 101.14(e)(6)). The purpose of this requirement is to prevent the use of health claims on foods with minimal nutritional value. The specific nutrients listed in 21 CFR 101.14(e)(6) are vitamin A, vitamin C, iron, calcium, protein, and fiber.[49]

[49] We note that the final rule entitled "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" (81 Fed. Reg. 33742; May 27, 2016) changed the mandatory declaration of vitamins and minerals as a percent of the RDI in 21 CFR 101.9(c)(8) from vitamin A, vitamin C, calcium, and iron to vitamin D, calcium, iron, and potassium. Therefore, vitamin D and potassium are now nutrients of public health significance. We plan to address, as appropriate and as time and resources permit, the impact of the changes in nutrient declarations in the final rule to other regulations, such as 21 CFR 101.14(e)(6), in separate rulemaking actions (see 81 Fed. Reg. 33742 at 33751).

Conventional Foods.
The 10 percent minimum content requirement applies to conventional foods that bear a magnesium and high blood pressure (hypertension) qualified health claim. For the purpose of this qualified health claim, the agency intends to exercise its enforcement discretion with respect to 21 CFR 101.14(e)(6) for the qualified health claim to be used on conventional food labels where the food contains 10 percent or more of the DV per RACC for the nutrients listed in 21 CFR 101.14(e)(6). FDA will also exercise its enforcement discretion if the food contains 10 percent of the DV per RACC for vitamin D or potassium.

Dietary Supplements.
The 10 percent minimum nutrient content requirement does not apply to dietary supplements (21 CFR 101.14(e)(6)).

V. Conclusions

Based on FDA's consideration of the scientific evidence and other information submitted with your petition, and other pertinent scientific evidence and information, FDA concludes that the current scientific evidence is appropriate for consideration of qualified health claims for consumption of magnesium and reduced risk of high blood pressure (hypertension), provided that the qualified health claims are appropriately worded to avoid misleading consumers.

The petition proposed the following model claim to be used on the labels or in the labeling of conventional foods and dietary supplements "high" in magnesium:

> "Supportive but inconclusive scientific evidence suggests that diets with adequate magnesium may reduce the risk of high blood pressure (hypertension), a condition associated with many factors."

The proposed claim includes qualifying language disclosing that "supportive but inconclusive" scientific evidence supports the claim. However, describing the level of evidence for the claim as "supportive" overstates and therefore mischaracterizes the strength of the evidence for a relationship between magnesium consumption and reduced risk of high blood pressure (hypertension). As discussed in section III of this letter, the evidence suggesting that intake of magnesium from conventional foods and dietary supplements may reduce the risk of high blood pressure (hypertension) is inconclusive and inconsistent.

Therefore, FDA has determined that further qualifying language should be included to convey the limits on the strength of the scientific evidence supporting the relationship and such qualifying language is necessary to prevent the claims from misleading consumers. Since FDA determined the strength of the scientific evidence supporting the claimed relationship is inconclusive and inconsistent, this qualifying language is being added to inform consumers about the level of science supporting the claim and prevent them from being misled about the strength of the supporting evidence.

Thus, FDA intends to consider exercising enforcement discretion for the following qualified health claims for conventional foods and dietary supplements:

> "Inconsistent and inconclusive scientific evidence suggests that diets with adequate magnesium may reduce the risk of high blood pressure (hypertension), a condition associated with many factors."
> "Consuming diets with adequate magnesium may reduce the risk of high blood pressure (hypertension). However, FDA has concluded that the evidence is inconsistent and inconclusive."
> "Some scientific evidence suggests that diets with adequate magnesium may reduce the risk of high blood pressure (hypertension), a condition associated with many factors. FDA has concluded that the scientific evidence supporting this claim is inconsistent and not conclusive."

FDA intends to consider exercising enforcement discretion for the above qualified health claims for when all other factors for enforcement discretion identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will support a qualified health claim for those claims that were denied, that will no longer support the use of the above qualified health claim, or that may raise safety concerns about the substances that are the subject of the claims.

Sincerely yours,

Claudine J. Kavanaugh -S

Digitally signed by Claudine J. Kavanaugh -S
Date: 2022.01.08 13:53:16 -05'00'

Claudine Kavanaugh, PhD, MPH, RD
Director
Office of Nutrition
and Food Labeling
Center for Food Safety
and Applied Nutrition

References

Agency for Healthcare Research and Quality, “Systems to rate the scientific evidence” (March 2002) [http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf] (accessed December 9, 2021).

Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663-694.

Altman, D., G. Carroli, L. Duley, B. Farrell, J. Moodley, J. Neilson, D. Smith and G. Magpie Trial Collaboration (2002). "Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial." Lancet **359**(9321): 1877-1890.

Ascherio, A., E. B. Rimm, E. L. Giovannucci, G. A. Colditz, B. Rosner, W. C. Willett, F. Sacks and M. J. Stampfer (1992). "A prospective study of nutritional factors and hypertension among US men." Circulation **86**(5): 1475-1484.

Baker, W. L., J. Kluger, C. M. White, K. M. Dale, B. B. Silver and C. I. Coleman (2009). "Effect of magnesium L-lactate on blood pressure in patients with an implantable cardioverter defibrillator." Ann Pharmacother **43**(4): 569-576.

