Results of the public consultation on the WHO draft guideline: use of lower-sodium salt substitutes[1]

Comments were received from the following individuals and organizations

Nongovernmental and consumer organizations and associations	
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Yuko Nagasaka	RESULTS Japan, Japan
Mark Barone, Eduardo Augusto Fernandes Nilson, Elton Junio Sady Prates, Hermelinda Pedrosa, Jaqueline Correia, Michely Arruda Bernardelli, Patrícia Vieira de Luca, Ronaldo Pineda-Wieselberg, Vinícius Batista Campos	Intersectoral Forum to Fight NCDs in Brazil (ForumDCNTs), Brazil
Toshihide Nishimura*	Umami Information Center, Japan
Margherita Caroli	Società Italiana di Pediatria Preventiva e Sociale, Italy
Mhairi Brown	World Action on Salt, Sugar and Health, United Kingdom of Great Britain and Northern Ireland
Kenji Shibuya	Tokyo Foundation for Policy Research, Japan
Paul Whelton*	World Hypertension League, United States of America

Private Sector (including industry/trade organizations and associations)	
Maria Teresa Scardigli	International Glutamate Technical Committee, Belgium
Caroline Campbell	Klinge Chemicals Ltd., United Kingdom of Great Britain and Northern Ireland

Academic/research	
Bruce Neal, Kathy Trieu, Laura Fisher, Claudia Selin Batz, Mhairi Brown, Anne Kelly, Leopold Aminde, Linda Cobiac, Inez Denham, Irene Deltetto, Kenji Shibuya, Dike Ojji, Emalie Rosewarne, Matti Marklund, Katrina Kissock, Polly Huang, Emma Feeny	The George Institute for Global Health, Australia†
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Lawrence J. Appel, Lyn M. Steffen, Tammy Brady, Matti Marklund, Megan Henry	Johns Hopkins University, United States of America

* Comments were submitted, but declaration of interest forms were not received.
† Affiliation of the primary submitter is noted. See the Annex for a full list of affiliations.

[1] At the time of the public consultation, the title of the draft guideline was “WHO guideline: use of low-sodium salt substitutes”.

Summary comments and WHO responses

Comments were compiled and summarized, and brief responses were prepared. Comments were organized into categories according to their content. Comments received without completed DOI forms were not included in this process. Original comments as received are attached in the Annex.

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1. Title and scope of the guideline

Summary comment	Response
Consider renaming the title of the guideline to: "WHO Guideline: use of potassium-enriched salts".	The title of the guideline has been revised to "WHO guideline: use of lower-sodium salt substitutes (LSSS)". - For the development of this guideline, LSSS interventions of any type were included in the systematic review (Brand 2022), provided they aimed to replace the dietary intake of any amount of sodium with another mineral or compound. - There is a Codex standard[2] that defines and reserves the term "low-sodium salt substitutes" for special dietary foods (sodium content is only 120mg/100g), while the salt substitutes discussed in the guideline are for use by the general population. - The salt substitutes discussed in the guideline are not necessarily 'low' in sodium but just 'lower' in sodium. The majority of trials included in the systematic review (23 out of 26 RCTs) investigated the effects of LSSS that replaced sodium with potassium. The sodium chloride (NaCl) and potassium chloride (KCl) contents of those LSSS ranged from 41 to 75 % and from 19 to 50 %, respectively. The scope of the recommendation clearly states that the recommendation in this guideline applies

[2] Standard for Special Dietary Foods with Low-Sodium Content (Including Salt Substitutes): CODEX STAN 53-1981. Rome: Food and Agriculture Organization of the United Nations; 2019 (https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXS%2B53-1981%252FCXS_053e.pdf).

Summary comment	Response
	to the use of LSSS in which NaCl is partially replaced by KCl.
The guideline should also consider umami and other glutamates (e.g. monosodium glutamate (MSG)) as part of LSSS intervention. For example, MSG contains about 12% sodium, which is less than half of that contained in regular salt (which is about 39%). So MSG has reduced sodium content.	Umami and other glutamates serve different purposes in many cases and have their own unique chemical compositions and different health considerations as compared to salt. Therefore, they were not included in the guideline. As noted in the scope section, the recommendation in this guideline applies to the use of LSSS in which NaCl is partially replaced by KCl.
Diabetes is not a condition that requires restriction of dietary potassium intake. Text suggesting that diabetes is a condition for which persons would be advised not to increase potassium intakes should be removed from the document.	The document has been revised, and diabetes is no longer listed as part of contraindications to the use of LSSS that contain potassium. Although diabetes often leads to high blood pressure, which further strains the kidneys and accelerates kidney damage, we agree that diabetes per se does not constitute a contraindication.
The recommendation on LSSS should not apply to infants and young children as they are vulnerable age groups.	The recommendation in the LSSS guideline does not apply to children (i.e. 2 to 18 years), which is clearly indicated in the recommendation itself and the scope section. WHO recommends exclusive breastfeeding for the first 6 months of life and introduction of nutritionally adequate and safe complementary (solid) foods at 6 months, together with continued breastfeeding up to 2 years of age or beyond. The WHO guideline for complementary feeding of infants and young children 6-23 months of age provides recommendations on complementary feeding of this specific age group.
The recommendation should leave open the potential for use of LSSS in manufactured food products. Manufactured food products make up large parts of diets in certain countries. While there is no direct evidence that LSSS prevents disease when used in manufactured food products, it would be expected to act similarly. The parallel is sodium reduction, where most data derive from reducing 'discretionary salt', yet taking sodium out of the food supply is a key component of WHO's SHAKE package on sodium reduction. Without positive guidance on the use of LSSS in reformulation, food manufacturers would have a reason to indefinitely stall their sodium/salt reduction programmes in favour of commercial gains.	Non-discretionary salt consumed as already present in manufactured foods or foods served at restaurants and other out-of-home settings is not included in the scope of the recommendation. This is because there was not enough evidence to substantiate such use of LSSS to include them in the recommendation. It was not possible to extrapolate the findings on discretionary LSSS use to non-discretionary use because the impacts on effectiveness and safety may vary depending on the degree and range of salt substitution as well as intakes of such foods, for which evidence was very limited at this stage. Moreover, considerations for the contextual factors would also differ from those associated with discretionary use of LSSS. For individuals at high risk, it could be challenging to avoid foods containing potassium in non-discretionary settings (when consuming manufactured foods or foods served at restaurants and other out-of-home settings). As noted in the "Research gaps and future initiatives" section, further research is needed to achieve a better understanding of the safety implications of widespread LSSS use (discretionary and non-discretionary) on

Summary comment	Response
	explicitly defined measures of hyperkalaemia; and evidence on the use of LSSS in manufactured foods and the implications for guidance on total potassium chloride intake. The guideline now contains as Annex 8 examples of various approaches adopted by certain countries regarding the LSSS use in manufactured foods, foods served at restaurants and other out-of-home settings. While such use of LSSS is beyond the scope of this guideline, the information is provided for reference purposes. Finally, as emphasized in the recommendation section, the use of LSSS is only one of many means in an overall strategy to reduce sodium intake. Food manufacturers should strive to implement a comprehensive package of actions for sodium reduction, as endorsed by Resolution WHA76(9) (2023).[3] SHAKE Technical Package for Salt Reduction[4] is currently updated to present a suite of action menus that will include LSSS use in appropriate settings. The updated SHAKE Package will be released in early 2025.

2. WHO guideline development process, GRADE framework

Summary comment	Response
WHO should make a *strong* recommendation, not a *conditional* recommendation, based on the robust beneficial effects and the absence of harms.	The recommendation was agreed as *conditional* by the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health. This was determined by considering the overall certainty of evidence, assessed as *low* according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance, as well as the uncertainty about the balance between the benefits and potential harms, especially in settings where a considerable proportion of the population may have undiagnosed conditions for which it would not be advisable to increase potassium intakes (e.g. some low-resource settings). For further details on benefits and harms, please see responses in the following sections. Furthermore, as per the GRADE framework, the other factors considered when formulating the recommendation and determining its strength included: the priority of the problem that the recommendation addresses; values and preferences related to the recommendation in different settings; the cost of the options available to public health officials and

[3] Tackling NCDs: best buys and other recommended interventions for the prevention and control of noncommunicable diseases, second edition. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/376624).

[4] The SHAKE technical package for salt reduction. Geneva: World Health Organization; 2016 (https://iris.who.int/handle/10665/250135).

	programme managers in different settings; feasibility and acceptability of implementing the recommendation in different settings; and the potential impact on equity and human rights. See the section on Evidence to recommendations and Annex 7 of the guideline for further details.

3. Interpretation and use of evidence

Evidence: overall certainty of evidence

Summary comment	Response
The totality of the evidence is misinterpreted as "*low* certainty evidence". It should be rated higher based on the robust beneficial effects and absence of harms.	Among the critical outcomes, the certainty of the evidence differed and was assessed as either *moderate, low* or *very low*. The WHO NUGAG agreed on selecting '*low*' as the overall certainty of evidence, informed by GRADE guidance[5]. Importantly, the '*low*' certainty is the summary assessment across all the critical outcomes, and this is with acknowledging that there is some evidence of benefit that was of *moderate* certainty.

Evidence: beneficial effects

Summary comment	Response
The draft guideline underestimates the quality of the evidence available for blood-pressure-lowering effects, which have comparable effects as seen in the WHO sodium and potassium guidelines. The evidence for the impact of LSSS on systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be reported as *high* certainty, not *moderate* certainty. In the wider context of our knowledge about the effects of sodium and potassium on blood pressure in diverse populations, there is a very strong rationale for expecting highly generalizable effects across the global population with huge potential for health gains. The draft guideline must acknowledge the important observation that blood pressure reduction was achieved universally with the use of LSSS and it would be expected in the long-term to reduce the risk of cardiovascular outcomes for all populations.	As shown in the GRADE evidence profiles table (Annex 6), the two blood pressure-related outcomes (changes in DBP and SBP) were downgraded by one for inconsistency because of substantial heterogeneity (I^2 = 88% for DBP, 78% for SBP), which was not explained by subgroup analyses (study duration, ethnicity, blood pressure status, type of LSSS, baseline sodium excretion) or meta-regression (type of LSSS, baseline sodium excretion, overall risk of bias). This judgement to downgrade for inconsistency follows the GRADE guidance. Since the LSSS guideline is informed by evidence from a set of studies that is distinct from those used for developing the 2012 WHO sodium guideline and potassium guideline, even though the effect size may be comparable, other aspects comprising the certainty of evidence (e.g. inconsistency, indirectness, imprecision, risk of bias) are different because we are looking at a different set of studies. Importantly, the LSSS guideline acknowledges the beneficial effects of LSSS throughout the text. For example, the executive summary section states that assignment to use LSSS compared to regular salt resulted in reductions in diastolic and systolic blood pressure and that the use of LSSS showed reductions in risks of non-

