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August 8, 2023

Robert M. Califf, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Re: Use of Salt Substitutes to Reduce the Sodium Content in Standardized Foods; proposed rule; docket no. FDA-2022-N-2226

Dear Commissioner Califf:

The American Kidney Fund appreciates the opportunity to comment on the Food and Drug Administration's (FDA) proposed rule on the use of salt substitutes to reduce the sodium content in standardized foods.

The American Kidney Fund (AKF) fights kidney disease on all fronts as the nation's leading kidney nonprofit. AKF works on behalf of the 37 million Americans living with kidney disease, and the millions more at risk, with an unmatched scope of programs that support people wherever they are in their fight against kidney disease—from prevention through transplant. Through programs of prevention, early detection, financial support, disease management, clinical research, innovation and advocacy, no kidney organization impacts more lives than AKF. AKF is one of the nation's top-rated nonprofits, investing 97 cents of every donated dollar in programs, and holds the highest 4-Star rating from Charity Navigator and the Platinum Seal of Transparency from GuideStar.

AKF appreciates the FDA's public health interest in reducing sodium across the food supply. Hypertension is the second most common cause of end-stage renal disease (ESRD), and about one in four people with kidney failure have it because of high blood pressure. Choosing foods lower in sodium is a key step in reducing the risk of high blood pressure and preventing kidney disease and other conditions in which hypertension is a leading cause, such as heart disease and stroke.

In this proposed rule, FDA is proposing to amend FDA's definitions and standards of identity (SOI) that specify salt as a required or optional ingredient in standardized foods. The amendments would permit the use of safe and suitable salt substitutes to replace some or all of the salt used in the manufacture of standardized foods. The proposed rule does not list specific salt substitutes, but instead covers ingredients or combinations of ingredients used as salt substitutes

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by food manufacturers currently or in the future. The proposed rule would not require manufacturers to replace salt with salt substitutes but would give them the option of using salt substitutes in standardized foods. The option to use salt substitutes would apply to 80 SOIs that specify salt as a required or optional ingredient, but because some SOI cross reference other SOI, 140 of the 250 SOIs currently established for a wide variety of standardized foods would be permitted to replace salt with salt substitutes.

Although the proposed rule does not list specific salt substitutes, potassium chloride is a commonly used salt substitute. If finalized, this proposed rule would provide a new means for manufacturers to reduce the sodium content of standardized foods while also increasing the potassium content. For the general population, this could have a beneficial effect on reducing the risk of high blood pressure.

However, for people with chronic kidney disease (CKD) and particularly later stage CKD, increased potassium intake is a concern because they are unable to excrete extra potassium, raising the risk of hyperkalemia. Additionally, patients taking renin–angiotensin–aldosterone system (RAAS) inhibitors and/or mineral corticoid antagonists (MRAs) are at increased risk for hyperkalemia. These medications are critical treatments for many people with CKD, heart failure (HF), diabetes, and hypertension. Because of this risk for people with CKD and because further research examining the potential impact of potassium chloride salt substitutes on the CKD population is needed, we recommend that the FDA not finalize the rule as proposed, or alternatively implement additional safeguards for people at risk of hyperkalemia.

Risk of hyperkalemia for people with CKD and current data on potassium

The Kidney Disease Outcomes Quality Initiative (KDOQI) *Clinical Practice Guideline for Nutrition in CKD* statement on potassium is that for adults with CKD stage 3-5D, "it is reasonable to adjust dietary potassium intake to maintain serum potassium within the normal range."[1] Regarding dietary and supplemental potassium intake for hyperkalemia or hypokalemia, KDOQI suggests that dietary or supplemental potassium intake for adults with CKD stage 3-5D "be based on a patient's individual needs and clinician judgment."[2] KDOQI's rationale for the guidance is due to high and low potassium levels being associated with muscular weakness, hypertension, ventricular arrhythmias and death, and therefore dietary consumption of potassium is of great clinical concern.[3]

KDOQI also notes in its justification that there is a scarcity of studies on the topic of dietary potassium and the CKD population, and they found no clinical trials on how diet modification can influence serum potassium levels in people with CKD.[4] A review of the literature backs this up.

Current data on the association between dietary potassium excretion and mortality and CKD progression in adults with CKD are mixed,[5] and the results of currently available studies indicate that

[1] Ikizler TA, Burrowes JD, Byham-Gray LD, et al; KDOQI Nutrition in CKD Guideline Work Group. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis. 2020;76(3)(suppl 1):S1-S107.
[2] Ibid.
[3] Ibid.
[4] Ibid.
[5] Ibid.

the course of renal diseases is still insufficiently documented.[6] Burnier further noted "it is rather obvious that potassium supplements should not be given to patients with advanced CKD (eGFR <45 mL/min/1.73 m2) because of the risk of hyperkalemia and perhaps the risk of accelerating the disease. But, in earlier CKD stages (stages 1–3a), whether potassium supplements are damaging or beneficial because they lower BP and reduce cardiovascular complications remains to be demonstrated, as observations suggesting a benefit rather than a risk are increasing. The only way to resolve this question will be to perform a randomized controlled prospective trial testing the administration of potassium supplements versus placebo in patients with CKD Stages 1–3."[7]

