DATE:	August 16, 2016
NAME OF PETITIONER:	The Center for Magnesium Education and Research, LLC
POST OFFICE ADDRESS:	13-1255 Malama Street Pahoa, HI 96778
SUBJECT OF PETITION:	Petition for the Authorization of a Qualified Health Claim for Magnesium and Reduced Risk of High Blood Pressure (Hypertension)
SUBMITTED TO:	Office of Nutrition, Labeling and Dietary Supplements (HFS-800) Center for Food Safety and Applied Nutrition Food and Drug Administration Harvey W. Wiley Federal Building 5001 Campus Drive College Park, MD 20740

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Petition for the Authorization of a Qualified Health Claim for Magnesium and Reduced Risk of High Blood Pressure (Hypertension)

I. INTRODUCTION

The undersigned, The Center for Magnesium Education & Research, LLC (the Center), submits this petition for a qualified health claim (QHC) in reference to the ability of magnesium to reduce the risk of high blood pressure (hypertension) in accordance with the guidance documents posted by the Food and Drug Administration (FDA) on July 10, 2003[1] and on January 2009[2]. This petition addresses all of the elements set forth in 21 C.F.R. § 101.70 for unqualified health claims. Proposed wording of the new claim is,

> 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 claim would apply to foods and dietary supplements that contain at least 20% Daily Value (DV) of magnesium per reference amount customarily consumed (RACC) and therefore qualify as a high source of this nutrient as defined in 21 C.F.R. §101.54(b). Foods and dietary supplements that are eligible for the proposed claim would also comply with all of the provisions of 21 C.F.R §101.14 except that tree nuts would be exempt from the total fat disqualifier level as defined in 21 C.F.R. §101.14(a)(4).

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[1] Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements. July, 2003. http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/QualifiedHealthClaimsPetitions/ucm096010.htm

[2] Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final. January, 2009 http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm073332.htm

A. Scientific basis for the proposed claim

A comprehensive review of the scientific literature shows that the predominance of evidence supports the proposed claim. This evidence is based on observational studies that suggest magnesium status and/or dietary intake is inversely associated with blood pressure in healthy individuals, controlled dietary intervention studies that show magnesium supplementation can lower blood pressure among healthy individuals (and especially those with mild to moderate hypertension), and by systematic review papers and meta-analyses that confirm such effects using data pooled from many studies. As will be discussed below, the Center strongly believes that this evidence more than justifies the proposed claim.

B. Statements from public health and professional organizations

Magnesium has received less attention than many other nutrients from the public health community; nevertheless this mineral is receiving increased visibility as part of dietary recommendations.

1. The Dietary Guidelines for Americans

The 2015-2020 *Dietary Guidelines for Americans* (DGAs) list magnesium as an important nutrient present in vegetables, grain products and dairy. In addition, the DGAs note that magnesium is an important nutrient in the Dietary Approaches to Stop Hypertension (DASH) diet which is one of the three healthy patterns recommended for the American population. The DGAs state,

> The DASH Eating Plan is high in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, beans, and nuts and is low in sweets, sugar-sweetened beverages, and red meats. It is low in saturated fats and rich in potassium, calcium, and **magnesium** (emphasis supplied), as well as dietary fiber and protein. It also is lower in sodium than the typical American diet, and includes menus with two levels of sodium, 2,300 and 1,500 mg per day. Additional details

> on DASH are available at http://www.nhlbi.nih.gov/health/health-topics/topics/dash.

2. The American Heart Association

The American Heart Association (AHA) makes a variety of nutrition and lifestyle recommendations to consumers. These recommendations include balancing energy intake with physical activity, eating a variety of nutritious foods from all the food groups, eating fewer nutrient-poor foods as well as choosing a healthy dietary pattern including fruits and vegetables, whole grains, skinless poultry and fish, foods that contain omega-3 fatty acids, dairy products that are low or free in fat and reducing foods that are high in *trans* fats, saturated fats, added sugars and sodium[3]. However, the AHA also specifically mentions magnesium as part of its recommendations for consumers,

> A diet that includes natural sources of potassium is important in controlling blood pressure because potassium lessens the effects of sodium. The recommended daily intake of potassium for an average adult is about 4,700 milligrams per day. But potassium should be considered as only part of your total dietary pattern. Factors such as salt intake, amount and type of dietary fat, cholesterol, protein and fiber, as well as minerals such as calcium and **magnesium** (emphasis supplied) may affect blood pressure. Researchers attribute changes in blood pressure to certain patterns of food consumption[4].

The AHA also recommends the DASH eating pattern (including magnesium) to consumers as part of its dietary recommendations.

> Keeping high blood pressure (also called hypertension) under control is crucial for heart health. Left uncontrolled, high blood pressure stretches and damages arteries, making your heart work harder, but less effectively. This can lead to heart disease, stroke and other problems.

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[3] http://www.heart.org/HEARTORG/HealthyLiving/HealthyEating/Nutrition/The-American-Heart-Associations-Diet-and-Lifestyle-Recommendations_UCM_305855_Article.jsp#.VzYaQ_krJD8

[4] http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/PreventionTreatmentofHighBloodPressure/Potassium-and-High-Blood-Pressure_UCM_303243_Article.jsp#.VzYdIPkrJhE

> Think about trying the DASH diet to control your high blood pressure. It has been proven to help lower blood pressure, especially in African-Americans and people diagnosed with hypertension. It was recently ranked in US News & World Report as the #1 best diet overall. It's easy to follow, nutritious and safe.
> Here's a breakdown of the foods that the DASH eating plan emphasizes:
>
> - Fruits
> - Vegetables
> - Whole-grain, higher-fiber foods
> - Fat-free and low-fat (1 percent) dairy products
> - Beans (like chickpeas, kidney beans, black-eyed peas, etc.)
> - Seeds, nuts, and vegetable oils
> - Skinless poultry and lean meats
> - Fish, especially fatty fish that have omega-3 fatty acids such as salmon, trout and herring (eat these at least twice a week)
>
> Compared to the typical American diet, the DASH eating plan has less red meat, sodium, sweets and sugary drinks. It's lower in saturated fat, trans fat and sodium. It also provides adequate protein and is rich in nutrients — like potassium, **magnesium** (emphasis supplied), calcium and fiber — that many of us fall short on. Many of the American Heart Association's recipes are compatible with a DASH eating plan[5].

In summary, the Center strongly believes that the preponderance of scientific evidence shows that increased intake of magnesium would have a beneficial effect on blood pressure; particularly among individuals at risk of hypertension. Furthermore, increased consumption of this nutrient would contribute to overall diet quality as a component of vegetables, whole grains, low-fat dairy and nuts as well as the DASH pattern. Availability of the proposed claim would call attention to this important nutrient which has the potential to meaningfully affect public health. We, therefore, respectfully request that FDA act swiftly approve this petition.

[5] http://sodiumbreakup.heart.org/change-way-eat-lower-blood-pressure/

II. **PRELIMINARY REQUIREMENTS**

Pursuant to 21 CFR § 101.70 (f), health claim petitions are required to, "…demonstrate that the substance of the proposed claim conforms to the definition of the term 'substance' in § 101.14 (a)(2)," and to explain, "…how the substance conforms to the requirements of § 101.14 (b)." The requirements of 21 CFR § 101.14 (b) that are applicable to substances to be consumed at other than decreased dietary levels are: 1) to demonstrate that the substance is, "… associated with a disease or health-related condition for which the general U.S. population…is at risk…"; 2) to show that the substance, "…contribute[s] taste, aroma, or nutritive value…"; and 3) to demonstrate that the substance is, "… a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify a 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."

A. Magnesium is a "substance" under 21 CFR § 101.14 (a)(2)

The definition of a "substance" under 21 CFR § 101.14 (a)(2) is, "…a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances." Magnesium is an essential nutrient, and clearly meets the regulatory definition of a "substance".

B. The U.S. population is at risk for developing high blood pressure

The most recent health statistics from the AHA (Mozaffarian et al., 2016) indicate the enormity of hypertension as a public health problem in the U.S. This report states,

> Based on 2009 to 2012 data, 32.6% of US adults 20 years of age or older have hypertension, which represents approximately 80.0 million US adults. African American adults have among the highest prevalence of hypertension in the world.

> Among non-Hispanic black men and women, the age-adjusted prevalence of hypertension was 44.9% and 46.1%, respectively.
>
> National Health and Nutrition Examination Survey (NHANES) data from 2009 to 2012 revealed that among US adults with hypertension, 54.1% were controlled, 76.5% were currently treated, 82.7% were aware they had hypertension, and 17.3% were undiagnosed.
>
> From 2003 to 2013, the death rate attributable to high blood pressure increased 8.2%, and the actual number of deaths rose 34.7% (National Heart, Lung, and Blood Institute tabulation). During this 10-year period, the corresponding values were a 14.4% and 30.9% increase in non-Hispanic whites; a 1.7% and 75.5% increase in Hispanics; and a 9.1% decrease and 18.4% increase in non-Hispanic blacks.

These data clearly show that the U.S. population is at risk for high blood pressure.

C. Magnesium contributes nutritive value to the diet

Magnesium is an essential nutrient. The Recommended Daily Allowance (RDA) of this nutrient ranges from 310-320 mg[6] per day for adult women 19 years of age or older and from 400-420 mg per day for adult men (Institute of Medicine, 1997). The Daily Value (DV) for nutrition labeling purposes is 400 mg per day. The availability of these standards clearly indicates that magnesium contributes nutritive value to the diet.

D. Magnesium is safe and lawful

As noted above, magnesium is an essential nutrient that is a safe (and necessary) component of the food supply. Several forms of this mineral are designated Generally Recognized as Safe (GRAS) by the FDA. These forms include: magnesium carbonate (21 C.F.R. §184.1425), magnesium chloride (21 C.F.R. §184.1426), magnesium hydroxide (21 C.F.R. §184.1428)

[6] To convert mg magnesium to mmol magnesium, multiply by 0.041~~7~~2. Both units are used throughout this document.

magnesium oxide (21 C.F.R. §184.1431), magnesium phosphate (21 C.F.R. §184.1434), magnesium stearate (21 C.F.R. §184.1440) and magnesium sulfate (21 C.F.R. §184.1443).

III. **SCIENTIFIC EVIDENCE SUPPORTING THE CLAIM**

A. Introduction/overview

The totality of the scientific evidence, based on a comprehensive review of the literature, provides convincing support of the proposed claim. The most dramatic evidence is provided by high or medium quality randomized, controlled trials (RCTs) among healthy subjects with pre- or mild to moderate hypertension. Eighty-eight percent of such studies provide direct or mixed support for the proposed claim. Studies with such subjects are more likely to report a beneficial effect of magnesium supplementation on blood pressure than studies with normal blood pressures as dictated by normal physiology (see E.1 of this section). Nevertheless, 54 percent of high and medium quality RCTs that examined normotensive and/or hypertensive subjects also provided direct or mixed support for the proposed claim. The consistency of this evidence is demonstrated by the fact that the most recent meta-analyses (published since 2012) reported that pooled data from studies that examined both normotensive and hypertensive or only hypertensive subjects showed that magnesium supplementation significantly lowered blood pressure (Kass et al., 2012, Rosanoff and Plesset, 2013, Zhang et al., 2016). Finally, the majority of epidemiologic data (especially prospective cohort and case-control studies) are consistent with the contention that adequate magnesium in food and/or supplements is beneficial in achieving or maintaining a healthy blood pressure. A detailed discussion of these conclusions is provided in the remainder of this section.

B. Mechanism of action

There is consensus in the scientific literature that the ultimate mechanism by which dietary magnesium beneficially affects blood pressure is through increased vasodilation and/or decreased vasoconstriction. These effects are exerted through multiple physiological pathways as discussed in numerous reviews (Resnick, 1999, Shechter, 2010, Houston, 2011, Kupetsky-Rincon and Uitto, 2012, Maier, 2012, Romani, 2013, Houston, 2014, Kolte et al., 2014, Das, 2015).

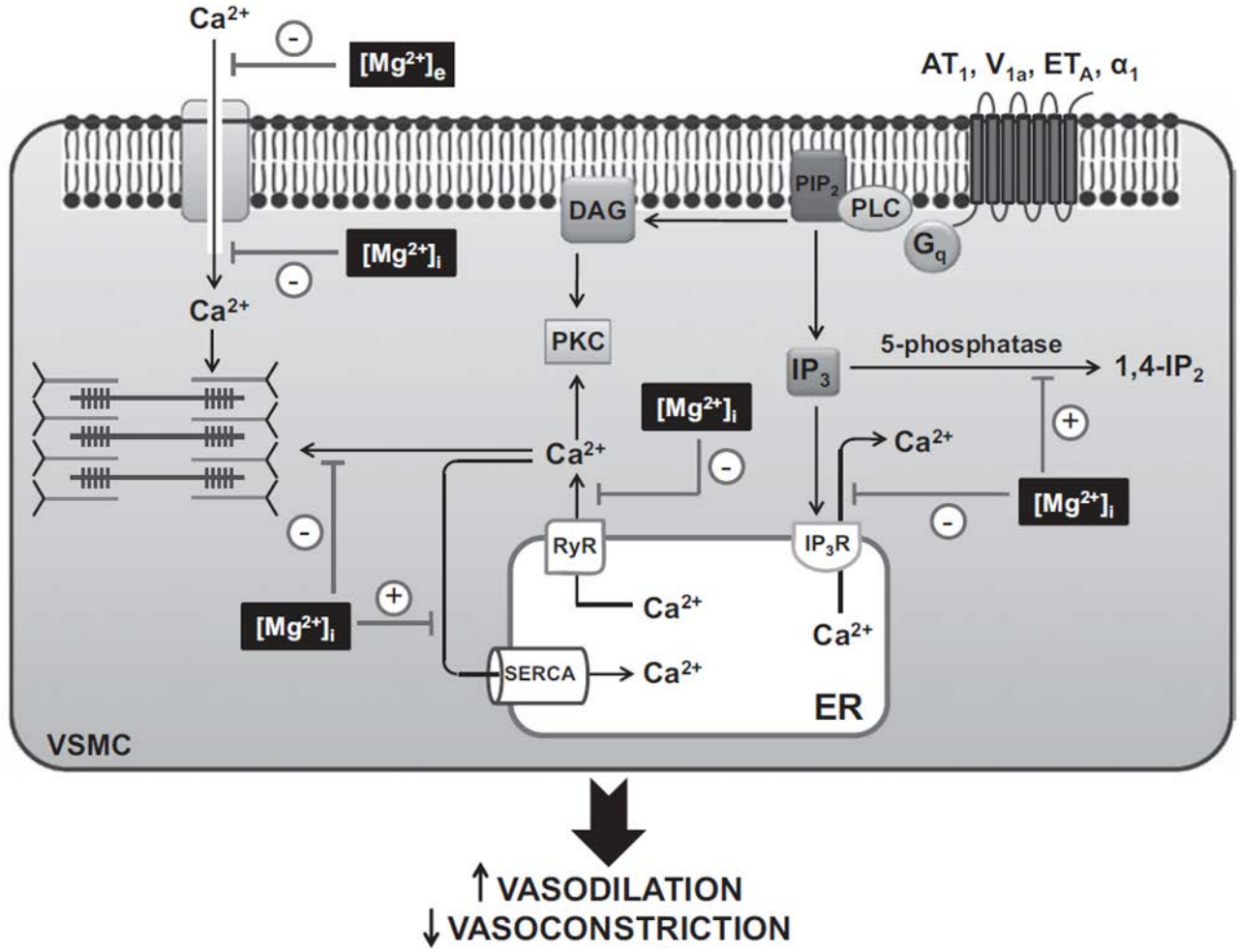
Acknowledgment of the important roles magnesium plays in blood pressure regulation through its effects on vascular function was noted in the Dietary Reference Intakes report on magnesium more than 20 years ago (Institute of Medicine, 1997). This publication states, "In normal subjects, experimental magnesium depletion results in increased urinary thromboxane concentration, angiotensin II-induced plasma aldosterone levels, and blood pressure- indicating a potential effect of magnesium deficiency on vascular function."

The ability of magnesium to dilate arteries was first demonstrated in dogs by Turlapaty and Altura (1980). Since that time, numerous ways in which magnesium interacts with other nutrients to lower blood pressure through increased vasodilation and/or decreased vasoconstriction have been identified.

The role of magnesium as a calcium channel blocker is one of the most important modes of action for affecting vascular function. This role is depicted graphically in Figure A. Briefly, dietary magnesium increases serum concentrations of this cation which, in turn, decreases the flow of calcium ions into vascular smooth muscle cells.

Figure A

Effects of extracellular and intracellular magnesium on vascular smooth muscle tone via modulation of calcium entry and intracellular signal transduction pathways



α1 indicates alpha 1 receptor; AT1, angiotensin 1 receptor; DAG, diacylglycerol; ER, endoplasmic reticulum; ETA, endothelin A receptor; IP3, inositol-1,4,5-trisphosphate; IP3R, IP3 receptor; 1,4-IP2, inositol 1,4-bisphosphate; PIP2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PLC, phospholipase C; RyR, ryanodine receptor; SERCA, sarcoendoplasmic reticulum Ca2+-ATPase; V1a, vasopressin 1a receptor; VSMC, vascular smooth muscle cell.
Source: Kolte et al., *Cardiology in Review* 2014;22:182

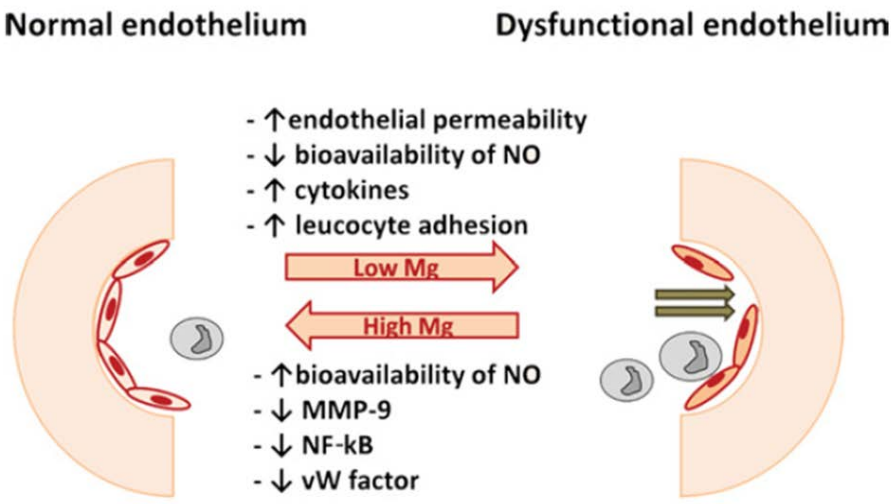
The decreased intercellular calcium concentration caused by this effect prompts numerous metabolic changes within the cell. As Kolte et al. (2014) describes, intercellular calcium ion has profound effects on angiotensin II, vasopressin, endothelin and epinephrine/norepinephrine which exert vasoconstrictor effects via stimulation of the alpha 1 receptor, the

angiotensin 1 receptor, the endothelin A receptor and the vasopressin 1a receptor. Activation of these receptors initiates the phospholipase C (PLC), inositol-1,4,5-triphosphate (IP_3), diacylglycerol (DAG), Ca^{2+} and protein kinase C (PKC) signal transduction pathways. Evidence also exists that the intracellular magnesium ion itself acts as a second messenger to modulate signal transduction following receptor ligand interaction by regulating G-protein activity, phospholipase C translocation and PKC activation. Elevated Mg^{2+} intercellular concentration stimulates IP_3 breakdown, inhibits IP_3-induced Ca^{2+} release from the sarcoplasmic reticulum and competes with intracellular calcium ion for cytoplasmic and reticular binding sites. Finally, intracellular magnesium activates the sarcoplasmic/endoplasmic reticular Ca^{2+} ATPase pump that sequesters intracellular calcium ions into the sarcoplasmic reticulum. The ultimate effect of these processes is that increased dietary magnesium results in an inhibition of calcium transport into the vascular smooth muscle cell coupled with increased intracellular magnesium which prompts the cascade of physiological events that leads to reduced blood pressure through increased vasodilation and decreased vasoconstriction.

Magnesium is also necessary to maintain a healthy endothelium which is critical for the regulation of blood pressure through vasoconstriction and vasodilation. As Kolte et al. (2014) state, “It is well accepted that endothelia dysfunction is central to the pathogenesis of atherosclerosis, thrombosis, hypertension and diabetes.”

Some of the roles that magnesium plays in this regard are depicted in Figure B taken from Maier (2012). This figure illustrates that magnesium balance within the endothelium contributes to the synthesis and bioavailability of nitric oxide (NO) which is intimately involved in arterial relaxation. In addition magnesium deficiency promotes oxidative stress which leads to the

Figure B
The role magnesium in endothelial function



NO (nitic oxide), MMP-9 (matrix metalloprotease-9), NF-κB (nuclear factor κB), wW factor (von Willebrand factor)
Source: Maier *Clinical Science* 2012;122:397

formation of free radicals including superoxide anions which activate pro-inflammatory and pro-thrombic pathways that contribute to endothelial dysfunction (Forstermann, 2008). Low extracellular magnesium has also been demonstrated to activate nuclear factor κB (NF-κB) which is an important regulator of pro-inflammatory genes (Ferre et al., 2010). Activation of this transcription factor results in the release of pro-inflammatory cytokines including interleukin-1α (IL-1α). IL-1α in turn induces various chemokines and adhesion molecules through the activation of NF-κB. Low magnesium also stimulates the secretion of platelet-derived growth factor-BB (PDGF-BB) which contributes to atherogensis (Lusis, 2000). Detailed explanations of the many roles magnesium plays in maintaining a healthy endothelium are available in Maier (2012) and Kolte et al. (2014).

Magnesium plays other roles in maintaining a healthy cardiovascular system in addition to its role in normalizing blood pressure through vasodilation and vasoconstriction. Specifically, this cation also exerts beneficial antiarrhythmic and anti-ischemic effects (Kolte et al., 2014). However, such effects are outside of the scope of the proposed claim because they operate independently of blood pressure.

In summary, there is a broad consensus in the literature that magnesium exerts its effect on blood pressure through the mechanism of vasodilation and vasoconstriction. This fact is illustrated by conclusions from review papers cited at the beginning of this section:

- Resnick (1999) stated, “Altogether, a cellular Mg deficiency, by decreasing the function of a wide range of enzyme cascades, membrane pumps, and ion channels, would be expected to impair cellular glucose disposal, concomitantly to exaggerate Ca-induced cell stimulation in general, and in the vasculature in particular, to promote vasoconstriction.”

- Shechter (2010) observed, “Magnesium supplementation improves…vascular tone, peripheral vascular resistance, afterload and cardiac output, reduces cardiac arrhythmias and improves lipid metabolism. Magnesium also reduces vulnerability to oxygen-derived free radicals, improves human endothelial function…”.

- Houston (2011) concluded, “Oral magnesium acts as a natural calcium channel blocker, increases nitric oxide, improves endothelial dysfunction, and induces direct and indirect vasodilation.”

- Das (2015) noted, “Low magnesium levels in serum and other extracellular fluids increase smooth muscle tension and narrow the lumens of arterioles and venules, resulting in

vasospasm. Thus magnesium-deficient diets are expected to raise blood pressure in rats and possibly, in humans and lead to the development of atherosclerosis and CAD [coronary artery disease]."

The Center concludes that the broad consensus in the literature cited above establishes that the mechanism by which magnesium exerts its beneficial effects on blood pressure is through vasoconstriction and vasodilation as mediated by a wide variety of physiological pathways. As will be discussed later in this section (see section III. E. 1), these physiological pathways function at all blood pressure levels, which justify the inclusion of studies that examine the effect of magnesium supplementation on blood pressure among hypertensive as well as normotensive subjects for substantiation of the proposed claim.

C. Systematic reviews and meta-analyses

The Center understands that FDA cannot rely on meta-analyses for the direct substantiation of health claims because sufficient detail on the individual studies included in such analyses is not available to assess the quality of the data. Nevertheless, meta-analyses conducted during the past 14 years (as evidence on the ability of magnesium to lower blood pressure has accumulated) provide strong evidence of such an effect based on the totality of the evidence.

1. Observational studies

No meta-analyses or systematic review papers were identified that examined the association between dietary magnesium intake/status and blood pressure, however Del Gobbo et al. (2013) conducted such an analysis for the incidence of cardiovascular disease (CVD). Dietary magnesium (per 200 mg/d increment) was associated with a 22 percent lower risk of ischemic heart disease (IHD) (RR=0.78, 95% CI 0.67-0.92) and fatal IHD up to a threshold of

approximately 250 mg magnesium per day (RR=0.73, 95% CI 0.62-0.86) but not for CVD (RR=0.89, 95% CI 0.75-1.05). Circulating magnesium (per 0.2 mmol/L[7] increment) was associated with a reduced risk of CVD (RR=0.70, 95% CI 0.56-0.88) and a trend for lower risk of IHD (RR=0.83, 95% CI 0.75-1.05) and fatal IHD (RR=0.61, 95% CI 0.37-1.00). This analysis included 16 studies among 313,041 individuals who had experienced 11,995 cases of CVD, 7,534 incidences of IHD and 2,686 fatal IHD events. Eleven prospective cohort studies provided data on dietary magnesium while nine studies examined circulating magnesium. As noted above, this meta-analysis did not examine blood pressure directly; nevertheless it provides additional support for the proposed claim because blood pressure is a major risk factor for CHD (including IHD) and dietary magnesium was found to be inversely associated with this parameter.

Another meta-analysis that provides tangential support for the proposed claim was conducted by Dibaba et al. (2014) who reported that magnesium intake was inversely associated with the incidence of metabolic syndrome (RR=0.69, 95% CI 0.59-0.81) based on six cross-sectional studies among 24,473 individuals who experienced 6,311 cases of metabolic syndrome. Studies were included if metabolic syndrome was the exposure of interest, but no specific criteria for defining this syndrome were employed. Nevertheless, this analysis showed that every 100 mg increment in dietary magnesium reduced the risk of metabolic syndrome by 17 percent (RR=0.83, 95% CI 0.77-0.89). Once again, this meta-analysis did not report on blood pressure *per se* (including baseline blood pressures) but this parameter is a component of the metabolic syndrome. Furthermore, metabolic syndrome is a risk factor for CHD (Ninomiya et al., 2004).

[7] To convert mmol magnesium per liter to mg/dL, multiply by 2.43. Both units are used throughout this document.

2. Intervention studies

Five meta-analyses and one systematic review paper were identified that examined the ability of magnesium supplementation to lower blood pressure. Three published peer-reviewed meta-analyses (Dickinson et al., 2006, Kass et al., 2012, Rosanoff and Plesset, 2013) and a very recent high-quality meta-analysis by Zhang et al. (2016) have shown statistically significant effects of magnesium supplementation on blood pressure based on pooled data. The first meta-analysis published in this area (Jee et al., 2002) did not report such findings, but was based on the limited amount of data available at the time. Additional evidence was provided by a non-quantitative analysis of intervention studies by Rosanoff (2010) that explored the importance of baseline blood pressure and other parameters in the ability of magnesium to affect blood pressure. Five of the meta-analyses noted above examined randomized controlled trials (RCTs) that were highly heterogeneous and one meta-analysis (Rosanoff and Plesset, 2013) which was very homogeneous but included non-controlled trials. The individual studies included in these publications as well as pooled outcome measures (where appropriate) are enumerated in Table I. A narrative discussion of the analyses is provided below.

Jee et al. (2002) was the first meta-analysis published on the effect of oral magnesium supplementation on blood pressure. This meta-analysis of 20 studies (1,220 participants) found a significant inverse dose-dependent effect of magnesium on blood pressure with reductions of 4.3 mm Hg SBP (systolic blood pressure) (95% CI 6.3 to 2.2; $p<0.001$) and of 2.3 mm Hg DBP (diastolic blood pressure) (95% CI 4.9 to 0.0; $p=0.09$) for each 10 mmol[8]/day increase in Mg dose. However, pooled net estimates of blood pressure change was small and insignificant (-0.6 mm for systolic blood pressure (95% CI: -2.2 to 1.0) and -0.8 mm for diastolic blood pressure

[8] To convert mmol magnesium to mg magnesium, multiply by 24.3. Both units are used throughout this document

Table I

Outcome measures and identity of the intervention studies included in meta-analyses that examined the effect of magnesium supplementation on blood pressure

Study citation [a, b] **Outcome measure**	**Systematic Review/Meta-Analysis**					
	Jee et al. (2002)	**Dickinson et al. (2006)**	**Rosanoff (2010)**	**Kass et al. (2012)**	**Rosanoff and Plesset (2013)**	**Zhang et al. (2016)**
Borrello et al. (1996)		x	x	x		x
Ferrara et al. (1992)	x	x	x	x		x
Henderson et al. (1986)	x	x	x	x		x
Lind et al. (1991)	x	x	x	x		x
Paolisso et al. (1992)		x	x	x	x	x
Walker et al. (2002)		x	x			
Witteman et al. (1994)	x	x	x	x		x
Zemel et al. (1990)	x	x	x	x		x
Kawano et al. (1998)	x	x	x	x		
Plum-Wirell et al. (1994)	x	x	x	x		x
Wirell et al. (1994)		x	x	x		x
Dyckner and Wester (1983)	x		x			
Reyes et al. (1984)	x		x			
Cappuccio et al. (1985)	x		x	x		
Saito et al. (1988)[c]	x		x	x		
Nowson and Morgan (1989)	x	x	x			
Patki et al. (1990)	x		x			x
TOHP (1992)	x		x			x
Widman et al. (1993)	x		x	x		x
Purvis et al. (1994)	x		x	x		x
Sanjuliani et al. (1996)	x		x	x		x
Itoh et al. (1997)	x		x	x		x
Sacks et al. (1998)	x		x	x		x
Doyle et al. (1999)	x		x	x		x
Lee et al. (2009)			x	x		x
Guerrero-Romero and Rodriguez-Moran (2009)			x	x	x	x
Michon (2002)			x		x	
Sebekova et al. (1992)			x		x	
Olhaberry et al. (1987)			x			x
Daly et al. (1990)			x			x
Wirell et al. (1993)			x			x
Rodriguez-Moran and Guerrero-Romero (2003)				x		x
Guerrero-Romero et al. (2004)				x		x
de Valk et al. (1998)						x
Wary et al. (1999)						x
Barbagallo et al. (2010)						x
Rodriguez-Hernandez et al. (2010)						x
Guerrero-Romero and Rodriguez-Moran (2011)						x
Mooren et al. (2011)						x

Cosaro et al. (2014)						x
Rodriguez-Moran and Guerrero-Romero (2014)						x
Simental-Mendia et al. (2014)						x
Shafique et al. (1993)			x			
Ruiz-Lopez et al. (1999)			x			
Cohen et al. (1984)			x			
Haga (1992)			x			
Motoyama et al. (1989)			x			
Sur and Maftei (2006)[d]			x			
Sibai et al. (1989)			x			
Sacks et al. (1995)			x			
Kisters et al. (1993)			x			
I squared	"High"	62%/47%	NA	80%+	0% (SBP); ?? (DBP	62.7%(SBP); 64.7% (DBP)
Change in SBP	-0.6 (n.s.)	-1.26 (n.s.)	NA	-3-4 mm Hedges G = 0.32 (p=0.00)	-18.7 (p<0.0001)	-2.08 (p=0.01)
Change in DBP	-0.8 (n.s.)	-2.13 (p=0.0007)	NA	- 2-3 mm Hedges G = 0.36 (p=0.00)	-10.9 (p<0.0001)	-1.83 (p+0.001)
Mean Mg dose (mmol/day)	15.4	17	NR	16.9	14	15.1
Range of Mg dose (mmol/day)	10 – 40	10 - 40	5 - 40	5 - 40	10.5 – 18.5	9.8 – 39.5
Mg dose effect	Yes	No	Yes	Yes	NR	No

[a] Studies in **bold** are these included as direct substantiation of the proposed claim (see Section III E)
[b] Some citations contain more than one comparison used in the meta-analyses
[c] The same data were published in Saito et al. (1988) and Hattori et al. (1988). Both citations were used depending on the meta-analysis
[d] Included one subject with Stage 2 hypertension at baseline, but this paper was not included in reviews other than Rosanoff (2010); the study employed teens rather than adults, and did not appear in a peer-reviewed journal.

(95% CI: -1.9 to 0.4)) leading the authors to conclude, "Adequately powered trials with sufficiently high doses of magnesium supplements need to be performed to confirm the inverse dose-response relationship observed in our study." Q statistics showed "substantial and significant heterogeneity" in effect size across trials.

Dickinson et al. (2006) conducted a meta-analysis limited to hypertensive subjects ($\geq$ 140/85 mm Hg) who received oral magnesium therapy for at least eight weeks. This analysis of 12 studies (545 participants) found no significant reduction in systolic blood pressure (mean difference:

-1.3 mm Hg, 95% CI: -4.0 to 1.5, I^2=67%) but a significant reduction in diastolic blood pressure (mean difference: -2.2 mmHg, 95% CI: -3.4 to -0.9, I^2=47%) with oral magnesium supplementation. These authors concluded,

> In view of the poor quality of included trials and the heterogeneity between trials, the evidence in favour of a causal association between magnesium supplementation and blood pressure reduction is weak and is probably due to bias. This is because poor quality studies generally tend to over-estimate the effects of treatment. Larger, longer duration and better quality double-blind placebo controlled trials are needed to assess the effect of magnesium supplementation on blood pressure. . .

Rosanoff (2010) published a non-quantitative analysis of all 44 studies (from 40 articles) available at that time which included 1,492 participants. This analysis used conservative criteria to classify the results of such studies as either "decrease" or "no change" in blood pressure. A "decrease" designation was assigned to studies that showed statistically significant decreases in both systolic and diastolic blood pressure from both baseline and control groups; while all other outcomes were designated as "no change." Each study was also designated as "treated" if greater than 50 percent of subjects were on uninterrupted anti-hypertension medication for a minimum of six months. All other studies were designated as employing "untreated" subjects. Studies were also categorized as to hypertension status with "hypertensive" studies showing greater than 45% of subjects with diastolic blood pressures of greater than 90 mm Hg at baseline, while all remaining studies were designated as employing "normotensive" subjects. Each study was assigned to one of three categories: hypertensive-treated subjects, hypertensive-untreated subjects, or normotensive subjects regardless of drug treatment. Each of these tables listed studies in order of ascending magnesium dose. This categorization of both low- and high-quality studies found that studies on hypertensive subjects treated with anti-hypertensive medications showed "decreases" in both systolic and diastolic blood pressure with oral magnesium

supplementation as low at 10 mmol/day, while studies on hypertensive subjects not treated with such medications required a daily magnesium dose two times as high (≥20 mmol/day) to show significant decreases in systolic and diastolic blood pressures. No studies on normotensive subjects, regardless of medication status or magnesium dose, showed significant decreases in systolic and diastolic blood pressure up to oral magnesium doses as high as 40 mmol/day using these very conservative criteria. This author concluded,

> Mg supplements above the RDA may be necessary to significantly lower high blood pressure in Stage I HT unless subjects have been continuously treated with anti-HT medications ≥ 6 months. Such medication use may lower by half the oral magnesium dose needed to significantly decrease high blood pressure. Oral Mg therapy may have no effect in studies with normotensive subjects.

The author went on to apply these findings to Jee et al. (2002), and Dickinson et al. (2006) which were the two meta-analyses that had been published at the time. Only 27.8% of all subjects in the Jee et al. (2002) study and just over half (52.3%) in the Dickinson et al. (2006) study would be expected to show a significant lowering of blood pressure based on their magnesium dose, use of medication and hypertensive status at baseline.

Kass et al. (2012) was the next meta-analysis that examined the effect of oral magnesium supplementation on blood pressure. This analysis included 22 studies among 1,173 normotensive and hypertensive participants and found significant beneficial effects of oral magnesium (using Hedges G) on both systolic (0.32, 95% CI: 0.23-0.41) and diastolic blood pressure (0.36, 95% CI: 0.27 – 0.44). This meta-analysis included 10 of the 12 studies in Dickinson et al. (2006) and 15 of the 20 studies used by Jee et al. (2002). Heterogeneity was high (I^2 = 81.9 – 87.7%), and, like Jee et al. (2002), this group found statistically greater efficacy

of magnesium supplementation at doses of at least 370 mg per day compared to lower doses. The authors concluded,

> Effect size increased in line with increased dosage. Although not all individual trials showed significance in BP reduction, combining all trials did show a decrease in SBP of 3-4 mm Hg and DBP of 2-3 mm Hg, which further increased with crossover designed trials and intake > 370 mg/day. To conclude, magnesium supplementation appears to achieve a small but clinically significant reduction in BP, an effect worthy of future prospective large randomized trials using solid methodology.

