DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 91 N-0095]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements; Sodium and Hypertension

AGENCY: Food and Drug Administration. HHS.

ACTON: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing its decision to authorize the use on the label or labeling of certain foods of health claims relating to an association between dietary sodium and high blood pressure. The agency has concluded that, based on the totality of the scientific evidence, there is significant scientific agreement among qualified experts that diets low in sodium may help lower blood pressure in many people. Therefore, FDA has concluded that claims on certain foods relating sodium reduction to reduced risk of high blood pressure are justified. This action is in response to provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) that bear on health claims, and is developed in accordance with the final rule on general requirements for health claims, which is published elsewhere in this issue of the **Federal Register**.

EFFECTIVE DATE: May 8, 1993.

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, 202-205-5375.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 27, 1991 (56 FR 60825), FDA proposed to authorize the use on food labeling of health claims relating diets low in sodium to lower blood pressure in some people. The proposed rule was issued under provisions of the 1990 amendments (Pub. L. 101-535) that bear on health claims and in accordance with the proposed general requirements for health claims for food (56 FR 60537, November 27, 1991). As amended in 1990, the Federal Food, Drug, and Cosmetic Act (the act) provides that a food 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 section 403(r)(3) or (r)(5)(D) of the act (21 U.S.C. 343(r)(3) or (r)(5)(D)).

Section 3(b)(1)(A) of the 1990 amendments specifically requires that the agency determine whether claims respecting 10 nutrient/disease relationships, meet the requirements of section 403(r)(3) or (r)(5)(D) of the act. The relationship between sodium and hypertension is one of the claims required to be evaluated. In the **Federal Register** of March 28, 1991 (56 FR 12932), FDA published a notice requesting scientific data and information on the 10 specific topic areas identified in the 1990 amendments. Relevant scientific studies and data received in response to this request were considered as part of the agency's review of the scientific literature on sodium and hypertension and were included in the proposed rule. Comments received in response to the notice and not specifically addressed in the proposed rule are summarized and addressed below.

In addition to evaluating the scientific evidence, the proposed rule identified qualifying and disqualifying criteria for foods bearing health claims on sodium and hypertension. The proposed rule also specified mandatory and optional information for health claim statements and provided a sample claim. FDA requested written comments in response to its proposed rule and solicited comments on several issues in particular. The agency asked whether foods with minimal nutritional value should be allowed to bear health claims and whether a statement of the recommended range of sodium intake (500 to 2,400 milligrams (mg) per day) should be required or remain optional. The agency requested comments on requiring the use of the terms "sodium" rather than "sodium chloride" and "high blood pressure" rather than "hypertension," and on allowing the terms "salt" in addition to "sodium" and "hypertension" in addition to "high blood pressure." The agency also requested comments on whether a statement indicating that identified hypertensives should consult their physicians should be allowed or required, on the safety of the recommendations to reduce sodium and salt intake, and on the proposed "Consumer Summary on Sodium and High Blood Pressure."

On January 30 and 31, 1992, FDA held public hearings on all aspects of the proposed rules published in response to the 1990 amendments, including health claims for sodium and high blood pressure (57 FR 239).

In response to its proposed health claim regulation on sodium and hypertension, the agency received approximately 100 comments from consumers, consumer advocacy groups, State health departments, organizations of health professionals, the food industry, and Government agencies. A number of comments were received that were more appropriately addressed in other documents, and these comments were forwarded to the appropriate docket for response.

II. General Comments

1. One comment noted that it is difficult to find a variety of foods that meet recommended dietary Sodium levels and expressed the hope that this regulation would encourage industry to provide more low sodium foods.

FDA strongly encourages innovation in providing consumers with a wider variety of choices. FDA's labeling and education initiatives in the early eighties resulted in a 60 percent increase in sodium content labeling from 1978 to 1988 (Ref. 46) and the introduction of additional low sodium products (Ref. 56). The current initiatives include not only sodium/hypertension health claims, but also mandatory sodium labeling, a daily value (DV) for sodium, sodium disqualifying levels for health claims, and sodium disclosure levels for nutrient content claims. FDA anticipates that these regulations will motivate manufacturers to develop and market a broader range of lower salt products for the American consumer.

2. Another comment argued that consumers will wrongly believe that consumption of foods with too much sodium to qualify for a sodium/hypertension health claim will necessarily lead to exceeding current dietary guidelines.

FDA disagrees. Rather, the agency believes that health claims will encourage the availability and consumption of foods that will help consumers meet dietary guidelines. Furthermore, auxiliary educational programs, consistent with the dietary guidelines philosophy, can help consumers understand that, by consuming a variety of foods, some higher in sodium and some lower in sodium, they can meet total dietary intake goals.

3. One comment opposed sodium restrictions on foods, arguing that restrictions would be likely to hinder the development of low fat foods and that reducing fat in the diet is more important than reducing sodium. The comment submitted supporting data from surveys in which nutritionists and

physicians rated their most important health concerns (Refs. 137 and 142). Although reduction in sodium intake was ranked as a "high priority" for good health (Ref. 142) and a "moderate priority" for improved heart health (Ref. 137), the comment noted that the survey results indicate that reducing fat was considered a higher priority than reducing sodium.

It was not clear whether the comment objected to sodium/hypertension health claims, to disqualifying levels for sodium on other health claims, or to both. In the 1990 amendments, Congress specifically identified sodium and hypertension as one often topics to be evaluated for health claims and did not limit claims to the highest priority health issues. FDA evaluated the totality of the scientific information and the extent of the scientific agreement among qualified experts and concluded that claims for sodium and hypertension should be allowed. In addition, the provisions of the 1990 amendments state that health claims may not be made on a food that contains a nutrient that increases the risk of a disease or health-related condition. Sodium was one of four nutrients identified by the agency as increasing the risk of a disease or health-related condition.

FDA disagrees that these survey results are relevant to its duty under the 1990 amendments with regard to health claims for sodium and hypertension. FDA need only establish that a relationship between sodium and hypertension is supported by the totality of the scientific evidence and by significant scientific agreement among experts qualified by experience and training to evaluate such evidence. A poll of scientists ranking sodium/hypertension concerns relative to fat/heart disease concerns does not contribute to this process.

FDA recognizes the importance of encouraging the development and use of more low fat foods. The agency has authorized two health claims that may appear only on foods low in fat (final rules on lipids and cardiovascular disease and on lipids and cancer health claims, published elsewhere in this issue of the **Federal Register**). Sodium is a disqualifying nutrient for these and other health claims, because diets high in sodium increase blood pressure in many people and, therefore, increase the risk of high blood pressure and associated risks of heart disease and stroke. (See the final rule on general requirements for health claims, published elsewhere in this **Federal Register**).

4. Several comments asserted that the agency adequately considered safety concerns regarding reductions in sodium intake in the proposed regulation. The Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) prepared a final independent evaluation of the scientific evidence on sodium and hypertension (Ref. 138) and submitted this as a comment. An earlier draft of the report (Ref. 108) was discussed in the proposed rule (56 FR 60825 at 60829). The FASEB report (Ref. 138) concluded that severe sodium chloride restriction (less than 20 milliquivalents (meq) or 460 mg sodium per day) may have adverse consequences, but that, in the absence of obvious salt-losing disorders, there is no evidence that avoiding high sodium chloride intakes would be deleterious to health. Other comments, including a review article (Ref. 144), disagreed with FDA's assessment, arguing that there is inadequate scientific evidence that curtailing sodium will safely reduce the risk of hypertension; that there is a growing body of scientific evidence that reducing sodium may put some healthy people at risk, that no populations with free access to salt choose such low levels and the risks of these levels have not been considered; that severe restriction in animals results in some risks; that in the older literature, extremely low sodium intake in humans resulted in some symptomatic distresses; and that FDA has no studies that demonstrate safety and efficacy of universal sodium restriction, especially in normotensives. The comments submitted no data demonstrating that daily dietary intakes of 2,400 mg sodium are unsafe.

The agency has considered and addressed the safety concerns and believes that the recommended goal of 2,400 mg per day is safe. The National Academy of Sciences, which recommended the 2,400 mg daily goal, is considering dropping the current target goal to 1,800 mg sodium per day (Ref. 62). Furthermore, the 1989 Recommended Dietary Allowances (Ref. 63) identify 500 mg sodium as a safe minimum daily intake for adults, and 2,400 mg is well above this safe minimum intake level. Other authoritative documents also agree that a moderate sodium intake is safe (Refs. 38, 43, and 62). Numerous experiments with low sodium diets have been conducted with no serious consequences. Finally, dietary guidelines since the early eighties (Refs. 9, 22, and 85) have recommended moderation in sodium intake with no ill effects. Given these conclusions, the lack of data demonstrating safety concerns with daily consumptions of 2,400 mg sodium, and the extreme difficulty in achieving an intake of sodium at or below the 500 mg per day minimum safe level in the U.S. diet, FDA concludes that there are no safety risks associated with use of the sodium/hypertension health claim.

5. A few comments from health professionals supported FDA's description of the special considerations and risks involving sodium losses during sustained exercise or training in hot temperatures. One comment specifically supported responding to these risks with education efforts as proposed by the agency.

FDA acknowledges these comments.

6. Some comments supported FDA's conclusion in the proposed rule that the study results (Refs. 33 and 72) that suggest some individuals may respond to sodium reduction with blood pressure increases rather than decreases may be due to random variations and require additional research to determine if the results of these few studies are significant and reproducible. Other comments disagreed. One comment stated that many people believe that the results of the INTERSALT study (Ref. 37) confirm this heterogeneous blood pressure response.

FDA acknowledges that there is wide variability in blood pressure response to changes in sodium intake, but disagrees that recommended sodium intake goals pose safety risks. The INTERSALT (Ref. 37) and other study results (Refs. 41, 44, 45, 76, 80, 94, 97, 100, 106, 107, 109, 121, 122, and 123), in spite of large background fluctuations and a dilution effect of including nonresponsive individuals, clearly show that reducing sodium intake has a measurable and beneficial effect on reducing average blood pressure. The agency encourages additional studies under controlled conditions; however, FDA disagrees that this normal variability, which commonly occurs with physiological measurements, calls into question the safety of current intake recommendations of 2,400 mg per day.

7. A few comments supported FDA's conclusion in the proposed rule that the possible adverse changes in plasma lipids in response to sodium restriction (Refs. 2, 40, 49, and 89) do not pose safety concerns for the general public consuming recommended intakes of sodium. One comment indicated that the sodium intakes in these studies were very low and that the observed effects could have been due to dehydration. Other comments disagreed. One comment, accompanied by three studies, accused FDA of failure to give

the plasma lipid studies proper consideration.

In preparing its proposal, FDA reviewed the plasma lipid studies submitted. Sodium intake levels in these studies were very low (460 and 780 mg daily) relative to current U.S. intakes (approximately 3,000 to 6,000 mg daily) and dietary guidelines (2,400 mg daily). Also, the intervention periods were very short (one week or less). The agency encourages additional research, but disagrees that a few studies involving sodium intakes of 460 to 780 mg daily are relevant or raise safety concerns for the general public consuming well in excess of this amount or for public health agency recommendations encouraging moderate sodium intakes of 2,400 mg per day.

8. One comment included recent study data (Ref. 91), which the comment believed linked reduced sodium intake to high plasma renin levels and risk of myocardial infarction.

FDA reviewed the study data submitted, and located a review article associated with the original study (Ref. 96). The incidence of myocardial infarction was low (27 instances in 1,717 subjects over 8.3 years) in a narrow and limited population group (predominantly nonwhite, hypertensive males with 20 percent excluded for renin levels outside the limits established for the study). Furthermore, sodium intakes per se were not evaluated in relationship to potential risk. It is unclear whether there is a causal relationship or whether renin levels simply serve as a marker for high risk. It is clearly premature to extrapolate the results of one study with a variety of limitations to the effects that a modest reduction in dietary sodium may have on the general population.

9. One comment mentioned that sodium restriction might precipitate sodium depletion in people with "wasting" nephropathy or chronic renal failure, but that it might also ameliorate their hypertension. The comment noted, further that, at this time, there is not enough information to know what might occur and that patients with these diseases need specific advice from their physicians.

FDA agrees that there is not enough Information to know if sodium restriction to 2,400 mg would pose any concern or be of any benefit with regard to "wasting" nephropathy or chronic renal failure. These are serious diseases and persons with these conditions should be under a physician's supervision and monitoring. Should these persons need to be concerned about their sodium intake, mandatory nutrition labeling of sodium content on all foods can help them meet specific dietary goals set by their physicians and health care consultants.

10. A couple of comments expressed concern that, in consuming low sodium foods, individuals might be missing important nutrients.

FDA disagrees. Many nutrient-rich foods are relatively low in sodium and will qualify for sodium/hypertension health claims (e.g., fruits, vegetables, and some dairy products). Additionally, substitute foods formulated to be low in sodium must be nutritionally equivalent to the foods that they are intended to replace (21 CFR 101.3(e)). Failure to maintain nutritional equivalency results in identification of the substitute food as an "imitation" product. With the mandatory labeling of a core set of nutrients, including sodium, for foods generally (see the final rule on mandatory nutrition labeling published elsewhere in this issue of the **Federal Register**), people consuming low sodium foods as part of a total diet can select a variety of foods and meet nutrient needs.

11. One comment stated that FDA has determined that current U.S. intakes of sodium are not safe. The comment argued, therefore, that current levels are not generally recognized as safe (GRAS), that the food industry should bear the burden of proof that current levels are safe, and that in the absence of such proof, FDA is obligated to require that salt levels be reduced and the food industry is obligated to lower the levels of salt currently being added to foods.

FDA disagrees. Salt has traditionally and historically been regarded as a GRAS substance (21 CFR 182.1), and the GRAS safety review in 1982 (47 FR 26590, June 18, 1982) deferred regulatory action until the impact of the sodium labeling initiatives (47 FR 26580, June 18, 1982; 49 FR 15510, April 18, 1984) could be assessed. The agency is not aware of any new data that would raise significant additional safety concerns. There is thus no basis for reopening the question of salts GRAS status at this time.

III. Statement of the Relationship of Sodium and Hypertension

In the proposed rule (56 FR 00825), FDA tentatively concluded that, based on the totality of the scientific evidence, there is significant scientific agreement among qualified experts that there is a relationship between sodium intake and high blood pressure. Some comments agreed with this conclusion, often providing no evidence. A few comments disagreed and provided specific reasons for their objections.

12. Several comments supported FDA's conclusion that there is sufficient evidence of and significant agreement about a relationship between sodium and hypertension. The FASEB report (Ref. 138) concluded that "both observational data and intervention trials document a small, but consistent effect of dietary sodium chloride on blood pressure." The report further noted that the association between sodium intake and blood pressure may be more meaningfully extrapolated to a population than applied to an individual, that additional studies are necessary to assess the dose-response relationship, and that human data provide no evidence that blood pressure at one age is related to salt intake at an earlier age. A submitted study by Espinel (Ref. 143) identified specific patients and levels of salt intake that triggered hypertension. The results were repeated between 2 months and 1 1/2 years later and remained stable and reproducible.

A few comments and a review article (Ref. 144) disagreed and noted that the scientific data on sodium and hypertension are variable, complex, inconsistent, and more complicated than previously accepted. These comments argued that the epidemiological (i.e., observational) evidence is weak and that information from a natural setting where individuals select their own diets provides no information on how alterations would affect blood pressure. They also argued that modification studies have been short-term, that there are few long-term maintenance studies and data, and that the data are insufficient to support significant long-term effects, including long-term blood pressure changes and reduced rates of stroke and cardiovascular disease. These comments noted that, in contrast, clinical trials of lifesaving drugs often last several years. They suggested that FDA erroneously cited the INTERSALT study to establish that a lifetime lowering of sodium chloride would lower risk of hypertension, and that FDA should avoid giving prescriptive recommendations on weak observational data.

These comments argued further that there is significant controversy regarding the relationship between sodium and hypertension and, therefore, insufficient scientific agreement to support a health claim. The comments noted that the FASEB Report (Ref. 108) concluded that the within-population study data were inconclusive or showed low correlation, and that there was only sparse or inconclusive long-term information

about the relationship. They observed that no consensus was reached at the Workshop on Salt and Hypertension (Ref. 103), and noted that the Dietary Guidelines Advisory Committee (Ref. 135) reported that such a lack of consensus, especially relative to guidance for nonhypertensives, was apparent. (Other comments indicated that, even though consensus was not an aim of the workshop, a large degree of consensus was exhibited.) The comments observed that FDA acknowledged in its proposal the highly polarized views at the Hypertension Workshop (Ref. 103) and the controversy over the interpretation of the INTERSALT results (Ref. 37). The comments argued that the intense and continuing nature of the debate over the relationship between sodium and hypertension evidences lack of significant scientific agreement. The comments accused FDA of not attempting to understand the controversy and change its public health policies, but rather simply dismissing new studies and asserting that there is significant agreement among scientists.

FDA agrees with the FASEB report that there is a small but significant effect of sodium on blood pressure and with the Espinel study results demonstrating that sodium intake can trigger hypertension. This position is consistent with the tentative conclusions reached in the proposal. FDA noted in the proposed rule that the science is complicated by the multi factorial nature of the blood pressure response and that blood pressure varies for each individual and among different individuals. Nonetheless, in spite of large average fluctuations in confounding variables and the resultant impact on blood pressure response, there continues to be a small, significant, and independent impact of sodium on blood pressure, which is supported by the FASEB report (Ref. 138), the National Academy of Sciences' Report (Ref. 62), the Surgeon General's Report (Ref. 43), the INTERSALT study (Ref. 37), and other recent studies (Refs. 41, 44, 45, 55, 71, 76, 80, 90, 94, 97, 100, 106, 107, 109, 121, 122, and 123).

FDA recognizes that data from carefully controlled clinical trials are stronger than data from human observational studies. The methodologic problems in observational studies are more difficult to address adequately,. and there are more individually negative observational studies than trials. Furthermore, pooling of studies is more difficult for observational studies, because of the need to control for confounding variables. Finally, most observational studies are cross-sectional, so they do not establish time-orders (i.e., cause precedes effect). However, despite these limitations, FDA contends that, in general, the human observational data support a relationship between sodium and hypertension. The recent, multinational INTERSALT study (Ref. 37) used carefully standardized methodologies and comprehensive data analysis. The study reported a significant relationship between sodium intake and systolic blood pressure (SBP) for the pooled within-center data and for changes in blood pressure with age for the across-center data. This conclusion is likewise supported by other authoritative reports (Refs. 43 and 62) and is consistent with and strengthened by the experimental evidence provided by randomized clinical trials.