Banjanin, N. and G. Belojevic (2018). "Changes of Blood Pressure and Hemodynamic Parameters after Oral Magnesium Supplementation in Patients with Essential Hypertension-An Intervention Study." Nutrients **10**(5).

Barbagallo, M., L. J. Dominguez, A. Galioto, A. Pineo and M. Belvedere (2010). "Oral magnesium supplementation improves vascular function in elderly diabetic patients." Magnes Res **23**(3): 131-137.

Barragan-Rodriguez, L., M. Rodriguez-Moran and F. Guerrero-Romero (2008). "Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial." Magnes Res **21**(4): 218-223.

Bashir, Y., J. F. Sneddon, H. A. Staunton, G. A. Haywood, I. A. Simpson, W. J. McKenna and A. J. Camm (1993). "Effects of long-term oral magnesium chloride replacement in congestive heart failure secondary to coronary artery disease." Am J Cardiol **72**(15): 1156-1162.

Beydoun, M. A., T. L. Gary, B. H. Caballero, R. S. Lawrence, L. J. Cheskin and Y. Wang (2008). "Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome." Am J Clin Nutr **87**(6): 1914-1925.

Bo, S., M. Durazzo, S. Guidi, M. Carello, C. Sacerdote, B. Silli, R. Rosato, M. Cassader, L. Gentile and G. Pagano (2006). "Dietary magnesium and fiber intakes and inflammatory and

metabolic indicators in middle-aged subjects from a population-based cohort." Am J Clin Nutr **84**(5): 1062-1069.

Borrello, G., P. Mastroroberto, F. Curcio, M. Chello, S. Zofrea and M. L. Mazza (1996). "The effects of magnesium oxide on mild essential hypertension and quality of life." Curr Therapeutic Res **57**(10): 767-774.

Bullarbo, M., H. Mattson, A. K. Broman, N. Odman and T. F. Nielsen (2018). "Magnesium Supplementation and Blood Pressure in Pregnancy: A Double-Blind Randomized Multicenter Study." J Pregnancy **2018**: 4843159.

Bullarbo, M., N. Odman, A. Nestler, T. Nielsen, M. Kolisek, J. Vormann and R. Rylander (2013). "Magnesium supplementation to prevent high blood pressure in pregnancy: a randomised placebo control trial." Arch Gynecol Obstet **288**(6): 1269-1274.

Cappuccio, F. P., N. D. Markandu, G. W. Beynon, A. C. Shore, B. Sampson and G. A. MacGregor (1985). "Lack of effect of oral magnesium on high blood pressure: a double blind study." Br Med J (Clin Res Ed) **291**(6490): 235-238.

Chidambaram, N., S. Sethupathy, N. Saravanan, M. Mori, Y. Yamori, A. K. Garg and A. Chockalingam (2014). "Relationship of sodium and magnesium intakes to hypertension proven by 24-hour urianalysis in a South Indian population." J Clin Hypertens (Greenwich) **16**(8): 581-586.

Choi, M. K. and Y. J. Bae (2013). "Relationship between dietary magnesium, manganese, and copper and metabolic syndrome risk in Korean adults: the Korea National Health and Nutrition Examination Survey (2007-2008)." Biol Trace Elem Res **156**(1-3): 56-66.

Cohen, L., A. Laor and R. Kitzes (1984). "Reversible retinal vasospasm in magnesium-treated hypertension despite no significant change in blood pressure." Magnesium **3**(3): 159-163.

Cosaro, E., S. Bonafini, M. Montagnana, E. Danese, M. S. Trettene, P. Minuz, P. Delva and C. Fava (2014). "Effects of magnesium supplements on blood pressure, endothelial function and metabolic parameters in healthy young men with a family history of metabolic syndrome." Nutr Metab Cardiovasc Dis **24**(11): 1213-1220.

Cunha, A. R., J. D'El-Rei, F. Medeiros, B. Umbelino, W. Oigman, R. M. Touyz and M. F. Neves (2017). "Oral magnesium supplementation improves endothelial function and attenuates subclinical atherosclerosis in thiazide-treated hypertensive women." J Hypertens **35**(1): 89-97.

Daly, N. M., K. G. D. Allen and M. Harris (1990). "Magnesium supplementation and blood pressure in borderline hypertensive subjects: A double blind study." Magnesium Bulletin **12**(4): 149-154.

de Araujo, C. A. L., J. G. Ray, J. N. Figueiroa and J. G. Alves (2020). "BRAzil magnesium (BRAMAG) trial: a double-masked randomized clinical trial of oral magnesium supplementation in pregnancy." BMC Pregnancy Childbirth **20**(1): 234.

Desai M, Stockbridge N, Temple R. Blood pressure as an example of a biomarker that functions as a surrogate. AAPS J 2006;8(1):E146-152.

de Valk, H. W., R. Verkaaik, H. J. van Rijn, R. A. Geerdink and A. Struyvenberg (1998). "Oral magnesium supplementation in insulin-requiring Type 2 diabetic patients." Diabet Med **15**(6): 503-507.

Doyle, L., A. Flynn and K. Cashman (1999). "The effect of magnesium supplementation on biochemical markers of bone metabolism or blood pressure in healthy young adult females." Eur J Clin Nutr **53**(4): 255-261.