Rosanoff and Plesset (2013) published a meta-analysis of two RCTs (Paolisso et al., 1992, Guerrero-Romero and Rodriguez-Moran, 2009) and five non-controlled studies reported in two publications (Sebekova et al., 1992, Michon, 2002) that employed subjects with baseline mean systolic blood pressure greater than 155 mmHg. This very selective analysis (135 subjects) showed remarkable homogeneity (I^2 = 0% for SBP) and reported highly significant decreases in both systolic (-18.7 mm Hg, 95% CI: -14.95 to -22.45; $p<0.0001$) and diastolic blood pressures (-10.9 mm Hg, 95% CI: -8.73 to – 13.1; $p<0.0001$). The authors discussed the three previously published meta-analyses (Jee et al., 2002, Dickinson et al., 2006, Kass et al., 2012) and two other non-high responder studies (Reyes et al., 1984, Sanjuliani et al., 1996) with high baseline systolic blood pressure and concluded,

> This uniform subset of seven studies showed a strong effect of Mg treatment in hypertension, which is in stark contrast to results of three other meta-analyses. Using non-uniform sets of studies, the small effects reported in previous meta-analyses may reflect a blending of dissimilar studies, which acted to seriously underestimate the potential of magnesium in hypertension in some (but not all) subjects. Within studies, blending of non-, moderate and high responder subjects in any one study might mask strong effects of magnesium treatment in some subjects.

Finally, the largest and most recent meta-analysis (Zhang et al., 2016) reported significant decreases of both systolic (2.08 mmHg; 95% CI: 0.49 – 3.68 P=0.01, I^2=62.7) and diastolic

blood pressure (1.83 mm Hg; 95% CI: 0.77 – 2.90 p=0.001, I^2=64.7) in pooled data from 33 high quality studies (2,500 participants) of oral magnesium therapy. This study confirms the findings of Kass et al. (2012) while also including meta-analysis of serum magnesium measured in 26 of the 33 studies. The authors concluded,

> In this meta-analysis of 34 randomized double-blind placebo-controlled trials involving a total of 2028 participants, we found that oral Mg supplementation led to a significant reduction in both systolic and diastolic BPs (2.00 and 1.78 mmHg, respectively), although systolic BP and diastolic BP responses differed slightly in dose- and duration-dependent manners, respectively. The BP-lowering effects of Mg supplementation were accompanied by elevated serum Mg levels. Greater reduction in both systolic and diastolic BPs also tended to be present in trials with high quality or low dropout rate. Taken together, our findings support a causal antihypertensive effect of Mg supplementation in adults.

3. Summary and conclusions

Collectively, the available meta-analyses provide strong evidence that magnesium supplementation has a significant effect on blood pressure. This finding is remarkable because the studies included in the highest quality meta-analyses (Jee et al., 2002, Kass et al., 2012, Dickinson et al., 2006, Zhang et al., 2016), employed a substantial number of subjects for whom the effect of magnesium supplementation on blood pressure is attenuated. Such subjects include those with normal blood pressures, hypertensive or pre-hypertensive subjects not taking anti-hypertensive medications (including the largest magnesium supplementation study (TOHP Study Group, 1992)) and/or those given low doses of magnesium. Furthermore, subjects with stage two or three hypertension (for whom a large magnesium effect on blood pressure would be expected) were excluded from such studies due to ethical concerns.

The one meta-analysis with high homogeneity (Rosanoff and Plesset, 2013) showed a very large effect of magnesium on blood pressure reduction among drug-treated hypertensive subjects with baseline systolic blood pressure of at least 155 mm Hg, but included studies not directly

applicable to the proposed claim because 64% of subjects were not compared to placebo controls. Nevertheless, this analysis illustrates the influence of baseline blood pressure on the magnesium response and provides additional support for the proposed claim.

Finally, the most recent meta-analysis (Zhang et al., 2016) is especially relevant to the proposed claim because it includes 32 of the 44 RCTs that meet FDA's quality standards for the substantiation of health claims and are submitted in this document as direct evidence for the proposed claim (see section III E below).

In conclusion, the Center believes that the available systematic reviews and meta-analyses, while not capable of substantiating the proposed claim in their own right, provide strong support that the totality of scientific evidence from dietary intervention studies demonstrates that magnesium supplementation has a beneficial effect on blood pressure in humans.

D. Observational studies

The majority of observational studies that examined the association between indicators of magnesium status (e.g., dietary intake, urinary excretion, serum concentrations) and blood pressure and/or incidence of hypertension provided direct or partial support for the proposed claim. Most of these studies employed a cross-sectional design; however a variety of ecological, case-control and prospective cohort studies have also been published. As FDA's January 2009, Guidance for Industry: Evidence-Based System for the Scientific Evaluation of Health Claims[9] indicates, observational studies are less convincing that randomized, controlled intervention studies because they are incapable of demonstrating a causal relationship. In addition, cross-sectional studies are the least convincing form of epidemiologic studies for within-population

[9] http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm

observations because dietary intake and disease status are measured at the same time so that it is not possible to determine whether dietary intake of the substance is a factor affecting the risk of the disease or a result of having the disease. In addition, cross-sectional studies calculate the prevalence of a disease based on exposure, and this may be a measure of survival of the disease rather than the risk of developing the disease. For these reasons, FDA has concluded that such studies "have the potential to mislead as errors of interpretation are very common" and consequently given them very little weight in the assessment of health claims. Case-control studies are slightly more convincing than cross-sectional studies, but they too are prone to confounding by limitations such as inability to know whether the consumption of the food or food component of interest was altered by the disease or knowledge of the disease. Therefore, the case-control study design does not control for changes in intake caused by or in response to the disease. Prospective cohort studies are the most convincing type of observational study because the intake of the substance precedes disease development. Therefore, this study design ensures that the subjects are not consuming the substance in response to having the disease. Nevertheless, as with all observational studies, the possibility of confounding by unrecognized variables can never be eliminated so that it is not possible for such studies to establish a cause and effect relationship.

Furthermore, observational studies that examine associations between magnesium status and blood pressure may be especially susceptible to confounding because the mechanisms by which this mineral affects blood pressure are complex and involve several other minerals including calcium, potassium and sodium (Houston, 2011, Kolte et al., 2014). They may also be influenced by myriad other factors including baseline blood pressure, magnesium status, use of anti-hypertensive medications and ethnicity. Therefore, the conclusions that can be drawn from

the epidemiologic literature are limited, and failure to observe an association certainly cannot be taken as evidence for a lack of causality. Nevertheless the presence of such associations provides evidence that the ability of dietary magnesium to reduce the risk of hypertension that is demonstrated by dietary intervention studies can also be observed in free living populations.

1. Studies that provide direct support for the proposed claim

As noted above, the majority of observational studies provide support for the proposed claim. Studies that provide direct support reported statistically significant inverse associations for all forms of blood pressure that were examined (i.e., systolic, diastolic) after correction for whatever potentially confounding variables were considered. Such support was provided by two prospective cohort studies, three case-control studies and six cross-sectional studies. These studies are discussed briefly below. Detailed information about these, and all other observational studies identified by our literature search, is presented in Table II (see page 42).

Two prospective cohort studies provided direct support for the claim. Witteman et al. (1989) examined the association between dietary magnesium (and other nutrients) and self-reported hypertension among 58,218 members of the Nurses' Health Study using a 61-item validated FFQ (food frequency questionnaire). The cohort, followed for four years, reported 3,275 cases of hypertension. Total dietary magnesium was inversely associated with incidence of hypertension (RR =0.72, 95% CI 0.62-0.98) after adjustment for energy and alcohol intake. Further adjustment for intakes of calcium, potassium and dietary fiber only slightly attenuated this association (RR=0.78, 95% CI 0.62-0.98). Dietary magnesium from cereals, dairy and remaining foods other than fruits and vegetables was also significantly inversely associated with incidence of hypertension.

Song et al. (2006) performed a prospective analysis of 23,349 participants of the Women's Health Study. A 131-item validated FFQ was used to collect dietary data. The mean follow-up period was 9.8 years during which time 8,544 cases of hypertension were reported. Dietary magnesium was inversely associated with risk of hypertension (RR=0.87, 95% CI 0.81-0.93; p for trend <0.0001) after adjustment for age and randomization treatment. This inverse association was attenuated (RR=0.93, 95% CI 0.86-1.02) but remained significant (p for trend =0.03) after further adjustment for a wide range of potentially confounding variables. Multivariate analysis of dietary magnesium intake (no supplements) was inversely associated with incident hypertension (RR=0.91, 95% CI 0.83-0.99, p for trend=0.002). This study provides strong evidence for the proposed claim.

The three case-control studies that provided direct support for the proposed claim were Sudhakar et al. (1999), Yang and Chiu (1999) and Panhwar et al. (2014). Sudhakar et al. (1999) studied 86 hypertensive Indian subjects, 77 of their first degree relatives, and 130 healthy controls matched to the hypertensive patients (>140/90 mmHg) as well as 130 separate controls matched to the relatives. The paper did not report blood pressure data and did not state whether the first degree relatives were hypertensive. Serum magnesium concentrations as well as erythrocyte intracellular magnesium concentration were lower ($p<0.01$) in the hypertensives compared to the controls. The same result was reported for first degree relatives compared to their controls.

Yang and Chiu (1999) studied 2,336 residents of Taiwan who died from hypertension and the same number of controls who died by other causes and examined correlations to levels of calcium and magnesium in drinking water from 322 municipalities. The concentration of magnesium in the water was significantly inversely associated with age and sex-adjusted hypertension death risk. The odds ratio for the highest versus the lowest quintile of magnesium

intake from drinking water was 0.80 (95% CI 0.67-0.95). Further adjustment for urbanization level or residence and calcium levels in drinking water strengthened the association (RR=0.63, 95% CI 0.047-0.84). Total magnesium intake was not reported.

Panhwar et al. (2014) conducted a cross-sectional study among 257 Pakistani hypertensive subjects and 166 normotensive controls matched for age, geographic location and socioeconomic status. The magnesium concentrations in hair were higher among controls than among hypertensives for both men (719 vs. 415 µg/g, respectively, p=0.001) and women (739 vs. 441 µg/g, respectively, p=0.001). Similar results were seen for serum magnesium (mg/L)[10] for both men (23.9 vs. 13.5, respectively, p=0.003) and women (24.4 vs. 13.9 mg/L, respectively, p=0.002), and for venous blood (83.8 vs. 61.5 mg/L respectively, p=0.012 for men and 87.2 vs. 63.9 mg/L, respectively, p=0.01 for women). Urinary magnesium was higher (p=0.001) among hypertensive males (99.6 mg/L) than normotensive males (63.6 mg/L). Similar findings were reported for hypertensive vs. normotensive females (102 vs. 68.9 mg/L, respectively, p=0.001). It is possible that the higher urinary magnesium concentrations in the hypertensive subjects were related to the use of anti-hypertensive medications such as diuretics**.**

Seven cross-sectional studies also provide direct support for the proposed claim. Joffres et al. (1987) reported that systolic and diastolic blood pressure were inversely associated (p=0.006 and p=0.008, respectively) with total magnesium intake in a cross-sectional analysis of 615 Japanese men. Magnesium supplement users had an average systolic and diastolic blood pressure of 4.0 and 1.2 mmHg lower than that of nonusers (p = 0.03 and 0.04, respectively).

[10] To convert to mg magnesium per liter to mmol/L multiply by 0.0412

Ideno and Kubena (1989) examined a small sample of 35 women and five men living in Texas. The abstract of the paper states, "Dietary magnesium and dietary calcium to magnesium ratio were directly related ($P<0.05$) to diastolic blood pressure." Very little data were presented in the paper, but the discussion notes there was a significant *inverse* correlation between magnesium intake and diastolic blood pressure ($r= -0.288$; p value not given). Contrary to the wording in the abstract quoted above, the data presented in the paper indicate that an increase in magnesium intake was associated with a decrease in diastolic blood pressure. No data on systolic blood pressure were provided. Dietary data were collected by the 24-hour recall method which may not reflect long-term consumption – especially in such a small study.

Van Leer et al. (1995) reported significant ($p<0.05$) inverse associations between dietary magnesium intake and systolic and diastolic blood pressure among 11,697 Dutch men and 9,224 women after adjustment for age, town, survey year, BMI (body mass index), heart rate as well as alcohol intake. A validated 70-item FFQ was used to obtain dietary information.

Song et al. (2005) conducted a cross-sectional analysis of 11,686 participants of the Woman's Health Study. History of hypertension was inversely associated ($p=0.01$) with magnesium intake. In addition, incidence of high blood pressure ($\geq$135/85 mmHg) was inversely associated with magnesium intake ($p<0.0001$) in this cohort.

Rasic-Milutinovic et al. (2012) examined 90 healthy blood donors living in Russia. Serum magnesium was negatively correlated with systolic (r=-0.226) and diastolic (r=-0.262) blood pressure (both $p<0.05$). However, lack of statistical power and the fact that these subjects were blood donors makes it very difficult to draw meaningful conclusions from this study.

Kim and Choi (2013) conducted a small cross-sectional study among 258 Korean adults. Dietary magnesium was significantly inversely associated with systolic (r=-0.1323, $p<0.05$) and non-significantly associated with diastolic blood pressure (r=-0.1091, $p>0.05$) after correction for age, sex, BMI and energy intake. Once again, limited conclusions can be drawn from this small cross-sectional study conducted in Asia.

2. Studies that provide mixed support for the proposed claim

The majority of observational studies identified in our literature search provided mixed support for the proposed claim. Such studies reported statistically significant protective associations between one or more magnesium-related parameters (e.g., dietary magnesium intake, serum magnesium concentration) and one or more parameters related to CHD (e.g., systolic and/or diastolic blood pressure, incidence of hypertension, incidence of CVD) after correction for all of the potentially confounding variables considered. However, such associations were not observed for all of the magnesium-related parameters examined.

Five prospective cohort studies provided such mixed support. Ascherio et al. (1992) studied the association between dietary magnesium (and other minerals) and hypertension in a cohort of 51,529 men who were participants in the Health Professionals' Follow-up Study. Hypertension was reported by 1,248 subjects during the four year follow-up period. Magnesium intake was inversely associated with risk of hypertension after adjustment for age, Quetelet's index (i.e., BMI) and alcohol consumption (RR comparing the bottom with the top category of intake was 1.49 (95% CI 1.15-1.92, p for trend =0.003)). Please note that this value represents a *protective* association for dietary magnesium. However, further adjustment for intakes of fiber and

potassium attenuated this association (RR=1.12[11], 95% CI 0.80-1.56). Magnesium intake was inversely associated with systolic (r=-3.37, p<0.001) and diastolic blood pressure (r=-3.09, p<0.0001). Analysis of baseline data showed systolic blood pressure was 2.08 mmHg higher (95% CI 1.52-2.64) in the lowest magnesium consumption category (<250 mg/d) while diastolic blood pressure was 1.67 mmHg higher (95% CI 1.20-2.05) in the same intake category (both significant). When magnesium, calcium, potassium and fiber were entered into the model simultaneously, analogous results were: systolic blood pressure 1.38 mmHg lower (95% CI 0.65-2.11) and diastolic blood pressure 0.96 mmHg lower (95% CI 0.47-1.45) in the lowest magnesium consumption category. Data for baseline systolic and diastolic blood pressure demonstrated a significant inverse association with dietary magnesium which was also inversely related to the change in blood pressure during the follow-up period among men who did not develop hypertension. This prospective cohort study provided suggestive evidence that dietary magnesium is inversely associated with hypertension. However, the data in this early study from the Health Professionals' Follow-up Study was presented in a very confusing fashion and were minimally corrected for potential confounding. Nevertheless, this study provides some evidence that supports the proposed claim.

Liao et al. (1998) studied 13,922 members of the Atherosclerosis Risk in Communities (ARIC) cohort living in four U.S. communities during a 4-7 year follow-up period. Serum magnesium concentrations among women and men who developed CHD were lower than among those who did not (p=0.002 for both), however there was no difference in dietary magnesium between these two groups. Serum magnesium was also significantly associated with reduced incidence of CHD in women (RR for quintiles from lowest to highest, 1.0, 0.92, 0.48 and 0.44 mEq/L, p for

[11] Please note the discussion section of the paper reports this value as 1.56, which appears to be a typographical error.

trend=0.009) and men (RR=1.00, 1.32, 0.95, and 0.73 ,p for trend = 0.07) after adjustment for sociodemographic characteristics, waist/hip ratio, smoking, alcohol intake, sports participation, use of diuretics, fibrinogen, total and high-density lipoprotein cholesterol levels, triglyceride concentrations and hormone replacement therapy. There were no such associations for dietary magnesium and the incidence of CHD (RR=0.69, 95% CI 0.45-1.05 for men and RR=1.32, 95% CI 0.68-2.55 for women). The paper noted that there was a low correlation between dietary and serum values of magnesium, which suggests the possibility of inaccuracies in dietary assessment of this cohort. The dietary assessment tool employed was not stated, but is likely that it was the 61-item Willett FFQ adapted for interviewer administration as described in Peacock et al. (1999).

Peacock et al. (1999) also reported data from the ARIC cohort based on 4,190 women and 3,541 men free of hypertension at baseline. Dietary magnesium was assessed using the Willett 61-item FFQ adapted for interviewer administration, and the subjects were followed for six years. Serum magnesium was inversely associated with incident hypertension in women (OR=0.76 for quartiles four vs one, 95% CI=0.58-0.99, p for trend =0.11) after adjustment for baseline age, race, ARIC field center, BMI, waist/hip ratio, diabetes status, education level and systolic blood pressure. There was no such association in men (OR=0.90, 95% CI 0.68-1.18, p for trend 0.50). There were no significant associations between dietary magnesium and hypertension in women (OR=0.69, 95% CI 0.69-1.43) or men (OR=0.98, 95% CI 0.68-1.41) after adjustment for all of the potentially confounding variables noted above. There are no obvious methodological issues with the study, however only about half of the original cohort was included. These data provide partial support for the proposed claim.

Peacock et al. (2010) reported 12 year follow-up data from 14,232 members of the ARIC cohort. The purpose of the study was to examine the association between serum magnesium and sudden

cardiac death, however data on incidence of hypertension were also provided. Dietary magnesium was associated positively with levels of serum magnesium (p=0.0008 by F test from ANOVA). Serum magnesium was inversely associated with the incidence of hypertension (p<0.0001 by F test from ANOVA). This condition was present in 43.8% of hypomagnesemic subjects and 33.6% of normomagnesemic subjects after adjustment for age, race, gender and field center. Multivariate adjusted serum magnesium was inversely associated with sudden cardiac death (RR=0.62 95% CI 0.42-0.93, p for trend = 0.006). The paper stated that dietary magnesium was not associated with CHD or sudden cardiac death after adjustment for possible confounding variables, but detailed data were not provided. No such calculation was made for incidence of hypertension. Similar to other reports form the ARIC cohort, this study provides some evidence of a protective association between serum magnesium and the incidence of hypertension.

Lutsey et al. (2014) reported data from the ARIC cohort with an average follow-up period of 20.6 years. Once again baseline data collected from 1987-89 showed inverse associations with serum magnesium and systolic blood pressure (127 and 119 mmHg for lowest (1.4 mEq/L[12]) vs. highest (1.8 mEq/L) quintiles, p for trend <0.0001)) as well as incident hypertension (52.5% vs. 26.4%, p for trend <0.001). No prospective associations for blood pressure were presented in this paper but serum magnesium was inversely associated with incidence of heart failure (RR=1.66, 95% CI 1.42-1.95, p for trend <0.0001) after adjustment for numerous potentially confounding variables including systolic blood pressure.

One case-control study also provided mixed support for the proposed claim. Rodriguez-Ramirez et al. (2015) studied 520 subjects with prehypertension and 401 normotensive controls (basis for

[12] To convert mEq magnesium per L to mmol/L, multiply by 0.5

selection not specified) living in Mexico. The subjects were drawn from a survey of 4,272 subjects living in six different Mexican cities. Serum magnesium was greater ($p<0.05$) among men without prehypertension (2.00 mg/dL)[13] than with this condition (1.79 mg/dL). Similar results were seen for women (2.01 vs. 1.78 mg/dL, respectively, $p<0.05$). Systolic and diastolic blood pressure were similar ($p=0.54$) between normo- and hypomagnesemic subjects without prehypertension (106.5/67.6 mmHg vs. 105.9/67.1 mm Hg) and between normo- and hypomagnesemic subjects with prehypertension (127/76.4 vs. 126.9/77.3, $p=0.90$). There was no difference between normomagnesemic subjects with and without prehypertension with respect to serum magnesium (2.04 vs. 2.09 mg/dL, respectively) however serum magnesium was greater (1.65 mg/dL) among hypomagnesemic subjects without prehypertension than those with this condition (1.43 mg/dL, $p<0.05$). There was a negative Pearson correlation rank between serum magnesium and systolic ($r=-0.152$, $p<0.0005$) and diastolic blood pressure ($r=-0.165$, $p<0.005$). Multiple logistic regression analysis indicated an association between hypomagnesemia and prehypertension (OR=1.77, 95% CI 1.3-4.4, $p<0.0005$). Adjusted multiple linear regression analysis showed that serum magnesium concentrations are inversely associated with systolic ($\beta=-6.39$, 95% CI -9.8 to -1.5) and diastolic blood pressure ($\beta=-2.6$, 95% CI -2.9 to -1.3) in the subjects with prehypertension, but not among normotensive individuals ($\beta=0.66$, 95% CI -1.7 to 3.0 and $\beta=-0.93$, 95% CI, -3.1 to 1.1 for systolic and diastolic blood pressure, respectively).

Finally, mixed support for the proposed claim was provided by 13 cross-sectional studies. Johnson et al. (1987) found that serum magnesium concentrations were inversely associated with systolic ($p<0.001$) but not diastolic blood pressure among women in a study of 62 U.S. residents

[13] To convert mg magnesium per dL to mmol/L, multiply by 0.411. Both units are used throughout this document.

living in Georgia. There was also a non-significant inverse association between dietary magnesium and blood pressure in this small study.

Karanja et al. (1987) reported that magnesium intake was lower ($p<0.05$) among 22 hypertensive women than 19 normotensive counterparts. No such difference occurred between eight normotensive and 21 hypertensive males in this very small study from Oregon.

Kesteloot and Joossens (1988) stated that multiple regression analysis yielded a significant negative correlation between dietary magnesium and systolic blood pressure among 3,891 women living in Texas. The partial regression coefficient for this association was -14.43, but the statistical analysis was unconventional and difficult to interpret. There was no such association among 4,167 men or in subsamples of this population that were not taking antihypertensive medication.

He et al. (1991) studied 400 men from four separate locations in population groups studied in southern China. There were no significant associations at the ecological level (among the 14 different villages studied) between dietary, serum or urinary magnesium and blood pressure. However, univariate and multivariate analysis at the individual level showed a significant inverse association between dietary magnesium and systolic and diastolic blood pressure ($p=0.0001$ for all) with no such associations for serum or urinary magnesium.

Ma et al. (1995) reported cross-sectional data from the U.S. based ARIC study cohort of 15,248 participants. Serum magnesium was inversely associated with systolic blood pressure among white and black men and among white women (all $p\leq0.01$) while no such association was observed for black women or for diastolic blood pressure in any of the groups. Dietary magnesium was inversely associated ($p\leq0.01$) with systolic blood pressure among white and

black women but not among their male counterparts. There were also significant associations of dietary magnesium with diastolic blood pressure for white and black women as well as black men. Data were adjusted for BMI and alcohol intake, but not for additional potentially confounding variables.

Bo et al. (2006) reported a cross-sectional analysis of 1,653 Italian adults. There was no association between magnesium intake and systolic blood pressure, but diastolic blood pressure was inversely associated with intake of this nutrient ($p<0.001$) after adjustment for energy intake.

Ford et al. (2007) reported data from the NHANES III study on 7,669 participants 20 years of age or older. The purpose of the study was to assess risk factors for metabolic syndrome. There was no significant association between magnesium intake and incidence of high blood pressure on an unadjusted basis. The third and fourth quintile of magnesium intake were, however, associated with this condition (RR=0.64, 95% CI 0.45-0.92, and RR=0.60, 95% CI 0.39-0.91, respectively) but there was no association for the upper quintile or for overall trend.

Beydoun et al. (2008) also conducted analyses from the NHANES studies. The study included 14,618 volunteers from surveys conducted in 1999-2000, 2001-2002 and 2003-2004. Dietary magnesium (per 100 mg) was inversely associated with diastolic blood pressure (-0.62, $P<0.05$) but not with systolic blood pressure (-0.39) among men after adjustment for age, sex, race, socioeconomic status, energy intake and physical activity. However, no such associations for systolic or diastolic blood pressure were noted for women (-0.31 and -0.29, respectively).

Choi and Bae (2013) studied 5,136 members of the Korea National Health & Nutrition Examination Survey (KHANES) from 2007-2008. Women subjects with hypertension had significantly lower magnesium intakes ($p<0.0001$) than subjects without this condition after

adjustment for age. No such association was reported in men (p=0.9499). The conclusions that can be drawn from this study in Korea are limited because the blood pressure data were not corrected for potentially confounding variables other than age.

Chidambaram et al. (2014) reported that urinary magnesium (mg per gram creatinine) was lower among hypertensive subjects (n=52) compared to 115 normotensive individuals (137.07 vs. 82.58) but not significantly so (p=0.262). However, this difference was significant among middle aged participants 40-59 years of age (112.95 vs. 85.35 mg, p=0.014). Data reporting in this small study was very limited.

Guasch-Ferre et al. (2014) reported that magnesium intake at baseline was not associated with prevalence of hypertension among 7,216 adults at high risk of CVD enrolled in the PREDIMED (Prevencion con Dieta Medeterranea) cohort in Spain. This study reported a variety of inverse associations between magnesium intake and cardiovascular events, cardiovascular mortality, cancer mortality and all-cause mortality, but did not report such findings individually for blood pressure.

Papanikolaou et al. (2014) analyzed data from five separate NHANES studies including 14,338 subjects at least 20 years of age during the period between 2001 and 2010. Subjects who consumed at least the EAR of magnesium from food alone had slightly, but significantly, (p=0.0279) lower systolic blood pressure than those who did not, but there was no such difference in diastolic blood pressure (p=0.718). The same outcome was observed for systolic (p=0.0297) and diastolic (p=0.6621) blood pressure based on magnesium intake from foods plus dietary supplements. There was a significant trend for lower systolic blood pressure with increasing quartile of magnesium consumption from foods plus supplements (p=0.0029) and

from foods alone (p=0.0074), however the magnitude of the change was very small (less than 2 mm Hg). There was a significant opposite trend for diastolic blood pressure with increasing magnesium intake from total diet (p=0.0168) and foods alone (p=0.0009), but once again, the absolute difference was very small. There was an inverse association for elevated blood pressure (OR=0.83, 95% CI 0.70-0.99, p=0.0673) and elevated systolic blood pressure (OR=0.81, 95% CI 0.68-0.97, p=0.0298) comparing the upper and lower quintiles of magnesium from food and supplements, but no such association was observed for diastolic blood pressure. Similar results were reported for magnesium intake from food alone which showed an inverse association for elevated blood pressure (OR=0.77, 95% CI 0.64-0.93, p=0.030) and systolic blood pressure (OR=0.77, 95% CI 0.65-0.93, p=0.0017) but not for diastolic blood pressure (OR=0.95, 95% CI 0.80-1.12). The large sample size and sophisticated sampling plan of the NHANES studies provides considerable statistical power and allows generalization to the entire U.S. population, but the study still suffers the shortcomings of cross-sectional methodology as noted previously.

Rotter et al. (2015) examined 313 Polish men aged 50-75 years of age. Serum magnesium was lower among 171 members of this cohort who had hypertension compared to normotensives (0.85 vs. 0.88 mmol/L, p=0.0001) and this parameter was inversely correlated with systolic (r=-0.15, p=0.006) but not diastolic blood pressure (r=-0.0004, p=0.99). Logistic regression modeling showed that serum magnesium was inversely associated with the incidence of hypertension (RR=0.84, 95%CI, 0.743-0.942; p=0.003).

3. Studies that did not provide support for the proposed claim

Two prospective cohort studies, six cross-sectional studies and one ecological study failed to provide support for the proposed claim. This category includes studies which may have reported significant protective associations between a magnesium-related parameter and blood pressure

based on unadjusted or partially adjusted data but which was no longer significant on a fully-adjusted basis.

The two prospective cohort studies that do not support the proposed claim were He et al. (2006) and Khan et al. (2010). He et al. (2006) studied 4,637 members of the Coronary Artery Risk Development in Young Adults (CARDIA) study who were 18 to 30 years of age at baseline for an average follow-up period of 15 years. Dietary data were obtained with a validated FFQ. Magnesium intake was not associated with systolic or diastolic blood pressure at baseline for black men and women; however both systolic ($p<0.01$) and diastolic ($p=0.04$) blood pressures were inversely associated with magnesium intake among white men and women. Total magnesium intake was inversely associated with elevated blood pressure (systolic blood pressure ≥130 mmHg, or diastolic blood pressure ≥85 mmHg) among all participants at the 15-year follow-up period (RR=0.78, 95% CI 0.63-0.97, p for trend <0.01) after correction for age, gender, race, education, smoking, physical activity history of diabetes, alcohol consumption and baseline BMI, but the association was attenuated (RR=0.87, 95% CI 0.69-1.10, p for trend=0.11) after further adjustment for dietary fiber, polyunsaturated fat, saturated fat, carbohydrates and total energy. This finding is not unexpected because associations between dietary fiber and magnesium have been reported (Hopping et al., 2010) and Lukaski et al. (2001) reported that there is a negative association between magnesium availability and saturated fat intake. Nevertheless, magnesium intake was inversely associated with incidence of the metabolic syndrome (RR=0.69, 95% CI 0.52-0.91, p for trend <0.01) after adjustment for all of the potential confounders noted above.

Khan et al. (2010) studied 3,531 middle-aged members of the Framingham Heart Study offspring cohort. There were 551 new cases of hypertension during the eight year follow-up period. The

study also examined CVD events using a 20-year follow-up period. Multivariate analysis showed that serum magnesium concentration was not associated with development of hypertension (RR=1.03, 95% CI 0.92 – 1.15) after 8 years. This study does not support the proposed claim; however no dietary data were reported, and there was only limited data on the distribution of serum magnesium concentrations (i.e., 0.58-0.99 mmol/L for men and 0.47-1.01 mmol/L for women). Nevertheless, the paper stated that 12 of 2,520 subjects had serum magnesium levels less than 0.61 mmol/L while 24 subjects had values greater than 90 mmol/L at baseline. These data are consistent with the notion that the population was dominated by magnesium replete individuals. In addition, the subjects were normotensive at baseline so that failure to observe a significant association with serum magnesium is not unexpected.

The six cross-sectional studies that did not provide evidence in support of the proposed claim are discussed briefly below. Hajjar et al. (2001) conducted an analysis among all individuals greater than 20 yrs (n=17,030) in the NHANES III study. Standardized daily intake of magnesium per calorie was inversely associated with mean systolic and diastolic blood pressure as well as pulse pressure ($p<0.01$). However multivariate analysis revealed no such significant associations.

McKeown et al. (2008) conducted a small cross-sectional study among 535 mature adults (60-72 years) living in Boston. There were no significant associations between dietary magnesium and blood pressure. Dietary magnesium was below the RDA and approximately one-third of the subjects were taking anti-hypertensive drugs which may have confounded the results. Dietary assessment of this small study was conducted by 3-day food record which may not reflect typical daily intake – especially among such a small study.

Kesteloot et al. (2011) reported data from the International Study of Macro- and Micro-Nutrients and Blood Pressure (INTERMAP) and the International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT) study consisting of 4,679 and 10,067 participants, respectively. The INTERMAP study was conducted from 17 populations in China, Japan, the United Kingdom and the U.S. while the INTERSALT study involved 52 centers from around the world. In the INTERSALT study, magnesium excretion was inversely associated with systolic blood pressure ($p<0.05$) and diastolic blood pressure ($p>0.0001$) after adjustment for age, gender, sample, weight and height. These associations remained significant ($p<0.05$ for SBP and $p<0.001$ for DBP) after further adjustment for special diet, physical activity, physician-diagnosed heart attack or stroke, history of hypertension and smoking. However, these associations were no longer statistically significant after additional adjustment for alcohol intake, 24-hour excretion of sodium and potassium, dietary cholesterol, saturated fatty acids, polyunsaturated fatty acids, calcium intake, magnesium intake and animal protein intake. Data from INTERMAP showed no statistically significant association between magnesium excretion and systolic blood pressure while diastolic blood pressure was inversely associated with this parameter ($p<0.0001$) after adjustment for the potentially confounding variables noted above, but not after further adjustment for alcohol intake and urinary excretion of sodium and potassium. Mean systolic blood pressures ranged from 117.2 (Japan) to 121.3 mmHg (China) and mean diastolic pressures ranged from 73.2 (China) to 77.3 mmHg (UK). Therefore, the lack of an association with fully-adjusted data from this mostly normotensive population is not unexpected. In addition, the heterogeneous nature of the populations included in multi-center global studies such as the ones reported in this paper limit their applicability to the general U.S. population.

Syedmoradi et al. (2011) studied 1,558 adults living in Iran. There was no association between serum magnesium and systolic (r=0.028, p=0.274) or diastolic blood pressure (r=0.042, p=0.101). However, these results are not surprising because the subjects had normal blood pressures and were magnesium replete.

Huang et al. (2012) reported marginal, but insignificant, associations between dietary magnesium concentrations and systolic (r=-0.123, p=0.074) and diastolic blood pressure (r=-0.128, p=0.065). There were also no associations between magnesium intake and systolic blood pressures greater than 130 mmHg or diastolic blood pressures greater than 80 mmHg (RR=0.60, 95% CI, 0.21-1.7, p-for trend=0.452) among 210 type-2 diabetic patients living in Taiwan. However, few conclusions can be made from this very small study due to lack of statistical power and the inability to extrapolate results from type-2 diabetic Asian subjects to the general U.S. population.

Guerrero-Romero and Rodriguez-Moran (2013) studied 427 adults living in Durango, Mexico who were divided into four categories: Normal weight (n=45), obese (n=253), metabolically-healthy obese (n=98) and metabolically obese normal weight (n=31). Multivariate analysis showed no association between serum magnesium and hypertension among non-obese (OR=0.11, 95% CI 0.11-12.41) or obese (OR=0.88, 95% CI 0.41-1.71) subjects. The limited statistical power of this small cross-sectional study (as illustrated by the very wide 95% CI of the non-obese subjects) makes it difficult to draw meaningful conclusions.

Finally, one population-based ecological study was identified that did not support the proposed claim. Yamori et al. (1992) reported blood pressure data from 48 centers in 20 countries. Twenty-four hour urinary magnesium was significantly inversely associated with systolic and diastolic blood pressure in 8.5 and 10.6 percent of these centers, respectively. There were no

other statistically significant associations observed between urinary magnesium concentration and systolic or diastolic blood pressures in any of the other centers. However, using data from the entire population (n=4,265), urinary magnesium was not significantly associated with systolic or diastolic blood pressure. The 2009 FDA Guidance document noted in the introduction concluded that ecological studies are the least reliable types of observational study.

4. Overall summary of observational studies capable of supporting the proposed claim

In summary, the observational studies that have examined the possible association between magnesium intake and/or status and CHD or its surrogate endpoints (including blood pressure) provide consistent support for the proposed claim. As shown in Table III, 79 percent of the 38 observational studies identified by our literature search provided positive or mixed support for the proposed claim. This figure includes 76 percent of the cross-sectional studies, 100 percent of the case-control studies and 78 percent of the prospective cohort studies. Consideration of only the prospective cohort studies and case-control studies (the two most reliable forms of observational studies) reveals that 11 out of 13 studies 85 percent of such studies provide direct or mixed support for the claim while only 15 percent failed to do so. The strongest support for the proposed claim is provided by the prospective cohort studies. Two such studies (Witteman et al., 1989, Song et al., 2006) were completely supportive while five studies (Ascherio et al., 1992, Liao et al., 1998, Peacock et al., 1999, Peacock et al., 2010, Lutsey et al., 2014) provided suggestive evidence that was consistent with the premise that magnesium is beneficially associated with the risk of CHD (or its surrogate endpoints including blood pressure). Only two prospective cohort studies provided data unsupportive of the proposed claim.