FDA acknowledges that long-term, prospective study data are limited and sometimes inconclusive. However, obtaining definitive, long-term human data on the development of hypertension may be difficult due to a wide variety of factors: (1) the long time necessary for the development of the disease, (2) the large sample and control populations needed for statistical significance, (3) the small absolute magnitude of the effect of sodium on blood pressure, (4) the wide variations in salt content in foods and food products, (5) the large day-to-day and year-to-year variability in dietary sodium intake, (6) the large fluctuations in blood pressure response in the individual, (7) the multifactorial response of blood pressure to a wide variety of nutritional and environmental factors, and (8) the ethical considerations of encouraging or maintaining long-term, high-sodium diets in a control population. The feasibility of obtaining definitive study data was discussed in greater detail in the proposed rule on general requirements for health claims (56 FR 60537 at 60548 through 60549). Nonetheless, although three long-term intervention studies were inconclusive (Refs. 42, 70, and 124), the abstract (Ref. 123) and the recently reported final study results (Ref. 145) of the 18-month Trials of Hypertension Prevention (TOHP) Collaborative Research Group, which were published subsequent to the proposed regulation, reported conclusively that a reduction in sodium intake reduced blood pressure in the sodium intervention group and also showed a trend towards a reduced incidence of hypertension. The 18-month followup of the Koopman study (Ref. 76) also documented reduced blood pressure in response to reduced sodium intake. The results of these clinical trials are thus consistent with and strengthen the INTERSALT results (Ref. 37), which are cross-sectional. Additionally, the INTERSALT study provides useful information for making limited inferences on long-term effects of sodium reductions on blood pressure. The INTERSALT study reported a statistically significant relationship between sodium intake and the slope of SBP and diastolic blood pressure (DBP) with age; i.e., the difference in blood pressure of older individuals in a population relative to younger individuals in the same population is greater in populations with high sodium intake than in populations with low sodium intake. The lack of definitive long-term studies is, therefore, not sufficiently problematic to disallow sodium/hypertension health claims, given the strength of the short-term clinical data relating sodium intake and blood pressure, the difficulties associated with obtaining long-term sodium/hypertension data, and the long history of support by authoritative bodies for public health policies encouraging all people to reduce their sodium intake.

Finally, FDA recognizes that, as is typical in science, there is a wide range of opinion regarding the relationship between sodium and hypertension, and consensus is rarely reached. A requirement for "significant scientific agreement" has not been interpreted by FDA to mean a requirement for consensus. (See final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**.) FDA believes that there is sufficient scientific evidence to provide strong support for a relationship between dietary sodium intake and high blood pressure, and that there is significant scientific agreement that the evidence supports the relationship. In the proposed rule, FDA summarized Government and authoritative reports that concluded that the evidence was sufficiently strong to support a relationship between salt or sodium and high blood pressure, and many of these reports recommended that sodium intake be decreased (Refs. 38, 43, 62, 63, and 85). The interim and final FASEB reports (Refs. 108 and 138) concluded that the totality of the data supports a relationship between dietary sodium chloride and blood pressure. The INTERSALT study (Ref. 37) reported evidence of a relationship between sodium and high blood pressure. Most authors supported the INTERSALT findings and favored sodium restriction

(Refs. 50, 52, 60, 69, 75, 111, and 114), whereas only a few authors considered the effect to be too small and opposed sodium restriction (Refs. 90 and 120). The other scientific studies evaluated in the proposed sodium/hypertension health claim regulation generally supported a relationship between sodium and high blood pressure, although a few were inconclusive or not supportive. Finally, most of the reports at the Hypertension Workshop (Ref. 103) supported reductions in dietary sodium intake (Refs. 94, 95, 97, 98, 102, 104, 105, and 113), while only a few were in opposition (Refs. 110 and 112). Vigorous, spirited debate is necessary to the scientific process and should be encouraged. However, despite the existence of differences of opinion, FDA concludes that, based on the totality of the scientific evidence, there is significant scientific agreement among qualified experts that diets high in sodium are associated with high blood pressure.

13. One comment questioned FDA's evaluation of the INTERSALT data (Ref. 37), indicating it was possibly serious abuse of the scientific data, including a possibly intentionally misleading interpretation. The comment stated that the INTERSALT authors, in their abstract, concluded both that there was no relationship between sodium intake in a society and the prevalence of hypertension within that society, and that there was a positive association between the level of sodium in a society's diet and the rate of rise in blood pressure with age. The comment argued that, if both statements are correct, then the societies with higher sodium, intakes must have had lower blood pressures earlier in life, could not have had more hypertension even after 40 years, and must have had lower blood pressures from 20 to 60 years of age.

The FASEB report (Ref. 138) summarized the results of the INTERSALT study, noting that, after adjustments for age and gender, sodium was significantly correlated with SBP in 39 of the 52 centers and with DBF in 33 of the 52 centers, and that there was a significant linear relationship between average sodium excretion and the slope of SBP with age for all 52 centers, which remained significant when four populations with low salt intakes were excluded.

FDA disagrees with the comment Criticizing FDA's evaluation of the INTERSALT study. The conclusions of both the FASEB report (Ref. 138) and the authors of the INTERSALT study are consistent with FDA's interpretation and not with those of the objecting comment. In the discussion, the INTERSALT study authors noted that some of the results across the centers were no longer statistically significant when the results from four centers with low sodium excretion were excluded. They attributed this to diminished statistical power due to an upper limit of sodium intake that was lower than anticipated, which resulted in a range of intakes too narrow to provide adequate detection sensitivity. They also noted that multiple confounding factors, such as climate, physical activity, and acculturation, would affect results across several centers but would be less likely to confound results within centers. The authors concluded by emphasizing that the data across the centers showed a significant positive association between sodium intake and the slope of increasing blood pressure with age for all 52 centers, which remained significant when the 4 populations with low salt intakes were excluded. These results are consistent with the findings within the centers. FDA believes that it has presented an accurate summary of the INTERSALT results that neither intentionally nor unintentionally misrepresented the authors' findings. FDA also believes that the INTERSALT study provides a useful piece of evidence for supporting the sodium/hypertension relationship that is consistent with and strengthens conclusions in recent consensus and authoritative reports (Refs. 43, 85, 62, and 63).

14. A couple of comments contended that, because there is controversy surrounding the interpretation of the INTERSALT data, FDA is legally and scientifically obligated to independently review the primary data tapes and to make the original data publicly available.

FDA disagrees and notes that it is not reviewing primary data for any of the studies it is evaluating. Rather, the agency reviewed and summarized publicly available scientific reports and publications of results from the INTERSALT study, including both significant and inconclusive findings (56 FR 60825 at 50829 through 60830). FDA considered all these results in determining whether the totality of scientific evidence supported a relationship between sodium and hypertension. This satisfied the agency's legal obligation to evaluate the publicly available scientific evidence and determine whether, based on the totality of that evidence, there is significant scientific agreement among qualified experts that a health claim for sodium and hypertension is supported. Since the primary data tapes from the INTERSALT study are not publicly available, the agency did not review that evidence. The agency does not have the authority to compel the release of these data.

15. One comment objected to the findings of the TOHP Collaborative Research Group study (Ref. 145) (see section VIII.A.5 of this document), which reported significant average decreases in blood pressure (1.7 millimeters of mercury (mm Hg) SBP; 0.9 mm Hg DBP) with average daily reductions in sodium of 55.19 millimoles (mmol) or 1,270 mg in 2, 182 normointensives over an 18-month period. The comment suggested that the study methodology was flawed because the sodium reduction intervention group was compared with unmasked nonintervention controls, because the sodium reduction group was compared with a subset (417 subjects) of the "usual care" control group (589 subjects), and because the authors failed to explain the drop in blood pressure of the control group, which was two-thirds of the decrease noted in the sodium reduction intervention group.

FDA disagrees. As the authors noted, achieving sodium reduction via dietary changes requires active and conscious cooperation of the intervention participants in changing shopping, cooking, and food selection behaviors. Therefore, it would not have been feasible to blind the study participants to the dietary changes necessary to reduce sodium intake. In addition, it would have been impractical to follow free-living participants who are blinded to sodium intake for an 18-month period. Most importantly, the study included blinding at the critical point, blood pressure measurement, that is, trained, certified observers, who were blinded to the dietary sodium status of the participants, took the blood pressure measurements of participants at 3, 6, 12, and 18 months. In addition, the success of the dietary sodium intervention and possible confounding factors were independently monitored at 6, 12, and 18 months by collecting 24-hour urine samples for sodium analysis, and weighing participants. With regard to the number included in the control group systematically and randomly assigned, the total cumulative number of controls was 589 generated as a result of conducting three separate intervention studies. Furthermore, as noted in Figure 1 in the article, the number of control subjects available for respective comparisons varied due to stratification by clinic and body mass index, and as noted on page 1,214 of the article, in clinics where both weight reduction and sodium reduction were

studied, a higher number of subjects were assigned to the control group to provide sufficient high-weight controls for comparison with the weight reduction intervention. Thus, it is inaccurate to conclude that 172 controls were excluded, since none of the three intervention groups had a control group of all 589 controls. Finally, although both the sodium reduction intervention and the control group experienced decreases in blood pressure, the sodium reduction intervention group's decrease in blood pressure relative to the control group was statistically significant. Furthermore, although the control group was not specifically instructed in ways of reducing sodium intake, the independent measures indicated that, at 18 months, the sodium intake of the control group had decreases by 11.33 mmol (260 mg) sodium as compared with 55.19 mmol (1.270 mg) in the sodium reduction intervention group. This reduction in sodium could account for some of the decrease in blood pressure observed in the control group. In conclusion, the epidemiologic study design was rigorous. The study results provide important insight into the relationship between sodium intake and blood pressure in a normotensive population and also into the long-term impact of sodium reduction on both blood pressure and the development of hypertension over time.

16. One comment objected to FDA's definition of normotension, SBP below 140 mm Hg and DBF below 90 mm Hg, arguing that this implies that blood pressures below 90 mm Hg are without risk. The comment noted that those with DBP between 80 and 90 mm Hg account for one third of cardiovascular disease response. The comment suggested that labels state that blood pressure should ideally be no more than 120 mm Hg SBP and 80 mm Hg DBF.

FDA disagrees. In the proposed rule, the agency acknowledged that the definitions of hypertension and normotension are based on correlations with risk of heart disease and stroke, differ by organization and purpose (Refs, 4, 17, 27, and 38), and are currently under review by the Joint National Committee of the National Heart, Lung, and Blood Institute at the National Institutes of Health. The definitions were changed in 1984 (Ref. 23) based on Public Health Service recognition that there is substantial risk associated with blood pressure levels between 140 and 160 mm Hg SBP and between 90 and 95 mm Hg DBP. These definitions will continue to be monitored; however, it would be very confusing to consumers if various government agencies used different definitions of hypertension and normotension. Consequently, FDA adopted the current Public Health Service definitions.

IV. Statement of the Significance of the Sodium and Hypertension Relationship

17. A few comments argued that the general population should be considered to be the general normotensive population, and that studies on hypertensives would, therefore, not be relevant. The comments suggested also that the data on normotensives are sparse, heterogeneous, and short-term, and that there is no clear, persuasive scientific evidence that healthy people in the general population would benefit from sodium reduction or that sodium increases the risk of hypertension in the general population. The comments concluded that the data do not support a recommendation that 200 million normotensives should reduce their daily sodium intake by half.

FDA disagrees with this assessment Under new § 101.14(b)(1), set out in the final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**, to qualify for a health claim a "substance must be associated with a disease or health related condition for which the general U.S. population, or an identified U.S. population subgroup (e.g., the elderly) is at risk." The general population is at risk for hypertension, and sodium consumption is associated with hypertension. One third of the adult, U.S. population is hypertensive (Ref. 85) and many of these are expected to benefit from sodium reduction. Furthermore, many normotensives are likely to benefit as well, because even in the range of normal blood pressures, mortality risk from stroke and heart disease decreases as blood pressures drop (Refs. 68, 69, and 114).

18. One comment opposed the sodium/hypertension claim, arguing that high blood pressure affects a large segment of the population, but that only a minority are salt sensitive and that this fact should be stated if claims are permitted. Other comments argued that there is wide variation among individuals in salt sensitivity, that many patients are not responsive to sodium, and that health claims should not be allowed because only 12.5 percent of the population, the salt-sensitive hypertensives, would benefit. Another comment said that sodium restriction would benefit a large portion of the population, 20 to 40 percent, and one comment argued that FDA should change its statement to indicate that "many" people, rather than "some," would be likely to benefit. One submitted study (Ref. 143) reported that 13 of 30 well-established hypertensive patients (DBP greater than 90 mm Hg) could control their blood pressure (DBP below 90 mm Hg) on a low salt diet (2 g salt or 780 mg sodium per day). The blood pressures of the remaining patients were reduced as well (SBP: from 173.3 to 164.1 mm Hg; DBP: 102.9 to 98.2 mm Hg) but not enough to return to normotensive levels. The FASEB report (Ref. 138) noted that, "(al)though it is clear that there is a marked heterogeneity of blood pressure responses to alterations of dietary NaCI in both the experimental animal and in man, currently, there is not a uniform definition of salt sensitivity of blood pressure." The report concluded that, "until more information is available, caution is recommended before arbitrarily classifying individuals as NaCI sensitive or NaCI resistant."

FDA recognized in its proposed rule that not all persons may be sensitive to salt. However, all salt-sensitive individuals, those with high blood pressures as well as those with normal blood pressures, are likely to benefit from sodium reductions, since mortality risk from stroke and heart disease drops as blood pressures decrease. Even within the range of normal blood pressures, the lower the blood pressure, the lower the risk (Refs. 68, 69, and 114).

Recognizing that the response varies widely between individuals and that not all people are likely to benefit, FDA originally proposed that health claims indicate that a low sodium diet is associated with lower blood pressure in "some people" (proposed § 101.74(c)(2)). Upon reconsideration, the agency agrees with the comment that suggests that more than "some" individuals are likely to profit from reducing sodium intake. The word "some" may erroneously lead consumers to believe that only a small percentage of the population will benefit and may discourage many people from following this dietary goal. Some scientists have estimated that 30 to 60 percent of hypertensives and 15 to 45 percent of normotensives are salt sensitive (Ref. 116) and would thus benefit from sodium reduction. Taken together, this represents a significant segment of the U.S. adult population. FDA is persuaded that these numbers may not be accurately conveyed by noting that "some" people may benefit from sodium reduction. The agency has therefore dropped the use of the qualifier from the regulation. The agency believes that requiring the use of "may" or "might" (new

§ 101.74(c)(2)(i)(A)) to describe the relationship between sodium intake and blood pressure conveys the meaning that not all individuals respond to sodium restriction with lower blood pressure levels. The statement of the significance of sodium in relation to high blood pressure now includes the following sentences at new § 101.74(b)(1): "The scientific evidence indicates that reducing sodium intake lowers blood pressure and associated risks in many but not all hypertensive individuals. There is also evidence that reducing sodium intake lowers blood pressure and associated risks in many but not all normotensive individuals as well." Consistent with other health claim regulations, the final rule specifically permits the inclusion in a claim of information on the number of people in the United States who have high blood pressure.

19. A few comments contended that moderate reductions of less than 100 mmol sodium (2,300 mg) sodium would have limited impact. A couple of these comments noted that the relationship between sodium and hypertension in the INTERSALT study was significant when all 52 centers were included, but not when only 48 centers were considered. The comment considered the sodium intake range in the 48 centers to be comparable to sodium intakes of Western diets, and argued that since the results were not significant in this group, sodium intake changes in this range would not have any significant effect. A few comments also stated that no populations with free access to salt voluntarily choose such low levels. A few comments suggested that reducing sodium intake significantly was not feasible in Western populations. Others disagreed. One comment noted that the public health benefit could be substantial because food habits are linked to preventable diseases. Another comment extrapolated its clinical findings to the total population and estimated that FDA's reference value of 2,400 mg for sodium could result in cost savings of $2.1 billion per year by reducing costs of hypertension medications for patients who can control their blood pressure by diet alone. They further noted that additional cost savings could be expected through reductions in medication dosages, medication side effects, hospitalization, and costs associated with stroke, heart disease, and kidney disease.

FDA agrees with the comments that suggest sodium restriction will have a significant impact. Average estimates of the effect of a reduction in sodium intake of 100 mmol (2,300 mg) per day on SBP range from 2.2 mm Hg (Ref. 37) to 5 to 10 mm Hg (Ref. 106). Since these are population averages and therefore composite figures, the individual impact for many people will be greater than average. Furthermore, estimates suggest that over a 30-year age span (i.e., 25 to 55 years of age), this reduction of 100 mmol per day corresponds to a reduction in mortality rate of 16 percent for heart disease and 23 percent for stroke (Refs. 69 and 114). Other estimates indicate that a 1,150 mg daily change in sodium intake over a 10-year age span (i.e., 50 to 59 years of age) would result in a 26 percent reduction in stroke and a 15 percent reduction in heart disease in Western populations (Ref. 107).

FDA agrees that there is significant potential benefit if moderate sodium intakes in the U.S. population can be achieved and maintained. This is a feasible goal, because it has been estimated that 90 percent of dietary sodium is from salt added during food processing and manufacturing (75 percent) and during food preparation and consumption (15 percent). Thus, only 10 percent of sodium is naturally occurring in food. The agency notes that populations that voluntarily choose to consume high levels of sodium also have high prevalence of hypertension and greater increases of blood pressure with age. FDA continues to believe that encouraging reductions in sodium intake will benefit millions of Americans.

20. One comment objected to health claims listing ways of reducing sodium without noting that the majority (75 percent) is added to foods in processing. and the most effective strategy to reduce sodium intake is to avoid high-sodium, processed foods.

In the proposed rule, FDA included ways to reduce sodium intake as part of the significance statement. § 101.74(b): "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." This information has been deleted from the final rule in order to make it consistent with the final rules authorizing other health claims. However, the same information is included in "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 85). This information is truthful and correct, and manufacturers may provide this or similar information as long as it is presented in a truthful and nonmisleading manner. Furthermore, FDA agrees that most sodium is added in manufacturing and processing; however, the agency has restricted sodium/hypertension health claims to foods naturally low or processed to be low in sodium and salt.

V. Requirements

FDA received many comments about its proposed disqualifying criteria for sodium and hypertension health claims. Some of these comments supported and some opposed the concept of disqualifying criteria, the selected nutrients, the proposed levels, and the per 100-gram (g) criterion.

FDA has made several changes that affect disqualifying criteria, and these changes are discussed more fully in the final rules on general requirement for nutrient content claims, general requirements for health claims, Reference Daily Intakes (RDI's) and Daily Reference Values (DRV's), and serving sizes, which are published elsewhere in this issue of the **Federal Register**. FDA has retained sodium, fat, saturated fat, and cholesterol as disqualifying and disclosure nutrients, but the levels have changed due to changes in serving sizes, in the caloric basis for DV's (from 2,360 to 2,000 kilocalories), in the cutoff percentage for disqualifying nutrients (from 15 percent to 20 percent of the DV), and in the density criteria for disqualifying nutrients (from per 100 g to per 50 g for foods with reference amounts of 30 g or less or two tablespoons or less). As discussed below, these changes have resulted in additional foods qualifying for sodium/hypertension health claims.

