

21 CFR Part 101

[Docket No. 91N-00951]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements; Sodium/Hypertension**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to authorize health claims on food labels and labeling that state that a low sodium diet is associated with lower blood pressure in some people. The agency reviewed the relationship between dietary sodium intake and hypertension under provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments). On the basis of this review, the agency tentatively concludes that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, and that the strength and consistency of the publicly available scientific evidence supports such claims. The agency's tentative conclusion is based on its review of the scientific literature and on review of conclusions and recommendations provided in Federal government and other authoritative documents.

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the 1990 amendments.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville MD 20857.

FOR FURTHER INFORMATION CONTACT: Ellen M. Anderson, Center for Food Safety and Applied Nutrition (HFF-266), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5375.

SUPPLEMENTARY INFORMATION:**I. Background***A. The Nutrition Labeling and Education Act of 1990*

On November 8, 1990, the President signed into law the 1990 amendments (Pub. L. 101-535), which amended the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorize the Secretary of Health and

Human Services (the Secretary) to issue regulations authorizing nutrient content and health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)).

Published elsewhere in this **Federal Register** is a proposed rule to establish general requirements for health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs, or nutritional substances (referred to generally as "substances") to a disease or health related condition on food labels and in labeling. In this companion document, FDA has tentatively determined that such claims would be justified for dietary supplements as well as conventional foods only if the agency determines based on the totality of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles) that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The 1990 amendments also require (section 3(b)(1)(A)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x)) that, within 12 months of their enactment, the Secretary shall issue proposed regulations to implement section 403(r) of the act (21 U.S.C. 343(r)), and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including sodium and hypertension, meet the requirements of section 403(r)(3) of the act (21 U.S.C. 343(r)(3)). In this document, the agency will consider whether a claim on food or food products, including conventional foods and dietary supplements, on the relationship between sodium and hypertension would be justified under the standard proposed in the companion document entitled "Food Labeling: General Requirements for Health Claims for Food: Proposed Rule."

*B. Sodium/Hypertension Relationship***1. Hypertension**

Hypertension, commonly referred to as high blood pressure, is a serious public health concern. One in three adults in the United States is hypertensive (Ref. 85) approximately 58

million adults (Ref. 23). Individuals with high blood pressure have an increased risk of developing stroke, heart disease, and several types of kidney disease (Refs. 43 and 62). Heart disease and stroke are 2 of the 10 leading causes of death in the United States (Ref. 43). In 1988, 35.3 percent of all deaths were attributable to heart disease and 7.9 percent to stroke (Ref. 82).

In spite of improvements in the awareness and control of hypertension and a decline in related mortality rates for heart disease and stroke, hypertension continues to be a serious public health problem. Developing strategies to lower blood pressure in the general population remains an important public health goal (Ref. 74).

2. Sodium and Salt

Sodium is an essential nutrient with a variety of physiological functions (Ref. 63). It is the major electrolyte of blood plasma and other noncellular fluid and is essential for maintenance of fluid and electrolyte balance within the body. Sodium is also necessary for normal kidney function, nerve conduction, and muscle contraction (Ref. 7).

Sodium requirements vary with age, physical activity, environmental factors, and pregnancy status. Estimates have been made for safe minimum daily requirements for sodium in healthy persons taking into account wide variations in climate and physical activity but not including an allowance for large or prolonged sweat losses. These estimates range from approximately 300 milligrams (mg) per day for children 2 through 5 years of age to 500 mg per day for adults over 18 years of age (Ref. 63). In the United States, sodium is generally consumed well in excess of bodily needs. Dietary intake estimates range from 3,000 to 6,000 mg per day (refs. 18, 34, 35, and 43).

3. Relationship Between Sodium and Hypertension

An association of salt intake with high blood pressure was first observed in 1904 (Ref. 1). Since then, considerable experimental evidence linking sodium intake to hypertension has accumulated (Ref. 14). This increasing body of evidence resulted in public health concerns about the high levels of sodium intake in the U.S. population (Refs. 3, 9, 11, 22, 43, 62, 63, and 85). Consequently, a series of recommendations for Americans to moderate or reduce their sodium consumption have been made (Refs. 43, 62, 63, and 85).

Despite widely accepted recommendations to reduce or moderate sodium intake, estimating the

effectiveness of sodium restriction in reducing blood pressure has proven difficult because high blood pressure has many causes, and blood pressure levels are affected by many factors. The 1990 amendments require FDA to review and evaluate the data on sodium and hypertension to determine whether health claims on this topic are appropriate.

C. Sodium: Regulatory History

Sodium and salt have long regulatory histories. Salt (sodium chloride) has been regulated as an ingredient (21 CFR 100.140) and a flavoring (21 CFR 101.22). It has traditionally and historically been regarded as a generally recognized as safe (GRAS) substance (21 CFR 182.1). Sodium has been regulated as an essential nutrient (21 CFR 107.10, 21 CFR 107.100, and current 21 CFR 101.9). However, in the early 1980's, concern over high sodium consumption led to the GRAS safety review of sodium chloride (June 18, 1982, 47 FR 26590) and to FDA regulations (June 18, 1982, 47 FR 26580; April 18, 1984, 49 FR 15510) to include sodium content information on nutrition labels (current 21 CFR 101.9), to define descriptive terms for "low sodium" and "reduced sodium" foods (current 21 CFR 101.13), and to permit sodium labeling without full nutrition labeling on foods used to regulate sodium intake (21 CFR 105.69).

The intent of these regulations was to provide guidelines for sodium and salt labeling on foods, to establish definitions for descriptor terms useful in labeling foods low in sodium and salt, and to encourage manufacturers to provide a greater number and variety of low sodium foods. The emphasis was on developing and maintaining policies appropriate for the general public so that consumers could structure their diets to meet individual health needs, and so that medical professionals could better manage those patients requiring control of dietary sodium intake. Two quotes summarize the agency position in 1982 to 1984. The first refers to the general public:

Adult intake of sodium in the United States is in excess of physiological needs, and it would be prudent for the general population to reduce sodium intake whenever possible. The role of excess dietary sodium in the development of hypertension needs to be defined more clearly, but there is no evidence that a moderate reduction in sodium intake for the general public would have any adverse effects, and there is a strong indication that such a reduction would be beneficial to a large segment of the population. (47 FR 26580 at 26581.)

The second quote refers to that portion of the U.S. population predisposed to hypertension:

Although many epidemiological studies indicate a relationship between sodium intake and the prevalence of hypertension, the evidence that sodium consumption is a major factor in causing hypertension is not fully conclusive. Nevertheless, the evidence is strong enough for most members of the medical and scientific community to conclude that a substantial portion of the U.S. population which is predisposed to hypertension would benefit from a reduction in dietary sodium. (47 FR 26580 at 26581.)

In the *Federal Register* of June 18, 1982 (47 FR 26590), FDA reviewed the GRAS status of sodium chloride. Regulatory action was deferred until the agency could assess the impact of sodium descriptor and labeling regulations and voluntary efforts of manufacturers to reduce the salt and sodium content of their products. It was recognized that salt occupies a unique place in the food supply because it occurs naturally in foods, has a wide variety of manufacturing uses, and has a long history of direct consumer use in food preparation and at the table. In addition, the level of dietary sodium recommended for different individuals varies widely, from severe sodium restriction for some hypertensive patients, to moderate restriction for others, to general recommendations to reduce sodium intake for the general public. FDA concluded that it would be impractical to set upper safe limits for salt in individual foods, and that it was more appropriate to provide sodium content information than to try to restrict sodium use. In the years following the sodium labeling initiatives, FDA has taken no further action on the GRAS status of salt.

Consideration of health claims for a sodium and hypertension relationship was first proposed by FDA in a repropounded rule on health messages published on February 13, 1990 (55 FR 5176). Sodium and hypertension was proposed as one of six possible topics most likely to be suitable for health claims.

Elsewhere in this issue of the *Federal Register*, FDA is publishing a supplementary proposal on mandatory nutrition labeling, Reference Daily Intakes (RDI's), and Daily Reference Values (DRV's) for nutrients. The proposed DRV for sodium is 2,400 mg. Also in this issue of the *Federal Register*, FDA is proposing a revision of nutrient content claims that include sodium content claims.

D. Evidence Considered in Reaching the Decision

The agency has reviewed relevant scientific evidence on sodium and hypertension. Federal government documents considered include the Surgeon General's Report on "Nutrition and Health" (Ref. 43), the U.S. Department of Agriculture's (USDA) and the Department of Health and Human Services, (DHHS) "Nutrition and Your Health—Dietary Guidelines for Americans" (Ref. 85), the National Institute of Health (NIH), National Heart, Lung, and Blood Institute's (NHLBI) "The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (Ref. 38), and the NIH/NHLBI Hypertension Workshop (Ref. 103).

The agency also reviewed additional documents prepared by recognized scientific bodies: The National Academy of Sciences/National Research Council's (NAS/NRC) "Diet and Health—Implications for Reducing Chronic Disease Risk" (Ref. 62), and the NAS/NRC "Recommended Dietary Allowances" (Ref. 63). FDA recently contracted with the Federation of American Societies for Experimental Biology (FASEB), Life Sciences Research Office (LSRO) to prepare an independent evaluation of the available scientific evidence on the relationship between sodium and hypertension. The agency has also considered the results of this "Sodium and Hypertension" review (Ref. 108). These reports considered the weight of the publicly available scientific evidence up until their publication, and they provided a foundation for studies published subsequently. The agency considered the results of animal studies to the extent that they clarified human studies or suggested possible mechanisms of action. FDA updated the evidence in these documents by reviewing relevant human studies that have become available since 1988. The agency evaluated one major, multinational investigation (Ref. 37), four clinical trials (Refs. 44, 70, 79, and 109), and three meta-analyses (Refs. 100, 106, and 107).

To ensure that its review of relevant evidence was complete, FDA requested, in the *Federal Register* of March 28, 1991 (56 FR 12932), scientific data and information on the 10 specific topic areas identified in section 3(b)(1)(A) of the 1990 amendments. The topic of sodium and hypertension was among the 10 subjects on which the agency requested information.

E. Comments Received in Response to FDA Request for Scientific Data and Information

FDA received 13 comments in response to the **Federal Register** request for data and information about the relationship between sodium and hypertension (56 FR 12932). One comment was a request for an extension for additional time for comments, and this request was denied because of the limited time available. Several provided comments about the general process of writing health claims. Others expressed opinions in support of or in opposition to sodium reduction or health claims for sodium and hypertension. Among those taking positions, a manufacturer and a trade association opposed reducing sodium intake and sodium/hypertension health claims. Reduced sodium intake and sodium/hypertension health claims were supported by a professional health association, a distributor of health foods, and a foreign government.

Comments from a trade association stated that health claims were inconsistent with the statutory requirements of the act. However, this comment was contained in a letter that was written before the enactment of the 1990 amendments which explicitly authorize health claims.

Comments from a State department of health, an association of State and territorial public health nutrition directors, a trade association, and a distributor of health foods included support for the 1990 amendments and the Surgeon General's report (Ref. 43). The comments favored requiring significant scientific agreement as a precondition to a health claim and suggested that FDA should authorize such claims only if other nutrient levels do not contradict the health benefits from the substance. These comments said that such claims should emphasize the total diet rather than individual foods, supplementation, or fortification. Some expressed concern that industry could abuse health claims or that the general public could misinterpret them. One suggested that FDA should do a literature search to obtain an impartial selection of data for review. Another emphasized that the public should continue to rely on modern medicine for the cure and mitigation of diseases. FDA believes that the proposed rule is responsive to these concerns.

Comments from a health food distributor and a professional health association made recommendations about levels of daily sodium intake. The health food distributor advised that adult sodium intake should not exceed 1,600 mg per day, while the professional

health association recommended that adult sodium intake should not exceed 3 grams (g) (3,000 mg) per day. In this issue of the **Federal Register**, as stated above, FDA is proposing a DRV of 2,400 mg of sodium per day. Comments concerning recommended daily sodium intakes are more appropriately discussed in response to the establishment of a DRV for sodium. Copies of these two comments have been placed under Docket No. 90N-0134.

A distributor of health foods recommended a two-tiered approach to establishing the maximum amount of sodium that a food could contain and still bear a health claim. It suggested an absolute value (less than 100 mg of sodium per 100 calories) and recommended a secondary criteria based on the naturally occurring sodium levels in the various food categories. The health food distributor emphasized the importance of maintaining standard levels of other important nutrients and suggested that sodium/hypertension health claims would be misleading on low sodium foods if other ingredients in the food caused increased hypertension. These issues have been addressed in the proposed regulation on general requirements for health claims published elsewhere in this issue of the **Federal Register**.

Comments from a trade association suggested that health claims should be national in scope and uniform nationwide, and that FDA should not proceed without the resources to adequately enforce any new regulations. Under the 1990 amendments, regulations established by FDA on health claims are national in scope. FDA is required to prepare appropriate regulations in response to the congressional mandate. The agency will enforce the food labeling regulations to the best of its ability with the resources available.

Comments from a trade association suggested that model label statements should be created by expert advisory committees, evaluated through consumer testing, and published in the **Federal Register** for public comment. Manufacturers will have the latitude to develop claims that meet the requirements of the rule. FDA has tentatively decided that, under the act, the appropriate course is for the agency to determine the requirements that a health claim must meet. In this and other documents, FDA is proposing to authorize health claims and is proposing a model claim. FDA is inviting public comment on that model claim as well as on the proposed rule.

Comments from both a State health department and a health food distributor

suggested that health claims should recognize the populations affected, refer to other factors that contribute to the disease, and emphasize the overall diet and lifestyle and not overstate the effectiveness of the nutrient or allow short descriptive statements separate from the total health claim. As discussed below and in the document on general principles for health claims, FDA's proposal is responsive to these concerns.

Several organizations sent in references for scientific studies. All recent and pertinent studies and comments concerning the scientific evaluation are included in the scientific review and summary elsewhere in this document.

A comment from a trade association included detailed objections to the Surgeon General's report (Ref. 43) and the NAS report (Ref. 62) and suggested that the documents were outdated, incorrect, incomplete, and biased. The comment concluded that the reports should not be given special consideration. FDA disagrees with these comments and believes that the documents are appropriate for consideration.

The Canadian Government also submitted a comment, outlining its position on the relationship of diet and nutrients to disease. The position reflects the work of the Canadian Scientific Review Committee (the Committee) (Ref. 84). The Committee reviewed the scientific data and recommended that the sodium content of the Canadian diet should be reduced. The report stated that there were insufficient data to support a quantitative recommendation. However, it concluded that a reduction in current sodium intakes of the Canadian population would involve no risk. Canada also pointed out that its Food and Drug Act expressly prohibits the sale or advertisement of foods represented to treat, prevent, or cure hypertension and other diseases.

II. Review of the Scientific Evidence

A. Introduction

Definitions of hypertension are related to both contracting, or systolic, blood pressure (SBP) and resting, or diastolic, blood pressure (DBP) measurements, are based on correlations with risk of heart disease and stroke, and differ by organization and purpose (Refs. 4, 17, 27, and 38). Currently, individuals with SBP greater than or equal to 140 millimeters of mercury (mm Hg) or DBP greater than or equal to 90 mm Hg or currently taking

antihypertensive medication are considered hypertensive. Those with SBP less than 140 mm Hg and DBP less than 90 mm Hg are considered normotensive (Refs. 17, 38, and 83). "High normal" DBP is defined as DBP between 85 and 89 mm Hg. All definitions are currently under review by the NIH/NHLBI Joint National Committee.

In considering the scientific evidence on the relationship between dietary sodium intake and hypertension, FDA reviewed three Federal government documents (Refs. 38, 43, and 85), a Federal government workshop (Ref. 103), and three other documents from recognized scientific bodies (Refs. 62, 63, and 108). FDA also reviewed the human studies that have become available since these documents were written. The agency included in its review English language reports of primary human studies involving sodium and hypertension specifically. FDA considered review articles and issues involving hypertension or other nutrients only as they related to the primary relationship between sodium and hypertension.

B. Federal Government Documents

1. "The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure"

"The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (Ref. 32) noted that research on hypertension prevention was in progress, and that recommendations for ways to prevent hypertension could not yet be made. It concluded that population studies suggest that low sodium intake, weight reduction, and moderation of alcohol consumption may contribute to prevention of age-related increases of blood pressure. The report noted that "high sodium intake plays a critical role in maintaining the elevated blood pressure of some hypertensive patients and in limiting the effectiveness of certain antihypertensive drugs," and that "some patients with mild or moderate blood pressure elevation may achieve control through moderate sodium restriction." The report observed that there is no easy way to identify specific individuals who would profit from sodium restriction and indicated that moderate sodium intake (approximately 1,500 to 2,500 mg per day) produced no serious adverse consequences.

2. "The Surgeon General's Report on Nutrition and Health," 1988

"The Surgeon General's Report on Nutrition and Health" (Ref. 43) observed that epidemiological studies have shown that, in populations with low sodium intake, blood pressure does not rise with age, and that populations with low blood pressure do not generally consume much salt. The report noted that the correlation between salt intake and blood pressure is not consistent in population studies, and that the associations among individuals within a population have been less consistent, which may be due to methodological reasons.