[5] GRADE Book: https://book.gradepro.org/

	fatal stroke, non-fatal acute coronary syndrome and cardiovascular death. The recommendation to suggest LSSS use is applicable to the extent supported by evidence not only on benefits but also on harms – i.e. adults in general populations, excluding individuals with kidney impairments or with other circumstances or conditions that might compromise potassium excretion. The recommendation does not apply to children or pregnant women. Generalizability beyond this is not supported by evidence. The majority of the studies assessing safety was of limited duration and did not provide evidence of long-term safety.
The recommendation should remove statements such as "LSSS compared to regular salt "probably, slightly" reduces systolic blood pressure." The same goes for the description of the other outcomes such as non-fatal stroke, non-fatal acute coronary syndrome, and heart disease death.	This approach followed the GRADE guidance on informative statements to communicate the findings of systematic reviews of interventions, where the statement combines the size and certainty of an effect on a particular outcome. That said, to avoid the risk of potentially misleading in the general context, this wording has been removed.
A threshold of clinically meaningful reduction in SBP was defined as 10 mmHg and in DBP as 5 mmHg in the systematic review. The selection of these thresholds appears arbitrary, and it is unreasonable to expect any dietary intervention to result in an overall blood pressure reduction of this magnitude. In fact, most classes of blood-pressure-lowering medications do not achieve this level of blood pressure reduction.	Importantly, the thresholds described in the published systematic review (Brand 2022) in relation to clinically meaningful reductions in blood pressure were <u>not</u> used by the guideline development group (WHO NUGAG Subgroup on Diet and Health) during their decision-making for the recommendation in this guideline. These thresholds did not inform the recommendation in the guideline as they were not included in the preliminary review report prepared for and used during the NUGAG meeting in November 2021 when decision-making occurred, and the NUGAG had agreed on their own judgement on the magnitude of the anticipated desirable effects (as reflected in the table in Annex 7) before the thresholds were written up in the published Cochrane review. These were only added to the Discussion section of the systematic review during the finalization of the Cochrane manuscript and strongly considered the population from which this evidence stemmed, namely a high CVD risk population, and effects on risk of major cardiovascular events, as described in the review.
The draft guideline recommendation should be based on similar outcomes as those considered in the WHO guideline on sodium and potassium intake. The WHO guideline on LSSS has failed to specify and report on key effectiveness outcomes. These should include composite cardiovascular disease outcomes as the primary focus of evaluation, which would produce *high* certainty evidence.	The subjects of the three WHO guidelines are closely related; however, the LSSS guideline addresses different questions than those addressed by the sodium and potassium guidelines. The sodium and potassium guidelines provide recommendations on the appropriate dietary intake levels of these nutrients, whereas the LSSS guideline provides a recommendation to inform policy decision-making on implementation of an intervention that combines sodium reduction and potassium supplementation. Since the questions are different, a set of studies reviewed in the systematic review that informed the development of the LSSS guideline was

	different from those used for the sodium and potassium guidelines. Therefore, outcomes were also reported differently. In the studies that supported the sodium and potassium guidelines, composite cardiovascular disease outcomes were used because they were reported by 9 studies (adults) and 4 studies (adults), respectively, whereas in the studies included in the WHO systematic review (Brand 2022) supporting the LSSS guideline, this was not the case. Only one study reported a composite outcome, and the remaining studies reported individual outcomes. It should be noted that the LSSS guideline well acknowledges the beneficial effects of LSSS, but what was critically missing was evidence on the safety of LSSS use, leading to the decision and agreement on the *conditional* recommendation. Therefore, even if analyses using composite cardiovascular disease outcomes had been done and effect estimates on these outcomes had been rated as *high* certainty evidence, this would not have changed the consensus that the recommendation should be *conditional*.
The draft guideline recommendation should be based on similar outcomes as those considered in the WHO guidelines on sodium and potassium intake. Hypertension and blood pressure control were included as outcomes when considering the overall recommendation for LSSS. Neither of these outcomes was considered in the guidelines for sodium and potassium.	Blood pressure was identified as one of the critical outcomes by NUGAG. As noted above, the evidence synthesis is largely informed by how the outcomes were reported in the primary studies. Blood pressure was reported in a few different ways (i.e. continuous blood pressure levels, hypertension prevalence and incidence (as reported, or SBP >140 mmHg or DBP >85 mmHg), and blood pressure control defined as achieving blood pressure threshold or 'control' as prespecified by study authors). To capture all relevant information, they were included in the evidence synthesis.
The WHO systematic review (Brand 2022) downgraded the evidence from *high* to *moderate* based on 'substantial heterogeneity', not explained by subgroup analyses. It is noteworthy that such heterogeneity occurred in the meta-analyses conducted by Aburto et al. in support of the WHO potassium guideline, which nonetheless gave a '*strong'* recommendation.	When assessing evidence on LSSS use, the blood pressure outcomes (DBP and SBP) were downgraded by one because of inconsistency due to substantial heterogeneity (i.e. high heterogeneity of effect sizes across studies; I^2 >50%) that was not explained by subgroup analyses (study duration, ethnicity, blood pressure status, type of LSSS, baseline sodium excretion) or meta-regression (type of LSSS, baseline sodium excretion, overall risk of bias). The decision to downgrade for inconsistency (and other criteria) followed the GRADE guidance. In the case of evidence on potassium intake (Aburto 2013 BMJ), substantial heterogeneity was dealt with differently at the time. Importantly, there have been advancements in the methodology for formulating recommendations on topics of public health importance over the past decade since the time the WHO potassium guideline was released.
The WHO systematic review used effect estimates that were unfavourable to salt substitutes when multiple estimates were available.	As specified in the methods section, 'When outcome data were reported at more than one point, we extracted data from the latest point available.' This approach was applied consistently across studies.

For example, in the China Salt Substitute Study (CSSS), the first LSSS trial in China, due to the investigators' inexperience, the salt already in use in the families were not sealed, and the effect on blood pressure appeared to have a significant time trend with the effect the largest at the end of the 1-year intervention. However, the systematic review selected the mean blood pressure between 3 months to 12 months, which was significantly smaller. The WHO systematic review also selected effect estimates from a subpopulation of a study that theoretically would have a lower effect in Hu 2018 (CSSS-2 study), a randomized trial with the main study on patients with hypertension and an ancillary study on the patients' family members. The WHO systematic review only selected results from the ancillary study on family members that included many people with normal blood pressure. Combining results of patients with high blood pressure and family members with normal blood pressure has diluted the effect estimate.	The objective of the LSSS guideline is to provide guidance on the LSSS use for the general population. Therefore, it is appropriate to collect information from as general a population as possible rather than limiting it to individuals with a specific condition (in this case hypertension). The recommendation was developed based on a comprehensively reported systematic review of evidence that was synthesized according to the transparent methods to analyse all data together and then to explore effect estimates further via predetermined subgroup and sensitivity analyses. This enables reviewing the totality of the available best evidence while allowing appraisal of the certainty of the evidence (the extent to which our confidence in an estimate of the effect is correct).
Potassium intake from food source is WHO's primary recommendation. However, the studies that informed the potassium guideline came mostly from supplementation trials, which contradicts with recommending potassium intake from food only. The draft guideline should identify potential benefits of potassium supplementation and consider the potential health benefits that LSSS use would have through reducing the population sodium/potassium ratio.	The WHO guideline on potassium intake recommends an increase in potassium intake from food, and not from supplements in tablet form or LSSS. Because of the safety of consumption of increased potassium via food, no upper limit was considered. The following are the reasons why potassium intake from food is recommended in the WHO guideline on potassium intake: - There is no evidence of adverse effects from increased potassium intake from foods in individuals with unimpaired potassium excretion; in individuals without renal impairment caused by medical conditions or drug therapy, the body is able to efficiently adapt and excrete excess potassium via the urine when consumption exceeds needs. Intervention trials, including potassium consumption as high as 400 mmol/day from food for several weeks and 115 mmol/day for up to a year, have not reported any adverse effects. There have been some isolated reports of acute toxicity from extremely high potassium intake in supplement form, but no reports of toxicity of potassium from consumption in food. - Most ingested potassium is excreted via the urine. Under conditions of extreme heat and

	intense physical activity that result in a high sweat production, potassium losses in sweat are increased and appreciable. However, acclimation occurs rapidly, and potassium losses via sweat are reduced quickly. Thus, most individuals can replace needed potassium through food consumption without the need for supplements or specially formulated products. - Potassium is commonly found in a variety of unrefined foods, especially fruits and vegetables. Food processing reduces the amount of potassium in many food products, and a diet high in processed foods and low in fresh fruits and vegetables is often lacking in potassium. Additionally, because fresh fruits, vegetables and beans are high in potassium, an increased intake of potassium can be achieved without increasing caloric intake if these foods replace foods lower in potassium levels in the diet. Examples of foods high in potassium can be found in Annex 2 of the WHO potassium guideline. - While the results suggest that an increase in potassium intake from either supplement or food has a beneficial effect on blood pressure, consistency in results from studies with increased potassium through dietary change supports the health benefit of potassium specifically, and not the conjugate anion found in the supplements used in the supplementation studies. Additionally, all cohort studies compared groups consuming different levels of potassium from foods. That said, the LSSS guideline acknowledges in the remarks section that the blood-pressure-lowering effect of LSSS is partly due to its potassium content, although the percentage of KCl in the LSSS did not modify the effect in the systematic.
The systematic review underlying the WHO guideline on LSSS used DBP rather than SBP to be the primary study outcome.	This is not correct. The systematic review examined both DBP and SBP because they were both part of the critical outcomes agreed by the NUGAG and prespecified in the PICO question.

Evidence: harms and safety

Summary comment	**Response**
The conclusions drawn about the inferred risks from hyperkalaemia go far beyond any of the evidence presented. There is no evidence of risk for the general healthy population. Conclusions	As noted in the LSSS guideline, caution is needed to interpret the finding of the systematic review that there was no meaningful increase in hyperkalaemia with LSSS when compared to regular salt. This is because the evidence on hyperkalaemia presented by the studies in the systematic review has several limitations, including

Summary comment	Response
about the likely overall balance of risks and benefits are not right.	that very few studies reported on hyperkalaemia, and that studies that did report on hyperkalaemia also used variable, in some cases unclear, criteria to define the condition. The information on hyperkalaemia events and other potassium-related measures was unreliable. Most studies assessing safety were of limited duration and did not provide evidence of long-term safety. Importantly, lack of evidence on safety was the case not only for people for whom increased potassium intakes would not be advisable (i.e. people excluded from studies because of their high risk of hyperkalaemia) but also for the generally healthy population, for whom studies were conducted. Based on these, the conclusions about the overall balance of risks and benefits are appropriate, and it is inaccurate to assert that there is no evidence of risk for the general healthy population.
The draft guideline should state that the slight increase in blood potassium seen with LSSS compared to regular salt (i.e. 0.12 mmol/L increase) is not clinically important for a normal range of blood potassium, and this should be considered when establishing the recommendation on LSSS use.	The document has been updated to include a discussion on the interpretation of the increase in blood potassium. A new sub-section has been added in the "Interpreting the evidence" section, citing a systematic review and meta-analysis of RCTs that evaluated the safety of increasing potassium intake with supplements on circulating potassium and renal function (Cappuccio 2016). The study showed that a short-term moderate increase in potassium intake using supplements (average 45 mmol or 1755 mg/day; range 22–140 mmol or 858–5460 mg/day) caused an increase in circulating potassium levels of 0.14 mmol/L (95% CI 0.09 to 0.19). This is comparable to that observed in the LSSS trials. The study also showed that potassium supplements did not seem to cause severe hyperkalaemia or deterioration in renal function in healthy people and patients whose kidney function is not impaired.
The draft guideline fails to report on the most likely level of population risk from hyperkalaemia and should incorporate the latest data, including those from China (Marklund 2020 BMJ) and India (Marklund 2022 Hypertension). These studies showed very high benefit-risk ratios, even under worst-case assumptions about harms from hyperkalaemia.	The WHO's contextual factor review (WHO 2023) included data from modelling studies, including Marklund 2020 BMJ. Marklund 2022 Hypertension was published after the contextual factor review was compiled. Results of this study were similar to those reported in the review supporting the formulation of the recommendation. While modelling studies can provide valuable insights, there are limitations due to assumptions made, and therefore the results should be interpreted carefully.
The draft guideline fails to identify that the proportion of the population likely at risk of hyperkalaemia (those with stage 4 or stage 5 kidney disease) is a fraction of 1% of the population. While some of these individuals in very resource poor settings may be	Patients with chronic kidney disease (CKD) stage 3b (GFR 30-44 mL/min/1.73 m^2: moderately to severely decreased) and above should be particularly careful with potassium intake due to the increased risk of hyperkalemia.