Table II
Summary of Observational Studies on Magnesium and Blood Pressure

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Joffres et al. (1987)	Cross-sectional assessment of a prospective cohort	Japanese men born between 1900-1919 living in Oahu in 1965 with no history of CVD or HTN. 615 subjects analyzed from 1980-1982 follow-up visit.	61 dietary variables collected by 24-hr recall along with questionnaire asking about brand names and dietary supplement use to be related to CHD, stroke or cancer at time of follow-up exam	Total Mg intake (Mg from foods and supplements) was strongly and inversely associated with SBP ($p=0.006$) and DBP ($p=0.008$). The largest decrease in blood pressure was noted from the 1st to the 2nd quartile of intake (SBP 4.6 mmHg, DBP 2.8 mmHg). Results were similar when dietary Mg without supplement was examined although the association with DBP was borderline ($p = 0.06$). An inverse association was also found between BP and Mg supplement. Supplement Mg users had an average SBP 4 mmHg and DBP 1.2 mmHg lower than nonusers ($p = 0.03$ and 0.04, respectively). Mg had the strongest association with BP in univariate and multi-variate analyses.	Small number of subjects. Japanese men living in Hawaii may not reflect the general US population due to different dietary habits, but detailed dietary information was not presented.	-
Johnson et al. (1987)	Cross-sectional	62 middle income residents aged 54-81 (6 blacks, 56 whites; 23 males, 39 females) from Evans County GA.	97 item FFQ developed by Caster and venous blood samples for calcium and Mg concentrations.	Mg intake (122-185 mg/d) was inversely related to BP in men and women but not statistically significant. Serum Mg (1.93-2.25 mg/dl) was inversely correlated to SBP in females ($p<0.05$).	Very small number of subjects. FFQ not validated.	-
Karanja et al. (1987)	Cross-sectional analysis of BL data from an RCT	48 hypertensive and 32 normotensives aged 21-70 were recruited from Outpatient clinic of the Oregon Health Sciences Univ.	Nutrient intakes assessed by means of three 24-hr recalls taken by dietitian and analyzed for 13 nutrients at Univ. Mass, Amherst.	Average intake of Mg in hypertensives: male 386 ±192 mg/d; females 223 ±45 mg/d. Normotensive: males 370 ±61 mg/d, females 305 ±122 mg/d. Hypertensive female subjects consumed significantly less ($p<0.05$) magnesium than did normotensive subjects.	Small sample size.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Kesteloot and Joossens (1988)	Cross-sectional	Nutritional survey in men and women aged 25-74 (mean 48 ±13 yrs) carried out from 1979-1984 in a randomly selected segment of the Belgian population (N=4,167 for men and N=3,891 for women).	Dietary intake of sodium, potassium, calcium, and Mg using 24-hour food records checked by a dietitian and correlated with blood pressure. Mg content of food items was obtained from the food composition tables of Paul and Southgate and from the Dutch food tables. Two BP determinations were made.	Mg intake for total group in men was 397 ±145 mg/d; women 306+100 mg/d. In the group not taking antihypertensives (untreated group) Mg intake in men was 401 ±145 mg/d and untreated women 312 ±100 mg/d. SBP/DBP for total group men, 136 ±18.1/82.2 ±12.1 mmHg, untreated 134.8 ±17.2/81.5 ±11.8 mmHg. SBP/DBP for total group women, 131.7 ±21.0/79.8 ±12.4 mmHg; untreated women, 128.3 ±18.8/78.4 ±11.7 mmHg. In multiple regression, a significant negative correlation was found between dietary calcium intake and DBP in men and between dietary Mg intake and SBP in women [partial regression coefficient -14.43].		-
Ideno and Kubena (1989)	Cross-sectional	35 women (28 white, 6 black and 1 Hispanic) and 5 men (4 white, 1 black) ages 65-86 (mean 76 yrs) were recruited from a congregate meal program or apartment complex in Bryan, Texas.	24-hour recall of dietary intake and information on other factors which could affect dietary intake, such as transportation and kitchen facilities.	45% of subjects had HTN, with 47.5% taking antihypertensive agents. Mg intake males 286 ±140 mg/d (82% RDA); females 336 ±239 mg/d (112% RDA). 38% of subjects reported using supplemental vitamins or minerals. Significant correlation between DBP and Mg intake (r= -0.288) p value not given. The abstract of the paper states, “Dietary magnesium and dietary calcium to magnesium ratio were directly related (P<0.05) to DBP.”	Small sample of elderly subjects. 24-hr recall may not reflect long-term consumption patterns	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Witteman et al. (1989)	Prospective cohort	98,462 predominantly white US female registered nurses, aged 34-59 yrs from the Nurses' Health Study. 58,218 women entered into final analysis. 3,275 incident cases of HTN were reported on the 1982 or 1984 questionnaire. Mean follow-up period = 4 years.	Semiquantitative FFQ of 61 food items, including alcoholic beverages. Mg intake was calculated only from food sources as information on supplementation was not available in 1980. BP defined by self-report in the previous 2 years.	Total dietary Mg inversely associated with HTN (RR for upper quintile (≥350 mg/d)=0.72; 95% CI 0.62-0.98) vs. lower quintile after adjustment for energy and alcohol. Further adjustment for intakes of Ca, K and fiber only slightly attenuated the association (RR=0.78, 95% CI 0.62-0.98). Mg intake also inversely associated with HTN from cereals (RR=0.88, 95% CI 0.80-0.96, p for trend 0.011), dairy (RR=0.86, 95% CI 0.78-0.95, p for trend = 0.002) and remaining foods other than fruits and vegetables (RR=0.82. 95% CI 0.72-0.92, p for trend = 0.002). Association of Mg intake from fruits and vegetables not significant (RR=0.88, 95% CI 0.74-1.05, p for trend 0.33).	This is the first report of significant protective association of Mg with hypertension in a large, well-conducted prospective cohort study. FFQ and adjustment for potentially confounding variables less extensive than in subsequent prospective cohort studies.	Ø
He et al. (1991)	Cross-sectional	Random subsample included 400 men >15 yrs from 4 population groups studied in Puge County, southern China: 119 Yi farmers (remote mountains), 114 Yi farmers (mountainside), 89 Yi migrants to lowlands, and 97 native residents of County seat - Han people.	Three 24-hour dietary recalls were conducted by trained dietitians on the same days as 24 hr urine sample collections (men only). Supplemental surveys also conducted regarding other foods consumed.	Ecological analysis (across all groups) found no significant correlation between dietary or urinary Mg and SBP (r= -0.18) or DBP (r=-0.45). Univariate and multivariate analysis showed an inverse association b/w dietary Mg and SBP (r=-0.170, p=0.0001) serum Mg and SBP (r=-0.263, p=0.0001,) but not urinary Mg and SBP (r=-0.203, p=0.281). Similar results were also reported for DBP (r=-0.178, p=0.0001, r=-0.254, p=0.0001, and r=-0.353, p=0.36, respectively). There was also a significant inverse relation of the Mg/creatinine ratio to both SBP (beta= -2.721, p=0.003) and DBP (beta= -4.052, p=0.0001). Multiple regression analysis yielded similar results to univariate.	Small sample size. The rural Chinese population does not reflect the general US population.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Yamori et al. (1992)	Population-based ecological study	Data from 48 centers in 20 countries. From each population, 100 men and 100 women aged 50-54 were randomly selected for BP, 24-hr urine collection, blood tests and medical interview.	Dietary Mg was not assessed.	In 4,265 subjects not on HTN meds collected 24 hr urine samples. 24-hr urinary Mg was significantly inversely associated with SBP in 8.5% of 47 centers and with which had such data (p-value not provided). DBP was significantly (p-value not provided) in 10.6% of such centers. The remaining centers showed non-significant positive or inverse associations with urinary Mg. Urinary Mg was not significantly associated with S/DBP among the entire population.	No dietary data. Only 100 subjects from each center. Within center analysis using multiple linear regression implied Mg may have a beneficial influence on BP.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Ascherio et al. (1992)	Prospective cohort	Health Professionals Follow-up Study of 51,529 subjects 40-75 yrs old initially recruited in 1986. 30,681 eligible men were followed for HTN incidence in the subsequent 4 years. The 1988 f/u questionnaire was returned by 29,306 (95.5%) of that sample and the 1990 f/u questionnaire by 27,698 (90.3%).	A semiquantitative FFQ of 131 items plus vitamin supplements was administered. Nutrients were adjusted for total caloric intake and for each calorie-adjusted nutrient, 5 levels of intake were analyzed. Analyses of HTN risk were based on 4-year cumulative incidence rates. Examined was the association between nutrient intakes in 1986 and BP reported in 1986 (baseline) and in 1990. Also assessed the associations of dietary factors and BP change from 1986 to 1990 using the 1990 pressure as dependent variable and 1986 BP as a covariate. Nutrients were added to the models as continuous variables to test for a linear trend between nutrient intakes and BP.	During the four years of f/u, 1,248 cases of HTN were diagnosed. The basic logistic model controlled for Quetelet's index (the same as BMI), age and alcohol consumption. Age adjusted RR comparing the bottom with the top category of intake was 1.49 (95% CI 1.15-1.92, p for trend =0.003)*. Similar data for multivariate-adjusted associations were no longer significant (RR=1.12**, 95% CI 0.80-1.56, p for trend = 0.66). Mg was inversely associated with SBP (r=-3.37, p<0.001) and DBP (r=-3.09, p<0.0001). Analysis of baseline data showed SBP was 2.08 mmHg higher (95% CI 1.52-2.64) in the lowest Mg consumption category (<250 mg/d) while DBP was 1.67 mmHg higher (95% CI 1.20-2.05) in the same intake category (both significant). When magnesium, calcium, potassium and fiber were entered into the model simultaneously analogous results were: SBP 1.38 mmHg lower (95% CI 0.65-2.11) and DBP 0.96 mmHg lower (95% CI 0.47-1.45). * This value represents an inverse (protective) association b/w Mg intake and hypertension because the highest consumption level (≥400 mg/d) was used as the reference point (RR=1.0). The current convention is to use the bottom intake level as the reference point. **The body of the paper notes this value to be 1.56 which the reviewer believes to be an error. The value 1.56 does not appear as a relative risk in the table referred to (Table1).	Paper uses modern FFQ developed by Willett. The results are presented in a confusing fashion, but support an inverse association b/w Mg and S/DBP both at baseline and during the 4-yr follow-up period. The data also provide suggestive evidence of such an association between Mg and hypertension but correction for potassium and fiber attenuated the result.	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Ma et al. (1995)	Cross-sectional	ARIC is a biracial cohort, aged 45-64 years at entry from 4 US communities (Forsyth county, NC; Jackson, MS (AA only); the Northwest suburbs of Minneapolis, MN, and Washington County, MD). This report included 15,248 participants, male and female, black and white.	Fasting serum Mg, lipids, fasting glucose and insulin, usual dietary intake by Willett 61 item FFQ. Prevalent HTN was defined as SBP≥140 mmHg and DBP ≥90 mmHg.	Mean serum Mg levels were significantly lower in participants with prevalent CVD, HTN, and diabetes than in those free of these diseases. In participants without CVD, serum Mg levels were also inversely associated w/ SBP (r=-0.06, p≤0.01) but not w/ DBP (r=-0.01) in white men and white women (identical values). Mg was also inversely associated with SBP in black men (r=0.08, p≤0.01) but not w/ DBP (r=-0.04). There were no associations between serum Mg and SBP or DBP in black women (r=-0.04 and 0.01, respectively). Dietary Mg was inversely associated (p≤0.01) with SBP and DBP in white and black women: SBP (r=-0.06 and -0.07, respectively) and DBP (r=-0.05 and -0.07, respectively). Dietary Mg was not associated with SBP in white or black men (r=0.01 and -0.04, respectively) while such an association for DBP was seen in black men (r=-0.09, p≤0.01) but not white men (r=-0.03).	Data were adjusted for BMI and alcohol intake, but not additional potentially confounding variables. Utilized the older 61-item Willett FFQ. Longitudinal data from this cohort are presented in subsequent publications summarized below (Peacock et al., 1999, Peacock et al., 2010, Liao et al., 1998).	Ø
Van Leer et al. (1995)	Cross-sectional	Monitoring Project on Cardiovascular Risk Factors with screening performed between 1987 and 1991 in Amsterdam, Doetinchem and Maastricht. Each year a new random sample of men and women aged 20-59 years was selected in each city. Sample was stratified according to gender and 5-year age groups. Total sample size 20,921; 11,697 men, 9224 women. Mean age of 41.5 yrs.	Usual dietary intake was assessed by using a validated, 70 food item self-administered semi-quantitative FFQ. Nutrient content evaluated based on Netherlands (NEVO) food table containing 1,300 foods. Average of 2 BP measures used for analysis.	Mean Mg intake: males 429 mg/d, females 359 mg/d. After adjustment age, town, survey year, significant inverse associations were observed between Mg and both SBP (r=-2.71, 95% CI -4.52 to -0.92 for men and r=-5.83, 95% CI -8.03 to -3.63 for women) and DBP (r=-5.43, 95% CI -6.73 to -4.13 for men and r=-5.62, 95% CI -7.12 to -4.15 for women). These associations remained significant after further adjustment for heart rate, BMI, alcohol and energy intake for both SBP (r= -6.74, 95% CI -9.74 to -3.74 for men and r=-7.83, 95% CI -12.2 to -3.43 for women) and DBP (r= -6.18, 95% CI -8.28 to -4.08 for men and r=-5.75, 95% CI -8.65 to -2.85 for women). The relation between Mg intake and BP was stronger than those between BP and intakes of potassium and calcium.		Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Liao et al. (1998)	Prospective cohort	Middle age adults from the Atherosclerosis Risk in Communities (ARIC) study (n=13,922; 7767 women, 6155 men) 45-64 year old free of baseline CHD with baseline serum Mg measures were evaluated from 4 US communities (Forsyth County, NC; Jackson, Miss (blacks only), Minneapolis, Minn. and Washington County, MD). Sample included approx. 27% blacks and 73% whites. The follow-up period was 4-7 years.	Details of dietary methodology not provided in this paper however it was likely the 61-item Willett FFQ adapted for interviewer administration described in Peacock et al. (1999) (see below). BP was measured 3 times in succession and the mean of the last 2 measurements was used for analysis.	Dietary Mg intake ranged from 39.9 to 485.1 mg/1000 kg and was significantly skewed to the right. Serum Mg levels ranged from 0.5 to 3.1 mEq/L and was normally distributed. Pearson correlation between serum Mg and dietary Mg was low; r=0.04 in women and r=0.09 in men. After adjustment for multiple sociodemographic factors and risk factors the RR of CHD across quartiles of serum Mg was 1.0, 0.92, 0.48 and 0.44 (p for trend=0.009) among women and 1.00, 1.32, 0.95, and 0.73 (p for trend = 0.07) among men. The adjusted RR of CHD for the highest vs. the lower quartile of dietary Mg was 0.69 in men (95% CI 0.45-1.05) and 1.32 in women (95% CI 0.68 to 2.55).	The paper stated that dietary Mg was associated negatively with most CHD risk factors but did not provide specific data. Limited information on dietary Mg and blood pressure. A subsequent paper from this cohort (Lutsey et al., 2014) reported significant protective associations b/w serum Mg and BP as well as incidence of heart failure after a follow-up period of 8-10 years.	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Peacock et al. (1999)	Prospective cohort	ARIC is a biracial cohort, aged 45-64 years at entry from 4 US communities (Forsyth county, NC; Jackson, MS (AA only); the Northwest suburbs of Minneapolis, MN, and Washington County, MD). This report included 7731 participants (4190 women and 3541 men) free of HTN at baseline (1987-89) and followed six years.	Fasting serum Mg was measured, and usual dietary intake was assessed with a Willett 61-item FFQ adapted for interviewer administration. BP was measured 3 times in succession and the mean of the last 2 measurements was used for analysis. Primary endpoint was incident HTN (defined as SBP≥140 mmHg and DBP ≥90 mmHg) at visit 3 and six years later. Used logistic regression (3 models) to calculate the multivariate adjusted odds ratio of incident HTN in relation to quartiles of serum Mg or dietary Mg.	Serum Mg levels ranged from 0.7 to 2.3 mEq/L and appeared to be normally distributed. Dietary Mg intake ranged from 31-864 mg/d and was skewed to the right. There was no linear association between serum and dietary Mg levels (Pearson correlation coeff. = 0.053). Over 6 years, 20% of women, 21% of men, 32% of AA and 18% of other ethnic groups became hypertensive. Women who developed HTN (n=822) had lower serum Mg levels (1.64±SEM 0.005 mEq/L) than did those who remained free of HTN (n=3368, 1.66±0.002 mEq/L). Men who developed HTN (n=755) had only slightly lower serum Mg levels than men (n=2786) without incident HTN (1.65±0.005 mEq/L vs. 1.66±0.003 mEq/L, respectively; p=0.08). In an adjusted model (baseline age, race and ARIC field center, BMI, waist/hip ratio, diabetes status, education level, SBP) for incident HTN in relation to quartiles of serum Mg or dietary Mg women continued to show a weak negative association between serum Mg and the odds of incident hypertension (OR=0.76 for quartiles 4 vs 1, 95% CI=0.58-0.99, p for trend =0.11), while there was no statistically significant association in men (OR=0.90, 95% CI 0.68-1.18). There were no significant associations b/w dietary Mg and HTN in women (OR=0.69, 95% CI 0.69-1.43) or men (OR=0.98, 95% CI 0.68-1.41) after adjustment for all of the potentially confounding variables noted above.	Only about half of the original ARIC cohort (n=15,248) reported by Ma et al. (1995) participated in this study. The primary emphasis of the ARIC study appeared to be serum (rather than dietary) Mg.	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Sudhakar et al. (1999)	Case-control	86 (42 male, 44 female) essential hypertensives living in India and their first degree relatives (77; 44 male, 33 females) and 240 sex and age matched controls (130 against hypertensives and 110 against first degree relatives). Age range not given.	No dietary data presented	Serum Mg levels were decreased (P<0.01) in hypertensive (0.86 mmol/L) when compared to matched controls (0.96 mmol/L). Serum Mg concentrations were 0.89 mmol/L in first degree relatives vs. 0.95 mmol/L in matched controls. Erythrocyte levels showed a similar pattern.	Indian subjects not reflective of the general US population.	-
Yang and Chiu (1999)	Population based, case-control	2,336 HTN deaths (by ICD-9 code) in Taiwan (1,500 men and 836 women) mean age 62.9 yrs from 1990 through 1994 and 2,336 controls (deaths from other causes) correlated to levels of calcium and Mg in drinking water of residents of 322 municipalities.	Four water samples (one for each season) were collected from 252 municipalities' water works. Water samples collected and measured by the Water Quality Research Ctr. of the Taiwan Water Supply Corp.	The concentration of magnesium in the water was significantly inversely associated with age and sex-adjusted hypertension death risk. The odds ratio for the highest versus the lowest quintile of Mg intake from drinking water was 0.80 (95% CI 0.67-0.95). Further adjustment for urbanization level or residence and calcium levels in drinking water strengthened the association (RR=0.63, 95% CI 0.047-0.84). Sig. protective dose-response effect on risk of death from HTN (X2 for trend = 29.05, P<.001). The increased Mg group had a 27% to 37% lower risk of death from HTN.	No dietary intake data. Subjects from Taiwan not reflective of general US population. Numerous possible confounding variables not control for.	-
Hajjar et al. (2001)	Cross-sectional	NHANES III sample on all individuals >20 yrs (n=17030). Mean age 48.8±0.2 yrs, 47% male, 42% white, 28% AA, 26% Hispanic and 4% other. Mean BMI 27.1±0.2.	24 hr recall data for sodium, potassium, calcium, Mg, protein, alcohol, and total energy and blood pressure.	Overall mean Mg intake was 280±1 mg/d; white 300±2 mg, AA 243±2; male 332±2, female 242±1. SBP was not associated with sodium, Mg, calcium or protein intake. SBP, DBP and pulse pressure (PP) was negatively associated with energy-adjusted Mg intake (P<0.001). In the final multivariate model S/DBP and PP were not associated with Mg intake.	Although NHANES is a high-quality study, the cross-functional design limits the conclusions that can be drawn.	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Song et al. (2005)	Cross-sectional [baseline analysis of RCT]	11,686 participants >45 yrs of age in the Women's Health Study free of CVD and cancer and had no use of postmenopausal hormones. Mean age range 51±6.5-53±7.7 across quintiles.	131-item semiquantitative FFQ obtained at baseline in 1993 and used Harvard Food Composition database. Total Mg represents the sum of Mg intake from both dietary and supplemental sources. Incident HTN based on self-reported BP, treatment and/or physician diagnosis.	Dietary sources of Mg accounted for 96% of intakes. Median intake of Mg was 326 mg/d. Approx. 1.5 fold difference in total Mg intake between the highest and lowest quintiles of intake (median: 422 mg/d in the higher quintile vs. 252 mg/d in the lowest). Number of participants with history of hypertension inversely associated with Mg intake (p for trend=0.01). Number of participants with elevated baseline BP (≥135/85 mmHg) across quintiles of Mg intake was inversely associated with Mg intake (p for trend<0.001).	Study was designed to examine the association of Mg intake with C-reactive protein & metabolic syndrome. Therefore, data on history of high blood pressure and elevated BL BP were not adjusted for potentially confounding variables.	-
Song et al. (2006)	Prospective cohort	23,349 participants >45 yrs of age in the Women's Health Study free of CVD and cancer and had no use of postmenopausal hormones. Mean age range 52-55 across quintiles. During mean follow-up period of 9.8 years, 8,544 cases of hypertension were reported.	131-item semiquantitative FFQ obtained at baseline in 1993 and used Harvard Food Composition database. Total Mg represents the sum of Mg intake from both dietary and supplemental sources.	Dietary sources of Mg accounted for 97% of intakes. Median intake of Mg from diet and supplements was 330 mg/d. Women in the highest quintile (median 434 mg/d) had a decreased risk for HTN (RR 0.87, 95% CI 0.81-0.93; p for trend <0.0001) compared with those in the lowest quintile (median 256 mg/d). This inverse association was attenuated (RR=0.93, 95% CI 0.86-1.02) but remained significant (p for trend =0.03) after further adjustment for known risk factors. Multivariate analysis of dietary Mg intake (no supplements) was inversely associated with incident hypertension (RR=0.91, 95% CI 0.83-0.99, p for trend=0.002).	The fact that Mg from foods was more strongly associated with hypertension than the intake of total Mg (including supplements) suggests that use of a health claim on foods could be particularly beneficial.	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Bo et al. (2006)	Cross-sectional	Middle-aged subjects (n=1,653) from a group of six family physicians in the Asti province of Italy.	Validated semiquantitative FFQ (from the European Prospective Investigation into Cancer and Nutrition (EPIC study) was used to assess average frequency and portion intake of 148 foods consumed during the 12 mo before examination. Dietary energy-adjusted Mg and fiber intakes were divided into tertiles to evaluate fiber intakes, metabolic variables, and hsCRP values.	Median Mg intake was 308 mg/d; 241.2 in lowest tertile to 397.9 in highest tertile. 52.3% of men and 30.8% of women consumed less than the recommended dietary amount for European populations (approx. 4 mg/kg). SBP was unchanged across tertiles of Mg intake (134.5±16 vs 132.6±16.6, P=0.09) where as DBP was significantly lower in the highest tertile (82.1±9.6) compared to the lowest tertile (84.2±9.1 of Mg intake ($p<0.001$).	Study was designed to examine the association of Mg and dietary fiber intake with metabolic indicators (e.g., metabolic syndrome), therefore, BL data on SBP and DBP were not adjusted for potentially confounding variables.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
He et al. (2006)	Prospective cohort	4637 participants from the CARDIA Study, a multicenter longitudinal study to evaluate role of CVD risk factors in 2363 black men and women and 2274 white men and women, aged 18-30 years were enrolled in 1985-1986. A total of 932 incident events occurred meeting BP criterion; 608 incident metabolic syndrome cases identified during a mean follow-up period of 15 years.	Dietary information was collected at baseline and year 7 via dietary history during an interviewer-administered quantitative FFQ. Foods and portion sizes were reported for consumption during the past month. Total Mg and dietary Mg intakes were recorded. Mg intakes reported as mg/1000 kcal.	Mg intake in black men and women ranged from 97.9±10.1 to 173.1±55.0 mg/1000 kcal lowest to highest quartile and were significantly different across quartiles ($p<0.01$). Mg intake in white men and women ranged 24.4±3.5 to 26.4±2.9 mg/1000 kcal lowest to highest quartile ($p<0.01$). Mg intake was not associated with S/DPB at BL for black men and women, however both SBP ($p<0.01$) and DBP ($p=0.04$) were inversely associated with Mg intake at BL among white men and women. AT 15 yr follow-up, total Mg intake was inversely associated with elevated BP (SBP ≥130 mmHg or DBP ≥85 mmHg) among all participants (RR=0.78, 95% CI 0.63-0.97, p for trend <0.01) after correction for age, gender, race, education, smoking, physical activity history of diabetes, alcohol consumption and BL BMI, but the association was attenuated (RR=0.87, 95% CI 0.69-1.10, p for trend=0.11) after further adjustment for dietary fiber, polyunsaturated fat, saturated fat, carbohydrates and total energy.	Magnesium intake inversely associated with metabolic syndrome (RR=0.69, 95% CI 0.52-0.91, p for trend <0.01) after adjustment for potentially confounding variables	+

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Ford et al. (2007)	Cross-sectional	7,669 non-pregnant participants in NHANES III dataset (1988-1994) > 20 yrs of age who had fasted for eight hours or more.	Trained interviewers administered a single 24-hour dietary recall to participants using the NHANES III Dietary Data Collection methodology.	The mean and median intakes of Mg were 310 and 276 mg/d, respectively. HBP was non-significantly (p=0.107) related to dietary Mg intake on an unadjusted basis. Adjustment of the data for age, sex, race, education smoking, C-reactive protein, alcohol, physical activity family history of early CHD, use of vitamin supplements, history of diabetes, dietary fat, carbohydrate, fiber and energy resulted in significant inverse associations for the third and fourth quintile compared to the first (RR=0.64, 95% CI 0.45-0.92, and RR=0.60, 95% CI 0.39-0.91, respectively), but not for the upper quintile (RR=0.61 (0.37-1.03). There was also no significant trend (p=0.169).	This study was designed to assess associations with the metabolic syndrome of which blood pressure in only one component. Significant protective associations for the 3rd and 4th quintiles compared to the first could suggest Mg intakes at the upper quintile (≥337 mg/d for women and ≥466 mg/d for men) were already adequate. These intakes are in excess of the RDA for Mg, but those at the lower quintiles were not.	Ø
Beydoun et al. (2008)	Cross-sectional	14,618 participants > 18 yrs of age in NHANES 1999-2000, 2001-2002 and 2003-2004 datasets were merged to examine the association between dairy consumption and body weight and metabolic syndrome.	NHANES provided one 24-hr recall for years 1999-2000 and 2001-2002 and 2 recalls for 2003-2004 and collected by trained staff. Nutrients were expressed as per 100 mg. BP (3-4) were collected in the mobile examination center in individuals over 50 yrs of age. Age, sex and ethnicity were considered as independent variables with dairy consumption and other health outcomes.	Mean intakes, all participants, was 283.2±2.6 mg/d. Intakes were lowest in non-Hispanic black men (235.6±3.3) and highest in all men 328.1±2.9. Mg intake of all women was 241.7±2.9 mg/d. Mean SBP, all participants, 122.5±0.3, and DBP 71.5±0.2 mmHg. Mg per 100 mg was significantly and inversely associated with DBP (-0.62, P<0.05) but not SBP (-0.39) among men after adjustment for age, sex, race, socioeconomic status, energy intake and physical activity. However, no such associations for SBP or DBP were noted for women (-0.31 and -0.29, respectively).	The study was designed to examine the association between dairy products and metabolic syndrome. The data presented for Mg were cursory. Mg data not adjusted for many of the potentially confounding dietary variables (e.g., macronutrients)	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
McKeown et al. (2008)	Cross-sectional	535 (179 men and 356 women) community-living adults aged 60 years (mean 72 yrs for men, 74 years for women) living in Boston, MA between the years of 1981 to 1984 were evaluated. 24% of participants were taking lipid lowering medication and 33% were taking BP medication.	Participants were instructed on how to keep a consecutive 3-d food record. Total Mg intake represents the sum of Mg intake from both supplements and dietary sources. Nurse practitioner obtained BP and medical history.	Dietary sources accounted for ~ 98% of total Mg intake. Median daily intake of total and dietary Mg was 298 and 293 mg, respectively, and in men and 251 mg and in 245 mg, respectively, in women. Between the lowest and highest quintile of Mg intake, there was almost a 200 mg/d difference in total Mg intake. Only 14.6% of participants in the study were taking supplements which included Mg. No statistically significant associations were observed between Mg intake and blood pressure (RR=0.44, 95% CI 0.18-1.04, p for trend =0.16) for upper quartile of Mg intake compared to the lowest.	The study was designed to examine the association between dairy products and metabolic syndrome. The data presented for Mg were cursory. Very small sample size for an observational study. 33% of subjects taking antihypertensive drugs likely confound any effect of Mg. 3-day food diaries may not reflect longer-term consumption – especially with such a small sample.	-
Khan et al. (2010)	Prospective cohort	3,531 middle-aged adult participants from the Framingham Study offspring cohort that participated in the second examination (1979-1982) were evaluated.	No dietary data presented. Serum Mg was measured along with physical exam and ascertainment of incident HTN (present at the fourth offspring examination that took place ~ 8 years later) and/or CVD.	At baseline, there were 772 (22%) of participants with prevalent HTN. The range of observed values for serum Mg was 1.41 to 2.40 mg/dL in men and 1.15 to 2.46 mg/dL in women. Between the baseline and follow-up examination (8 yrs), a total of 551 participants (22%) developed hypertension. In age- and sex-adjusted logistic regression analyses, serum Mg was not significantly associated with incident HTN (adjusted OR per SD [0.15 mg/dL] increment in serum Mg= 0.96, 95% CI 0.87-1.06, p=0.39). Results were similar after multivariable adjustment (RR=1.03, 95% CI 0.92-1.15, p for trend= 0.61).	Dietary data not presented. Data on serum Mg was limited. However, 12/2,520 subjects had serum Mg <0.61 mmol/L and 24 subjects had values >90 mmol/L which suggests a magnesium replete population at baseline.	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Peacock et al. (2010)	Prospective cohort	AIRC is a biracial cohort, aged 45-64 years at entry from 4 US communities. This report included 14,232 participants free of HTN at baseline (1987-89) and followed for an average of 12 years.	Usual dietary intake over the last year was collected using an adapted version of the Willett 61-item FFQ. Serum Mg was measured (visits 1 and 2) along with physical exam and ascertainment of incident sudden cardiac death.	Dietary Mg (mg/d) was 251 in hypomagnesemic subjects (<1.5 mEq/L) and 254 in normomagnesemic subjects (1.55-1.6 mEq/L). Dietary Mg intake was associated positively with levels of serum Mg ($p=0.0008$ by F test from ANOVA). Serum Mg inversely associated with incidence of HTN ($p<0.0001$ by F test from ANOVA). HTN present in 43.8% of hypomagnesemic subjects and 33.6% of normomagnesemic subjects. These values were adjusted for age, race, gender and field center only. Multivariate adjusted serum Mg inversely associated with sudden cardiac death (RR=0.62 95% CI 0.42-0.93, p for trend = 0.006). The paper stated that dietary Mg was not associated with CHD or sudden cardiac death after adjustment for possible confounding variables but detailed data were not provided. No such calculation was made for incidence of HTN.	The study was designed to assess the association b/w Mg intake/serum concentrations and sudden cardiac death. Therefore, detailed analysis of the possible association with HTN was not reported. However an earlier publication with six years of follow-up data from this cohort reported no such associations (Peacock et al., 1999).	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Kesteloot et al. (2011)	Cross-sectional	The International Study of Macro- and Micro-Nutrients and Blood Pressure (INTERMAP, 1996-1999) comprised 4,679 persons aged 40-59 years from 17 population samples in China, Japan, the United Kingdom, and the US. The International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT, 1985-1987) comprised 10,067 persons aged 20-59 years from 52 samples around the world. Both general population and workforce samples were included. Whenever possible, individuals were selected randomly from population lists and stratified by age and gender to obtain approximately equal numbers.	BP was measured twice at each clinic visit in INTERMAP (8 measurements in total) and in INTERSALT. Two timed 24-hour urine specimens were obtained from all INTERMAP participants; for all INTERSALT participants who had a single timed 24-hour urine specimen collected. In INTERMAP, dietary data were collected at each visit by a trained interviewer using the in-depth multipass 24-hour recall model. All food and drink consumed in the previous 24 hours, including supplements were recorded.	In the INTERMAP study, dietary Mg intake ranged from 134.4 mg/1,000 kcal (Japan) to 154.6 mg/1,000 kcal (China). Mean SBP ranged from 117.2 mmHg (Japan) to 121.3 mmHg (China); mean DBP ranged from 73.2 mmHg (China) to 77.3 mmHg (UK). Mean urinary Mg excretion ranged from 3.2 mmol (78.3 mg) per 24 hrs (Japan) to 4.2 mmol (103.3 mg) per 24 hours (United States). Data from INTERSALT showed that Mg excretion was inversely associated with SBP ($p<0.05$) and DBP ($p>0.0001$) for a decrement of +2 standard deviations after adjustment for age, gender, sample, weight and height. These associations remained significant ($p<0.05$ for SBP and $p<0.001$ for DBP) after further adjustment for special diet, physical activity, physician-diagnosed heart attack or stroke, history of HTN and smoking. However, these associations were no longer statistically significant after adjustment for additional potentially confounding variables. Data from INTERMAP showed no statistically significant association b/w Mg excretion and SBP while DPB was inversely associated with this parameter ($p<0.0001$) after adjustment for the potentially confounding variables noted above, but not after further adjustment for alcohol intake and urinary excretion of Na and K .	Many of the subjects in these studies reside in countries with large differences in habitual diet that do not reflect the general US population.	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Syedmoradi et al. (2011)	Cross-sectional	1558 participants (754 males, 804 females) aged 20-80 years are drawn from the Tehran Lipid and Glucose study (TLGS), between 2006 and 2007 using a multi-stage stratified cluster random sampling technique.	Serum Mg samples were drawn and analyzed by atomic absorption spectrophotometry. Blood pressure was measured twice in a sitting position after 15 minutes of rest.	Serum Mg was not significantly correlated with SBP (r=0.028, p=0.274) or DBP (r=0.042, p=0.101).	Lack of a correlation b/w serum Mg and BP could be due to a low prevalence of hypomagnesima in the overall population (4.6%) and the fact that the participants were normo-tensive (mean BP for men=115/76 mmHg, mean BP for women=109/72 mm Hg). No dietary data were provided. Data from the Iranian population does not reflect the general US population.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Huang et al. (2012)	Cross-sectional	Study involved 210 type 2 diabetes patients aged 65 years and above living in rural area of central Taiwan. Inclusion criteria: type 2 diabetes for more than 6 mos, no change in any medications in past 3 mos, stable lifestyle for past 3 mos.	Dietary intake was assessed using 24-hour recall. In addition, questionnaires of typical dietary pattern were also applied in the survey to assess patients' daily dietary intake. 24-hr dietary recalls and a week of typical dietary pattern were collected via interview by registered dietitian. Mg and other nutrient intake were analyzed using Taiwan Nutrition Database. Serum Mg was measured using methylthymol blue method.	88.6% of patients had a Mg intake less than the dietary reference intake (mean 3.6+1.7 mg/kg) (DRI) and 37.1% had hypomagnesemia (serum magnesium <0.75 mmol/L). Mg intake was not significantly correlated with BP either by diet (p=0.344) or serum level (p=0.669); however, it did show marginal inverse associations with SBP (r= -0.123; p=0.074) and DBP (r=-0.128; p=0.065). On adjusted analysis (for metabolic parameters, body fat percentage and body mass index) mean of SBP showed marginal linear trend with quartile of Mg intake (p for trend <0.089). However, Mg intake was not associated with SBP ≥130 or DBP ≥80 (RR=0.60, 95% CI, 0.21-1.70, p for trend =0.452.	Subjects were Type-2 diabetics living in Taiwan which do not reflect the healthy US population. Very small N for this cross-sectional study.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Rasic-Milutinovic et al. (2012)	Cross-sectional	90 healthy blood donors aged 18-52 years (mean 34.57±10.56), 30 from each of three municipalities in Serbia (Soft water: Banovci, Grocka and hard water: Pozarevac).	Total water hardness, Mg and calcium concentrations, electroconductivity and total dissolved solids were measured in water samples from public water supply systems as part of the National Monitoring Prograrmme of Drinking Water Quality from Public Water Supply Systems from 2003-2004. Water samples from individual wells were not considered. BP was recorded (2 separate readings) and blood samples taken for serum minerals and routine chemistry.	The median content of Mg in the water supply from Pozarevac was significantly higher (42.25 mg/L) and the ratio of Ca/Mg was significantly lower than the level in the water supply in Grocka (2.36 vs. 4.98; $p<0.05$). The median content of Mg in the water supply system did not differ between Pozarevac and Banovci, and neither did the ratio of Ca/Mg. The mean SBP did not differ between groups; DBP showed significant differences between groups being lowest in the subjects from Pozarevac (78.30±4.87 mmHg); and significantly different from Grocka (81.66±5.86 mmHg; $p=0.03$). The mean serum Mg was the highest in the group from Pozarevac (0.87±0.09 mmol/L), and the serum Ca/Mg ratio was lowest in the serum of the same subjects (1.23±0.13). Serum magnesium was negatively correlated with systolic ($r=-0.226$) and diastolic ($r=-0.262$) blood pressure (both $p<0.05$). The serum Ca/Mg ratio were also associated w/ DBP after adjustment for confounders (age, gender, BMI) only total cholesterol and serum Mg levels were independent predictors of DBP. In stepwise multivariate linear regression, 23% of the variation in DBP was explained by the serum Mg.	No dietary data were presented. Very small number of subjects. Russian population probably not reflective of the general, healthy US population.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Choi and Bae (2013)	Cross-sectional	The data sets are from the 2007-2008 Korea National Health & Nutrition Examination Survey (KHANES) of 14,338 individuals from 6,000 households. Included in this analysis are 5,136 subjects aged 19 years and older (2,084 men and 3,052 women). [KHANES uses a rolling sampling design that involves a complex, stratified, multistage, probability-cluster survey of a representative sample of the non-institutionalized civilian Korean population. Survey data are compiled through a health interview, health examination and a nutrition survey.]	Trained dietitians interviewed each subject to collect dietary data via 24-hr recalls. The daily Mg, Mn, and Cu intakes from foods (those subjects taking supplement had been excluded) were estimated using a mineral database produced by previous studies and the food composition table of the National Rural Living Science Institute, Korea. The database covered 92.4% of the food intake for Mg.	Women subjects with hypertension had significantly lower Mg ($p<0.0001$) than subjects without this condition after adjustment for age. No such association was reported in men ($p=0.9499$).	The study was designed to assess the association between Mg and other minerals and metabolic syndrome. Therefore, the data pertaining to BP were limited and not corrected for potentially confounding variables other than age. The Korean population does not reflect the general, healthy US population.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Guerrero-Romero and Rodriguez-Moran (2013)	Cross-sectional	Men and non-pregnant women aged 20-65 years (mean 41.5+13.7 yrs). 274 women or 64.2% and 153 men or 35.8% from the general population of Durango, Mexico were invited to participate. 427 subjects were enrolled and allocated into groups with and without obesity. Among non-obese subjects, a subgroup of metabolically obese normal weight (MONW) (n=31) and metabolically healthy obese (MHO) (n=98) were evaluated.	A standardized interview, clinical examination and laboratory tests were obtained. Serum Mg was measured by colorimetric method.	Multivariate analysis showed no association b/w serum Mg and hypertension among non-obese (OR=0.11, 95% CI 0.11-12.41) or obese (OR=0.88, 95% CI 0.41-1.71) subjects.	This study was designed to primarily to examine the differences b/w metabolically obese normal weight and healthy-obese subjects and very little data were presented on BP. Very small N. No dietary data were presented.	-
Kim and Choi (2013)	Cross-sectional	258 healthy men/women Korean adults 20-64 years (mean 49 yrs) not taking supplements or any medications.	Ht, Wt, BMI, lipid profile, systolic and diastolic BP measured. Dietary intakes assess via 3 - 24 hr recalls on nonconsectuve days through personal interview. Mineral intakes calculated from Korean database of frequently consumed foods.	After adjusting for age, sex, BMI, and energy intake, Mg intake had a significant negative correlation (r=-0.1323; $p<0.05$) with SBP and a non-significant inverse correlation with DBP (r=-0.1091, $p>0.05$).	Very small N. Subjects were normotensive and lean. The Korean diet cannot be extrapolated to the average American Diet.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Chidambaram et al. (2014)	Cross-sectional	The Healthy Eating Asians Remain Together (HEART) study is the second generation of the WHO-CARDIAC study. A total of 168 subjects, 90 men and 78 women aged 30-39, 40-49 and 50-59 years randomly selected from a community list in Annamalai Nagar, Tamil Nadu, India.	No description of how the diet data were ascertained.	Urinary magnesium (mg per gram creatinine) was lower among hypertensive subjects (n=52) compared to 115 normotensive individuals (137.07 vs. 82.58) but not significantly so (p=0.262). This difference was significant among middles aged participants (40-59 years of age; 112.95 vs. 85.35 mg, p=0.014).	Small sample size of Indian subjects who do not reflect the healthy US population. No dietary or specific BP data presented. This study boarders on being totally inapplicable to the proposed claim due to incompleteness.	-
Guasch-Ferre et al. (2014)	Cross-sectional [baseline of RCT]	PREDIMED (Prevencion con Dieta Medeterranea) is a multicenter, randomized clinical trial conducted in Spain comparing 3 dietary interventions in 7,216 adults at high CVD risk in men (aged 55-80 y) and women (aged 60-80 yr). Subjects were free of CVD at enrollment.	Dietary Mg intake (energy adjusted) was assessed by a validated baseline 137-item FFQ completed by trained dietitians. Spanish food composition tables were used to estimate energy and nutrient intake.	Median Mg intakes across tertiles were: 312, 341, and 442 mg/d (p=0.05). Prevalence of HTN was not significantly different across tertiles of Mg intake (p=0.14).	Hypertension not individually assessed at BL. Those taking anti-hypertensive drugs or who had been previously diagnosed were deemed hypertensive. BL data on Mg intake were adjusted for energy intake but no other potentially confounding variables. Although PREDIMED is prospective intervention trial, no data on the association between Mg intake and incidence of hypertension were presented during the 4.8 year follow-up period described in this paper.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Lutsey et al. (2014)	Prospective cohort	ARIC is a biracial cohort, aged 45-64 years at entry from 4 US communities. This report included 14,709 subjects aged 45-64 at baseline (1987-89) observed after a mean follow-up period of 20.6 yrs.	Mg was measured at baseline (visits 1 and 2).	Baseline data collected from 1987-89 showed inverse associations with serum Mg and SBP (127 and 119 mmHg for lowest (1.4 mEq/L) vs. highest (1.8 mEq/L) quintiles, p for trend <0.0001) as well as incident HTN 52.5% vs. 26.4%, p for trend <0.001). These data have been presented in other forms in previous ARIC papers (Peacock et al., 2010, Liao et al., 1998). No prospective associations for blood pressure were presented in this paper but serum Mg was inversely associated with incidence of heart failure (RR=1.66, 95% CI 1.42-1.95, p for trend <0.0001) after adjustment for numerous potentially confounding variables including SBP.	No dietary data were presented in this report.	Ø
Panhwar et al. (2014)	Case-control	N=257 (120 F) hypertensive and 166 healthy (82F) control subjects 30-60 years living in Hyderabad city, Pakistan. Hypertensive subjects had BP >130/96 mm Hg and admitted to hospital for uncontrolled HTN and had earlier history of HBP. There were no significant differences in height, weight or age. Approximately 50% of the hypertensive subjects were taking blood pressure lowering drugs.	Dietary information was obtained by "questionnaire" but no specifics were provided. Mg was analyzed in hair, serum, venous blood, and morning urine samples. Additional data on sample collection (e.g., fasting) were not provided.	Mg concentrations in hair were higher among controls vs. hypertensives for both men (719 vs. 415 µg/g, respectively, p=0.001) and women (739 vs. 441 µg/g, respectively, p=0.001). Similar results were seen for serum Mg (mg/L) for both men (23.9 vs. 13.5, respectively, p=0.003) and women (24.4 vs. 13.9 mg/L, respectively, p=0.002), and for venous blood (83.8 vs. 61.5 mg/L respectively, p=0.012 for men and 87.2 vs. 63.9 mg/L, respectively, p=0.01 for women). Urinary mg was higher (p=0.001) among hypertensive males (99.6 mg/L) than normotensive males (63.6 mg/L). Similar findings were reported for hypertensive vs. normotensive females (102 vs. 68.9 mg/L, respectively, p-0.001).	Pakistani subjects do not reflect the general US population. Study did not report dietary intake data. Conditions of sample collection not well specified and may not reflect overall exposure (e.g., morning urine samples instead of 24-hour samples)	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Papanikolaou et al. (2014)	Cross-sectional	Analysis from five NHANES datasets (2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010) were combined for these analyses. The combined sample included 14,338 participants, aged >19 years of age, who had complete 24-h dietary intake data. Analyses were limited to men and non-pregnant/non lactating women >20 yrs of age.	The nutrient intakes for NHANES 2001-2008 are from the USDA Food and Nutrient Database for Dietary Studies 3.0 and intake data from What We Eat in America. The NHANES 2001-2010 data were analyzed examining the relationship between diabetes and related health factors with the intake of Mg from food and Mg from food plus supplements.	Adults with adequate intake (meeting the EAR) of Mg from food had significantly lower SBP (-0.54%, p=0.0279) compared to adults with inadequate intake (not meeting the EAR) of Mg from food, but this difference was less than 1%. No significant difference was noted for DBP among adults with adequate vs. inadequate intake of Mg from foods (p=0.718). Adults with adequate intake of Mg from food plus supplements had significant differences in SBP (-0.56%, p=0.0297) compared to adults with inadequate intakes of Mg from food plus supplements. No significant difference was noted for DBP among adults with adequate and inadequate intake of Mg from food plus supplements (p=0.6621). As Mg intake from food (1st quintile <238.8 mg/d to fourth quintile >341.3 mg/d) increased, SBP decreased (p=0.0074) and DBP increased significantly (p=0.0009) across quintiles of Mg intake, a difference of 2% from lowest to highest quintile. Mg intake from food plus supplements noted similar significant trends (p=0.0029 as from food alone with less than a 2% difference in intakes (SBP lower w/ increasing consumption (p=0.0029) and DBP higher (p=0.0168)). Higher dietary intake of Mg from foods was associated with significantly reduced odds ratios at the fourth quintile for elevated BP (OR=0.77, 95% CI 0.64-0.93) for elevated SBP (OR=0.77, 95% CI 0.65=0.93, p=0.002) but not for elevated DBP (OR=0.95, 95% CI 0.80-1.12, p=0.2580). Higher dietary intake of Mg from food plus supplements was associated with significantly reduced odds ratio for elevated SBP (OR=0.81, 95% CI 0.68-0.97, p=0.0298, but not for elevated BP (OR=0.83, 95% CI 0.70-0.99, p=0.0673) or DBP (OR=0.95, 95% CI 0.80-1.13, p=0.7520).	Although NHANES is a high-quality study, the cross-functional design limits the conclusions that can be drawn.	Ø