The report observed that long-term clinical studies have shown that 40 percent of hypertensive patients and 30 percent of mildly hypertensive patients could control their blood pressures by reducing sodium intake below 1,150 and 1,720 mg per day, respectively. It further noted that the effect of sodium restriction has been less well studied in normotensive populations as compared to hypertensive populations. There are fewer studies of normotensive individuals, and the studies have been small in size and short in duration. A few studies have indicated that dietary sodium restriction in normotensive adults or infants can result in small blood pressure decreases.

The report observed that intervention studies have suggested that sodium restriction and weight control can be beneficial in helping control hypertension in mildly hypertensive individuals who have discontinued their antihypertension medication.

The Surgeon General's Report on Nutrition and Health" concluded that "[d]ietary factors that clearly contribute to high blood pressure include obesity and excessive intake of sodium and alcohol," and that "[s]tudies indicate a relationship between a high sodium intake and the occurrence of high blood pressure and stroke."

The report observed that the average sodium consumption by U.S. adults (4,000 to 6,000 mg per day) significantly exceeds the range that NRC estimated in 1980 as would be a safe and adequate daily intake (1,100 to 3,300 mg). It noted that there is no easy way to identify individuals who would profit from sodium restriction, and that some individuals appear to respond to sodium restriction and are considered "salt-sensitive" and others do not respond and are considered "salt-resistant." The report observed that there is no practical way of distinguishing the two groups other than by measuring the blood pressure response itself. It

concluded that moderate reduction of dietary sodium would not be harmful and might be of significant benefit to that portion of the population at risk of developing hypertension. The report suggested that most Americans should consider reducing their sodium intake by choosing foods with less sodium, using less sodium in food preparation, and adding less sodium at the table.

3. "Nutrition and Your Health—Dietary Guidelines for Americans," 1990

In 1990, "Nutrition and Your Health—Dietary Guidelines for Americans" (Ref. 85) made seven nutrition recommendations for the U.S. population. Among other suggestions, it stated that Americans should "[u]se salt and sodium in moderation" and recommended that Americans choose foods with less sodium, use less sodium in food preparation, and add less sodium at the table.

4. Summary

These three Federal government documents acknowledged a relationship between sodium intake in excess of physiological need and the prevalence of hypertension. There was agreement that limiting dietary sodium may benefit a portion of the population with elevated blood pressures, i.e., be of benefit for some hypertensive individuals. Dietary Guidelines and the Surgeon General's report also indicated that in addition to benefiting individuals identified as hypertensive, moderation of dietary sodium might also benefit the portion of the normotensive population at risk of developing hypertension.

C. Federal Government "Workshop on Salt and Blood Pressure," 1989

On November 1 and 2, 1989, NHLBI sponsored a "Workshop on Salt and Blood Pressure" to review the scientific evidence on the relationship between sodium and blood pressure, to consider the variability in human response, to review research findings relative to clinical and public health policies, and to provide recommendations for future research (Ref. 103). Three articles that resulted from this workshop (Refs. 109, 111, and 114) are discussed elsewhere in this document. Positions and opinions expressed at the meeting were highly polarized on the value of salt restriction. A wide range of topics was presented, and the scientific discussions reflected the controversy surrounding this topic. Some participants at the conference supported reducing sodium intake and argued that the relationship is scientifically supported (Refs. 94, 97, and

113), that many hypertensives are "salt-sensitive" (Ref. 95), that there are no negative consequences of decreased sodium intake (Ref. 98), and that since the target population cannot be identified easily or cheaply (Ref. 104), a population approach, which is often used for nutrition policies (Ref. 99), is necessary (Ref. 104). Some indicated that reductions in sodium intake are possible because interventions have been successful and have made significant contributions to treatment and prevention (Ref. 98). Others contended that only expensive, labor-intensive interventions with highly motivated participants have been successful (Ref. 105), and that the most pragmatic approach would be to alter the sodium content of the entire food supply (Refs. 102 and 105).

Other participants opposed reducing sodium intake and contended that more research is necessary because electrolytes other than sodium may affect hypertension (Ref. 110). Some indicated that sodium restriction affects people in very different ways, and that some individuals might be closer to a critical deficit of extracellular fluid or might have more difficulty reconstituting losses after acute salt-depleting stress. They argued that sodium reduction should be used only for individuals at risk and for those in whom it has proven effective (Ref. 112). Some asserted that long-term, substantial reductions in sodium intake have not been successfully achieved in comparative trials (Ref. 113).

D. Other Documents and Statements

1. "Diet and Health—Implications for Reducing Chronic Disease Risk," 1989

The NAS "Diet and Health—Implications for Reducing Chronic Disease Risk" (Ref. 62) observed that cross-cultural, epidemiological studies show that blood pressure does not increase with age, and that there is a low prevalence of hypertension in populations with low sodium intake. However, the relationship between low sodium intake and low blood pressure or low incidence of hypertension has been less consistent in epidemiological studies within individual cultures. The report noted that INTERSALT, a large, multinational, pooled study, showed both a small but significant positive correlation between sodium excretion and mean SBP and also a significant positive correlation between sodium excretion and increases in blood pressure that occur with age (Ref. 37).

The report observed that small, short-term clinical studies suggest that sodium restriction is related to reductions in

blood pressure in normotensive individuals. However, these results have not been confirmed in long-term, prospective, controlled trials in normotensive populations.

The report noted that animal studies support the conclusions from human studies. High salt intake appears to promote the development of high blood pressure in some animal models, especially when renal defects reduce the ability of the kidney to excrete salt. The report noted that these findings suggest that high-salt diets in combination with reduced sodium excretion may be related to the development of hypertension in humans. It further noted that, once high blood pressure is induced by high sodium intake, it cannot necessarily be reversed by resumption of a moderately low intake, due probably to irreversible changes in the kidney.

"Diet and Health—Implications for Reducing Chronic Disease Risk" concluded that: "[b]lood pressure levels are strongly and positively correlated with the habitual intake of salt," and that "the weight of evidence supports the contention that intake of sodium is an important factor in the occurrence of hypertension." The report recommended that total daily salt intake should be not greater than 6 g (2,400 mg sodium), with a possible future goal of 4.5 g salt (1,800 mg sodium). It suggested reducing salt and sodium intake by choosing low sodium foods and using less sodium in food preparation and at the table. The report observed that there is a wide variability in genetic susceptibility to salt-induced hypertension, that some people are more salt-responsive ("salt-sensitive") than others, and that there is no reliable way to identify individuals in the population who would benefit from sodium restriction. It concluded that limiting dietary sodium may be of significant benefit to that portion of the population at risk of developing hypertension and noted that the recommended intake levels would not be harmful to the general public.

2. "Recommended Dietary Allowances," 1989

"Recommended Dietary Allowances," 10th Edition (Ref. 63) noted that: "[s]ustained overconsumption of sodium, particularly as salt, has been related to development of hypertension in sensitive individuals." It supported the recommendation of the NAS Report to limit daily sodium intake to 2,400 mg. It noted that 500 mg sodium per day is a safe minimum intake for adults, and that there is no known advantage in consuming large amounts of sodium.

3. "Dietary Sodium Chloride and Blood Pressure," 1991

FASEB recently prepared an independent evaluation of the available scientific evidence on the relationship between sodium and hypertension (Ref. 108). The FASEB report concluded that the association between increased sodium or salt intake and increased blood pressure is due to sodium and chloride in combination, and that the increase is mitigated by the presence of potassium and calcium ions. It indicated that the most convincing evidence comes both from studies across populations and from controlled clinical trials which have shown a small, significant positive correlation between dietary sodium chloride intake and blood pressure for hypertensive and normotensive individuals.

The FASEB report noted that studies within populations have been inconclusive or have shown a low correlation. The report noted that there was little long term information about the effect of dietary sodium intake on the development of hypertension, and that the available data have been inconclusive. The report concluded that observational data and intervention trials document a small, but consistent effect of dietary sodium chloride on blood pressure.

4. Summary

There is general agreement among the three authoritative documents that there is a relationship between sodium intake and hypertension.

E. Review of the Scientific Evidence Since the Authoritative Reports

1. INTERSALT, 1988

INTERSALT (Ref. 37) was a large, multinational investigation of the relationship between electrolytes, including sodium, and blood pressure (Table 1). The intent was to apply highly standardized methods across varied populations, to examine the major confounding factors, and to evaluate the relationships in individuals (Ref. 64). The study involved 10,079 adults in 52 population centers around the world (Refs. 37, 50 through 54, 58, 59, and 64). Within-individual variability in sodium excretion was estimated using data from a random sampling (8 percent) of individuals who provided two 24-hour urine collections. The within-center data were pooled, and a statistically significant relationship between sodium intake and increased SBP was reported. A relationship between sodium intake and DBP was significant under some analysis conditions and not others.

Similar results were found when the data were analyzed by gender and by age (Ref. 51), and when the normotensive population was considered independently (Ref. 50).

The across-center data analysis considered relationships between sodium intake and blood pressure and between sodium intake and trends in blood pressure with age. The data were analyzed with and without four isolated population centers, two Brazilian Indian (Yanomamo and Xingu), the Papua New Guinean, and the Kenyan. These four centers had exceptionally low median sodium intakes (ranging from 5 to 1,100 mg per 24 hours) and the lowest average blood pressures of all 52 centers (SBP of 103 mm Hg, DBP of 63 mm Hg) (Ref. 58). The relationship between sodium intake and blood pressure, across centers, was strongly dependent on the inclusion or exclusion of these four populations. When these populations were included, the relationship between sodium intake and blood pressure was positive and significant. Results were negative and significant or inconclusive when these four populations were excluded from the analysis. The relationship between sodium intake and trends in blood pressure with age was positive and significant under all analysis conditions. The four centers with exceptionally low sodium intakes had little or no upward slope of blood pressure with age and low prevalence of hypertension (5 percent in Kenya, absent in remaining three centers) (Ref. 58). The Yanomamu Indians consumed as little as 1 mg of sodium in 24 hours and appeared healthy and physically active with no evidence of malnutrition or protein deficiency (Ref. 59).

The INTERSALT Cooperative Research Group analysis included adjustments for age, sex, potassium excretion, body mass index, and alcohol intake. The group estimated that an average sodium reduction of 100 millimole (mmol) per day (2,300 mg sodium) would correspond to an average reduction in SBP and DBP of 2.2 mm Hg and 0.1 mm Hg, respectively, on a population basis. In addition, assuming a cumulative effect over time, the group estimated the difference that this 2,300 mg reduction in sodium would have on the age-related increase in blood pressure that is characteristic of Western populations. It calculated that the average blood pressure would increase more slowly and, after 30 years (from 25 to 55 years of age), would be 9.0 mm Hg (SBP) and 4.5 mm Hg (DBP) lower than it would have been with a diet higher in sodium. The INTERSALT Cooperative Research Group concluded

that even these small changes in blood pressure could result in important public health benefits when applied to the population as a whole.

In recent years, there have been many published opinions on the INTERSALT findings. In reviewing the totality of publicly available scientific evidence, FDA also included these articles and considered the INTERSALT findings in this total context. The arguments were similar to those expressed at the government workshop discussed above. Several authors supported sodium restriction and emphasized the predicted benefits on a population basis (Refs. 52, 60, 69, 75, 111, and 114). Two authors objected to sodium restriction, contended that it is unclear whether the relationship is nonexistent or small with negligible benefit, and expressed concern about potential adverse effects of sodium restriction (Refs. 90 and 120).

The Stamlers, et al. (Refs. 69 and 114) used the INTERSALT data (Ref. 37) to estimate that the 2.2 mm Hg reduction in SBP would correspond to a 4 percent reduction in coronary mortality and a 6 percent reduction in stroke mortality, or 12,000 fewer U.S. deaths each year for people in the age range from 45 to 64. They estimated that the 9 mm Hg reduction in the expected increase in blood pressure from age 25 to 55 would correspond to a 16 percent reduction in deaths from coronary heart disease (CHD) and a 23 percent reduction in deaths from stroke. R. Stamler estimated that 85 percent of the American population have some risk for mortality associated with blood pressure levels (Ref. 114).

2. Clinical Trials (Table 2)

Many of the studies considered involved hypertensive subjects. Dustan and Kirk (Ref. 121) investigated sodium depletion (210 mg sodium per day) and loading (varied by body weight, added 90 mg sodium per kilogram (kg) per day) in 31 hypertensive and 84 normotensive subjects. The authors reported that in hypertensives and some normotensives, mean arterial blood pressure fell with sodium depletion and rose with sodium loading. In other normotensives, blood pressure remained stable throughout. The study phase was very short (4 days sodium depletion, and 3 days sodium loading), and the sodium loading was administered intravenously which introduced additional uncontrolled variability. In addition, the sodium depletion regime was very extreme, allowing only 210 mg sodium per day.

Lasaridis et al. (Ref. 55) studied the responses of 18 (10 male, 8 female) hypertensive patients to controlled diets low (1,150 mg per day) and high (4,600

mg per day) in sodium. Average supine blood pressure rose significantly (6.7 mm Hg). Average standing blood pressure rose (5.0 mm Hg), but the increase was not significant. The study size (18 subjects) was small.

The Australian National Health and Medical Research Council Dietary Salt Study Management Committee (Ref. 44) conducted an 8-week, double blind, placebo-controlled intervention study with 103 (86 male, 17 female) mildly hypertensive subjects (DBP: 90 to 100 mm Hg). Lower and statistically significant decreases in SBP (average decrease of 6.1 versus 0.6 mm Hg) and DBP (average decrease of 3.7 versus 0.9 mm Hg) were observed in the low sodium intake group (1,840 mg sodium per day) as compared to the normal sodium intake group (3,680 mg sodium per day). A large range of variation in individual response was observed but not confirmed.

The Australian National Health and Medical Research Council Dietary Salt Study Management Committee (Ref. 45) continued the intervention study into a crossover design. Eighty eight (73 male, 15 female) subjects continued into the second phase of the study. Similar decreases in SBP (average decrease of 6.0 versus 0.1 mm Hg) and DBP (average decrease of 4.1 versus 0.4) were observed for the low and high sodium intake groups when the data were analyzed as a parallel design identical to that of the first study (Ref. 44). When individual response was considered in accordance with the crossover design of this second study, the average reduction was 3.6 mm Hg (SBP) and 2.1 mm Hg (DBP) in the placebo phase (1,840 mg dietary sodium per day) versus the diet phase (1,840 mg dietary sodium plus 1,840 mg sodium chloride tablets per day).

Koopman et al. (Ref. 76) conducted an intervention trial in 28 mild to moderate hypertensives (average initial SBP of 144.5 mm Hg and DBP of 95.4 mm Hg) to encourage reduced sodium diets through dietary counseling and feedback from results from urinary sodium excretion. At the end of 18 months, the average sodium had decreased by 510 mg per 24 hours (from 3,590 to 3,080 mg), accompanying average decreases in SBP of 3.7 mm Hg and in DBP of 4.0 mm Hg. In general, over the 18 months, the sodium intake and blood pressure decreased over the first 6 months and then remained at the lower levels for the rest of the trial period. Four subjects dropped out because of high blood pressure. This was a small study (18 subjects) with no untreated control group (CG).

In another study of mildly hypertensive subjects, Luft et al. (Ref. 79) used a placebo controlled, crossover study design to investigate sodium effects on blood pressure of 10 mildly hypertensive (SBP > 140 mm Hg or DBP > 90 mm Hg) and 10 normotensive (SBP < 140 mm Hg and DBP < 90 mm Hg) subjects (10 male, 10 female) (10 black, 10 white). Sodium chloride (1,810 mg sodium per day) or sodium bicarbonate (1,810 mg sodium per day) supplements were supplied with a controlled basal diet (1,380 mg sodium per day). During the sodium chloride intake period, no statistically significant change in blood pressure was observed in either the mildly hypertensive or the normotensive group. The SBP of the mildly hypertensive group was decreased by 5 mm Hg during the sodium bicarbonate intake period. The population size was small (2 groups of 10 subjects).

In another study involving 20 (11 male, 9 female) (5 black, 15 white) mild hypertensives (DBP: 90 to 110 mm Hg), MacGregor et al. (Ref. 122) investigated blood pressure response in a crossover study involving three levels of sodium intake determined by urinary excretion (1,130 mg, 2,480 mg, and 4,370 mg sodium per 24 hours). Blood pressure increased stepwise with sodium intake (SBP: 147, 155, and 163 mm Hg; DBP: 91, 95, and 100 mm Hg). The differences were statistically significant and were not affected by the order of sodium intake.

Several studies involved normotensive subjects. In addition to the two studies considered above (Refs. 79 and 121), Mascioli et al. (Ref. 109) conducted a double blind, placebo controlled, crossover study involving 48 (79 percent male) (1 black, 47 white) normotensive (SBP < 150 mm Hg; DBP: 80 to 89 mm Hg; not on antihypertensive medication or diagnosed as hypertensive) subjects, randomized into two groups, ingesting sodium capsules (2,210 mg sodium per day) or a placebo in addition to a low sodium diet (monitored as less than 805 mg sodium per 8-hour overnight urine collection). In 65 percent of the participants, SBP was higher during the sodium chloride intake period than during the placebo period (Group 1: 4.3 mm Hg higher, 126.4 versus 122.1 mm Hg; Group 2: 2.8 mm Hg higher, 121.4 versus 118.5 mm Hg). In 69 percent of the participants, DBP was higher during the sodium chloride intake period than during the placebo period (Group 1: 2.7 mm Hg higher, 78.8 versus 76.1 mm Hg; Group 2: 1.8 mm Hg higher, 78.5 versus 76.6 mm Hg). The study used timed, overnight, 8-hour urine excretion to assess adherence to low sodium diet.