Summary comment	Response
undiagnosed, the majority are likely to be aware of their risk and already advised to avoid salt and products high in potassium.	A systematic review and meta-analysis showed that the global mean CKD prevalence of stages 3–5 was 10.6% (95%CI 9.2–12.2%) (Hill 2016 PLOS ONE). Unfortunately, the analysis of stages 3a and 3b separately was not possible due to a lack of reporting and studies. The number of patients affected by CKD has been rising due to aging and an increasing burden of risk factors for CKD such as diabetes and hypertension, which are the two most common causes of CKD worldwide (KDIGO 2024 clinical practice guideline for the evaluation and management of CKD). GBD studies have shown that CKD has emerged as a leading cause of worldwide mortality (Kovesdy 2022 Kidney international suppl). Therefore, we should be careful with assessing the impact of CKD on hyperkalaemia. We disagree with the point made that "the majority are likely to be aware of their risk and already advised to avoid salt and products high in potassium". Approximately 850 million people worldwide are estimated to have kidney disease, most of whom live in low-income and lower-middle-income countries, and a large proportion of these individuals lack access to kidney disease diagnosis, prevention or treatment. As many as 9 out of 10 individuals with CKD in resource-poor settings with weak primary care infrastructure are unaware that they have this condition and therefore do not seek treatment (Francis 2024 Nature reviews nephrology).
The choice of key safety outcomes is inappropriate, and evidence of risks is overinterpreted. WHO should review the evidence and draft guideline considering more appropriate and patient-centred outcomes for harms, to ensure that safety in terms of *moderate* strength evidence of no effect on clinical hyperkalaemia events and no effect on sudden death are appropriately identified and included in the assessment. Clinical hyperkalaemia, arrhythmia, sudden cardiac death (or sudden death), and total mortality would be more appropriate and focused on true harm.	Evidence on safety was very limited. It should be noted that the evidence on hyperkalaemia presented in the studies in the systematic review has several limitations. Very few studies reported on this important safety outcome, and studies that did report on hyperkalaemia also used variable, in some cases unclear, criteria to define the condition. Other potassium-related outcomes presented in most of these studies were not rigorously collected and reported. Therefore, the information on hyperkalaemia events and other potassium-related measures was unreliable. Consequently, serum potassium was considered probably the most relevant available outcome for safety. Most studies included in the review had strict inclusion and exclusion criteria with regard to risk factors for hyperkalaemia. All included trials specifically excluded participants in whom an increased intake of potassium could cause harm, for example, people with kidney disease, impaired renal function or those using potassium-sparing medications. Further, studies assessing safety were of limited duration and did not provide evidence on long-term safety. Finally,

Summary comment	Response
	NUGAG considered that the undesirable effects and safety concerns may vary with access to health care. Therefore, it was agreed that the undesirable effects varied depending on the setting and population. Sudden death was not examined as a safety outcome. While it is an outcome of clinical relevance, there are several downsides, including that it is a relatively rare event and it may not occur frequently enough to provide meaningful data, that it would be difficult to determine the direct cause of sudden death as it may be influenced by multiple factors, and that monitoring for sudden death requires rigorous follow-up and extensive data collection (only 1 study reported on this outcome). Total mortality also has an issue of non-specificity. WHO encourages the research community to generate more reliable evidence around the safety of LSSS, which is identified as the key area of future research. See the section on "Research gaps and future initiatives".
When looking at the potential harms to higher-risk individuals, it is necessary to take into consideration that a number of the trials, including the SSaSS trial, which was the largest and looked at hard cardiovascular outcomes, only excluded people who self-identified as having kidney disease or taking a potassium-sparing diuretic and found no evidence of harm. The LSSS guideline should consider the same exclusions as the SSaSS trial – people with known advanced kidney disease or taking a potassium-sparing diuretic.	Developing WHO recommendations requires robust data on both safety and benefits. WHO is unable to recommend LSSS to those people for whom safety was not properly assessed and confirmed. The pragmatic approach, as noted in the comment, which may have been useful in conducting RCTs, unfortunately, did not provide appropriate data for assuring safety. It is possible that hyperkalemic episodes were missed because they relied on self-reporting to record hyperkalaemia events.
The current WHO potassium guideline provides a *strong* recommendation to increase potassium intake among adults, without considering potential effects on serum potassium and hyperkalemia risk in the general population or in high-risk individuals. The draft LSSS guideline considers effects on serum potassium, hyperkalaemia and hypokalaemia as primary outcomes, and refers to the uncertainties in these outcomes as a justification for the *conditional* recommendation.	The two guidelines have different objectives. The potassium guideline provides recommendations on the appropriate dietary intake levels of potassium. The LSSS guideline provides a recommendation to inform policy decision-making on the implementation of an intervention that combines sodium reduction and potassium supplementation. The potassium guideline identified renal function and adverse effects as critical outcomes. In the LSSS guideline, potassium-related outcomes, including hyperkalaemia, were identified as critical, as concerns have been raised about the safety of LSSS that contain potassium. The recommendation was assessed as *conditional* because the overall certainty of evidence was *low* according to the GRADE guidance and there was

Summary comment	Response
	uncertainty about the balance between the benefits and potential harms. With a *conditional* recommendation, policy-makers will have to assess the importance of the concern about harm in their own setting, whereas a *strong* recommendation would imply that there were no concerns at all with universal implementation of LSSS.
WHO should conclude that salt substitutes are generally safe, considering that salt substitutes have been on the global market for over 50 years and only few cases of clinical hyperkalaemia with severe clinical manifestations were reported to be associated with the use of salt substitutes that contain potassium.	Currently, there is an evidence gap on safety, and the evidence base does not support the statement. As noted in the Research gaps and future initiative section, further research is needed to achieve a better understanding of the safety implications of widespread LSSS use (discretionary and non-discretionary) on explicitly defined measures of hyperkalaemia. See the Research gaps and future initiative section.

Evidence: new/additional studies, consistency of systematic review supporting the guideline with other reviews

Summary comment	Response
The WHO systematic review and the draft guideline did not consider two safety evaluations of LSSS (≤40% KCl) in elderly hospitalized patients (Karppanen 1984 J Cardiovasc Pharmacol) or heart failure patients (Bistola 2020 Clinical Nutrition ESPEN) or a recently published cluster RCT conducted in elderly care facilities (Yuan 2023 Nature Medicine), which all reported no adverse clinical outcomes of LSSS use.	Bistola 2020: This prospective, controlled study was included in the search of the WHO systematic review. It did not meet the inclusion criteria of the systematic review as it is a non-randomised intervention study. Karppanen 1984: The paper reporting on 3 studies was included in the search of the systematic review. Two studies were ineligible based on the comparisons they investigated (they did not comparatively analyse LSSS with NaCl), and the third was also ineligible because it did not report on any outcomes rated as critical nor important by NUGAG (reported on serum creatinine, blood glucose, total cholesterol). Importantly, this paper did not report on hyperkalaemia or other safety outcomes apart from the blood potassium that was reported in the first study. Regarding Yuan 2023, please see our response immediately below.
WHO should review and incorporate the latest data and evidence from a cluster RCT (Yuan 2023). The recommendations should be updated accordingly.	Yuan 2023 was published after the publication of the WHO systematic review (Brand 2022). This trial would have been eligible for inclusion in the systematic review. The crucial question was whether the new study would add data on safety in a significant manner, as the current evidence base notably lacks such data, contributing to the uncertainty about the balance between the benefits and potential harms. Additional analyses were conducted incorporating data for relevant primary outcomes reported on by Yuan 2023. Since these analyses did not

Summary comment	Response
	result in consequential changes to pooled effects or certainty of evidence on which the recommendation is based, the WHO systematic review will not be formally updated for the guideline at this time. Yuan 2023 reported broad beneficial effects of LSSS, including major cardiovascular events, as well as a statistically significant increase in hyperkalaemia, although not associated with adverse clinical outcomes.
WHO should revise the draft guideline considering the analysis in the Yin 2022 systematic review. There are discrepancies between studies included in the WHO systematic review and the Yin 2022 review.	Yin 2022 (systematic review) was published after the publication of the WHO systematic review (Brand 2022). There are some important discrepancies in the data included, which cannot be explained by the difference in the inclusion criteria of the two studies as described below. **1) Hyperkalaemia:** - Yin 2022 only reported narratively on hyperkalaemia and did not report a meta-analysis for hyperkalaemia. Extract from Yin 2022: "There were two studies that reported no difference in hyperkalaemia events between randomised groups including SSaSS, which recorded 331 clinical hyperkalaemia events. [Neal 2021; Li 2016]" - Yin 2022 used the clinical hyperkalaemia events data from Neal 2021 in a different manner from the WHO systematic review. The WHO systematic review only included 'definite' and 'probable' hyperkalaemia events reported in Neal 2021. Neal 2021 did not report event data per group for 'possibly' hyperkalaemia, only events per 1000 person-years. Neal 2021 reported "There were two participants who had definite or probable hyperkalemia (one in the salt-substitute group and one in the regular-salt group). An additional 313 participants, including 302 who died and 11 who had a nonfatal event, were identified as having possible hyperkalemia." From the Neal 2021 Supplementary Appendix, 'definite' or 'probable' hyperkalaemia were defined as "Elevated serum K >5.5mmol/L and typical ECG changes documented in medical notes"; 'possibly' hyperkalaemia was defined as "Self-reported serum K >5.5mmol/L or ECG changes but no supporting documentation to verify". - Li 2016 did not report usable hyperkalaemia event data (as reported in Table 5 of the WHO systematic review on trials without usable data). The study authors were contacted by the reviewers but were unresponsive. - The WHO systematic review additionally included 20 hyperkalaemia events reported in the Zhang 2015 conference abstract, where nursing houses were randomized into 2 groups: normal salt (control group) and potassium-containing salt (intervention group). It is not clear why these data were not included in Yin 2022.

Summary comment	Response
	2) Blood potassium: - Yin 2022 included blood potassium data from 2 studies: Geleijnse 1994 and Omvik 1995. The WHO systematic review included four additional trials in the meta-analysis for blood potassium (Allaert 2017, Kawasaki 1998, Pereira 2005, Zhang 2015). • Allaert 2017 assessed the effect of LSSS with 3% of sodium replaced by chitosan and did not meet the Yin 2022 inclusion criteria. • Kawasaki 1998 investigated a 'reduced sodium mineral' salt (22.9 % Na; 10.1 % K; 1.2% Mg per g) intervention; it is not clear why these data were not included in Yin 2022. • Pereira 2005 investigated an intervention with 50% NaCl and 50% KCl; it is not clear why these data were not included in Yin 2022. • Zhang 2015, a conference abstract, investigating a potassium-containing salt (NaCl:KCl = 1:1). It is not clear why these data were not included in Yin 2022. **3) Adverse events attributable to hyperkalaemia** - Yin 2022 reported narratively on serious adverse events attributable to hyperkalaemia. Extract from Yin 2022: "…six reported no serious adverse events attributable to hyperkalaemia. [CSSS 2007; Zhao 2014; Mu 2003; Sarkkinen 2011; Suppa 1988; Yu 2021]" - All six studies cited in Yin 2022 were included in the WHO systematic review. However, those papers did not report on serious adverse events attributable to hyperkalaemia, and it is not clear where these data were obtained from in Yin 2022 to make the above statement.
Some studies were not included in Yin 2022 that were included in the WHO systematic review. Reasons for studies being excluded from Yin 2022 were, for example, that the "salt substitute" was not low sodium as it included 97% NaCl, or that the intervention was not LSSS but rather 'reduced salt bread'. While the majority of studies examined LSSS where potassium replaced some of the sodium, one intervention looked at the use of salt-reduced bread (Toft 2020) and another replaced regular salt with a salt where NaCl was combined with 3% chitosan (Allaert 2013). It would have been more methodologically sound to exclude these studies.	The initial scope of the evidence search was set out to be as broad as possible so that the recommendation could be as generalizable as possible. First, evidence needs to be collected, analyzed and appraised, and this evidence then feeds into the evidence-to-decision processes and the potential recommendation. The eligibility criteria of the review developed by the WHO NUGAG state: 'LSSS interventions/exposures of any type or duration were included, provided they aimed to replace the dietary intake of any amount of sodium with another mineral or compound. Studies investigating either discretionary (i.e. salt on table or added during cooking) or non-discretionary use of LSSS (i.e. included during food manufacturing), or both, were included.' We recognize the heterogeneity in the interventions used in the studies included in the systematic review, and multiple subgroup analyses were therefore conducted to explore if and how effects on outcomes were impacted by such heterogeneity.

Summary comment	Response
	Included studies could be different because the inclusion criteria were different, but we note that several papers had been omitted in Yin 2022, the reasons for which are unclear. Those are: Arzilli 1986; Kawasaki 1998; Li 2014; Mu 2009; Pan 2017; Zhang 2015. On the contrary, Yin 2022 included two studies that were not included in the WHO systematic review as they did not meet the inclusion criteria: Mickelsen 1977 (non-randomised study) and Barros 2015 (quasi-randomised controlled trial).
WHO defines that LSSS in this recommendation refers to products where NaCl is partially replaced with KCl in varying amounts. However, the systematic review included studies with no KCl or products with only 3% of NaCl replaced with KCl. This is not appropriate.	As noted above, the initial scope of the evidence search was set out to be as broad as possible. It was after the evidence was synthesized that the scope of the recommendation was determined (i.e. products with its NaCl replaced by KCl). Therefore, the inclusion of studies in the WHO systematic review was appropriate.
WHO should not include in the systematic review Omvik 1995 and Suppa 1988 because they used salt substitutes only as table salt. In addition, the intervention used in the Omvik study was mainly a salt-restricted diet for 6 months.	The two studies met the eligibility criteria of the review developed by the WHO NUGAG as noted above (i.e. LSSS interventions of any type were included in the systematic review, provided they aimed to replace the dietary intake of any amount of sodium with another mineral or compound). Therefore, they were included. As for Omvik 1995, the salt-restricted diet was considered as a co-intervention common to both groups, with the only difference being the use of LSSS or regular salt.
WHO should not include in the review the China Rural Health Initiative Sodium Reduction Study (CRHI SRS) by Li 2016 because they used health education rather than salt substitutes as the study intervention.	The additional intervention component in this study was the education programme, where the judgement was made that most of the components be predominantly aimed at promoting LSSS use instead of regular salt rather than being predominantly focused more broadly on reducing sodium intake by, for example, avoiding high-salt foods (based on Table 1 of Li 2013 Am Heart J).
Following recent publications on umami should be considered for the guideline development: - Nomura 2021 Health. - Nakamura 2022 Food Sci Nutri. - Nomura 2022 Public Health Nutr. - Tanaka 2023 BMC Public Health.	As noted above, umami was not included as an intervention in the LSSS guideline.