Dyckner, T. and P. O. Wester (1983). "Effect of magnesium on blood pressure." Br Med J (Clin Res Ed) **286**(6381): 1847-1849.

Eriksson, J. and A. Kohvakka (1995). "Magnesium and ascorbic acid supplementation in diabetes mellitus." Ann Nutr Metab **39**(4): 217-223.

Farvid, M. S., M. Jalali, F. Siassi, N. Saadat and M. Hosseini (2004). "The impact of vitamins and/or mineral supplementation on blood pressure in type 2 diabetes." J Am Coll Nutr **23**(3): 272-279.

Ferrara, L. A., R. Iannuzzi, A. Castaldo, A. Iannuzzi, A. Dello Russo and M. Mancini (1992). "Long-term magnesium supplementation in essential hypertension." Cardiology **81**(1): 25-33.

Ferre, S., E. Baldoli, M. Leidi and J. A. Maier (2010). "Magnesium deficiency promotes a pro-atherogenic phenotype in cultured human endothelial cells via activation of NFkB." Biochim Biophys Acta **1802**(11): 952-958.

Flegal, K. M. (1999). "Evaluating epidemiologic evidence of the effects of food and nutrient exposures." Am J Clin Nutr **69**(6): 1339S-1344S.

Ford, E. S., C. Li, L. C. McGuire, A. H. Mokdad and S. Liu (2007). "Intake of dietary magnesium and the prevalence of the metabolic syndrome among U.S. adults." Obesity (Silver Spring) **15**(5): 1139-1146.

Geleijnse, J. M., J. C. Witteman, A. A. Bak, J. H. den Breeijen and D. E. Grobbee (1994). "Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension." BMJ **309**(6952): 436-440.

Guerrero-Romero, F. and M. Rodriguez-Moran (2009). "The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, placebo-controlled clinical trial." J Hum Hypertens **23**(4): 245-251.

Guerrero-Romero, F. and M. Rodriguez-Moran (2011). "Magnesium improves the beta-cell function to compensate variation of insulin sensitivity: double-blind, randomized clinical trial." Eur J Clin Invest **41**(4): 405-410.

Guerrero-Romero, F. and M. Rodriguez-Moran (2013). "Serum magnesium in the metabolically-obese normal-weight and healthy-obese subjects." Eur J Intern Med **24**(7): 639-643.

Guerrero-Romero, F., H. E. Tamez-Perez, G. Gonzalez-Gonzalez, A. M. Salinas-Martinez, J. Montes-Villarreal, J. H. Trevino-Ortiz and M. Rodriguez-Moran (2004). "Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial." Diabetes Metab **30**(3): 253-258.

Gullestad, L., L. O. Dolva, E. Soyland, A. T. Manger, D. Falch and J. Kjekshus (1992). "Oral magnesium supplementation improves metabolic variables and muscle strength in alcoholics." Alcohol Clin Exp Res **16**(5): 986-990.

Haga, H. (1992). "Effects of dietary magnesium supplementation on diurnal variations of blood pressure and plasma Na+, K(+)-ATPase activity in essential hypertension." Jpn Heart J **33**(6): 785-800.

Hajjar, I. M., C. E. Grim, V. George and T. A. Kotchen (2001). "Impact of diet on blood pressure and age-related changes in blood pressure in the US population: analysis of NHANES III." Arch Intern Med **161**(4): 589-593.

Hattori, K., K. Saito, H. Sano and H. Fukuzaki (1988). "Intracellular magnesium deficiency and effect of oral magnesium on blood pressure and red cell sodium transport in diuretic-treated hypertensive patients." Jpn Circ J **52**(11): 1249-1256.

Hatzistavri, L. S., P. A. Sarafidis, P. I. Georgianos, I. M. Tziolas, C. P. Aroditis, P. E. Zebekakis, M. I. Pikilidou and A. N. Lasaridis (2009). "Oral magnesium supplementation reduces ambulatory blood pressure in patients with mild hypertension." Am J Hypertens **22**(10): 1070-1075.

He, J., G. S. Tell, Y. C. Tang, P. S. Mo and G. Q. He (1991). "Relation of electrolytes to blood pressure in men. The Yi people study." Hypertension **17**(3): 378-385.

He, K., K. Liu, M. L. Daviglus, S. J. Morris, C. M. Loria, L. Van Horn, D. R. Jacobs, Jr. and P. J. Savage (2006). "Magnesium intake and incidence of metabolic syndrome among young adults." Circulation **113**(13): 1675-1682.

Henderson, D. G., J. Schierup and T. Schodt (1986). "Effect of magnesium supplementation on blood pressure and electrolyte concentrations in hypertensive patients receiving long term diuretic treatment." Br Med J (Clin Res Ed) **293**(6548): 664-665.

Hill A.B., The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300

Huang, J. H., Y. F. Lu, F. C. Cheng, J. N. Lee and L. C. Tsai (2012). "Correlation of magnesium intake with metabolic parameters, depression and physical activity in elderly type 2 diabetes patients: a cross-sectional study." Nutr J **11**: 41.

Ideno, K. T. and K. S. Kubena (1989). "Nutrition, physical activity, and blood pressure in the elderly." J Nutr Elder **9**(2): 3-15.