Mtabaji et al. (Ref. 80) investigated blood pressure response to salt intake in 30 normotensive, black male Tanzanians. In the group on the low sodium diet (1,200 mg per 24 hours), the average mean arterial blood pressure decreased from 87 to 81 mm Hg, whereas, in the group on the high sodium diet (7,750 mg per 24 hours), the average mean arterial blood pressure increased from 86 to 89 mm Hg. The high sodium diet phase was excessively high in sodium (7,750 mg per day).

Three studies, from Scotland (Ref. 41), Japan (Ref. 71), and Belgium (Ref. 42), were cross sectional. The Scottish heart health study (Ref. 41) investigated the relationship of blood pressure to sodium in 7,354 (3,754 male, 3,600 female) free-living subjects from 22 districts in Scotland. The study concluded that there was a weak, positive correlation between sodium and SBP (males: 0.025, females: 0.055) and between sodium and DBP (males: 0.026, females: 0.052) in both sexes. Sodium intake was not independently significant after multivariate analysis. Single sodium measurements in cross sectional studies do not assess previous or habitual sodium intake habits.

Takemori et al. (Ref. 71) considered sodium intake and blood pressure response in 7,441 Japanese females from 88 urban (3,933 subjects) and 81 rural (3,508 subjects) municipalities including all prefectures in Japan. The authors concluded that an increase of 2,300 mg sodium per day was related to an increase in SBP of 4.5 mm Hg (urban: 4.1 mm Hg; rural: 4.9 mm Hg) and to an increase in DBP of 1.6 mm Hg (urban: 1.2 mm Hg; rural: 2.0 mm Hg). Spot urine and predictive equations were used to estimate 24-hour sodium which added uncertainty to the results.

Staessen et al. (Ref. 42) conducted a 5-year, cross sectional, intervention trial in two Belgian towns (12,000 and 9,000 inhabitants). A mass media campaign to avoid salt was implemented in one of the two towns, and the second town received no information and served as a control. Data from a random sampling of 777 males and 733 females were analyzed. There were decreases in average urinary sodium, SBP, and DBP for men in the intervention town, and the trends in the control town were not significantly different. In women, sodium decreased in the intervention town and increased in the control town; whereas SBP and DBP decreased similarly in both towns. No conclusions about the relationship between sodium intake and blood pressure could be made. There was a large range of variability in the results, and no

independent assessment was made of what information was available to inhabitants in the control town.

Three of the studies were intervention trials. Stamler et al. (Ref. 70) conducted a 5-year, dietary, multiple intervention trial involving 201 subjects with high normal blood pressure (DBP: 80 to 89 mm Hg). The intervention group (IG) was encouraged to reduce alcohol and sodium intakes (goal: 1,800 mg sodium per day or less), reduce weight, and increase physical activity. The intervention group significantly modified their behavior in three of these four categories relative to the control group (CG), increased frequent, moderate physical activity, weight reduction, and sodium reduction (IG: drop of 25 percent from 3980 to 3040 mg sodium per day; CG: drop of 6 percent from 4,300 to 4,060 mg sodium per day). Both groups showed similar reductions in alcohol consumption. After 5 years, the incidence of hypertension (IG: 9 percent; CG: 19 percent), the average SBP (IG: decrease of 2.6 mm Hg from 122.5 to 119.8 mm Hg; CG: decrease of 1.3 mm Hg from 122.7 to 121.5 mm Hg), and the average DBP (IG: decrease of 1.3 mm Hg from 82.5 to 81.2 mm Hg; CG: decrease of 0.1 mm Hg from 82.6 to 82.5 mm Hg) were significantly lower in the IG as compared to the CG. After multiple regression analysis, the independent effect of reduced sodium intake on lowering blood pressure was not statistically significant. Appropriate statistical tools were used to assess the effect; however, the analysis was complicated due to the four simultaneous interventions.

The Hypertension Prevention Trial Research Group (Ref. 124) conducted a dietary counseling intervention involving 841 subjects randomized into four intervention groups and a control. The four interventions involved dietary counseling to encourage reduced calories, reduced sodium, reduced sodium and calories in combination, and reduced sodium and increased potassium. Sodium and blood pressure were reduced in all groups, including the control group. In the sodium only intervention group, sodium was reduced significantly at 6 months and marginally at 3 years. Blood pressure was generally lower in the sodium only intervention group than in the control group, but the decreases were not statistically significant.

The Trials of Hypertension Prevention (TOHP) Collaborative Research Group (Ref. 123) investigated seven nonpharmacological interventions (weight loss and exercise; sodium restriction; stress management; and

supplementation with four nutrients: calcium, magnesium, potassium, and fish oil) relative to a control population, in 2,182 subjects with high normal blood pressure (DBP: 80 to 89 mm Hg). After 18 months, there was a 39 percent reduction in sodium in the sodium restriction population, and SBP and DBP were reduced by 1.5 and 0.8 mm Hg, respectively. The authors concluded that weight loss and sodium restriction were the most promising nonpharmacological interventions.

3. Meta-Analyses

FDA evaluated five meta-analyses (Refs. 94, 97, 100, 106, and 107) which analyzed the effect of sodium intake on blood pressure (table 3). Meta-analyses combine data collected using a wide variety of methodologies, and this complicates data analysis and assessment.

Cutler et al. (Ref. 94) considered 23 randomized clinical trials involving 1536 subjects. Net reductions in sodium ranged from 375 to 3,319 mg sodium, and average pooled reductions in blood pressure were 2.5 mm Hg (SBP) and 1.6 mm Hg (DBP). When hypertensive and normotensive subjects were considered separately, the net reduction was 1.9 mm Hg (DBP: 2.6 mm Hg) and smaller for the normotensive subjects (SBP: 1.7 mm Hg, DBP: 1.0 mm Hg). The results were statistically significant for SBP and DBP reductions in hypertensive subjects after including adjustments for inverse variance weights.

Whitton et al. investigated the combined results of 14 observational studies involving 12,500 (7,799 male, 6,136 female) subjects in 16 populations. The authors concluded that an average reduction of 2,300 mg sodium per day was related to average reductions in SBP and DBP of 3.7 and 2.0 mm Hg, respectively. Regression coefficients were somewhat larger in women than in men.

Three meta-analyses from one group (Refs. 100, 106, and 107) considered the relationship of sodium intake to blood pressure among populations, within populations, and from clinical trials of salt reduction. In the analysis among populations (47,000 subjects) (Ref. 106), 12 economically undeveloped and 12 economically developed communities were considered separately. The authors developed a model to analyze the relationship of blood pressure to sodium intake. The variability in blood pressure increases with age was controlled by age-stratified analysis. On a population basis, the analysis showed small but consistent increases in blood pressure with increases in sodium intake for both

economically developed and undeveloped populations. The magnitude of the increase was greater for older people and for those with higher initial blood pressures. A difference of sodium intake of 100 mmol per day (2,300 mg) was associated with an average change in SBP of 5 mm Hg (ranging from 3 to 7 mm Hg) for those 15 to 19 years of age and of 10 mm Hg (ranging from 6 to 15 mm Hg) for those 60 to 69 years of age. The magnitude of the change was greatest for those with higher initial blood pressure. Smaller changes were observed for those with lower initial blood pressure, but some change was observed in even the lowest blood pressure range.

The within-population analysis of 14 studies (Ref. 100) tested the model developed in the first paper. Using a concept previously applied to 24-hour dietary recall data (Ref. 5), the analysis demonstrated that there is considerable day-to-day variability in sodium intake, determined that a single 24-hour excretion study underestimates the true variance, and used two studies of daily variation to estimate the magnitude of the bias. After adjustment for bias, the magnitude of the correlation between blood pressure and sodium excretion for the within-population data agreed with the estimates of the correlation for the among-population data in the first paper.

The authors noted that for a small effect, such as the change in blood pressure with sodium intake, very large sample sizes are required to produce statistically significant results because of the substantial random error in measuring sodium intake and the wide range of blood pressures associated with each level of sodium intake. The authors estimated that a study would need to include 400 hypertensive subjects and 400 normotensive subjects to have a 50 percent probability of detecting such a small effect. Doubling the sample size would increase the probability to 80 percent. The authors concluded that, when estimates of the correlation of sodium intake and blood pressure are based on 24-hour dietary intake data, the estimates of the true correlation are too low, and the relationship is stronger than previously reported.

The third analysis included data from 68 crossover trials and 10 randomized controlled trials (Ref. 107). The authors concluded that lower sodium intake was associated with reduced blood pressure in those with high and normal initial blood pressure levels. The authors estimated that, in people between 50 and 59 years of age, a 50 mmol per day (1,150 mg) reduction in sodium intake would lower SBP by an average of 5 mm

Hg in the total population and by 7 mm Hg in those with initially high blood pressures. They also estimated that these lower blood pressure levels for the entire population would result in a 26 percent reduction in stroke and a 15 percent reduction in heart disease in Western populations.

Sodium intake was associated with blood pressure. Studies of 4 weeks or less showed smaller differences than studies that lasted 5 weeks or longer.

Taken together, the three meta-analyses concluded that the correlation between sodium intake and blood pressure is stronger than previously estimated, and that the INTERSALT study, among others, underestimated the magnitude of the correlation. The meta-analyses supported the conclusion that modest sodium intake is related to lower blood pressure on a population basis and suggested a beneficial effect on an individual basis, the magnitude depending on the age and the existing blood pressure of the individual.

4. Summary

FDA reviewed the totality of available human studies published since the authoritative documents. One of the studies showed a decrease in blood pressure with increased sodium bicarbonate intake in 10 mildly hypertensive subjects (Ref. 79). For the other subjects in the study and for all subjects during the sodium chloride intake period, the results were inconclusive. The results of the 5-year study involving four simultaneous interventions, the results of the 5-year intervention in two Belgian towns, and the results of the 3-year dietary counseling intervention were also inconclusive (Refs. 42, 70, and 124). However, the large, multinational INTERSALT study (10,079 subjects) (Ref. 37), 11 other recent studies (Refs. 41, 44, 45, 55, 71, 76, 80, 109, 121, 122, and 123), and 5 meta-analyses (Refs. 94, 97, 100, 106, and 107) supported the relationship between sodium intake and blood pressure levels.

F. Summary and Conclusions

There was significant scientific consensus among the three Federal government documents (Refs. 33, 43, and 85), most of the position papers presented at the Federal government workshop (Ref. 103), and the other documents of recognized scientific bodies (Refs. 62, 63, and 108) that high dietary sodium intake, particularly as sodium chloride, is related to the prevalence of hypertension, and that diets that are low in sodium will be

associated with low occurrences of hypertension.

FDA updated the evidence in the documents described above by reviewing the totality of available human studies published since these documents. One study (Ref. 79) was negative in mildly hypertensive subjects, and four studies (Refs. 42, 70, 79, and 124) showed no effect or were inconclusive with respect to a relationship between sodium intake and blood pressure. The other studies (Refs. 37, 41, 44, 45, 55, 71, 76, 80, 94, 97, 100, 106, 107, 109, 121, 122, and 123) supported the conclusions reached in earlier government and authoritative reviews which recognized a link between sodium intake and hypertension. Based on its review, FDA tentatively concludes that the contradictory or inconclusive studies are insufficient to affect the consensus among the government documents and other reviews discussed above.

In summary, the effect of changes in dietary sodium on blood pressure is small but statistically significant. Changes in sodium intake are associated with changes in blood pressure across a wide range of normotensive and hypertensive blood pressures. Thus, reductions in sodium intake have broad applicability. The magnitude of the effect varies widely, with benefit for some but not for all individuals. This variability is typical of nutrient and chronic disease relationships. The responsiveness of some individuals is thought to be the result of a "salt sensitivity"; however, the difficulty in identifying these individuals makes it impractical to predict those individuals most likely to benefit by moderation or reduction in sodium intake. There is some indication that different sodium salts may produce different blood pressure responses, and thus, increasing emphasis is being placed on the potential importance of the chloride ion in combination with the sodium ion in producing blood pressure increases. Additional research is needed in this area. However, because most sodium in foods is in the form of sodium chloride, this issue has little practical impact on public health policies.

G. Tentative Decision To Authorize a Health Claim Relating Sodium and Hypertension

FDA reviewed the publicly available scientific data and authoritative documents on the association between dietary sodium intake and hypertension. On the basis of this review, the agency tentatively concludes that there is significant scientific agreement among experts who by training and experience

are qualified to evaluate such evidence to support health claims that high sodium intake is related to the prevalence of hypertension. The basis for this decision is threefold: (1) The strength and the scientific evidence relating high sodium intakes to the prevalence of hypertension; (2) the extent and significance of the likely public health benefit; and (3) the safety of expected dietary changes.

1. Scientific Evidence Is Sufficient to Support the Relationship

Proposed § 101.14(c) states that a health claim may be made if the Secretary determines, "based on the totality of publicly available scientific evidence (including evidence from well designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by the evidence." A companion document, published elsewhere in this issue of the **Federal Register**, considered this requirement and is proposing this standard for health claims for both conventional foods and dietary supplements.

In the case of sodium and hypertension, the "totality of publicly available scientific evidence" included three Federal government documents derived through consensus-building processes (Refs. 38, 43, and 85), a Federal government workshop (Ref. 103), three other documents prepared by recognized scientific bodies (Refs. 62, 63, and 108), one major international epidemiological investigation (Ref. 37), 17 clinical trials (Refs. 41, 42, 44, 45, 55, 70, 71, 76, 79, 80, 94, 97, 109, 121 through 124), and five meta-analyses (Refs. 94, 97, 100, 106, and 107).

In determining whether there was "significant scientific agreement," FDA first looked for consistency in the conclusions and recommendations of the relevant Federal government documents. The agency then considered the contribution of the Federal government workshop, other recent authoritative documents, and all pertinent human studies available since 1988. In considering the value of particular studies and assessing the quality of the research that produced the data, FDA took into consideration the relevance of study objectives for examining the relationship of sodium to hypertension, the experimental design of the study, the treatment of resultant data, and the statistical significance of the conclusions.

In reviewing the recent primary research, the agency looked for general agreement or disagreement with the conclusions and policy of the Federal government and other comprehensive, authoritative documents and evaluated whether inconsistencies in results from newer studies were sufficient to cause the agency to reverse or modify the conclusions reached in those earlier review documents.

Throughout its evaluation, FDA focused primarily on human studies because the public health issue is hypertension in humans, and especially in Americans. In addition, FDA concentrated on the relationship between the nutrient, sodium, and the disease, hypertension. FDA is aware that a wide range of variables, in addition to sodium intake, have been reported to affect hypertension. Among others, these include chloride, calcium, and magnesium ions; chemical forms of sodium other than sodium chloride; the ratio of serum sodium to serum potassium; alcohol consumption; and obesity. Given the severe time constraints and other specific requirements of the 1990 amendments, FDA limited its evaluation of the scientific data to, the relationship between "sodium" and "hypertension." The agency considered these other issues to be peripheral, and they were addressed only if they related directly to interpretation of the relationship between sodium and hypertension.

In general, the Federal government documents (Refs. 38, 43, and 85), the Federal government workshop (Ref. 103), and the other documents (Refs. 62, 63, and 108) were in agreement that sodium intake specified as sodium chloride in the FASEB document) is related to the prevalence of hypertension. While the effect of the average change in blood pressure in response to sodium restriction is "small" in magnitude, much larger benefit can be expected for persons at greater risk because of already elevated blood pressure levels or because of a predisposition or sensitivity to the adverse effects of salt. Many of the documents noted that there is some indication that, in addition to benefiting many hypertensive individuals, reduced sodium levels may reduce blood pressures and associated risks in some normotensive individuals as well.

In research published subsequent to the documents described above, a few of the human studies showed no effect. However, most of the studies supported the previous conclusions of a link between sodium and hypertension. Thus, the more recent studies were

generally consistent with the conclusions reached by earlier government and authoritative reviews.

FDA tentatively concludes that, having reviewed the relevant, publicly available, scientific evidence, there is significant scientific agreement among experts qualified by scientific training and experience to evaluate claims on a relationship between sodium and hypertension that such claims are supported by the evidence.

2. Public Health Impact

The prevalence of hypertension in the U.S. population is very high, with about one in three adults classified as hypertensive (Ref. 85). As many as 58 million people in the United States have elevated blood pressure (SBP equal to or greater than 140 mm Hg and/or DBP equal to or greater than 90 mm Hg) (Refs. 23 and 38), and only one-quarter to one-third of these individuals have their blood pressure under control (Ref. 74).