Romero-Gonzalez et al. outlined the mixed landscape of current observational studies on potassium in diets and CKD, and concluded "a note of caution regarding the recent publication of the SSaSS [Salt Substitute and Stroke Study] trial and the use of salt substitutes, particularly in patients with a limited capacity to increase K+ secretion in response to an exogenous load, particularly in the context of 'occult' CKD, HF, and in patients taking RAASis and/or MRAs."[8] Notably, the SSaSS trial excluded people with known serious kidney disease or who were on a potassium-sparing diuretic. Romero-Gonzalez et al. also concluded that "broadcasting and encouraging global public health policies on the beneficial use of salt substitutes rich in K+ without appropriate warnings may not be desirable."[9]

Greer et al. noted: "there is considerably less evidence regarding the effects of potassium-enriched salt on serum potassium levels and the occurrence of hyperkalemia in people with chronic kidney disease and others at risk for hyperkalemia. In this context, additional empirical research on the effect of potassium-enriched salt substitutes on serum potassium levels, as well as a robust modeling exercise to estimate the population-wide impact of replacing traditional salt with potassium-enriched salt substitutes are needed. Promotion of potassium-enriched salt substitutes as a public health strategy to reduce sodium intake should be accompanied by efforts to safeguard those populations with conditions that impair potassium excretion."[10]

Recommendation

Due to the risk of hyperkalemia for the CKD population and the need for further research on the impact of potassium chloride salt substitutes on people with CKD, we recommend the FDA not finalize the rule as proposed. We believe this is a reasonable recommendation given that the FDA proposal does not require the use of salt substitutes to replace salt where salt is required or optional in

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[6] Michel Burnier, Should we eat more potassium to better control blood pressure in hypertension?, Nephrology Dialysis Transplantation, Volume 34, Issue 2, February 2019, Pages 184–193, https://doi.org/10.1093/ndt/gfx340

[7] Ibid.

[8] Romero-González G, Bover J, Arrieta J, Salera D, Troya M, Graterol F, Ureña-Torres P, Cozzolino M, Di Lullo L, Cippà PE, Urrutia M, Paúl-Martinez J, Boixeda R, Górriz JL, Ara J, Bayés-Genís A, Bellasi A, Ronco C. The "FIFTY SHADOWS" of the RALES Trial: Lessons about the Potential Risk of Dietary Potassium Supplementation in Patients with Chronic Kidney Disease. J Clin Med. 2022 Jul 8;11(14):3970. doi: 10.3390/jcm11143970. PMID: 35887733; PMCID: PMC9318835.

[9] Ibid.

[10] Raquel C. Greer, Matti Marklund, Cheryl A.M. Anderson, Laura K. Cobb, Arlene T. Dalcin, Megan Henry, and Lawrence J. Appel, Potassium-Enriched Salt Substitutes as a Means to Lower Blood Pressure Benefits and Risks, Hypertension Volume 75, Issue 2 Feb 2020 https://doi.org/10.1161/HYPERTENSIONAHA.119.13241Hypertension. 2020;75:266–274

standardized foods. The FDA notes that "salt is a relatively inexpensive ingredient, and we would not expect manufacturers to begin using salt substitutes based on cost cutting considerations alone at this time."[11] The FDA also notes that they currently lack data on potential industry responses to the proposed rule and the extent to which manufacturers would use the increased flexibility to use salt substitutes.[12] Taken together, there is a reasonable expectation that if finalized, the rule would not result in an immediate change in the use salt substitutes. But given the risk of hyperkalemia for the CKD population and others, such as patients taking RAAS inhibitors and/or MRAs, and the need for further research on the effect of potassium chloride in these populations, it would be prudent to take the time for more research to be conducted.

Alternatively, if FDA were to proceed with finalizing the proposed rule, we recommend that safeguards be put in place to address concerns regarding increased potassium in standardized foods for the CKD population and those taking RAAS inhibitors and/or MRAs. Specifically, we would urge FDA to explore labeling requirements that would make it clearer to individuals that a product now uses potassium chloride as a salt substitute, if a manufacturer has opted to change its previous formulation. Many people with CKD read nutrition labels to monitor their potassium intake, and any increase in potassium due to the use of a salt substitute would be captured there. But we are concerned that individuals may reach for their usual brand of a standardized food, and not look at the back of the label because they assume nothing has changed. Therefore, greater clarity on the front of the label that potassium chloride is now used would be beneficial for consumers who need to monitor their potassium intake.

Thank you for the opportunity to provide comments on this proposed rule.

Sincerely,

LaVarne A. Burton
President and CEO

[11] Federal Register, 21159
[12] Ibid.