Institute of Medicine (2005). Dietary Supplements: A Framework for Evaluating Safety, Chapter 7, Categories of Scientific Evidence – In Vitro Data. . Washington, D.C., The National Academies Press.

Institute of Medicine (IOM) (1997). Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride, Chapter 6: Magnesium. Washington DC;.

Itoh, K., T. Kawasaka and M. Nakamura (1997). "The effects of high oral magnesium supplementation on blood pressure, serum lipids and related variables in apparently healthy Japanese subjects." Br J Nutr **78**(5): 737-750.

Joffres, M. R., D. M. Reed and K. Yano (1987). "Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu heart study." Am J Clin Nutr **45**(2): 469-475.

Johnson, M. A., S. P. Dooley, W. O. Caster and C. G. Hames (1987). "The relationship between dietary calcium adn blood pressure in the elderly." J Clin Exp Gerontol **9**(2): 89-102.

Joris, P. J., J. Plat, S. J. Bakker and R. P. Mensink (2016). "Long-term magnesium supplementation improves arterial stiffness in overweight and obese adults: results of a randomized, double-blind, placebo-controlled intervention trial." Am J Clin Nutr **103**(5): 1260-1266.

Kass, L. S. and F. Poeira (2015). "The effect of acute vs chronic magnesium supplementation on exercise and recovery on resistance exercise, blood pressure and total peripheral resistance on normotensive adults." J Int Soc Sports Nutr **12**: 19.

Kass, L. S., P. Skinner and F. Poeira (2013). "A pilot study on the effects of magnesium supplementation with high and low habitual dietary magnesium intake on resting and recovery from aerobic and resistance exercise and systolic blood pressure." J Sports Sci Med **12**(1): 144-150.

Katz, A., T. Rosenthal, C. Maoz, E. Peleg, R. Zeidenstein and Y. Levi (1999). "Effect of a mineral salt diet on 24-h blood pressure monitoring in elderly hypertensive patients." J Hum Hypertens **13**(11): 777-780.

Kawano, Y., H. Matsuoka, S. Takishita and T. Omae (1998). "Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures." Hypertension **32**(2): 260-265.

Kesteloot, H. and J. V. Joossens (1988). "Relationship of dietary sodium, potassium, calcium, and magnesium with blood pressure. Belgian Interuniversity Research on Nutrition and Health." Hypertension **12**(6): 594-599.

Kesteloot, H., I. Tzoulaki, I. J. Brown, Q. Chan, A. Wijeyesekera, H. Ueshima, L. Zhao, A. R. Dyer, R. J. Unwin, J. Stamler and P. Elliott (2011). "Relation of urinary calcium and magnesium excretion to blood pressure: The International Study Of Macro- And Micro-nutrients And Blood Pressure and The International Cooperative Study On Salt, Other Factors, And Blood Pressure." Am J Epidemiol **174**(1): 44-51.

Khan, A. M., L. Sullivan, E. McCabe, D. Levy, R. S. Vasan and T. J. Wang (2010). "Lack of association between serum magnesium and the risks of hypertension and cardiovascular disease." Am Heart J **160**(4): 715-720.

Kim, H. N., S. H. Kim, Y. M. Eun and S. W. Song (2018). "Effects of zinc, magnesium, and chromium supplementation on cardiometabolic risk in adults with metabolic syndrome: A double-blind, placebo-controlled randomised trial." J Trace Elem Med Biol **48**: 166-171.

Kim, J. E., C. S. Shin, Y. C. Lee, H. S. Lee, M. Ban and S. Y. Kim (2015). "Beneficial effect of intravenous magnesium during endoscopic submucosal dissection for gastric neoplasm." Surg Endosc **29**(12): 3795-3802.

Kim, M. H. and M. K. Choi (2013). "Seven dietary minerals (Ca, P, Mg, Fe, Zn, Cu, and Mn) and their relationship with blood pressure and blood lipids in healthy adults with self-selected diet." Biol Trace Elem Res **153**(1-3): 69-75.

Kisters, K., C. Spieker, M. Tepel and W. Zidek (1993). "New data about the effects of oral physiological magnesium supplementation on several cardiovascular risk factors (lipids and blood pressure)." Magnes Res **6**(4): 355-360.

Kohvakka, A., O. Luurila, A. Gordin and S. Sundberg (1989). "Comparison of potassium alone and potassium-magnesium supplementation in patients with heart failure using hydrochlorothiazide." Magnesium **8**(2): 71-76.

Kosucu, M., E. Tugcugil, E. Arslan, S. Omur and M. Livaoglu (2020). "Effects of perioperative magnesium sulfate with controlled hypotension on intraoperative bleeding and postoperative ecchymosis and edema in open rhinoplasty." Am J Otolaryngol **41**(6): 102722.

Lee, S., H. K. Park, S. P. Son, C. W. Lee, I. J. Kim and H. J. Kim (2009). "Effects of oral magnesium supplementation on insulin sensitivity and blood pressure in normo-magnesemic nondiabetic overweight Korean adults." Nutr Metab Cardiovasc Dis **19**(11): 781-788.

Liao, F., A. R. Folsom and F. L. Brancati (1998). "Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study." Am Heart J **136**(3): 480-490.