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Rodriguez-Ramirez et al. (2015)	Case-control	A population-based sample was first recruited from six Mexican cities in order to determine the prevalence of pre-hypertension among 20-65 yr old individuals. This effort resulted in a sample of N=4,272 (N=2,921F) subjects. The incidence of pre-HTN (120-139/80-89 mmHg) was 37.5% while 13.6% were hypertensive. A case-control comparison was conducted among N=520 subjects with pre-HTN and 401 controls. These subjects were selected from the above cross-sectional sample based on their pre-HTN status and the availability of serum Mg data which were obtained on only 21.5% of the sample due to economic constraints. Other criteria for selecting the controls were not stipulated.	Dietary data were not obtained. The study was designed to examine the possible association b/w hypomagnesemia and pre-HTN.	Serum Mg was greater ($p<0.05$) among men without pre-HTN (2.00 mg/dL) than with (1.79 mg/dL). Similar results were seen for women (2.01 vs. 1.78 mg/dL, respectively, $p<0.05$). SBP and DBP were similar ($p=0.54$) between normo- and hypomagnesemic subjects without pre-HTN (106.5/67.6 mmHg vs. 105.9/67.1 mm Hg) and between normo- and hypomagnesemic subjects with pre-HTN (127/76.4 vs. 126.9/77.3, $p=0.90$). There was no difference b/w normomagnesemic subjects with and without pre-HTN with respect to serum Mg (2.04 vs. 2.09 mg/dL, respectively) however serum Mg was greater (1.65 mg/dL) among hypomagnesemic subjects without pre-HTN than those with this condition (1.43 mg/dL, $p<0.05$). There was a negative Pearson correlation rank b/w serum Mg and SBP (r=-0.152, $p<0.0005$) and DBP (r=-0.165, $p<0.005$). Multiple logistic regression analysis (adjusted for age, sex, smoking, BMI, waist circumference, fasting glucose, total cholesterol HDL-C, TG and serum Mg) indicated an association b/w hypomagnesemia and pre-HTN (OR=1.77, 95% CI 1.3-4.4, $p<0.0005$). Adjusted multiple linear regression analysis showed that serum Mg concentrations are inversely associated with SBP (β=-6.39, 95% CI -9.8 to -1.5) and DBP (β=-2.6, 95% CI -2.9 to -1.3) in the subjects with pre-HTN, but not among normotensive individuals (β=0.66, 95% CI -1.7 to 3.0 and β=-0.93, 95% CI, -3.1 to 1.1 for SBP and DBP, respectively.	No dietary data. No data on selection of control subjects other than availability of serum Mg data. Only 21.5% of the subjects had serum Mg data.	-

Author	Design	Population Characteristics	Dietary Parameters and Study Endpoints	Summary of Results	Comments	FDA Quality Score
Rotter et al. (2015)	Cross-sectional	313 men aged 50-75 years (mean 61.3±6.3) recruited from primary health care centers in the cities from Szczecin in north-western Poland during March 2013-Feb 2014. 16% were smokers. Hypertension in 171 patients (54.6%) Those on testosterone, steroids, thyroid medications or on cancer treatment were excluded. 155.7% were on statins.	Height, weight, BMI and waist-hip ratios calculated, blood pressure and serum Mg concentrations. No dietary data recorded.	Serum Mg was lower (0.85±0.11 mmol/L) in 171 men with hypertension compared to 0.88 mmol/L among normotensives (p=0.0001) and was correlated with SBP (r=-0.15, p=0.006) but not DBP (r=-0.0004, p=0.99). In subjects with hypertension, the Mg level was significantly lower than in men without hypertension (P=0.0001). There was no difference in Mg levels between the obese and non-obese men. Logistic regression model showed that serum Mg was inversely associated with incidence of hypertension (RR=0.84, 95%CI, 0.743-0.942; p=0.003).	Very small N. Mean BP was in the pre-hypertensive range (135/84 mmHg). Not clear whether association b/w serum Mg and incidence of hypertension was corrected for potentially confounding variables. Polish population may not generalize to the US population.	-

Table III
Classification of Observational Studies by Support for the Proposed Claim

Study Quality	Positive Support	Mixed Support	Unsupportive
Prospective cohort	**Witteman (89)*** **Song (06)**	**Ascherio (92)** **Liao (98)** **Peacock (99)** **Peacock (10)** **Lutsey (14)**	**He (06)** **Khan (10)**
Case-control	Sudhakar (99) Yang and Chiu (99) Panhwar (14)	Rodriguez-Ramirez (15)	
Cross-sectional	Joffres (87) Ideno and Kubena (89) **Van Leer (95)** Song (05) Rasic-Milutinovic (12) Kim and Choi (13)	Johnson (87) Karanja (87) Kesteloot and Joossens (89) He (91) **Ma (95)** Bo (06) **Ford (07)** **Beydoun (08)** Choi and Bae (13) Chidambram (14) Guasch-Ferre (14) **Papanikolaou (14)** Rotter (15)	**Hajjar (01)** McKeown (08) **Kesteloot (11)** Syedmoradi (11) Huang (12) Guerrero-Romero and Rodriguez-Moran (13)
Prospective cohort	2	5	2
Case-Control	3	1	0
Cross-Sectional	6	13	6
Cohort + Case-Control	5	6	2
Total (all)	11	19	8

*Studies in **bold type** received a medium or high FDA quality rating

As noted previously, the study by He et al. (2006) reported that total magnesium intake was inversely associated with blood pressure at 15 years follow-up among 4,637 members of the CARDIA study (RR=0.78, 95% CI 0.63-0.97, p for trend <0.01) after correction for age, gender, race, education, smoking, physical activity history of diabetes, alcohol consumption and baseline BMI, but the association was no longer statistically significant after further adjustment for dietary fiber, polyunsaturated fat, saturated fat, carbohydrates and total energy (RR=0.87, 95% CI 0.69-1.10, p for trend=0.11). Nevertheless, this study is not incompatible with the notion that dietary magnesium is inversely associated with blood pressure under certain conditions. The other unsupportive prospective cohort study was that of Khan et al. (2010) who reported that serum magnesium was not associated with incidence of hypertension among 3,531 members of the Framingham Heart Study Cohort after eight years of follow-up. However, no dietary information about magnesium or other nutrients was provided so it is not possible to determine the range and or adequacy of this nutrient among the subjects. In addition, the subjects were 78% normotensive at baseline so that failure to observe a significant association between serum magnesium and blood pressure was not surprising. In conclusion, as noted earlier, observational studies are far less persuasive than dietary intervention studies for the evaluation of health claims due to inaccuracies in dietary assessment, characteristics of the population and the likelihood of unrecognized confounding variables. Furthermore, the complex mechanism by which magnesium interacts with other dietary components to help regulate blood pressure makes evaluation of such studies difficult because complete dietary data are often lacking and/or not considered in statistical adjustment of the data. Therefore, the lack of an observed association is no guarantee that such a relationship would not exist under other conditions, and by no means proof that magnesium does not have a direct effect on blood pressure. Nevertheless, observation

of such associations is evidence that the effects seen in controlled intervention studies do occur among free-living populations. The Center believes the fact that a large majority of observational studies reported evidence of such associations is compelling support for the proposed claim.

E. Intervention studies

1. Introduction

The totality of scientific evidence from dietary intervention studies that meet FDA's criteria for the substantiation of health claims provides compelling support for the proposed claim. These studies used a randomized, placebo-controlled design that allows the effect of magnesium supplementation on blood pressure to be identified. The studies employed a physiological dose and examined healthy human subjects who were normotensive, pre-hypertensive and/or moderately hypertensive. Detailed information about the design, results and pertinent comments about these studies are provided in Table IV (page 89).

In accordance with 21 C.F.R. § 101.70(c) and 21 C.F.R. § 101.70(d), the Center declares that to the best of its knowledge, all non-clinical studies relied upon in this petition were conducted in compliance with the good laboratory practice regulations set forth in 21 C.F.R. Part 58. Moreover, all clinical or other human investigations relied upon were either conducted in accordance with the requirements for institutional review set forth in 21 C.F.R. Part 56 or were not subject to such requirements in accordance with 21 C.F.R. §§ 56.104 or 56.105, and were conducted in compliance with the requirements for informed consent set forth in 21 C.F.R. Part 50.

The Center contends that studies in moderately hypertensive individuals are germane to the proposed claim because (as described above) the mechanisms by which magnesium helps to regulate blood pressure are the same in normotensive and hypertensive individuals. The agency's January 2009, Guidance for Industry: Evidence-Based System for the Scientific Evaluation of Health Claims[14] states,

> FDA considers evidence from studies with subjects who have the disease that is the subject of the claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence demonstrates 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 and healthy people.

FDA applied this principle for its review of intervention studies submitted as substantiation for the calcium and blood pressure QHC. The enforcement discretion letter pertaining to this claim[15] states, "Because the mechanism by which calcium may reduce blood pressure in normotensive and hypertensive subjects is considered to be the same (Hatton and McCarron, 1994), hypertensive subjects were considered in this review."

There are many similarities between the blood pressure-related mechanisms noted by Hatton and McCarron (1994) for calcium and those described previously for magnesium. Multiple mechanisms by which calcium exerts such effects noted by this review include vascular contractility and relaxation, alterations in the sodium-potassium-ATPase activity, interaction with magnesium to affect intracellular concentrations and membrane transport, modulation of inflammatory markers and altered prostaglandin synthesis. All of these mechanisms, which ultimately affect blood pressure in both the normotensive and hypertensive states, also apply to

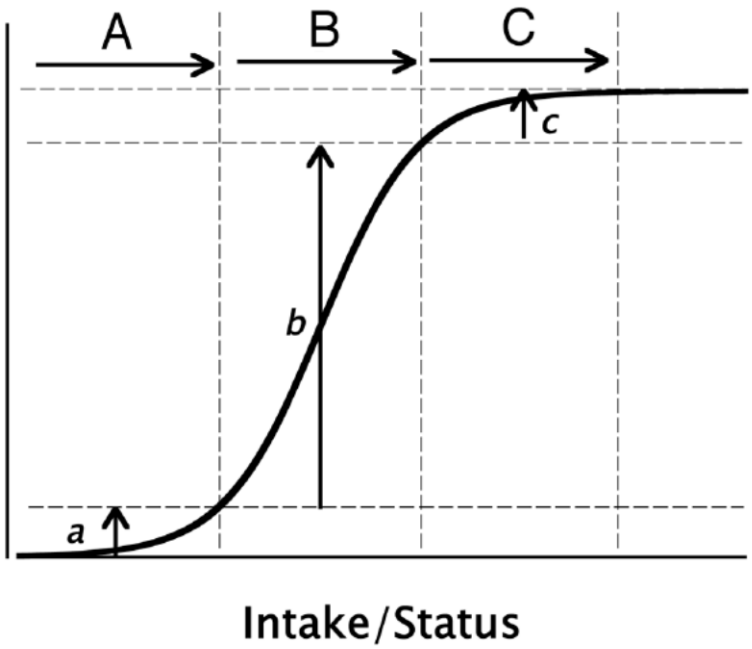
[14] http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm
[15] http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm073030.htm

magnesium as discussed earlier (Resnick, 1999, Shechter, 2010, Houston, 2011, Kupetsky-Rincon and Uitto, 2012, Maier, 2012, Houston, 2014, Kolte et al., 2014). In conclusion, the Center strongly believes that the rationale used by FDA to justify the inclusion of studies that employ moderately hypertensive subjects for evaluation of the calcium and hypertension QHC is equally applicable to magnesium; and provides more than enough regulatory precedent to justify the inclusion of such studies for evaluation of the proposed claim.

As noted above, all of the studies discussed in this section meet the basic criteria provided in FDA's January 2009, Guidance for Industry: Evidence-Based System for the Scientific Evaluation of Health Claims. However, even well-designed RCTs that examine the effect of nutrients (such as magnesium) on outcome measures (such as blood pressure) can fall prey to false negative results due to the very nature by which nutrients exert their beneficial effects. A variety of reasons why such false negatives may occur were eloquently discussed by Lappe and Heaney (2012). Perhaps the most relevant of such reasons as applied to the proposed claim is the sigmoid curve by which virtually all nutrients exert their physiological effects (see Figure C). At low intakes (or low nutrient status) there is little or no response because insufficient amounts of the nutrient are present to exert an effect. However, when a threshold level is reached, there is a fairly rapid rise in the beneficial effect until a plateau is reached at adequate intake levels. Increased intake of the nutrient once the plateau is reached results in little or no additional effect (and may even cause harm, albeit usually by a different mechanism).

This situation is directly applicable to the proposed claim where magnesium is the nutrient and blood pressure is the physiological response. As noted above, magnesium is one of the nutritional factors involved in blood pressure regulation. If all other factors are held constant, an

Figure C
Physiological response curve for nutrients



Source: Lappe and Heaney, *Dermato-Endocrinology* 2012;4:95

inadequate dose of magnesium would result in elevated blood pressure. Increasing the dose of magnesium will have little effect (if any) on blood pressure until the threshold of nutritional adequacy is approached. Once this threshold is reached, however, a rapid decrease in blood pressure can be expected until normal levels are achieved. Once again, even a substantial increase in magnesium intake once blood pressure has been normalized will result in very little, if any, change.

This principle is critical to evaluation of the intervention studies discussed in Table IV because only studies that provided magnesium in a sufficient dose to subjects with inadequate status would be expected to yield observable results. Specifically, a study that provided an inadequate dose of magnesium to hypertensive subjects would not be expected to result in significant changes in blood pressure even though a higher dose of magnesium would exert such an effect

(i.e., a false negative result). Furthermore, supplemental magnesium provided to a replete individual would also not be expected to result in a significant effect because the physiological plateau for blood pressure with respect to this mineral has already been reached, and providing extra magnesium beyond its requirement would result in little or no change in blood pressure (i.e., also a false negative result). It is therefore important to recognize the hypertensive status of the subjects as well as their magnesium status and the dose provided.

Magnesium status is difficult to measure in routine settings. Plasma or serum magnesium concentrations below 0.75 mmol/L are an indication of frank deficiency while those between 0.75 and 0.85 mmol/L may also be deficient, but a urinary loading test that assesses retention and/or excretion is necessary to confirm such a state (Arnaud, 2008). A recent review paper that discusses biochemical parameters used to assess magnesium status (Rosanoff et al., 2016) states that the criterion for low "normal" serum magnesium varies widely and ranges from 0.6 to as high as 0.75 mmol/L; however increasing that range to 0.80 – 0.85 mmol/L has been suggested to accommodate the chronic latent magnesium deficit subpopulation. For the purpose of discussion in this petition, a plasma/serum concentration of magnesium of 0.75 mmol/L or less will be considered to be an indication of frank inadequacy and 0.80 mmol/L or more will be considered an indication of replete magnesium status.

Urinary excretion typically increases after supplementation of magnesium (Witkowski et al., 2011), and this measure can be used to verify compliance among subjects in clinical trials. Therefore, magnesium supplementation studies that did not observe an increase in urinary excretion suggest that poor subject compliance may have occurred which may also result in a false negative outcome.

A discussion of the magnesium supplementation studies that were identified that are capable of substantiating health claims is provided below.

2. Studies capable of substantiating health claims

a. Studies that provide direct support for the proposed claim

As noted above, the totality of the evidence from controlled magnesium supplementation studies provides convincing support for the proposed claim. Fourteen high or medium quality studies provided strong or suggestive evidence that magnesium supplementation has beneficial effects on blood pressure. Additional support was provided by eight low quality studies.

Direct support for the proposed claim was provided by the high quality studies of Guerrero-Romero and Rodriguez-Moran (2011) and Rodriguez-Moran and Guerrero-Romero (2014). Guerrero-Romero and Rodriguez-Moran (2011) reported that blood pressure after three months of supplementation with 26 mmol/d of $MgCl_2$ was 109/70 mmHg compared to 113/74 mmHg after placebo among 106 normotensive healthy adults living in Mexico ($p=0.03$ and 0.04 for systolic and diastolic BP, respectively.

Similar results were reported by Rodriguez-Moran and Guerrero-Romero (2014) who found that supplementation with 15.7 mmol/d of $MgCl_2$ for four months resulted in blood pressures of 109/69 mmHg compared to 117/77 mmHg for the placebo group ($p=0.03$ and 0.01 for systolic and diastolic BP, respectively).

Direct support was also provided by four medium quality studies. Daly et al. (1990) reported beneficial effects on supplementation with 10.3 mmol/d MgO for 12 weeks among 40 normo- and borderline hypertensive subjects living in Colorado. Change in blood pressure in the magnesium group after 12 wks of treatment (-12.6±12.2 / -7.5±9.1 SEM) was much larger than

change in the control group (-0.9±11.5 / -1.6±4.9 SEM). In addition, slopes of individual linear regression lines for decrease in SBP and DBP were significantly greater in the magnesium group than the control group (p=0.007 and 0.02, respectively).

Widman et al. (1993) found that SBP (p=0.0051) and DBP (p=0.0075) were lower after the magnesium treatment vs. placebo among 17 mostly untreated hypertensive subjects living in Sweden using a randomized cross-over protocol with 12 week treatment periods. This study employed an escalating dose of magnesium of 15, 30 and 40 mmol/d for three weeks each.

Borrello et al. (1996) studied 83 hypertensive subjects living in Italy who received a relatively small dose of MgO. The paper reported the dose to be 10 mmol/d, however ambiguity in the paper suggests it was 5.25 mmol/d. Nevertheless, SBP and DBP after the magnesium treatments were lower than the placebo. The paper stated that the significance for SBP vs. the placebo was $p<0.01$. A numerical value for the difference in DBP was not provided, but the author noted a "weak significance". Blood pressures at the end of the magnesium and placebo treatment periods were 148.5/87.5 and 155.2/93.2 mmHg, respectively.

Finally Guerrero-Romero and Rodriguez-Moran (2009) reported that BP after magnesium supplementation (141/80 mmHg) was lower than after placebo treatment (150/84 mmHg) (p=0.03 and 0.02 for systolic and diastolic BP, respectively) after four months of an 18.5 mmol daily dose of $MgCl_2$.

Direct support for the proposed claim was also provided by six low quality studies. Factors that contributed to the low quality rating of these studies included a very small number of subjects, a short intervention period (i.e., eight weeks or less), and/or failure to use a true placebo in the control group. Dyckner and Wester (1983) reported a significant decrease from baseline in

supine SBP and DBP (both, $p<0.001$) and in standing SBP and DBP (both, $p<0.05$) in the magnesium group (n=20) with no significant change in the non-treated control group (n=19) after the provision of 15 mmol/d magnesium aspartate for six months to 20 of 39 hypertensive subjects living in Sweden.

Reyes et al. (1984) reported that supplementation of 15.8 mmol $MgCl_2$ per day among 21 hydrochlorothiazide-treated hypertensives living in Uruguay resulted in a significantly lower supine ($p<0.005$) and standing ($p<0.01$) SBP as well as supine and standing DBP ($p<0.05$ for both) after three weeks compared to placebo-supplemented controls.

Paolisso et al. (1992) observed that SBP was lower among 18 magnesium supplemented Italian hypertensive subjects compared to placebo control subjects (159 vs. 171 mmHg, $p<0.04$). Diastolic blood pressure was also lower in the supplemented group (89 vs. 95 mmHg, $p<0.05$).

Sanjuliani et al. (1996) supplemented 15 Brazilian hypertensives with 24.7 mmol/d MgO and a placebo each for three weeks using a randomized cross-over design. BPs after the magnesium treatment (151/103 mmHg) decreased ($p<0.01$) compared to baseline (159/107 mmHg) while BP values after the placebo treatment (161/106 mm Hg) were not significantly different than baseline values. No statistics were provided that compared the magnesium and placebo treatments at the end of the intervention periods. However, the change in SBP with magnesium vs. the placebo was greater than that compared to the baseline so it can be inferred that decreasing systolic blood pressure with magnesium was significantly different than with the placebo. The change in DBP was slightly less after magnesium supplementation compared to the placebo (2.8 mmHg) than after the baseline period (3.8 mmHg) so that statistical significance

for DBP is likely but cannot be unambiguously inferred. Nevertheless, this paper provides direct support for the proposed claim.

Kawano et al. (1998) reported lower systolic and diastolic BP after magnesium supplementation vs. a control period (no placebo was provided) when measured in an office environment (144.9/88.3 vs. 148.6/90.0 mmHg, $p<0.01$ for systolic and $p<0.05$ for diastolic) in the home environment (134.4/85.4 vs. 136.4/86.8 mmHg, $p<0.05$ for both) during 24-hour ambulatory measurements (131.2/79.6 vs. 133.7/81.0, $p<0.01$ for systolic, $p<0.05$ diastolic) and ambulatory blood pressure during the day (135.2/82.5 vs. 137.7/84.0, $p<0.05$ for both) among 62 hypertensive Japanese subjects given 20 mmol/d MgO for eight weeks using a randomized cross-over design. There were no differences in BP for the magnesium vs. control periods when measured at night (123.4/73.6 vs. 125.9/74.8).

Finally, direct support for the proposed claim was provided by the low quality study of Kass et al. (2013). These investigators found the supplementation of 12.5 mmol MgO per day for 14 days lowered resting SBP (115.1±9.5 vs. 124.5±3.9, $p<0.05$), post-exercise SBP (122.6±15.3 vs. 139.1±4.5, $p<0.05$) and recovery SBP (5 min post exercise) (110.4±9.2 vs. 121.6±6.1, $p<0.05$) among 16 healthy young men living in the UK. The exercise challenge used in this study was 30 minutes of cycling with one kg load at maximal capacity to achieve the greatest distance. The post-exercise values were obtained after five minutes of rest.

b. Studies that provide mixed support for the proposed claim

Eight high or medium quality studies and two low quality trials provided mixed support for the proposed claim. The high quality study of Witteman et al. (1994) reported that the change in DBP from baseline between the magnesium and placebo groups (-3.4 mmHg) was statistically

significant (95% CI, -5.6 to -1.3 mmHg) at six weeks after supplementation of 20 mmol/d magnesium aspartate in a study of 91 women with untreated borderline hypertension living in Holland. However, no such difference was observed in the change from baseline between the two groups for SBP after six weeks (-2.4 mmHg, 95% CI, -6.7 to 1.2)[16] of supplementation. There were also no significant differences in this parameter after three weeks of supplementation.

Seven medium quality studies also provided suggestive support for the proposed claim. Lind et al. (1991) reported no treatment effects on supine or standing SBP or DBP upon supplementation of 49 Swedish adults with pre- or mild hypertension with 15 mmol/d of a combination of magnesium lactate and magnesium citrate for six months. However, individual changes in blood pressure with such supplementation were related to pretreatment urinary magnesium excretion. This measure was correlated to both supine SBP ($r=0.29$, $p<0.05$) and DBP ($r=0.28$, $p=0.05$). The investigators noted, "In other words, a beneficial effect of magnesium supplementation was seen only in the subjects with low pretreatment levels of urinary magnesium excretion." These results are consistent with the concept discussed earlier that beneficial effects of nutrient supplementation will only be observed among subjects with inadequate intakes (Lappe and Heaney, 2012).

Plum-Wirell et al. (1994) conducted a randomized cross-over study among 39 Swedish adults with moderate untreated hypertension. Supplementation of 15 mmol/d magnesium aspartate for two months did not affect blood pressure compared to a placebo among the entire group. However, supine and standing SBP was significantly lower ($p=0.037$ and $p=0.004$, respectively) among the subgroup of participants who received the placebo first. Data on the DBP outcomes

[16] There was an error in Table 3 of the paper. The difference was incorrectly reported as -2.7 mmHg

for this group were not reported. This effect may have been at least partially due to the fact that body weight at baseline was higher in this subgroup and weight loss occurred during the intervention period. Serum magnesium concentrations at baseline were 0.79 mmol/L for the placebo period and 0.81 mmol/L for the magnesium period and did not increase with magnesium supplementation; however urinary magnesium concentration did increase upon supplementation. It is possible the subjects in this study were not deficient enough in magnesium to exert an overall effect. In addition, Rosanoff (2010) has reported that 15 mmol/d magnesium supplementation is too low to affect BP in untreated hypertensives.

Wirell et al. (1994) reported no effect of magnesium supplementation (15 mmol/d) for eight weeks on blood pressure among 40 hypertensive Swedish subjects treated with beta-blockers using a randomized, placebo-controlled, cross-over protocol. However, paired statistical analyses that compared the magnesium and placebo periods revealed lower supine (-7 mmHg, $p=0.005$) and standing (-6 mmHg, $p=0.028$) SBP when subjects received the placebo first. No data for DPB were provided. Both urinary and serum magnesium (as well as serum potassium) increased with supplementation. However, baseline mean serum magnesium concentrations were 0.83 mmol/L which suggests the status of this cation may have been too far into the adequate range to respond to further supplementation.

Purvis et al. (1994) reported that SBP was significantly lower (7.37 mmHg, $p\leq0.006$) after supplementation with 15.8 mmol magnesium per day for four weeks compared to a placebo among 33 non-insulin dependent diabetic (NIDDM) subjects living in Florida. There were no such differences for DBP (-2.27 mmHg, 95% CI, -6.40 to 1.86) in this randomized cross-over study. The baseline BP was not reported, but blood pressures after the placebo period (142/80

mmHg) suggest the subjects were normotensive. No values were reported for serum or urinary magnesium concentrations.

Eriksson and Kohvakka (1995) conducted a randomized, placebo-controlled, cross-over study among 29 insulin dependent type-2 diabetic patients (IDDM) and 31 NIDDM subjects. Twenty-five mmol/d magnesium (form not reported) was used to supplement the diets and two grams of ascorbic acid was used as the placebo. The intervention periods were 90 days after a 90 day run-in period. Magnesium supplementation resulted in lower ($p<0.05$) systolic and diastolic BP among the IDDM group (132/77 vs. 143/82 mmHg, respectively). There were no such differences in the NIDDM group. Plasma magnesium values increased slightly (but not significantly) in the IDDM group after magnesium supplementation while urinary values increased. Both plasma and urinary magnesium concentrations increased in the NIDDM group.

Lee et al. (2009) reported no overall effect of supplementation with 12.3 mmol/d MgO for 12 weeks among 155 normotensive Koreans. Blood pressure at the end of the intervention for the magnesium group was 119/81 vs. 123/83 mmHg for the placebo group. However, the decrease in SBP was greater in the subgroup of subjects in the intervention group (n=8, -17.1 mmHg) with baseline SBPs of ≥140 mmHg compared to those in the control group (n=16, -6.7 mmHg, $p=0.016$). No such differences were observed for subgroups with lower baseline systolic blood pressures. In addition, the decrease in DBP with magnesium supplementation was more than with the placebo in both the baseline DBP=80 to 90 mmHg and ≥90 mmHg subgroups (-3.4 vs. -0.8 mmHg, $p=0.043$ and -3.4 vs. -0.8 mmHg, $p=0.023$, respectively) when compared to baseline subgroups with <80 mmHg diastolic blood pressures. These data are a direct demonstration that the effectiveness of magnesium supplementation is directly associated with baseline blood pressures as noted previously.

Mooren et al. (2011) reported no overall difference in blood pressure after supplementation with 15 mmol/d magnesium aspartate for six months compared to a placebo among 52 normotensive Germans, however the difference in DBP with magnesium supplementation was almost significant ($p=0.0561$). In addition, both SBP and DBP decreased ($p<0.05$) compared to baseline after magnesium supplementation while no such change occurred among the placebo group. Final BPs in the magnesium group were 131.4/81.6 mmHg compared to 133.1/83.2 mmHg in the placebo group. These results are impressive because the subjects were normotensive.