Uncontrolled high blood pressure is a serious public health problem because it is associated with mortality from heart disease and stroke, which were ranked as the first and third leading causes of death respectively in the United States in 1987 (Ref. 43). In 1988, 35.3 percent of all deaths were attributable to heart disease and 7.0 percent to stroke (Ref. 82). Individuals with uncontrolled high blood pressure have seven times the risk of developing a stroke and three to four times the risk of developing CHD as persons with normal blood pressure levels (Ref. 74).

Though mortality risk is greatest for hypertensives, normotensives are also at risk, and the higher the blood pressure, the greater the risk (Refs. 69 and 114). A recent, followup, surveillance study of the men screened for the Multiple Risk Factor Intervention Trial (Refs. 68 and 114) showed age-standardized death rate among middle-aged (35 to 57 years of age) U.S. men to be directly proportional to SBP across all blood pressure ranges. Not only did hypertension appear to be a risk factor for premature death, but below average blood pressure appeared to have a beneficial effect on survival. The death rate among hypertensive men (SBP greater than 160 mm Hg) was 41.7 deaths per 1,000; the death rate among those with high normal blood pressure (SBP from 135 to 139 mm Hg) was 20.5 deaths per 1,000; and the death rate among those with low normal blood pressure (SBP from 115 to 119 mm Hg) was 14.9 deaths per 1,000. Because there is a continuum of risk across all blood pressure levels, reducing blood pressure

has the potential to benefit the entire population.

In the adult U.S. population, the prevalence of hypertension varies with age, gender, and race (Refs. 27, 43, 57, and 62). High blood pressure and related risks increase sharply with age. Less than 1 percent of individuals under 18 years of age are hypertensive, whereas 23 percent of those from 45 to 64 years of age and 38 percent of those over 65 years of age are hypertensive (Ref. 81). Hypertension commonly occurs in males at a younger age than in females. However, as people age, the prevalence of hypertension increases more rapidly in women and eventually surpasses that of men (Ref. 57). The group with the highest prevalence of hypertension is non-Hispanic blacks, and both males and females are at risk (Refs. 27 and 57). In those over 65 years of age, 52 percent of blacks and 37 percent of whites are hypertensive (Ref. 81).

Changes over time in mean blood pressure and in the prevalence of hypertension have been estimated using data from three large national health surveys. These changes were estimated using an earlier definition of hypertension: SBP equal to or greater than 160 mm Hg and/or DBP equal to or greater than 95 mm Hg and/or currently taking antihypertensive medication (Ref. 27). Although the data from these surveys show that, between 1960 and 1980, the prevalence of hypertension among black adults decreased from 34 to 29 percent, this difference was not statistically significant. There was no decrease of hypertension among white adults during the 20-year period. Average SBP decreased by 5 and 10 mm Hg in white and black adults, respectively. The greatest improvement was among older adults. The data suggest a trend toward lower average blood pressure in the U.S. population that has been attributed to increased public awareness, diagnosis, and treatment. The prevalence of undiagnosed hypertension decreased from 52 to 29 percent, medical treatment of hypertension increased from 30 to 45 percent, and the proportion of individuals with hypertension whose condition was medically controlled increased from 39 to 52 percent.

Recognition of the continuum of mortality risk across all blood pressures prompted recent changes in the clinical definition of hypertension. The current definition identifies hypertension as SBP greater than 140 mm Hg or DBP greater than 90 mm Hg or currently taking antihypertensive medication. Based on this definition, DHHS, in its "Year 2000 Health Objectives for the Nation" (Ref.

74), established a goal for reducing uncontrolled high blood pressure such that at least 50 percent of people with high blood pressure would have their blood pressure under control, a 108 percent increase. Achievement of this goal is expected to have a major effect on reducing the number of deaths from CHD and stroke, two other Year 2000 objectives.

Blood pressure is regulated by a complex process involving multiple factors that are not well understood. Sodium intake, alcohol consumption, and obesity are considered the major dietary factors that influence the development of hypertension in genetically susceptible individuals (Refs. 38, 43, and 62). Nonpharmacological approaches to controlling hypertension have included sodium restriction, alcohol restriction, and weight control (Ref. 29). Thirty to 60 percent of hypertensives and 15 to 45 percent of normotensive individuals respond to sodium reduction and are considered "salt sensitive" (Ref. 116).

The most common source of dietary sodium in the U.S. food supply is sodium chloride or common table salt. The terms "salt" and "sodium" have frequently been used interchangeably although salt (sodium chloride) is only 39 percent sodium by weight. Additional food sources of sodium include sodium bicarbonate or baking soda, baking powder, monosodium glutamate, sodium nitrite, and sodium citrate. Additional sources of sodium include drinking water and sodium-containing drugs (Ref. 16).

In addition to providing sodium to meet nutrient needs of individuals, salt has important uses in foods. Salt is added to a wide variety of foods to enhance and improve flavor. In pickling brines and salted meats, salt helps retard spoilage by inhibiting bacterial growth. In food processing, sodium salts promote curd formation in cheeses, serve as leavening agents in chemically-leavened baked goods, control the growth of yeast in yeast-leavened baked goods, and help to solubilize muscle proteins in some processed meat products (Refs. 6, 7, 8, and 10). Some of the sodium used for these functions can be reduced without unduly affecting the final food product (Ref. 13).

Sodium intake is a small, but significant risk factor for high blood pressure. It has been estimated that reducing sodium intake by 100 mmol per day (2,300 mg) would correspond to an average reduction in SBP and DBP of 2.2 mm Hg and 0.1 mm Hg respectively, on a population basis (Ref. 37), resulting in a 4 percent reduction in CHD mortality

and a 6 percent reduction in stroke mortality each year (Refs. 69 and 114). Assuming a cumulative effect over time, it has been estimated that reducing sodium intake by 160 mmol per day (2,360 mg), from the age of 25 to 55, would correspond to a 16 percent reduction in CHD mortality and a 23 percent reduction in stroke mortality (Refs. 69 and 114). Other estimates suggest that a 50 mmol per day (1,150 mg) reduction in sodium intake, from the age of 50 to 59, would result in a 15 percent reduction in heart disease and a 26 percent reduction in stroke (Ref. 107).

Based on the weight of the evidence that high dietary sodium intake increases the prevalence of high blood pressure, several authoritative groups have recently recommended that Americans reduce or moderate their sodium intake: "Nutrition and Your Health—Dietary Guidelines for Americans" (Ref. 85), "The Surgeon General's Report on Nutrition and Health" (Ref. 43), and "Diet and Health—Implications for Reducing Chronic Disease Risk" (Ref. 62). "Diet and Health—Implications for Reducing Chronic Disease Risk" recommended limiting daily salt intake to 6 g or less (2,400 mg sodium). This recommendation serves as the basis for the proposed DRV for sodium in the proposal on mandatory nutrition labeling published elsewhere in this issue of the Federal Register. Current consumption is estimated at between 3,000 and 6,000 mg sodium per day (Refs. 18, 34, 35, and 43), approximately 25 to 150 percent above the maximum level recommended.

It has been estimated that 90 percent of the sodium in foods is from added salt (75 percent added during processing and manufacturing and 15 percent added during preparation and consumption). Therefore, only 10 percent of dietary sodium is attributable to the natural salt and sodium content of foods (Refs. 34 and 35). Because approximately 90 percent of the sodium in foods is added, reduction in sodium consumption is an achievable goal.

FDA has long recognized that sodium is a risk factor contributing to high blood pressure, and the agency first outlined its position concerning sodium and hypertension in 1982 to 1984 in the proposed sodium claim and labeling regulation (47 FR 26586) and in the discussion on the GRAS status of salt (47 FR 26596). FDA concluded that sodium consumption should be reduced in the general population because sodium intake was in excess of biological requirements, that moderate sodium intake would have no adverse effects, and that a large portion of the

population would benefit. The agency emphasized that the policy was intended for the general public so that consumers could make informed decisions about their diets.

FDA has monitored sodium labeling since the first Food Label and Package Survey (FLAPS) in 1976 to 1978 (Ref. 25), and sodium education initiatives were included as part of The National High Blood Pressure Education Program, begun in 1981 by FDA and NHLBI (Ref. 47). The labeling and education initiatives resulted in more sodium content labeling on foods (an increase of nearly 60 percent between 1978 and 1988) (Ref. 46), the introduction of more products with lower sodium levels by manufacturers (Ref. 56), greater public awareness of the relationship between sodium and hypertension (up from 12 to 34 percent between 1979 and 1982) (Refs. 47 and 56), an increase in the number of consumers who have seen sodium reduced products and in the number who have purchased such products (Ref. 56), lower sales of table salt (down by 13 percent) (Ref. 47), and an increase in sodium avoidance dieting (practiced by approximately 40 percent of survey population) (Ref. 78).

In conjunction with sodium content in the nutrition label and the use of sodium content claims, the sodium/hypertension health claims, described in this proposal, will provide additional assistance to consumers in implementing the dietary guidelines and in understanding the nature of the relationship between sodium and hypertension. These regulations will be supplemented by extensive, educational initiatives. Such efforts have proven effective in the past in encouraging responsive actions by manufacturers (Refs. 46 and 56), in increasing consumer awareness (Refs. 47 and 56), and in affecting consumer purchasing habits and behaviors (Refs. 56 and 78).

In summary, because high sodium intake is related to the prevalence of high blood pressure, and because high blood pressure is related to increased risk of heart disease and stroke, reduction and moderation in sodium intake have the potential for having a significant impact on the health of the general U.S. population. Although average changes in salt and sodium intake are associated with changes in average blood pressure that are small in magnitude, the overall potential effect on health care costs and morbidity and mortality rates is quite significant. Persons who are sensitive to sodium would be expected to benefit significantly, and at the recommended levels, there is no apparent risk for those

who are not sensitive to sodium. Reductions in sodium intake are feasible within current dietary patterns, both through potential changes in food formulations and through the potential for altered consumer awareness and behavior in food selection and in decreased use of discretionary salt.

3. Safety

Minimum average adult requirements for sodium, under conditions of maximum adaptation and without active sweating, have been estimated to be 115 mg per day (Ref. 63). A safe minimum intake has been estimated to be 500 mg per day (Ref. 63), more than three times the minimum requirements. This estimate takes into account wide variations in patterns of physical activity and climatic exposure but does not include an allowance for large amounts of sodium loss from sweating. Current sodium intakes in the U.S. population are thought to be 5 to 10 times higher, well in excess of physiological needs (Refs. 18, 34, 35, and 43).

The DRV proposed for sodium (2,400 mg per day) represents a 20 to 60 percent reduction below current estimates of sodium intake (3,000 to 6,000 mg per day) (Refs. 18, 34, 35, and 43). The DRV is well in excess of the safe minimum intake, and NAS has noted that there is no known advantage in consuming large amounts of sodium (Ref. 63). Reductions in sodium intake, in response to Dietary Guidelines to use salt and sodium in moderation (Ref. 85), to the proposed DRV for sodium, or to sodium/hypertension health claims in this proposed rule, are unlikely to pose a safety risk given the large gap between current intakes (3,000 mg to 6,000 mg sodium per day) and minimum safe levels (500 mg sodium per day) and the wide margin between the proposed goal (2,400 mg sodium per day) and the minimum safe intake levels (500 mg sodium per day).

Sodium is naturally present in many foods, albeit frequently in small amounts. A diet that includes a variety of foods is likely to remain above the minimum safe intake level even without additional salt or sodium being added. Moderate sodium intake, below current consumption levels, is a reasonable public health objective for the general population. This policy would benefit a large segment of the population and would maintain adequate sodium intake for biological functions.

Recommendations to reduce sodium intake are likely to result in reduced chloride intake because sodium chloride, or "salt," is the most common

form of dietary sodium. Reduced chloride intake is not likely to pose a safety concern because dietary chloride deficiencies do not occur under normal circumstances, and the safe minimum intake of chloride was formulated jointly with sodium and salt minimum intakes (Ref. 63).

Of some concern is the loss of sodium as salt during periods of heavy sweating from high temperatures or vigorous physical activity (Ref. 30). Sodium losses can be significant under such conditions and tend to be more severe in individuals who are not acclimated to the temperature or conditioned to the level of activity (Refs. 20 and 30).

Illness can result from heat exhaustion, primarily as a result of salt depletion, and if accompanied by unreplaced fluid losses, can lead to potentially fatal heatstroke (Ref. 30). The concerns over excessive sweat losses led to recent experiments investigating the impact of dietary sodium on the adaptation of soldiers to high temperatures and vigorous exercise (Refs. 117, 118, and 119). Subjects consumed either 4 g salt (1,600 mg sodium) or 8 g salt (3,200 mg sodium) per day, and fluid losses were replaced frequently. Heat acclimation was safely achieved by all subjects, though subjects on the lower salt diet reported more symptoms of heat illness during the first few days, and Johnson (Ref. 118) recommended that higher sodium intakes may be beneficial during the first few days of heat acclimation.

Reports of heat exhaustion tend to involve isolated situations with excessive temperatures or extreme activity levels (Ref. 30). When making health policy recommendations, FDA must balance concerns about hypertension, which affects one third of the U.S. population, against safety concerns under conditions of extreme sweat losses. Heat acclimation was safely achieved on the controlled, low salt diet (1,600 mg sodium per day), and FDA is recommending a DRV for sodium (2,400 mg per day) that is well in excess of 1,600 mg per day. FDA's policy to encourage moderation in sodium intake provides for a wide safety margin. It is the agency's position that concerns about excessive sweat losses should be part of educational efforts aimed at groups that experience heavy physical exertion and especially at those who work with people under conditions of high temperature or vigorous exercise, such as military personnel, sports coaches, and officials involved in exercise programs in hot regions of the nation.

A few studies suggest that some individuals may respond to sodium

reduction with blood pressure increases instead of decreases (Refs. 33 and 72). As with many physiological measurements, a heterogeneous distribution may be the result of random variation, especially because the magnitude of the blood pressure lowering effect is small. Additional studies are needed under controlled conditions to determine whether these results are significant and reproducible.

There are a few studies in which plasma lipids were associated with increased sodium restriction (Refs. 40, 49, and 89) and another study that was inconclusive (Ref. 2). The intervention periods in these studies were very short (1 week or less), and the sodium restriction was extreme (460 mg and 780 mg as compared with the 2,400 mg DRV recommended by FDA). FDA believes that these studies are so few in number, so short in duration and conducted under such extremely restricted conditions that they have no bearing on public health recommendations for the general public.

Between 1982 and 1984, FDA concluded that moderate sodium intake would not have any adverse effects on the general public (47 FR 26580). After reviewing the scientific evidence related to sodium and hypertension and the safety issues relevant to moderate dietary sodium, FDA reaffirms that moderate sodium intake is unlikely to pose a safety concern in the U.S. population. Recommendations to moderate sodium intake have been part of public health policy guidelines for more than 10 years (Refs. 9, 22, and 85) with no adverse effects. There is significant agreement among the authoritative documents that moderate sodium intake would not be harmful (Refs. 38, 43, and 62), and serious problems have not been observed in populations that traditionally consume low amounts of salt (Ref. 69). In addition, the review of the scientific evidence indicates that high sodium intakes pose a significant health risk to a large number of people (Refs. 43 and 62).

FDA welcomes any additional information or data on the safety of sodium and salt intake and will continue to monitor the safety implications of all public policy recommendations.

III. Provisional Requirements for Health Claims

A. Relationship

FDA is proposing in § 101.74 to authorize health claims on the relationship of dietary sodium and hypertension on food labels and labeling. The agency has identified

several key points that it considers essential for helping consumers to understand this relationship. These points are made in § 101.74(a).

The definition of hypertension used in § 101.74(a) is taken from U.S. DHHS/PHS/NIH reports (Refs. 23 and 38). It defines hypertension as SBP of more than 140 mm HG or DBP of more than 90 mm HG. The regulation also distinguishes sodium from salt.

Proposed § 101.74(a) describes the relationship between sodium and hypertension. Based on its review of the available scientific evidence, FDA states that high sodium intake is related to the prevalence of hypertension and to the increase of blood pressure with age. The agency also states that low sodium intake is related to low prevalence of hypertension and to a low rise or no increase of blood pressure with age.

A substantial amount of human and animal data indicate that high potassium intake may be related to reduced blood pressure levels (Refs. 38, 43, and 62). In addition, high sodium-potassium ratios have been positively correlated with blood pressure levels (Refs. 43 and 62), and NAS (Ref. 62) noted that low sodium intake in combination with high potassium intake "is associated with the lowest blood pressure levels and the lowest frequency of stroke in individuals and populations." FDA considered including potassium intake information in sodium/hypertension health claims. However, because of time and resource constraints, the lack of evidence for a quantitative ratio, and safety concerns involving potassium supplementation and fortification (21 CFR 201.306), FDA at this time has limited the relationship statement to sodium and hypertension. This is the topic that FDA was directed to address in section 3(b)(1)(A)(vi) of the 1990 amendments.

B. Significance

In summarizing the significance of reductions and moderation in sodium intake relative to the reduction in the prevalence of hypertension in the general U.S. population and within the total dietary context, FDA has identified in proposed § 101.74(b) several key points that it considers essential for helping consumers in understanding this nutrient and disease relationship.