Lind, L., H. Lithell, T. Pollare and S. Ljunghall (1991). "Blood pressure response during long-term treatment with magnesium is dependent on magnesium status. A double-blind, placebo-controlled study in essential hypertension and in subjects with high-normal blood pressure." Am J Hypertens **4**(8): 674-679.

Liu, L., L. Liu, Y. Ding, Z. Huang, B. He, S. Sun, G. Zhao, H. Zhang, T. Miki, S. Mizushima, K. Ikeda, Y. Nara and Y. Yamori (2001). "Ethnic and environmental differences in various markers of dietary intake and blood pressure among Chinese Han and three other minority peoples of China: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study." Hypertens Res **24**(3): 315-322.

Lumme, J. A. and A. J. Jounela (1989). "The effect of potassium and potassium plus magnesium supplementation on ventricular extrasystoles in mild hypertensives treated with hydrochlorothiazide." Int J Cardiol **25**(1): 93-97.

Lutsey, P. L., A. Alonso, E. D. Michos, L. R. Loehr, B. C. Astor, J. Coresh and A. R. Folsom (2014). "Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study." Am J Clin Nutr **100**(3): 756-764.

Lutsey, P. L., L. Y. Chen, A. Eaton, M. Jaeb, K. D. Rudser, J. D. Neaton and A. Alonso (2018). "A Pilot Randomized Trial of Oral Magnesium Supplementation on Supraventricular Arrhythmias." Nutrients **10**(7).

Ma, J., A. R. Folsom, S. L. Melnick, J. H. Eckfeldt, A. R. Sharrett, A. A. Nabulsi, R. G. Hutchinson and P. A. Metcalf (1995). "Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study." J Clin Epidemiol **48**(7): 927-940.

McGarvey, S. T., S. H. Zinner, W. C. Willett and B. Rosner (1991). "Maternal prenatal dietary potassium, calcium, magnesium, and infant blood pressure." Hypertension **17**(2): 218-224.

McKeown, N. M., P. F. Jacques, X. L. Zhang, W. Juan and N. R. Sahyoun (2008). "Dietary magnesium intake is related to metabolic syndrome in older Americans." Eur J Nutr **47**(4): 210-216.

Mooren, F. C., K. Kruger, K. Volker, S. W. Golf, M. Wadepuhl and A. Kraus (2011). "Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects - a double-blind, placebo-controlled, randomized trial." Diabetes Obes Metab **13**(3): 281-284.

Mortazavi, M., F. Moeinzadeh, M. Saadatnia, S. Shahidi, J. C. McGee and A. Minagar (2013). "Effect of magnesium supplementation on carotid intima-media thickness and flow-mediated dilatation among hemodialysis patients: a double-blind, randomized, placebo-controlled trial." Eur Neurol **69**(5): 309-316.

Motoyama, T., H. Sano and H. Fukuzaki (1989). "Oral magnesium supplementation in patients with essential hypertension." Hypertension **13**(3): 227-232.

National Academies of Sciences, Engineering and and Medicine (2019). Dietary Reference Intakes for Sodium and Potassium. Washington, DC:.

National Research Council (2011). Reference Manual on Scientific Evidence: Third Edition. Washington, DC**:** 220.

FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Validated Surrogate Endpoint. 2017 Sep. [https://www.ncbi.nlm.nih.gov/books/NBK453484/] (accessed June 30, 2021).

Nowson, C. A. and T. O. Morgan (1989). "Magnesium supplementation in mild hypertensive patients on a moderately low sodium diet." Clin Exp Pharmacol Physiol **16**(4): 299-302.

Olhaberry, J., A. J. Reyes, T. N. Acosta-Barrios, W. P. Leary and G. Queiruga (1987). "Pilot evaluation of the putative antihypertensive effect of magnesium." Magnesium Bulletin **9**: 181-184.

Panhwar, A. H., T. G. Kazi, H. I. Afridi, F. N. Talpur, S. Arain and N. Kazi (2014). "Distribution of potassium, calcium, magnesium, and sodium levels in biological samples of Pakistani hypertensive patients and control subjects." Clin Lab **60**(3): 463-474.

Paolisso, G., G. Di Maro, D. Cozzolino, T. Salvatore, A. D'Amore, D. Lama, M. Varricchio and F. D'Onofrio (1992). "Chronic magnesium administration enhances oxidative glucose metabolism in thiazide treated hypertensive patients." Am J Hypertens **5**(10): 681-686.

Papanikolaou, Y., J. brooks and V. L. Fulgoni (2014). "Dietary magnesium usual intake is associated with favorable diabetes-related physiological outcomes and reduced risk of metabolic syndrome: An NHANES 2001-2010 analysis." J Human Nutr & Food Science **2**(4): 1038-1046.

Patki, P. S., J. Singh, S. V. Gokhale, P. M. Bulakh, D. S. Shrotri and B. Patwardhan (1990). "Efficacy of potassium and magnesium in essential hypertension: a double-blind, placebo controlled, crossover study." BMJ **301**(6751): 521-523.

Peacock, J. M., A. R. Folsom, D. K. Arnett, J. H. Eckfeldt and M. Szklo (1999). "Relationship of serum and dietary magnesium to incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study." Ann Epidemiol **9**(3): 159-165.