Finally, two low quality study also provided suggestive support for the proposed claim. Itoh et al. (1997) conducted a randomized, placebo-controlled study among 41 Japanese normotensive subjects given 22.5 mmol/d $Mg(OH)_2$ or a placebo for four weeks. Compared to baseline, mean SBP with Mg therapy decreased significantly after two weeks ($p<0.01$) and at four weeks ($p<0.05$) as did the mean DBP ($p<0.01$ at 2 wks, $p<0.05$ at 4 wks). In the placebo group there was no significant change of SBP or DBP from baseline during the study. There were no differences in SBP between the two groups at the end of the study (magnesium vs. placebo group, 125 vs. 122 mmHg) but final systolic blood pressure as percent of run-in systolic blood pressure was lower in the magnesium group (95.6% vs. 101.6%, $p<0.05$) compared to the placebo group. No such differences were observed for final diastolic blood pressure as a percent of run-in diastolic pressure.

Kass and Poeira (2015) conducted two separate placebo-controlled cross-over studies among physically active normotensive subjects given 12.5 mmol/d magnesium supplements for one week (“acute” dose, N=7 subjects) or four weeks (“chronic” dose, N=6). Within each trial subjects undertook both the magnesium intervention and placebo intervention with a one week washout period. Blood pressure measurements were recorded before and after a bench press

challenge at 50% 1-RM to fatigue on two separate days. Dietary intake was above the DRI for all groups [range 368±173 to 551±347 mg/d]. Resting systolic blood pressure from day one and day two significantly decreased with acute magnesium supplementation ($p = 0.031$) compared to the placebo which had exhibited an increase in systolic blood pressure v. baseline ($P = 0.047$). Significant day two reductions in systolic blood pressure were noted between acute treatments of magnesium supplementation compared to the placebo ($p = 0.016$). Chronic magnesium supplementation showed no significant reduction in resting systolic blood pressure on days one or two. Post bench press systolic blood pressure for chronic magnesium supplementation resulted in significant reductions on day one ($p=0.016$) and day two ($p= 0.016$) whereas acute magnesium supplementation resulted in a reduction of systolic blood pressure only on day two ($p = 0.047$) compared to the placebo. Resting diastolic blood pressure showed no differences between the placebo or magnesium treatments. Post diastolic blood pressure also showed no differences between days one and two for the acute group; however the chronic group showed a decrease in diastolic pressure for the post bench press treatment on day two. The authors concluded there appears to be no benefit in long term magnesium supplementation for those who have adequate dietary intake, but there are some benefits for taking an acute dose before intense exercise.

c. Studies that do not provide support for the proposed claim

Twelve high or medium quality studies and 11 low quality studies did not provide support for the proposed claim. However, there are compelling explanations for these null findings. As noted above, studies that employed normotensive subjects as well as those that used magnesium replete individuals would not be expected to show a significant effect of magnesium supplementation on blood pressure. These conditions apply to all but seven of the null studies (Henderson et al.,

1986, Nowson and Morgan, 1989, Zemel et al., 1990, TOHP Study Group, 1992, de Valk et al., 1998, Walker et al., 2002, Rodriguez-Moran and Guerrero-Romero, 2003). However, four of these studies (Nowson and Morgan, 1989, de Valk et al., 1998, TOHP Study Group, 1992, Rodriguez-Moran and Guerrero-Romero, 2003) employed pre- or hypertensive subjects who were not taking antihypertensive medications and provided doses of magnesium that ranged from 10 to 18.5 mmol/d. As noted previously, Rosanoff (2010) has observed that a dose of at least 20 mmol (480 mg) magnesium per day is necessary to illicit a significant decrease in blood pressure under these conditions. Table V indicates the studies that fall into each of these three categories as well as the studies that provide positive and partial support for the proposed claim.

In addition, two of the seven null studies noted above reported that serum magnesium did not increase in the supplemented group, which suggests the dose used was inadequate to alter magnesium status (Henderson et al., 1986, Zemel et al., 1990) and one such study was designed for another purpose and had serious methodological issues as described below (Walker et al., 2002). Therefore, as noted above, the totality of evidence from randomized controlled trials provides convincing support for the proposed claim. Furthermore, none of the studies that failed to support the claim reported adverse effects of magnesium supplementation on blood pressure. Additional discussion on the two high quality studies that did not support the claim and the remaining three studies that did not fit into one of the three broad categories noted above is provided below.

The two high quality studies that did not support the proposed claim were The Trials of Hypertension Prevention (TOHP) (1992) and Sacks et al. (1998). The TOHP study reported no significant difference in the change in blood pressure from baseline between 227 pre-hypertensive subjects given 15 mmol of magnesium diglycine per day for six months (-2.87/-3.0

mmHg) and 234 controls given a placebo (-2.67/-2.95 mmHg). Baseline blood pressures were 124.9/83.8 mmHg for the magnesium group and 125.4/83.9 mmHg for the placebo group. Serum magnesium concentrations increased by 0.02 mmol/L after six months while those of the placebo group decreased by the same amount so that the net difference between the two groups was 0.04 mmol/L ($p<0.01$). However, the baseline serum magnesium concentration was 0.78 mmol/L (reported by Yamamoto et al. (1995)) which means the final mean serum magnesium value was 0.80 mmol/L which may still have been suboptimal. It is therefore likely that the dose of magnesium used in this study was insufficient to achieve optimal status. The paper intentionally provided a dose that "could potentially be attained by diet change alone" rather than a larger supplemental dose. More importantly, baseline blood pressures were near normal in this study (the range for pre-hypertension is 120-130/80-89 mmHg) and the subjects were not taking anti-hypertensive medication. As noted above, Rosanoff (2010) observed that magnesium supplementation of at last 20 mmol (480 mg) may be necessary to affect blood pressure among such a group (i.e., not treated with anti-hypertensive medications) based on the literature. Nevertheless, this well-designed and executed study does not provide direct support for the proposed claim.

The other high quality study that did not provide support for the proposed claim was Sacks et al. (1998). This study reported no significant difference in blood pressure after supplementation with 14 mmol magnesium lactate per day for 16 weeks among 50 normotensive female residents of Boston compared to 100 placebo-supplemented controls. No subjects were taking anti-hypertensive medications. There were also no changes in systolic or diastolic blood pressure compared to baseline in either group. Baseline intake of dietary magnesium was estimated to be 239 mg/d (75% of the RDA for women 31-70 years), but serum magnesium concentrations were

not reported. Urinary magnesium increased ($p<0.01$) compared to the placebo in the magnesium supplemented group. The null results of this study are not surprising given the normotensive status of the participants and the low magnesium dose considering their "unmedicated" status. It would have been interesting to know the baseline serum magnesium concentrations as an indicator of overall status of this nutrient.

The medium quality study that did not fit into one of the three categories noted above was Henderson et al. (1986). This study was conducted among 40 hypertensive (mean baseline blood pressure of the magnesium and placebo groups 154/87 mmHg and 157/93 mmHg, respectively) supplemented with 12.4 mmol/d magnesium oxide for six months. The subjects were treated with potassium depleting diuretics for at least six months. There was no significant change in blood pressure (final blood pressure in the magnesium group was 150/88 mmHg compared to 154/92 mmHg in the placebo group). Baseline serum magnesium was marginally deficient (0.78 mmol/L) and did not increase upon supplementation (0.81 mmol/L after six months, $p>0.05$). Diastolic blood pressure in the magnesium group was lower than the placebo group at baseline (87 vs. 93 mmHg, $p=0.02$). The fact that serum magnesium did not increase during this study suggests that the relatively low dose employed was inadequate to materially affect magnesium status and largely explains the null result.

The two low quality studies that reported null results and did not fit onto one of the three categories noted above were published by Zemel et al. (1990) and Walker et al. (2002) . Zemel et al. (1990) employed a very small number of subjects (seven in the experimental group and six in the control group) who were supplemented with 40 mmol/d of magnesium or a placebo for three months. The subjects had mild hypertension (mean supine blood pressure of the magnesium and placebo groups was 145/90 and 140/89 mmHg, respectively) and were

required to have not taken anti-hypertensive medication for at least three months. Mean serum magnesium concertation was 0.72 mmol/L in the supplementation group and did not increase significantly during the experiment. Urinary magnesium concentration also did not increase in the group that received magnesium. There were no significant changes in supine or standing systolic or diastolic blood pressure. The final supine blood pressure in the magnesium and placebo groups was 148/92 and 139/90 mmHg, respectively. Once again, the fact that magnesium supplementation did not affect serum (or urinary) magnesium levels suggests that the dose was insufficient to illicit a blood pressure response. This finding is surprising given the relatively large (40 mmol/d) dose. Few details about the subjects were provided and it is possible that the null result was due to inadequate statistical power.

The study by Walker et al. (2002) also reported no effect of magnesium supplementation on blood pressure. This study was designed to examine the effect of supplementation with Hawthorn extract, with or without magnesium, on blood pressure among subjects with mild essential hypertension. The study employed a small number of subjects (nine in the magnesium group and 10 in the placebo group) and may have been underpowered to observe the hypothesized effect. Magnesium (24.7 mmol/d) was provided as an amino acid chelate but the exact form was not specified. There was a substantial decrease in both SBP and DBP in the placebo group, which prompted the authors to conclude, “There was a strong placebo effect which confounded the interpretation of results.” In addition, the magnesium group had a substantially higher intake of this mineral than the other groups (485±79.5 mg/d vs. 346.2±27.3 for placebo, 355.7±32.3 for Hawthorn, and 339.3±26.2 for the Mg + Hawthorn group) which led the authors to speculate that the magnesium group may have been replete at baseline. All of

these factors could have been related to ineffective randomization due to the small number of subjects.

3. Overall summary of intervention studies capable of substantiating the proposed claim

In summary, studies that meet FDA's criteria for the ability to substantiate health claims provide consistent support for the proposed claim. As depicted in Table V, 54% of high or medium quality studies (14 out of 26) provide direct support for the claim. However, when studies which would reasonably be expected to yield null results because they were conducted among normotensive and or magnesium replete subjects, or employed a dose of less than 20 mmol magnesium per day among unmedicated pre- or hypertensive subjects are excluded, 93% of high and medium quality studies (14 out of 15) provide direct or suggestive support for the proposed claim. Furthermore, null results from the remaining medium quality study (Henderson et al., 1986) can be explained by the fact that the dose of magnesium employed was inadequate because it did not increase serum levels of this nutrient. Therefore, the Center strongly believes that the totality of evidence from controlled intervention studies provides strong, consistent support for the proposed claim.

Table IV

Summary of Dietary Intervention Studies on Magnesium and Blood Pressure

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Dyckner and Wester (1983)	Parallel RCT	Mg 20(16F) Cont. 19 (10F) 100% finished the study	Sweden. Mg group: HT (N=18) and/or congestive heart failure (N=4); Cont: HTN (n=17), congestive heart failure (N=5). All patients on diuretics ≥ 1 y. All stayed on meds throughout study and all received K supplementation.	Mg group - supine: 152/93 standing: 145/93. Control grp - supine: 154/90 standing: 152/91	HT	15 mmol/d Mg aspartate HCl for 6 mo	Significant ↓ from BL in supine SBP and DBP ($p<0.001$) and in standing SBP and DBP ($p<0.05$) in Mg test group; no NSC in BP from BL in control group. Final Mg - supine: 140±15 / 85±7; standing: 139±18 / 87±10. Final Control - supine: 154±28 / 86±13; standing: 154±27 / 89±12.	No placebo reported. Subjects on drugs and ~30% had congestive heart failure. Relatively long duration of 6 mo. 19 of 20 subjects receiving Mg showed decrease in BP; 3 had to have Mg dose reduced due to low BP and dizziness, and 3 had to have thiazide dosage reduced during study. No significant change in heart rate before and after Mg treatment.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Reyes et al. (1984)	Parallel, double-blind, RCT	Mg 13 Cont. 8	Montevideo, Uruguay. Ambulatory white patients (17 females, 4 males) aged 42-82 y (mean=56.8±2.6 y) with uncomplicated HT (SDP 100 - 140). After a 4 wk washout, all subjects instructed to consume a low Na diet (≤130 mmol Na/day) and given hydrochlorothiazide for 7 weeks. Subjects then randomized into Group A (n=13) receiving Mg plus the hydrochlorothiazide and Group B (n=8) who received only the hydrochlorothiazide. Exclusion criteria: secondary or renal HT, congestive cardiac failure, history or evidence of cerebrovascular impairment, serum creatinine > 1.5 mg/dl, hypert- or hypokalaemia; gout or history of gout; hepatic insufficiency or history of same; diabetes; rheumatic conditions requiring drug therapy; any severe systemic disease; pregnancy; lactating mothers; women taking contraceptive steroids; patients on psychotropic drugs; patients considered uncooperative.	Group A (Mg): 156.1/111.5 Group B Placebo (identity not specified): 160/108.7	HT	15.8 mmol/d $MgCl_2$ (Slow-Mag) for 3 wks	Supine and standing SBP in thiazide + Mg group lower than thiazide alone group ($p<0.005$ and $p<0.01$, respectively). Supine and standing DBP in thiazide + Mg group also lower than thiazide alone group ($p<0.05$ for both). Values are mean±SEM. Supine and standing: SBP in Mg group (A) decreased (from 156.1±2.1 to 145.4±3.3) significantly from thiazide treated baseline ($p<0.005$) as did the placebo group (B) (from 160.0±2.7 to 147.5±3.7 $p<0.02$). DBP in Mg group also decreased (from 111.5±3.0 to 104.4±3.9) significantly from the thiazide treated baseline ($p<0.05$) while decrease in placebo group (from 108.7±5.1 to 105.0±4.2) was not significant.	All subject taking drugs. Study reports numerical results in abstract, presumably combined for supine and erect measurement, but only provides graphic results, for supine separated from erect, in paper. Graphs show that greatest BP reductions occurred during the 7 wks of thiazide treatment before the randomization (both supine and erect, SBP and DBP decreased, $p<0.02$).	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Cappuccio et al. (1985)	Cross-over, double-blind RCT	17 100% finished the study	London. 9 men and 9 women, 14 white and 3 black, mean age was 51.7 y (33 - 66). Essential HT with DBP 90-114; no meds for 2 mos (3 mos w/o diazides); excluded were plasma creatinine > 120 µmol/L; IHD or cerebrovascular disease, oral contraception or any other drug;	Lying: 154/100 Standing: 156/106 after 2 mos run-in.	HT	15 mmol/d Mg aspartate-HCl and placebo (identity not specified) for 1 mo treatments w/ no wash-out	No significant change in either standing or lying SBP or DBP with Mg treatment. Final standing at 4 wks: Mg periods 157±17.7 /105±7.83, placebo periods 154±18.1 /106±7.42. Final lying at 4 wks: Mg periods 154±14 /98±9.07, placebo periods 151±18.1 /97±8.24	Small cross-over RCT on untreated essential HT subjects with dose of Mg found to not decrease BP significantly in untreated subjects. There was no treatment order effect. Urinary ($p<0.001$) and plasma Mg rose ($p<0.02$) during Mg study periods. Variances reported in SEM have been converted to SD in this spreadsheet. BL plasma Mg was in the normal range of 0.89 mmol/L and may have accounted for the null result due to a BP threshold effect.	Ø
Henderson et al. (1986)	Parallel, blinded RCT	Mg 20 Cont. 20 98% finished the study	Denmark (multi-center). HT treated with K depleting diuretics for > 6 mos and DBP <105. Excluded if serum creatinine ≥200 micromol/l; any evidence of cardiac failure; chronic diarrhea; use of Mg containing drugs. Mean age 62; 75% of subjects had been taking diuretics for >2 y. No difference between Mg and placebo groups in age, sex,duration of diuretic treatment, serum electrolytes or SBP.	Mg group: 154/87 Placebo group (identity not specified): 157/-93. DBP > (p=0.02) in Mg vs. placebo	HT	12.4 mmol/d MgO for 6 mo	No significant change in BP. Final Mg group 150±20 / 88±7 placebo group 154±22 /92±6. Baseline serum Mg in the supplementary group was 0.78 mmol/L and 0.81 mmol/L in the placebo group.	DBP of Mg group differed significantly from DBP of placebo group before treatment (87 vs. 93 mmHg, p=0.02). NSC vs. BL in serum Mg. At baseline, using mean and S.D. 69% of the study's Mg test group had DBP≤90, i.e. normotensive while 75 % had SBP>140. No report of how compliance with study was assessed.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Olhaberry et al. (1987)	Parallel, double blind RCT	Mg 7 Cont. 7	Montevideo, Uruguay. Uncomplicated mild essential hypertensive patients ages 24-64, untreated with anti-HT meds, given a very low Na diet during study. Excluded were patients with antecedents of cardiac, hepatic, endocrine, metabolic, renal, gastrointestinal rheumatic or systemic disorders or any feature suggestive of Mg deficiency as well as psychotics, and patients on oral contraceptives. All had normal EKG, supine HR, chest x-rays, serum creatinine, serum K ad serum Mg (0.81 to 1.13 mmol/L).	Mg group: supine= 153/100 Erect= 153/100. Placebo group (identity not specified): supine= 150/ 100 Erect= 151/ 101.	HT	15.78 mmol/d $MgCl_2$ for 4 wks	No significant differences in BP were shown between the groups throughout the study. Both groups showed significant decreases in SBP vs baseline with p values from $p<0.05$ to $p<0.001$, depending upon supine, erect, Mg or placebo group. Final BP - Mg group: supine 138±4 / 97±6; erect 140±8 / 98±5. Placebo group: supine 130±3 / 93±3; erect 133±3 / 93±3. Variance values are SEM.	Subjects were co-prescribed Mg supplementation or placebo with a daily diet containing 70 - 100 mmol Na, i.e. 1610 to 2300 mg Na/day. The paper stated, "No significant differences between corresponding mean values of blood pressure occurred between the groups during treatment", however the statistics reported compared outcomes for the two treatments vs. BL, not compared to each other. If the comparison stated in the paper was actually vs. BL and not between groups, it is possible that the low Na diet confounded the results. Both groups began study with normal plasma ranges for Na, K and Mg. There were no significant changes in blood electrolytes except that the placebo group showed a significant decrease (to 0.86 mmol/L) in plasma Mg by end of study ($p<0.05$). Compliance was measured by pill count which the paper characterized as "unreliable". Lack of compliance could have been a factor since the subjects were required to take six pills per day.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Nowson and Morgan (1989)	Parallel, double blind, RCT	Mg 12 Cont. 13 100% finished the study	Parkville, Australia. All subjects had mild HT, untreated, and were placed on a very low Na diet (50-70 mmol Na/day) for 4 wks before Mg phase of the trial; Mg group was 7 males & 5 females age 62.7±2.1 y (50-77 y); Ct group was 10 males & 3 females age 62.6±1.7 y (51-71 y); Ct group body wt > Mg group, i.e. 85±4 kg vs 72±3 kg (p<0.02).	Values are approximate since they were presented only graphically Mg group: At wk 0- Standing: ~157/98 Supine: ~155/91 At wk 4: Standing: ~148/93 Supine: ~144/86 Placebo group (identity not specified) At wk 0- Standing: ~157/96 Supine: ~148/90 At wk 4: Standing: ~149/97 Supine: ~145/90 The supine placebo group appeared to have lower BL SBP at wk 0 than the other measures at that time.	Mild HT untreated	10 mmol/d Mg aspartate for 8 wks preceded by a 4-wk low-sodium run-in w/o Mg	The abstract reported NSD b/w groups at the end of the intervention period, but statistics were not provided. Changes from BL were reported based on wk 4 data (i.e., end of the run-in on low Na diet). These results were presented in a very confusing way: "Comparing the last placebo BL measurement with the last measurement on supplementation, there was a change in supine BL of -2±3 / -3±2 (p<0.4) in the placebo group. In the Mg group there was a change in supine pressure of 2±2 / 1±2 (p<0.6). The change in erect pressures in the placebo group was 1±2 / -1±2 (p<0.6) and in the Mg group 0±3 / 3±2 (for DBP p<0.02) but final Mg erect DBP did not differ from that of placebo group)." Plasma Mg concentrations not provided, but the paper stated the plasma concentrations did not increase with magnesium supplementation.	Low dose of Mg used. Small N. Design of the study that added supplementation of Mg to a low-sodium diet after four weeks likely a serious confounder of the study. Numerical baseline and final BP values with variance not reported; results given in figure. Subjects were all given a very low Na diet for a 4 week run-in before Mg supplementation or placebo was given, so BPs at start of Mg therapy or placebo were in the 145-151 range for SBP and 85 - 96 range for DBP. During the low-Na run in, SBP's decreased then leveled off during both the Mg and placebo test phases except for supine Ct SBP which was lower than all other SBP means at start of low-Na run in and decreased during the placebo test phase (See Fig. 1). DBPs of Mg groups all decreased during low-Na run-in, then leveled off or even raised during Mg phase. Ct group DBP remained level during run-in, then erect remained level but supine decreased during the placebo test phase. Dose of 10 mmol/day Mg shown to be inadequate to decrease BP in untreated HTs (Rosanoff, 2010).	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Daly et al. (1990)	Parallel, double blind, RCT	Mg 20 Cont. 20 95% finished the study	Ft. Collins, Colorado. Borderline HT with SBP>140 and/or DBP>90, untreated with anti-HT medications for at least one year prior to study. Excluded: pregnancy, mental incapacitation, alcohol or drug addiction, congestive heart failure, myocardial infarction within one year, angina pectoris, kidney stones within 10 yrs, history of cerebrovascular accident, parathyroid dysfunction or taking Ca or Mg supplements. Mg group was 8 men, 12 women, mean age 57 to start.	Mean and SEM: Mg group: 144±11 /85±9 Placebo (gelatin) group: 141±12 /83±8	Border-line HT/NT	10.3 mmol/d MgO for 12 wks	Change in BP in Mg group after 12 wks of treatment (-12.6±12.2 / -7.5±9.1) was much larger than change in control group (-0.9±11.5 / -1.6±4.9) . Variance is SEM. At 12 wks the decrease in mean SBP in Mg group was significantly greater than in control group (p=0.004) but changes in MAP or DBP showed no significant difference. However, slopes of individual linear regression lines for decrease in SBP, DBP and MAP over 12 wk trial showed decreases in SBP, DBP and MAP were significantly greater in the Mg group (p=0.007/0.02/0.015).	This study graphs SBP, DBP and MAP for each week during the study for both Mg and Ct groups. The Mg group showed a decrease in SBP compared to control starting at week 9, enlarging by wk 12 to a significant difference from control. A similar pattern was seen with MAP, but difference at wk 12 did not reach significance. 16/19 (84%) subjects receiving Mg vs 9/16 (56%) subjects receiving placebo showed a decrease in SBP and DBP. And, two additional ct subjects showed a slight decrease in DBP only. Variances are SEM.	Ø
Patki et al. (1990)	Cross-over, double-blind RCT	37 100% finished the study	Pune, India. Adults (mean age 49.9 yrs) attending cardiology unit at Sassoon General Hospitals, India; Supine DBP 90 to 110 after one month w/o any treatment. Mg was given in combination with potassium supplement during one phase of this 3-phase cross-over trial (placebo, K supplement, K+Mg supplement).	Pre-K+Mg supplement period: Supine 158.0±12.6 / 100.2±4.9 Standing 150.0±9.6 / 98.8±5.1	HT	20 mmol/d $MgCl_2$ + 60 mmol/d K and placebo (identity not specified) for 8 wk treatments w/ 2-wk wash-outs	**After placebo:** Final Supine: 155.7/97.6; Final Standing: 156.4/98.1 **After K:** Final Supine: 143.6/84.5 Final Standing:143.2/84.9 (all p<0.001, placebo vs K) **After K+Mg** Final Supine: 146.8 /88.0 Final Standing: 146.1/87.6 (all p<0.001, placebo vs K + Mg). NSD K vs. K+Mg. Baseline serum Mg=0.88 mmol/L.	Indian subjects probably not reflective of the general US. Population. The paper stated, "The difference in BP among treatment groups was not affected by the order in which the drugs were given" which suggests there was no carry over effect from the cross-over. When K+Mg combination's effect on BP was compared with placebo's effect, there was significant decrease in both SBP and DBP, standing and supine (p<0.001). There were no changes in serum Mg and urinary Mg was not measured, but serum cholesterol decreased when either K alone or K + Mg supplements were administered.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Zemel et al. (1990)	Parallel, double-blind, RCT	Mg: 7 Cont. 6 100% finished the study	Detroit, MI. Adults aged 20 - 69 y, with uncomplicated mild-to-moderate essential HT and normal renal function. To qualify for study, DBP between 85 - 100 and SBP<180 with no anti-HT meds for at least 3 months. At baseline, placebo group subjects had higher mean cholesterol, triglyceride and LDL cholesterol and lower HDL concentrations than did Mg group subjects, differences which persisted throughout the study.	Mean ±SEM Mg group: supine - 145±4 / 90±2 MBP 111±4. Standing - Mg group: 142±4 / 96±1 Placebo (identity not specified) group: supine - 140±5 / 89±2 MBP 108±4 Standing - 136±6 / 90±2 (Standing MBP values not reported.)	Mild HT untreated	40 mmol/d Mg aspartate HCl for 3 mo after 3-wk placebo run-in period	There were no significant changes in supine or standing SBP, DBP or MBP in either the placebo or Mg group. Final Mg group: supine 148±6 /92±2 MBP 112±4; standing 147±6 / 93±3. Final Placebo group: supine 139±5 / 90±4 MBP 108±3; standing 141±4 / 95±2. (NSD b/w groups at end of treatments). Standing MBPs mot reported. Values are SEM.	Effectiveness of the randomization in this small study was suspect. At baseline, the Mg group had a significantly higher standing DBP than the placebo group ($p<0.05$) as well a significantly lower PRA ($p<0.05$). In addition, the placebo group had higher total cholesterol ($p<0.05$), triglyceride (NSD) and LDL cholesterol (ns) plus lower HDL cholesterol (NSD) than did Mg group, and these differences remained throughout the study. The total cholesterol/HDL cholesterol ratios (calculated from values in Table 2) remained "high" for placebo group (all >3.5 and up to 5.5 and 5.8) throughout study while ratios of Mg group were all in normal range (<3.5) except for 1 month measurement when it rose to 3.69. Authors speculate that Mg lowers BP "only in states of magnesium deficiency," vaguely suggesting that subjects of Mg group were perhaps Mg replete (while control group was perhaps not). Other nutrients besides Mg can alter BP when deficient, i.e. Ca, K. It is reasonable to assume that Mg therapy in HT Mg replete subjects will not lower a high BP. In this study, final intracellular Ca was significantly higher in Mg group than placebo group, but no significant differences were seen in intracellular Na, K or Mg, PRA, in serum or urinary Ca, Mg, Na or K, or BP between Mg and placebo groups. Both groups showed 95 - 97% compliance in taking the supplement or placebo.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Lind et al. (1991)	Parallel, double-blind, RCT	Mg 49 Cont. 22	Uppsala, Sweden. Adults with DBP≥95 or DBP 85 - 94 plus SBP≥165 with or without antihypertensive medication from a health screening. Excluded were CVD, impaired kidney function or alcoholic abuse. Mg treatment group was 49% male age 60±9.4 y, placebo group was 59% male age was 62±7.8 y	Supine: Mg group - 151±14 / 91.8±6.2; Placebo (noted as free of Mg and Ca but identity not specified) group - 148±12 / 93.1±5.1. Standing: Mg group - 149±16 / 96.3±6.8; Placebo group - 146±15 / 98.3±6.4. Of 71 subjects randomized, 45 showed mild hypertension (DBP>90) and 26 showed high-normal BP.	Mild HT or pre-HT	15 mmol/d Mg lactate + Mg citrate for 6 mo.	At 6 mos there was no significant change in BP with Mg treatment: **Supine** Mg group 152±14 / 89.1±7.4 Placebo group 146±11 / 88.9±7.3 **Standing** Mg group 151±16 / 97±7.2 placebo group 145±15 / 97.1±8. When analyzed separately, subjects with pretreatment DBP>90 showed same n.s. results for BP. However, pretreatment Mg excretion correlated to the change in SBP ($r=0.29$; $p<0.05$) and DBP ($r=0.28$; $p<0.05$).	There were no overall treatment effects for S/DBP, however, beneficial effects of Mg on BP was seen in subjects with low pretreatment levels of urinary Mg excretion (also high pretreatment levels of serum K). This observation suggests that subjects with suboptimal Mg intake/status benefited from the supplementation. Hypotensive effect of Mg was mainly seen in subjects who, on Mg treatment, increased their urinary Na excretion and raised their serum Mg levels. Mg treatment induced a 30% increase in urinary Mg excretion.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Ferrara et al. (1992)	Parallel, double-blind RCT	Mg 13 Cont. 13 54% finished the study	Naples, Italy. Men and women (age 35 - 60 yrs) with mild to moderate essential HT and within 20% of ideal body weight and no chronic disease, non-pregnant, non-lactating. Excluded were BP>180/114, oral contraceptives.	Supine - Mg group: 156±12 / 97±4. Placebo group (identify not specified): 158±13 / 93±3. Standing - Mg group: 155±10 /102±5. Placebo group: 151±6 / 100±2.	HT	15 mmol/d Mg pidolate for 6 mo.	Both Mg and placebo groups showed significant lowering of both supine SBP and DBP and standing DBP from their baseline values (all $p<0.01$). However the placebo group's final supine SBP and standing SBP and DBP were all significantly LOWER than the Mg group final values (all $p<0.01$). Final **supine** BP values: for Mg group: 149±8 / 90±3 ($p<0.01$ from baseline); for control group: 141±8 / 89±3 ($p<0.01$ from BL and from Mg group for SBP). Final **standing** BP values: for Mg group: 155±11 / 96±5 (no change from baseline but $p<0.01$ vs placebo); for control group: 140±9 / 91±5 ($p<0.01$ vs baseline and vs Mg group for DBP). Baseline plasma Mg=0.9 mmol/L in both groups.	High dropout rate (53%) resulting in low N – especially for a parallel study. The study had a power to detect a ΔDBP of 6.8 mmHg. There was a large placebo effect, larger than the Mg effect, in this very small study (n=7 for each group), but there is no discussion of this placebo effect by authors. BP values dropped in both Mg and placebo groups, more so, significantly, in the placebo groups. Subjects dropped out during study because their BP rose to <180/114. Thus, lower BP, the range more difficult to show a significant decrease especially with few subjects, was emphasized in this study. This small study's results are included in 3 major meta-analyses, and since the change in BP with placebo is subtracted from change in BP with Mg, it is included in meta-analysis calculations as a rise in BP with Mg, even though Mg therapy showed a significant decrease in both SBP and DBP from baseline. Study appears, to me, faulty due to large placebo effect which may be due to even one outlier subject in placebo group in this small study. Unfortunate that authors nor reviewers demanded discussion of these unexpected placebo results.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Paolisso et al. (1992)	Parallel, double-blind RCT	Mg 9 Cont. 9 100% finished the study	Naples, Italy. Essential HT on thiazide diuretics > 1 y. Age = 63 ± 3 y, none with renal impairment or papilloedema or family history of diabetes. No drug use besides thiazide for at least 4 wks. 24 newly diagnosed untreated HT patients matched to age, gender, BMI, lean body mass and waist/hip ratio served as controls but were not given Mg. Mean dietary Mg intake 324±13 mg/day.	Baseline BP for 18 Thiazide treated HTs later randomized to 8 wks Mg or placebo (identify not specified): 173±9 / /96±4. For untreated "controls (n=24) who were not randomized nor received Mg treatment: 188±9 / 104±4.	HT	15.8 mmol/d Mg Pidolate for 8 wks	Mg therapy significantly lowered both SBP and DBP compared with placebo: SBP lower in Mg group (171 ± 8 v 159 ± 4, p<0.04); DBP lower in Mg group (89 ± 5 vs. 95 ± 3, p<0.05).	Small N. All subjects in randomization receiving drug therapy. Mg therapy significantly raised urinary Mg, plasma Mg, rbc Mg, rbc K and glucose uptake while significantly lowering rbc Na.	-
TOHP Study Group (1992) Also Yamamoto et al. (1995) and Whelton et al. (1995)	Parallel, double-blind, RCT	Mg 227 Cont. 234 93% (206 Mg 224 Ct) finished the study	10 USA clinics. Healthy men and women, age 30-54 yr, with high normal DBP (80-89) free of anti-HT meds for 2 months. Mean wt = 82.7±14.3 kg. Excluded were those with clinical or lab evidence of CVD or other life-threatening/disabling disease; conditions that would contraindicate intervention; evidence of unwillingness or inability to comply with intervention or procedures.	Mg group: 124.9±8.0 / 83.8±2.7 Placebo (identify not specified) group: 125.4±8.8 / 83.9±2.8	Pre-HTN	15 mmol/d Mg diglycine for 6 mo	Change from Baseline BP for Mg group: -2.87±6.6 / -3.0±4.54; for placebo group: -2.67±7.24 / -2.95±5.21, both NSC.	This largest trial of Mg for blood pressure showed no significant decrease in either SBP or DBP in these NT subjects with Mg supplementation of 15 mmol/day for 6 months. Mg groups showed significant increase in both urinary Mg excretion (p<.01) and serum Mg (p<0.01) at both 3 and 6 month measurements however the absolute change was in sMg @ 6 mo was only 0.02 mmol/L. BL sMg was 0.78 mmol/L (Yamamoto et al., 1995) so final value was only 0.80 mmol/L. ITT analysis (dropouts assigned ΔBP=0) was not materially different than the per-protocol analysis reported. Estimated intake of Mg (from 24-hr recall data) was 260 mg/d). Null results not unexpected due to a dose of less than 20 mg Mg in unmedicated subjects.	+