The requirement that foods meet the "low sodium" content claim requirements was inadvertently removed from the proposed regulation and a notice to that effect appeared in Corrections to Proposed Regulations (57 FR 8180, March 6, 1992). It has been added to the final rule as new §101.74(c)(2)(ii).

21. Several comments supported FDA's requirement that, in order to qualify for sodium/hypertension health claims, foods must meet the qualifying criterion for "low sodium" foods. Comments also favored allowing health claims only on foods that make a nutritional contribution to the diet. One comment supported requiring foods to meet the "very low sodium" (35 mg sodium) rather than the "low sodium" (140 mg sodium) criterion before being allowed to bear sodium/hypertension health claims. It argued that this would be consistent with prior FDA practices and with scientific evidence that only primitive societies with sodium intake levels at or below this level can avoid developing hypertension. The comment further argued that the only appropriate

target population for sodium/hypertension health claims is individuals on medically restricted diets, that the medical evidence suggests that only salt-sensitive hypertensives would benefit from sodium restriction, and that the INTERSALT (Ref. 37) data showed no effect for diets between 2,300 mg and 4,600 mg sodium per day. The comment concluded that 15 to 26 servings of "very low sodium" foods would provide a daily intake of only 525 to 910 mg sodium, and that this intake level corresponds to the intakes of low sodium populations that had little or no hypertension, and would, therefore, be low enough to have an impact on blood pressure.

FDA disagrees with these comments and contends that restricting sodium/hypertension health claims to "low sodium" foods is consistent with prior agency initiatives that emphasized developing and maintaining policies appropriate for the general public (47 FR 26580, June 18, 1982; and 49 FR 15510, April 18, 1984). The agency does not agree that the only appropriate target population is individuals on medically restricted diets. Furthermore, as discussed in comments 17 and 18 of this document, FDA disagrees that only hypertensives would benefit from reduced sodium intakes. Estimates suggest that 15 to 45 percent of normotensives are likely to benefit from salt (sodium) reduction (Ref. 116). Even within "normal ranges," lower blood pressures are generally associated with reduced mortality risk for the normotensive population as well as for the hypertensive population (Refs. 68, 69, and 114). In addition, 15 to 26 servings of "low sodium" foods would provide from 2,100 to 3,640 mg sodium per day. This is consistent with the DV for sodium of 2,400 mg, published elsewhere in this issue of the **Federal Register**. This is also consistent with FDA's policy that health claims are intended for the general population. Conversely, requiring foods bearing health claims to meet requirements for "very low sodium" could result in a sodium intake from 525 to 910 mg sodium per day, a value more appropriate for therapeutic diets than for diets for the general population. FDA is encouraging the entire population to moderate sodium intake, but the goal for the United States is not to try to reach the sodium intake levels of primitive societies. Although the INTERSALT data cited in the comment on the relationship between sodium and blood pressure were generally inconclusive when the four populations with the lowest sodium intakes were excluded, the data on the relationship between sodium intake and trends in blood pressure with age remained positive and significant.

The definition of "low sodium" requires that foods contain less than 140 mg sodium per reference amount and per 50 g for foods with reference amounts of 30 g or less or 2 tablespoons or less. The "per 50 g" criterion is a change from the proposed criterion of "per 100 g," and this change is discussed in further detail in the final rule on general requirements for nutrient content claims, which is published elsewhere in this issue of the **Federal Register**.

In the companion document on general requirements for health claims, FDA is also prohibiting claims on foods lacking naturally occurring nutrients (i.e., in order to bear health claims, foods must naturally contain a minimum of 10 percent of the RDI or DRV for one of six specified nutrients: Protein, fiber, vitamin A, vitamin C, calcium, and iron). The changes in the qualifying criteria for "low sodium," in the disqualifying levels for fat, saturated fat, and cholesterol, and in the restrictions to foods with naturally occurring nutrients have resulted in the qualification of some additional foods for sodium/hypertension health claims and the disqualification of foods lacking significant naturally occurring nutrients. Examples of foods that may bear sodium/hypertension claims include several additional fish and shellfish products, egg substitutes, and a few skim milk cheeses. Examples of foods that would have qualified for health claims under the proposed rules but no longer qualify include beverages such as carbonated soft drinks, coffees, and teas; most candies, cookies, baked goods, and icings; margarines and salad dressings; sweeteners; most jams and jellies; a few canned fruits; and a few canned and raw vegetables.

22. One comment argued that foods allowed to bear sodium/hypertension health claims should have a calorie restriction, since obesity is a risk factor for high blood pressure.

FDA disagrees. Sodium/hypertension health claims are intended for the general population and not merely for those who need to restrict their caloric intake. It would be a disservice to restrict health claims to low calorie foods, since many people who are at risk for high blood pressure and can benefit from consuming foods that are low in sodium may not need to consume foods low in calories. In addition, although everyone is encouraged to consume a diet low in sodium, individuals can select a variety of foods with different sodium and calorie contents to meet their dietary needs.

23. Some comments approved of the model health claim message. Others expressed concern that, by including too much information, claims would become overly burdensome and ineffective and would discourage manufacturers from using them and consumers from reading them. One comment suggested a simpler claim: "A low sodium diet can help to lower blood pressure in some people with high blood pressure."

FDA appreciates the concern about long and burdensome messages and has discussed this issue in the final rule on general requirements for health claims published elsewhere in this issue of the **Federal Register**. Upon reconsideration, the agency has made several changes that will simplify claims and limit the amount of required information, while assuring that claims are clear and nonmisleading to consumers. The proposed regulation would have imposed the following requirements on health claims: "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" (proposed § 101.74(c)(2)); and "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" (proposed §101.74(c)(3)).

These requirements have been simplified to require that claims use the words "may" or "might" (§ 101.74(c)(2)(i)(A)) (see comment 18 of this document); that the disease and nutrient terms be "high blood pressure" (§ 101.74(c)(2)(i)(B)), and "sodium" (§ 101.74(c)(2)(i)(C)), respectively (this is consistent with the proposed rule); and that claims not state any degree of risk reduction (§ 101.74(c)(2)(i)(D)) (see comment 26 of this document). The agency believes that simplifying the relationship statement will make the message shorter and easier for consumers to understand. In order to be consistent with other regulations, FDA has used wording associating diets low in sodium "to reduced risk of high blood pressure" rather than the wording suggested in the comment "to lower blood pressure." This phrasing more accurately captures the relationship

between sodium intake and high blood pressure than the proposal, which would have permitted claims to note the "association" or "relation" of sodium to blood pressure. In addition, as discussed in comment 18 of this document, the wording "in some people" has been deleted.

24. One comment opposed identifying specific risk populations in health claims and argued that other populations would assume they do not need to be concerned. Others argued that the inclusion of risk populations and dietary risk factors made claims too long and burdensome. Still others provided data on other dietary factors, such as the potassium, calcium, magnesium, or chloride ion content or the ratio of sodium to potassium (Refs. 15, 19, 21, 24, 26, 28, 32, 36, 39, 61, 65, 66, 67, 73, 77, 86, 88, 101, 110, and 115) or suggested that these other dietary factors should be discussed and acknowledged in health claims as dietary risk factors.

FDA recognizes that high blood pressure is a multifactorial disease and that research has indicated that other nutrients may be associated with high blood pressure. However, in the 1990 amendments, Congress directed the agency to evaluate, within a short period of time, the relationship between sodium and hypertension. Thus, FDA's present assessment of the scientific evidence is limited to this relationship. References in a sodium/hypertension health claim to other specified nutrients would constitute a health claim for these nutrients and would not be allowed unless authorized through the petition process set out in the final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**.

FDA is concerned that allowing the unrestricted listing of risk factors for high blood pressure other than sodium intakes could result in risk factors of little relative importance or with minimal scientific support being included on labels. Depending on the context in which they are discussed, information on risk factors other than sodium can be misleading. However, the agency is also concerned that consumers could be misled into overemphasizing the impact of sodium on blood pressure or into believing that high blood pressure can be controlled by sodium restriction alone. Proposed § 101.74(c)(3) would have required health claims to include information identifying populations at greatest risk of developing hypertension and other risk factors associated with high blood pressure.

Upon reconsideration, FDA has chosen to limit the mandatory health claim requirement for sodium and hypertension to a short statement containing the minimum essential information and to allow additional information on an optional basis. Under the final regulation, claims must indicate that the development of high blood pressure depends on many factors. This requirement is intended to prevent consumers from being misled that sodium intake alone is connected with high blood pressure. However, in order to permit shorter claims, the final regulation dose not require that specific risk factors be identified. FDA has listed major risk factors for which there is general scientific agreement in § 101.74(d)(1). Under that section, a claim "may identify one or more of the following risk factors for development of high blood pressure in addition to dietary sodium consumption: family history of high blood pressure, growing older, alcohol consumption, and excess weight." FDA encourages manufactures to provide useful and accurate information on risk factors, but advises that, if specific information about disease risk is included in health claims, then the information must of course be presented in a truthful and nonmisleading manner.

VI. Optional Information

25. One comment supported encouraging 2,400 mg sodium as a maximum intake recommendation for the public at large, and another agreed that current intakes of sodium are well in excess of need and recommendations. Another comment strongly opposed including a statement that sodium intake should not exceed 2,400 mg, indicating that this value is a reference level, not a maximum intake level.

In response to comments urging the agency to shorten health claims and to provide more consistent regulations, FDA has decided to retain this information, but to move it to the significance statement. While most people should target their sodium intakes within the 500 to 2,400 mg range, a very few individuals may need more than the minimum because of excessive sweat losses, and some high calorie consumers may find 2,400 mg impossible to meet. Section 101.74(d)(2) will permit the inclusion of information from the significance statement in a health claim. Consequently, proposed § 101.74(d)(1) has been deleted, and the following sentence has been added to the significance statement in § 101.74(b)(4): "Sodium is an essential nutrient, and experts have recommended a safe minimum level of 500 mg sodium per day and an upper level of 2,400 mg sodium per day, the FDA Daily Value for sodium."

26. Comments from both health professionals and trade associations strongly supported requiring that sodium/hypertension health claims contain a statement that individuals with high blood pressure should consult their physicians for medical advice and treatment. There were no comments opposing this statement or requesting that it remain optional, as proposed. although some comments expressed general objections to the length of health claims.

In the proposal, FDA expressed concern that some people might 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, especially since many people are aware of the dangers of hypertension (Ref. 56) and can easily learn their blood pressure levels by visiting a health professional or using "do it yourself" machines in grocery stores or shopping malls. Requiring the statement about physician consultations as part of the health claim might give consumers the erroneous impression that there is no benefit in making recommended dietary changes unless they have been identified as hypertensive. On the other hand, FDA remains concerned about hypertensives foregoing needed medical diagnosis and treatment. Specifically, definitions of hypertension or normotension in terms of blood pressure readings could encourage self-diagnosis, and information relating specific sodium intakes to specific reductions in blood pressure could encourage self-treatment. To decrease the likelihood of self-diagnosis or treatment based on health claims, in new § 101.74(c)(2)(i)(D) FDA has specifically prohibited claims from including any information on the degree of risk reduction for high blood pressure associated with sodium reduction. The agency has also has removed the following quantitative statements from the significance statement in new §101.74(b):

> 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.

FDA has decided to limit the information required in health claims to that which is essential. Therefore, the agency has retained the physician consultation statement as optional information, § 101.74(d)(7). However, should manufacturers choose to include information that could increase the likelihood of consumers self-diagnosing or self-treating their hypertension, that information must be presented in a clear and nonmisleading manner. For example, claims should not overemphasize the importance of sodium in reducing blood pressure. In addition, should manufacturers include specific information that would assist consumers in self-diagnosing their hypertension, such as definitions of either high or normal blood pressure, then the physician consultation statement would be mandatory, and this requirement has been included in new §101.74(d)(7):

> The claim may state that individuals with high blood pressure should consult their physicians for medical advice and treatment. If the claim defines high or normal blood pressure, then the health claim must state that individuals with high blood pressure should consult their physicians for medical advice and treatment.

Because high blood pressure is a serious disease that often has no outwardly observable symptoms, FDA encourages manufacturers to include a physician referral statement as a public service, and requires it when health claims include information that could encourage self-diagnosis or treatment.

27. The agency proposed to permit the optional use of the term "salt" in addition to the term "sodium" in health claims. However, because of recent studies, and the increasing body of evidence identifying sodium chloride rather than sodium alone as the active substance in affecting blood pressure, the agency specifically requested comments regarding the appropriateness of selecting sodium rather than sodium chloride as the specified nutrient and on allowing the term "salt" in addition to the term "sodium" in health claims. One comment objected to allowing the term "salt" in addition to the term "sodium," arguing that FDA policies have been based on sodium, that the 1990 amendments specify sodium, that it would be arbitrary and capricious to indicate sodium chloride without providing a scientific basis, that consumers would consider the two interchangeably, and that it would undermine previous education efforts. Other comments provided data on sodium salts other than sodium chloride and argued that the effect of sodium on blood pressure was due not to sodium alone but rather to sodium in combination with chloride. One coment noted that only studies involving sodium as the chloride salt have resulted in demonstrable increases in blood pressure. The comment urged the agency to permit salt/hypertension health claims and not sodium/hypertension health claims. The FASEB report (Ref. 138) concluded that "the impact of dietary sodium on blood pressure depends on the provision of sodium as the chloride."

After considering the comments and data submitted in response to the proposed rule, FDA has concluded that these issues are very complex. Salt or sodium chloride is the major source of sodium in foods, and over the years most of the studies investigating the effect of sodium on blood pressure have involved either increasing or decreasing sodium chloride intake (56 FR 60825, Table 2, Refs. 44, 45, 80, 109, 121, 122). Many dietary guidance discussions, policies, and recommendations refer to both sodium and salt (Refs. 43, 62, and 85), and the use of the term "salt" would make claims more understandable to many people. For these reasons, the agency has decided to make final its proposal to permit the optional use of the term "salt" in addition to "sodium."

FDA acknowledges that some studies and reviews indicate that sodium chloride and other sodium salts have distinct effects on blood pressure (Refs. 31, 43, 48, 79, 87, and 92). The agency recognizes that, if it is true that "salt" and not "sodium" is implicated in high blood pressure, products containing other sources of sodium may be incorrectly considered to promote high blood pressure. At present, however, there is not significant scientific agreement that only sodium chloride affects blood pressure, as evidenced by the fact that authoritative documents have not limited their recommendations to salt. Limiting health claims to "salt" would represent a significant policy change and would have implications for many other regulations. FDA has therefore concluded that a thorough review of all the data and an opportunity for public comment are required before such a shift. If concerned parties believe that, based on the totality of the publicly available scientific evidence, there is significant scientific agreement that sodium chloride, and not just sodium, is associated with high blood pressure, they should petition the agency for a change in the regulation.

28. No comments were received regarding FDA's tentative decision to allow the term "hypertension" in addition to the term "high blood pressure." Consequently, FDA has retained this provision in the optional information section of the regulation, although the numbering has changed from § 101.74(d)(4) to (d)(5).

29. Comments to the public docket on sodium and hypertension strongly supported Consumer Summaries. One comment recommended developing additional summaries to target specific audiences. A few comments suggested specific changes in the wording provided in the proposed rule. However, comments to the public docket for the general requirements for health claims generally opposed Consumer Summaries.

FDA acknowledges the interest expressed by comments in the consumer summaries. However, the agency has been persuaded by the comments received overall relative to health claims (See the general requirements for health claims final rule published elsewhere in this **Federal Register**). FDA notes that considerable educational efforts are planned and Consumer Summaries as part of the preamble and not in the codified language had limited utility.

VII. Model Health Claims

30. Several comments approved the model health claim for sodium and hypertension. Others objected to its length or to specific required information, and these comments have been addressed in comments 18, 23, 24, and 27 of this document. FDA has provided new model health claims to illustrate changes made in the proposed regulations.

VIII. Additional Scientific Data

To assure that significant new evidence had not become available subsequent to the proposal, FDA updated its review of the scientific evidence with human studies that were directly relevant to the proposed rule or became available after publication of its proposal (see Table).

A. Review of Scientific Studies and Data

1. Relationship of sodium intake to blood pressure

Pavek and Pavek (Ref. 146) conducted an intervention study in 35 mild, untreated hypertensives (15 males, 20 females) to determine the blood pressure sensitivity to 72-hour salt depletion achieved through a low salt diet consisting of unprocessed rice, potatoes, fruits, vegetables, and 2 liters (L) of tap water. Oscillometric,

auscultatory, and ambulatory blood pressure measurements were taken, and sodium intake was determined by 24-hour urine collections. Average 24-hour urinary sodium decreased by 17.5 mmol (400 mg), and average body weight by 3.1 percent. Average SBP decreased significantly (Oscillometric: 147.3 to 134.8 mm Hg; Auscultatory: 148.0 to 134.4 mm Hg; and Ambulatory Oscillometric: 138.6 to 130.4 mm Hg). Average DBP changed little, and only oscillometric measurements were statistically significant. Determination of individual salt sensitivity varied greatly and depended on the type of blood pressure measurement considered.

Dustan and Kirk (Ref. 125) investigated the effect of sodium depletion (9 meq or 210 mg sodium diet) followed by sodium loading (9 meq or 210 mg sodium plus 3.88 meq or 90 mg sodium per kilogram (kg)) in 51 normotensivo white (19 male, 32 female), 18 normotensive black (7 male, 16 female), and 21 hypertensive black (5 male, 16 female) patients and the effect of sodium loading followed by sodium depletion in 11 normotensive white (2 - male, 9 female), 16 normotensive black (6 male, 10 female), and 19 hypertensive black (4 male, 15 female) patients. The order of sodium loading and depletion did not affect mean arterial pressure in normotensive white patients (blood pressure did not vary) or in hypertensive black patients (blood pressure rose during sodium loading and fell during sodium depletion). Mean arterial pressure in normotensive black patients did not vary when sodium depletion was followed by sodium loading, but when the order was reversed, mean arterial pressure fell during sodium depletion and rose during sodium loading.

A study by Elliott et al. (Ref. 126) analyzed data collected as part of a random sample of 58 subjects aged 40 or above (29 male, 29 female) from a North London population that included diabetics (6 subjects) and individuals taking antihypertensive medication (5 subjects) or diuretics (3 subjects). SBP was significantly and positively related to 24-hour urinary sodium excretion and remained significant after adjustment for age, sex, and body mass index. DBP was significantly related to 24-hour urinary sodium excretion; however, the significance was borderline after adjustment for age and sex and insignificant after additional adjustment for body mass index. The reliability of complete 24-hour urine collection was monitored by para-aminobenzoic acids and the significance of the results was greater in the subgroup identified as having the most complete urine collections. The within-individual variation in sodium intake was estimated from data on 11 subjects who completed two 24-hour collections. A reduction of 50 mmol (1, 150 mg) sodium was associated with lower SBP and DBP of 5.3 and 1.4 mm Hg, respectively.