Peacock, J. M., T. Ohira, W. Post, N. Sotoodehnia, W. Rosamond and A. R. Folsom (2010). "Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study." Am Heart J **160**(3): 464-470.

Plum-Wirell, M., B. G. Stegmayr and P. O. Wester (1994). "Nutritional magnesium supplementation does not change blood pressure nor serum or muscle potassium and magnesium in untreated hypertension. A double-blind crossover study." Magnes Res **7**(3-4): 277-283.

Purvis, J. R., D. M. Cummings, P. Landsman, R. Carroll, H. Barakat, J. Bray, C. Whitley and R. D. Horner (1994). "Effect of oral magnesium supplementation on selected cardiovascular risk factors in non-insulin-dependent diabetics." Arch Fam Med **3**(6): 503-508.

Rasic-Milutinovic, Z., G. Perunicic-Pekovic, D. Jovanovic, Z. Gluvic and M. Cankovic-Kadijevic (2012). "Association of blood pressure and metabolic syndrome components with magnesium levels in drinking water in some Serbian municipalities." J Water Health **10**(1): 161-169.

Rasnake CM, Trumbo PR, Heinonen TM. Surrogate endpoints and emerging surrogate endpoints for risk reduction of cardiovascular disease. Nutr Rev 2008;66(2):76-81.

Reyes, A. J., W. P. Leary, T. N. Acosta-Barrios and W. H. Davis (1984). "Magnesium supplementation in hypertension treated with hydrochlorothiazide." Curr Therapeutic Res **36**(2): 332-340.

Rodriguez-Hernandez, H., M. Cervantes-Huerta, M. Rodriguez-Moran and F. Guerrero-Romero (2010). "Oral magnesium supplementation decreases alanine aminotransferase levels in obese women." Magnes Res **23**(2): 90-96.

Rodriguez-Moran, M. and F. Guerrero-Romero (2003). "Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial." Diabetes Care **26**(4): 1147-1152.

Rodriguez-Moran, M. and F. Guerrero-Romero (2014). "Oral magnesium supplementation improves the metabolic profile of metabolically obese, normal-weight individuals: a randomized double-blind placebo-controlled trial." Arch Med Res **45**(5): 388-393.

Rodriguez-Moran, M., L. E. Simental-Mendia, C. I. Gamboa-Gomez and F. Guerrero-Romero (2018). "Oral Magnesium Supplementation and Metabolic Syndrome: A Randomized Double-Blind Placebo-Controlled Clinical Trial." Adv Chronic Kidney Dis **25**(3): 261-266.

Rodriguez-Ramirez, M., M. Rodriguez-Moran, M. A. Reyes-Romero and F. Guerrero-Romero (2017). "Effect of oral magnesium supplementation on the transcription of TRPM6, TRPM7, and

SLC41A1 in individuals newly diagnosed of pre-hypertension. A randomized, double-blind, placebo-controlled trial." Magnes Res **30**(3): 80-87.

Rodriguez-Ramirez, M., L. E. Simental-Mendia, M. Gonzalez-Ortiz, E. Martinez-Abundis, A. Madero, O. Brito-Zurita, R. Perez-Fuentes, C. Revilla-Monsalve, S. Islas-Andrade, M. Rodriguez-Moran and F. Guerrero-Romero (2015). "Prevalence of Prehypertension in Mexico and Its Association With Hypomagnesemia." Am J Hypertens **28**(8): 1024-1030.

Romani, A. (2013). Magnesium in Health and Disease. Interrelations between Essential Metal Ions and Human Diseases. A. Sigel and H. Sigel, Springer Science. **13:** 49-79.

Rooney, M. R., A. Alonso, A. R. Folsom, E. D. Michos, C. M. Rebholz, J. R. Misialek, L. Y. Chen, S. Dudley and P. L. Lutsey (2019). "Serum magnesium and the incidence of coronary artery disease over a median 27 years of follow-up in the Atherosclerosis Risk in Communities (ARIC) Study and a meta-analysis." Am J Clin Nutr.

Rotter, I., D. Kosik-Bogacka, B. Dolegowska, K. Safranow, B. Karakiewicz and M. Laszczynska (2015). "Relationship between serum magnesium concentration and metabolic and hormonal disorders in middle-aged and older men." Magnes Res **28**(3): 99-107.

Rylander, R. and M. J. Arnaud (2004). "Mineral water intake reduces blood pressure among subjects with low urinary magnesium and calcium levels." BMC Public Health **4**: 56.

Sacks, F. M., L. E. Brown, L. Appel, N. O. Borhani, D. Evans and P. Whelton (1995). "Combinations of potassium, calcium, and magnesium supplements in hypertension." Hypertension **26**(6 Pt 1): 950-956.

Sacks F.M., Willett W.C., Smith A., Brown L.E., Rosner B., Moore T.J. "Effect on Blood Pressure of Potassium, Calcium, and Magnesium in Women with Low Habitual Intake". Hypertension. 1998;31:131-138.

Sanjuliani, A. F., V. G. de Abreu Fagundes and E. A. Francischetti (1996). "Effects of magnesium on blood pressure and intracellular ion levels of Brazilian hypertensive patients." Int J Cardiol **56**(2): 177-183.