Evidence: GRADE assessments, certainty in the evidence, strength of the recommendation

Summary comment	Response
To avoid confusing the intended audience, the recommendations must be *strong* to be consistent with WHO guidelines on sodium and potassium	While the LSSS guideline needs to be considered in the context of the WHO guidelines on sodium and potassium intakes, the nature of the intervention discussed is different. The sodium and potassium guidelines provide

Summary comment	Response
intakes, which are relevant to this LSSS guideline. The blood-pressure-lowering effects observed in LSSS trials are stronger than those observed in the studies supporting the WHO guidelines on sodium and potassium intakes. In keeping with WHO's guidance on sodium and potassium intakes, the draft guideline should state that using LSSS "lowers stroke, coronary syndrome and heart disease" (*strong* recommendation).	recommendations on the appropriate dietary intake levels of these nutrients, whereas the LSSS guideline provides a recommendation to inform policy decision-making on implementing an intervention that combines sodium reduction and potassium supplementation. The LSSS guideline considered evidence from studies that specifically addressed questions on LSSS. Furthermore, the formulation of a recommendation takes into account not only evidence on beneficial effects but also harms and other contextual factors, which also differ by intervention. All these factors need to be considered to determine the strength of a recommendation.
The draft guideline should have a *strong* overall recommendation, with areas of uncertainty identified through *conditional* recommendations for subgroups or settings. For example, 1) a *strong* recommendation for LSSS use in generally healthy adult populations and clinical settings, 2) a *conditional* recommendation for children and pregnant women, 3) a *conditional* recommendation for avoidance among population groups such as those with advanced kidney disease or in very remote settings where healthcare diagnostic facilities are absent.	It is challenging at the global level to define the settings or subpopulations where the conditions apply due to differences across countries in the way systems are set up. A *conditional* recommendation, by definition, gives each country the ability to assess their own situation, design and implement an adequate and safe approach. This will require substantial discussion and involvement of various stakeholders. Please refer to the "Translation and implementation" section of the guideline, outlining key considerations by policy-makers and programme managers when discussing the implementation of the recommendation on LSSS use at a country level. There was a paucity of data for children (in particular, no studies in children examining discretionary use of LSSS) and no data for pregnant women. Therefore, no conclusion can be drawn for these groups and the recommendation does not apply to them.
Conclusions about the likely overall balance of risks and benefits presented in the contextual factors narrative review do not align with the quantitative evidence and data in the systematic review. In particular, the conclusions drawn about the inferred risks from hyperkalaemia go far beyond any of the evidence presented. The draft guideline should explicitly define how the overall balance of benefits and risks was determined.	The NUGAG Subgroup on Diet and Health concluded that the balance between desirable and undesirable effects probably favours the intervention (i.e. LSSS use in comparison to not using LSSS) while noting uncertainty about the balance between the benefits and potential harms, particularly in settings where a considerable proportion of the population may have undiagnosed kidney disease for which it would not be advisable to increase potassium intakes. For undesirable effects, adverse events were very varied and, therefore, were not pooled in the systematic review. Very few studies reported on hyperkalaemia, and studies that did report on this important safety outcome also used variable, in some cases unclear, criteria to define the condition. Other potassium-related measures presented in most of these studies were not rigorously collected and reported. Therefore, the information on hyperkalaemia events and other

Summary comment	Response
	potassium-related measures was unreliable. Consequently, serum potassium was considered probably the most relevant outcome for safety. Considerations were that patients with overt kidney disease were excluded by the included trials, and that the majority of studies assessing safety were of limited duration and did not provide evidence of long-term safety. In addition, the undesirable effects may vary with access to health care. Overall, NUGAG concluded that the undesirable effects varied depending on the setting and population. The above is explained in the revised section on the balance of desirable and undesirable effects.

Evidence: general, others

Summary comment	Response
The priority public health message should be to reduce discretionary salt use, which is especially important for countries where discretionary use is a major source of sodium intake. The use of LSSS is only one of many means in an overall strategy to reduce sodium intake. This is also the case for manufactured food products, and policy measures such as implementation of voluntary sodium targets for packaged foods as well as front-of-pack labelling play a crucial role in reducing population sodium intake.	Noted and agreed. This is included throughout the guideline. Regarding manufactured foods, please refer to the "Translation and implementation" section and the SHAKE Technical Package, which includes a comprehensive action package for sodium reduction. The updated version of SHAKE will be published in early 2025.
WHO should not base its recommendation on a review that aggregated all studies with substantial heterogeneity together using a simple statistical synthesis. The review included studies with a wide variation in the KCl content of salt substitutes, study duration, and studies that examined non-discretionary use.	The recommendation was developed based on a comprehensively reported systematic review of evidence that was synthesized according to the transparent methods to analyse all data together and then to explore effect estimates further via predetermined subgroup and sensitivity analyses. This enables reviewing the totality of the best available evidence while allowing appraisal of the certainty of the evidence (the extent to which our confidence in an estimate of the effect is correct).
The guideline did not differentiate the efficacy studies from the effectiveness studies.	WHO guidelines on diet and health make recommendations based on an assessment of the effectiveness of exposures or interventions, not efficacy.

4. Wording of the recommendation, remarks

Summary comment	Response

The term 'limited' in the primary recommendation may cause confusion among consumers, and it should be removed from the guideline recommendation.	The recommendation wording has been revised as follows (the term 'limited' has been deleted): "To reduce blood pressure and risk of cardiovascular diseases, WHO has recommended reducing sodium intake to less than 2 g/day (*strong* recommendation). In this context, using less regular table salt is an important part of an overall sodium reduction strategy. If choosing to use table salt, WHO suggests replacing regular table salt with lower-sodium salt substitutes that contain potassium (*conditional* recommendation)".
Making the recommendation contingent on access to care limits its applicability, especially considering that this guideline focuses exclusively on discretionary salt, which is the largest source of sodium intake in most low- and middle-income countries.	Evidence on safety was limited, particularly for people at high risk of hyperkalaemia. The recommendation clearly states that it does not apply to individuals with contra-indications to higher potassium intakes. The issue, however, is that in some low-resource settings, a considerable proportion of the population who may not be aware of having these conditions, and there may be individuals with undiagnosed kidney disease for whom higher potassium intakes over the long term might be of concern, and might require medical supervision and periodic assessment over time. Therefore, the use of LSSS should be implemented in settings with adequate access to health care, where conditions in which increased potassium intakes are potentially harmful (e.g. kidney disease) would not go undiagnosed for a long time. As rightly pointed out, those low-resource settings (e.g. low- and middle-income countries) are exactly where discretionary salt tends to be a major source of sodium intake. Further research is needed to generate evidence on safety to inform the applicability of the recommendation to such populations/settings.
Suggesting that LSSS should not be used to prepare meals for households with children and pregnant women is overly restrictive and would likely limit the usefulness of this intervention.	The remark is <u>not</u> advising against LSSS use in a household with *any* children and pregnant women. The remark advises against LSSS use in a household with people (including children or pregnant women) at risk for hyperkalaemia. The wording is now clarified and reads as follows: "if a member in a household (including children and pregnant women) is at risk for hyperkalaemia, LSSS should not be used to prepare a family meal to be eaten by the member."

5. Implementation of the recommendation

Summary comment	Response
The feasibility section rightly notes that LSSS is not widely available and is more expensive than regular salt. However, while the uptake of LSSS is not currently widespread, government investment in this sector and promotion of LSSS would	Noted. When a government discusses the implementation of LSSS use, feasibility issues need to be considered, and what measures could potentially mitigate such issues.

Summary comment	Response
increase demand and availability and might also lower prices.	
Equity and human rights: Despite higher costs of LSSS, LSSS is highly cost-effective and averts substantial burden of disease and associated healthcare costs. Early and wider uptake and use of LSSS is likely to bring down its cost. Strategies such as government subsidies might be feasible and could decrease the differential effects within a country. Further, since low- and middle-income countries disproportionately consume sodium from discretionary sources, LSSS interventions have the potential to increase equity between countries.	Noted. As noted in the "Evidence to recommendations" section, NUGAG judged that using LSSS is probably cost-effective. When a government discusses the implementation of LSSS use, equity and human rights issues need to be considered, and what measures could potentially mitigate such issues.
Implementation considerations: Advocacy, training and meetings can be delivered through digital platforms; the overall costs are minimal and thus not relevant in this context. Moreover, it is often civil society organizations that lead such efforts.	The use of virtual means and assistance from civil society organizations could indeed reduce the cost to the government. However, there are still administrative costs for implementation, including securing adequate resources, hiring and training personnel and organizing such meetings, among others.
Target audience: It would be useful to define the roles and responsibilities of each target audience, including the role of industry in both the manufacturing of LSSS and the sourcing of potassium for such manufacture.	The recommendation is *conditional*, meaning that substantial discussion and involvement of various stakeholders is needed, including about setting-specific issues, before a *conditional* recommendation can be adopted as policy and appropriately implemented. Therefore, the roles and responsibilities of each target audience would be best defined within such a policy discussion, taking into account specific contexts and issues of the country.
Priority of the problem: It would be useful also to include the potential benefits of salt reduction including the Global Burden of Diseases (GBD) estimates on the number of deaths attributed to high sodium intake every year.	GBD data has been added.
Given the potential adverse impacts for people with kidney disease, there should be some type of label on low sodium salt indicating the potassium content. Some potential additional labels include: - This product contains potassium. If you have been told to limit potassium in your diet, please consult your doctor or other health care professional before use.	Noted. The document now lists warning labels as one of the key considerations by policy-makers and programme managers when discussing the implementation of the recommendation on the LSSS use at a country level. See the "Translation and implementation" section.

Summary comment	Response
- This product contains potassium. Persons with kidney disease should consult their doctor or other health care professional before using.	

6. General comments /others

Summary comment	Response
The implied negative position the WHO seems to be taking on LSSS in this guidance is a missed opportunity for providing a tool to governmental policymakers when tackling NCD reduction.	A *conditional* recommendation does not mean that WHO advises against LSSS use. LSSS can be used where appropriate. The recommendation can be interpreted as "Implement the recommendation to use LSSS if safety considerations can be accounted for, and monitor carefully because of potential risks of hyperkalaemia or other indicators of impaired potassium excretion that would be contraindications to LSSS use". WHO is currently updating the SHAKE Technical Package for Salt Reduction, and this updated document will include the use of LSSS in appropriate settings as part of a comprehensive action package for sodium reduction. WHO welcomes future research that would fill in the evidence gap, which may allow for wider implementation of LSSS.
There should be uniformity in naming this product category, and this is not addressed adequately in the guideline.	Although establishing a harmonized name for these products is not the objective of this guideline, we recognize the importance, and international forums, such as Codex, could provide an opportunity for such efforts.
There is an inconsistency in recommendations between the LSSS draft guideline and the WHO Global Report on Sodium Intake Reduction.	The WHO Global Report on Sodium Intake Reduction used LSSS that contain potassium as one example of potential areas of research and innovation where countries may explore ways to increase the availability and use, as appropriate. This is coherent with the *conditional* recommendation given in the LSSS guideline, which will require substantial discussion and involvement of various stakeholders to discuss the implementation of the recommendation on the LSSS use.

Annex: Original comments as received during the call for comments

Comments are listed in the order in which they were received.