Khaw and Barrett-Conner (Ref. 128) examined the relationship between blood pressure and sodium estimated from dietary recall data in upper middle class white Southern Californian subjects (584 men and 718 women). Age-adjusted SBP and DBP correlated significantly with dietary sodium intake in men but not in women and with the sodium/potassium ratio in both men and women. The relationship persisted over the entire range of blood pressures and dietary intakes. The authors concluded that the results support the hypothesis that dietary sodium and potassium are related to blood pressure within a population.

He et al. (Ref. 139) investigated! the relationship of 4 dietary ions, including sodium, to blood pressure in 4 population groups of Southern Chinese men from the Sichuan Province: 119 Yi farmers from remote villages in the high mountains, 114 Yi farmers from lower elevation, mountainside villages, 89 Yi people who had migrated to the county seat, and 97 Han people who were native residents of the county seat. Dietary and urinary sodium were significantly and positively correlated with SBP and DBP, even after controlling for age, body mass index, heart rate, alcohol, and total energy intake. Analysis at the individual level confirmed these results.

Forte et al. (Ref. 132) studied the effect of a health education program on salt reduction and blood pressure response in two matched rural Portuguese communities (150 of approximately 800 subjects studied in each community) with initially high daily salt intakes (360 mmol or 8,300 mg sodium). The health education program in the intervention community emphasized adding less salt in the kitchen, eating less cod fish and fewer sausages, and adding less salt to home-baked bread. In addition, local bakers were asked to reduce the salt added to bread by 50 percent during the 2-year trial. Mean sodium intake fell in the intervention community (364 mmol or 8,370 mg to 202 mmol or 4,640 mg) and rose slightly in the control community (352 mmol or 8, 100 mg to 371 mmol or 8,530 mg). In the intervention community, average blood pressure decreased (SBP: decrease of 3.6 mm Hg at one year and 5.0 mm Hg at 2 years, DBP: decrease of 5.0 mm Hg at 1 year and 5.1 mm Hg DBP at 2 years); however, in the control community, average SBP rose and DBP remained constant.

2. Risk factors for high blood pressure

Beretta-Piccoli (Ref. 134) studied total exchangeable sodium in 62 normotensive (SBP < 130 mm Hg, DBP < 90 mm Hg) Swiss males with and without a family history of hypertension (31 subjects each, matched by age, height, and weight) on a normal daily sodium intake (150 mrnol or 3,400 mg) and, in a subgroup of 23 subjects (13 with and 10 without a family history of hypertension), Beretta-Piccoli studied the adaptation of exchangeable sodium to variations in dietary sodium intake (low urinary sodium of 17 mmol or 390 mg versus high urinary sodium of 270 mmol or 6,200 mg). In the first, matched study, blood pressures tended to be higher in the group with a family history of high blood pressure. In the second, subgroup study, blood pressures increased with sodium intake in all subjects, but the magnitude of increase was greater in subjects with a family history of hypertension (SBP: 119 to 126 mm Hg, DBP: 76 to 80 mm Hg) than in those without (SBP: 112 to 113 mm Hg, DBP: 69 to 71 mm Hg).

3. Hypertensives versus norrnotensives

In addition to the Dustan study (Ref. 125) considered above, two additional studies investigated differences in responses for hypertensives and normotensives. Gill et al. (Ref. 127) investigated various hormonal changes in response to various dietary sodium levels. The study classified 19 patients with normal rerun idiopathic hypertension as salt-sensitive (mean arterial pressure increases of 8 to 14 percent) (8 patients) or salt-resistant (mean arterial pressure changes from -7 to +7 percent) (11 patients) as compared with 5 normotensive subjects (mean arterial pressure changes from -3 to +7 percent). Subjects were fed a constant isocaloric diet supplemented with sodium chloride to provide 3 dietary levels of sodium intake: 9 meq (200 mg), 109 meq (2,500 mg), and 249 meq (5,700 mg). Average mean arterial blood pressures on the low sodium relative to the high sodium diet changed from 79 to 83 mm Hg in the normotensive subjects, from 104 to 114 mm Hg in the salt-sensitive hypertensive patients, and remained balanced at 114 mm Hg in the salt-resistant hypertensive patients.

Weinberger and Fineberg (Ref. 141) conducted 3 studies in Indiana. The first investigated the reproducibility of determining salt-sensitivity in 28

normotensive (BP < 140/90) and hypertensive (antihypertension therapy or BP ≤ 140/90 on at least 3 occasions) subjects. Salt-sensitivity was defined in terms of response to sodium chloride infusion (change from 2 L of 0.9 percent sodium chloride to 10 mmol or 230 mg sodium per day) where mean arterial blood pressure responses of 10 mm Hg or greater, of 5 mm Hg or less, and of 6 to 10 mm Hg were classified as salt-sensitive, salt-resistant, and indeterminant, respectively. The authors reported that the majority (18 of 28) were consistent in their responses. The second study investigated the influence of age on blood pressure response to the salt-sensitivity procedure described above in 430 normotensive and 230 hypertensive subjects. Sodium sensitivity increased progressively with age in hypertensive subjects but not in normotensive subjects until they reached 60 years of age and older. The third study assessed changes in blood pressure over 10 or more years in subjects classified initially using the salt-sensitivity procedure described above: 13 hypertensives (10 salt-sensitive, 2 salt-resistant) and 18 normotensives (6 salt sensitive, 12 salt-resistant).

4. Salt sensitivity

In addition to the Gill study (Ref. 127) and the Weinberger study (Ref. 141) considered above, two other studies investigated the salt sensitivity issue. Sullivan et al. (Ref. 130) studied 65 borderline hypertensive (DBP generally below 90 mm Hg but greater than 90 mm Hg on at least 3 occasions) and 92 normotensive subjects to investigate different characteristics of sodium-sensitive and sodium-resistant individuals. Many parameters were studied while subjects followed their usual diets, 10 meq (230 mg) sodium/60 meq potassium diets, and 200 meq (4,600 mg) sodium per 60 meq potassium diets. Sodium sensitivity was defined as a 5 percent increase in blood pressure between the low sodium and the high sodium states; the prevalence of sodium sensitivity was higher in blacks (27 percent of normotensives and 50 percent of borderline hypertensives) than in whites (15 percent of normotensives and 29 percent of borderline hypertensives). Sodium depletion and repletion had a variable effect on blood pressure, and mean blood pressure rose 6.5 percent in those identified as sodium sensitive as compared with 0 percent in those identified as sodium resistant.

Espinel (Ref. 143) conducted a 3-phase dietary salt intervention trial to characterize the response of 30 well-established adult hypertensive patients (DBP greater than 90 mm Hg) to dietary salt. The unrestricted-salt phase certified the presence of hypertension and documented the customary salt intake. The restricted-salt phase (2 g salt) (<34 mmol salt or 780 mg sodium) identified 13 patients, who were considered salt-sensitive, who could control their DBP (below 90 mm Hg) on a salt-restricted diet containing less than 2 g salt per day (SBP: from 177.1 to 145.1 mm Hg; DBP: from 105.4 to 82.0 mm Hg). The blood pressures of the remaining patients were reduced as well (SBP: from 173.3 to 164.1 mm Hg; DBP: from 102.9 to 98.2 mm Hg) but not enough to return to normotensive levels. In the salt-step phase, salt was added to the diet established during the restricted-salt phase in a stepwise manner (increases of 1 g salt or 390 mg sodium; each step lasting at least 3 days) to determine the level of salt that triggered hypertension in individual patients. This level was termed the Salt Hypertension Threshold for that patient and in the 13 patients ranged from 3 to 16 g salt (1,200 to 6,200 mg sodium) per day. The test was repeated between 2 months and 1 1/2 years later and the results remained stable and reproducible.

5. Long-term effect

The results of an 18-month trial on normotensives, the TOHP Collaborative Research Group study abstract (Ref. 123) was included in the proposed regulation, and the final study results are summarized here (Ref. 145). The TOHP Collaborative Research Group study included 7 nonpharmacologic interventions, 3 life-style changes (weight reduction, sodium reduction, and stress management), and 4 nutritional supplements (calcium, magnesium, potassium, and fish oil) in 2, 182 normotensive (DBP from 80 to 89 mm Hg) subjects (70 percent male). The sodium-reduction intervention emphasized shopping, cooking, and food selection behavior aimed at reducing sodium intake, and at 18 months had achieved average daily reductions of 55.19 mmol sodium (1,270 mg) as compared to 11.33 mmol sodium (260 mg) in the control group from initial baseline values of 154.6 mmol (3,550 mg) and 156.4 mmol (3,600 mg) in the two groups, respectively. Statistically significant average decreases in blood pressure were reported in the intervention group as compared with the control group for both DBP (decrease of 0.9 mm Hg) and SBP (decrease of 1.7 mm Hg).

Joosens and Kesteloot (Ref. 147) reanalyzed data from 3,328 subjects collected as part of 6 Belgian surveys conducted between 1967 and 1986. Six of the surveys included blood pressure data and five included 24-hour sodium excretion data. Between 1967 and 1986, the mean standardized sodium excretion decreased from 265 to 160 mmol in men (6, 100 to 3,700 mg) and from 208 to 160 mmol in women (4,800 to 3,700 mg). Mean SBP decreased from 169 to 142 mm Hg in men and from 171 to 147 mm Hg in women. The prevalence of hypertension (SBP > 159 mm Hg) decreased from 51 to 21 percent in men and from 66 to 22 percent in women, and severe hypertension (SBP > 220 mm Hg) nearly disappeared. During the same period, body mass index increased 1.1 kg/m^2 in men and was unchanged in women. Since increased weight is associated with increases in blood pressure, the observed decreases in blood pressure could not be ascribed to changes in weight. The proportion of subjects receiving treatment for hypertension increased from 10 to 36 percent in men and from 18 to 41 percent in women. The increased treatment would account for some of the observed decreases in blood pressure, but the authors concluded that treatment alone could not account for all of the observed changes in blood pressure. The authors used the correlation between sodium intake and blood pressure from the INTERSALT study (Ref. 37) and the observed decrease in sodium intake In Belgium from 1967 to 1986 in order to estimate the expected corresponding decrease in SBP. Considered together, the increase in treatment and the decrease in sodium intake were considered sufficient to explain the observed decreases in blood pressure. Methodologies in the six studies were similar but not identical, adding to the uncertainties.

6. Sodium chloride versus other sodium salts

Shore et al. (Ret. 129) conducted a randomized, crossover study to investigate the blood pressure response of six hypertensives (DBP between 90 to 110 mm Hg) on low sodium diets of 10 mmol (230 mg) sodium and 80 mmol potassium with the addition of either sodium chloride (120 mmol or 2,760 mg total daily sodium) or sodium potassium (122 mmol or 2,800 mg total daily sodium). Urinary sodium excretion was similar during both periods. However, blood pressures increased when sodium chloride was added to the diet, but not when sodium phosphate was added.

7. Effect on medication requirements

Weinberger et al. (Ref. 131) investigated whether free-living

hypertensive patients could reduce their medication by individualized dietary counseling aimed at moderately reducing their dietary sodium intake. Only 98 of the original 114 individuals completed the study and maintained significant reductions in mean sodium intake for 30 weeks. Those who achieved the 80 mmol (1,800 mg) sodium goal were more likely to have a reduction in a number of medications than those not reaching the goal.

In an observer-blind, controlled trial, Little et al. (Ref. 140) compared the effect of a low sodium, low fat, high fiber diet against the individual components of the diet in reducing the amount of antihypertensive medication required by 196 patients with established hypertension. Medication reductions were 64 percent and significant on the combination diet, 45 percent and insignificant on the low sodium diet, and 33 percent on the control diet; 57.5 percent of patients on the combination diet stopped all medication as compared with 24 percent on the control diet.

8. Effect of sodium intake on medicated patients

Carney et al. (Ref. 136) used a randomized, double-blind, crossover study design to investigate the effect of 100 mmol (2,300 mg) of sodium chloride on blood pressure control in 11 patients with mild to moderate hypertension successfully treated with various hypotensive agents. No significant changes in supine or erect blood pressure were observed in these medicated patients.

9. Studies in children

An intervention study by Ellison et al. (Ref. 148) involved reducing the sodium intake of students by 15 to 20 percent through changes in food purchasing and preparation practices in two boarding high schools. Each school served alternately as the control or the intervention school, for one school year. Early in the year, blood pressures increased above baseline; however, as the year progressed blood pressures in the intervention school dropped and remained below baseline. The average SBP and DBP, adjusted for sex and initial blood pressure, were reduced by 1.7 and 1.5 mm Hg, respectively, on the low sodium diet when measured from the beginning to the end of the school year. Changes in sodium intake were calculated from 24-hour food diaries completed periodically during the year, and no independent measurements were made to document changes in sodium intake

A longitudinal study by Geleijnse at al. (Ref. 149) collected blood pressure and electrolyte data annually from 233 Netherlands children ranging in age from 5 to 17 years old (108 boys, 125 girls) for an average period of 7 years in order to investigate the association between sodium and potassium intake and the change in blood pressure over time. No significant association between sodium intake and the change in blood pressure over time was observed. Mean 24-hour sodium intakes were calculated values and were based on six timed, overnight urine collections.

Miller et al. (Ref. 150) conducted an intervention study in Indiana with 64 male and 84 female white, normotensive children to determine if modest dietary restriction in childhood results in heterogeneous changes in blood pressure response. Families received instruction to assist them in restricting their dietary sodium to 60 mmol (1,380 mg) per day. Average sodium decreased from 112.9 mmol (2,600 mg) to 53.4 mmol (1,230 mg) in boys and from 91.1 mmol (2,090 mg) to 41.1 mmol (940 mg) in girls. Changes in SBP were not significant for either boys or girls, but girls showed a decrease in DBP ($p<0.05$) and in mean arterial pressure.

Rocchini et al. (Ref. 133) studied blood pressure changes in 60 obese and 18 nonobese adolescents (10 to 16 years of age) on high salt diets (> 250 mmol or 5.700 mg sodium) per day and low salt diets (< 30 mmol or 700 mg sodium) per day with the caloric content held constant. In the obese adolescents, there was a statistically significant decrease in blood pressure on the low sodium diet (mean arterial pressure change from 92 to 80 mg Hg), but no significant change was observed in the nonobese adolescents (mean arterial pressure change from 76 to 77 mm Hg). The study was repeated on 51 of the obese adolescents after 20-week weight loss program. The 36 subjects who lost at least 1 kg of body weight (average weight loss 7.5 kg) had a reduced sensitivity of blood pressure to sodium (mean arterial pressure change from 82 to 81 mm Hg) as compared to the 15 subjects who lost less than 1 kg of body weight (mean arterial pressure change from 89 to 79 mm Hg).

B. Conclusions from Scientific Studies and Data

In assessing the new scientific evidence, FDA has considered whether the evidence significantly challenges any of its tentative conclusions presented in the proposed rule.

The agency has determined that, although one study was inconclusive (Ref. 125), the scientific evidence continues to support a relationship between sodium and hypertension in adults (Refs. 123, 126, 127, 128, 132, 134, 139, 141, 146, and 147). In particular, the 3-year study on nonpharmacologic interventions (Ref. 145) strengthens previously limited evidence on the benefits of long-term sodium reduction in reducing blood pressure. In addition, the Espinel study (Ret. 143) demonstrates the wide variability in blood pressure response to sodium and the long-term individual reproducibility. The studies on children sometimes showed an effect (Ref. 148), sometimes showed no effect (Ref. 149), and sometimes showed an effect in certain population subgroups but not in others (Refs. 133 and 150). The one study involving a nonchloride sodium salt (Ref. 129) showed an effect for sodium chloride but not for sodium phosphate, which supports the contention that sodium chloride and not sodium per se is important in blood pressure response (see comment 27 of this document).

In conclusion, the new scientific evidence strengthens the conclusion reached in the proposed regulation that, based on the totality of the scientific evidence, there is significant scientific agreement that the evidence supports health claims that diets low in salt and sodium may help lower blood pressure in many people.

IX. Conclusions

FDA has responded to all comments received in response to the proposed sodium/hypertension health claim regulation. In addition, the agency has reviewed all additional scientific studies received in comments or independently identified and has determined that the new studies strengthen the conclusions reached in the proposed regulation. After considering the comments and the new scientific studies, the agency concludes that health claims for sodium and hypertension should be authorized.

The agency has decided that the regulations for the authorized health claims are most useful if they follow a consistent format and require only information that the agency considers essential. Therefore, the agency has made a number of editorial changes in the proposed codified material of the sodium and hypertension health claim to make it more consistent with other authorized claims.

X. Economic Impact

In its food labeling proposals of November 27, 1991 (56 FR 60366 et seq.), FDA stated that the food labeling reform initiative, taken as a whole,

would have associated costs in excess of the $100 million threshold that defines a major rule. Thus, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA developed one comprehensive regulatory impact analysis (RIA) that presented the costs and benefits of all of the food labeling provisions taken together. That RIA was published in the **Federal Register** of November 27, 1991 (56 FR 60856), and along with the food labeling proposals, the agency requested comments on the RIA.

FDA has evaluated more than 300 comments that it received in response to the November 1991 RIA. FDA's discussion of these comments is contained in the agency's final RIA published elsewhere in this issue of the **Federal Register**. In addition, FDA will prepare a final regulatory flexibility analysis (RFA) subsequent to the publication of the food labeling final rules. The final RFA will be placed on file with the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, and a notice will be published in the **Federal Register** announcing its availability.

In the final RIA, FDA has concluded, based on its review of available data and comments, that the overall food labeling reform initiative constitutes a major rule as defined by Executive Order 12291. Further, the agency has concluded that although the costs of complying with the new food labeling requirements are substantial, such costs are outweighed by the public health benefits that will be realized through the use of improved nutrition information provided by food labeling.

XI. Environmental Impact

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

XII. References

The following references have been pieced 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 Generates de Medicine*, 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.

3. Select Committee on Nutrition and Human Needs, "Dietary Goals for the United States," 2d ed., U.S. Senate, 95th Cong., 1st sess., U.S. Government Printing Office, Washington, 1977.

4. World Health Organization, "Arterial Hypertension," Report of a WHO Expert Committee, Technical Report Series 628, World Health Organization, Geneva, 1978.

5. Beaton, G. H., et al., "Sources of Variance in 24-hour Dietary Recall Data: Implications for Nutrition Study Design and Interpretation," *American Journal of Clinical Nutrition*, 32:2456-2559, 1979.

6. LSRO, "Evaluation of the Health Aspects of Sodium Chloride and Potassium Chloride as Food Ingredients," SCOGS-102, FASEB, Bethesda, MD, 1979.

7. Modem Nutrition in Health and Disease, 6th ed., R. S. Goodhart, and M. E. Shils (eds.), Lea and Febiger, Philadelphia, PA, pp. 362-377, 833-835, 1003-1004, 1006-1020, 1024, and 1031-1032, 1980.