Sebekova, K., V. Revusova, D. Polakovicova, J. Drahosova, D. Zverkova and R. Dzurik (1992). "Anti-hypertensive treatment with magnesium-aspartate-dichloride and its influence on peripheral serotonin metabolism in man: a subacute study." Cor Vasa **34**(5-6): 390-401.

Shafique, M., A. Misbah ul and M. Ashraf (1993). "Role of magnesium in the management of hypertension." J Pak Med Assoc **43**(4): 77-78.

Sibai, B. M., M. A. Villar and E. Bray (1989). "Magnesium supplementation during pregnancy: a double-blind randomized controlled clinical trial." Am J Obstet Gynecol **161**(1): 115-119.

Simental-Mendia, L. E., M. Rodriguez-Moran and F. Guerrero-Romero (2014). "Oral magnesium supplementation decreases C-reactive protein levels in subjects with prediabetes and hypomagnesemia: a clinical randomized double-blind placebo-controlled trial." Arch Med Res **45**(4): 325-330.

Simental-Mendia, L. E., M. Rodriguez-Moran, M. A. Reyes-Romero and F. Guerrero-Romero (2012). "No positive effect of oral magnesium supplementation in the decreases of inflammation in subjects with prediabetes: a pilot study." Magnes Res **25**(3): 140-146.

Song, Y., P. M. Ridker, J. E. Manson, N. R. Cook, J. E. Buring and S. Liu (2005). "Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older U.S. women." Diabetes Care **28**(6): 1438-1444.

Song, Y., H. D. Sesso, J. E. Manson, N. R. Cook, J. E. Buring and S. Liu (2006). "Dietary magnesium intake and risk of incident hypertension among middle-aged and older US women in a 10-year follow-up study." Am J Cardiol **98**(12): 1616-1621.

Spilker, B. (1991). Guide to Clinical Studies. New York, New York**:** 59-64, 497-501, 497-501

Stamler, J., P. Elliott, L. Appel, Q. Chan, M. Buzzard, B. Dennis, A. R. Dyer, P. Elmer, P. Greenland, D. Jones, H. Kesteloot, L. Kuller, D. Labarthe, K. Liu, A. Moag-Stahlberg, M. Nichaman, A. Okayama, N. Okuda, C. Robertson, B. Rodriguez, M. Stevens, H. Ueshima, L. V. Horn and B. Zhou (2003). "Higher blood pressure in middle-aged American adults with less education-role of multiple dietary factors: the INTERMAP study." J Hum Hypertens **17**(9): 655-775.

Sudhakar, K., M. Sujatha, V. B. Rao, A. Jyothy and P. P. Reddy (1999). "Serum and erythrocyte magnesium levels in hypertensives and their first degree relatives." J Indian Med Assoc **97**(6): 211-213.

Sur, G. and O. Maftei (2006). Role of magnesium in essential hypertension in teenagers. Advances in Magnesium Research -- New Data. P. J. Porr, M. Nechifor and J. Durlack. Montrouge, France, John Libbey Eurotext**:** 55-60.

Syedmoradi, L., A. Ghasemi, S. Zahediasl and F. Azizi (2011). "Prevalence of hypo- and hypermagnesemia in an Iranian urban population." Ann Hum Biol **38**(2): 150-155.

Taylor, D. R., J. Constable, M. Sonnekus and F. J. Milne (1988). "Effect of indapamide on serum and red cell cations, with and without magnesium supplementation, in subjects with mild hypertension." S Afr Med J **74**(6): 273-276.

TOHP Study Group (1992). "The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I." JAMA **267**(9): 1213-1220.

Toprak, O., H. Kurt, Y. Sari, C. Sarkis, H. Us and A. Kirik (2017). "Magnesium Replacement Improves the Metabolic Profile in Obese and Pre-Diabetic Patients with Mild-to-Moderate Chronic Kidney Disease: A 3-Month, Randomised, Double-Blind, Placebo-Controlled Study." Kidney Blood Press Res **42**(1): 33-42.

U.S. Department of Health and Human Services and U.S. Department of Agriculture (2020-2025). Dietary Guidelines for Americans 2020-2025. Washington, DC, U.S. Government Printing Office.

U.S. Food and Drug Administration. (January 2009). "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims ", from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims.

U.S. Food and Drug Administration. "Memorandum to the File (Docket No. FDA-2016-Q-3770): Mean Arterial Pressure as a Surrogate Endpoint" 2021.
Van Leer, E. M., J. C. Seidell and D. Kromhout (1995). "Dietary calcium, potassium, magnesium and blood pressure in the Netherlands." Int J Epidemiol **24**(6): 1117-1123.

Vickovic, S., M. Pjevic, A. Uvelin, D. Pap, D. Nikolic and I. Lalic (2016). "Magnesium Sulfate as an Adjuvant to Anesthesia in Patients with Arterial Hypertension." Acta Clin Croat **55**(3): 490-496.

Vongpatanasin, W., P. Peri-Okonny, A. Velasco, D. Arbique, Z. Wang, P. Ravikumar, B. Adams-Huet, O. W. Moe and C. Y. C. Pak (2016). "Effects of Potassium Magnesium Citrate Supplementation on 24-Hour Ambulatory Blood Pressure and Oxidative Stress Marker in Prehypertensive and Hypertensive Subjects." Am J Cardiol **118**(6): 849-853.