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Kisters et al. (1993)	Parallel RCT Blind-ing not stated	Mg 37 Cont. 32 100% finished the study	Munster, Germany. Subjects were hyperlipidemic but normotensive with normal renal function. Mean age in the Mg group was 47.9±9.3 and in the placebo group 49.8±10 y. All subjects were on a Kcal and cholesterol restricted diet.	Baseline Mg group: 129.1±12.6 / 82±2.9; Placebo (identity not specified) group: 128.2±10.9 / 82.2±3.4	NT	20.6 mmol/d Mg hydrogen aspartate for 4 wks	No significant difference in BP b/w groups in these NT subjects. Final BP for Mg group: 123.3±12.4 / 81.5±2.8; for placebo group: 122.9±4.7 / 81.7±2.8. Baseline plasma Mg approximately 0.985 mmol/L in both groups (estimated from graph in the paper).	Energy-restricted diet not reflective of normal dietary practice. Weight loss has profound effect on BP and may have overshadowed any effect of Mg on this outcome. Results in this paper were reported graphically. Numerical results for BP here are from personal communication from author. Both groups showed significant weight loss (2.9 kg) during intervention; triglycerides were significantly lower with the Mg intervention than the placebo ($p<0.05$), and intracellular Mg was significantly higher with Mg intervention ($p<0.05$). However, no significant change in either SBP or DBP was shown in these normotensive subjects with Mg intervention of 20 mmol/day for 4 wks.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Widman et al. (1993)	Cross-over, double-blind, RCT	17 94% finished the study	Umea, Sweden. Patients with mild essential HT (DBP>90), age 50±6yrs. Excluded were severe HT (DBP>115), IHD, stroke, serum creatinine >130 µmol/L, atrioventricular block II or III; related cancer, diabetes, psychosis or signs of other serious mental illness.	Mg treatment: 154±10.7 / 100.2±4.2 Placebo (identify not specified other than the manufacturer – Emgesan, Kabi Pharmacia) treatment: 154.6±15.5 / 97.6±6.6	HT mostly untreated	15, 30 & 40 mmol/d $Mg(OH)_2$ 12 wks each arm (3 wks each at 15, 30 and 40 mmol Mg/day, consecutively). Also 3-wk placebo treatment. 3-wk wash-out at cross-over	Mg treatment lower for SBP (p=0.0051) and DBP (p=0.0075) vs. placebo. Mg treatment arms also showed significant decreases in both SBP (p=0.031) and DBP (p=0.0001) vs baseline values. Placebo arms showed ns decrease from baseline for SBP (p=0.089) and DBP (p=0.081). BP results - After 15 mmol Mg/day for 3 wks - Mg group: 151.6±16.8 / 95.6±5.0; placebo group: 150.7±14.9 / 96.2±7.1. After 30 mmol Mg/day for 3 wks (after 3 wks at 15 mmol/day) - Mg group: 148.7±17.4 / 94.0±7.3; placebo (after 6 wks): 149.5±17.1 / 94.5±6.1. After 40 mmol Mg/day for 3 wks (following 3 wks of 15 mmol/day then 3 wks of 30 mmol/day) - Mg group: 146.1±16.5 / 92.0±6.6; Placebo group (after 9 wks): 153.0±19.3 / 97.6±6.6. Descending trend in BP occurred after 30 mmol/day Mg [Rosanoff, 2010].	This is the only oral Mg therapy trial that used titration, i.e. increasing doses of Mg from 15 to 30, then 40 mmol/day, consecutively. Mg treatment arms consisted of 3 wks at 15 mmol Mg/day followed by 3 wks at 30 mmol Mg/day then 3 wks at 40 mmol Mg/day. Placebo arms were 9 wks. Three week washout at cross-over. This cross-over trial was not corrected for cross-over effect. It is possible that the high Mg intake before final placebo period partially repleted subjects who had been Mg deficient, thus minimizing difference between Mg and placebo arms for which statistics were all calculated together. When 30 mmol Mg period BP is t-tested against Mg and placebo baseline values, both SBP and DBP show significant decreases with Mg (p<0.01) (Rosanoff, 2010).	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Wirell et al. (1993)	Cross-over, double-blind RCT	36 100% finished the study	Umea, Sweden. 19 men, 17 women with mild to moderate HT; all subjects on Thiazides at least 2 months and throughout study (one taking chlorthalidon and 35 had received thiazide e.g. bendroflumethiazide for at least 2 mos: median 4.5 mos, mean 20.8 mos, range 2 - 168 mos, age 29 -62 yr, median age = 46 y.	Supine: 143±11.6 / 95.6±5.7; MAP = 119.3±7.5	HT	15 mmol/d Mg aspartate-HCl and placebo (identity not specified) for 8 wks	No significant change in SBP, DBP or MAP for supine or standing BP. Only supine values reported. Final supine BP - After Mg: 141.5±11.3 / 94.4±6.7; MAP = 117.9±8.4. After placebo: 142.7±11.6 / 93.7±8.7; MAP = 118.2±9.1.	Cross-over trial corrected for carry-over effect; randomization method not reported. If anti-HT med status was really <6 months, then Mg dosage is too low (i.e. <20 mmol/day) to show a significant decrease in BP (Rosanoff, 2010). Both serum and urinary Mg increased with Mg supplementation (42% subjects had serum Mg < 0.80 mmol/l at start of study), but Mg therapy had no effect on serum Na, K or Cl , urinary Na, K or Cl, or muscle Mg, K, Na or Cl.	Ø
Plum-Wirell et al. (1994)	Cross-over, double blind, RCT	39 100% finished the study	Umea, Sweden. Mild to moderate untreated essential HT, i.e. DBP between 95 and 110, supine (age 20-59 yrs). HT diagnosed 3 - 120 months (median = 19 months) before study. 34 (87%) subjects were treatment naïve, 3 used no meds for 2 yrs, 2 used meds for 6 and 1 month, respectively. Exclusion criteria: serum creatinine > 150 µmol/L; myocardial infarction or unstable angina within 3 mos; grade II or III atrioventricular block; cardiac failure class NYHA class IV; pregnancy; malignancy; diabetes; rheumatic disease; collagenosis; alcohol abuse; unable to cooperate.	Placebo periods: supine 150.7±14.3 / 97.9±7.6; standing 151.4±16.3 / 106.2±7.8; Mg periods: supine 149.9±17.7 /95.7 ±8.0; standing 149.0±19.6 / 103.9±8.8; subgroup (n=18) of placebo first: supine SBP 152.2±15.7; standing SBP 153.5±17.8	HT	15 mmol/d Mg aspartate HCl and placebo (identify not specified) for 2 mo w/ no wash-out	No significant change in either SBP or DBP in whole group (n=39): final placebo periods: supine 149.9±9.4 / 97.5±9.9, standing 147.5±19.0 / 105.3±11.3; Magnesium periods: supine 147.5±15.3 / 95.3±9.2; standing 147.2±18.4 / 104.5±9.5. Subgroup receiving placebo first (n=18) showed significant decrease in both standing SBP (final SBP = 144.1±20.3 p=0.004) and supine SBP (final SBP=146.1±17.0 p=0.037).	There was no testing for carry-over effect reported in this cross-over trial on mostly untreated subjects; dose of Mg was only 15 mmol/day which was shown to be inadequate to significantly lower SBP and DBP in untreated subjects (Rosanoff, 2010). In the subgroup with a significant decrease in SBP, starting body weight was greater than the other groupings, and their weight loss during the study was three times that of the other groups. Urinary Mg rose significantly on Mg supplementation (p<0.009) and decreased significantly on placebo (p=0.048). There were no changes in serum Mg or K, urinary K or muscle Mg or K. Urinary Na decreased on Mg treatment (p<0.005).not on placebo. Serum Mg at BL was 0.79 mmol/L (for placebo period) and 0.81 mmol/L (Mg period) and did not increase with Mg supplementation.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Purvis et al. (1994)	Cross-over, double-blind, RCT	33 85% finished the study	Tallahassee, Florida. Adults (28 - 84 y, mean age 53.8±12.8 y) with NIDDM controlled with diet or oral hypoglycemics plus total serum cholesterol ≥5.2 mmol/L. 24 women (85.7%) and 16 black (57.1%). BMI range was 21.3 - 50.6 kg/m^2, mean = 32.2±7.1. Excluded were people with serum creatinine > 179 mmol/L, those taking diuretics, beta-blockers, lipid lowering drugs or Mg containing antacids, or had history of alcohol abuse, dementia or other conditions that might lead to non-compliance of non-stability during the study.	NR	NT?	15.8 mmol/d $MgCl_2$ and placebo (identify not specified) for 4 wks. There were 2-wk placebo run-in and wash-out periods.	Mg supplementation resulted in lower SBP (-7.37 mm Hg) ($p<0.006$), and NSD in DBP (-2.27 mm Hg 95% CI, -6.4 to 1.86). Impact of Mg supplementation on BP was variable and dependent on the individual. The most dramatic improvement was from 162/82 to 130/66 but another subject had a rise of 8 mm Hg in SBP during active treatment with Mg. After Mg treatment BP: 134.4±4.82 / 77.73±3.06. After placebo treatment BP: 141.51±4.63 / 80±2.43. Values are SE.	This study appears to be on a group with diabetes but normal BP, i.e. perhaps Mg def. but with no HT. This is presumed as the baseline BP values are not reported. Correspondence with authors also has produced no starting BP, but "after placebo" values support presumption of NT at start of study. It is not expected that oral Mg therapy will significantly decrease both SBP and DBP in studies on mostly NT subjects (Rosanoff, 2010). This study reports the high individual variation in BP responses to Mg therapy which is not mentioned in most studies.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Wirell et al. (1994)	Cross-over, double-blind, RCT	40 98% finished the study	Umea, Sweden. Subjects with mild to moderate HT (HT diagnosed for a median time of 31 months, range 3 - 180 months), on beta-blockers for a median of 24 months (range 1 - a168 months, mean = 42±months). Subjects aged 26 - 69 yrs, mean age = 35.4yrs. Exclusion criteria: patients treated with drugs containing Mg or any non-beta-blocker meds, Serum creatinine >150 µmol/L, any serum Na and/or K outside normal values; recent myocardial infarction (within 3 months study start) or cardiac failure, pregnancy, malignancies, diabetes, rheumatic diseases, collagenoses, unable to cooperate, DBP>110 and SBP>190.	n=18 starting with placebo arm: Standing: 143.9±17.6 / /105.5, 10.4; Supine: 148.8±14 / 95±6.2. n=21 starting with Mg arm: Standing: 147±26 / /103.1±7.5; Supine: 147±18.7 / 95.1±8.1.	HT	15 mmol/d Mg aspartate and placebo (identify not specified) for 8 wks w/ no wash-out period	Using a paired statistical analysis (comparing data from same patients during Mg and placebo periods) showed a significant decrease in supine (p=0.005) and standing (p=0.028) SBP with Mg when it was supplemented AFTER placebo. But, using overall change in BP by either Mg or placebo using independent statistics there was no significant change in any BP parameter measured.	Subjects were taking beta-blockers. Cross-over study with no washout and no reported test for carry-over effects; using statistics with change in BP that "pair" each subject's Mg and placebo results showed a significant decrease of -6 to -7 in SBP with Mg, but usual overall analysis showed no change. Both serum Mg and K increased with Mg supplementation as did urinary Mg. There was no Mg effect on muscle Mg or K or urinary K. Note that subjects with very high BP were excluded from study. Subjects were Mg replete according to serum values (0.83 mmol/L at BL).	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Witteman et al. (1994)	Parallel, double-blind RCT	Mg 47 Cont. 44 100% finished the study	Zoetermeer, Holland women with untreated HT, i.e. SBP≥140 but <185 or DBP±90 but <105. Excluded were any secondary HT, history of major CVD, IDDM, chronic diarrhea, major changes in diet, use of anti-HT drugs in last 6 mos, use of drugs known to interfere with mineral metabolism or platelet activity.	Mg group: 146.2*±13.6 / 89.4±6.7 Placebo (identify not specified) group: 146.4±11.2 / 90.0±7.0 *As reported in Table 3 of publication.	Border-line HT	20 mmol/d Mg aspartate HCl for 6 mo	Final BP values for Mg group: 143.8±14.0 / 86.1±7.0; Final BP values for Ct group: 146.6±13.5 / 90.1±6.9; n.s. change in SBP -2.7** (95%CI -6.7, 1.2); significant change in DBP -3.4 (95% CI -5.6, -1.3). **As reported in Table 3 of publication. Note, change in SBP in Mg group reported as -2.7 but calculation results in -2.4.	The study shows the highly variable results for BP with Mg or placebo by displaying individual data. There was a trend towards lower SBP with Mg compared with placebo group as shown in Fig 2 of the % distribution of SBP change, but it was n.s. upon statistical test. Similar trend for DBP in Fig 3 that was significant when tested statistically. Note that subjects with very high BP, i.e. SBP>185 or DBP>105, were excluded from the study, and these are the subjects for whom oral Mg therapy shows largest Mg effect on BP (Rosanoff and Plesset, 2013, Lee et al., 2009). Urinary Mg ↑ more in Mg vs. placebo group ($p<0.0001$). NSC in serum Mg but a trend in that direction.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Eriksson and Kohvakka (1995)	Cross-over, double-blind RCT	60 93% finished the study	Helsinki, Finland. Outpatient diabetics on a weight-maintaining diet. 29 had IDDM (age 43±2 yrs, BMI 24.1±0.6, duration of diabetes 19±2 yrs) while 27 had NIDDM (age 61±2 yrs, BMI = 28.9±0.8, duration of diabetes 10±1 yrs).	IDDM group: 138±4 / 82±2. NIDDM group: 149±3 / 87±2.	NT in IDDM; mildly HT in NIDDM.	25 mmol/d Mg form not reported and 2 g. ascorbic acid (AA) placebo for 90 days after 90 day run-in period. There was a 4-wk wash-out b/w treatments	Mg therapy significantly reduced SBP and DBP ($p<0.05$) in IDDM group compared with Ascorbic Acid therapy. IDDM group: after Mg: 132±3 / 77± 2 ($p<0.05$ vs baseline and AA phase results for both SBP and DBP), after Ascorbic Acid: 143±4 / 82±2. There was no significant change in BP with Mg in the NIDDM group: after Mg: 151±4 / 86±2, after Ascorbic Acid: 155±3 / 88±2.	Use of AA as a placebo questionable. Insulin-dependent diabetic subjects do not reflect the heathy US population. This cross-over study had a 90-day run in, followed by two 90-day cross-over treatment phases with a 4-wk washout period in between. Treatment phases were either with Mg therapy (600 mg/day) or Ascorbic Acid (AA) therapy (2 g/day). IDDM and NIDDM subject groups were analyzed separately. In IDDM patients, Mg therapy showed significant decreases in both SBP and DBP and a significant rise in daily urinary Mg but no changes in HbA1c, blood glucose, cholesterol, HDL-cholesterol triglycerides or plasma Mg was seen with either Mg or AA therapy. In NIDDM patients AA therapy showed significant decreases in HbA1c, blood glucose, cholesterol, and triglycerides with no changes in SBP or DBP and significant rise in daily urinary Mg excretion while Mg therapy only showed significant rises in plasma Mg and daily urinary Mg and no changes in BP.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Borrello et al. (1996)	Parallel, double-blind, RCT	Mg 42 Cont. 41 100% finished the study	Catanzaro, Italy. Untreated mild HT on a normal salt diet. All were treatment naïve. Excluded were patients with any renal, hepatic, metabolic, or hematologic clinical dysfunction. Mg group: mean age = 51 yr, Placebo group, mean age=49 yr	Mg group: 155±13 / 93±4; Placebo (identify not specified) group: 156±11 / 92.5±4.3.	HT	10* mmol/d MgO for 12 wks *Actual dose used was probably 5.25 mmol/d (see comment)	SBP showed a significant decrease vs. BL after 12 wks of Mg therapy and was lower than the placebo (both $p<0.01$), while DBP showed a decrease from BL and was lower than the placebo group but numerical statistics were not provided. The authors reported as "weak significance". 24-hr monitoring of BP showed no significant differences between the 2 groups. Final Mg group: 148.5±7.1 / 87.5±6.3; Final Placebo group: 155.2±8.2 / 93.2±4.5.	Serum ($p<0.001$) and Urinary ($p<0.05$) Mg significantly increased with 12 wks of Mg therapy when tested against placebo. Quality of Life (by a 5-point Likert-style scale) showed significant improvement with Mg therapy ($p<0.05$) compared with both baseline and placebo that was confirmed clinically with improvements in respiratory functions, reduced frequency of chest pain, and improved psychosocial activities. Methods describe supplement as "200 mg Mg oxide (19.86 mEq of elemental Mg each day)", but 200 mg MgO provides 10 mEq rather than 19.86 mEq of elemental Mg; thus the Mg dose is probably 5 mmol rather than 10 mmol Mg/day.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Sanjuliani et al. (1996)	Cross-over , double-blind RCT	15 100% finished the study	Rio de Janeiro, Brazil. 7 men and 8 women, aged 35-65 yr, with mild to moderate primary HT (DBP 95-114) with all anti-HT meds interrupted 2 wks prior and throughout study; subjects had no history of heart, kidney, GI, metabolic disease or secondary HT.	Mean ±SEM: 158.8±3.64 / 106.5±1.28 MBP=123.8±1.95	HT	24.7 mmol/d MgO and placebo (identify not specified) for 3 wks after 2-wk run-in period w/ no drugs and normal Na. No wash-out period.	Final BP values after Mg arm: 151.2±4.62 ($p<0.05$ vs. BL) / 102.7±2.35 ($p<0.01$vs. BL) MBP=117.9±2.79 ($p<0.01$vs. BL); Final BP values after Placebo arm: 160.5±4.02 (ns vs. BL) / 105.5±4.02 (ns vs. BL) MBP=124.0±2.56 (ns vs. BL). Values are SEM. BP values after Control (BL): 158.8±3.64 / 106.5±1.28, MBP=123.8±1.95. Values are SEM. No stats for Mg vs. Placebo	Small N. Intervention period of three weeks may be too short – especially for the second arm of the cross-over with no wash-out period. Statistics based on a "control" phase which appeared to be BL values at the end of the run-in period. No direct statistics comparing the Mg and placebo treatments at the end of the intervention periods. However, ΔSBP was greater vs. P than BL so it can be inferred that Mg was significantly different than the placebo. The ΔDBP was slightly less after Mg vs. P (2.8 mmHg) than after BL (3.8 mmHg) so that statistical significance for DBP cannot be inferred but is likely. Even though Mg arm showed significant decreases in SBP, DBP and MBP, BP reductions were not homogeneous: 40% (i.e. 6 subjects) showed large changes in blood pressure; the other 60% (9 subjects) showed little, slightly positive or no change in BP. Thus, total change in SBP for all 15 subjects was (-7.6) (15) = -114. Since just about all this change occurred in only 6 subjects, then each of those 6 had an approximate SBP change of - 114/6 = -19. This is the magnitude of change seen in other studies with high starting BP (Rosanoff and Plesset, 2013), several of which have no proper control groups. There was no Cross-over effect.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Itoh et al. (1997)	Parallel, double-blind RCT	Mg 23 Cont. 18 80% finished the study (8 subjects from the control group did not)	Japan. Healthy active Japanese adults who were normotensive or borderline HT with normal glucose but some had moderately elevated cholesterol (up to 6.96 mmol/L). Mean age was 66±18 for placebo group and 64±9 y for Mg group. Food samples were collected for the last 2 days of each treatment period.	Mg group: 130±14 / 77±9; Placebo (identity not specified) group: 121±15 / 74±12.	NT	22.5 mmol/d (men) or 17 mmol/d (women) $Mg(OH)_2$ for 4 wks w/ 1-wk run-in.	4 wk values, Mg group: 125±13 / 75±10. Placebo group: 122±16 / 73±10. Compared to baseline, mean SBP with Mg therapy decreased significantly after 2 wks ($p<0.01$) and at 4 wks ($p<0.05$) as did the mean DBP ($p<0.01$ at 2 wks, $p<0.05$ at 4 wks). In the placebo group there was no significant change of SBP or DBP from baseline during the study. Compared with placebo group's change in BP, final SBP as a % of baseline decreased significantly with Mg therapy (95.6% vs. 101.6%, $p<0.05$) but DBP did not. However, mean SBP was *higher* ($p<0.05$) vs. the placebo at 2 and 4 wks in the Mg treatment but DBP was *lower* after the Mg treatment than placebo at both of these times ($p<0.05$).	Japanese subjects not reflective of US. High drop-out rate in placebo group may have led to apparent differences in BL values that are possible confounders. Compared to BL in this study on normotensive adults, both SBP ($p<0.05$) and DBP ($p<0.05$) decreased with Mg but there was NSC in placebo group. However, compared with placebo results, Mg effect on SBP alone was sig ($p<0.05$) but only when % of BL value compared with placebo group. Mean BL SBP/DBP for Mg group was 9/3 mm Hg higher than placebo (NSD) so mean SBP and DBP for Mg group NSD from final SBP and DBP for placebo group. Subjects asked to not change dietary habits during the study, and all meds were kept constant "when necessary". However, Mg group pulse pressure (calculated from data) at BL (53) was higher than placebo group (47), and at the end of the 4 wk study, these two values had merged with the Mg group pulse pressure ending at 50; that of placebo group at 49. However, a change of 3 mm Hg or 2 mm Hg for pulse pressure given the SDs of about 10% of means may not be significant. Urinary Mg ↑ ($p<0.0001$) as did urinary Na ($p<0.05$) in the Mg group vs. to the run-in values. NSC for placebo group in these urinary changes for Mg or Na. Compared to BL serum Mg rose ($p<0.01$) as did serum K ($p<0.01$) in the Mg group; NSCs in placebo group. Serum Na ↓ ($p<0.05$) in the Mg group while ↑ ($p<0.05$) in placebo group.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
de Valk et al. (1998)	Parallel, double-blind RCT	Mg 25 Cont. 25 68% finished the study (18 Mg, 16 Ct.)	Utrecht, The Netherlands. Patients with onset of Type 2 DM when >40 yrs on at least 1 yr adequate control of DM with oral medication and use of insulin for at least 6 months. Subjects on regular diet and regular insulin regimen or co-medication throughout study. Excluded: age >80 yrs, use of Mg compounds within past 3 months, use of K-sparing diuretics, renal impairment or GI disease. 50 subjects began study (used for baseline values), 16 dropped out leaving 34 patients (18 in Mg group, 16 in Placebo group) for final analysis.	Intention to treat baselines (n=25 for each group) Mg group: 162.6±23.3/ 84±11.5. Placebo (identity not specified) group: 157.4±23.6/ 83±14.2.	HT	15 mmol/d Mg aspartate-HCl for 3 mo	There was NSD for Mg vs. placebo for S/DBP but there was a trend (p=0.051) for lower DBP in the control group. Mg group: 158.7±20 / 82.9±8.3. Control group: 146.9±21.8 / 77.1±8.4. On-treatment analysis.	Insulin-dependent diabetic subjects do not reflect healthy US population. This study had a high dropout rate: it began with 50 subjects, 25 in test and 25 in placebo group. Final numbers were 18 Mg groups and 16 control group. Although Mg therapy showed a modest but significant increase in plasma Mg ($p<0.05$) and Mg excretion ($p=0.004$) there was no change in rbc Mg and no significant differences in glycaemic control (glucose, or HbA1c, both $p=0.8$) or blood pressure. However, baseline urinary Mg and glucose excretion were correlated ($r=+0.45$, $p=0.012$) and the modestly higher plasma Mg after Mg supplementation was associated with an increase in urinary Mg excretion with a similar degree of glucosuria. DBP in placebo group showed high trend ($p=0.051$) towards a lowering effect. Thus, this study had a slight placebo effect on DBP. This study showed a strong placebo effect: SBP decreased 10.5 mmHg and DBP decreased 5.9 mmHg in the placebo group.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Kawano et al. (1998)	Cross-over RCT	62 97% finished the study	Osaka, Japan. Men and women with mild to moderate essential HT, 35 - 74 yrs old, 40 treated and 20 untreated, with office SBP>140 and/or DBP>90. Meds continued unchanged throughout study. No placebo given, just no treatment besides usual meds during control phases of cross-over.	NR	HT	20 mmol/d MgO and usual diet (no treatment) for 8 wks, no wash-out period mentioned	All values SEM. After control period: Office: 148.6±1.6 / 90.0±0.9; Home: 136.4±1.3 / 86.8±0.9; Ambulatory BP for 24-hr: 133.7±1.3 / 81.0±0.8; for day: 137.7±1.3 / 84.0±0.8; for night: 125.9±1.9 / 74.8±1.1. After Mg period: Office: 144.9±1.7 / 88.3±0.9; Home: 134.4±1.4 / 85.4±0.8; Ambulatory BP measured for 24-hr: 131.2±1.1 / 79.6±0.8; for daytime: 135.2±1.3 / 82.5±0.9; for night: 123.4±1.5 / 73.6±0.9. Decreases in Office and 24-hr SBP with Mg were $p<0.01$ while decreases with Mg in Office DBP, Home SBP and DBP and 24-hr DBP were $p<0.05$. Table 4 reports SBP and DBP for women and men for office, home and 24-hr: men showed significant decreases in all SBP and DBP measurements with Mg compared to controls while women showed non-significant decreases in all measurements.	Japanese subjects do not reflect the general US population. Lack of placebo a serious concern. Office SBP and DBP used to determine HT status, Stage 1 HT was inclusion criterion; but no baseline measurements were reported for the 5 categories of BP measurements (office, home, 24-hr, day, night), all of which except night BP showed significant decrease between Mg therapy and control periods by end of study. 67%of subjects were treated with anti-hypertensive medications. In multiple regression analysis, baseline level of 24-hr BP, both SBP and DBP, was an independent determinant for the change in 24-hr BP: Subjects showing control period SBP≥134 and/or DBP≥81were more likely to show decrease in BP ($p<0.05$) during Mg period than subjects with lower ct period BP, and older subjects, men and those taking anti-HT meds showed tendency toward greater BP reduction with Mg.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Sacks et al. (1998)	Parallel, double-blind RCT	Mg 50 Cont. 103 Overall 93% finished the study but data for Mg and Cont. groups not given separate-ley	Boston, Massachusetts. White nurses, mean age 39±4.4, mean BMI 23.5±3.5, consuming <30% of K, Mg and Ca intakes by FFQ. Excluded were DBP<65 or SBP>160 or DBP>95, HT, BMI>32, IDDM, CVD, renal failure, medications affecting BP, weight loss diets, use of nutritional supplements of Ca, Mg or K, alcohol intake>50g/d.	ABP Mg group: 117±10 / 74±7; Placebo (identify not specified) group: 115±8 /73±6	NT	14 mmol/d Mg lactate for 16 wks	Change in BP from baseline, Mg group: -0.5±4.8 -0.5±4.4 Placebo group: 0.4±5.6 / 0.3±4.8. There was no significant difference between groups. Baseline intake of Mg was estimated to be 239 mg/d (75% of the RDA for women 31-70 years of age).	The study used ambulatory BP measurements which were shown in Hatzistavri 2009 to be more sensitive to statistical analysis than one-point measurements of BP. However, these subjects were NT at baseline, and subjects with SBP>160 or DBP>95 were excluded from participation. Thus these subjects had much lower SBP and DBP than in the Hatzistavri study, even though their Ca, Mg and K intakes were low. The low baseline SBP and DBP are those of subgroups shown in Lee et al., 2009 to have no significant decrease with Mg therapy. (See also Kawano, et al., for effect of starting BP on change in s4-hr BP with Mg.) Urinary Mg ↑ w/ supplementation vs. placebo ($p<0.01$) as did urinary Ca ($p<0.05$) but no data on serum concentrations. No subjects were taking anti-HT meds, and Mg dose was <20 mmol/day.	+
Doyle et al. (1999)	Cross-over, double-blind RCT	26 100% finished the study	Cork, Ireland. Healthy females (mean age 23, range 20-28 y), with mean BMI 22.2 (range 17 - 27.1). No chronic illness, no history of bone or articular disease; and no intake of nutritional supplements or medicines that could affect bone or cartilage metabolism	No baseline values reported, but inclusion required SBP<140 and DBP<85.	NT	10 mmol/d $Mg(OH)_2$ for 28 days and placebo (identify not specified) w/ no wash-out period	No significant difference b/w groups in BP. Final BP Mg group: 111.5±8.7 / 75.4±7.9, Final BP for placebo group: 113.3±8.6 / 76.9±5.8.	Subjects during "placebo" period had dietary Mg levels of 11.3 mmol/day, and during Mg period had this supplemented with 10 mmol Mg /day as $Mg(OH)_2$ for a total Mg intake of 21.6 mmol/day. There was no ↑in serum Mg. BL sMg was 0.76 mmol/L (~replete) despite low dietary intakes. In 28 days on each arm, there was no significant difference in SBP or DBP between Mg and placebo arms in these normotensive subjects. Also, a carry-over effect was evident in the rbc Mg contents, so analysis of data for Mg treatment effect was not possible according to authors. Urinary Mg was significantly raised with Mg supplementation.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Wary et al. (1999)	Parallel, double-blind, RCT	Mg 15 Cont. 15 100% finished the study but there were 2 replace-ments	Orsay Cedex, France. Healthy male adults (age 23.7±4.5 yrs) all within 10% of ideal body weight and free from individual history of diabetes, dyslipidaemia, spasmophilia, HT and CVD events. During trial subjects took no other medications and restricted cigarettes (< 5/day) and alcohol (<600 kcal/day).	Supine, Mg group: 113±12 / 69±8 ; Placebo (identify not specified) group: 116±11 / 68±5. Standing: Mg group 127±11 / 76±7, Placebo group: 126±11 / 77±5.	NT	12 mmol/d Mg lactate (plus 5 mg pyridox-ine) for 28-35 days	Final BP, supine: Mg group 111±8 / 68±7; control group 115±7 / 69±6. Standing: Mg group 121±12 / 76±5, control 127±7 / 76±5. No significant differences between groups.	Mg supplement also contained 5 mg pyridoxine, while the placebo did not (Aybak et al., 1995). THIS FACT MAY DISQUALIFY THIS PAPER PER A REPORT THAT PYRIDOXINE MAY LOWER BP (This paper has been ordered). Normotensive subjects No changes in BP were seen with Mg therapy in these normotensive, healthy adult males. Only urinary Mg significantly increased in the Mg therapy group although measured were reported for plasma Mg, RBC Mg, Plasma ionized Mg, Intracellular free Mg in skeletal muscle and brain Mg. None of these measures were significantly affected by Mg supplementation. Two subjects replaced due to non-compliance.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Walker et al. (2002)	Parallel, double-blind RCT	Mg 9 Cont. 10 N=36 for entire study includ-ing non-Mg groups. 100% finished the study	Reading, UK. Mild HT, DBP = 85 to 100. 18 males and 18 females. Mean age range for 4 groups = 48.8 to 53.3 y. Mean BMI range for 4 groups = 25.5 to 29.1. mean dietary Mg intake range for 4 groups 339.3 to 485.0. Randomized to 4 groups: A, cellulose placebo (N=10); B, magnesium (N=9); C, hawthorne placebo (N=7); D, magnesium + hawthorne (N=10). Exclusion criteria were heart disease, renal insufficiency, and any prescribed meds for HT or Mg supplements, pregnancy.	NR numerically. Bar graph only of resting baseline BP. Baseline BP after stress (values are SE): Placebo (identity not specified) 154.5±4.1 / 100.0±4.5; Mg group 150.0±3.5 / 95.7±2.2; Hawthorn 146.3±6.0 / 93.1±3.8; Mg + Hawthorn 148.5±4.4 / 96.73.3.	NT to mild HT	24.7 mmol/d AA chelate of Mg for 10 wks	No significant changes in BP for Mg or Hawthorn and all 4 groups showed decreases in BP over the course of the study. Resting BP results are given in a bar graph so numerical values are not reported. Numerical results below are given for 10 wk BP after stress. BP after stress (mean ±SEM): Placebo, 139.6±4.4 / 92.2±3.7; Mg group, 141.0±3.1 / 93.6±2.4; Hawthorn group, 139.1±5.5 / 91.4±4.6; Mg + Hawthorn group, 139.1±3.9 / 90.8±3.3.	Small N – especially for a parallel study. A strong placebo effect confounded interpretation of results. Mg group had a much higher dietary Mg intake (485±79.5 mg/d) than the other 3 groups (346.2±27.3 for placebo, 355.7±32.3 for Hawthorn, and 339.3±26.2 mg/d for Mg + Hawthorn group) and authors speculate Mg group was Mg replete at BL, thus limiting effect of oral Mg therapy. Resting BP values are in a bar graph only. The only actual numerical results for this study are for after stress and after exercise measurements of BP. These numerical results have been (erroneously) used in meta-analyses. In the after stress measurements, the Mg group's BL pulse pressure much lower than other 3 groups (43.7 vs 51.8, 53.2 and 54.5) while all ending (10 wk) pulse pressures were similar (47.4 vs 48.3, 47.7 and 47.4). In after exercise measurements, Mg group substantial ↓ in both SBP and DBP at 5 wks before a substantial rise in SBP after exercise at 10 wk. For these after exercise measurements, starting pulse pressure was > in both Mg groups (70.6 and 72.5 vs 58.5 and 55 for control groups) and these high pulse pressures remained > than the controls after 10 wk of Mg. The resting measurements would require a grid and much enlarging of bar graph to get any accurate/precise readings. However, these bar graphs show there was a ↓ in both SBP & DBP with Mg that was NSD from similar ↓s in the placebo groups, perhaps a greater decrease in DBP with Mg + Hawthorn than Hawthorn alone.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Rodriguez-Moran and Guerrero-Romero (2003)	Parallel, double-blind RCT	Intent to Treat: Mg 35 Cont. 37 88% finished the study: Mg (32) Ct. (31)	Durango, Mexico. Type 2 diabetics with serum Mg ≤0.74 mmol/l. Excluded were subjects with chronic diarrhea, alcohol intake ≥30 g/day; use of diuretic and/or Ca antagonist drugs, use of Mg supplements; reduced renal function. Mean age: Mg group=59.7, Ct group=54.1; mean BMI: Mg group=27.6, Ct group=28.6.	Mg group 148.3±32.3 / 86.3±17 Placebo (identify not specified) group 138.1±25.6 / 80.5±14.6	Border-line HT to NT	18.5 mmol/d $MgCl_2$ for 16 wks	No significant differences in either SBP or DBP b/w groups. Final BP values: Mg group 140.2±28.1 / 82.7±16.4 Placebo group 135±19.6 / 79.1±13.5	Type-2 diabetics do not reflect the healthy US population. Both SBP and DBP values tended to decrease (but not significantly so) in Mg group as well as placebo group, and decreases in Mg group (-8.1/-3.6) were larger than those of placebo group (-3.1/-1.4) but not statistically significant in this study on essentially normotensive subjects. Serum Mg was deficient at baseline and rose significantly in Mg group from 0.64 to 0.74 mmol/L ($p<0.05$) but not in placebo group; fasting glucose, and HbA1c decreased significantly in both Mg and placebo groups, but significantly more so with Mg ($p<0.05$); and fasting insulin significantly increased with Mg ($p<0.05$) over the rise seen in placebo group. The Mg dose <20 mmol/day may have been insufficient to cause a decreases in BP in this study as observed by Rosanoff (2010).	Ø
Guerrero-Romero et al. (2004)	Parallel, double-blind, RCT	Mg 30 Cont. 30 100% finished the study	Durango, Mexico. Apparently healthy subjects with insulin resistance (HOMA-IR index ≥3.0) and hypomagnesemia (serum Mg ≤0.74 mmol/L). Mean age: Mg group=43.0, Ct group=42.2; mean BMI: Mg group=29.3, Ct group=29.1.	Mg group: 110±8.4 / 73±7.5. Placebo (identify not specified) group: 111±12 / 73±9.0.	NT	12.5 mmol/d $MgCl_2$ for 3 mo	No significant differences in either SBP or DBP b/w groups. Final Values - Mg group: 108±8.1 / 72.3±7.4; Control group: 110±11 / 72.4±8.9.	There were no significant changes in BP with Mg in these normotensive subjects. However, fasting glucose, fasting insulin, HOMA-IR index, total cholesterol and triglycerides all decreased significantly with Mg, both from baseline ($p<0.05$) and when compared with placebo group ($p<0.01$). At the same time, HDL-cholesterol and serum Mg both were significantly raised from baseline values with Mg treatment ($p<0.05$) as well as when compared with placebo group values ($p< 0.01$).	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Barragan-Rodriguez et al. (2008)	Parallel, double-blind RCT	Mg 12 Cont. 11 91% finished the study	Durango, Mexico. Wlederly subjects, aged ≥60 yrs, with type 2 diabetes and newly diagnosed depression. Excluded were Widowhood or divorce in last 6 mos, alcoholism, degenerative illnesses of nervous central system, diagnosis of diabetes ≤ 6 mos, chronic diarrhea, use of diuretics, reduced renal function, previous or current treatment with antidepressants. During study, all subjects received glibenclamide and a low fat diet.	Mg group: 134.1±19.2/ 77.2±3.9; Impramine group: 141.0±20.1/ 84.7±6.1.	NT by mean BPs but 10 in Mg group and 8 in Impra-mine group had HT at baseline.	18.7 mmol/d $MgCl_2$ for 12 wks	No significant differences b/w groups were observed. Sub-analysis of HT subjects not reported. Final BP values for Mg group: 135.2±20.5 / 77.0±3.6; Impramine group: 143.7±19.9 / 87.6±6.4.	No true placebo group (impramine). Depressed diabetic subjects do not reflect the normal US population Both groups showed lower Yasavage and Brink score indicating improvement of depression in groups taking Mg as well as Imipramine. Mg group showed lower triglycerides and higher HDL-cholesterol and serum Mg than did the impramine, non-Mg group. There were no significant changes in SBP or DBP in this study on NT subjects and no sub-group analysis of any HT subjects.	-
Guerrero-Romero and Rodriguez-Moran (2009)	Parallel, double-blind RCT	Mg 42 Cont. 40 96% finished the study	Durango, Mexico. Diabetic hypertensive adults, age 40 - 75 yrs, with decreased serum Mg (≤0.74 mmol/L). Subjects withdrawn from all meds one wk before trial. Glibenclamide started and individually adjusted for glucose control. All subjects received 25 mg captopril daily during study. Excluded were chronic diarrhea or alcohol intake >30g/day, use of diuretics and/or calcium antagonist drugs, previous oral Mg supplementation, ischemic diseases and renal damage. Randomization. BMI of both Mg and placebo groups was 29.5.	Mg group: 161.1±26.0 / 88.4±14.5; Placebo (identify not specified) group: 154.5±21.2 / 84.9±12.4	HT	18.5 mmol/d $MgCl_2$ for 4 mo	Mg therapy showed significant decreases in SBP (p=0.03) and DBP (p=0.02) compared with placebo group. Final BP for Mg group: 140.7±11.9 / 79.7±7.1; Placebo group: 149.8±20.6 / 83.8±9.7.	SBP and DBP were primary endpoints. Diabetic subjects do not reflect healthy US population. There were no measured differences in Mg group vs placebo group at baseline other than significantly higher serum Na in Mg group (p<0.05). After study period, Mg groups showed significantly higher HDL-cholesterol (p=0.04) and serum Mg (p=0.002) compared with placebo group.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Lee et al. (2009)	Parallel, double-blind RCT	Mg 75 Cont. 80 100% finished the study	Busan, So. Korea. Adults age 30-60 y with BMI≥23 who had not taken any supplements or medications for 4 wks. Excluded were those with SBP > 160 or DBP > 110 (for safety reasons), pregnant or suffering from any chronic illness.	Mg group: 124.7±12.3/ 83.5±9.68 Placebo (identify not specified) group: 126.7±13.5/ 83.3±9.55	NT	12.3 mmol/d MgO for 12 wks	SBP decreased significantly ($p<0.001$) from baseline in both groups by 12 wks. DBP significantly decreased from baseline only in the Mg group ($p=0.006$). When whole Mg group was statistically compared with whole placebo group, there was no significant decrease of BP with Mg intervention (119/81 in Mg grp vs. 123/83 in the placebo grp. However, **analysis of subjects sub-grouped by starting BP showed a significant decrease in BP with Mg:** Subjects with starting SBP>140 (Mg group, n=8; placebo group, n=16) showed a significant decrease in SBP with Mg ($p=0.016$) compared with placebo (-17.1 vs. -7.7 mmHg); Subjects with starting DBP=80-90 (Mg group, n=27; placebo group, n=29) showed a significant decrease in DBP with Mg ($p=0.043$) compared with placebo (-3.4 vs. -0.8 mmHg); subjects with starting DBP≥90 (Mg group, n=24; placebo group, n=25) showed a significant decrease in DBP with Mg ($p=0.023$) compared with placebo (-3.4 vs. -0.8 mmHg).	Korean subjects do not reflect the healthy US population. This study is one of two that broke out results by starting BP, showing that subjects with high starting BP show larger decreases in BP than subjects with a lower BL BP. Both placebo and Mg groups showed ↓s in this study, but only subgroups of those with higher BL BP showed significantly > decreases of BP with Mg. Subjects with quite high BL BP, i.e. SBP>160 and DBP>110 were excluded "for safety". Oral Mg studies for BP, in general, eschew subjects with higher BP that will not be medicated or given Mg treatment for ethical reasons. Possibly an overall but unintended outcome is the minimization of the effect of Mg for high BP as those subjects that will show the largest decreases in BP are left out of controlled studies for safety reasons. See Rosanoff & Plesset, 2013 that chose such trials for a meta-analysis (SBP>155) and heterogeneity I^2 was 0 when all other meta-analyses of HT studies with oral Mg therapy have shown high heterogeneity. Note also that in subgroup analysis, those with starting DBP<80 showed an INCREASE in DBP with Mg where placebo did not, suggesting that oral Mg therapy "normalizes" blood pressure, raising a low BP and decreasing a high BP. However, when overall mean for overall Mg and placebo group are statistically analyzed, "no change" in BP is the conclusion that thoughtful sub-group analysis contests.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Rodriguez-Hernendez et al. (2010)	Parallel, RCT	Mg 20 Cont. 18 79% finished the study (Mg15 Ct. 15)	Durango, Mexico. Non-hypertensive obese women aged 30 - 65 yrs. Hypomagnesemic (≤0.74 mmol/L) women received Mg supplementation in the study while normomagnesemic women (>0.74 mmol/L) did not. 20 - 25% were diabetic (4 in Mg group; 3 in Ct) and continued their diabetic medications throughout the study. Excluded were chronic diarrhea, alcohol intake > 30 g/day, use of diuretics, previous oral Mg supplementation, hepatic disease or renal damage.	Mg group (hypomagne-semic) 124.6±16.8 / 82.3±12.1; Control group (normomag-nesmic) 117.0±14.8 / 78.0±15.9	NT	18.5 mmol/d $MgCl_2$ for 4 mo	No significant change in BP for either group: Mg group (hypomagnesemic at baseline, normomagnesemic by final) 116.3±10.8 / 76.3±10.3; Control group (normomagnesemic) 112.4±15.1 / 75.7±9.8.	Lack of placebo is a serious concern. Oral Mg therapy showed no changes in BP in these NT subjects. Basal serum Mg for Mg group (hypomagnesemic) was 1.7±0.2 mg/dL (0.7 mmol/L) and for Control group (normomagnesemic) was 1.9±0.1 mg/dL (0.78 mmol/L). Final serum Mg for Mg group was 1.9±0.2 mg/dL (0.78 mmol/L) and for final Control was also 1.9±0.2 mg/dL.	-
Guerrero-Romero and Rodriguez-Moran (2011)	Parallel, double-blind RCT	Mg 54 Cont. 52 92% finished the study (49Mg 48 Ct)	Durango, Mexico. Apparently healthy men and non-pregnant women who were non-diabetic, normotensive with serum Mg ≤0.7 mmol/L and age 40-65 y. Excluded were pregnancy, chronic diarrhea, alcohol intake > 30 g/day, impaired renal function, diabetes, prior diagnosis or current treatment for HT or a BP ≥140/90, use of diuretics or Mg supplements for last 6 mos. .	Mg group: 117.2±12.0 / 73.8±9.4; Placebo group (50 mL inactive solution using water as a solvent): 115.9±17.2 / 73.8±9.6.	NT	26 mmol/d $MgCl_2$ for 3 mo	Final BP for Mg group: 108.9±9.5 / 70.3±9.1; Placebo group: 113.1±10.1 / 74.1±8.9. There was no statistical different in BP values between Mg group and placebo at start of study. By end of Mg treatment the Mg group showed lower SBP (p=0.03) and lower DBP (p=0.04) than placebo group.	In this study of NT but Mg deficient subjects, Mg therapy significantly lowered SBP and DBP, fasting glucose, fasting insulin and HOMA-B index while raising serum Mg significantly.	+