Survey response 1

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SUBMISSION TO THE CONSULTATION ON DRAFT WORLD HEALTH ORGANIZATION GUIDELINE ON USE OF LOW-SODIUM SALT SUBSTITUTES

About this submission

The George Institute for Global Health, a World Health Organization (WHO) Collaborating Centre for Population Salt Reduction, is pleased to contribute to the public consultation on the Draft WHO Guideline on the use of low-sodium salt substitutes (LSSS) (Draft Guideline), with endorsement from the organisations listed below.

The George Institute has led twenty years of research into the health benefits of this approach to sodium reduction, culminating in the completion of the China Salt Substitute and Stroke Study (SSaSS) in 2021. With this and related studies, we now have evidence to indicate that a large-scale switch to LSSS is feasible and very likely to generate considerable health gains, be acceptable to consumers, affordable to industry, easy for governments to support, and sustainable in the long-term.

For the first time, we have a feasible way to reduce the huge global burden of disease caused by excess consumption of dietary sodium, including cardiovascular disease (CVD) – a challenge that all stakeholders, including governments across the globe have previously been unable to achieve using other methods of sodium reduction.

We congratulate the WHO for developing the Draft Guideline at this pivotal moment, and for identifying areas for action to implement LSSS.

However, to support Member States across WHO regions, it is critical that the Draft Guideline reflects up-to-date evidence which is interpreted appropriately from a clinical and population health standpoint. **Our submission identifies several issues of significant concern which we encourage the WHO to address**, including:

- Flaws in the design and interpretation of the systematic review and meta-analysis;
- Inconsistencies between the Draft Guideline and WHO's guidance on sodium and potassium intake;
- Serious underestimation of the quality of the evidence available for effects of LSSS on blood pressure reduction;
- Misinterpretation of the likely overall balance of benefits and risks.

The George Institute and the organisations listed below welcome further engagement on the Draft Guideline and stand ready to collaborate to address the evidence gaps and other considerations identified in this submission.

Overall clarity of the Guideline

The Draft Guideline has many strengths, including its transparent approach to analysing the totality of existing evidence, and the commissioning of a systematic review and meta-analysis that outline questions and gaps that should be addressed by future research. However, there are **important flaws in aspects of the design and interpretation of the systematic review and meta-analysis and other relevant factors in the Draft Guideline** that undermine the overall conclusion. Several elements could be revised to improve the overall clarity of the Guideline:

1. ***Inconsistency between the Draft Guideline and the related WHO guidance on sodium and potassium intake***
   A comparison of the Draft Guideline for LSSS and WHO's guidance on sodium intake and potassium intake shows important inconsistencies in the outcomes reviewed and interpretations made (see Table 1). For example, in the Draft Guideline, hypertension and blood pressure control were examined and considered as separate outcomes when justifying the recommendation. Neither hypertension nor blood pressure control were examined as outcomes for WHO's Guidelines on sodium intake and potassium intake. Hypertension and blood pressure control are problematic outcomes because they are binary outcomes. This affects the statistical power to detect effects and does not capture the variability of blood pressure change (e.g., blood pressure control of <140 mmHg for those with a systolic blood pressure of 142 mmHg is very different compared to those with 160 mmHg) making it difficult to interpret. Similarly, the Draft Guideline examined change in blood potassium, hyperkalaemia, and hypokalaemia as outcomes, but these were not considered in WHO's Guideline on potassium intake. The Draft Guideline also focuses highly inappropriately on subgroups of cardiovascular events (e.g., fatal separate from non-fatal, no overall assessment of cardiovascular events) while the WHO guidelines on sodium intake and potassium intake both considered composite cardiovascular disease outcomes.

   Recommendation: The Draft Guideline recommendation should be based on similar outcomes as those considered in WHO's guidance on sodium and potassium intake. These should include composite cardiovascular disease outcomes as the primary focus of evaluation.

2. **Inconsistency in the interpretation of blood pressure effects between the recommendations in the Draft Guideline for LSSS and WHO's guidelines for sodium and potassium intake**
   WHO's Guideline for sodium intake for adults and children makes a strong recommendation for sodium reduction effects on blood pressure, based on smaller reductions in blood pressure

assessed in fewer people compared to the data available for LSSS (see Table 1). WHO's Guideline for sodium intake rightly recognises that a 'modest reduction' in systolic and diastolic blood pressure would have 'important public health benefits' (page 17). In contrast, despite larger blood pressure reductions being found when using LSSS compared to regular salt, the draft LSSS guidelines conclude LSSS "probably slightly reduces diastolic and systolic blood pressure" (page 7). In addition, there is more compelling evidence of the health benefits of LSSS on cardiovascular disease and death than there is for the effects of sodium and potassium intake on clinical outcomes. Both the sodium and potassium guidelines make *strong* overall recommendations. The *conditional* recommendation for LSSS (which effectively combines the two) is contradictory.

Recommendation: To avoid confusing the intended audience, the Draft Guideline recommendations must be consistent with those of other relevant guidelines and should therefore make a "strong" recommendation for the effect of LSSS on blood pressure and remove statements such as LSSS compared to regular salt "probably slightly reduces diastolic and systolic blood pressure".

Table 1. Comparison of the Draft Guideline and WHO's Guidelines on sodium intake, and potassium intake, for adults and children

Outcomes	WHO Guideline	Effect	n*	Quality of evidence
Change in SBP (mmHg)	Low-sodium salt substitutes	MD 4.76 lower (6.01 to 3.50 lower)	21,414	Moderate
	Sodium	MD 3.39 lower (4.31 to 2.46 lower)	6,736	High
	Potassium	MD 3.06 lower (4.70 to 1.42 lower)	1,892	High
Change in DBP (mmHg)	Low-sodium salt substitutes	MD 2.43 lower (3.50 to 1.36 lower)	20,830	Moderate
	Sodium	MD 1.54 lower (2.11 to 0.98 lower)	6,736	High
	Potassium	MD 2.84 lower (4.66 to 1.01 lower)	1,892	High
Cardiovascular disease *(In the Draft Guideline, cardiovascular mortality and events were separate outcomes, whereas in the WHO sodium and potassium intake guidelines, composite cardiovascular*	Low-sodium salt substitutes	Rate ratio 0.77 (0.60 to 1.00) – reduced cardiovascular mortality with LSSS interventions	23,200	Moderate
		Rate ratio of 0.70 (0.52 to 0.94) – reduced non-fatal acute coronary syndrome events with LSSS interventions	20,995	Moderate
	Sodium	RR 0.84 (0.57 to 1.23) – decreased risk of composite cardiovascular disease with decreased sodium intake	720	Moderate
		RR 1.12 (0.93 to 1.34) – increased risk of composite cardiovascular disease with increased sodium intake	46,483 (from cohort studies)	Very low

disease was considered)	Potassium	RR 0.88 (0.70 to 1.11) – decreased risk of composite cardiovascular disease with increased potassium intake	29,067 (from cohort studies)	Very low
Stroke *(In the Draft Guideline, non-fatal stroke and stroke mortality were examined separately, whereas in the WHO sodium and potassium intake guidelines, overall stroke was considered)*	Low-sodium salt substitutes	RR 0.90 (0.80 to 1.01) for non-fatal stroke when comparing LSSS with regular salt	21,250	Moderate
		Rate ratio 0.64 (0.33 to 1.25) for stroke mortality	21,423	Very low
	Sodium	Only 1 inconclusive RCT. RR 1.24 (1.08 to 1.43) - based on cohort studies, there was an increased risk of **all** strokes with increased sodium intake	72,878 (from cohort studies)	Very low
	Potassium	RR 0.79 (0.68 to 0.93) - based on cohort studies, there was a decreased risk of stroke with increased potassium intake	97,152 (from cohort studies)	Low

**Number of participants from randomised controlled trials unless otherwise specified.*

3. ***Misinterpretation of the totality of the data as "low certainty evidence"***
   The overall recommendation in the Draft Guideline is based on "evidence of *low* certainty overall". This conclusion is driven by uncertainty regarding the effect size on blood pressure and conclusions of low certainty evidence about efficacy and safety. However, there is compelling evidence of blood pressure reduction in all LSSS studies, and the wrong cardiovascular outcomes have been reported on in the systematic review. In addition, the conclusions about potential harms are not justified by the LSSS Systematic Review findings, which indicate moderate quality evidence of a small, clinically unimportant increase in blood potassium; moderate quality evidence of "little to no difference in…hyperkalaemia"; and very low-quality evidence of no hypokalaemia events and adverse events when comparing LSSS with regular salt. The latter fails to identify the moderately strong evidence about absence of effects on sudden death.

   Recommendation: For consistency with WHO's guidelines for sodium intake and potassium intake, the Draft Guideline should have a strong overall recommendation, with areas of uncertainty identified through conditional recommendations for subgroups or settings. For example, the recommendation for LSSS should be strong for adults, and conditional for children. There should be strong recommendations for LSSS use in general healthy adult populations and clinical settings, with a conditional recommendation for avoidance among population groups such as those with advanced kidney disease or in very remote settings where healthcare diagnostic facilities are absent.

4. ***Inconsistency in clinical effects between the Draft Guideline for LSSS, and WHO's sodium and potassium intake Guidelines***
   WHO's existing guidance is to reduce sodium intake "to reduce blood pressure, stroke and coronary heart disease in adults (strong recommendation)", and "increase potassium intake from food to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease (strong recommendation)". This is inconsistent with the recommendation for LSSS, which combines these

two effects and provides stronger evidence for LSSS than for either sodium or potassium alone. The LSSS recommendations of "probably slightly reduces diastolic and systolic blood pressure" (with moderate evidence), and "probably slightly lowers stroke, coronary syndrome, and heart disease" (moderate evidence) are wrong in this context.

Recommendation: In keeping with WHO's guidance on sodium and potassium intake, the Draft Guideline should state that use of LSSS "lowers stroke, coronary syndrome and heart disease" (strong recommendation).

5. ***Misinterpretation of the change in blood potassium data in the Systematic Review***
"The meta-analysis showed small, important effects on blood potassium on average between LSSS and regular salt groups (MD 0.12, 95%CI 0.07 to 0.18, I2 = 0%, 784 participants, 6 RCTs, moderate-certainty evidence)" (page 27). There is no justification provided in this paragraph for the clinical- or population-level importance attributed to this slight increase, in contrast to previous paragraphs about systolic and diastolic blood pressure, where the importance was illustrated through estimates of population impact. Further, in the LSSS Systematic Review, the conclusion explicitly states that "a small pooled mean difference in blood potassium between LSSS and regular salt indicated a small increase in this outcome for the LSSS group. This was not considered to be clinically important (moderate-certainty evidence) given its impact on the upper end of a 'normal' blood potassium level would not reach levels indicative of moderate hyperkalaemia."

Recommendation: The Draft Guideline should state that the slight increase in blood potassium seen with LSSS compared to regular salt is not clinically important, and this should be considered when establishing the recommendation on use of LSSS.

6. ***Failure to identify potential benefits of potassium supplementation***
The Draft Guideline considers the effect of LSSS on population sodium intake but neglects the potential effect LSSS would have on population potassium intake. WHO recommends a minimum intake of 3510 mg/day of potassium for adults for the prevention of disease. In most populations, this level of potassium intake is not achieved.[i] In fact, many studies now suggest that the sodium/potassium ratio is more important than sodium or potassium intake alone.[ii]

Recommendation: The Draft Guideline should consider the potential health benefits use of LSSS would have through reducing the population sodium/potassium ratio.

7. ***The term 'limited' in the primary recommendation may cause confusion among consumers***
The use of "limited" in the Draft Guideline recommendation may confuse the intended audience. Stating that "WHO suggests the limited use of low-sodium salt substitutes as a replacement for discretionary salt use" may be interpreted as indicating that discretionary salt is better to consume.

Recommendation: The term "limited" should be removed from the Guideline recommendation, which should instead read: "WHO suggests the use of low-sodium salt substitutes as a replacement for discretionary salt use when it contributes to reducing sodium intake to below 2 g/day in adults."

8. ***Failure to report on most likely level of population risk from hyperkalaemia***
The Draft Guideline infers significant uncertainty about the likely overall balance of benefits and risks with use of LSSS. This is inconsistent with the data, including government assessments which suggest blood pressure lowering benefits for most in the population, with corresponding long-term reductions in cardiovascular risks.[iii] In contrast, the Draft Guideline fails to identify that the

proportion of the population likely at risk of hyperkalaemia (those with stage 4 or stage 5 kidney disease) is a fraction of 1% of the population.