This section states that hypertension is a public health concern because it is a risk factor for CHD and stroke. This statement is based on the Surgeon General's Report (Ref. 43) and the NAS Report (Ref. 62). The recognition that there is a continuum of risk across the range of blood pressures, which is reflected in this provision, was

documented in the followup surveillance study of the men screened for the Multiple Risk Factor Intervention Trial (Refs. 68 and 114). The agency has included a statement from Dietary Guidelines on the prevalence of high blood pressure in the United States in this section to provide some indication of the magnitude of the problem and the number of Americans currently affected (Ref. 85).

Based on FDA's evaluation of the scientific evidence, proposed § 101.74(b) goes on to state that reduced sodium intake may benefit some but not all hypertensives and possibly some but not all normotensives. The range of percentages in § 101.74(b) of responsive hypertensive and normotensive individuals that respond to sodium reduction was taken from the Sullivan review (Ref. 116). The regulation recognizes, however, based on the Surgeon General's report (Ref. 43), the NAS report (Ref. 62), and "Dietary Guidelines" (Ref. 85) that there are no practical biological markers for identifying responsive individuals.

The regulation goes on to list the populations most at risk for hypertension and most likely to benefit from sodium reduction. These populations were identified in the Surgeon General's report (Ref. 43), the NAS report (Ref. 62), and the National Health and Nutrition Examination Survey (Ref. 27). It then lists the risk factors for hypertension other than sodium intake. These factors are mentioned in the Surgeon General's report (Ref. 43) and the NAS report (Ref. 62). The statement that the magnitude of the effect is "small" but statistically significant is based on FDA's evaluation of the scientific evidence, which is summarized in section II. of this document. Proposed § 101.74(b) goes on to cite the estimated magnitude of the change in blood pressure in response to a change in dietary sodium intake. The agency took this information from the conclusions of the INTERSALT study (Ref. 37). The estimated reductions in mortality cited in proposed § 101.74(b) were taken from the Stamler's analysis of the impact that the change in blood pressure would have on a population-wide basis (Refs. 69 and 114). This section concludes with recommendations for ways to reduce sodium intake, which were taken from "Dietary Guidelines" (Ref. 85), the Surgeon General's report (Ref. 43), and the NAS report (Ref. 62).

In discussing the magnitude of the effect of a change in sodium intake, the agency uses the words "estimate" and "approximate" to indicate that the

values cited are based on the best information available and are close to but not identical to the actual and true values. FDA would consider changing these estimates only if newer estimates that were based on better data and that were significantly different from these values were presented to it.

C. General Requirements

In § 101.74(c)(1), FDA is requiring that for a food to bear a health claim on the topic of sodium and hypertension, it must meet the general requirements for health claims set forth in proposed § 101.14, published elsewhere in this issue of the *Federal Register*. Under this regulation, a sodium/hypertension health claim is prohibited if any of the specified disqualifying nutrient levels are exceeded. This requirement assures that sodium/hypertension health claims may not appear on foods and food products that contain 11.5 g or more of fat per reference amount commonly consumed, per label serving size, or per 100 g, 4 g or more of saturated fat per reference amount commonly consumed, per label serving size, or per 100 g, and 45 mg or more of cholesterol per reference amount commonly consumed, per label serving size, or per 100 g. There are also disqualifying criteria for sodium: 360 mg or more of sodium per reference amount commonly consumed, per label serving size, or per 100 g. However, to qualify to make a sodium/hypertension health claim under proposed § 101.74(c)(2), it must contain 140 mg or less of sodium per serving and per 100 g. A more thorough discussion of the criteria for identifying risk nutrients and the levels of these nutrients allowed in foods that bear health claims is included in the document on general requirements for health claims, published elsewhere in this issue of the *Federal Register*.

The requirement that a food must meet the "low sodium" definition to bear a sodium/hypertension health claim assures that such claims will appear only on foods and food products that contain 140 mg or less of sodium per serving and per 100 g. A more thorough discussion of the "low sodium" criteria and the rationale for the established sodium content levels is presented in the adjectival descriptor document published elsewhere in this issue of the *Federal Register*. Should additional considerations or evidence prompt the establishment of a different definition for "low sodium," only the descriptor document will require revision.

FDA used the qualifying criteria and the disqualifying criteria, described above, to identify foods that would likely be allowed to bear sodium/

hypertension health claims (Ref. 93). Examples of foods qualifying for sodium/hypertension health claims include tuna and salmon without added salt; most fruits and vegetables, except for canned and frozen vegetables processed with salt; lowfat milk (2 percent or less fat), evaporated milk, lowfat yogurt with fruit, cottage cheese, ice milk, sherbet, and nondairy dessert toppings and cream substitutes; most flours, meals, grains, and pastas (except for egg pastas); and breakfast cereals such as shredded wheat, low sodium corn flakes, frosted shredded (mini-sized) wheat, puffed rice, sugar crisp, wheat germ, and many prepared cereals such as cream of wheat, cream of rice, and grits. In addition to these types of foods, several other food types would qualify for sodium/hypertension health claims including beverages such as carbonated soft drinks, coffee, tea, some fruit juices, drinks, and punches; some candies, cookies, baked goods, and icings; jams, jellies, and other sweeteners; and margarines and salad dressings without added salt. Given the minimal nutrition value of many of these foods, FDA requests comments as to whether they should be allowed to bear a health claim.

D. Relationship Statement

In the companion document on general principles for health claims published elsewhere in this issue of the *Federal Register*, FDA is proposing to require that claims present an accurate representation of the nutrient/disease relationship. Consequently, based on the scientific evidence regarding the relationship between sodium and hypertension, in § 101.74(c)(2), FDA is proposing that sodium/hypertension health claims must state that a low sodium diet is associated with lower blood pressure in some people, or that a high sodium diet is associated with higher blood pressure in some people. Because sodium reduction helps lower blood pressure in some but not all individuals, FDA is proposing that health claims acknowledge this fact. It is the agency's position that, without such an acknowledgement, the health claim would be misleading to those people whose blood pressures do not respond to sodium reduction.

E. Populations at Greatest Risk and Dietary Risk Factors

In § 101.74(c)(3), FDA is proposing to require that health claims acknowledge that many factors are associated with the development of high blood pressure. Thus, under this proposal, claims will be required to identify high risk populations

and dietary risk factors associated with hypertension. Those most at risk of developing hypertension, and consequently most likely to benefit from sodium restriction, include the elderly and those with family histories of high blood pressure, which may encompass individuals in specific racial or gender groups (Refs. 27, 43, 57, and 62). In addition to dietary sodium intake, alcohol consumption and obesity are identified, modifiable, dietary risk factors for hypertension (Refs. 43 and 62). Consequently, achieving weight control and reducing alcohol consumption have been recommended to assist in lowering blood pressure levels in the general population (Ref. 85). This additional information on populations and risk factors provides a broader context for the nutrient/disease relationship. Presentation of this information will ensure that consumers are aware that, in addition to sodium intake, there are many other factors that contribute to the development and control of hypertension.

IV. Optional Health Claim Information

A. Sodium as an Essential Nutrient

Sodium is an essential nutrient, and it is important that consumers include sodium in their total diets. On the other hand, NAS has recommended a safe, minimum level of 500 mg sodium per day (Ref. 63) and an upper limit of 2,400 mg sodium per day (Ref. 63). Elsewhere, in this issue of the Federal Register, FDA is proposing to establish a DRV for sodium of 2,400 mg per day for use in nutrition labeling. Yet, while some sodium is required for good health, excessive intake of sodium is unnecessary and may be harmful. For consumers to understand the significance of the sodium contained in a food that is qualified to bear a sodium/hypertension health claim in relation to the total daily intake goal, FDA considered requiring that sodium/hypertension health claims state that adults should consume at least 500 mg but not more than 2,400 mg sodium per day. However, in an attempt to keep health claims short and not overwhelm consumers with information, FDA is tentatively proposing in § 101.74(d) (1) to allow, but not to require, quantitative limits for sodium intake. The agency requests comments on whether this additional information will be beneficial to consumers, and whether it should be required on health claims or remain optional.

B. Consultation of Physicians

Many people are now aware of the dangers of high blood pressure (Ref. 56). With the ready availability of "do it

yourself" machines to measure blood pressure levels in grocery stores and shopping malls and the common practice of having blood pressure levels checked each time an individual visits a physician or health professional, many people now know what their blood pressure levels are. FDA is concerned that some individuals may attempt to use the ready-availability of sodium labeling, and in particular sodium/hypertension health claims, to self-medicate or treat their hypertension without consulting a physician. For this reason, the agency considered requiring that health claims state that individuals with high blood pressure should consult their physician for specific medical advice and guidance.

Health claims that result from this regulation are intended for the general healthy public, however. Hypertension is a serious medical condition. It is FDA's view that any individual with an identified medical problem should be under the care of a physician, and that health claims are not intended as a substitute for individual patient/doctor care and especially not for individuals with identified medical diseases or health-related conditions. The agency has tentatively decided to include this information as an optional element, § 101.74(d) (2), and requests comments.

C. Sodium and Salt

FDA is proposing in § 101.74(d) (3), to allow manufacturers to use the term "salt" in addition to the term "sodium," both of which have been incorporated into "Dietary Guidelines" to use salt and sodium in moderation. Salt, which is 39 percent sodium by weight, is the most common source of dietary sodium and is a more familiar term to the general public than sodium. A recent FDA survey found that approximately 70 percent of the survey population generally understood that sodium and salt are related (Ref. 1982). Respondents frequently used "sodium" and "salt" interchangeably, which is technically incorrect but functionally effective because reducing salt intake also reduces sodium intake. The available evidence suggests, however, that sodium is the nutrient most clearly implicated in hypertension. Furthermore, in the proposed nutrition labeling document published elsewhere in this issue of the Federal Register, FDA is proposing to use the term "sodium" in the nutrition label to inform consumers of the sodium content of a food. Therefore, allowing use of the term "salt" in a sodium/hypertension health claim, rather than the term "sodium," would be potentially confusing to consumers because it would be inconsistent both with the

nutrition label and with the strongest scientific evidence for linking dietary factors to hypertension. Conversely, using the term "salt" in addition to the term "sodium" would seem less likely to be misleading and may actually be useful to those consumers who are unfamiliar with the more technical term but who wish to reduce their sodium intake. Therefore, the agency is proposing to allow the use of the term "salt" if the term "sodium" is also used.

The agency is aware that a few recent studies and reviews suggest that the chloride ion, rather than or in addition to the sodium ion, may be important in the development of high blood pressure (Refs. 31, 48, 79, 87, and 92). Early studies with sodium chloride attributed blood pressure increases to the chloride ion; however, in the 1950's the sodium ion was considered to be more important (Refs. 14 and 43). Because many of the studies that investigated the relationship between sodium and hypertension used sodium chloride as the source of dietary sodium, these studies do not distinguish the effects of sodium from the effects of sodium chloride.

In the early and mid-1930's, studies with various sodium salts found that while sodium chloride raised blood pressure levels in sensitive individuals and animals, other sodium salts had no effect (Refs. 31 and 43). The recent studies (Refs. 79 and 87) are inconclusive with respect to chloride or indicate that the sodium and chloride ions have different roles. Recent reviews (Refs. 48 and 92) suggest that sodium and chloride together produce larger blood pressure changes, and that the ion that is associated with the sodium may greatly influence the subsequent blood pressure response. To date, the studies involving humans have been few in number and small in size. Consequently, at this time, there is insufficient information available for drawing substantive conclusions or for changing public health policy recommendations. Nonetheless, these results raise important questions, and FDA encourages additional research to determine the independent and combined effect of sodium and of chloride on blood pressure.

Sodium chloride is the major source of dietary sodium. Because FDA's policy of encouraging sodium reduction will also result in chloride reduction, the policy remains prudent regardless of whether sodium, chloride, or sodium chloride is determined to be important in relationship to hypertension. In addition, compliance is simplified because sodium content is identified on the labeling and

verification would involve detection of sodium alone. The agency requests data and comments on the appropriateness of selecting sodium rather than sodium chloride as the specified nutrient and on the appropriateness of allowing the term "salt" in addition to the term "sodium" on sodium/hypertension health claims.

D. High Blood Pressure and Hypertension

In § 101.74(d)(4), FDA is proposing to allow manufacturers to use the term "hypertension" in addition to the term "high blood pressure." Hypertension is a broader term which encompasses persons with untreated high blood pressure levels as well as persons with "normal" levels as a result of effective treatment. Hypertension is also the disease specified in section 3(b)(1)(A)(vi) of the 1990 amendments. The term "high blood pressure" means nearly the same thing as hypertension and individuals with controlled high blood pressure are frequently considered to have high blood pressure even though, technically, the blood pressure levels are in the normal range. The term "high blood pressure" is less technical and more familiar to consumers since blood pressure measurement is included in routine physical examinations, and blood pressure response is used to monitor the treatment of hypertension. Because simple, uncomplicated terminology is useful for assuring that health claims are clear and understandable to consumers, FDA is proposing to require the use of the term "high blood pressure" and to allow for the optional addition of the term "hypertension." The agency requests comments on the appropriateness of this proposed usage.

E. Additional Information

In § 101.74(d)(5), FDA is proposing to allow manufacturers to develop sodium/hypertension health claims that provide factual information about hypertension, including information contained in the "Relationship" and "Significance" statements included as part of the regulation and estimates of the number of people in the United States who are affected with high blood pressure or hypertension. It is FDA's policy that one of the purposes of health claims is to inform and educate the general public. Consequently, manufacturers should be allowed to include accurate, factual information in their health claims about the prevalence and seriousness of hypertension for the U.S. population. FDA is proposing to limit the additional information allowed to that contained in these statements because they are based on FDA's review of the scientific

evidence concerning sodium and hypertension. By using an approximate estimate of prevalence, such as "one in three" adults, updating this estimate is likely to be less of a problem than if a more precise estimate were used.

F. Model Health Claim

FDA is including in proposed § 101.74(c) a model health claim on sodium and hypertension. The agency is including this model to assist manufacturers in formulating an appropriate claim.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a) (11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Effective Date

FDA is proposing to make these regulations effective 6 months after the publication of a final rule based on this proposal.

VII. Comments

Interested persons may, on or before February 25, 1992, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

VIII. Economic Impact

The food labeling reform initiative, taken as a whole, will have associated costs in excess of the \$100 million threshold that defines a major rule. Therefore, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA has developed one comprehensive regulatory impact analysis (RIA) that presents the costs and benefits of all of the food labeling provisions taken together. The RIA is published elsewhere in this issue of the *Federal Register*. The agency requests comments on the RIA.

Appendix to the Preamble—Consumer Health Message Summary—Sodium and High Blood Pressure

The following Appendix is a proposed consumer summary on sodium and hypertension. FDA solicits comments on

this document as explained in the proposal on the general requirements for health claims published elsewhere in this issue of the *Federal Register*.

Appendix—Consumer Summary on Sodium and High Blood Pressure

Sodium and High Blood Pressure

Under the provisions of the recent Nutrition Labeling and Education Act of 1990, manufacturers may put clear information on the food label about the relationship between a nutrient, such as sodium, and a disease or health-related condition, such as hypertension. To prevent consumers from being misled, FDA allows only truthful label statements about diet and health relationships that are firmly supported by the current scientific evidence. There is agreement that the scientific evidence is strong enough to allow health claims about the relationship between sodium in the diet and hypertension.

Many consumers have said that health claims on food labels could be useful to them in making improvements in their diets. However, label space is often limited. Therefore, the label statement may refer to an attached pamphlet, or other adjacent labeling that provides additional information about the health claims that appear on the label of the food product itself.

In addition to allowing health claims about the relationship between sodium and hypertension, FDA is allowing health claims about the relationship between calcium and osteoporosis, saturated fat and cholesterol and cardiovascular disease, and fat and cancer. For information about these other diet and health relationships, write to: (to be supplied by manufacturer).

What is Hypertension?

Hypertension means high blood pressure, a condition in which your blood pressure goes up and stays above a normal level. Blood pressure measures the force of blood against the artery walls as the heart pumps blood through the body.

When you get your blood pressure checked, you are given two numbers. The first number (systolic pressure) is the force of blood against the artery walls when the heart beats. The second number (diastolic pressure) is the force on the artery walls when the heart relaxes between beats. Currently, people with systolic blood pressure of 140 or more millimeters of mercury (mm Hg) and/or diastolic blood pressure of 90 or more mm Hg are considered to have high blood pressure.

Why is There Concern About Hypertension?

In the United States, about one in three adults has high blood pressure. The disease affects approximately 58 million people and is a public health concern primarily because it is a major risk factor for death from coronary heart disease and stroke. Risk of death increases steadily as blood pressure increases. People with high blood pressure levels are at greatest risk, and the lower the blood pressure the lower the risk.

Hypertension occurs more frequently among persons with a family history of high blood pressure, elderly men and women of all races, black men and women, and men at an earlier age than women. In the U.S., hypertension and its related risks increase with age. Less than 1 percent of people below age 18, about 23 percent of people between ages 45 through 64, and about 38 percent of people over 65 have hypertension.

Primarily because of increased public awareness and treatment of the disease, hypertension has decreased somewhat in the U.S. population in recent years; nevertheless it remains a serious public health concern.

What Is the Cause of Hypertension?