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Mooren et al. (2011)	Parallel, double-blind RCT	Mg 27 Cont 25 90% finished the study	Giessen, Germany. Subjects with metabolic syndrome who were normomagnesemic, overweight, insulin resistant, and non-diabetic (as tested by oral glucose tolerance test). Inclusion criteria: BMI≥25 kg/m^2; 30 to 70 yrs; decreased insulin sensitivity as fasting plasma glucose ≤6.94 mmol/l, venous plasma glucose 2h after glucose load <11.11 mol/l and serum insulin 2 h after oral glucose load >434.78 pmol/l.	Mg group: 137.7±14.9 / 85.3±9.4. Placebo (identify not specified) group: 134.8±15.0 / 82.5±9.6.	NT	15 mmol/d Mg aspartate-HCl for 6 mo	No significant difference in SBP or DBP with Mg compared with placebo in these NT subjects, but the DBP difference in Mg group compared with placebo was close to significance (p=0.0561). Both SBP and DBP of Mg group decreased significantly (p≤0.05) from baseline while there was no such change in the placebo group. Final of Mg group: 131.4±16.4 / 81.6±9.8. Final Control group: 133.1±21.9 / 83.2±12.1.	Fasting plasma glucose and Indices for insulin resistance (ISI Matsuda and ISI-HOMA) were significantly improved by Mg intake, but there was no effect of Mg for cholesterol or triglyceride measurements nor serum insulin either fasting or after oral glucose load.	Ø
Simental-Mendia et al. (2012)	Parallel, double-blind RCT	26 total (initial alloca-tion not given 85% finished the study (11 Mg, 11 Ct.)	Durango, Mexico. Apparently healthy men & non-pregnant women 20-65 years w/ newly diagnosed prediabetes, inflammation and hypomagnesemia enrolled. Exclusion criteria: smoking, alcohol intake, acute or chronic inflammatory disease, acute or chronic infection, glomerulopathies, renal disease, malignancy, diabetes, hypertension, cardiovascular disease, intake of statins, anti-inflammatory drugs or magnesium supplements.	Mg: 116.9±7.6/ 66.7±6.9 Placebo (lactose): 118.4±8.2/ 71.8±7.5	NT	15.7 mmol/d $MgCl_2$ for 3 mo	NSD b/w treatments at the end of the intervention. Final BP for Mg=115.5±18.0/65.6±10.4 (p=0.84); Placebo=114.0±9.7/66.6±8.6 (p=0.72)	Normotensive subjects. sMg increased in these hypomagnesemic subjects w/ Mg (0.74 mmol/L at BL to 0.86 mmol/L after supplementation) (p=0.03).	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Kass et al. (2013)	Parallel, RCT No placebo	Mg 8 Cont. 8 100% finished the study	Hertfordshire, UK Healthy males 19-24 yr. w/ normal BP (110/70 to 135/85) exercising for ≥4 hr/wk. Exclusion criteria: any medication, any supplement 72 hr before BL testing, any ailment or injury that affects performance, negative health screen. BP measured in resting state and after 30 min exercise (cycling) w/ 1 kg load at maximal capacity to achieve greatest distance.	Mg: 122.75±7.09/ 71.13±10.06 Cont: 125.25±70.75 ±7.09	NT	12.5 mmol/d MgO for 14 d	Mg vs. control resulted in lower resting SBP (115.1±9.5 vs. 124.5±3.9, p<0.05), post-exercise SBP (122.6±15.3 vs. 139.1±4.5, p<0.05) and recovery SBP (5 min post exercise) (110.4±9.2 vs. 121.6±6.1, p<0.05).	Normotensive, young active subjects. Small N and short intervention period makes these significant results very impressive. Lack of placebo a concern, however probably less so for post-exercise outcomes because of physiological nature of response.	-
Cosaro et al. (2014)	Cross-over, double-blind RCT	16 88% finished the study	Verona, Italy. Males aged 23 to 33 with good health and family history of Met Syndrome and/or T2D in at least one first degree relative. Excluded were BP>140/90, use of antihypertensive treatment, diabetes, obesity (BMI>30), use of lipid-lowering drugs or continuous therapy with nonsteroidal inflammatory drugs, use of vitamins or micro-nutrients, previous CVD event or disease, chronic renal insufficiency, chronic inflammatory liver disease, kidney disease, malignancies, GI dysfunction with hypo-mobility, smoking>5 cigarettes/day.	Pre-Mg: 126.0±13.1 / 71.4±5.9; Pre-placebo: 117.2±7.5 / 69.7±4.1	NT	16.2 mmol/d Mg pidolate and placebo (lactose) for 8 wks w/ ≥4-wk wash-out	No significant difference in BP. SBP post Mg =123.7±13.2; SBP post placebo = 117.2±7.5 (p=0.40). DBP post Mg = 71.4±4.5; DBP post placebo = 69.7±4.1(p=0.31). Baseline plasma Mg=0.81 mmol/L in the Mg group and 0.83 mmol/L in the placebo group.	NSC in BL plasma (p=0.50) or urinary Mg (p=0.35) due to supplementation. Also NSD b/w groups in plasma ((p=0.93) or urinary Mg (p=0.17). Mg hawthorn for 8 weeks did not change any investigated parameters in these healthy NT men who were offspring of patients with MetX and/or T2DM. 4 wks washout period between two 8-wk arms of cross-over. In this small cross-over trial, significant reduction of CRP was seen during placebo phases, and there was a significant increase in Flow Mediated Dilatation during placebo phases. No significant changes were seen in BP, any lipid measurements, glucose, insulin, HOMA-IR, HbA1c in either Mg phase or placebo phase.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Rodriguez-Moran and Guerrero-Romero (2014)	Parallel, double-blind RCT	Mg 25 Cont. 24 96% finished the study	Durango, Mexico. Metabolically obese, normal weight subjects (MONW), i.e. non-obese subjects (BMI ≥20, <25) that are "metabolically obese" in that they have insulin resistance (HOMA-IR index ≥3, hyperglycemia (fasting glucose ≥100 mg/dL), hypertriglyceridemia (TG≥150 mg/dL) and/or high BP (SBP≥140 and DBP≥90), both men and non-pregnant women age 20-60y with hypomagnesemia (serum Mg ≤1.8 mg/dL, i.e. 0.74 mmol/L), aged 20 - 60 yrs. Excluded were BMI≥25, smoking, alcohol intake, acute or chronic diseases, new diagnosis of diabetes or intake of oral supplements and/or vitamins.	Mg group: 111.3±14.5 / 71.5±6.6; Placebo (identify not specified) group: 112.3±17.1 / 71.4±9.3.	NT	15.7 mmol/d $MgCl_2$ for 4 mo	Final BP, Mg group: 109.4±12.4 / 68.8±7.4; Placebo group: 116.6±11.5 / 76.8±7.6. While the two groups did not differ statistically in either SBP or DBP at start of the study, they were different in both SBP (p=0.03) and DBP (p=0.01) by end of the treatment period.	Subjects in both groups counseled to consume a diet of 40% CHO, 40% lipid and 20% protein and to exercise at least 30 min 3x per week. At start of study there were no significant differences between groups. At end of study, those receiving Mg showed significantly lower SBP, DBP HOMA-IR index, fasting glucose and triglycerides. In addition, serum Mg levels were significantly higher in the intervention group and remained unchanged in the control group. In general, subjects receiving Mg showed significant improvement of all components of the MONW phenotype.	+

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Simental-Mendia et al. (2014)	Parallel, double-blind RCT	Mg 31 Cont. 31 92% finished the study	Durango, Mexico. Adults 18-65 yrs with new diagnosis of prediabetes and hypomagnesemia. Participant advised to consume a diet with 40% CHO, 40% lipids and 20% protein and advised to perform physical activity for at least 30 min 3x per week. Excluded were smokers, alcohol intake, acute or chronic inflammatory disease, acute or chronic infection, glomerulopathies, renal disease, malignancy, diabetes, HT, cardiovascular diseases, intake of statins, anti-inflammatory drugs or Mg supplements.	Mg group: 114.8±31.1 / 76.9±12.9; Placebo group (30 ml of 1% $NaHCO_3$ solution): 115.7±21.4 / 72.3±10.5.	NT	15.7 mmol/d $MgCl_2$ for 3 mo	No significant difference b/w groups in BP. Final BP for Mg group: 117.5±18.6 / 75.0±14.5; Placebo group: 123.4±22.2 / 76.9±10.8. p=0.28/0.57.	Normotensive subjects. Use of sodium bicarbonate as a placebo inappropriate as this compound is a source of sodium which can affect BP, however the amount was probably trivial. This study was a follow up to an earlier trial (Simental-Mendia et al., 2012). There were no significant changes in SBP or DBP in either group in this NT study of low serum Mg subjects, however there was a significant rise in serum Mg with Mg supplementation plus a significant decrease in fasting glucose (p=0.007) and 2 hr post-load glucose (p=0.03) with Mg supplementation. Serum CRP after Mg treatment was significantly lower than that of the placebo group (p=0.01) even though the serum CRP in the placebo group decreased significantly from its basal level, perhaps due to the diet and activity advisory given in this study.	Ø

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Kass and Poeira (2015)	Two Cross-over, double-blind RCTs. Acute and chronic dosing studies run in parallel	Acute 7 Chronic 6 100% finished the study	Hertfordshire AL, UK. 7 males and 6 females recruited from recreational running, cycling and triathlete clubs. Six subjects were allocated to acute intervention group (1 week) and 7 to chronic intervention group (4 weeks). Within each trial subjects undertook both the Mg intervention and placebo intervention with a one week washout. Mean age chronic group [40.8±6.2], mean age acute group [=35.8±6.2]. BP measures and augmentation index (Aix) were recorded pre and post bench press at 50% 1-RM to fatigue on day 1 and day 2. 4-day weighted food and beverage diary collected at baseline and post intervention.	Resting BP pre bench press challenge: Placebo chronic group day1= 119±7/85±7; day 2 =121±8/78±8; Placebo acute group day 1= 120±5/75±7; day 2= 125±2/79±6 Mg chronic group day 1= 118±6/79±6; day 2= 118±7/75±7 Mg acute group day 1= 122±4/75±4 day 2= 117±7/74±5.	NT	12.5 mmol/d from Mg citrate	No significant differences between placebo and Mg groups for anthropometric data, VO_2max, heart rate, and dietary intake data. Dietary intake was above the RNI for all groups [range 368±173 to 551±347 mg/d]. Resting SBP from day 1 and 2 significantly decreased with acute Mg (P = 0.031), vs. placebo with a significant increase in SBP (P = 0.047). Significant day 2 reductions in SBP noted between acute treatments of Mg vs. placebo (P = 0.016). Chronic Mg showed no significant reduction in resting SBP on day 1 or day 2. Post bench press SBP for chronic Mg resulted in significant SBP reductions; on day 1 (P =0.016) and day 2 (P = 0.016) whereas acute Mg reduction occurred only on day 2 (P = 0.047) vs. placebo. Resting DBP showed no differences between placebo or Mg groups. Post DBP showed no differences between day 1 to day 2 for acute group, however the chronic group showed a decrease in DBP for post bench press on day 2.	Low statistical power due to small N (7 in acute study and 6 in chronic study). No data on serum or urinary magnesium so no way to assess adequacy of dose as judged by physiological responses. Highly fit athletically active subjects not reflective of general US population. Cardiovascular responses to the bench press were significantly enhanced by Mg supplementation reducing resting SBP and DBP with the greatest effect seen with acute Mg supplementation for rest and post exercise. Similarly, SBP, DBP and augmentation index showed a significantly greater and more consistent reduction in response to the acute Mg supplementation, as opposed to the minimal effects induced by chronic Mg supplementation.	-

Literature Citation	Design	N	Description of Subjects/Intervention	Baseline BP	HT Status	Mg Dose/ Duration	Summary of Results	Comments	FDA Score
Joris et al. (2016)	Parallel, double-blind RCT	Mg 26 Cont. 25	Netherlands - healthy overweight and slightly obese men and post-menopausal women, 45 - 70 yrs, non-diabetic, non-smokers with stable body weight (BMI between 25 and 35. Excluded was use of proton pump inhibitors, anti-HT medications or medications affecting lipid or glucose metabolism, no active CVD drug or alcohol abuse. Subjects agreed to abstain from dietary supplements 1 mo prior to study and during study.	Mg group: Office Brachial 130±15 / 82±8; mean 24-hr ambulatory 124±11 / 78±8. Placebo group: Office Brachial 126±14 / 81±7; mean 24-hr ambulatory 125±12 / 80±8	NT	14.4 mmol/d Mg Citrate for 24 wks	NO significant change in BP. Mg group: Office Brachial 126±14 / 79±8; mean 24-hr ambulatory 123±11 / 78±9. Placebo group: Office Brachial 123±12 / 79±7; 24-hr ambulatory 125±13 / 79±9.	There were no significant changes in SBP or DBP in either group in this NT study of healthy overweight and slightly obese adults. Study was designed to measure oral Mg therapy's effect on arterial stiffness as measured by carotid-to-femoral pulse wave velocity (PWVc-f) which significantly improved after 24 wks of oral Mg therapy compared to placebo group ($p<0.01$). Also at 24 wks, urinary Mg rose in the Mg group ($p<0.001$) but serum Mg did not ($p<0.1$). Authors suggest a trend toward higher serum Mg in the Mg group, but both groups showed healthy serum Mg (0.84-0.85 mmol/L) as well as normotensive BP values at baseline.	Ø

Table V
Classification of Magnesium Intervention Studies by Support for the Proposed Claim

Study Quality	Positive Support	Partial Support	Null Studies			
			All Null Studies	Expected Null Result Categories		
				Normotensive subjects	Magnesium replete subjects	Unmedicated pre- and hypertensive subjects ≤20 mmol/d dose
High	Guerrero-Romero (11)	Witteman (94)	TOHP (92)			X
	Rodriguez-Moran (14)		Sacks (98)	X		X
Medium	Daly (90)	Lind (91)	Cappuccio (85)		X	
	Widman (93)	Plum-Wirell (94)	Henderson (86)*			
	Guerrero-Romero (09)	Wirell (94)	Wirell (93)		X	
	Borrello (96)	Purvis (94)	Doyle (90)	X		
		Eriksson (95)	Rodriguez-Moran (03)			X
		Lee (09)	Guerrero-Romero (04)	X		
		Mooren (11)	Simental-Mendia (12)	X		
			Cosaro (14)	X	X	
			Simental-Mendia (14)	X		
			Joris (16)	X	X	
Low	Dyckner (83)	Ioth (97)	Olhaberry (87)		X	
	Reyes (84)	Kass & Poeira (15)	Nowson & Morgan (89)			X
	Paolisso (92)		Patki (90)		X	
	Sanjuliani (96)		Zemel (90)*			
	Kawano (98)		Ferrara (92)		X	
	Kass (13)		Kisters (93)	X	X	
			de Valk (98)			X
			Wary (99)	X	X	
			Walker (02)			
			Barragan-Rodrigues (08)	X		
			Rodriguez-Hernandez (10)	X		
Total (all)	12	10	23			
Total (High/Med)	6	8	12			

*No rise in serum Mg with Mg supplementation: presume dose inadequate for BP reduction.

4. Studies that do not meet FDA's quality criteria for the ability to substantiate health claims, but assessed the effect of magnesium and blood pressure in healthy people

Multiple studies were identified that did not meet FDA's criteria for the substantiation of health claims. Most of these studies were not randomized and/or reported results compared to baseline, without the use of a suitable control group. Nevertheless, such studies are of some interest because they assessed the effect of magnesium on blood pressure in healthy humans with normal or moderately elevated blood pressure. These studies are noted briefly below.

Taylor et al. (1988) reported that supplementation of 17.7 mmol magnesium per day for eight weeks among South African adults with moderate hypertension who had previously been given indapamide or a placebo for eight weeks did not affect blood pressure.

Hattori et al. (1988) found that blood pressure was lower ($p<0.05$) after supplementation with 25 mmol magnesium per day for four weeks than it was after four weeks subsequent administration of a placebo in a study of 20 hypertensive Japanese subjects. These data were also published by Saito et al. (1988).

Motoyama et al. (1989) reported lower mean blood pressure ($p<0.001$) after supplementation with 24.7 mmol magnesium per day for four weeks among 21 Japanese subjects with essential hypertension. There was an increase in mean blood pressure ($p<0.001$) after provision of a placebo for four weeks.

Haga (1992) supplemented 17 Japanese adults with mild-to-moderate essential hypertension and eight normotensive controls with 25 mmol magnesium per day for two weeks. Blood pressure decreased compared to baseline in the hypertensive subjects ($p<0.05$) but not in the normotensive controls.

Shafique et al. (1993) reported that supplementation of Pakistani adults with 10 mmol magnesium per day for up to four months resulted in lower supine ($p<0.001$) and standing ($p<0.01$) blood pressure compared to baseline.

Sebekova et al. (1992) found that systolic blood pressure was lower compared to baseline among Slovakians given 10.5 mmol magnesium per day for two and three months ($p<0.001$ and $p<0.01$, respectively) compared to baseline values. Similar results were obtained with diastolic blood pressure ($p<0.01$ after both two and three months).

Yokota et al. (2004) supplemented the diet of type-2 diabetic Australian subjects with 300 ml of magnesium-containing lake water (total of 12.5 mmol/d) for 30 days. Systolic, diastolic and mean blood pressure decreased compared to baseline ($p<0.01$, $p=0.038$ and $p<0.01$, respectively).

Hatzistavri et al. (2009) reported that supplementation with 25 mmol magnesium per day for 12 weeks along with lifestyle modification resulted in significant reductions in systolic, diastolic and mean blood pressure measured during the day, night and over 24-hours (all $p<0.001$) compared to baseline among 48 Greek subjects with mild hypertension. In addition, blood pressures after such supplementation were significantly lower compared to a similar group given only lifestyle modifications.

Barbagallo et al. (2010) did not find a difference in blood pressure among 60 elderly diabetic subjects living in Italy given 15.3 mmol magnesium per day for four weeks compared to subjects given a placebo using a non-randomized design, but did show a rise ($p<0.05$) in flow-mediated dilation in the magnesium group compared to the controls.

Finally Kisters et al. (2012) found that systolic and diastolic blood pressures decreased ($p<0.05$) after supplementation with 10 to 20 mmol magnesium per day for 12-15 weeks compared to baseline among 18 untreated borderline hypertensive subjects living in Germany. Blood pressure data for the normotensive subjects were not reported.

In conclusion, eight of the ten studies discussed above that did not use a fully randomized, placebo-controlled design reported beneficial effects of magnesium supplementation on blood pressure in healthy normo- and/or moderately hypertensive individuals. These data are not rigorous enough to substantiate the proposed claim; however they do provide additional evidence that magnesium is capable of beneficially affecting blood pressure.

5. Magnesium studies not applicable to the proposed claim

Numerous studies were identified that examined the effect of magnesium supplementation on blood pressure but were not applicable to the proposed claim. These studies are listed below in the spirit of providing FDA with the totality of the evidence.

a. Studies in unhealthy subjects

The following papers were excluded because the subjects were not applicable to the healthy U.S. population targeted by the proposed claim. Two papers used subjects with congestive heart failure (Kohvakka et al., 1989, Bashir et al., 1993), one study examined

subjects with implantable cardioverter defibrillators (Baker et al., 2009) one study examined alcoholics (Gullestad et al., 1992), two studies used pregnant subjects (Altman et al., 2002, Bullarbo et al., 2013), one paper studied infants (McGarvey et al., 1991), and finally Mortazavi et al. (2013) studied hemodialysis patients.

b. Studies with multiple interventions

The following studies were excluded because the effect of magnesium on blood pressure could not be isolated due to multiple components of the intervention (Margetts et al., 1986, Lumme and Jounela, 1989, Singh, 1990, Singh et al., 1991, Geleijnse et al., 1994, Sacks et al., 1995, Katz et al., 1999, Liu et al., 2001, Tikkanen et al., 2001, Stamler et al., 2003, Farvid et al., 2004, Rylander and Arnaud, 2004, Sur and Maftei, 2006, Wu et al., 2006).

c. Studies excluded for miscellaneous reasons

Two studies were excluded because they were published in Polish (Michon, 2002) or available only in abstract form (Ruiz-Lopez et al., 1999).

F. Overall summary and conclusions regarding scientific evidence germane to the proposed claim

As noted in the introduction to this section, the Center believes the totality of scientific evidence provides convincing support for the proposed claim. Forty-five RCTs were identified by our literature search that were eligible to substantiate the proposed claim based on FDA's 2009 guidance document. The most persuasive of this evidence was furnished by 82 percent (14/17) of the high or medium quality RCTs that reported some evidence that magnesium supplementation lowered blood pressure among individuals with pre- or mild hypertension and/or those with suboptimal magnesium status. Such

evidence was also provided by 54 percent (14/26) of high or medium quality studies that included subjects with normal blood pressure and/or optimal magnesium status. The consistency of these findings is illustrated by the fact that a Cochrane review (Dickinson et al., 2006) and all three meta-analyses published subsequent to it (Kass et al., 2012, Rosanoff and Plesset, 2013, Zhang et al., 2016) reported pooled data that showed magnesium supplementation significantly reduced systolic and/or diastolic blood pressure. These findings are especially persuasive because many of the studies included in these analyses involved normotensive and/or magnesium replete subjects who are less likely to respond to supplementation than their anti-hypertensive drug-treated counterparts. Further, suggestive evidence was provided by eight of 10 studies that reported significant beneficial effects of magnesium supplementation on blood pressure, but failed to employ a rigorous control group.

Additional support for the proposed claim was provided by the epidemiologic evidence. Seventy-nine percent of the 38 observational studies identified by our literature search reported at least some evidence that magnesium intake and/or status was inversely associated with blood pressure in free-living humans. The strongest of such support was furnished by the 78 percent of prospective cohort studies that reported such findings. As FDA has observed, observational data are less compelling than RCTs because they cannot establish a causal relationship. Nevertheless, supportive findings from such studies help confirm that that the beneficial effects of magnesium supplementation seen under controlled conditions also occur in free-living individuals.

In conclusion, the Center strongly believes that the totality of scientific evidence provides more than enough justification for use of the proposed claim, and we respectfully request

that the agency use its enforcement discretion to permit dissemination of this important information to the American population.

IV. **OTHER SCIENTIFIC SUMMARY CONSIDERATIONS**

A. Is there an optimum level of magnesium to be consumed beyond which no benefit would be expected?

As explained previously (see section III. A. 1), no additional beneficial effect of magnesium supplementation on blood pressure would be expected after an adequate physiological status of this nutrient is reached. As explained by Lappe and Heaney (2012), essential nutrients exert their physiological effects over a narrow range as their status moves from deficient to replete. Therefore, individuals with normal blood pressure, or those with elevated blood pressure due to some cause other than magnesium deficiency, would not be expected to benefit from increased magnesium intake due to the claim. However, nutritional adequacy with respect to magnesium can only be maintained with habitually adequate intakes. Therefore, knowledge about the benefits of adequate dietary magnesium (as the proposed claim would foster) is important for the population as a whole.

B. Is there any level at which an adverse effect from magnesium occurs for any segment of the population?

The tolerable upper intake level (UL) of magnesium (Institute of Medicine, 1997) for non-food sources of magnesium is 350 mg per day for adolescents older than nine years of age and adults. However, the IOM noted that this UL was based on limited data, and observed, “Although a few studies have noted mild diarrhea and other mild gastrointestinal complaints in a small percentage of patients at levels of 360 to 380 mg

(15.0 to 15.8 mmol) per day, it is noteworthy that many other individuals have not encountered such effects even when receiving substantially more than this UL of supplementary magnesium, as indicated previously."

The RCTs submitted as substantiation for the proposed claim are consistent with the IOM's conclusion that side effects from doses of magnesium in excess of the UL are often not observed. None of these 44 studies reported significant adverse effects due to magnesium supplementation. Sixteen studies specifically indicated that there were no magnesium-related side effects (Borrello et al., 1996, Cappuccio et al., 1985, de Valk et al., 1998, Guerrero-Romero and Rodriguez-Moran, 2011, Itoh et al., 1997, Joris et al., 2016, Lee et al., 2009, Mooren et al., 2011, Olhaberry et al., 1987, Paolisso et al., 1992, Plum-Wirell et al., 1994, Reyes et al., 1984, Wary et al., 1999, Widman et al., 1993, Wirell et al., 1993, Wirell et al., 1994) with doses as high as 26.6 mmol (638 mg) per day. Thirteen of these controlled studies did not mention the occurrence of adverse effects due to magnesium supplementation of up to 25 mmol (600 mg) per day (Barragan-Rodriguez et al., 2008, Doyle et al., 1999, Dyckner and Wester, 1983, Eriksson and Kohvakka, 1995, Ferrara et al., 1992, Guerrero-Romero et al., 2004, Kass et al., 2013, Kisters et al., 1993, Rodriguez-Moran and Guerrero-Romero, 2014, Sanjuliani et al., 1996, Walker et al., 2002, Zemel et al., 1990). Several studies reported that subjects dropped out of the study for minor conditions that may or may not have been due to magnesium supplementation: Henderson et al. (1986) reported that one subject in the magnesium group (12.5 mmol/d) left the study due to hypokalemia, Simental-Mendia et al. (2012) reported one drop out due to diarrhea in the group that received 15.9 mmol magnesium per day, Daly et al. (1990) noted that one subject in the magnesium group

(20.8 mmol/d) and one in the placebo group left the study due to diarrhea, and vomiting prompted one subject who had been receiving 18.75 mmol/d to withdraw from the study conducted by Rodriguez-Hernandez et al. (2010) . No other studies reported that subjects withdrew due to adverse effects of magnesium supplementation although minor issues such as loose stools (TOHP Study Group, 1992, Sacks et al., 1998) or other forms of minor discomfort were reported (Rodriguez-Moran and Guerrero-Romero, 2003, Cosaro et al., 2014, Patki et al., 1990, Guerrero-Romero and Rodriguez-Moran, 2009).

In conclusion, no serious adverse reactions to magnesium supplementation were reported among participants receiving up to 40 mmol per day in the RCTs submitted as substantiation for the proposed claim. The adverse effects that were reported were minor, transient and were often reported in both experimental and control groups. Should such effects occur among consumers who begin magnesium supplementation in response to the claim, they can easily be addressed by discontinuing such supplementation or lowering magnesium dose. No reports of adverse effects of magnesium from food were identified; and no UL exists for this source of the nutrient. Therefore, it is extremely unlikely that consumers who respond to the claim by increasing their intake of magnesium-containing foods will experience adverse effects. Therefore, the Center strongly believes that the potential occurrence of minor adverse effects due to increased magnesium consumption is greatly overshadowed by the potential benefit of reduced risk of hypertension.

C. Are there certain populations that must receive special considerations

Hypermagnesimia had been reported in dialysis patients although the lack of adequate magnesium nutrition among patients with impaired renal function has also been reported

(Alhosaini and Leehey, 2015). The challenges and opportunities related to magnesium nutrition in chronic kidney disease have been reviewed (Guerrera et al., 2009, Kanbay et al., 2010) and patients in this category should be given special consideration. Hypermagnesimia has also been reported among elderly subjects who abuse magnesium-containing cathartics or antacids (Onishi and Yoshino, 2006). However, the Center is not aware of segments of the healthy population who must be given special consideration with respect to this nutrient.

D. What other nutritional or health factors (both positive and negative) are important to consider when consuming magnesium?

Magnesium is an essential nutrient and serves as a required cofactor for more than 300 enzyme systems including those involved in energy metabolism through glycolysis and oxidative phosphorylation (Institute of Medicine, 1997). In addition to its role in blood pressure as discussed in this document, considerable data suggest that magnesium has beneficial effects on glucose metabolism and could reduce the risk of type-2 diabetes (Rodriguez-Moran et al., 2011). Magnesium has also been suggested to be of potential benefit for a wide variety of health related conditions including eclampsia and preeclampsia, arrhythmias, asthma, migraine and dysmenorrhea (Guerrera et al., 2009).

As noted previously, magnesium interacts with a variety of other nutrients including calcium and vitamin D. It has been suggested that calcium and vitamin D supplementation could adversely affect magnesium status in free living individuals (Rosanoff et al., 2016, Deng et al., 2013).

In conclusion, magnesium is an essential nutrient that has the potential to beneficially affect not only blood pressure but a variety of other health related conditions. The Center is aware of no known areas of concern pertaining to the consumption of magnesium in the range of the Daily Reference Intakes.

E. Prevalence of hypertension in the U.S. population and relevance of the claim in the context of the total daily diet.

As noted earlier in this document (see section II B), approximately 80 million Americans currently have hypertension including an estimated 17 million cases that are undiagnosed (Mozaffarian et al., 2016). It is likely that multiple etiologies are responsible for this high incidence of hypertension; however inadequate magnesium intake could very well be one of the factors that is involved.

Suboptimal magnesium intake is prevalent among certain segments of the U.S. population. Data from the 2003-2006 NHANES from 8,860 adults (19 years of age or older) show that mean daily intake of magnesium from foods among non- dietary supplement users was only 268 mg/d for men and 234 mg/d among women (Bailey et al., 2011). Magnesium intake from foods among supplement users was higher ($p \leq 0.003$) for both men (350 mg/d) and women (267 mg/d) than among non-supplement users. Mean intake of magnesium from both foods and supplements among supplement users was also higher ($p \leq 0.003$) among both men (449 mg/d) and women (387 mg/d) than among non-supplement users. The mean percentage of individuals who failed to consume the EAR for magnesium among non-supplement users was 63 and 69 among men and women, respectively. Analogous data for total magnesium intake (from foods and supplements) among supplement users was 22 and 19 percent for men and women, respectively. More

recent data from a meta-analysis of observational cohort and longitudinal studies that presented data on the habitual intakes of older adults 65 years or greater (ter Borg et al., 2015) showed that mean intake of magnesium among this group was only 296 mg/d among men and 294 mg/d among women. The percentage of men and women who failed to consume the EAR of this nutrient was 73 and 41percent, respectively. These data clearly show that both the incidence of hypertension and suboptimal magnesium intakes are highly prevalent in the U.S. The Center strongly believes that the potential of the proposed claim to focus attention on both of these public health issues makes it highly relevant within the context of the entire diet.

V. **OTHER DIETARY CONSIDERATIONS**

As noted above, suboptimal intakes of magnesium are prevalent among adults (Bailey et al., 2011) and older adults (ter Borg et al., 2015) in the U.S. Therefore, educating consumers about the benefits of magnesium has the potential to improve diet quality by increasing the intake of this nutrient. In addition, foods that are good sources of magnesium tend to be nutrient dense and have the potential to increase the quality of the diet in other areas as well. The magnesium content of a selection of popular foods that are significant sources of this nutrient are presented in Table VI.

Only foods and dietary supplements that are excellent sources of magnesium (at least 20% DV) will be eligible to bear the proposed claim. However, the Center strongly believes that availability of the claim will call attention to the benefits of increased magnesium intake and prompt greater consumer interest and demand for such foods. Therefore, manufacturers will have an incentive to use the “good source” nutrient content claim on foods (including many of those in Table VI) that qualify for the proposed claim.

Table VI
Foods that are significant sources of magnesium

Food	Serving size	Magnesium content per serving	
		(mg)	(% DV)
Almonds	30 g RACC	81	20
Banana	1 cup sliced	40	10
Brown rice	45 g RACC	64	16
Black beans	½ cup	60	15
Cashews	30 g RACC	88	22
Chard	1 cup	150	38
Dark chocolate	1 oz.	41	10
Edamame	1 cup frozen, prepared	99	25
Green peas	1 cup, cooked	42	10
Oats	45 g RACC	80	20
Spinach	1 cup, cooked	157	39
Yogurt, vanilla	1 cup	39	10

VI. **NATURE OF THE FOOD ELIGIBLE TO BEAR THE CLAIM**

The Center proposes that foods and dietary supplements eligible to bear the proposed claim meet the definition of excellent source of magnesium (21 C.F.R. §101.54(b)) as specified in the general requirements for health claims (21 C.F.R. §101.14(d)(1)(vii)).

In addition, the Center proposes that such foods and dietary supplements meet all of the general requirements for health claims specified in 21 C.F.R. §101.14 with the exception that tree nuts (e.g., almonds, cashew nuts) not be required to meet the total fat disqualifier level of no more than 13.0 grams per RACC and per 50 grams as specified in 21 C.F.R. §101.14(a)(4). The imposition of this requirement would disqualify one of the most important food sources of magnesium from bearing the claim with no sound nutritional reason for doing so.

A. Tree nuts are nutrient dense foods recommended by the 2015-2020 *Dietary Guidelines for Americans*

The 2015-2020 DGAs specifically identify nuts as one of the protein foods that are a component of the healthy dietary pattern recommended for Americans along with vegetables, fruits, whole grains, fat-free or low-fat dairy and healthy oils.

One of the reasons that nuts are included in this recommended dietary pattern is that they are characterized as nutrient dense foods. Specifically, the DGAs state,

> All vegetables, fruits, whole grains, seafood, eggs, beans and peas, unsalted **nuts** (emphasis supplied) and seeds, fat-free and low-fat dairy products, and lean meats and poultry—when prepared with little or no added solid fats, sugars, refined starches, and sodium—are nutrient-dense foods. These foods contribute to meeting food group recommendations within calorie and sodium limits. The term "nutrient dense" indicates the nutrients and other beneficial substances in a food have not been "diluted" by the addition of calories from added solid fats, sugars, or refined starches, or by the solid fats naturally present in the food.