8. Niven, C. F. Jr., "Technology of Sodium in Processed Foods: General Bacteriological Principles, With Emphasis on Canned Fruits and Vegetables, and Dairy Foods," in "Sodium and Potassium in Foods and Drugs," Conference Proceedings, White, P. L. and S. C. Crocco (eds.), *American Medical Association*, Chicago, IL, pp. 45-60, 1980.

9. "Nutrition and Your Health: Dietary Guidelines for Americans," Home and Garden Bulletin No. 232, U.S. Department of Agriculture (USDA), Department of Health and Human Services (DHHS), 1980.

10. Vetter, J. L., "Technology of Sodium in Bakery Products" in "Sodium and Potassium in Foods and Drugs," Conference Proceedings, White, P. L. and S. C. Crocco (eds.), *American Medical Association*, Chicago, IL, pp. 61-65, 1980.

11. Subcommittee on Investigations and Oversight of the Committee on Science and Technology, "Sodium in Food and High Blood Pressure," Serial M, U.S. House of Representatives, 97th Cong., 1st sess., U.S. Government Printing Office, Washington, DC, 1981.

12. Heimbach, J. T., "Public Understanding of Food Label Information," Division of Consumer Studies, FDA, 1982.

13. Marsh, A. C., "Processes and Formulations that Affect the Sodium Content of Foods," *Food Technology*, pp. 45-49, July 1983.

14. Porter, G. A., "Chronology of the Sodium Hypothesis and Hypertension," *Annals of Internal Medicine*, 98:720-723, 1983.

15. Resnick, L. M., J. H. Laragh, J. E. Sealey, and M. H. Alderman, "Divalent Cations in Essential Hypertension," *New England Journal of Medicine*, 309:888-891, 1983.

16. Shank, F. R., L. Larsen, F. E. Scarbrough, J. E. Vandorveen, and A. L. Forbes, "FDA Perspective on Sodium," *Food Technology*, pp. 73-78, July 1983.

17. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, "The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure," *Archives of Internal Medicine*, 144;1045-1057, 1984.

18. Pennington, J. A. T., D. B. Wilson, R. F. Newell, B. F. Harland, R. D. Johnson, and J. E. Vanderveen, "Selected Minerals in Foods Surveys, 1974 to 1981/82," *Journal of the American Dietetic Association*, 84:771-780, 1984.

19. Resnick, L. M., R. K. Gupta, and J. H. Laragh, "Intracellular Free Magnesium in Erythrocytes of Essential Hypertension: Relation to Blood Pressure and Serum Divalent Cations," *Proceedings of the National Academy of Sciences of the United States of America*, 81:6511-6515, 1984.

20. Armstrong, L. E., R. W. Hubbard, P. C. Szlyk, W. T. Matthew, and I. V. Sils, "Voluntary Dehydration and Electrolyte Losses During Prolonged Exercise in the Heat," *Aviation, Space, and Environmental Medicine*, pp. 765-770, August 1985.

21. MacGregor, G. A., "Sodium is More Important than Calcium in Essential Hypertension," *Hypertension*, 7:628-637, 1985.

22. "Nutrition and Your Health: Dietary Guidelines for Americans," 2d ed., Home and Garden Bulletin No. 232, USDA, DHHS, 1985.

23. Subcommittee on Definition and Prevalence of the 1984 Joint National Committee, Final Report, "Hypertension Prevalence and the Status of Awareness, Treatment, and Control in the United States," *Hypertension*, 7:457-468, 1985.

24. Weinsier, R. L. and D. Norris, "Recent Developments in the Etiology and Treatment of Hypertension: Dietary Calcium, Fats and Magnesium," *American Journal of Clinical Nutrition*, 42:1331-1338, 1985.

25. Division of Consumer Studies, "Trends in Sodium labeling of Supermarket Foods 1978-1986—Food Label and Package Survey (FLAPS)," FDA, Center for Food Safety and Applied Nutrition, 1986.

26. Kaplan, N. M. and R. B. Meese, "The Calcium Deficiency Hypothesis of Hypertension: A Critique," *Annals of Internal Medicine*, 105:947-955, 1986.

27. National Center for Health Statistics, Drizd, T., A. L. Dannenberg, and A. Engel, "Blood Pressure Levels in Persons 18-74 Years of Age in 1976-80, and Trends in Blood Pressure From, 1960 to 1980 in the United States," Vital and Health Statistics, Data from the National Health and Nutrition Examination Survey, Series 11, No. 234, DHHS Pub. No. (PHS) 86-1684, DHHS. Public Health Service (PHS), U.S. Government Printing Office, Washington, DC, July 1986.

28. Resnick, L. M., J. P. Nicholson, and J. H. Laragh. "Calcium Metabolism in Essential Hypertension: Relationship to Altered Renin System Activity," *Federation Proceedings*, 45:2739-2745, 1986.

29. Subcommittee on Nonpharmacologic Therapy of the 1984 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, Final Report, "Nonpharmacologic Approaches to the Control of High Blood Pressure," National Heart, Lung, and Blood Institute,

National Institutes of Health, *Hypertension*, 8:444-467, 1986.

30. Knochel, J. P. and G. Reed, "Disorders of Heat Regulation" in Clinical Disorders of Fluid and Electrolyte Metabolism, 4th ed., M. H. Maxwell, C. R. Kleeman, and R. G. Narins (eds.) McGraw Hill, New York, pp.1197-1232, 1987.

31. Kurtz, T.W., H. A. Al-Bander, R. C. Morris, Jr., "'Salt-Sensitive' Essential Hypertension in Men—Is the Sodium Ion Alone Important?", *New England Journal of Medicine*, 317:1043-1048, 1987.

32. McCarron, D. A., and C. D. Morris, "The Calcium Deficiency Hypothesis of Hypertension," *Annals of Internal Medicine*, 107:919-922, 1987.

33. Miller, J. Z., M. H. Weinberger, S. A. Daugherty, N. S. Fineberg, J. C. Christian, and C. E. Grim, "Heterogeneity of Blood Pressure Response to Dietary Sodium Restriction in Normotensive Adults," *Journal of Chronic Disease*, 40:245-250, 1987.

34. Sanchez-Castillo, C. P., W. J. Branch, and W. P. T. James, "A Test of the Validity of the Lithium-marker Technique for Monitoring Dietary Sources of Salt in Man," *Clinical Science*, 72:87-94, 1987.

35. Sanchez-Castillo, C. P., S. Warrender, and W. P. T. James, "An Assessment of the Sources of Dietary Salt in a British Population," *Clinical Science*, 72:95-102, 1987.

36. Gruchow, H. W., K. A. Sobocinski, and J. Barboriak, "Calcium intake and the Relationship of Dietary Sodium and Potassium to Blood Pressure," *American Journal of Clinical Nutrition*, 48:1463-1470, 1988.

37. The INTERSALT Cooperative Research Group, "Intersalt: An International Study of Electrolyte Excretion and Blood Pressure: Results for 24-Hour Urinary Sodium and Potassium Excretion," *British Medical Journal*, 297:319-328, 1988.

38. 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," *Archives of Internal Medicine*, 148:1023-1038, 1988.

39. Luft, F. C. and M. H. Weinberger, "Review of Salt Restriction and the Response to Antihypertensive Drugs—Satellite Symposium on Calcium Antagonists," *Hypertension*, 11 (Suppl I) 1-229-I-232, 1988.

40. Masugi, F., T. Ogihara, K. Hashizume, T. Hasagawa, K. Sakafuchi, and Y. Kumahara, "Changes in Plasma Lipids and Uric Acid with Sodium Loading and Sodium Depletion in Patients with Essential Hypertension," *Journal of Human Hypertension*, 1:293-298, 1988.

41. Smith, W. C. S., L K. Crombie, R. T. Tavendale, S. K. Gullard, and H. D. Tunstall-Pedoe, "Urinary Electrolyte Excretion, Alcohol Consumption, and Blood Pressure in the Scottish Heart Health Study," *British Medical Journal*, 297:329-330, 1988.

42. Staessen, J., C. J. Bulpitt, R. Fagard, J. V Joossens, P. Lijnen, and A. Amery, "Salt Intake and Blood Pressure in the General Population: A Controlled Intervention Trial in Two Towns," *Journal of Hypertension*, 6:965-973, 1988.

43. Surgeon General's Report on "Nutrition and Health," DHHS, PHS, U.S. Government Printing Office, Washington, DC, pp. 1-20, 139-175, 1988.

44. Australian National Health and Medical Research Council Dietary Salt Study Management Committee, "Fall in Blood Pressure with Modest Reduction in Dietary Salt Intake in Mild Hypertension," *Lancet*, pp. 399-402, February 25, 1989.

45. Australian National Health and Medical Research Council Dietary Salt Study Management Committee, "Effects of Replacing Sodium Intake in Subjects on a Low Sodium Diet: A Crossover Study," *Clinical and Experimental Hypertension—Theory and Practice*, A11:1011-1022, 1989.

46. Bender, M., "Status of Nutrition and Sodium Labeling on Processed Foods: 1988—Food Label and Package Survey (FLAPS)." Division of Consumer Studies, Center for Food Safety and Applied Nutrition, FDA, 1989.

47. Blumenthal, D., "The Health-Diet Link—Charting a Rising Awareness," FDA Consumer, pp. 23-27, October 1989.

48. Boegehold, M. A. and T. A. Kotchen, "Relative Contributions of Dietary Na+ and Cl- to Salt-Sensitive Hypertension," *Hypertension*, 14:579-583, 1989.

49. Egan, B. M. and A. B. Weder, "Deleterious Effects of Short-Term Dietary NaCI Restriction in Man: Relationship to Salt-Sensitivity Status," presented at American Heart Association's Scientific Sessions in New Orleans, LA, November 15, 1989.

50. Elliott, P., "The INTERSALT study: An Addition to the Evidence on Salt and Blood Pressure, and Some Implications," *Journal of Human Hypertension*, 3:289-298, 1989.

51. Elliott, P., A. Dyer, and R. Stamler, on behalf of the INTERSALT Co-operative Research Group, "The INTERSALT Study: Results for 24 Hour Sodium and Potassium, by Age and Sex," *Journal of Human Hypertension*, 3:323-330, 1989.

52. Elliott, P., et al, "The INTERSALT Study: Main Results. Conclusions and Some Implications," *Clinical and Experimental Hypertension—Theory and Practice*, All:1025-1034, 1989.

53. Elliott, P., et al., "Sodium, Potassium, Body Mass, Alcohol, and Blood Pressure in Three United Kingdom Centers (the INTERSALT Study)," *European Journal of Clinical Nutrition*, 44:637-645, 1990.

54. Hashimoto, T., et al., "Urinary Sodium and Potassium Excretion, Body Mass Index, Alcohol Intake and Blood Pressure in Three Japanese Populations," *Journal of Human Hypertension*, 3:315-321, 1989.

55. Lasaridis, A., et al., "The Effects of Daily Sodium Intake on the Relationship of Blood Pressure, Renal Plasma Flow and Natriuresis in Essential Hypertension," *Journal of Hypertension*, 7 (Suppl.) S180-S181, 1989.

56. Levy, A. S. and J. T. Heimbach, "Recent Public Education Efforts About Health and Diet," FDA, Division of Consumer Studies, Washington, DC, 1989.

57. LSRO, "Nutrition Monitoring in the United States—An Update Report on Nutrition Monitoring," FASEB, prepared for the DHHS, PHS, and the USDA, Food and Consumer Services, DHHS Publication No. (PHS) 89-1255, PHS, Washington, U.S. Government Printing Office, September 1989.

58. Mancilha Carvalho, J. J., et al., "Blood Pressure in Four Remote Populations in the INTERSALT Study," *Hypertension*, 14:238-246, 1989.

59. Mancilha Carvalho, J. J., de R. Oliveira, and R. J. Esposito, "Blood Pressure and Electrolyte Excretion in the Yanomamo Indians, an Isolated Population," *Journal of Human Hypertension*, 3:309-314, 1989.

60. Marmot, M. G. and P. Elliott, "Public Health Measures for Blood Pressure Control in the Whole Community," *Clinical and Experimental Hypertension—Theory and Practice*, All:(5 and 6), pp. 1171-1186, 1989.

61. Moore, T. J., "The Role of Dietary Electrolytes in Hypertension," *Journal of the American College of Nutrition*, 8 (Suppl.), 68S-80S, 1989.

62. The National Academy of Science's Report, "Diet and Health—Implications for Reducing Chronic Disease Risk," Committee on Diet and Health, Food and Nutrition Board, Commission on Life Sciences, National Research Council, National Academy Press, Washington, DC, pp. 3-40, 413-430, 549-561, 1989.

63. Subcommittee on the Tenth Edition of the Recommended Dietary Allowance's, Food and Nutrition Board, Commission on Life Sciences, National Research Council, "Recommended Dietary Allowances," 10th ed., National Academy Press, Washington, DC, pp. 247-261, 1989.

64. Rose, G. and J. Stamler, on behalf of the INTERSALT Cooperative Research Group, "The INTERSALT Study; Background, Methods and Main Results," *Journal of Human Hypertension*, 3:283-288, 1989.

65. Saito, K., H. Sano, Y. Furuta, and H. Fukuzaki, "Effect of Oral Calcium on Blood Pressure Response in Salt-loaded Borderline Hypertensive Patients," *Hypertension*, 13(3):219-226, 1989.

66. Sowers, J. R., "Dietary Calcium Effects in Salt-sensitive Hypertension," *Clinical Nutrition*, pp. 158-163, 1989.

67. Sowers, J. R., P. Zemel, P. Standley, J. Kraniak, and M. B. Zemel, "Role of Calcium in Modulating Salt Sensitivity" in Salt and Hypertension: Dietary Minerals, Volume Homeostasis and Cardiovascular Regulation, Springer Verlag, New York, pp. 169-175, 1989.

68. Stamler, J., J. D. Neaton, and D. N. Wentworth, "Blood Pressure (Systolic and Diastolic) and Risk of Fatal Coronary Heart Disease," *Hypertension*, 13 (Suppl. I) 2-12, 1989.

69. Stamler, J., G. Rose, R. Stamler, P. Elliott, A. Dyer, and M. Marmot, "INTERSALT Study Findings—Public Health and Medical Care Implications," *Hypertension*, 14:570-577, 1989.

70. Stamler, R., et al., "Primary Prevention of Hypertension by Nutritional-Hygienic Means—Final Report of a Randomized, Controlled Trial," *Journal of the American Medical Association*, 262:1801-1807, 1989.

71. Takemori, K., S. Mikami, S. Nihira, and N. Sasaki, Tohoku, *Journal of Experimental Medicine*, 158:269-281, 1989.

72. Alderman, M. H. and B. Lamport, "Moderate Sodium Restriction—Do the

Benefits Justify the Hazards?", *American Journal of Hypertension*, 3:499-504, 1990.

73. Ernst, F. A., C. O. Enwonwu, and R. A. Francis, "Calcium Attenuates Cardiovascular "Reactivity to Sodium and Stress in Blacks," *American Journal of Hypertension*, 3:451-457, 1990.

74. DHHS, PHS, "Healthy People 2000-National Health Promotion and Disease Prevention Objectives," DHHS Pub. No. (PHS) 91-50213, U.S. Government Printing Office, Washington, DC, 1990.

75. Kaplan, N. M., "New Evidence on the Role of Sodium in Hypertension—The INTERSALT Study," *American Journal of Hypertension*, 3:168-169, 1990.

76. Koopman, H., C. Spreeuwenberg, R. F. Westerman, and A. J. M. Donker, "Dietary Treatment of Patients with Mild to Moderate Hypertension in a General Practice: A Pilot Intervention Study. (2) Beyond Three Months," *Journal of Human Hypertension*, 4:372-374, 1990.

77. Kurtz, T. W. and R. C. Morris, Jr., "Sodium-Calcium Interactions and Salt-Sensitive Hypertension," *American Journal of Hypertension*, 3:152S-155S, 1990.

78. Levy, A. S. and T. Guthrie, "Prevalence and Distribution of Sodium Avoidance Dieting Behavior in the U.S.: 1982-1988," Center for Food Safety and Applied Nutrition, 1990.

79. Luft, F. C., M. B. Zemel, J. A. Sowers, N. S. Fineberg, and M. H. Weinberger, "Sodium Bicarbonate and Sodium Chloride: Effects on Blood Pressure and Electrolyte Homeostasis in Normal and Hypertensive Man," Journal of Hypertension, 8:663-670, 1990.

80. Mtabaji, J. P., Y. Nara, and Y. Yamori, "The Cardiac Study in Tanzania: Salt Intake in the Causation and Treatment of Hypertension," *Journal of Human Hypertension*, 4:80-81, 1990.

81. National Center for Health Statistics, Adams, P. F. and V. Benson, "Current Estimates from the National Health Interview Survey, 1989" in "Vital and Health Statistics," Data from the National Health Survey, DHHS Pub. No. (PHS) 90-1504, DHHS, PHS, Centers for Disease Control, Series 10, No. 176, p. 84, October 1990.

82. National Center for Health Statistics, "Advance Report of Final Mortality Statistics, 1988," Final Data from the National Center for Health Statistics, Monthly Vital Statistics Report, DHHS, PHS, Centers for Disease Control, vol. 39, No. 7, Supplement, p. 20, November 28, 1990.

83. National Center for Health Statistics, "Health, United States, 1989," DHHS Pub. No. (PHS) 90-1232, DHHS, PHS, Centers for Disease Control, U.S. Government Printing Office, Washington, DC, pp. 25-27, 1990.

84. "Nutrition Recommendations—The Report of the Scientific Review Committee," Catalog Number H49-42/1990E, Canadian Government Publishing Centre, Ottawa, Canada, 1990.

85. "Nutrition and Your Health: Dietary Guidelines for Americans," 3d ed., "Home and Garden Bulletin No. 232," USDA, DHHS, 1990.

86. Oparil, S., J. M. Wyss, R. Yang, H. Jin, and Y. Chen, "Dietary Ca2+ Prevents NaCI-sensitive Hypertension in Spontaneously Hypertensive Rats by a Sympatholytic Mechanism," *American Journal of Hypertension*, 3(8):179S-188S, 1990.

87. Passmore, J. C. and A. E. Jimenez, "Separate Hemodynamic Roles for Chloride and Sodium in Deoxycorticosterone Acetate-salt Hypertension," *Proceedings of the Society for Experimental Biology and Medicine*, 194:283-288, 1990.

88. Resnick, L. M., "The Effects of Sodium and Calcium in Clinical Hypertension: Mediating Role of Vitamin D Metabolism," The Biology and Medicine of Signal Transduction," Nishizuka, Y. et al. (eds.), Raven Press, New York, 1990.

89. Sharma, A. M., H. R. Arntz, A. Kribben, S. Schattenfroh, and A. Distler, "Dietary Sodium Restriction: Adverse Effect on Plasma Lipids," *Klinische Wochenschrifts*, 68;664-668, 1990.