In most people with high blood pressure the cause is unknown. Regulation of blood pressure by the body is a complex process that is not completely understood. Probably a variety of factors influence the development of hypertension in people whose heredity makes them susceptible to the disease.

Currently, scientists generally agree that three major diet-related factors have an effect on blood pressure—obesity or being overweight, excessive sodium in the diet, and excessive alcohol consumption.

The terms "salt" and "sodium" often are used interchangeably, although salt (which is sodium chloride) is only part sodium. Salt is our most common source of dietary sodium.

Studies of populations around the world provide the primary basis for associating dietary sodium with hypertension. In populations that have diets low in sodium, high blood pressure is less common than in populations with diets high in sodium. Scientists believe that dietary sodium is related to hypertension, and that diets which are lower in sodium will be associated with lower frequency of hypertension.

These studies also indicate, that in populations with diets low in sodium, blood pressure increases less rapidly or does not increase at all with age. This

contrasts sharply with the blood pressure increases with age that are seen in the U.S. Less salt in the diet may be particularly appropriate for people who are at increased risk for developing hypertension in later life, such as blacks and those with either a family history of high blood pressure or current high normal blood pressure levels. The blood pressure of some—but not all—people will be lowered by decreasing dietary sodium. Persons whose blood pressure is decreased by lowering sodium are considered "salt sensitive." There is no practical way to identify the "salt-sensitive" people in the population, to predict who might develop high blood pressure, or to determine who will benefit from reducing dietary sodium. Authorities currently recommend that most people use salt and sodium only in moderation. Reduction in sodium will benefit those people whose blood pressure rises with high salt intake. No harmful effect is known to occur from moderately reducing dietary sodium.

Do Most People Eat Too Much Salt and Sodium?

Sodium is an essential nutrient that is required by the body. The National Academy of Sciences has set a minimum safe amount for adults of 500 milligrams (mg) per day under normal temperature and activity conditions. People who lose a lot of sodium and water through sweat need to drink extra water and in rare cases replace the lost salt. The Academy has stated that there is no known advantage in consuming large amounts of sodium in excess of body needs. Most Americans consume several times the minimum amount of sodium needed.

The U.S. Public Health Service has set a national health goal for the public to use salt and sodium in moderation. To do this, people are encouraged to prepare foods without adding salt, to avoid salt at the table, and to make a habit of purchasing foods that are low in sodium or modified to lower sodium content.

Which Foods Are Sources of Sodium?

Sodium in the diet comes from many sources. Small amounts of sodium are found naturally in many foods, so if you eat a variety of foods, you'll easily get the minimum safe amount.

However, your salt intake can increase dramatically depending on the choices you make. Salt is added for flavoring and preserving during processing of many foods, but products are often available in a "low sodium" version as well. Salt may also be added during cooking at home, or by yourself at the table. In addition to table salt, many substances added to foods, such

as baking soda, baking powder, sodium nitrite, and monosodium glutamate (MSG), contain sodium.

A good way to learn about the amount of sodium in foods is to read nutrition labels. Most foods now have nutrition information on their labels. The amount of sodium in a serving of food is listed in milligrams. FDA has established "Daily Values" for several nutrients, including sodium, that are important in diet and health relationships. The daily value is intended to help consumers determine how a single serving of a food contributes to the total amount of nutrient for the day. The daily value for sodium is 2,400 mg, based on a report from the National Academy of Science. Therefore, a food that contains 600 mg sodium per serving would provide about one-quarter of the daily recommended value for sodium. When you add up the sodium from all the foods you eat in a day, it should total less than 2,400 mg.

What Do Label Claims About Sodium Mean?

In addition to the amount of sodium per serving on the nutrition label, you may see other kinds of claims about sodium on some food packages. There are two kinds of label claims—nutrient content claims and health claims.

Nutrient content claims may be made about the amount of sodium the food contains. For example, a food that contains 35 mg sodium or less per serving may be labeled "very low sodium." Foods that contain 5 mg or less of sodium per serving may be labeled "sodium free" or "no sodium," and foods that contain 140 mg sodium or less per serving may be labeled "low sodium." A reduced sodium claim on a food label indicates that the sodium content has been reduced by 50 percent or more compared to the regular product.

Some foods that are low in sodium may contain one or more nutrients that may increase the risk of a diet-related disease other than high blood pressure. For example, a low sodium food could be high in saturated fat which has a relationship to elevated blood cholesterol and heart disease. A content claim about sodium cannot be made on such foods without indicating the presence of the other nutrient, for example, "Low sodium; see nutrition label for saturated fat content."

Health claims are those made about the relationship between the nutrient, sodium, and the disease, hypertension. Health claims of this type may appear only on foods that qualify as "low sodium." In addition, the food must not contain any other nutrient that FDA has determined increases the risk of a diet-

related disease or health condition other than hypertension. For example, a health claim could not appear on a "low sodium" food that contains a high amount of saturated fat, because saturated fat has a relationship to heart disease.

Many foods are eligible to make sodium and hypertension claims. For example, at least some products in each of the following categories of foods can make such claims: Fruits and vegetables; fruit juices and drinks; milk and dairy products; breakfast cereals; cereal grains (such as rice); pasta products (such as spaghetti); flours; legumes (peas and beans); nuts and seeds; and seafood.

Other Diet-Related Risk Factors for Hypertension

In addition to sodium, there are at least two other diet-related factors for hypertension over which a person has control—body weight and alcohol consumption. Increased body weight is related to increased blood pressure, and blood pressure falls when weight is reduced. Weight loss is recommended for all overweight persons, particularly those with hypertension. People who regularly consume large amounts of alcohol have higher blood pressure than people who don't drink or who drink only in moderation. Authorities recommend maintaining a healthy weight and drinking alcoholic beverages in moderation, if at all.

Facts to Keep in Mind

It's the total combination of foods that you eat regularly—both the kinds and the amounts—that's important in terms of good nutrition. Eating particular foods or one specific food isn't a magic key that will assure you have a more healthy diet.

Eating a healthy diet, in itself, doesn't guarantee good health. A healthy diet, however, is an important part of a healthy lifestyle that includes, for example, regular physical exercise, not smoking, not drinking alcoholic beverages to excess, and not abusing drugs.

In addition to what you eat, many factors may affect your own chance of developing a particular disease. Among these are your heredity, your environment, and the health care you receive. Our knowledge about most diet-health relationships is incomplete and will improve as scientific knowledge increases. However, enough is known today about some of these relationships to encourage specific dietary practices that are believed to be beneficial.

IX. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Ambard, L., and E. Beaujard, "Causes de L'hypertension Arterielle," *Archives Generales de Medecine*, 1:520-533 (1904).

2. Kirkendall, W.M., W.E. Conner, F. Abboud, S.P. Rastogi, T.A. Anderson, and M. Fry, "The Effect of Dietary Sodium Chloride on Blood Pressure, Body Fluids, Electrolytes, Renal Function, and Serum Lipids of Normotensive Man," *Journal of Laboratory and Clinical Medicine*, 87:418-434, 1976.

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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under the authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR Part 101 is revised to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355, 371).

2. Section 101.74 is added to subpart F to read as follows:

§ 101.74 Health claims: sodium and high blood pressure.

(a) *Relationship between sodium and high blood pressure.*

As used here, hypertension, or high blood pressure, means systolic blood pressure of greater than 140 millimeters of mercury (mm Hg) or diastolic blood pressure of greater than 90 mm Hg. Normotension, or normal blood pressure, is a systolic blood pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg. Sodium is specified here as the chemical entity or mineral "sodium" and is distinguished from sodium chloride or salt, which is 39

percent sodium by weight. The scientific evidence from epidemiological, clinical, and animal data establishes that high sodium intake is related to the prevalence of hypertension or high blood pressure and to the increase of blood pressure with age, and that low sodium intake is related to low prevalence of hypertension or high blood pressure and to a low rise or no increase of blood pressure with age.

(b) *Significance of sodium in affecting high blood pressure.* High blood pressure is a public health concern primarily because it is a major risk factor for mortality from coronary heart disease and stroke. There is a continuum of mortality risk that increases as blood pressures rise.

Individuals with high blood pressure are at greatest risk, and individuals with moderately high, high normal, and normal blood pressure are at steadily decreasing risk. The 1990 "Dietary Guidelines for Americans" states that: "In the United States, about one in three adults has high blood pressure." The scientific evidence from clinical data indicates that reducing sodium intake lowers blood pressure and associated risks in some but not all hypertensive individuals; approximately 30 to 60 percent respond to sodium reduction. There is some evidence that reducing sodium intake lowers blood pressure and associated risks in many but not all normotensive individuals as well: approximately 15 to 45 percent respond to sodium reduction. There are no practical genetic markers to identify responsive individuals. The populations at greatest risk for high blood pressure, and those most likely to benefit from sodium reduction, include those with family histories of high blood pressure, the elderly of all genders and races, males because they develop hypertension earlier in life, and black males and females. Sodium intake, alcohol consumption, and obesity are identified risk factors for high blood pressure. On a population-wide basis, the indications from epidemiological and clinical data are that reducing the average sodium intake would have a small but statistically significant effect on reducing the average blood pressure. Estimates suggest that reducing sodium intake by 100 millimoles (mmol) per day (2,300 mg of sodium or approximately one rounded teaspoon of salt) would correspond to an average lowering of blood pressure of approximately 2.2 mm Hg systolic and 0.1 mm Hg diastolic. Because these are population-wide

estimates, the magnitude of the effect for sensitive individuals would be greater. Estimates suggest that, for the age range from 25 to 55, a 100 mmol per day (2,300 milligrams (mg) per day) lower lifetime intake of sodium would correspond to a reduction in mortality rates of approximately 16 percent for coronary heart disease and 23 percent for stroke. In order to reduce sodium intake, individuals can choose foods with less sodium and salt, reduce the amount of sodium and salt used in food preparation and cooking, and reduce the amount of salt added at the table.

(c) *Specific requirements.* A food label or labeling may contain a sodium/hypertension health claim provided that:

(1) The health claim for a food or food product meets all the general requirements of § 101.14 for health claims.

(2) The health claim states that a low sodium diet is associated with or related to lower blood pressure in some people. Alternatively, the health claim can state that a high sodium diet is associated with or related to higher blood pressure in some people.

(3) The health claim identifies the populations at greatest risk of developing high blood pressure as being the elderly and those with family histories of high blood pressure and states that other dietary risk factors associated with high blood pressure include alcohol consumption and excess weight.

(d) *Optional information.* Sodium/hypertension in health claims may provide additional information:

(1) The health claim may state that sodium is an essential nutrient or necessary for good health, and that the total intake of sodium should be at least 500 mg per day but not more than 2,400 mg per day.

(2) The health claim may state that individuals with high blood pressure should consult their physicians for medical advice and treatment.

(3) In specifying the nutrient, the health claim may include the term "salt" in addition to the term "sodium".

(4) In specifying the disease, the health claim may include the term "hypertension" in addition to the term "high blood pressure".

(5) The health claim may include information from paragraphs (a) and (b)

of this section, which include summaries of the relationship between sodium and high blood pressure and of the significance of sodium reduction in affecting high blood pressure.

(e) *Sample health claim.* High blood pressure is associated with many factors, including a family history of the disease, growing older, being overweight, drinking too much alcohol, and diets high in sodium. A low sodium diet is associated with lower blood pressure in some people.

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

Note: The following tables will not appear in the annual Code of Federal Regulations.

TABLE 1.—INTERSALT STUDIES

Reference	Study design and duration	Subjects	Base diet	Other factors	Results	Assessment and comments
INTERSALT Cooperative Research Group (1988). (Ref. 37)	Cross sectional study. Sodium (Na) intake determined by single 24-hour urine collection blood pressure determined by average of 2 seated measurements. Repeated urine collections for 8% of subjects to estimate within-individual variability.	10,079 subjects from 52 population centers in 32 countries. (5,045 males, 5,034 females). (Goal of 200 at each center, 25 in each of 8 age and sex groups).	Normal diets ranging from 5 mg Na per day to 5,560 mg Na per day.	Single Na measurement does not assess previous or habitual Na intake habits. Subjects on antihypertensive medication included thereby reducing the effect of Na on blood pressure. Urine collection probably not complete in all subjects. Confounding factors: age, sex, body mass index, alcohol intake, and potassium intake. Significance sometimes lost after adjustment for confounding factors.	Within centers: Na significantly related to SBP and DBP. Across 52 centers Na significantly related to SBP, to DBP, and to changes in SBP and DBP with age. Across 48 centers: Na significantly related to change in DBP with age and significantly and negatively related to DBP. Estimated that 2300 mg less Na per day corresponds to lower SBP (2.2 mm Hg), lower DBP (0.1 mm Hg), and lower change of SBP (9.0 mm Hg) and DBP (4.5 mm Hg) with age from 25 to 45 years of age.	Large scale International Standard assessments Little data loss (approximately 3%). Study methods consistent within and across populations. Within center relationships and across center changes in relationships with age were consistent. Across center relationships depended on inclusion or exclusion of 4 population centers
Elliott (1989). (Ref. 50)	INTERSALT study design. Analysis of normotensive subjects.	Normotensive subjects from INTERSALT population (SBP < 140 mm Hg, DBP < 90 mm Hg, not on antihypertensive medication).	Normal diets	Multiple regression analysis adjusted for age, sex, potassium intake, alcohol intake, and body mass index. Corrected for individual variability of Na excretion ("reliability") (see below).	Na intake significantly related to blood pressure: 2300 mg change in Na intake corresponded to 2.10 mm Hg change in SBP after multiple regression analysis to adjust for confounding factors.	Regression coefficient similar to findings with the total INTERSALT population. Total population: 2300 mg change in Na intake corresponded to 2.17 mm Hg change in SBP.
Elliott (1989). (Ref. 51)	INTERSALT study design. Analysis of all INTERSALT data by age and sex.	10,079 subjects: (5045 males, 5034 females). (Goal of 100 males and 100 females from each of 52 centers, 25 in each age category: 20-29, 30-39, 40-49, and 50-59).	Same as INTERSALT	Multiple linear regression analyses in 52 centers, pooled, weighted, adjusted for potassium intake, alcohol intake, and body mass index, and adjusted for age or sex as appropriate. Corrected for individual variability of Na excretion ("reliability") by estimating the degree of regression dilution using data from 8% of subjects who returned and provided second set of data.	Within centers: Average Na intake related to SBP and DBP in men and in women, to SBP for men and women combined in 4 age categories, and to DBP in only the oldest age category. Across centers associations influenced by 4 centers with low Na intake.	Associations stronger for women than for men and for the older age categories.
Elliott (1989). (Ref. 52)	INTERSALT study design. Main results and implications for public health policy.	Same as INTERSALT	Same as INTERSALT	Some subjects were on antihypertensive medication which would give artificially low blood measurements and underestimate any effect of Na on blood pressure. Only simple adjustments were used to correct for bias toward zero. Some populations had been subjected to health campaigns to reduce Na intake which would underestimate current blood pressure effects due to previous habits.	The higher the center's median Na excretion, the steeper the slope of blood pressure with age.	Authors suggest that small clinical changes could result in large benefits to a population, especially in the cumulative effects over a lifetime. Authors conclude that the study gave "powerful qualitative tests . . . poor quantitative estimates of the size of these relationships"
Elliott (1989). (Ref. 53)	INTERSALT study design. Analysis of data from three United Kingdom centers (Belfast, Birmingham, and South Wales). Data collection in 1985.	598 subjects: (299 men, 299 women)	Normal diets Na ranging from 730 mg to 9,040 mg per 24 hours. Averages: Belfast: 3,470 mg Na per 24 hours. Birmingham: 3520 mg Na per 24 hours. South Wales: 3500 mg Na per 24 hours.	43 subjects excluded (41 for incomplete urine collection and 2 for pregnancy).	SBP positive and significantly related to Na in 2 of 3 centers (p<0.06) (Belfast, South Wales) and inconclusive in third. DBP relationship inconclusive in 3 centers.	Authors recommend modest increase in K and reductions in Na, obesity, and heavy alcohol drinking and suggest these lifestyle changes could result in downward shift of population blood pressure and prevalence of hypertension.