Walker, A. F., G. Marakis, A. P. Morris and P. A. Robinson (2002). "Promising hypotensive effect of hawthorn extract: a randomized double-blind pilot study of mild, essential hypertension." Phytother Res **16**(1): 48-54.

Wary, C., C. Brillault-Salvat, G. Bloch, A. Leroy-Willig, D. Roumenov, J. M. Grognet, J. H. Leclerc and P. G. Carlier (1999). "Effect of chronic magnesium supplementation on magnesium distribution in healthy volunteers evaluated by 31P-NMRS and ion selective electrodes." Br J Clin Pharmacol **48**(5): 655-662.

Whelton, P. K., J. Buring, N. O. Borhani, J. D. Cohen, N. Cook, J. A. Cutler, J. E. Kiley, L. H. Kuller, S. Satterfield, F. M. Sacks and et al. (1995). "The effect of potassium supplementation in persons with a high-normal blood pressure. Results from phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group." Ann Epidemiol **5**(2): 85-95.

Whelton, P. K., S. K. Kumanyika, N. R. Cook, J. A. Cutler, N. O. Borhani, C. H. Hennekens, L. H. Kuller, H. Langford, D. W. Jones, S. Satterfield, N. L. Lasser and J. D. Cohen (1997). "Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results

from phase 1 of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group." Am J Clin Nutr **65**(2 Suppl): 652S-660S.

Widman, L., P. O. Wester, B. K. Stegmayr and M. Wirell (1993). "The dose-dependent reduction in blood pressure through administration of magnesium. A double blind placebo controlled cross-over study." Am J Hypertens **6**(1): 41-45.

Wilson EB. 1990. An Introduction to Scientific Research. Dover Publications, New York. pp. 46-48.

Wirell, M. M., P. O. Wester and B. G. Stegmayr (1993). "Nutritional dose of magnesium given to short-term thiazide treated hypertensive patients does not alter the blood pressure or the magnesium and postasium in muscle -- A double blind cross-over study." Magnesium Bulletin **15**(2): 50-54.

Wirell, M. P., P. O. Wester and B. G. Stegmayr (1994). "Nutritional dose of magnesium in hypertensive patients on beta blockers lowers systolic blood pressure: a double-blind, cross-over study." J Intern Med **236**(2): 189-195.

Witteman, J. C., W. C. Willett, M. J. Stampfer, G. A. Colditz, F. M. Sacks, F. E. Speizer, B. Rosner and C. H. Hennekens (1989). "A prospective study of nutritional factors and hypertension among US women." Circulation **80**(5): 1320-1327.

Witteman J.C., Grobbee D.E., Derkx F.H., Bouillon R., de Bruijn A.M., Hofman A. "Reduction of Blood Pressure with Oral Magnesium Supplementation in Women with Mild to Moderate Hypertension". Am J Clin Nutr. 1994;60:129-135

Workinger, J. L., R. P. Doyle and J. Bortz (2018). "Challenges in the Diagnosis of Magnesium Status." Nutrients **10**(9).

Wu, G., H. Tian, K. Han, Y. Xi, Y. Yao and A. Ma (2006). "Potassium magnesium supplementation for four weeks improves small distal artery compliance and reduces blood pressure in patients with essential hypertension." Clin Exp Hypertens **28**(5): 489-497.

Yamamoto, M. E., W. B. Applegate, M. J. Klag, N. O. Borhani, J. D. Cohen, K. A. Kirchner, E. Lakatos, F. M. Sacks, J. O. Taylor and C. H. Hennekens (1995). "Lack of blood pressure effect with calcium and magnesium supplementation in adults with high-normal blood pressure. Results from Phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group." Ann Epidemiol **5**(2): 96-107.

Yamori, Y., Y. Nara, S. Mizushima, M. Mano, M. Sawamura, M. Kihara and R. Horie (1992). "International cooperative study on the relationship between dietary factors and blood pressure: a preliminary report from the Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. The CARDIAC Cooperative Study Research Group." Nutr Health **8**(2-3): 77-90.

Yang, C. Y. and H. F. Chiu (1999). "Calcium and magnesium in drinking water and the risk of death from hypertension." Am J Hypertens **12**(9 Pt 1): 894-899.

Yokota, K., M. Kato, F. Lister, H. Ii, T. Hayakawa, T. Kikuta, S. Kageyama and N. Tajima (2004). "Clinical efficacy of magnesium supplementation in patients with type 2 diabetes." J Am Coll Nutr **23**(5): 506S-509S.

Zemel, P. C., M. B. Zemel, M. Urberg, F. L. Douglas, R. Geiser and J. R. Sowers (1990). "Metabolic and hemodynamic effects of magnesium supplementation in patients with essential hypertension." Am J Clin Nutr **51**(4): 665-669.

Zhou, B., J. Webster, L. Y. Fu, H. L. Wang, X. M. Wu, W. L. Wang and J. P. Shi (2016). "Intake of low sodium salt substitute for 3years attenuates the increase in blood pressure in a rural population of North China - A randomized controlled trial." Int J Cardiol **215**: 377-382.