Further, while some of these individuals in very resource poor settings may be undiagnosed, the majority are likely to be aware of their risk and already advised to avoid salt and products high in potassium. Recent modelling studies for China and India show very high benefit risk ratios, even under worst case assumptions about harms from hyperkalaemia.[iv][v]

Recommendation: The Draft Guideline should incorporate the latest data, including those from China and India. See references at the end of the submission.

9. ***Inconsistency in recommendations between LSSS draft guideline and the WHO Global Report on Sodium Intake Reduction***
The Draft Guideline recommendation is inconsistent with WHO's recently published 2023 Global Report on Sodium Intake Reduction which recommends countries "explore ways to increase the availability and use of potassium enriched low-sodium salt substitutes" on page 45 (under the section 'The Way Forward').

Recommendation: To avoid confusing countries, the Draft Guidelines should have consistent recommendations about the use of low-sodium salt substitutes with recently published WHO reports – in line with our "strong" recommendation at point 2 and other commentary throughout this document.

Adaptation and implementation of the Guideline

The Draft Guideline sets out a range of useful implementation considerations, including on cost, use by policymakers and programme managers, and how it can be translated into country-specific dietary guidelines.

We recommend that the implementation considerations be further strengthened by:

- **Page 13**: Leave open the potential for use of LSSS in manufactured food products, as these make up large parts of certain country diets. While there is no direct evidence that LSSS prevents disease when used in manufactured food products, it would be expected to act similarly. The parallel is sodium reduction, where most data derive from reducing 'discretionary salt', yet taking sodium out of the food supply is a central plank of WHO's SHAKE package.
- **Page 38 – Equity and human rights**: While the higher costs of LSSS may discourage use for certain income levels within a country, evidence suggests the use of LSSS is highly cost effective and averts substantial burden of disease and associated healthcare costs.[vi] The utility in low- and middle-income countries (LMICs) is likely to be high, given LMICs' greater use of discretionary salt, which is currently the target of the Draft Guideline, and early and wider uptake and use of LSSS is likely to bring down its cost.
- **Page 46 – Implementation considerations:** We understand that policy makers need to be aware of the costs incurred in relation to LSSS use, but advocacy, training and meetings can be delivered through digital platforms; the overall costs are minimal and thus not relevant in this context. Moreover, it is often civil society organisations that lead such efforts.
- **Page 15 – Target audience:** To further aid implementation of the Draft Guideline and use of LSSS, it would be useful to define the roles and responsibilities of each target audience,

including the role of industry in both the manufacturing of LSSS and the sourcing of potassium for such manufacture.

Context-specific issues that have not yet been captured.

Nil comments.

Any errors of fact or missing data

The WHO has thoroughly analysed the data prior to inclusion in the Draft Guideline and we would like to comment on the **appropriateness of the methods used to develop the Draft Guideline, and on the LSSS Systematic Review of the effects of LSSS on health outcomes.**

<u>Appropriateness of the methods used to develop the Draft Guideline</u>:

10. ***WHO's scoping review*** concluded that, at the time, there was not an existing systematic review that comprehensively covered the relevant studies, and that a new systematic review was needed to be able to develop a guideline for the use of LSSS as a replacement for regular salt. There are now multiple systematic reviews and meta-analyses in this field, and a major new outcome trial was reported this month.

    Recommendation: WHO should review and consider the findings of these analyses, because there are important differences in conclusions. WHO should review and incorporate data from:
    - *Yin X, Rodgers A, Perkovic A, et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. Heart 2022;108: 1608-1615.*
    - *Yuan Y, et al. Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster randomised trial. Nature Medicine. 2023 April 14; NCT03290716.*

    Recommendation: The Draft Guideline should incorporate the latest data and evidence of the effects on the most appropriate outcomes. The primary recommendations should be updated accordingly.

11. ***WHO considered contextual factors that may affect the use of LSSS*** in a narrative review. However, the qualitative process by which the information has been synthesised for the draft guideline does not appear to have delivered key conclusions about the likely overall balance of risks and benefits that are aligned with the quantitative data and evidence derived from the LSSS Systematic Review. In particular, the conclusions drawn about the inferred risks from hyperkalaemia go far beyond any of the evidence presented.

    Recommendation: The Draft Guideline should explicitly define how the overall balance of benefits and risks was determined.

12. ***A well-conducted systematic review and meta-analysis*** is clearly the right way to summarise the relevant data to inform the Guideline. However, we have significant concerns about key aspects of the methods used for the WHO-commissioned LSSS Systematic Review (see below). As a result of these methods, the conclusions about LSSS that are drawn from the systematic review do not appear to reflect the evidence available and are at odds with other reviews of the same data.

    Recommendation: The WHO should seek an update to the systematic review that incorporates all available data and reports on the most important outcomes. The primary recommendations in the Draft Guideline should be updated accordingly.

The LSSS Systematic Review of the effects of LSSS on health outcomes

There are significant weaknesses in the design and interpretation of the systematic review, that raise serious questions about the integrity of the summary data upon which the Draft Guideline is based:

13. ***A failure to understand the clinical and public health importance of small-to-moderate differences in blood pressure***

    The authors pre-specified a clinically meaningful reduction in blood pressure as a fall of at least 10mmHg. This is a huge effect. A clinically meaningful reduction is smaller and an effect meaningful to public health smaller still. From a clinical perspective, a 10mmHg fall is more than what is achieved with most blood pressure lowering drugs and, for example, twice the magnitude of the fall in blood pressure observed in a meta-analysis of trials of the antihypertensive drugs class ACE inhibitors (4mmHg).[vii] Of note, the blood pressure reduction achieved with ACE inhibitors was associated with reductions in stroke (20%) heart failure (21%), acute coronary syndrome (13%) and major cardiovascular events (17%). Regarding public health effects, a recent modelling study showed that a 3.0mmHg lower population-wide blood pressure in China, less than a third of that deemed meaningful in the review, would prevent almost a million strokes and heart attacks each year in China.[viii] In the SSaSS trial, a mean SBP reduction of 3.3 mmHg was associated with a 14% reduction in strokes and 12% reduction in mortality.[ix]

    Recommendation: WHO should review the evidence for differences in blood pressure from a lower clinically meaningful reduction (i.e., 4mmHg), and from a meaningful public health reduction (i.e., 2mmHg). The George Institute would be happy to assist in this review.

14. ***Failure to clearly specify and report on key efficacy outcomes***

    For large-scale trials and meta-analyses of interventions targeting cardiovascular outcomes through blood pressure lowering, there are well established sets of outcomes for evaluation. Specifically, the usual primary clinical efficacy outcome would be total major cardiovascular events comprising cardiovascular death, non-fatal stroke, and non-fatal acute coronary syndrome (ACS). Secondary outcomes would typically be total stroke (fatal and non-fatal), total ACS (fatal and non-fatal), total heart failure (fatal and non-fatal) and cardiovascular death. Sudden deaths, arrhythmias, hospitalisations, and procedures may also be reported. Separate reporting of fatal and non-fatal events would usually be an exploratory analysis. In the LSSS Systematic Review the interpretation of the effects on clinical outcomes is based primarily on separate review of subsets of fatal and non-fatal outcomes. This hugely impacts on the statistical power to detect effects and means the conclusions of benefit for clinical outcomes are deemed of lower quality evidence – and are directly at odds with another systematic review that focuses on the most appropriate outcomes (total cardiovascular events, total stroke, total acute coronary syndrome) and fatal and non-fatal events combined, that identifies strong protective effects of LSSS on multiple clinical outcomes.

    Recommendation: WHO should review the Draft Guideline considering the analysis in Yin X, Rodgers A, Perkovic A*, et al.* The George Institute has also updated this analysis with subsequently published data (specifically, the DECIDE-SALT Study by Yuan Y *et al*), which shows similarly clear and significant reductions of 11% in overall mortality, 14% in CVD mortality, and 11% in Major Adverse Cardiovascular Events (MACE).[x]

    We note further that some studies were not included in Yin et al.'s above mentioned paper that were included in the LSSS Systematic Review. Reasons for studies being excluded from Yin et al.'s paper were, for example, that the "salt substitute" was not low sodium as it included 97% NaCl,

or that the intervention was not LSSS but rather 'reduced salt bread'. **The George Institute would be happy to assist in a review of this evidence to fully understand the impact on the main conclusions**.

15. ***Serious underestimation of the quality of the evidence available for effects of LSSS on intermediate outcomes***
    The LSSS Systematic review and Draft Guideline acknowledge the central role of blood pressure reduction in mediating the effect of LSSS on cardiovascular outcomes. However, while the interpretation of the effects of LSSS on blood pressure in the WHO-commissioned review highlights the heterogeneity of effect sizes between studies, it fails to acknowledge the reduction in both systolic and diastolic blood pressure observed in all studies. Hence, there is little to no uncertainty about whether LSSS lowers blood pressure, while the magnitude of reduction differs, as expected. It is the fact of blood pressure reduction in all studies and all populations that matters and should be highlighted, not the secondary matter of the difference in the size of the effect between studies. Differences in the size of effect between studies are to be expected because studies included different populations and tested different LSSS – for example LSSS that included 97% Na Cl in the WHO-commissioned review.

    Recommendation: The Draft Guideline must acknowledge the important observation that blood pressure reduction was achieved universally with the use of LSSS and would be expected in the long-term to reduce the risk of cardiovascular outcomes for all populations. The evidence for effects of LSSS on blood pressure should be assessed as "important" and "strong". Further, in the wider context of our knowledge about the effects of sodium and potassium on blood pressure in diverse populations, there is a very strong rationale for expecting highly generalisable effects across the global population with huge potential for health gains, which should be acknowledged in the Guideline.

16. ***Inappropriate choice of key safety outcomes and over-interpretation of evidence of risks***
    The key safety outcomes for the main risk selected for the LSSS Systematic Review (biochemical hyperkalaemia) are not well chosen – clinical hyperkalaemia, arrhythmia, sudden cardiac death (or sudden death), and total mortality would be more appropriate and more patient-centred than the blood potassium levels, and biochemical hyperkalaemia focused on. Further, the overview found evidence of a small increase in serum potassium but no evidence of any other harm, yet the guideline concluded major uncertainty about the likely balance of benefits and risks.

    Recommendation: WHO should review the evidence and Draft Guideline considering more appropriate and patient-centred outcomes for harms, to ensure that safety in terms of moderate strength evidence of no effect on clinical hyperkalaemia events and no effect on sudden death are appropriately identified and included in the assessment.

17. ***Misinterpretation of likely overall balance of benefits and risks***
    Assessment of appropriate outcomes would have identified *strong* evidence of benefits for blood pressure and cardiovascular protection with *moderate* quality evidence for an absence of harms in use of LSSS. As it stands, the overview identifies positive effects for multiple serious clinical outcomes, and clear adverse effects for no clinical outcomes and one biochemical outcome but weights the two about the same in the overall interpretation.

    Recommendation: Based on the evidence the recommendation for LSSS should be assessed as "strong", not "conditional".

In addition to the key messages and recommendations above, **we recommend that several elements be refined to improve the Draft Guideline**:

- **Pages 10 and 12**: A stronger focus on the role of potassium within LSSS is needed in the Draft Guideline. For example, in relation to statements such as: "Recently, use of [LSSS] has gained increased attention as a potential strategy to reduce sodium intake"; and "…increasing potassium intake should not be the purpose of using LSSS containing KCl." These statements, as relevant, neglect the potential importance of increasing potassium intake for CVD prevention in most people, and focus only on the potential harm from hyperkalaemia for a few.
- **Page 23**: Table 1 title should read LSSS intervention compared to regular salt in adult (≥18 years), not (<18 years).
- **Page 36 - Feasibility**: There is some repetition in paragraphs 1 and 3.

Other comments

The WHO plays a significant role in providing normative guidance, technical assistance and sharing information and country experiences to improve health for all. Beyond the comments made above, we would specifically like to reiterate our support for the processes established within the development of the Guideline to manage conflicts of interest in external peer reviews and this public consultation process. This is crucial to the integrity of such guidelines and the optimisation of their downstream impacts on public health.

As an independent medical research institute and WHO CC for Population Sodium Reduction, the identification of pending questions and gaps in the current evidence to be addressed by future research is extremely helpful for The George Institute for Global Health. We stand ready to work with partners to address these gaps.

About The George Institute for Global Health

The George Institute – a leading independent global medical research institute – was established in Sydney, with additional major centres in China, India, and the UK, and an international network of experts and collaborators. Our mission is to improve the health of millions of people worldwide by using innovative approaches to prevent and treat the world's biggest killers: non-communicable diseases (NCDs) and injury.