90. Swales J. D., "Studies of Salt Intake in Hypertension—What Can Epidemiology Teach Us?", *American Journal of Hypertension*, 3:645-649, 1990.

91. Alderman, M. H., S. Madhavan, W. L. Ooi, H. Cohen, J. E. Sealey, and J. H. Laragh, "Association of the Renin-Sodium Profile with the Risk of Myocardial Infarction in Patients with Hypertension," *New England Journal of Medicine*, 324:1098-1104, 1991.

92. Boegehold, M. A. and T. A. Kotchen, "Importance of Dietary Chloride for Salt Sensitivity of Blood Pressure," *Hypertension*, 17 (Suppl. I), pp. 1158-1161, 1991.

93. Crane, N., memorandum of October 23, 1991.

94. Cutler, J. A., D. Follmann, P. Elliott, and I. Suh, "An Overview of Randomized Trials of Sodium Reduction and Blood Pressure," *Hypertension*, 17 (Suppl. I), I-27-1-33, 1991.

95. Dustan, H. P., "A Perspective on the Salt-Blood Pressure Relation," *Hypertension*, 17 (Suppl. I), I-166-I-169, 1991.

96. Dzau, V. J., "Renin and Myocardial Infarction in Hypertension," New England Journal of Medicine, 324:1128-1130, 1991.

97. Elliott, P., "Observational Studies of Salt and Blood Pressure," *Hypertension*, 17 (Suppl. I), 1-3-I-8, 1991.

98. Elmer, P. J., R. H. Grimm, Jr., J. Flack, and B. Laing, "Dietary Sodium Reduction for Hypertension Prevention and Treatment," *Hypertension*, 17(Suppl.I), I-182-I-189, 1991.

99. Ernst, N. D., "Health Promotion Roles of the Federal Government and Food Industry in Nutrition and Blood Pressure," *Hypertension*, 17 (Suppl. I), I-196-1-200, 1991.

100. Frost, C. D., M. R. Law, and N. J. Wald, "By How Much Does Dietary Salt Reduction Lower Blood Pressure? II—-Analysis of Observational Data Within Populations," *British Medical Journal*, 302:815-818, 1991.

101. Hamet, P., E. Mongeau, J. Lambert, F. Bellavance, M. Daignault-Gelinas, M. Ledoux, and L. Whissell-Cambiotti, "Interactions Among Calcium, Sodium, and Alcohol Intake As Determinants of Blood Pressure," *Hypertension*, 17 (Suppl. I), I—150-I-154, 1991.

102. Hegsted, D.M., "A Perspective on Reducing Salt Intake," *Hypertension*, 17 (Suppl. I), I-201-I-204, 1991.

103. *Hypertension*, 17 (Suppl. I), I-1-I 221, 1991.

104. Kuller, L. H., "Research and Policy Directions—Salt and Blood Pressure," *Hypertension*, 17 (Suppl. I), I-211-I-215 1991.

105. Kumanyika, S., "Behavioral Aspects of Intervention Strategies to Reduce Dietary Sodium," *Hypertension*, 17 (Suppl. I), 1-190-1-195, 1991.

106. Law, M. R., C. D. Frost, and N. J. Wald, "By How Much Does Dietary Salt Reduction Lower Blood Pressure? I—Analysis of Observational Data Among Populations," *British Medical Journal*, 302:811-815, 1991.

107. Law, M. R., C. D. Frost, and N. J. Wald, "By How Much Does Dietary Salt Reduction Lower Blood Pressure? Ill—Analysis of Data From Trials of Salt Reduction," *British Medical Journal*, 302:819-824, 1991.

108. LSRO, Kotchen, T., "Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships: 4. Sodium and Hypertension," prepared for the Center for Food Safety and Applied Nutrition, 223-88-2124, Task Order No. 9, FASEB, November 1991.

109. Mascioli, S., R. Grimm, Jr., C. Launer, K. Svendsen, J. Flack, N. Gonzalez, P. Elmer, and J. Neaton, "Sodium Chloride Raises Blood Pressure in Normotensive Subjects," *Hypertension*, 17 (Suppl. I), I-21-I-26, 1991.

110. McCarron, D. A., "A Consensus Approach to Electrolytes and Blood Pressure—Could We All Be Right?", *Hypertension*, 17 (Suppl. I), 1-170-1-172, 1991.

111. Page, L. B., "Commentary on Epidemiological Studies and Intervention Trials," *Hypertension*, 17 (Suppl. I), I-34-I35, 1991.

112. Pecker, M. S. and J. H. Laragh, "Dietary Salt and Blood Pressure—A Perspective," *Hypertension*, 17 (Suppl. I), I-97-1-99, 1991.

113. Prineas, R. J., "Clinical Interaction of Salt and Weight Change on Blood Pressure Level," *Hypertension*, 17 (Suppl. I), I-143-I-149, 1991.

114. Stamler, R., "Implications of the INTERSALT Study," *Hypertension*, 17 (Suppl. I). I-16-I-20, 1991.

115. Sullivan, J., "Session V. Environmental/Metabolic Modifiers of Salt-Blood Pressure Relation," *Hypertension*, 17 (Suppl. I), I-173-I-174, 1991.

116. Sullivan, J. M., "Salt Sensitivity: Definition, Conception, Methodology, and Long-term Issues," *Hypertension*, 17 (Suppl. I), I-173-I-174, 1991.

117. Armstrong, L. E., R. W. Hubbard, E. W. Askew, and R. P. Francesconi, "Responses of Soldiers to 4 g and 8 g NaCI Diets During 10 Days of Heat Acclimation," in press.

118. Francesconi, R., et al., "Endocrinological Responses to Dietary Salt Restriction During Heat Acclimation," in press.

119. Johnson, R. F. and D. J. Merullo "Reevaluation of Sodium Requirements for Work in the Heat: Subjective Reports of Heat Illness," in press.

120. Folkow, B., "Salt and Hypertension," *News in Physiological Sciences*, 5:220-224, 1990.

121. Dustan, H. P. and K. A. Kirk, "'Corcoran Lecture: The Case for or Against Salt in Hypertension," *Hypertension*, 13:696-705, 1989.

122. MacGregor, G. A., N. D. Markaudu, G A. Sagnella, D. R. Singer, and F. P. Cappuccio, "Double-blinded Study of Three Sodium intakes and Long-term Effects of Sodium Restriction in Essential Hypertension," *Lancet*, pp. 1244-1247, November 25, 1989.

123. The TOHP Collaborative Research Group, "Results of the Trials of Hypertension Invention (TOHP)," abstract.

124. The TOHP Collaborative Research Group, "The Hypertension Prevention Trial: Three-year Effects of Dietary Changes on Blood Pressure," *Archives of Internal Medicine*, p. 150, 1990.

125. Dustan, H. P. and K. A. Kirk, "Relationship of Sodium Balance to Arterial Pressure in Black Hypertensive Patients, " *American Journal of Medical Science*, 295:378-383, 1988.

126. Elliott, P., R. D. Forrest, C. A. Jackson, and J. S. Yudkin, "Sodium and Blood Pressure: Positive Associations in a North London Population with Consideration of the Methodological Problems of Within-population Surveys," *Journal of Human Hypertension*, 2:89-95, 1988.

127. Gill, J. R., H. G. Guellber, C. R. Lake, D. L. Lakatua, and G. Lan, "Plasma and Urinary Catecholamine In Salt-Sensitive Idiopathic Hypertension," *Hypertension*, 11:312-319, 1988.

128. Khaw, K. and E. Barrett-Connor, "The Association Between Blood Pressure, Age, and Dietary Sodium and Potassium: A Population Study," *Circulation*, 77:53-61, 1988.

129. Shore, A. C., N. D. Markandu, and G. A. MacGregor, "A Randomized Crossover Study to Compare the Blood Pressure Response to Sodium Loading With and Without Chloride in Patients With Essential Hypertension," *Journal of Hypertension*, 6:613-617, 1988.

130. Sullivan, J. M., R. L. Prewitt, and T. K. Rafts, "Sodium Sensitivity in Normotensive and Borderline Hypertensive Humans," *American Journal of Medical Science*, 295:370-377, 1988.

131. Weinberger, M. H., S. J. Cohen, J. Z. Miller, F. C. Luft, C. E. Grim, and N. S. Fineberg, "Dietary Sodium Restriction as Adjunctive Treatment of Hypertension," *Journal of the American Association*, 259:2561-2565, 1988.

132. Forte, J. G., J. M. P. Miguel, M. J. P. Miguel, F. Padua, and G. Rose, "Salt and Blood Pressure: A Community Trial," *Journal of Human Hypertension*, 3:179-184, 1989.

133. Rocchini, A. P., et al. "The Effect of Weight Loss on the Sensitivity of Blood Pressure to Sodium in Obese Adolescents," *New England Journal of Medicine*, 321:580-585, 1989.

134. Beretta-Piccoli, C., "Body Sodium in Normal Subjects Predisposed to Hypertension," *Journal of Cardiovascular Pharmacology*, 16 (Suppl. 7):S52-S55, 1990.

135. Dietary Guidelines Advisory Committee, *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans*, 1990 to the Secretary of Agriculture and the Secretary of Health and Human Services, Report reproduced by the Human Nutrition Information Service, USDA, Hyattsville, MD, U.S. Government Printing Office, June, 1990.

136. Carney, S. L., A. H. Gillies, A. J. Smith, and S. Smitham, "Increased Dietary Sodium Chloride in Patients Treated with Antihypertensive Drugs," *Clinical and Experimental Hypertension—Theory and Practice*, A13:401-407, 1991.

137. Delaney, L. and C. London, "Knock Out Heart Disease—What Doctors Say Matters Most," pp. 33-42, April 1991.

138. LSRO, Kotchen, T., "Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships; 4. Sodium and Hypertension" prepared for the Center for Food Safety and Applied Nutrition, FDA, GHHS, FDA Contract No. 223-88-2124, Task Order No. 9, FASEB, December, 1991.

139. He, J., G. S. Tell, Y. Tang, P. Mo, and G. He, "Relation of Electrolytes to Blood Pressure in Men—The Yi People Study," *Hypertension*, 17:378-385, 1991.

140. Little, P., G. Girling, A. Hasler, and A. Trafford, "A Controlled Trial of a Low Sodium, Low Fat High Fibre Diet in Treated Hypertensive Patients: Effect on Antihypertensive Drug Requirement in Clinical Practice," *Journal of Human Hypertension*, 5:175-181, 1991.

141. Weinberger, M. H. and N. S. Fineberg, "Sodium and Volume Sensitivity of Blood Pressure—Age and Pressure Change Over Time," *Hypertension*, 18:67-71, 1991.

142. Zarrow, S. and C. London, "The New Diet Priorities," Prevention, pp. 33-36 and 118-120, September 1991.

143. Espinel, C. H., "The Salt Step Test: Its Usage in the Diagnosis of Salt-Sensitive Hypertension and in the Detection of the Salt Hypertension Threshold," *Journal of the American College of Nutrition*, 11(5):526-531, 1992.

144. Muntzel, M. and T. Drueke, "A Comprehensive Review of the Salt and Blood Pressure Relationship," *American Journal of Hypertension*, 5:1S-42S 1992.

145. The TOHP Collaborative Research Group, "The Effects of Nonpharmacologic Interventions on Blood Pressure of Persons with High Normal Levels—Results of the Trials of Hypertension Prevention. Phase 1," *Journal of the American Medical Association*, 267:1213-1220, 1992.

146. Pavek, K. and E. Pavek, "Salt Sensitivity of Blood Pressure in Patients with Primary Hypertension," *Journal of Cardiovascular Pharmacology*, 16 (Suppl. 8):S59-S61, 1990.

147. Joosens, J. V. and H. Kesteloot, "Trends in Systolic Blood Pressure, 24-Hour Sodium Excretion, and Stroke Mortality in the Elderly in Belgium," *The American Journal of Medicine*, 90 (Suppl. 3A):3A-5S-3A-11S, 1991.

148. Ellison, R. C, et al., "Effects on Blood Pressure of a Decrease in Sodium Use in Institution Food Preparation: The Exeter-Andover Project," *Journal of Clinical Epidemiology*, 42:201-208, 1989.

149. Geleijnse, J. M., D. E. Grobbee, and A. Hofman, "Sodium and Potassium Intake and Blood Pressure Change in Childhood," *British Medical Journal*, 300:899-902, 1990.

150. Miller, J. Z., et. al., "Blood Pressure Response to Dietary Sodium Restriction in Healthy Normotensive Children," *American Journal of Clinical Nutrition*, 47:113-119, 1988.

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 authority delegated to the Commissioner of Food and Drugs, 21 CFR part 101 is amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFH part 101 continues 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, 701 of the Federal Food, Drug, and Cosmetic Act (21 U. S.C. 321, 331, 342, 343, 348, 371).

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

§ 101.74 Health claims: sodium and hypertension.

(a) *Relationship between sodium and hypertension (high blood pressure).* (1) Hypertension, or high blood pressure, generally means a systolic blood pressure of greater than 140 millimeters of mercury (mm Hg) or a 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 electrolyte "sodium" and is distinguished from sodium chloride, or salt, which is 39 percent sodium by weight.

(2) The scientific evidence establishes that diets high in sodium are associated with a high prevalence of hypertension or high blood pressure and with increases in blood pressure with age, and that diets low in sodium are associated with a low prevalence of hypertension or high blood pressure and with a low or no Increase of blood pressure with age.

(b)) *Significance of sodium in relation to high blood pressure.* (1) High blood pressure is a public health concern primarily because it is a major risk factor for mortality from coronary heart disease and stroke. Early management of high blood pressure is a major public health goal that can assist in reducing mortality associated with 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 scientific evidence indicates that reducing sodium intake lowers blood pressure and associated risks in many but not all hypertensive individuals. There is also evidence that reducing sodium intake lowers blood pressure and associated risks in many but not all normotensive individuals as well.

(2) 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, males because they develop hypertension earlier in life than females, and black males and females. Although some population groups are at greater risk than others, high blood-pressure is a disease of public health concern for all population groups. Sodium intake, alcohol consumption, and obesity are identified risk factors for high blood pressure.

(3) Sodium intakes exceed recommended levels in almost every group in the United States. One of the major public health recommendations relative to high blood pressure is to decrease consumption of salt. On a population-wide basis, reducing the average sodium intake would have a small but significant effect on reducing the average blood pressure, and, consequently, reducing mortality from cardiovascular disease and stroke.

(4) Sodium is an essential nutrient, and experts have recommended a safe minimum level of 500 milligrams (mg) sodium per day and an upper level of 2,400 mg sodium per day, the FDA Daily Value for sodium.

(c) *Requirements.* (1) All requirements set forth in § 101.14 shall be met.

(2) Specific requirements, (i) *Nature of the claim.* A health claim associating diets low in sodium with reduced risk of high blood pressure may be made on the label or labeling of a food described in paragraph (c)(2)(ii) of this section. provided that:

(A) The claim states that diets low in sodium "may" or "might" reduce the risk of high blood pressure;

(B) In specifying the disease, the claim uses the term "high blood pressure";

(C) In specifying the nutrient, the claim uses the term "sodium";

(D) The claim does not attribute any degree of reduction in risk of high blood pressure to diets low in sodium; and

(E) The claim indicates that development of high blood pressure depends on many factors.

(ii) *Nature of the food.* The food shall meet all of the nutrient content requirements of § 101.61 for a "low sodium" food.

(d) *Optional information.* (1) The claim may identify one or more of the following risk factors for development of high blood pressure in addition to dietary sodium consumption: Family history of high blood pressure, growing older, alcohol consumption, and excess weight.

(2) The claim may include information from paragraphs (a) and (b) of this section, which summarizes the relationship between dietary sodium and high blood pressure and the significance of the relationship.

(3) The claim may include information on the number of people in the United States who have high blood pressure. The sources of this information must be identified, and it must be current information from the National Center for Health Statistics, the National Institutes of Health, or "Nutrition and Your Health: Dietary Guidelines for Americans," U.S. Department of Health and Human Services (DHHS) and U.S. Department Of Agriculture (USDA), Government Printing Office.

(4) The claim may indicate that it is consistent with "Nutrition and Your Health: U.S. Dietary Guidelines for Americans, DHHS and USDA, Government Printing Office.

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

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

(7) The claim may state that individuals with high blood pressure should consult their physicians for medical advice and treatment. If the claim defines high or normal blood pressure, then the health claim must state that individuals with high blood pressure should consult their physicians for medical advice and treatment.

(e) *Model health claims.* The following are model health claims that may be used in food labeling to describe the relationship between dietary sodium and high blood pressure:

(1) Diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors.

(2) Development of hypertension or high blood pressure depends on many factors. (This product) can be part of a low sodium, low salt diet that might reduce the risk of hypertension or high blood pressure.