Hashimoto (1989) (Ref. 54)	INTERSALT study design. Analysis of data from three Japanese centers (urban Osaka, rural Tochigi, semi-rural Toyama).	591 subjects: (295 men, 296 women)	Normal diets Average Na of 4,300 mg per 24 hours Averages: Osaka: 3,870 mg Na per 24 hours. Tochigi: 4,150 mg Na per 24 hours. Toyama: 4,890 mg Na per 24 hours.	9 subjects excluded for incomplete data. High within-individual variation. Public health campaigns to reduce Na intake resulted in declines in Na consumption, Blood Pressure, prevalence of hypertension, and stroke mortality. 16.7 normotensives and 47.4 hypertensives receiving medical treatment reported reducing salt intake.	SBP negative and significantly related to Na in 1 center ($p < 0.001$). (Osaka), positive and significantly related to Na in 1 center ($p < 0.05$). (Toyama) and inconclusive in third DBP negative and significantly related to Na in 1 center ($p < 0.01$). (Osaka) and inconclusive in other two.	Authors recommend further reductions in Na, increases in K, and reductions in heavy drinking.
Mancilla-Carvalho (1989). (Ref. 58)	INTERSALT study design. Analysis of data from four remote populations with low ??? (NaCl) intake. (Yanomano and Xingu Indians in Brazil, rural Kenya, and rural Papua New Guinea).	731 subjects: Yanomano Indians: 195 subjects. Xingu Indians: 198 subjects. Papua New Guinea: 162 subjects Kenya: 176 subjects	Normal diets Median Na: tanomano Indians: 5 mg Na per 24 hours. Xingu Indians: 130 mg Na per 24 hours. Papua New Guinea: 620 mg Na per 24 hours. Kenya: 1,180 mg Na per 24 hours.	Average body weight low relative to other 48 centers. No or low average alcohol intake. Group variability largest in Kenya population. Authors noted that within-center association between Na and blood pressure was unlikely due to small variations in average Na and blood pressure. Adults were physically active and healthy with no signs of malnutrition or protein deficiency.	Four populations had lowest average blood pressure compared to other 48 centers (SBP of 103 mm Hg vs 120 mm Hg, DBP of 63 mm Hg vs 74 mm Hg). Four populations had little or no upward slope of blood pressure with age. Hypertension in 5% of Kenyan population and absent in other populations. Four populations had low average Na relative to other 48 centers (1-3 grams NaCl vs 9 grams NaCl).	Authors noted that when other centers had low average body weights and alcohol intake, but high Na intake (2,760 to 4,830 mg), the prevalence of hypertension ranged from 8 to 19%.
Mancilla-Carvalho (1989). (Ref. 59)	INTERSALT study design. Analysis of data from Yanomano Indians, a seminomadic population from the Brazilian, Amazon rainforests. Data collected July 1986.	195 subjects: (99 males, 96 females)	Normal diets Average Na of 21 mg per 24 hours. Range from 1 mg to 614 mg per 24 hours. Diet of local crops and game supplemented by wild fruits and insects. Banana and manioc staple foods. Little salt, refined sugar, alcohol, milk or dairy products in diet.	Low average body mass index, calcium intake, total fat and saturated fat. High K intake, fiber. No alcohol intake. Almost no obesity. Relatively high physical activity and endurance. No physical signs of evident malnutrition or protein deficiency. Na not considered in correlation analysis because non-normal distribution made it inappropriate. May have eaten some food from investigators.	Average SBP 96.0 mm Hg (range from 78 to 128 mm Hg). Average DBP 60.6 mm Hg (range from 37 to 86 mm Hg). Low average blood pressure. No hypertension. No increases of blood pressure with age.	
Rose (1989) (Ref. 64)	INTERSALT study design. Summary of background, methods, and main results. Designed to apply highly standardized methods across varied populations, to examine major confounding factors, and to evaluate the relationships in individuals.	INTERSALT populations ...	Same as INTERSALT	Planned study to be large enough to observe an effect. Planned standardized methods to allow for appropriate pooling of results. Planned analysis methodology to deal with confounding factors. Planned random repeat urine collections to estimate within-individual variability ("reliability").	Na excretion significantly related to blood pressure in individuals and to rise of blood pressure with age.	2 years for planning, funding, and recruitment of centers. Regional training meetings in 1984-1985. Field work and laboratory analyses completed in 1987.

TABLE 2.—SODIUM/HYPERTENSION STUDIES

Reference	Study design and duration	Subjects	Treatment or intervention	Intake of test material	Base diet	Other factors	Results	Assessment and comments
Australian National Health and Medical Research Council Dietary Salt Study Management Committee (1989a). (Ref. 44)....	Double blind, placebo controlled, clinical intervention trial. 6 weeks: run-in phase. 8 weeks: diet phase. Subjects seen every 2 weeks and 24-hr urine provided at each visit. During diet phase, all subjects monitored and counseled to keep dietary Na intake to below 1840 mg Na per day. NaCl or placebo added to low Na base diet.	103 mildly hypertensive subjects (DBP: 90–100 mm Hg). (86 male, 17 female). (Average age: 58.4 years). Randomized into two groups.	Study population: 8 (10 mmol) slow release NaCl tablets per day. Control population: 8 placebo tablets per day.	1840 mg Na per day.	Low Na diet (< 1840 mg Na per day monitored by 24-hr urine collection and dietary counseling).	2 centers..... 8 subjects dropped out. Large range of individual variation SBP of study and control populations approached same value near end of study DBP of study and control populations approached each other but remained distinct at end of study. Confounding factors: age, sex, weight, initial blood pressure, center.	Blood pressure of low Na group reduced an average 6.1 (SBP) and 3.7 (DBP) mm Hg in the study population relative to 0.6 (SBP) and 0.9 (DBP) mm Hg reduction in the control population (p < 0.005). Results remained significant after multi-variant analysis to adjust for age, weight, and initial blood pressure.	Sound methodology Skewed sex ratio, but approximately equal distribution to each group Dietary Na restriction produced heterogeneous response in individuals, but confirmatory studies in "responder" and "nonresponder" populations have not been done.
Australian National Health and Medical Research Council Dietary Salt Study Management Committee (1989b). (Ref. 45)....	Double blind, placebo controlled, clinical intervention trial. Continuation of previous study and study design to include crossover phase. 6 weeks: run-in phase. 8 weeks: diet phase 1. 8 weeks: diet phase 2.	88 mildly hypertensive subjects (DBP: 90–100 mm Hg). (73 male, 15 female). (Average age: 58.6 years). Randomized into two groups.	Study population: 8 (10mmol) slow release NaCl tablets per day. Control population: 8 placebo tablets per day.	1840 mg Na per day.	Low Na diet (< 1840 mg Na per day monitored by 24-hr urine collection and dietary counseling).	2 centers..... 15 subjects dropped out between two diet phases. 79 subjects completed study. Confounding factors: age, sex, weight, initial blood pressure, center, order of treatment.	Blood pressure of low Na group reduced an average 6.0 (SBP) and 4.1 (DBP) mm Hg in the study population relative to 0.1 (SBP) and 0.4 (DBP) mm Hg reduction in the control population (p < 0.001). Blood pressure reduced an average 3.6 (SBP) and 2.1 (DBP) mm Hg in the NaCl diet phase vs the placebo diet phase. Differences independent of order of treatment. Statistical significance greater for DBP than for SBP.	Sound methodology

TABLE 2.—SODIUM/HYPERTENSION STUDIES—Continued

Reference	Study design and duration	Subjects	Treatment or intervention	Intake of test material	Base diet	Other factors	Results	Assessment and comments
Dustan (1989). (Ref. 121)	Clinical intervention trial. Protocol 1: 3 days: Na depletion phase, 3 days: Na loading phase. Protocol 2: 3 days: Control phase, 3 days: Na loading phase, 4 days: Na depletion phase. Na determined by 24-hour unna excretion blood pressure determined 4 times per day	Protocol 1: 69 normotensives and 21 hypertensives. Protocol 2: 27 normotensives and 19 hypertensives. 12 normotensives and 9 hypertensives participated in both protocols. Hypertensives were either untreated or had not received antihypertensive medication for at least 1 month.	Na depletion phase: Furosemide (1 mg per kg) taken as 2 divided doses. Na loading phase: Isotonic saline (3.88 mM NaCl per kg per day) supplied intravenously over 4 hrs.	Na loading phase: 90 mg Na per kg per day.	Controlled diets. Control phase: 3450 mg Na per day (assumed as diet since was not clear). Na depletion and loading phases: 210 mg Na per day.	Only Na loading performed intravenously which introduces variability. Low Na phase was extreme: Only 210 mg per day.	Protocol 1: Mean arterial blood pressure in hypertensives fell and rose with Na (116 to 104 to 110 mm Hg). Mean arterial blood pressure in normotensives remained stable throughout (84 to 83 to 81 mm Hg). Protocol 2: Mean arterial blood pressure in hypertensives and some normotensives rose and fell with Na (107 to 111 to 98 mm Hg and 83 to 87 to 82 mm Hg). Separate analysis of subjects who participated in both protocols suggested that sequence was not important.	Short study Low Na diet was extreme Population differed between two protocols. Means of administering Na differed between different phases.
Hypertension Prevention Trial Research Group (1990). (Ref. 124)	Intervention trial (parallel design) 3 years Na determined by timed, overnight, urine collection blood pressure determined as average of 2 measurements Individuals received dietary counseling (once a week for 10 weeks, then every other week for 4 weeks, then every other month for the duration of the study).	841 subjects (DBP 78-89 mm Hg) (no antihypertensive medication or evidence of cardiovascular disease) (65.3% male) (82.2% white) (Average age: 38.6 years) Randomized into 5 groups.	4 intervention groups and a control. 5 groups: 1) Reduce calories, 2) Reduce Na, 3) Reduce calories and Na, 4) Reduce Na and increase K, 5) Control.	N/A.....	Group goal of 50% reduction in average dietary NA Individual goal of less than 1610 mg/d.	Multippliers used to estimate 24-hour Na from timed, overnight, urine collections. All groups, including the control, had reductions in Na excretion and in blood pressure during follow-up. Largest sustained reduction in Na occurred on the group encouraged to reduce both Na and calories. Intervention populations blood pressure levels were lower than those of the control population.	Na reduction statistically significant at 6 months (p = 0.002) and marginal at 3 years (p = 0.053) blood pressure reductions generally below those of control population, but changes were not statistically significant.	Authors note that maintaining dietary changes in free-living populations is difficult.

TABLE 2.—SODIUM/HYPERTENSION STUDIES—Continued

Reference	Study design and duration	Subjects	Treatment or intervention	Intake of test material	Base diet	Other factors	Results	Assessment and comments
Koopman (1990). (Ref. 76).....	Clinical intervention trial. Dietary counseling and feedback, follow-up from 3 to 18 months Na determined monthly by 24-hr excretion blood pressure determined monthly. Participants asked to return for evaluation at 18 months.	28 mild to moderate hypertensives (average initial SBP: 144.5 mm Hg, average initial DBP: 95.4 mm Hg).	Dietary counseling and feedback monthly. Dietary counseling and Na and blood pressure measurements ended at 12 months.	N/A.....	Low Na diets encouraged.	7 subjects dropped out (4 for high DBP, 2 for suspected angina, and 1 for stroke). During 1st 3 months of study, participants had been divided into an intervention and a control group. Control group participants received dietary counseling from 3 to 12 months. Intervention group participants received counseling from 0 to 12 months..	Average Na decrease of 510 mg per 24 hrs (p<0.05). Average decrease in SBP of 3.7 mm Hg (p<0.05). Average decrease in DBP of 4.0 mm Hg (p<0.01). Na and blood pressure decrease during first 6 months then leveled off at lower values.	Small study. No untreated control group followed throughout
Lasaridis (1989). (Ref. 55).....	Clinical intervention trial. 2 days: adaptation period. 5 days: low Na diet. 5 days: high Na diet. Blood pressure (supine and standing) determined 3 times per day. Na determined by 24-hr urine excretion.	18 hypertensive patients. (10 males, 8 females). (Average age: 47.3 years). (Age range: 30-64 years of age).	N/A.....	N/A.....	Controlled low Na diet: 1150 mg Na per day. Controlled high Na diet: 4600 mg Na per day.	Blood pressure determined by automated device. Patients on high Na diet had an average increase in body weight of 1.3 kg (p<0.01). "Responders" (8 patients with a change in mean supine blood pressure >8 mm Hg). Low-renin patients (6 patients with plasma renin activity <3 ng/ml per hr during Na deprivation). "Responders" were virtually all low-renin patients.	Average Na rose from 1180 to 4440 mg Na per day (p<0.001). Average supine blood pressure rose 6.7 mm Hg (from 102.7 to 109.4 mm Hg) (p<0.001). Average standing blood pressure rose 5.0 mm Hg (from 107.6 to 112.6 mm Hg) (not significant).	Small study Not clear if patients were receiving or had received antihypertensive medication. Low-renin patients appeared to respond better to changes in Na.
Luft (1990). (Ref. 79).....	Placebo controlled crossover trial. Phase 1: 4 days: low Na diet. 7 days: low Na diet plus mineral water with NaCl or NaHCO3. Phase 2: 4 days: low Na diet. 7 days: low Na diet plus mineral water with NaHCO3 or NaCl. All urine collected. Phase 1 and Phase 2 conducted a month apart	10 mildly hypertensive subjects (blood pressure >140/90 mm Hg) and 10 normotensive subjects (blood pressure <140/90 mm Hg) (10 male, 10 female) (10 black, 10 white) (Average age: 36 years) Randomized into two groups.	NaHCO3 Phase: 3 liters per day of mineral water containing NaHCO3 (26.2 mmol/l Na, 33.03 mmol/l HCO3, and 4.23 mmol/l Cl). NaCl Phase: 3 liters per day of mineral water containing NaCl (26.2 mmol/l Na and 36.07 mmol/l Cl).	1810 mg Na per day.	Controlled low Na diet containing 1380 mg Na per day. All foods prepared and eaten at research center. Same food eaten for each meal every day during both phases of study.	Blood pressure determined by automated device. NaHCO3 mineral water contained 12.69 mmol Cl per day. Base diet contained 60 mmol Cl per day. NaCl increased calcium excretion whereas NaHCO3 did not.	NaCl intake period: Blood pressure did not change in hypertensive or normotensive subjects. NaHCO3 intake period: SBP decreased by 5 mm Hg in hypertensive subjects (p<0.05). SBP did not change in normotensive subjects. DPB did not change in hypertensive or normotensive subjects.	Small sample size NaCl and NaHCO3 may differ in their effects on blood pressure.

TABLE 2.—SODIUM/HYPERTENSION STUDIES—Continued

Reference	Study design and duration	Subjects	Treatment or intervention	Intake of test material	Base diet	Other factors	Results	Assessment and comments
MacGregor (1989). (Ref. 122)	Double blind, placebo controlled, crossover trial. 2 months: observation, 4 weeks: low Na diet phase, 1 month: 1st diet phase, 1 month: 2nd diet phase, 1 month: 3rd diet phase, 12 months: follow up. Diet phases included total daily diets of 1150, 2300, and 4600 mg Na. Blood pressure determined as average of 5 measurements. Na determined as average of 2 24-hr urine collections.	20 subjects with mild hypertension (DBP: 90-110). (11 men, 9 women). (15 whites, 5 blacks). (Average age: 57 years). (Age range: 42-72 years).	1150 mg Na phase: 16 placebo tablets per day. 2300 mg Na phase: 7 (10 mmol) slow release NaCl tablets plus 9 placebo tablets per day. 4600 mg Na phase: 16 (10 mmol) slow release NaCl tablets per day.	1150 mg Na phase: 0 mg Na per day. 2300 mg Na phase: 1610 mg Na per day. 4600 mg Na phase: 3680 mg Na per day.	Low Na diet (690-1150 mg Na per day) monitored by 24-hr urine collection and dietary counseling.	Excluded patients with renal failure, ischaemic heart disease, cerebrovascular disease, and those taking oral contraceptives or other drugs. Weight increased as Na increased, but change was not significant. 16 to 20 (1 moved, 3 medicated) controlled blood pressure by salt restriction alone for the year following the study (Na of 1420 mg per 24 hr, SBP of 142 mm Hg, DBP of 87 mm Hg).	Na in 3 phases was 1130, 2480, and 4370 mg per 24-hr. SBP in 3 phases was 147, 155, and 163 mm Hg. DBP in 3 phases was 91, 95, and 100 mm Hg. Average change in blood pressure from lowest to highest Na intake was 16 mm Hg SBP and 9 mm Hg DBP ($p < 0.001$).	Blood pressure differences were not affected by the order in which the Na intake was altered. Necessary to have some salt-free products (i.e. salt-free bread) in order to reach the dietary Na intake of 690-1150 mg Na per day.
Mascioli (1991). (Ref. 109)	Double blind, placebo controlled, crossover trial. Phase 1: 4 weeks: NaCl or placebo capsules. Phase 2: 4 weeks: placebo or NaCl capsules. Phase 1 preceded by 2 weeks of testing and 8 weeks of dietary counseling to achieve low Na diet. 2 week washout period (placebo capsules) between phases. Low Na diet continued throughout.	48 normotensive subjects. (SBP < 150 mm Hg, DBP: 80-89). (47 white, 1 black). (79% male)..... (Average age: 52 years) Randomized into two groups.	Intervention phase: 6 (16 meq) NaCl capsules per day Control Phase: 6 placebo capsules per day.	2210 mg Na per day.	Low Na diet (<805 mg Na per timed overnight, 8-hr urine excretion assessed prior to Phase 1 by 5 consecutive overnight urine collections below 805 mg Na).	23% of initial participants excluded for high urine Na levels. 2 subjects dropped out. Blood pressure measured every 2 weeks (twice at each visit) 8-hr urine measured at beginning of Phase 1 and at end of each phase. Subjects lost weight and blood pressure dropping during diet only phase.	Average SBP 3.6 mm Hg higher during NaCl treatment period as compared with placebo period ($p < 0.001$). Average DBP 2.3 mm Hg higher during NaCl treatment period as compared with placebo period ($p < 0.005$). 65% and 69% of participants experienced an increase of SBP and DBP, respectively, when on NaCl capsules as compared with placebo capsules.	Sound methodology Estimated 3-6 mm Hg increase in SBP and 2-4 mm Hg increase in DBP associated with 2300 mg increase in Na intake.