Tree nuts are also widely recommended as part of a diet designed to manage the risk of CHD by professional organizations. For example, the AHA[17] recommends a healthy dietary pattern than includes nuts. Specifically, recommendations directed to consumers on the organization's website[18] state,

> To get the nutrients you need, eat a dietary pattern that emphasizes:
> - Poultry, fish and **nuts** (emphasis supplied),
> - Fruits, vegetables,
> - Whole grains,
> - Low-fat dairy products,
> - While limiting red meat and sugary foods and beverages.

[17] http://www.heart.org/HEARTORG/GettingHealthy/HealthierKids/HowtoMakeaHealthyHome/Dietary-Recommendations-for-Healthy-Children_UCM_303886_Article.jsp
[18] http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/HealthyEating/The-American-Heart-Associations-Diet-and-Lifestyle-Recommendations_UCM_305855_Article.jsp

The proposed claim pertains to hypertension rather than CHD *per se*, however both of these conditions are important to overall cardiovascular health and it is therefore appropriate to recommend nuts as part of an overall heart-healthy diet – including reduced risk of hypertension.

B. FDA has established a strong regulatory precedent for exempting foods from the total fat disqualifier level for CHD-related health claims

FDA has granted numerous exemptions from the total fat disqualifier (as well as the "low fat" requirement when necessary) for QHCs related to cardiovascular disease. Specifically, such exemptions were made for the QHCs for olive oil, canola oil, and corn oil and reduced risk of CHD. The agency's rationale for granting this exemption for olive oil was,

> Olive oil exceeds the disqualifying total fat level because it is essentially entirely fat. However, the MUFAs from olive oil and CHD qualified health claim will inform consumers that they might lower their risk of CHD by consuming foods containing MUFAs from olive oil in place of similar foods high in SFAs, while not increasing caloric intake. FDA believes this type of dietary information will help consumers maintain healthy dietary practices by providing consumers with information that can facilitate reductions of saturated fat and cholesterol intake without increasing total calorie consumption. Furthermore, FDA concurs with current dietary guidelines that consuming diets low in saturated fat and cholesterol is more important in reducing CHD risk than consuming diets low in total fat. Therefore, FDA has decided not to consider, in the exercise of its enforcement discretion, that olive oil meet the disqualifying total fat level to bear a MUFAs from olive oil and CHD qualified health claim.

The Center agrees with this rationale and notes that the observation that consuming diets lower in saturated fat is more important than consuming diets low in total fat is particularly relevant. This conclusion has become widely accepted in the public health

community and is evident in the fact that the 2015-2020 DGAs do not impose a quantitative limit on total fat content of the diet.

In conclusion, the Center respectfully requests that the agency exempt tree nuts from the total fat disqualifier level for the purposes of making the proposed claim. Nut products that choose to bear the claim would include the disclosure statement that complies with 21 C.F.R. § 101.13(h) (i.e., "See nutrition information for fat content."). As noted above, all other foods and dietary supplements bearing the claim would be required to meet the provisions of 21 C.F.R §101.14 in their entirety.

VII. **LABELING REQUIREMENTS**

Foods eligible to bear the proposed claim would be required to declare the magnesium content per serving in the Nutrition Facts panel, as stipulated in 21 C.F.R. § 101.9(c)(8). In addition, as noted previously, the appropriate disclaimer statement “[see nutrition information for total fat]” will also be provided immediately adjacent to the claim with no intervening material as specified in 21 C.F.R. § 101.13(h), when the claim is used on tree nut products as appropriate.

VIII. **ENVIRONMENTAL IMPACT STATEMENT**

The Center chooses to avail itself of the categorical exclusion with respect to an environmental impact assessment provided by 21 CFR § 25.32(p). Accordingly, an environmental impact assessment is not required for this submission.

IV. **CONCLUSIONS**

In conclusion, the Center strongly believes that the totality of available scientific evidence supports the proposed QHC for magnesium and reduced risk of hypertension. The preponderance of such evidence clearly demonstrates that adequate intake of magnesium lowers blood pressure in the general U.S. population. This effect is particularly robust among individuals with mildly elevated blood pressure, but is also statistically significant based on pooled data from studies that include normotensive subjects (Kass et al., 2012, Zhang et al., 2016). The hypotensive effects of magnesium supplementation observed in the intervention studies was corroborated by the majority of observational studies (especially prospective cohort studies) that showed magnesium intake and/or status was inversely associated with blood pressure and/or the incidence of high blood pressure. These findings are consistent with the fact that magnesium is known to be one of the nutrients that are critical for the regulation of blood pressure by acting on vascular smooth muscle cells and the endothelium. Finally, NHANES data show that current intakes of magnesium are suboptimal among many members of the U.S. population (Bailey et al., 2011, ter Borg et al., 2015) and availability of the claim would call attention to this important nutrient and act as an incentive for food and dietary supplement manufacturers to help educate consumers in this area. In conclusion, the Center respectfully requests that FDA allow the use of the proposed claim as quickly as possible.

X. CERTIFICATION

We hereby certify that to the best of our knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information known to us to be pertinent to the evaluation of the proposed qualified health claim.

Respectfully submitted,

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XI. **REFERENCES**

Alhosaini, M. & Leehey, D.J. (2015). Magnesium and Dialysis: The Neglected Cation. *American journal of kidney diseases : the official journal of the National Kidney Foundation,* 66**:** 523-31

Altman, D., Carroli, G., Duley, L., Farrell, B., Moodley, J., Neilson, J., Smith, D. & Magpie Trial Collaboration, G. (2002). Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet,* 359**:** 1877-90

Arnaud, M.J. (2008). Update on the assessment of magnesium status. *Br J Nutr,* 99 Suppl 3**:** S24-36

Ascherio, A., Rimm, E.B., Giovannucci, E.L., Colditz, G.A., Rosner, B., Willett, W.C., Sacks, F. & Stampfer, M.J. (1992). A prospective study of nutritional factors and hypertension among US men. *Circulation,* 86**:** 1475-84

Aybak, M., Sermet, A., Ayyildiz, M.O. & Karakilcik, A.Z. (1995). Effect of oral pyridoxine hydrochloride supplementation on arterial blood pressure in patients with essential hypertension. *Arzneimittel-Forschung,* 45**:** 1271-3

Bailey, R.L., Fulgoni, V.L., 3rd, Keast, D.R. & Dwyer, J.T. (2011). Dietary supplement use is associated with higher intakes of minerals from food sources. *Am J Clin Nutr,* 94**:** 1376-81

Baker, W.L., Kluger, J., White, C.M., Dale, K.M., Silver, B.B. & Coleman, C.I. (2009). Effect of magnesium L-lactate on blood pressure in patients with an implantable cardioverter defibrillator. *Ann Pharmacother,* 43**:** 569-76

Barbagallo, M., Dominguez, L.J., Galioto, A., Pineo, A. & Belvedere, M. (2010). Oral magnesium supplementation improves vascular function in elderly diabetic patients. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 23**:** 131-7

Barragan-Rodriguez, L., Rodriguez-Moran, M. & Guerrero-Romero, F. (2008). Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: a randomized, equivalent trial. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 21**:** 218-23

Bashir, Y., Sneddon, J.F., Staunton, H.A., Haywood, G.A., Simpson, I.A., Mckenna, W.J. & Camm, A.J. (1993). Effects of long-term oral magnesium chloride replacement in congestive heart failure secondary to coronary artery disease. *Am J Cardiol,* 72**:** 1156-62

Beydoun, M.A., Gary, T.L., Caballero, B.H., Lawrence, R.S., Cheskin, L.J. & Wang, Y. (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**:** 1914-25

Bo, S., Durazzo, M., Guidi, S., Carello, M., Sacerdote, C., Silli, B., Rosato, R., Cassader, M., Gentile, L. & Pagano, G. (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**:** 1062-9

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

Bullarbo, M., Odman, N., Nestler, A., Nielsen, T., Kolisek, M., Vormann, J. & Rylander, R. (2013). Magnesium supplementation to prevent high blood pressure in pregnancy: a randomised placebo control trial. *Arch Gynecol Obstet,* 288**:** 1269-74

Cappuccio, F.P., Markandu, N.D., Beynon, G.W., Shore, A.C., Sampson, B. & Macgregor, G.A. (1985). Lack of effect of oral magnesium on high blood pressure: a double blind study. *Br Med J (Clin Res Ed),* 291**:** 235-8

Chidambaram, N., Sethupathy, S., Saravanan, N., Mori, M., Yamori, Y., Garg, A.K. & Chockalingam, A. (2014). Relationship of sodium and magnesium intakes to hypertension proven by 24-hour urianalysis in a South Indian population. *Journal of clinical hypertension (Greenwich, Conn),* 16**:** 581-6

Choi, M.K. & Bae, Y.J. (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). *Biological trace element research,* 156**:** 56-66

Cohen, L., Laor, A. & Kitzes, R. (1984). Reversible retinal vasospasm in magnesium-treated hypertension despite no significant change in blood pressure. *Magnesium,* 3**:** 159-63

Cosaro, E., Bonafini, S., Montagnana, M., Danese, E., Trettene, M.S., Minuz, P., Delva, P. & Fava, C. (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**:** 1213-20

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

Das, U.N. (2015). Nutritional factors in the prevention and management of coronary artery disease and heart failure. *Nutrition,* 31**:** 283-91

De Valk, H.W., Verkaaik, R., Van Rijn, H.J., Geerdink, R.A. & Struyvenberg, A. (1998). Oral magnesium supplementation in insulin-requiring Type 2 diabetic patients. *Diabet Med,* 15**:** 503-7

Del Gobbo, L.C., Imamura, F., Wu, J.H., De Oliveira Otto, M.C., Chiuve, S.E. & Mozaffarian, D. (2013). Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr,* 98**:** 160-73

Deng, X., Song, Y., Manson, J.E., Signorello, L.B., Zhang, S.M., Shrubsole, M.J., Ness, R.M., Seidner, D.L. & Dai, Q. (2013). Magnesium, vitamin D status and mortality: results from US National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III. *BMC Med,* 11**:** 187

Dibaba, D.T., Xun, P., Fly, A.D., Yokota, K. & He, K. (2014). Dietary magnesium intake and risk of metabolic syndrome: a meta-analysis. *Diabet Med,* 31**:** 1301-9

Dickinson, H.O., Nicolson, D.J., Campbell, F., Cook, J.V., Beyer, F.R., Ford, G.A. & Mason, J. (2006). Magnesium supplementation for the management of essential hypertension in adults. *Cochrane Database Syst Rev***:** CD004640

Doyle, L., Flynn, A. & Cashman, K. (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**:** 255-61

Dyckner, T. & Wester, P.O. (1983). Effect of magnesium on blood pressure. *Br Med J (Clin Res Ed),* 286**:** 1847-9

Eriksson, J. & Kohvakka, A. (1995). Magnesium and ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab,* 39**:** 217-23

Farvid, M.S., Jalali, M., Siassi, F., Saadat, N. & Hosseini, M. (2004). The impact of vitamins and/or mineral supplementation on blood pressure in type 2 diabetes. *J Am Coll Nutr,* 23**:** 272-9

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

Ferre, S., Baldoli, E., Leidi, M. & Maier, J.A. (2010). Magnesium deficiency promotes a pro-atherogenic phenotype in cultured human endothelial cells via activation of NFkB. *Biochim Biophys Acta,* 1802**:** 952-8

Ford, E.S., Li, C., Mcguire, L.C., Mokdad, A.H. & Liu, S. (2007). Intake of dietary magnesium and the prevalence of the metabolic syndrome among U.S. adults. *Obesity (Silver Spring),* 15**:** 1139-46

Forstermann, U. (2008). Oxidative stress in vascular disease: causes, defense mechanisms and potential therapies. *Nat Clin Pract Cardiovasc Med,* 5**:** 338-49

Geleijnse, J.M., Witteman, J.C., Bak, A.A., Den Breeijen, J.H. & Grobbee, D.E. (1994). Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension. *BMJ,* 309**:** 436-40

Guasch-Ferre, M., Bullo, M., Estruch, R., Corella, D., Martinez-Gonzalez, M.A., Ros, E., Covas, M., Aros, F., Gomez-Gracia, E., Fiol, M., Lapetra, J., Munoz, M.A., Serra-Majem, L., Babio, N., Pinto, X., Lamuela-Raventos, R.M., Ruiz-Gutierrez, V. & Salas-Salvado, J. (2014). Dietary magnesium intake is inversely associated with mortality in adults at high cardiovascular disease risk. *J Nutr,* 144**:** 55-60

Guerrera, M.P., Volpe, S.L. & Mao, J.J. (2009). Therapeutic uses of magnesium. *Am Fam Physician,* 80**:** 157-62

Guerrero-Romero, F. & Rodriguez-Moran, M. (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**:** 245-51

Guerrero-Romero, F. & Rodriguez-Moran, M. (2011). Magnesium improves the beta-cell function to compensate variation of insulin sensitivity: double-blind, randomized clinical trial. *Eur J Clin Invest,* 41**:** 405-10

Guerrero-Romero, F. & Rodriguez-Moran, M. (2013). Serum magnesium in the metabolically-obese normal-weight and healthy-obese subjects. *European journal of internal medicine,* 24**:** 639-43

Guerrero-Romero, F., Tamez-Perez, H.E., Gonzalez-Gonzalez, G., Salinas-Martinez, A.M., Montes-Villarreal, J., Trevino-Ortiz, J.H. & Rodriguez-Moran, M. (2004). Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. *Diabetes & metabolism,* 30**:** 253-8

Gullestad, L., Dolva, L.O., Soyland, E., Manger, A.T., Falch, D. & Kjekshus, J. (1992). Oral magnesium supplementation improves metabolic variables and muscle strength in alcoholics. *Alcoholism, clinical and experimental research,* 16**:** 986-90

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

Hajjar, I.M., Grim, C.E., George, V. & Kotchen, T.A. (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**:** 589-93

Hatton, D.C. & Mccarron, D.A. (1994). Dietary calcium and blood pressure in experimental models of hypertension. A review. *Hypertension,* 23**:** 513-30

Hattori, K., Saito, K., Sano, H. & Fukuzaki, H. (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**:** 1249-56

Hatzistavri, L.S., Sarafidis, P.A., Georgianos, P.I., Tziolas, I.M., Aroditis, C.P., Zebekakis, P.E., Pikilidou, M.I. & Lasaridis, A.N. (2009). Oral magnesium supplementation reduces ambulatory blood pressure in patients with mild hypertension. *Am J Hypertens,* 22**:** 1070-5

He, J., Tell, G.S., Tang, Y.C., Mo, P.S. & He, G.Q. (1991). Relation of electrolytes to blood pressure in men. The Yi people study. *Hypertension,* 17**:** 378-85

He, K., Liu, K., Daviglus, M.L., Morris, S.J., Loria, C.M., Van Horn, L., Jacobs, D.R., Jr. & Savage, P.J. (2006). Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation,* 113**:** 1675-82

Henderson, D.G., Schierup, J. & Schodt, T. (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**:** 664-5

Hopping, B.N., Erber, E., Grandinetti, A., Verheus, M., Kolonel, L.N. & Maskarinec, G. (2010). Dietary Fiber, Magnesium, and Glycemic Load Alter Risk of Type 2 Diabetes in a Multiethnic Cohort in Hawaii. *The Journal of Nutrition,* 140**:** 68-74

Houston, M. (2011). The role of magnesium in hypertension and cardiovascular disease. *Journal of clinical hypertension (Greenwich, Conn),* 13**:** 843-7

Houston, M. (2014). The role of nutrition and nutraceutical supplements in the treatment of hypertension. *World journal of cardiology,* 6**:** 38-66

Huang, J.H., Lu, Y.F., Cheng, F.C., Lee, J.N. & Tsai, L.C. (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. & Kubena, K.S. (1989). Nutrition, physical activity, and blood pressure in the elderly. *Journal of nutrition for the elderly,* 9**:** 3-15

Institute of Medicine (1997). Calcium and Related Nutrients: Overview and Methods. *National Academy of Sciences Press, Washington, DC,*

Itoh, K., Kawasaka, T. & Nakamura, M. (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**:** 737-50

Jee, S.H., Miller, E.R., 3rd, Guallar, E., Singh, V.K., Appel, L.J. & Klag, M.J. (2002). The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. *Am J Hypertens,* 15**:** 691-6

Joffres, M.R., Reed, D.M. & Yano, K. (1987). Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu heart study. *Am J Clin Nutr,* 45**:** 469-75

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

Joris, P.J., Plat, J., Bakker, S.J. & Mensink, R.P. (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,*

Kanbay, M., Goldsmith, D., Uyar, M.E., Turgut, F. & Covic, A. (2010). Magnesium in chronic kidney disease: challenges and opportunities. *Blood purification,* 29**:** 280-92

Karanja, N., Morris, C.D., Illingworth, D.R. & Mccarron, D.A. (1987). Plasma lipids and hypertension: response to calcium supplementation. *Am J Clin Nutr,* 45**:** 60-5

Kass, L., Weekes, J. & Carpenter, L. (2012). Effect of magnesium supplementation on blood pressure: a meta-analysis. *Eur J Clin Nutr,* 66**:** 411-8

Kass, L.S. & Poeira, F. (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., Skinner, P. & Poeira, F. (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. *Journal of sports science & medicine,* 12**:** 144-50

Katz, A., Rosenthal, T., Maoz, C., Peleg, E., Zeidenstein, R. & Levi, Y. (1999). Effect of a mineral salt diet on 24-h blood pressure monitoring in elderly hypertensive patients. *J Hum Hypertens,* 13**:** 777-80

Kawano, Y., Matsuoka, H., Takishita, S. & Omae, T. (1998). Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. *Hypertension,* 32**:** 260-5

Kesteloot, H. & Joossens, J.V. (1988). Relationship of dietary sodium, potassium, calcium, and magnesium with blood pressure. Belgian Interuniversity Research on Nutrition and Health. *Hypertension,* 12**:** 594-9

Kesteloot, H., Tzoulaki, I., Brown, I.J., Chan, Q., Wijeyesekera, A., Ueshima, H., Zhao, L., Dyer, A.R., Unwin, R.J., Stamler, J. & Elliott, P. (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**:** 44-51

Khan, A.M., Sullivan, L., Mccabe, E., Levy, D., Vasan, R.S. & Wang, T.J. (2010). Lack of association between serum magnesium and the risks of hypertension and cardiovascular disease. *Am Heart J,* 160**:** 715-20

Kim, M.H. & Choi, M.K. (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. *Biological trace element research,* 153**:** 69-75

Kisters, K., Spieker, C., Tepel, M. & Zidek, W. (1993). New data about the effects of oral physiological magnesium supplementation on several cardiovascular risk factors (lipids and blood pressure). *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 6**:** 355-60

Kisters, K., Wessels, F., Nguyen, M.Q., Mitchell, A., Geremmler, B., Funke, C., Baraliakos, X., Kask, B., Hausberg, M., Hunger, R., Liebscher, D.-H., Liebscher, U. & Tokmak, F. (2012). Magnesium therapy in borderline hypertension. *Trace Elements & Electrolytes,* 29**:** 113-6

Kohvakka, A., Luurila, O., Gordin, A. & Sundberg, S. (1989). Comparison of potassium alone and potassium-magnesium supplementation on patients with heart failure using hydrochlorothiazide. *Magnesium,* 8**:** 71-6

Kolte, D., Vijayaraghavan, K., Khera, S., Sica, D.A. & Frishman, W.H. (2014). Role of magnesium in cardiovascular diseases. *Cardiology in review,* 22**:** 182-92

Kupetsky-Rincon, E.A. & Uitto, J. (2012). Magnesium: novel applications in cardiovascular disease--a review of the literature. *Ann Nutr Metab,* 61**:** 102-10

Lappe, J.M. & Heaney, R.P. (2012). Why randomized controlled trials of calcium and vitamin D sometimes fail. *Dermato-endocrinology,* 4**:** 95-100

Lee, S., Park, H.K., Son, S.P., Lee, C.W., Kim, I.J. & Kim, H.J. (2009). Effects of oral magnesium supplementation on insulin sensitivity and blood pressure in normo-magnesemic nondiabetic overweight Korean adults. *Nutr Metab Cardiovasc Dis,* 19**:** 781-8

Liao, F., Folsom, A.R. & Brancati, F.L. (1998). Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J,* 136**:** 480-90

Lind, L., Lithell, H., Pollare, T. & Ljunghall, S. (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**:** 674-9

Liu, L., Liu, L., Ding, Y., Huang, Z., He, B., Sun, S., Zhao, G., Zhang, H., Miki, T., Mizushima, S., Ikeda, K., Nara, Y. & Yamori, Y. (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**:** 315-22

Lukaski, H.C., Bolonchuk, W.W., Klevay, L.M., Milne, D.B. & Sandstead, H.H. (2001). Interactions among dietary fat, mineral status, and performance of endurance athletes: a case study. *Int J Sport Nutr Exerc Metab,* 11**:** 186-98

Lumme, J.A. & Jounela, A.J. (1989). The effect of potassium and potassium plus magnesium supplementation on ventricular extrasystoles in mild hypertensives treated with hydrochlorothiazide. *Int J Cardiol,* 25**:** 93-7

Lusis, A.J. (2000). Atherosclerosis. *Nature,* 407**:** 233-41

Lutsey, P.L., Alonso, A., Michos, E.D., Loehr, L.R., Astor, B.C., Coresh, J. & Folsom, A.R. (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**:** 756-64

Ma, J., Folsom, A.R., Melnick, S.L., Eckfeldt, J.H., Sharrett, A.R., Nabulsi, A.A., Hutchinson, R.G. & Metcalf, P.A. (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**:** 927-40

Maier, J.A. (2012). Endothelial cells and magnesium: implications in atherosclerosis. *Clin Sci (Lond),* 122**:** 397-407

Margetts, B.M., Beilin, L.J., Vandongen, R. & Armstrong, B.K. (1986). Vegetarian diet in mild hypertension: a randomised controlled trial. *Br Med J (Clin Res Ed),* 293**:** 1468-71

Mcgarvey, S.T., Zinner, S.H., Willett, W.C. & Rosner, B. (1991). Maternal prenatal dietary potassium, calcium, magnesium, and infant blood pressure. *Hypertension,* 17**:** 218-24

Mckeown, N.M., Jacques, P.F., Zhang, X.L., Juan, W. & Sahyoun, N.R. (2008). Dietary magnesium intake is related to metabolic syndrome in older Americans. *Eur J Nutr,* 47**:** 210-6

Michon, P. (2002). [Level of total and ionized magnesium fraction based on biochemical analysis of blood and hair and effect of supplemented magnesium (Slow Mag B6) on selected parameters in hypertension of patients treated with various groups of drugs]. *Annales Academiae Medicae Stetinensis,* 48**:** 85-97

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

Mortazavi, M., Moeinzadeh, F., Saadatnia, M., Shahidi, S., Mcgee, J.C. & Minagar, A. (2013). Effect of magnesium supplementation on carotid intima-media thickness and flow-mediated dilatation among hemodialysis patients: a double-blind, randomized, placebo-controlled trial. *European neurology,* 69**:** 309-16

Motoyama, T., Sano, H. & Fukuzaki, H. (1989). Oral magnesium supplementation in patients with essential hypertension. *Hypertension,* 13**:** 227-32

Mozaffarian, D., Benjamin, E.J., Go, A.S., Arnett, D.K., Blaha, M.J., Cushman, M., Das, S.R., De Ferranti, S., Després, J.-P., Fullerton, H.J., Howard, V.J., Huffman, M.D., Isasi, C.R., Jiménez, M.C., Judd, S.E., Kissela, B.M., Lichtman, J.H., Lisabeth, L.D., Liu, S., Mackey, R.H., Magid, D.J., Mcguire, D.K., Mohler, E.R., Moy, C.S., Muntner, P., Mussolino, M.E., Nasir, K., Neumar, R.W., Nichol, G., Palaniappan, L., Pandey, D.K., Reeves, M.J., Rodriguez, C.J., Rosamond, W., Sorlie, P.D., Stein, J., Towfighi, A., Turan, T.N., Virani, S.S., Woo, D., Yeh, R.W. & Turner, M.B. (2016). Heart Disease and Stroke Statistics—2016 Update: A Report From the American Heart Association. *Circulation,* 133**:** e38-e360

Ninomiya, J.K., L'italien, G., Criqui, M.H., Whyte, J.L., Gamst, A. & Chen, R.S. (2004). Association of the Metabolic Syndrome With History of Myocardial Infarction and Stroke in the Third National Health and Nutrition Examination Survey. *Circulation,* 109**:** 42-46

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

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

Onishi, S. & Yoshino, S. (2006). Cathartic-induced fatal hypermagnesemia in the elderly. *Internal medicine (Tokyo, Japan),* 45**:** 207-10

Panhwar, A.H., Kazi, T.G., Afridi, H.I., Talpur, F.N., Arain, S. & Kazi, N. (2014). Distribution of potassium, calcium, magnesium, and sodium levels in biological samples of Pakistani hypertensive patients and control subjects. *Clinical laboratory,* 60**:** 463-74

Paolisso, G., Di Maro, G., Cozzolino, D., Salvatore, T., D'amore, A., Lama, D., Varricchio, M. & D'onofrio, F. (1992). Chronic magnesium administration enhances oxidative glucose metabolism in thiazide treated hypertensive patients. *Am J Hypertens,* 5**:** 681-6

Papanikolaou, Y., Brooks, J. & Fulgoni, V.L. (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**:** 1038-46

Patki, P.S., Singh, J., Gokhale, S.V., Bulakh, P.M., Shrotri, D.S. & Patwardhan, B. (1990). Efficacy of potassium and magnesium in essential hypertension: a double-blind, placebo controlled, crossover study. *BMJ,* 301**:** 521-3

Peacock, J.M., Folsom, A.R., Arnett, D.K., Eckfeldt, J.H. & Szklo, M. (1999). Relationship of serum and dietary magnesium to incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol,* 9**:** 159-65

Peacock, J.M., Ohira, T., Post, W., Sotoodehnia, N., Rosamond, W. & Folsom, A.R. (2010). Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J,* 160**:** 464-70

Plum-Wirell, M., Stegmayr, B.G. & Wester, P.O. (1994). Nutritional magnesium supplementation does not change blood pressure nor serum or muscle potassium and magnesium in untreated hypertension. A double-blind crossover study. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 7**:** 277-83

Purvis, J.R., Cummings, D.M., Landsman, P., Carroll, R., Barakat, H., Bray, J., Whitley, C. & Horner, R.D. (1994). Effect of oral magnesium supplementation on selected cardiovascular risk factors in non-insulin-dependent diabetics. *Archives of family medicine,* 3**:** 503-8

Rasic-Milutinovic, Z., Perunicic-Pekovic, G., Jovanovic, D., Gluvic, Z. & Cankovic-Kadijevic, M. (2012). Association of blood pressure and metabolic syndrome components with magnesium levels in drinking water in some Serbian municipalities. *Journal of water and health,* 10**:** 161-9

Resnick, L. (1999). The cellular ionic basis of hypertension and allied clinical conditions. *Prog Cardiovasc Dis,* 42**:** 1-22

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

Rodriguez-Hernandez, H., Cervantes-Huerta, M., Rodriguez-Moran, M. & Guerrero-Romero, F. (2010). Oral magnesium supplementation decreases alanine aminotransferase levels in obese women. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 23**:** 90-6

Rodriguez-Moran, M. & Guerrero-Romero, F. (2003). Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care,* 26**:** 1147-52

Rodriguez-Moran, M. & Guerrero-Romero, F. (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**:** 388-93

Rodriguez-Moran, M., Simental Mendia, L.E., Zambrano Galvan, G. & Guerrero-Romero, F. (2011). The role of magnesium in type 2 diabetes: a brief based-clinical review. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 24**:** 156-62

Rodriguez-Ramirez, M., Simental-Mendia, L.E., Gonzalez-Ortiz, M., Martinez-Abundis, E., Madero, A., Brito-Zurita, O., Perez-Fuentes, R., Revilla-Monsalve, C., Islas-Andrade, S., Rodriguez-Moran, M. & Guerrero-Romero, F. (2015). Prevalence of Prehypertension in Mexico and Its Association With Hypomagnesemia. *Am J Hypertens,* 28**:** 1024-30

Romani, A. (2013). Magnesium in Health and Disease. IN Sigel, A. & Sigel, H. (Eds.) *Interrelations between Essential Metal Ions and Human Diseases.* Springer Science.

Rosanoff, A. (2010). Magnesium supplements may enhance the effect of antihypertensive medications in stage 1 hypertensive subjects. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 23**:** 27-40

Rosanoff, A., Dai, Q. & Shapses, S.A. (2016). Essential Nutrient Interactions: Does Low or Suboptimal Magnesium Status Interact with Vitamin D and/or Calcium Status? *Advances in Nutrition: An International Review Journal,* 7**:** 25-43

Rosanoff, A. & Plesset, M.R. (2013). Oral magnesium supplements decrease high blood pressure (SBP>155 mmHg) in hypertensive subjects on anti-hypertensive medications: a targeted meta-analysis. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 26**:** 93-9

Rotter, I., Kosik-Bogacka, D., Dolegowska, B., Safranow, K., Karakiewicz, B. & Laszczynska, M. (2015). Relationship between serum magnesium concentration and metabolic and hormonal disorders in middle-aged and older men. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 28**:** 99-107

Ruiz-Lopez, M.F., Gil-Extremera, B., Maldonado-Martin, A., Huertas-Hernandez, F., Caeballos-Atienza, R., Munfloz-Parra, F., Cruz-Benayas, M.A., Leon-Espinosa-Monteros, M.T., Cobo-Martinez, F. & Soto-Mas, J.A. (1999). Blood pressure and metabolic syndrome in essential hypertensive patients treated with losartan or verapamil after oral magnesium supplement. *Am J Hypertens (Abstract),* 12**:** 182A

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

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

Sacks, F.M., Willett, W.C., Smith, A., Brown, L.E., Rosner, B. & Moore, T.J. (1998). Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. *Hypertension,* 31**:** 131-8

Saito, K., Hattori, K., Omatsu, T., Hirouchi, H., Sano, H. & Fukuzaki, H. (1988). Effects of oral magnesium on blood pressure and red cell sodium transport in patients receiving long-term thiazide diuretics for hypertension. *Am J Hypertens,* 1**:** 71S-74S

Sanjuliani, A.F., De Abreu Fagundes, V.G. & Francischetti, E.A. (1996). Effects of magnesium on blood pressure and intracellular ion levels of Brazilian hypertensive patients. *Int J Cardiol,* 56**:** 177-83

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

Shafique, M., Misbah Ul, A. & Ashraf, M. (1993). Role of magnesium in the management of hypertension. *JPMA The Journal of the Pakistan Medical Association,* 43**:** 77-8

Shechter, M. (2010). Magnesium and cardiovascular system. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 23**:** 60-72

Sibai, B.M., Villar, M.A. & Bray, E. (1989). Magnesium supplementation during pregnancy: a double-blind randomized controlled clinical trial. *Am J Obstet Gynecol,* 161**:** 115-9

Simental-Mendia, L.E., Rodriguez-Moran, M. & Guerrero-Romero, F. (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**:** 325-30

Simental-Mendia, L.E., Rodriguez-Moran, M., Reyes-Romero, M.A. & Guerrero-Romero, F. (2012). No positive effect of oral magnesium supplementation in the decreases of inflammation in subjects with prediabetes: a pilot study. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 25**:** 140-6

Singh, R.B. (1990). Effect of dietary magnesium supplementation in the prevention of coronary heart disease and sudden cardiac death. *Magnesium and trace elements,* 9**:** 143-51

Singh, R.B., Rastogi, S.S., Mani, U.V., Seth, J. & Devi, L. (1991). Does dietary magnesium modulate blood lipids? *Biological trace element research,* 30**:** 59-64

Song, Y., Ridker, P.M., Manson, J.E., Cook, N.R., Buring, J.E. & Liu, S. (2005). Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. *Diabetes Care,* 28**:** 1438-44

Song, Y., Sesso, H.D., Manson, J.E., Cook, N.R., Buring, J.E. & Liu, S. (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**:** 1616-21

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

Sudhakar, K., Sujatha, M., Rao, V.B., Jyothy, A. & Reddy, P.P. (1999). Serum and erythrocyte magnesium levels in hypertensives and their first degree relatives. *Journal of the Indian Medical Association,* 97**:** 211-3

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

Syedmoradi, L., Ghasemi, A., Zahediasl, S. & Azizi, F. (2011). Prevalence of hypo- and hypermagnesemia in an Iranian urban population. *Annals of human biology,* 38**:** 150-5

Taylor, D.R., Constable, J., Sonnekus, M. & Milne, F.J. (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**:** 273-6

Ter Borg, S., Verlaan, S., Hemsworth, J., Mijnarends, D.M., Schols, J.M., Luiking, Y.C. & De Groot, L.C. (2015). Micronutrient intakes and potential inadequacies of community-dwelling older adults: a systematic review. *Br J Nutr,* 113**:** 1195-206

Tikkanen, M.J., Hogstrom, P., Tuomilehto, J., Keinanen-Kiukaanniemi, S., Sundvall, J. & Karppanen, H. (2001). Effect of a diet based on low-fat foods enriched with nonesterified plant sterols and mineral nutrients on serum cholesterol. *Am J Cardiol,* 88**:** 1157-62

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**:** 1213-1220

Turlapaty, P.D. & Altura, B.M. (1980). Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. *Science,* 208**:** 198-200

Van Leer, E.M., Seidell, J.C. & Kromhout, D. (1995). Dietary calcium, potassium, magnesium and blood pressure in the Netherlands. *Int J Epidemiol,* 24**:** 1117-23

Walker, A.F., Marakis, G., Morris, A.P. & Robinson, P.A. (2002). Promising hypotensive effect of hawthorn extract: a randomized double-blind pilot study of mild, essential hypertension. *Phytotherapy research : PTR,* 16**:** 48-54

Wary, C., Brillault-Salvat, C., Bloch, G., Leroy-Willig, A., Roumenov, D., Grognet, J.M., Leclerc, J.H. & Carlier, P.G. (1999). Effect of chronic magnesium supplementation on magnesium distribution in healthy volunteers evaluated by 31P-NMRS and ion selective electrodes. *British journal of clinical pharmacology,* 48**:** 655-62

Whelton, P.K., Buring, J., Borhani, N.O., Cohen, J.D., Cook, N., Cutler, J.A., Kiley, J.E., Kuller, L.H., Satterfield, S., Sacks, F.M. & 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**:** 85-95

Widman, L., Wester, P.O., Stegmayr, B.K. & Wirell, M. (1993). The dose-dependent reduction in blood pressure through administration of magnesium. A double blind placebo controlled cross-over study. *Am J Hypertens,* 6**:** 41-5

Wirell, M.M., Wester, P.O. & Stegmayr, B.G. (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**:** 50-54

Wirell, M.P., Wester, P.O. & Stegmayr, B.G. (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**:** 189-95

Witkowski, M., Hubert, J. & Mazur, A. (2011). Methods of assessment of magnesium status in humans: a systematic review. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium,* 24**:** 163-80

Witteman, J.C., Grobbee, D.E., Derkx, F.H., Bouillon, R., De Bruijn, A.M. & Hofman, A. (1994). Reduction of blood pressure with oral magnesium supplementation in women with mild to moderate hypertension. *Am J Clin Nutr,* 60**:** 129-35

Witteman, J.C., Willett, W.C., Stampfer, M.J., Colditz, G.A., Sacks, F.M., Speizer, F.E., Rosner, B. & Hennekens, C.H. (1989). A prospective study of nutritional factors and hypertension among US women. *Circulation,* 80**:** 1320-7

Wu, G., Tian, H., Han, K., Xi, Y., Yao, Y. & Ma, A. (2006). Potassium magnesium supplementation for four weeks improves small distal artery compliance and reduces blood pressure in patients with essential hypertension. *Clinical and experimental hypertension (New York, NY : 1993),* 28**:** 489-97

Yamamoto, M.E., Applegate, W.B., Klag, M.J., Borhani, N.O., Cohen, J.D., Kirchner, K.A., Lakatos, E., Sacks, F.M., Taylor, J.O. & Hennekens, C.H. (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**:** 96-107

Yamori, Y., Nara, Y., Mizushima, S., Mano, M., Sawamura, M., Kihara, M. & Horie, R. (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. *Nutrition and health,* 8**:** 77-90

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

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

Zemel, P.C., Zemel, M.B., Urberg, M., Douglas, F.L., Geiser, R. & Sowers, J.R. (1990). Metabolic and hemodynamic effects of magnesium supplementation in patients with essential hypertension. *Am J Clin Nutr,* 51**:** 665-9

Zhang, X., Li, Y., Del Gobbo, L.C., Rosanoff, A., Wang, J.W. & Song, Y. (2016). Effects of magnesium supplementation of blood pressure: A meta-analysis of randomized double-blind placebo-controlled trials. *Hypertension (in press),*