Dated: December 17,1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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

BILLING CODE 4160-01-F

TABLE

Sodium/Hypertension

Study	Study Design	Subjects	Methods	Results	Comments
eretta- iccoli (1990) Ref. 134)	Survey of exchangeable body sodium (Na) in normotensive men with and without a family history of hypertension Study done in Switzerland	62 healthy, normotensive males (SBP ‹ 130 mm Hg, DBP ‹ 90 mm Hg) (31 with a family history of hypertension, 31 without a family history of hypertension) Subjects matched by age, height, and weight Subgroup of 23 (13 with and 10 without a family history of hypertension)	Mean total exchangeable Na was measured by isotope dilution The study of exchangeable Na in the total group was carried out with subjects on a normal Na intake (150 mmol or 3,400 mg per day) The adaptation of exchangeable Na to variations in dietary Na intake, carried out in the study measurements at the end of a 70day low-salt phase (17 mmol or 390 mg per day) and of a 7-day high salt phase (270 mmol or 6,200 mg per day)	Investigation of 62 subjects on normal Na intake: Blood pressure (BP) was higher in the group of normotensive men with a family history of hypertension (p ‹ 0.005), but age, urinary Na excretion, plasma rennin activity, and aldosterone levels or creatine clearance were comparable Exchangeable Na did not differ significantly between the two groups and was unrelated to arterial pressure or to plasma rennin activity Investigation of subgroup of 23 subjects varying the Na intake: At the end of the low-Na phase, there was no significant difference in BP, heart rate, body weight, exchangeable Na, plasma Na and potassium, or creatinine clearance between subjects with and without a family history of hypertension The change from a low-Na diet to a high-Na diet resulted in significant and comparable rises in body weight and exchangeable Na in the two groups, comparable values for Na-dependant suppression of rennin, andgiotensin II, aldosterone, and plasma catecholamines, and no changes in heart rate, plasma Na and potassium, or creatine clearance Supine SBP and DBP increased with Na intake in all subjects but more in subjects with a family history of hypertension (SBP: from 119 to 126 mm Hg, DBP: from 76 to 80 mm Hg) as compared to those without a family history of hypertension (SBP: from 112 to 113 mm Hg, DBP: from 69 to 71 mm Hg)	Findings suggest that exchangeable body Na is normal and adapts normally to variations in dietary Na intake in normotensive subjects with familial predisposition to hypertension The authors concluded that exchangeable body Na depletion in early hypertension appears to be a secondary rather than a primary event

TABLE 1--CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Carney (1991) (Ref. 136)	Randomized double-blind crossover study to evaluate the effect of additional sodium chloride (NaCl) compared with a placebo on BP control over a 6 week period before changing to the other trial arm for an additional 6 week period	11 patients with mild to moderate essential hypertension satisfactorily treated with diverse hypotensive agents (BP stable and well controlled for at least 6 months with no evidence of renal, cardiac, hepatic, or endocrine disease) (5 men, 6 women) Age range: 30 to 65 years	Patients were kept on normal diets and randomly assigned to 6 week periods of additional Na (100 mmol or 2,300 mg slow Na (10 NaCl tablets per day) or a placebo with a subsequent crossover Body weight, pulse, and supine and erect BP (mean of two readings) were measured at 1, 2, 4, and 6 weeks of each trial arm Blood collections and 24-hour urine collections were taken at study commencement, and 1, 6, 7, and 12 weeks	Tablet compliance was excellent There were no significant changes in mean supine or erect BP with increased NaCl in patients on various hypotensive drugs	Findings suggest that excess ditary Na does not jeopardize BP control in patients on various hypotensive drugs
Dustan (1988) (Ref. 125)	Intervention study to investigate the quantitative importance of Na balance to arterial pressure changes produced by changes in Na intake Conducted at the University of Alabama Hospital	Protocol 1: 51 normotensive white patients (19 males, 32 females) 18 normotensive black patients (7 males, 11 females) 21 hypertensive black patients (5 males, 16 females) Protocol 2: 11 normotensive white patients (2 males, 9 females) 16 normotensive black patients (6 males, 10 females) 19 hypertensive black patients (4 males, 15 females)	Protocol 1: A 3-day control period (150 mg or 3,400 mg Na intake per day) followed by 4 days of salt depletion (SD) (low-Na diet of 9 meq or 210 mg Na per day) and furosenide (1 mg/kg given on the first day) followed by 3 days of salt loadingPABA (SL) (low-Na diet continued plus 25 mL/kg of isotonic NaCl solution or 3.88 meq or 90 mg per kg per day) given intravenously Protocol 2: Same as Protocol 1 except the sequence of Na intake changes was reversed For both protocols, Na balance was calculated by subtracting urinary Na excretion from Na intake and expressed in meq per Kg, either positive or negative	Protocol 1: Mean arterial pressure of the two normotensive groups were comparable in the control period and varied little during SD and SL Mean arterial pressures of the hypertensive group fell during SD and returned toward control values during SL Na balance data were comparable for the three groups, except the hypertensive lost more Na during SD than the normotensive Protocol 2: Mean arterial pressures of the normotensive whilte group varied little during SD and SL Mean arterial pressures of both the normotensive and the hypertensive black groups fell during SD and rose during SL Na balance data were comparable for the two normotensive retained less Na during SL and did not lose more Na during SD than the normotensives Spearman correlation coefficients indicated that there was no significant relationship between arterial pressure changes and Na losses during SD or Na retention during SL in either protocol or any group	The authors noted that group averages obscured the heterogeneity of the BP response Spearman correlations suggest that salt-sensitive (SS) hypertension results not from the magnitude of Na retention, but from the pressor mechanisms evoked

TABLE--continued

Study	Study Design	Subjects	Methods	Results	Comments
Elliott (1988) (Ref. 126)	Data collected as part of a 1983 to 1984 survey in North London, England	58 subjects (29 men, 29 women) Age: 40 years and above Age range: 41 to 87 years Mean age: 57.9 years Diabetics (6 subjects) and people taking antihypertensive medication (5 subjects) and diuretics (3 subjects) were included in the study	Na determined by 24-hour urinary Na excretion BP determined as the average of 2 measurements, 1 at each of 2 visits and average of 8 1/2 months apart	SBP significantly related to 24-hour Na excretion, and results remained significant after adjustment for age, sex, and body mass index DBP significantly related to 24-hour Na excretion, and results were borderline after adjustment for age and sex and not significant after adjustment for age, sex, and body mass index Para-aminobenzoic acid (PABA) was used to monitor reliability of complete 24-hour urine collection and the statistical significance was greater for the subgroup of "complete collectors" as monitored by PABA	Eleven subjects provided two 24-hour urine collections to estimate the within-individual variability Only 50% of subjects were classified as "complete collectors" by PABA excretion
Ellison (1989) (Ref. 148)	Nonrandomized, concurrently controlled, longitudinal study Application of intervention in two boarding high schools Each school served alternatively as the control or the intervention school for 1 school year	BP monitored among 341 subjects during control years and 309 subjects during intervention years	The Na intake of students was reduced by 15 to 20% through changes in food purchasing and preparation practices Students were not asked to change their usual eating habits Changes in Na intake were determined by 24-hour food diaries which the students completed periodically during the study BP determined weekly as the average of 2 of 3 measurements	Average SBP reduced by 1.7 mm Hg (95% confidence intervals (CI) = -0.6, -2.9, p=0.003) on low-Na diet Average DBP reduced by 1.5 mm Hg (95% CI= -0.6, -2.5, p=0.002) on low-Na diet Values were adjusted for gender and initial BP	There was no control for possible difference in exercise levels among students at two schools There was no independent measurement of urinary Na excretion from the beginning to the end of the year to document changes in the Na intake BP increased above baseline early in the year and then fell and remained below baseline later in the year

TABLE -- continued

Study	Study Design	Subjects	Methods	Results	Comments
Espinal (1992) (Ref. 143)	Three-phase dietary salt intervention trial to characterize the response of hypertensive patients to dietary salt	30 well-established adult hypertensives (DBP › 90 mm Hg on 3 visits)	Salt-Step Test in three Phases (medications and substances that might alter BP or salt balance were discontinued during the three phases) Phase 1: Unrestricted-salt phase: No restrictions on salt intake to certify the presence of hypertension and to document customary salt intake Phase 2: Restricted-salt phase: Low salt diet (2 g salt per day, i.e. ‹ 34 mmol or 780 mg Na per day) to identify SS patients who could maintain DBP ‹ 90 mm Hg on 2 g salt per day Phase 3: Salt-step phase: Diet established in Phase 2 (2 g salt per day) continued and salt added stepwise (each step lasting at least 3 days) in 1 g increments (390 mg Na) to determine the level of salt that triggered hypertension in individual patients (Salt Hypertension Threshold)	The 13 patients classified as SS (DBP ‹ 90 mm Hg on salt-restricted diet) experienced large BP decreases between Phases 1 and 2 (SBP: from 177.1 to 145.1 mm Hg; DBP: from 105.4 to 82.0 mm Hg) The Salt Hypertension Threshold for the 13 SS patients ranged from 3 to 16 g salt (1,200 to 6,200 mg Na) per day, and the results, which were repeated in 11 patients at intervals between 2 months and 1 1/2 years later, remained stable and reproducible (i.e., they agreed for each patient within 2 g salt or 780 mg Na per day) The remaining 17 patients experience smaller BP decreases between Phases 1 and 2 (SBP: from 173.3 to 164.1 mm Hg; DBP: from 102.9 to 98.2 mm Hg) Body weight decreased in all but 2 patients in the restricted-salt phase and increased in all patients until thresholds were reached	The independent contribution of weight changes was not evaluated, thus, it is not clear whether the observed BP changes are the result of lower salt intake, lower weight, or a combination of the two The author noted that the individuality of responses and the broad range of thresholds could explain why some patients respond to fixed salt dosages and others do not and concluded that the Salt-Step Test may be useful in providing specific, individualized guidelines for dietary salt restriction
Forts (1989) (Ref. 132)	Study to evaluate the effect of a health education program on salt reduction and BP in two matched rural communities in Portugal Initial salt intake was high (about 360 mmol or 8,300 mg Na individuals were bypertensive (DBP = or › 95 mm Hg)	2 villages, each with about 800 inhabitants A stratified random sample of 150 people was drawn from each village, comprised of 25 subjects of each gender in each of 3 age groups (15 to 34, 35 to 54, and 55 to 69 years)	In the intervention community there was a vigorous health education effort to reduce salt intake Duplicate BP readings were obtained from each individual at the beginning of the study, at 12 months, and at 24 months	In the intervention community, average SBP and DBP fell by 3.6 and 5.0 mm Hg, respectively, at 1 year and by 5.0 and 5.1 mm Hg, respectively, at 2 years In the control community, average SBP rose an DBP remained stable	The authors noted that the difference in trends between the two communities was highly significant and seemed to indicate that , at least in this high-intake population, a decrease in salt consumption seemed to have resulted in a sizeable decrease in average BP

TABLE --continued

Study	Study Design	Subjects	Methods	Results	Comments
Geleijnse (1990) (Ref. 149)	Longitudinal study of a cohort of children in a suburban town in the Netherlands to assess the association between Na and potassium intake and BP	233 children (108 boys, 125 girls) Age range: 5 to 17 years at entry Randomly selected from participants in an epidemiological population survey for determining risk factors for cardiovascular disease Children with established hypertension were excluded	At least 6 yearly examinations were made during an average followup period of 7 years Mean 24-hour Na and potassium was calculated from 6 timed overnight urine samples during the year, and the sodium/potassium ratio was calculated BP was determined at each visit as the average of 2 readings Individual slopes of BP over time were calculated by linear regression analysis	No significant association was observed between Na excretion and the change in BP over time Figures were adjusted for gender, initial age, change in height, change in body weight, and potassium intake Boys mean 24-hour Na ranged from 61.5 to 251.5 mmol (1,400 to 5,800 mg) The mean yearly rise in SBP for the whole group was 1.95 mm Hg	Dietary potassium and the ratio of dietary Na to potassium were related to the rise in BP in children, and the authors concluded that these values may be important in the early pathogenesis of primary hypertension Higher potassium levels were associated with lower mean SBP slopes over time Higher sodium/potassium ratios were associated with greater changes in SBP
Gill (1988) (Ref. 127)	Intervention trial in which patients with normal renin, idiopathic hypertension were compared with normotensive subjects after consuming Na intakes of 9, 109, and 249 meq (200, 2,500, and 5,700 mg) per day for 7 days	19 patients with normal renin idiopathic hypertension (antihypertensive medications discontinued) (14 women, 10 men) (20 to 75 years of age) 5 normotensive subjects without a family history of hypertension (3 women, 2 men) (20 to 62 years of age)	All subjects housed on a metabolic unit and fed a constant isocaloric diet containing 9 meq (200 mg) Na Supplements of NaCl were given as follows: 100 meq (2,300 mg Na) per day for 7 days (normal Na intake of 109 meq or 2,500 mg Na); no supplement for 7 days (low Na intake of 9 meq or 200 mg Na); and 240 meq (5,500 mg) per day for 8 days (high Na intake of 249 meq or 5,700 mg Na)	Hypertensive subjects were classified as SS (mean arterial pressure increases of 8 to 14%) or salt-resistant (SR) (mean arterial pressure changes of -7 to +7%) in response to changes in Na intake Mean BP on the low-Na relative to the high-Na diet increased in the SS hypertensive subjects (from 104 to 114 mm Hg), and the normotensive subjects (from 79 to 83 mm hg), and remained balanced in the SR hypertensive subjects (114 mm Hg) (due to classification scheme in which BP increases and decreases were set to be equal)	The authors noted that supernormal Na retention and a failure to suppress adrenergic activity may explain, in part, the phenomenon of salt sensitivity of BP in SS patients and may also be factors in the pathogenesis of hypertension in this subset of individuals

TABLE -- CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
He (1991) (Ref. 139)	Study to investigate the relationship of Na, potassium, calcium, and magnesium to BP in 4 groups of Southern Chinese men with a wide range of electrolyte intakes Study conducted in Puge County, Sichuan Province, People's Republic of China	4 groups of men: 119 high-mountain Yi farmers, 114 mountainside Yi farmers, 89 Yi people who had migrated to the county seat, 97 Han people who were native residents of the county seat	Four electrolytes were measured in the diet, blood serum, and urine	Na excretion was 73.9 mmol (1,700 mg) per 24 hours in high-mountain Yi farmers, 117.9 mmol (2,700 mg) per 24 hours in mountainside Yi farmers, 159.4 mmol (3,700 mg) per 24 hours in Yi migrants, and 186.0 mmol (4,300 mg) per 24 hours in the Han people In ecological correlation analysis, dietary and urinary Na were significantly and positively correlated with both SBP and DBP, whereas serum Na showed no relationship to BP Analysis at the individual level confirmed the results seen at the ecological level These findings persisted after controlling for age, body mass indices, heart race, alcohol, and total energy intake In multiple regression analysis, an increase in Na intake of 100 mmol (2,300 mg) per day corresponded to an increase of 2.3 mm Hg SBP and 1.8 mm Hg DBP	The authors noted that the results are consistent with the view that a diet low in Na may prevent the development of hypertension

TABLE -- continued

Study	Study Design	Subjects	Methods	Results	Comments
Joossens (1991) (Ref. 147)	SBP data from 6 Belgian surveys conducted between 1967 and 1986 were reanalyzed	3,328 subjects 1967 study: 510 subjects 1972 study: 366 survivors of 1967 study 1973 to 1977 study: 143 subjects 1980 to 1984 study: 1,803 subjects 1979 to 1986 study: 344 subjects 1986 study: 162 subjects Range of mean age of 6 groups: 70 to 81 years	All Na determination from 24-hour urine samples were performed using the same methods and in the same laboratory used in the INTERSALT study (Ref. 37) Data were analyzed by age groups and the age groups used were the same as those used in the INTERSALT study	Values are for the change between 1967 and 1986: The mean standardized 24-hour Na excretion decreased from 265 to 188 mmol (6,100 to 3,700 mg) in men and from 208 to 160 mmol (4,800 to 3,700 mg) in women Mean age decreased from 159 to 142 mm Hg in men and from 171 to 147 mm Hg in women The prevalence of hypertension (SBP above 159 mm Hg) decreased from 51% to 21% in men and 66% to 22% in to 21% in men and 66% to 22% in women, and severe hypertension (SBP › 220 mm Hg) nearly disappeared The proportion of subjects receiving treatment for hypertension increased from 10% to 36% in men and from 18% to 41% in women SBP was significantly and independently related to Na excretion in the 1967 and 1972 studies	Methodologies were similar but not identical between the studies, and difference would increase variability Only SBP was considered because DBP decreases with age in the elderly During the same period, body mass index increased 1.1 kg/m^2 in men and remained unchanged in women, therefore decreases in BP cannot be ascribed to changes in body mass index Treatment for hypertension increased, and Na intake decreased The authors calculated that the increase in hypertension treatment and the decrease in Na intake, taken together, could account for the observed changes in SBP, but that neither factor alone was sufficient The authors concluded that the decrease in SBP in Belgium was influenced by the combined effects of more and better treatment for hypertension and a decrease in Na intake

TABLE -- continued

Study	Study Design	Subjects	Methods	Results	Comments
Khaw (1988) (Ref. 128)	Cross-sectional examination of the relationship between dietary Na and potassium intake and BP estimated from 24-hour dietary recall among members of a defined geographical region in Southern California	584 men and 718 women Ages: 30 to 79 years Geographically defined, upper middle class, white population	A 24-hour dietary recall was obtained by a certified dietician The raw 24-hour dietary recall data were coded for nutrient intake by the Nutrition Coordinating Center, University of Minnesota, using their 1993 computerized data base	Age-adjusted SBP and DBP correlated significantly with dietary Na intake in men, but not in women, and with the sodium/potassium ratio in both men and women The relationship was apparent over the whole range of BP and dietary intakes A marked age gradient was apparent in men; the regression slope for BP versus sodium/potassium ratio increasing with increasing age, suggesting increasing sensitivity to dietary sodium/postassium ratio with age Adjustments for intakes of other dietary variables; including calories, protein, carbohydrates, saturated fat, alcohol, calcium, and fiber; did not alter the relationship. Adjustments for body mass index reduced the strength of the association in women but not in men	The authors noted that the results support the hypothesis that Na and potassium are related to BP within a population
Little (1991) (Ref. 140)	Observe-blind controlled trial studying the effect of a low-Na, low-fat, high-fiber diet in allowing a reduction of antihypertensive medication as compared with the effect produced by the individual components of this diet Study conducted in the United Kingdom	196 Patients with established hypertension (DBP > 95 mm Hg on at least 3 occasions)	Patients were allocated to the following groups, keeping the observer blind to group allocation: Group A (control): no change in diet (n=41_ Group B (high-fiber diet): 40 to 45 g soluble and insoluble fiber per day (n=42) Group C (low-Na diet): 40 to 50 mmol (920 to 1,150 mg) Na per day (n=30) Group D (low-fat diet): 23 to 25% calories as fat per day with no change to the P/S or M/S ratios (n=43) Group E (combination low-Na, low-fat, high-fiber diet) 40 to 45 g fiber, 40 to 50 mmol (920 to 1,150 mg) Na, 23 to 25% calories as fat per day (n=40)	In the control group, a 33% reduction in medication was possible, with 24% of patients off medication altogether The low-fat, high-fiber, and low-Na groups showed larger reductions in medication (38%, 47%, and 45%, respectively, but the results were not significant when compared with the control group The combination group had the largest medication reduction (64%) and the difference was highly significant when compared with the control group, and significantly more patients in this group stopped their medication altogether (57.5%) when compared with the control group	The authors noted that the findings are significant because negative side effects of drug treatment may be reduced by lowering drug doses and making corresponding changes in diet