TABLE 2.—SODIUM/HYPERTENSION STUDIES—Continued

Reference	Study design and duration	Subjects	Treatment or intervention	Intake of test material	Base diet	Other factors	Results	Assessment and comments
Mtabaji (1990). (Ref. 30)....	Clinical intervention trial. 3 days: control phase. 7 days: diet phase. One group on Low Na diet other on normal diet plus Na as consomme soup. Blood pressure determined daily. Na determined by 24-hr Na excretion.	30 normotensive Tanzanian black male subjects Randomized into two groups.	High Na group: 250mmol NaCl per day as consomme soup.	High Na group: 5750 mg Na.	Control phase: Diet of unspecified Na content. Low Na group: 1150 mg Na per day. High Na group: Normal diet of unspecified Na content.	Blood pressure determined by automated device. Ages of participants not specified.	Significant difference between two groups within 4-5 days ($p < 0.001$). Low Na group: Na of 1200 mg per day. Mean arterial blood pressure fell from 87 to 81 mm Hg. High Na group: Na of 7750 mg per day. Mean arterial blood pressure rose from 86 to 89 mm Hg.	Control diet and normal diet of unknown Na content. Single population: High Na diet phase was excessively high in Na (7750 mg per day).
Smith (1988). (Ref. 41)....	Cross sectional study. Part of Scottish heart health study. Data collected from 1984-1986. Na intake determined by single 24-hr urine collection. Blood pressure determined by average of 2 measurements.	7354 subjects from 22 districts in Scotland (3754 males, 3600 females). (Age range: 40-59 years) Subjects chosen at random.	N/A.....	N/A.....	Normal diets.....	Single Na measurement does not assess previous or habitual Na intake habits. 74% response rate, 17.5% excluded (generally for failure to provide urine). 1.6% excluded due to antihypertensive medication. Confounding factors: age, body mass index, pulse rate, alcohol consumption, potassium intake.	Weak, positive correlation between Na and blood pressure in both sexes. Na correlation with SBP 0.025 for males and 0.055 for females. Na correlation with DBP 0.026 for males and 0.052 for females. Na not independently significant after multivariate analysis.	Large study population. Single community (Scotland).

TABLE 2.—SODIUM/HYPERTENSION STUDIES—Continued

Reference	Study design and duration	Subjects	Treatment or intervention	Intake of test material	Base diet	Other factors	Results	Assessment and comments
Staessen (1988). (Ref. 42) ...	Cross sectional intervention trial. 5 years (1979-1985). Mass media campaign to avoid salt directed mainly at women in one town. Control town was observed. Urinary Na excretion and blood pressure determined at beginning and end of intervention.	Intervention town of 12,000 and control town of 9,000 Belgian inhabitants. 2211 subjects examined (5 and 10% random sample at baseline in control and intervention town, respectively; doubled at follow-up). Previous participants excluded from follow-up. Data from 1697 subjects analyzed. (777 males, 733 females) with and without 187 subjects on antihypertensive medication.	Intervention town (IT): Leaflets sent to all homes, posters displayed, radio and newspaper ads run. Active support from Town Council, local health officials and practitioners, and insurance organizations. Local bakers and restaurants asked to prepare low-salt foods. Women's clubs, health education courses, and children's homework targeted. Control town (CT): Salt not mentioned as a health hazard.	N/A.....	Normal diets.....	Data from teens excluded (464 subjects). Data excluded if urine volume or creatinine excretion outside limits (50 subjects). Blood pressure determined as average of 10 measurements collected at 2 home visits 2-5 weeks apart. Na determined by 24-hr urine extraction. Baseline and follow-up data taken on different subjects.	The trends in Na, SBP, and DBP in men and women were similar between the two towns except for Na in women which was significantly lower in the IT than in the CT. Na changes ranged from +180 mg in females in CT to -410 mg in females in IT. SBP changes ranged from -4.4 mm Hg in males in CT to -9.1 mm Hg in females in IT. DBP changes ranged from +1.8 mm Hg in males in CT to -2.8 in females in IT.	Large range of variation in results affects interpretation (eg.: change in Na in females in control town was +180 ±210 mg). No independent assessment of information available to subjects in control town between 1979 and 1985 regarding Na an health hazards. 'Inconclusive.
Stamler, R. (1989). (Ref. 70).....	Intervention trial 5 years. Intervention subjects: Extensive dietary and lifestyle counseling varying from 2 visits per week initially to 4 visits per year. Control subjects: 2 visits per year Blood pressure measured 2 times per year Na from urinary excretion measured 1 time per year.	201 hypertension prone subjects (high normal DBP: 85-89 mm Hg) or (high normal DBP: 80-84 plus 10-49% overweight) and/or (rapid resting pulse rate >80 beats per min). Randomized into two groups (102 intervention subjects and 99 control subjects).	Intervention goals: 1) Reduce daily NA intake, 2) Reduce alcohol intake, 3) Reduce overweight, 4) Increase moderate physical activity.	N/A.....	Goal of <1800 mg Na per day. 13% of intervention subjects achieved Na intervention goal. Average Na intake reduced by 24% in intervention group (drop from 3980 mg/day to 3040 mg/day) vs 6% in control group (drop from 4300 mg/day to 4060 mg/day)(p<0.001).	Multiple interventions. Blood pressure measure at worksite and at office and worksite measurements used for comparison. 24-hr NA estimated from timed, 8-hr Na excretion and multipliers. Statistically significant changes in 3 of 4 interventions: NA intake, alcohol intake, and weight reduction. Statistically significant relationship with blood pressure in one of 4 interventions: weight reduction.	19% of control subjects and 9% of intervention subjects developed hypertension (DBP >90 mm Hg or medication). SBP: Reduction of 2.6 mm Hg (from 122.5 to 119.8 mm Hg) in intervention group vs 1.3 mm Hg in control group (from 122.7 to 121.5 mm Hg). DBP: Reduction of 1.3 mm Hg (from 82.5 to 81.2) in intervention group vs 0.1 in control group (from 82.8 to 82.5 mm Hg). Relationship between Na and blood pressure not independently significant.	Appropriate statistical tools used. Low dropout rate: 87% participatin; at least 4 years

TABLE 2.—SODIUM/HYPERTENSION STUDIES—Continued

Reference	Study design and duration	Subjects	Treatment or intervention	Intake of test material	Base diet	Other factors	Results	Assessment and comments
Takemori (1989). (Ref. 71).....	Cross sectional study Na intake determined by spot urine. Blood pressure determined by single measurement. Data collected in 1985.	7,441 Japanese females from 88 urban and 81 rural municipalities including all prefectures in Japan. (3933 urban subjects, 3508 rural subjects). (3 age groups between 40 and 69 years of age).	N/A.....	N/A.....	Normal diet averaging 3720 mg Na per day.	History of being hypertensive or on antihypertensive medicine not considered. Confounding factors: age, height, weight, potassium.	Increase of 2300 mg Na per day related to increase of 4.5 mm Hg SBP (urban: 4.1 mm Hg, rural: 4.9 mm Hg) and an increase of 1.6 mm Hg DBP (urban: 1.2 mm Hg, rural: 2.0 mm Hg).	Spot urine and predictive equations used to estimate 24-hr Na adds to uncertainty of results. Single population.
Trials of Hypertension Prevention (TOHP) Collaborative Research Group (Abstract) (1991). (Ref. 123)	Clinical intervention trial. Investigation of 7 nonpharmacological interventions in persons with high normal blood pressure. Checked at 6, 12, and 18 months into study.	2182 subjects with high normal blood pressure. (DBP: 80-89 mm Hg). (Age range: 30-54 years) randomized to 1 of 8 groups.	7 interventions (3 lifestyle changes for 18 months, 4 nutrition supplements for 6 months) and 1 control). 1) weight loss and exercise, 2) NA restriction, 3) stress management, 4) calcium supplementation, 5) magnesium supplementation, 6) potassium supplementation, 7) fish oil supplementation, 8) control.	None.....	None.....	None.....	39% reduction in Na at 18 months. SBP 1.5 mm Hg lower at 18 months (p=0.05). DBP 0.8 mm Hg lower at 18 months (p=0.07).	Authors suggest that weight loss and Na restriction are the most promising nonpharmacological interventions for hypertension control.

TABLE 3.—SODIUM/HYPERTENSION META-ANALYSES

Reference	Study design and duration	Subjects	Other factors	Results	Assessment and comments
Cutler (1991) (Ref. 94).....	Meta-analysis of 23 randomized clinical trials published before January 1990. Analyzed separately for hypertensives, normotensives, and total subjects.	Total: 23 trials with 1536 subjects. Data for hypertensive and normotensive subjects analyzed separately and together.	Excluded trials with confounded designs. Excluded 2 trials for Na intake outside the usual ranges for Na. Magnitude of results was reduced slightly when inverse variance weights were included. All results statistically significant except for DBP in normotensives after including an adjustment for inverse variance weights.	Hypertensives: Net reductions in Na ranged from 1290 to 2410 mg. Average pooled reductions in blood pressure were 4.9 mm Hg (SBP) and 2.6 mm Hg (DBP). Normotensives: Net reductions in Na ranged from 370 to 3910 mg. Average pooled reductions in blood pressure were 1.7 mm Hg (SBP) and 1.0 mm Hg (DBP). Totals: Net reductions in Na ranged from 370 to 3910 mg. Average pooled reductions in blood pressure were 2.9 mm Hg (SBP) and 1.6 mm Hg (DBP).	Studies used a variety of different methodologies (unstandardized). Selected only randomized trials which eliminates selection bias. Authors indicate there is evidence for a dose-response relationship between Na and blood pressure.
Elliott (1991)..... (Ref. 97).....	Meta-analysis of 14 observational studies in 16 populations. Only studies that provided 24-hr urine and blood pressure data and published quantitative regression or correlation estimates.	12,503 subjects (7099 men, 6136 women).....	Excluded studies that compared hypertensives with normotensives. Excluded studies that just reported significance without quantification. Data corrected for within-individual variability in Na ("reliability") using INTERSALT estimate. 2 studies of only men, 1 study of only women, 2 studies of only combined data for women and men combined.	Reduction of 2300 mg Na related to reduction in SBP of 3.7 mm Hg and in DBP of 2.0 mm Hg. Regression coefficients somewhat larger in women than in men.	Variety of study designs (unstandardized methodology).
Frost (1991)..... (Ref. 100).....	Meta-analysis of 14 published studies of blood pressure and Na intake. 24 hour Na excretion. One blood pressure measurement. 24 hour intake of Na adjusted due to common underestimation.	12,773 people from Europe, Asia, and the United States.	None.....	2 mm Hg decrease in blood pressure for every 100 mmol decrease in 24 hour Na intake. Weak effect within populations—reduced Na intake reduced blood pressure slightly. Unclear how study controlled for confounding factors. One of three studies suggesting that Na reduction reduces SBP and the risk of mortality due to hypertension.	Variety of study methodologies (unstandardized).
Law (1991a)..... (Ref. 106).....	Meta-analysis:..... 12 developing 12 developed communities Cross sectional studies	47,000 people from 24 communities.	Developed versus developing communities. Confounders: Potassium, alcohol, and body mass linked to Na. These varied between, but not within, the two groups. Blacks excluded from study because blood pressure in these communities were higher than for communities with similar Na intake. The effect was measured in both developing and developed communities.	Blood pressure varied according to intake. The change in blood pressure was relative to the age and existing blood pressure. It appeared that there was not a lower Na threshold below which no effect was measured.	Variety of study methodologies (unstandardized).
Law (1991b)..... (Ref. 107).....	Meta-analysis of 78 published studies that recorded the effect of salt restriction on blood pressure. Variable duration: Researchers subdivided the data from studies that recruited both subjects with high blood pressure and subjects with normal blood pressure to allow separate assessment of the effect of salt restriction for each category.	Not stated.....	Some of the trials were not randomized which could introduce bias.	Salt reduction lowered blood pressure in persons with high blood pressure and in those with normal blood pressure. In people aged 50-59, a reduction in daily Na intake of 50 mmol (about 3 g salt), after a few weeks, lowered SBP by an average of 5 mm Hg and by 7 mm Hg in those with high blood pressure DBP was lowered by about half this amount.	Variety of study methodologies (unstandardized). Authors suggest that the effect of moderate dietary salt reduction on mortality from stroke and ischemic heart disease would be substantial. Authors concluded that the effect of salt reduction on blood pressure was larger than previously reported. Unclear exactly how authors controlled for confounding factors in this study.

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21 CFR Parts 5, 20, 100, 101, 105, and 130

[Docket No. 91N-0219]

RIN 0905-AD08

Regulatory Impact Analysis of the Proposed Rules to Amend the Food Labeling Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Regulatory impact analysis statement.

SUMMARY: The Food and Drug Administration (FDA) is publishing herein the regulatory impact analysis (RIA) that it has prepared under Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354) on the costs and benefits of the food labeling regulations that FDA is currently proposing to amend. FDA is issuing these proposals (published elsewhere in this issue of the *Federal Register*) in response to the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) and as part of the Secretary of Health and Human Services' (the Secretary's) food labeling reform initiative. The agency has prepared this comprehensive RIA document for these proposals because, when taken together, they constitute a major rule.

DATES: Written comments by February 25, 1992.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Richard A. Williams, Jr., Center for Food Safety and Applied Nutrition (HFF-303), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-485-0271.

SUPPLEMENTARY INFORMATION: FDA is publishing herein its RIA of the proposed rules to amend the food labeling regulations. This document analyzes both the costs and the benefits, including the impact on small businesses, of FDA's proposals (published elsewhere in this issue of the *Federal Register*) to reform the food label in response to the 1990 amendments and the Secretary's food labeling initiative. This analysis was

prepared by the Economics Section of the Office of Compliance in FDA's Center for Food Safety and Applied Nutrition (CFSAN).

The food labeling reform initiative, taken as a whole, will have associated costs in excess of the \$100 million threshold that defines a major rule. Therefore, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA has developed one comprehensive RIA that presents the costs and benefits of all of the food labeling proposals taken together. FDA requests comments on the RIA.

I. Introduction

The 1990 amendments amend the Federal Food, Drug, and Cosmetic Act (the act) to expand the coverage of nutrition labeling to all food products (except meat and poultry), produce more ingredient labeling, regulate health claims, and standardize nutrient content claim definitions and serving sizes. The 1990 amendments require that the nutrition information on both the food label and on eating establishment menus be readily understandable by the public. These changes to the food label are the most comprehensive changes to be proposed in 53 years. FDA has proposed implementing regulations for the 1990 amendments and estimated the costs and benefits of the proposed changes and regulatory options within the act. However, even before the 1990 amendments were enacted FDA believed that the food label could be improved and was engaged in proposing a series of similar regulations.

In order to evaluate the need for Federal intervention, FDA examined the market for food label information and found that less than the optimal amount of nutrition information was being produced because consumers cannot, independently, determine the nutritional quality of food, thus leading to insufficient incentives for manufacturers to reveal the nutrient content of their products or produce nutritious food. FDA undertook two studies to determine the costs and benefits of these proposed regulations, by engaging a contractor, Research Triangle Institute (RTI). These studies were done over a period of 3 years under the direction of the Economics Section of CFSAN.

A. Costs of the 1990 Amendments

The cost study consisted of both interviews with food manufacturers and a mailed survey. The result was a generic model which can be applied to any regulation mandating a label change. Categories of costs include administrative, analytical, printing,

inventory, and reformulation.

Administrative costs are management costs which are often high because of the prominence of the food label as an advertising tool for packaged foods. Analytical costs are costs of testing products for nutrient composition to comply with labeling provisions. Printing costs are the costs of printing new labels which may be either glue-on labels or the food package itself. These costs may include redesign costs where extensive labeling changes are undertaken. In the model, estimates of printing costs take into account normal firm relabeling.

Inventory costs are the costs of disposal of existing labels where firms have inventories that outlast the compliance period, i.e., the period of time between issuance of a final rule and its effective date. Inventories of labels, both glue-on labels and packages, range from only a few months to well over 10 years in the food industry. The last cost category reformulation includes the costs of reformulating products and introducing new ones in response to labeling regulations and market testing those products. No estimate of these costs is given because they depend on marketing decisions and are impossible to predict. Moreover, they do not result directly from these proposed rules. Regardless, FDA expects a substantial benefit to be derived from such reformulations, which are likely to make foods more nutritious. In all cost categories, except administrative costs, the costs of relabeling products produced and labeled in foreign countries cannot be separated from those produced and labeled domestically. Thus, administrative costs considered are domestic costs only, and printing, inventory, and analytical costs are considered multinational.

FDA estimates that about 17,000 domestic food manufacturers and 257,000 labels will be affected by the regulations promulgated in response to the 1990 amendments. In addition, approximately 96,000 food service firms might be required to alter their menus if they are not in compliance with health claims or descriptors regulations. The majority of the costs will occur in the first year. Recurring costs are assumed to continue 20 years into the future and are discounted back to the present at a rate of 5 percent.

The individual regulations may be divided into the following separable categories: (1) Mandatory ingredient labeling for standardized foods and certified colors; (2) "voluntary" (see section III.E. of this document) labeling