Our work aims to generate effective, evidence-based, and affordable solutions to the world's biggest health challenges. We research the chronic and critical conditions that cause the greatest loss of life and quality of life and the most substantial economic burden, particularly in resource-poor settings.

Our Food Policy team works to reduce death and disease caused by diets high in salt, harmful fats, added sugars, and excess energy. The team conducts multi-disciplinary research with a focus on generating outputs that will help governments and industry deliver a healthier food environment for all.

The George Institute for Global Health

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Survey response 2

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Comments by Resolve to Save Lives on the Draft WHO guideline: use of low-sodium salt substitutes

Summary of evidence

The summary of evidence given by WHO in its Draft Guidelines is thorough and based on the commissioned systematic review by Brand et al. Unfortunately, some of the elements in the design and interpretation of the systematic review have led to a recommendation by the NUGAG that is less protective of health than justified by the level of evidence and will likely be a deterrent to low sodium salt substitutes (LSSS) uptake by governments, resulting in avoidable loss of life. One reason for these insufficiently protective recommendations is that the conclusions drawn by the Guidelines committee are too narrowly reliant on the systematic review, ignoring broader work documenting the health harms of excess sodium and insufficient potassium intake.

Overall, overly restrictive language of the guidelines is a barrier to large scale implementation of LSSS interventions in healthy populations and an opportunity to prevent millions of deaths from heart disease. Recommendations should be rephrased as (i) strong recommendation for the general population of healthy adults, based on moderate to high certainty evidence; (ii) Conditional recommendations for subgroups such as children and pregnant women; (iii) Conditional recommendation for avoidance among groups with advanced kidney disease.
Our comments on the evidence summary are grouped by the design, findings and interpretation of the systematic review.

Design of systematic review

- *Different exposures combined together*: The guidelines acknowledge that the review combines multiple different types of exposures. While the majority of studies examine LSSS where potassium replaces some of the sodium, one intervention looked at the use of salt-reduced bread (Toft, 2020) and another replaced regular salt with a salt where NaCl was combined with 3% chitosan (Allaert, 2013). While the systematic review authors did multiple subgroup analyses to make sense of this data, it would have been more methodologically sound to exclude these studies.

- *Expectations of clinical significance:* The systematic review pre-specified that a reduction in SBP of 10mmHg was clinically significant, therefore leading it to conclude that the changes due to low sodium salt were “slight”. A 10 mmHg drop in BP is a very high bar even for a clinical intervention (higher than what is seen with drugs such as ACE inhibitors and other anti-hypertensive medications, for instance) (Law, 2003). For a population/public health intervention rather than a clinical intervention, this level of impact is unheard of. Further, the strong recommendations for sodium intake reduction and potassium intake increases in the WHO Guidelines on Sodium and Potassium intake respectively are based on smaller SBP reductions (see Table 1).

- *Outcomes*:

- Cardiovascular endpoints: the pre-specified cardiovascular outcomes of the meta-analysis were overly precise, leading to lower power to detect an effect. For instance, when looking at cardiovascular endpoints, the main outcome is usually a composite outcome of total cardiovascular events. The systematic review had 12 primary outcomes. When looking at cardiovascular outcomes specifically, it separated fatal and non-fatal outcomes (e.g. fatal stroke, non-fatal stroke), greatly reducing the statistical power of the review and therefore the strength of the evidence. These outcomes are different from what was used in the WHO Sodium and Potassium Guidelines and inconsistent with standard best practice in cardiovascular research.
- Safety endpoints: the safety outcomes for the main risk selected for the WHO-commissioned review (hyperkalaemia and changes in blood potassium) are also problematic. Clinically significant hyperkalaemia, arrhythmia, sudden cardiac death (or sudden death) and total mortality would be more appropriate and focused on true harm. The overview found evidence of a small increase in serum potassium but no evidence of any other harm. This has led to the overstatement of the potential harms of the intervention, particularly among the general population. Biochemical hyperkalaemia is a blood test result and can be due to hemolysis of a blood sample during the collection or transport, or may, if valid, be clinically insignificant and not the cause of any health harm.

<u>Findings of systematic review</u>

- *Moderate certainty around the impact on blood pressure*: All of the trials (with the exception of Toft et al. 2020, which looked at salt-reduced bread) found a reduction in SBP compared to control (mean -4.76 mmHg, 95% CI: -6.01, -3.5) and all but one (Li et al, 2016) found a reduction in DBP compared to control (mean: -2.43 mmHg; 95% CI: -3.5, -1.36). This evidence is strong, highly consistent and of greater magnitude than that found for the impact of either sodium or potassium in the WHO's *Guideline: Sodium Intake for Adults and Children* and *Guideline: Potassium Intake for Adults and Children.* It is also based on a bigger sample size (see table 1 below). **Given this, the evidence for the impact of LSSS on SBP and DBP should be reported as High certainty, not Moderate certainty.**

Table 1. Comparison of WHO's draft guideline on low-sodium salt substitutes and WHO's published guidelines on sodium intake and potassium intake.

Outcomes	WHO Guideline	Effect	n	Certainty of evidence
Change in SBP (mmHg)	Low-sodium salt substitutes	-4.76 mmHg (-6.01 to -3.5)	21,414	Moderate
	Sodium	-3.39 mmHg (-4.31 to -2.46)	6,736	High
	Potassium	-3.06 mmHg (-4.70 to -1.42)	1,892	High
Change in DBP (mmHg)	Low-sodium salt substitutes	2.43 mmHg (-3.5 to -1.36)	20,830	Moderate
	Sodium	1.54 mmHg (-2.11 to -0.98)	6,736	High
	Potassium	2.84 mmHg (-4.66 to -1.01)	1,892	High

- *Moderate certainty around hyperkalaemia:* At the same time, the evidence around hyperkalaemia was given a grade of moderate certainty. This contradicts the findings of the systematic review itself, which found that LSSS non-significantly increases hyperkalaemia (RR 1.04, 95% CI 0.46 – 2.38) and concluded that "LSSS interventions likely result in little to no

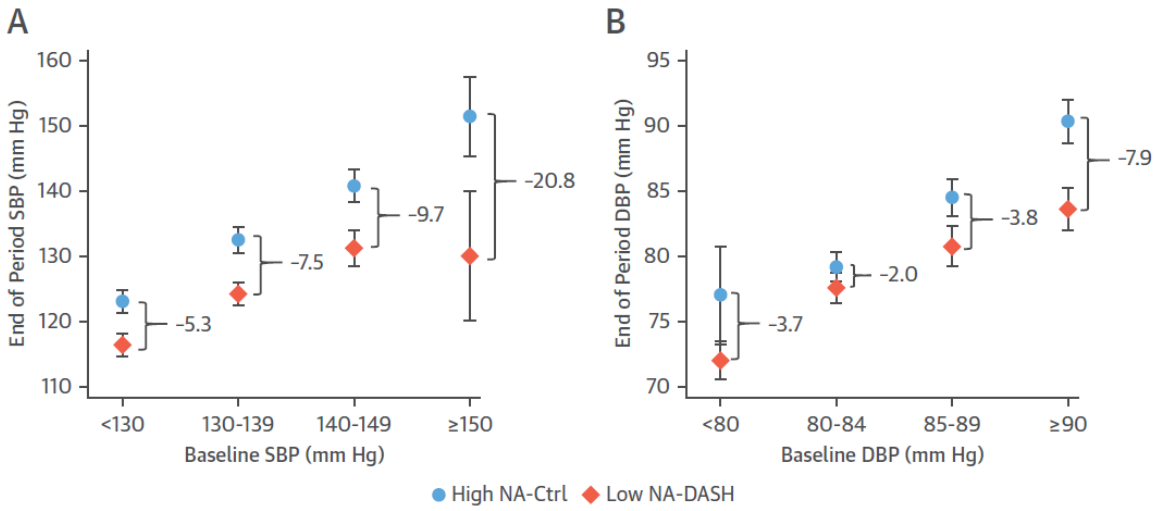
difference in hyperkalaemia." (p. 5). Given this, we suggest that the grading makes it clear that there is moderate certainty evidence that there is no relationship to hyperkalaemia in populations without advanced kidney disease.

Interpretation of the systematic review

- *Generalizability to people known to be at risk of high blood potassium*: The guidelines correctly note that the trials included in the systematic review attempted to exclude people at high risk of harm due to hyperkalaemia, making it difficult to understand the potential harm in high-risk populations. However, as noted in the guidelines, the populations excluded did differ between the trials, with some trials such as the SSASS trial (Neal, 2021) and the more recent trial in India (Yu, 2021) taking a pragmatic approach and only excluding people who self-reported chronic kidney disease or the use of a potassium sparing diuretic. (The Draft Guidelines note that 7 trials had participants at possible risk of hyperkalaemia and 4 at unclear risk). Importantly, despite having a smaller number of exclusions, these trials did not have evidence of harm. Finally, it should be considered that globally, most studies show that people underconsume potassium. The guidelines should consider what populations of potential concern were included in some of the trials (e.g. people with type 1 and type 2 diabetes) to better understand the generalizability of the evidence. We recommend the guidelines consider the same exclusions as the SSASS trial – people with known advanced kidney disease or taking a potassium sparing diuretic.

- *Lack of evidence for people without elevated blood pressure:* The Draft Guidelines correctly note that the evidence of impact is lower for people without hypertension, largely due to the fact that most of the trials focus on hypertensive populations and the fact that the effect size appears to be lower. A lower effect size is consistent with the existing evidence on the impact of salt reduction on blood pressure (as well as anti-hypertensive medications on blood pressure). The figure below, from the DASH-Sodium trial shows that there is a linear relationship between baseline SBP and DBP and the magnitude of BP reduction compared to control (Juraschek, 2018). Further, in the wider context of our knowledge about the effects of sodium and potassium on blood pressure in diverse populations there is a very strong rationale for expecting highly generalisable effects across the global population with huge potential for health gains. This is consistent with the WHO Guidelines on both sodium and potassium which apply to all populations, regardless of hypertension status.

FIGURE 1 The Combined Effects of Low Sodium and the DASH Diet According to BP



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- *Generalizability of the evidence depending on the implementation of LSSS:* The draft guidelines suggest that because the large majority of the studies included in the guidelines examine discretionary sodium, the results of the guidelines cannot be generalized beyond this. However, in many cultures, soy sauce, fish sauces and other condiments are a major source of discretionary sodium and are added to food either by home cooks or at the table, similarly to salt. While the exact intervention would differ depending on the source of the LSSS, the scientific link between using LSSS instead of salt should be unchanged. The major consideration would be that in non-discretionary settings (e.g. packaged foods, restaurant foods), it would be difficult for high risk individuals to opt out of products containing potassium.

- *Children, pregnant women, and household:*
    - This section rightly points out that the implementation of low sodium salt interventions is likely to happen at the household level, as home cooked food is a major source of discretionary sodium. For high-risk individuals, such as those with impaired kidney function, the recommendation is clear that LSSS shouldn't be used as the main discretionary salt in the household.
    - However, the implications for households containing pregnant women and children is less clear. While we understand that the trials included in the systematic review did not include pregnant women at all and had limited inclusion of children, the Draft Guidelines should take into account the larger body of evidence around sodium and potassium intake in these populations to assess whether there is potential risk. If there is no indication of risk, then suggesting that LSSS shouldn't be used to prepare meals for households with children and pregnant women is overly restrictive and would likely limit the usefulness of this intervention. In the WHO Potassium Guidelines, for instance, the recommendation to increase potassium intake is a strong recommendation for adults, and a conditional recommendation for children. For LSSS there could be strong recommendations for LSSS use in adult populations without advanced kidney disease and conditional recommendations in children and pregnant women given the lack of studies explicitly including these populations.