TABLE -- continued

Study	Study Design	Subjects	Methods	Results	Comments
Miller (1988) (Ref. 150)	Intervention study to determine whether modest dietary Na restriction in childhood results in heterogeneous changes in BP response Study conducted in Indiana	149 healthy, normotensive children (64 boys, 85 girls)	Baseline BP and 24-hour urinary Na were determined prior to Na restriction to serve as control data Families received instructions designed to aid them in restricting their dietary Na intake to a goal of 60 mmol (1,300 mg) per day	Na excretion was decreased during the study period in both boys (from 112.9 mmol 2,600 mg to 53.5 mmol or 1,230 mg) and girls (from 91.1 mmol or 2,090 mg to 41.1 mmol or 940 mg) Changes in SBP were not significant in either sex but females showed a decrease ($p < 0.05$) in DBP and mean actual pressures Because BP in children is correlated with age and body size, multiple linear regression was used to adjust BP levels for age and weight, and these analyses yielded small but significant decreases in SBP, DBP, and arterial pressures	The authors noted that the results suggest that compliance with modest Na restriction does not consistently lower BP in normotensive children
Pavek (1990) (Ref. 146)	Intervention study Objective measures of BP sensitivity to a 72-hour salt depletion were evaluated Salt-sensitivity was defined as a decrease in DBP after salt depletion and was estimated by both 24-hour ambulatory and office BP measurements Study conducted in Sweden	35 mild hypertensives (15 men and 20 women) Mean age: 48 years Mean body mass index: 25.2 Active, working patients with mild, untreated hypertension were recruited from a screening of public health service employees The duration of known increase of BP was 7.3 years	Salt depletion started with a morning furosemide (60 mg) tablet and continued for 72 hours with a low-salt diet consisting of unprocessed rice, potatoes, fruits, vegetables, and about 2 L of tap water Na determined by 24-hour urine collection BP determined before and after salt depletion; 24-hour ambulatory BP was recorded 3 times per hour on the left arm using an oscillometric monitor; and 6 pairs of sitting auscultatory and oscillometric pressures were recorded in random order in the mornings, at the start, and at the end of the 24-hour BP recordings	Average 24-hour Na decreased by 17.5 mmmol (400 mg) Average body weight decreased by 31.1% Average SBP decreased significantly using all 3 types of BP measurements Average DBP changed little, and a statistically significant decrease was observed only by the oscillometric method.	Study duration was short (72 hours) Individual estimate of salt-sensitivity varied widely and were dependent on the type of BP measurement employed

TABLE --CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Rocchini (1989) (Ref. 133)	Study to measure BP response in obese and nonobese adolescents after successive 2-week periods of a high-salt diet and low-salt diet, and to compare results for a subset of the obese adolescents before and after a 20-week weight-loss program	60 obese adolescents (10 to 16 years old) (Mean age: 13 years) 18 nonobese adolescents (10 to 16 years old) (Mean age: 12.5 4 years)	Sensitivity to Na was evaluated by giving all subjects a high-salt diet (> 250 mmol or 5,700 mg Na per day) for two weeks, followed by a low-salt diet (< 30 mmol or 700 mg Na per day) for two weeks The low-salt diet was formulated to contain the same caloric intake as the high-salt diet To assess compliance with the diets, 24-hour food records were reviewed and 24-hour urine samples were collected on the day before the outpatient testing A subset of the obese adolescents (51 subjects) were also studied before and after a 20-week weight-loss program	When changed from the high-salt to the low-salt diet, the obese group had a significant decrease in mean arterial pressure (form 92 to 80 mm Hg) relative to insignificant change in the nonobase group (from 76 to 77 mm Hg) ($p < 0.001$) After the weight-loss program, the 36 subjects who lost more than 1 kg of body weight (average weight loss 7.5 kg) had a reduced sensitivity of BP to Na	The authors noted that the results support the hypothesis that the BP of obese adolescents is sensitive to dietary Na intake, and that this sensitivity may be due to the combined effects of hyperinsulinemia, hyperaldosteronism, and increased activity of the sympathetic nervous system that are characteristic of obesity
Shore (1988) (Ref. 129)	Randomized, crossover study to investigate the effect of supplementing a low-Na diet with either NaCl or sodium phosphate Study conducted in the United Kingdom	6 hypertensive outpatients (DBP between 90 to 110) with no history of, and no clinical, or biochemical evidence of renal or heart disease Patients had either received no antihypertensive medication or such medication had been withdrawn for at least 2 weeks prior to the study Patients had DBP between 90 and 110 mm Hg when receiving no medication	A low-salt diet (10 mmol or 230 mg Ma and 80 mmol potassium) was provided After 5 days on the low-salt diet, the diet was supplemented with Na for an additional period of 5 days, followed by another 5-day period of the low-salt diet alone, and a second supplementation period of 5 days The Na load was given as NaCl (daily Na intake 120 mmol or 2,760 mg) or as Na in the presence of other anions, mainly phosphate (daily Na intake 122 mmol or 2,800 mg) Three patients received NaCl supplementation first	With both Na salts, urinary Na excretion increased The calculated amount of Na retained was similar for both the NaCl and the sodium phosphate periods Increases in BP occurred with the addition of NaCl to the low-salt diet; however, no change in BP occurred with the addition of sodium phosphate	Difference in the distribution of the retained Na may have contributed to the BP responses The authors noted that these findings suggest that the anion may be important in the BP response to Na loading in patients with essential hypertension

TABLE 2--continued

Study	Study Design	Subjects	Methods	Results	Comments
Sullivan (1988) (Ref. 130)	Dietary intervention study to identify normotensive and borderline hypertensive individuals whose BP rose in response to increased dietary Na, to determine the hemodynamic mechanism causing the increase in BP, to identify other characteristics of the Na-or salt-sensitive (SS) individual, and to determine of the Na-induced increases in BP persisted with time	65 borderline hypertensive subjects (DBP generally < 90 mm Hg, but > 90 mm Hg on at least 3 occasions) 92 normotensive subjects	Subjects were studied while following their usual diets followed by 4 days of a 10 meq (230 mg) Na and 60 meq potassium diet, and again after 2 days of their usual diets followed by 4 days of a 200 meq (4,600 mg) Na and 60 meq potassium diet After examining the distribution of responses, a 5% increase in BP from the 230 mg Na to the 4,600 mg Na state was selected as a measure of SS A subset of normotensive subjects, chosen from the Na-resistant normotensive subjects who agree to participate, followed a daily diet containing about 200 meq (4,600 mg) Na and were followed for 12 months	The prevalence of SS was higher in blacks than in whites and greater in hypertensives than in normotensives Mean BP rose on the high-salt diet as compared with the low-salt diet in the SS population (increase of 6.5%) as compared with the Na-resistant population (0%) BP was not found to rise during the long-term study because total peripheral resistance fell proportionately	The authors speculated that there may be a genetic basis for the response to Na, because the observed changes resembled those reported in the Dahl SS rat
Trials of Hypertension Prevention (TOHP) Collaborative Research Group (1992) (Ref. 123)	Randomized control, multicenter trials	2,182 normotensive (DBP: 80 to 89 mm Hg) subjects (70% men) Age: 30 to 54 years Average age: 43 years	Three life-style change groups (weight reduction, Na reduction, and stress management) were each compared with unmasked nonintervention controls over 18 months Four nutritional supplement groups (calcium, magnesium, potassium, and fish oil) were each compared singly, in double-blind fashion with placebo controls over 6 months The primary outcome measure was change in DBP from baseline to final followup, measured by blinded observers Secondary outcome measures were changes in SBP and intervention compliance measures Na reduction interventions focused on shopping, cooking, and food selection behaviors aimed at reducing intake of Na No recommendations regarding Na were given to weight reduction participants	In the Na-reduction and weight-reduction groups, both DBP and SBP were consistently reduced in the active intervention groups when compared to the controls In the Na-reduction group, the mean decrease in the Na excretion was constant at about 55 to 60 mmol (1,300 to 1,400 mg) per 24 hours at 6, 12, and 18 months At the end of the study, the BP decreases in the Na-reduction group were 0.9 mm Hg DBP ($p<0.01$), while in the weight reduction group, they were 2.3 mm Hg DBP and 2.9 mm Hg SBP ($p<0.01$ for both) Changes in BP for stress management were small and inconsistent in direction	Compliance with the three life-style interventions was satisfactory, both in terms of attendance at counseling sessions and in reaching specific goals The authors concluded that the magnitude of the BP reductions with changes in body weight and Na intake could have a substantial benefit in reducing the incidence of hypertension, and on cardiovascular morbidity and mortality

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Weinburger (1991) (Ref. 141)	Three studies to classify subjects as SS or SR, to evaluate the relationship of SS and SR to age, and to evaluate the changes in BP over time of individuals classified as SS or SR Used a Na and volume expansion and contraction protocol in making both cross-sectional and longitudinal observations Study conducted in Indiana	Study 1: 28 hypertensive (antihypertensive medication or BP > 140/90) and normotensive (BP < 140/90) subjects Study 2: 230 hypertensive and 430 normotensive subjects Study 3: 13 hypertensive (10 SS, 3 SR) and 18 normotensive (6 SS, 12 SR)	Rapid Na-sensitivity test described: Comparison of BP response after rapid increase in extracellular fluid volume and Na balance using and intravenous infusion of 2 L saline (0.9%) over 4 hours versus Na and volume depletion induced by intake of 10 mmol or 230 mg Na and furosemide over 1 day A SS response was defined as a decrease in mean arterial pressure of 10 mm Hg or greater, and a SR response was defined as a change in mean arterial pressure of 5 mm Hg or less Study 1: The BP response was studied twice within a 12-month period Study 2: The BP response was studied to evaluate the influence of age Study 3: BP changes over a period of 10 years or more were studied	Study 1: The BP response was reproducible in 28 individuals who were tested twice within a 12-month period (r=.56; p < 0.002) Study 2: Salt-sensitivity of BP increased significantly with increasing age in the entire population (n=660; r= -0.38; p < 0.001) and was more striking in hypertensive subjects in whom a progressive increase in SS with decades was seen then in the normotensives in whom SS was not seen until the sixth decade Study 3: SS subjects had a significantly greater increase in SBP and DBP over time than SR subjects	The authors noted that salt-sensitivity appears to be a reproducible phenomenon that is related to the age-associated increase in BP which is characteristic of industrialized societies The authors noted that salt-sensitivity can be shown to be a predictor of subsequent, age-related BP increase

[FR doc. 92-31521 Filed 12-28-92; 8:45 a.m.]
BILLING CODE 4160-01-c

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Smith et al., 1990 (Ref. 121)	The effects of high fat diet and CCK-receptor antagonist on growth of human pancreatic tumor cells in nude mice	Male 5 to 6-week old Athymic nude mice 15/groups	Diet 4.3% fat chow diet 20.3% fat diet: 4.3% fat in the chow + 16% CO Mice were injected w/SW-1990 human pancreatic adenocarcinoma cell line and fed the diets for 23 days. The effects of dietary fat and CCK-receptor antagonist L364718 on pancreatic tumor development examined	Among L364718 untreated animals, the high fat diet significantly increased tumor volume and protein content in tumor, compared to the chow diet L364718 significantly decreased tumor yield; endogenous CCK (cholecystokinin) may promote the growth of pancreatic tumor in mice	FA composition of chow diet not reported. The chow diet may have provided insufficient linoleic acid for tumor growth Tumor cells, assayed in vitro, were used
Longnecker et al., 1990 (Ref. 122)	To measure the development of pancreatic neoplasms in elastase-1-simian virus transgenic mice	Elastase 1 simian virus transgenic mice Strain Tg (Ela-1, SV4oE) Bri1 18 Female and male 11 to 23/groups	Diet chow: 5-6% fat AIN-76A: 5% CO Hi-fat: 20% CO Diets were fed for 22 to 23 weeks. At autopsy, incidence and multiplicity of the tumor examined	Incidence of exocrine carcinoma: significantly reduced by chow diet No difference between AIN-76A and high fat diets Incidence of islet cell tumor: no difference among groups	Genetically transformed, transgenic mice were used: extrapolation of results to human is questionable Extremely low total fat Linoleic acid content of the chow diet is not known
Oth et al., 1990 (Ref. 131)	The modulation of CD4 expression in lymphoma transplanted to mice fed n-3 PUFA	Adult AKR mice	Diet No fat, basal diet I 1% FO II 1% BT III 4% FO IV 4% BT V 6% FO VI 6% BT VII 8% FO VIII 8% BT IX 16% FO X 16% BT FO: 23 7% SFA, 30.3% n-3 FA, 1.3% linoleic acid Experimental diets were fed for 6 weeks before and 2 weeks after tumor xenograft by intraperitoneal transplantation. RDM-4 tumors in ascites were harvested and examined. Cell surface markers tested as well	Considerably (statistics not tested) faster tumor growth in the FO-fed donor than in the BT- or no-fat-fed donors Significantly reduced CD4 cell surface marker in the FO groups than BT groups; other markers such as CD8, H2K, Thy-1, and LFA-1 markers were not affected No effects of total fat	Both BT and FO Diets may not have provided adequate linoleic acid for tumor growth

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Ayachi et al., 1990 (Ref. 130)	To test the suspectability of lymphoma cells to lymphokine-activated killer (LAK) cells in mice fed high fat, fish oil diets	AKR mice	Diet 4% FO 4% HBT 8% FO 8% HBT 16% FO 16% HBT n-6 FA content HBT: 0.1 wt% FO: 2.2 wt% Mice were fed the diets for 6 weeks before and 12 to 15 weeks after the intraperitoneal graft of RDM4 lymphoma cells	Tumor yield was significantly greater in the FO group than in the HBT group FO increased resistance of lymphoma cells to lysis by lymphokine activated killer cells in vitro No effect of total fat	Experimental diets may not have provided adequate linoleic for growth of tumor and the mice Total fat in 4 to 8% fat diets was unrealistically low Due to the limitation in dietary linoleic acid, results are not useful for evaluating the effect of fat
Locniskar et al., 1991 (Ref. 127)	To compare the effects of fish, coconut, and corn oils on skin tumor promotion by benzoyl peroxide in mice	Weanling Female SENCAR mice 30/groups	Diet: 10% total fat CCO / CO / MO (wt%) A 8.5 / 1.5 / - B 7.5 / 1.5 / 1.0 C 4.5 / 1.5 / 4.0 D - / 1.5 / 8.5 E - / 10.0 / - Mice were fed 5% CO diet for 3 weeks treated with an initiator, 7,12-DMBA, fed 10% CO diet for 52 weeks, and treated with benzoylperoxide (promoter) biweekly. Latency, incidence, and Ornithine decarboxylase (ODC), vascular permeability, and hyperplasia of the dorsal skin were also examined	Papilloma Significantly higher cumulative tumor probability in Diet A than Diet B, D, and E, but not C. Papilloma yield was significantly greater in Diet A or Diet C than Diet B, D, and E (Tumor probability was mathematically calculated) Carcinoma Significantly higher tumor incidence and cumulative tumor probability in Diet A and Diet E: no difference in incidence among Diet B, C and D. Carcinoma yield not reported No difference in ODC activities or vascular permeability among groups. Significantly greater hyperplasia in Diets B and C than Diets A, D, and E	Low total fat in the diets Except Diet E, all the diets many have provided inadequate linoleic acid for tumor growth. Diet E with adequate linoleic acid resulted in the longest latency period, lowest tumor incidence, and least tumor yield The results suggest that growth of skin tumor may not require 4% dietary linoleic acid and that the effect of dietary fat on tumorigenesis is site-specific In the 10% fat diet, high PUFA in the diet showed a protective effect and high SFA in the diet showed a promoting effect while the effect of n3 FA-rich diet was intermediate

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Layton et al., 1991 (Ref. 128)	To measure effects of type of dietary fat on phorbol-ester-elicited tumor promotion in mouse skin	Female SENCAR and DBA/2 mice 4-week old 30 mice/groups	Diet Initiation period: 5 wt% total fat CO CCO C18:2n-6 all 1.7% 3.3% 1.0% promotion period: 15 wt% total fat CO CCO C18:2n-6 I 1.0 14 0.8 II 3.6 11.4 2.2 III 6.0 9.0 3.5 IV 7.9 7.1 4.5 V 9.9 5.1 5.6 VI 12.5 2.5 7.0 VII 15. 0. 8.4 7,12-DMBA initiated and 12-0-tetradecancyl-phorbol-13-Acetate(TPA)-promoted papilloma development determined	Papilloma incidence: No difference among groups Signficant inverse correlation between CO level and papilloma yield (r= 0.92), 5.4 tumors versus 11.7 tumors per mouse; 15% CO versus 10% CO in SENCAR mice). Similar results found in DBA/2 mice The results suggest that increasing dietary CO or decreasing SFA may suppress skin tumor in mice TPA elevated epidermal PGE2 in all diet groups: the extent was negatively correlated with dietary CO	The effect of total fat not tested Low PUFA/high SFA diet significantly enhanced DMBA- and TPA-induced skin tumor-yield than high PUFA/low SFA diet; this result is inconsistent with the 4 to 5 wt% linoleic acid requirement found in mammary and pancreatic tumorigenesis in rats. The results suggest that the effect of dietary fat may be specific for tumor sites
Jenski et al., 1991 (Ref. 143)	To measure the release of cytosolic components from leukemic cells inoculated into mice fed menhaden oil or coconut oil	BALB/c mice Female and male 4/groups	Diet I 10% MO + basal chow diet II 10% CCO + basal chow diet III 20% MO + ICN fat free diet IV 20% HCO + ICN fat free diet Mice were fed the diets for 5 weeks, inoculated intraperitoneally with murine leukemia cell line T27A, and fed the diets for 1 week Membrane permeability of tumor cells was examined in vitro by examining 51CR release from the cells	Increased membrane permeability in the MO groups The enhanced membrane permeability was correlated with n-3 FA (DHA and EPA) incorporated into the tumor cells	Diets may not have provided adequate linoleic acid for optimal tumor growth Tumor development not measured. Eradication of tumor was measured indirectly by measuring cell permeability intravenously

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Hietanen et al., 1990 (Ref. 120)	To test the modulation of dietary fat, varied in the quality and the quantity, of the oxidative stress and chemical-induced liver tumors in rats	Male wistar rats 4-week old	Diet SSO land (wt%) I 2 0 II 1 III 12.5 0 IV 1 11.5 V 25 0 VI 1 24 Rats were fed for 10 weeks prior and 33 weeks after the N-nitrosodimethylamine (NDMA) administration by gavage Tumor prevalence as well as plasma lipids and lipid peroxidation were measured	High-PUFA diet (25% SSO) significantly elevated tumor incidence compared to low PUFA diet (2% SSO), (80% versus 42%; 25% SSO versus 2% SSO) Fat type did not significantly affect tumor incidence High-PUFA diets (25% or 12.5% SSO) reduced plasma cholesterol and TG concentration compared to high SFA diets (25% or 12.5% lard diets)	Except 12.5% SSO and 25% SSO diets, all diets may have provided inadequate linoleic acid for tumor growth Nonisocaloric diets used: body weight changes were not significantly different among groups Due to limitations in study design, the effect of dietary fat on cancer development cannot be evaluated

Abbreviations
BCO: black currant seed oil
BO: borage oil
BS: beef suet
BT: beef tallow
Ca: calcium
CO: corn oil
CCO: coconut oil
DMBA: 7, 12-dimethylbenzanthracene
DMH: 1, 2-dimethylhydrazine
EPA: eicosapentaenoic acid
EFA: essential fatty acid
FO: fish oil
FA: fatty acid
HBT: hydrogenated beef tallow
HCO: hydrogenated corn oil
i.p.: intraperitoneal
MO: menhaden oil
MUFA: monounsaturated fatty acid
NFDM: nonfat dried milk
PO: palm oil
PUFA: polyunsaturated fatty acid
PrO: primrose oil
RR: relative risk
SSO: sunflower seed oil
SFA: saturated fatty acid
SBO: soybean oil
SO: safflower oil

[FR Doc. 92-31520 Filed 12-28-92; 8:45am]
BILLING CODE 4160-01-C