Evidence to recommendations

- *Overall certainty in the evidence*: The decision to grade the evidence as overall being "low" despite the impact on SBP, DBP, and non-fatal stroke, non-fatal acute coronary syndrome, and cardiovascular mortality all being of moderate certainty is not supported by the evidence and should be changed. Given the literature cited above, the evidence linking LSSS to SBP and DBP is actually of high certainty, not low certainty, and there is no evidence of risk for the general population. **Accurate analysis of the relevant scientific literature indicates that the overall certainty of the evidence for LSSS is at least moderate and potentially high.**

- *Balance of desirable and undesirable effects.*
    - As noted above, we do not agree that the beneficial effect would be "small" as stated in the Draft Guidelines. At a population level, this has the potential to save millions of lives. The modelling paper by Marklund et al estimates that in China it would save 450,000 lives per year (Marklund, 2020).
    - The only potential harm found was an increase in blood potassium, which the authors of the systematic review themselves concluded: "was not considered to be clinically important (moderate-certainty evidence) given its impact on the upper end of a 'normal' blood potassium level would not reach levels indicative of moderate hyperkalaemia."
    - Even when looking at the potential harms to higher risk individuals, it is necessary to take into consideration that a number of the trials, including the SSASS trial which was the largest and looked at hard cardiovascular outcomes, only excluded people who self-identified as having kidney disease or taking a potassium-sparing diuretic and found no evidence of harm. For interventions targeting discretionary sodium (or condiments, which as mentioned above function in many cultures as a source of discretionary sodium), people in these two categories can opt to not consume LSSS, thereby reducing the potential risks.

- *Priority of the problem:* It would be useful to also include the potential benefits of salt reduction including the fact that the Global Burden of Diseases currently estimates that approximately 1.8 million deaths are attributed to high sodium intake every year. Additionally modelling studies suggest that LSSS could save 450,000 lives annually in China and between 200,000 to 350,000 (Marklund, 2020 and 2022) annually in India.

- *Feasibility:*
    - The feasibility section rightly notes that LSSS is not widely available and is more expensive than regular salt. However, while uptake of LSSS is not currently widespread, government investment in this sector and promotion of LSSS would increase demand, availability and might also lower prices. In China, where the market for LSSS is relatively well developed, a survey of major online retailers found more than 75 LSSS on the market, at a wide range of price points (unpublished data). Recent analyses have found that not only are LSSS interventions expected to be cost effective, they are expected to be cost saving (Li, 2022), potentially creating incentives for government and private sector investment and subsidization.
    - Further, the Draft Guidelines appear to argue against LSSS because unlike reducing salt intake overall, use of LSSS would not help people get used to the taste of lower salt foods. Further, they suggest that promotion of LSSS might be confusing in the context of previous messages to reduce salt intake. While these are valid points, the recent

WHO Global Report on Sodium intake Reduction found that current strategies are not sufficient. Few countries are implementing comprehensive sodium reduction programs. While behavior change interventions, the only other available tool to reduce discretionary sodium intake, have shown impact in clinical trial settings, their impact on population sodium intake has been limited so far (Hyseni, 2017).

- Finally, this section mentions that not all trials have shown that LSS decreased sodium intake; while true, even those that don't show a decrease in sodium intake do find an impact on critical health outcomes such as SBP and DBP (Bernabe-Ortiz, 2020).

- *Acceptability:* The sentence: "*At an individual level, because adhering to the recommendation to not use LSSS and reduce sodium intake, might require for some a reduction in the overall saltiness of the diet, particularly for those accustomed to saltiness in certain types of food and beverages, acceptability of the recommendation may be low*" is unclear. It seems to be saying that the recommendation is to not use LSSS, which is not the case.

- *Equity and Human Rights*: While the higher costs of LSSS may discourage use by lower income individuals, particularly in LMICs, LSSS is a cost saving intervention (Li, 2022). Because of this, strategies such as government subsidies might be feasible and could decrease the differential effects within a country. Further, since LMICs disproportionately consume sodium from discretionary sources, LSSS interventions have the potential to increase equity between countries.

Recommendations and supporting information

The Draft Guidelines recommendation is: WHO suggests the limited use of low-sodium salt substitutes as a replacement for discretionary salt use when it contributes to reducing sodium intake to below 2 g/day in adults (*conditional* recommendation1, based on *low* certainty evidence).

Strength of the recommendation:

As noted above, the evidence for LSSS is in some ways stronger than that for either potassium intake or sodium intake alone (both in terms of effect size and sample size included in the evidence review, see table 1) and therefore the conditional recommendation is inconsistent with the previous guidelines on sodium and potassium intakes. Based on our comments above, we believe that the WHO recommendation should be a strong recommendation for the general population of healthy adults, based on moderate to high certainty evidence. Areas of uncertainty can be identified through conditional recommendations for subgroups such as children and pregnant women. Further there should be a conditional recommendation for avoidance among groups with advanced kidney disease.

Limited use:

The use of "limited" in the Draft Guideline recommendation is confusing and could be interpreted as indicating that regular salt is better to consume. Given the lack of evidence of adverse events in the trials included in the systematic review, there is no reason to recommend that the use is limited in the general population. We recommend that the guideline instead read: "WHO suggests the use of low-sodium salt substitutes as a replacement for discretionary salt use when it contributes to reducing sodium intake to below 2 g/day in adults."

Discretionary sodium:

This recommendation should apply to condiments used at home as well as discretionary salt, since they are used very similarly and are a major source of sodium intake in a number of countries.

Access to care:

Making the recommendation contingent on access to care limits its applicability. Especially considering that this guideline focusses exclusively on discretionary salt which is the largest source of sodium intake in most LMICs.

Other comments:

Given the potential adverse impacts for people with advanced kidney disease, we do think that there should be some type of label on low sodium salt indicating the potassium content. Some potential additional labels include:

- This product contains potassium. If you have been told to limit potassium in your diet, please consult your doctor or other health care professional before use.
- This product contains potassium. Persons with kidney disease should consult their doctor or other health care professional before using.

Survey response 3

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IGTC Comments on 'DRAFT WHO GUIDELINE ON USE LOW-SODIUM SALT SUBSTITUTES'

Dear Sir/Madam,

The International Glutamate Technical Committee (IGTC) is an international non-profit organization focusing on the science of glutamates since its establishment in 1970. The IGTC is also a long-standing observer at the Codex Alimentarius Commission.

The IGTC understands that the WHO has put forward *a public consultation: draft WHO guideline on use of low-sodium salt substitutes*, published on 23 March 2023.

Firstly, the IGTC would like to express its respect towards the public health objective of this guideline, which aims to facilitate reducing mean population sodium intake by 30% by 2025.

We recognize that the prevention and control of noncommunicable diseases by utilizing low-sodium salt substitutes, which are alternatives to regular salt (sodium chloride) both as an ingredient of pre-packaged foods and salt added to food and beverages, are part of many combined actions that should be conducted by different stakeholders.

The IGTC also understand that successful implementation of sodium reduction strategies can only be achieved if the food remains acceptable to consumers in terms of palatability.

However, currently, there is no perfect salt substitute that has the salty taste and flavor enhancing property the same as table salt. Therefore, it is very difficult to achieve recommended sodium intake of WHO 2 g/day by using only one salt substitute such as KCl. It may be achieved by combination of different ingredients and technologies.

It is within this context that the IGTC would like to humbly offer its comments in relation to this guideline, which must have a significant impact on glutamates, an ingredient which can be used as a salt substitute.

1. Glutamate – Its Function and Safety

Glutamic acid is a non-essential amino acid, and its anionic glutamate form is the primary compound that is responsible for providing umami taste, which is one of the five basic human tastes. As such, glutamate can be found naturally at significant levels in a wide variety of foods including anchovies, ripened cheeses, tomatoes and many other foods that have a savory taste (Yamaguchi & Ninomiya, 2000).

With the knowledge of its taste and flavor enhancing properties, purified glutamate salts are also manufactured and used in food. It can be added by foodservice providers or consumers directly during the cooking process, as well as by food manufacturers during food processing.

The most common form of purified glutamate salt produced is monosodium glutamate (MSG), due to its stability and relatively low production cost. MSG is produced by the fermentation of raw materials that are rich in carbohydrate, such as molasses and syrups from sugarcane, sugar beets or cassava.

The typical use level of MSG is 0.1 to 0.8% of the food (Beyreuther, 2007). Its use is generally self-limiting since excess addition of MSG actually reduces palatability and consumer acceptability.

The safety of MSG has also been extensively studied and evaluated by international scientific bodies such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which assigned an "ADI not specified" for MSG. Furthermore, due to its long history of safe use in food, the US Food and Drug Administration (FDA) since 1958 also considered MSG to be a substance that is 'Generally Recognized as Safe' (GRAS).

2. MSG and Sodium Reduction

Regular table salt contains approximately 39% sodium while MSG only contains 12% sodium (Maluly, 2017). When taking this fact into account together with its flavor enhancing qualities, MSG and other glutamates can be an important tool to facilitate sodium reduction without sacrificing palatability of reduced sodium food.

There is accumulating experimental evidence to support the use of MSG and other glutamates to contribute for the sodium reduction in food. These studies have been conducted in many different countries and regions, as well for a wide variety of foods including prepared dishes, soups, processed meats, and cheeses. Therefore, this indicates that MSG can be used for sodium reduction purposes irrespective of differences in food culture or dietary habits.

Recognition of this has resulted in scientific bodies and academic professional associations, such as the Institute of Medicine (IOM) and Academy of Nutrition and

Dietetic (AND), to support the use of MSG as one of the options for implementing sodium reduction efforts[1].

In addition to that, we would like to provide some other analysis and clinical studies related to this matter to show umami substances in clear extent could help salt intake in below 5 g/d, the WHO's recommendation (Nomura, 2018; Tanaka, 2023; Halim, 2020; Crowe-White, 2022).

3. Comments to the proposed guideline

Although MSG was not initially included as a low-sodium substitute in the draft Guideline in reference, it is clearly stated with this purpose in the document *"Review of contextual factors to inform the development of the WHO guideline on the use of low-sodium salt substitutes"*, which well evaluated the studies that prove the effectiveness of this substance in the sodium reduction in a daily diet.

Besides that, IGTC understand that there was an undervaluation in the totality of data as *'low certainty evidence'*, which was based upon the determination of the effect on blood pressure as moderate. However, it has been quantitatively proven in humans the strong correlation between blood pressure and other disorder. For example, a meta-analysis of 147 randomized trials using blood pressure lowering drugs reported the correlation between the reduction of blood pressure with the risk of cardiovascular events, even estimated reduction of blood pressure was moderate (Law, 2009).

The association between sodium intake and various cardiovascular diseases has already been recognized also by WHO in other guideline *"Guideline: sodium intake for adults and children"*. So, the certainty of the evidence should be upgraded with consideration of the scientific consistency with other statements issued by this same organization.

At latest, the IGTC would like to note that it is difficult to conduct clinical trials over a long period with many groups, and there are limitations in the study design setting to examine the effects of sodium reduction in a daily diet.

4. Suggestions from the IGTC

Based on the above, the IGTC would like humble provide the following suggestions to this for this highly renowned WHO:

[1] A summary of these experimental studies and the references to statements by the IOM and AND are attached in the IGTC Statement on 'Glutamate Contributes to the Reduction of Dietary Sodium Intake'.

i. Inclusion of glutamic acid and its salts such as monosodium glutamate (MSG) as a low-sodium salt substitutes in the *Annex 7: Evidence to recommendation table,* mainly in the *Acceptability* factor.

ii. Reconsideration of the level of certainty in a higher-level score considering that there is enough evidence to state the correlation between the reduction of blood pressure with the risk of cardiovascular events and importance of moderate reduction of blood pressure in public health.

The IGTC would like to thank you in advance for your kind consideration of its comments and for the possibility to consider its suggestions.

Should you have any questions, please do not hesitate to contact us for further information or discussion.

We look forward to hearing your views on this matter.

Sincerely yours,

Ms. Maria Teresa Scardigli
Chair of IGTC

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Glutamate Contributes to the Reduction of Dietary Sodium Intake

The World Health Organization (WHO) recommendation on sodium consumption for adults is 2 g sodium/day (equivalent to 5 g salt/day). However, most people consume much more with the current mean global sodium consumption estimated to be at 3.95 g sodium/day (Mozaffarian et al. 2014). Since high sodium intake is reported to be associated with various non-communicable diseases (NCDs) such as hypertension, cardiovascular disease and stroke, the reduction of sodium intake is a very important public health concern around the world (WHO, 2003).

While sodium reduction in the diet is an important objective, when salt (NaCl) levels are reduced in foods, its palatability is also generally decreased. Monosodium glutamate (MSG) is a flavour enhancer that contains about 12% sodium, which is less than half of that contained in regular table salt at about 39%. Therefore, by the addition of an appropriate amount of MSG, the palatability of low salt foods can be recovered with the overall sodium content of the food being substantially reduced.

Further reduction in dietary sodium can also be achieved through the use of other forms of glutamate, such as calcium di-glutamate (CDG) and monomagnesium di-glutamate (MDG), which do not contain sodium. These other forms of glutamate have been shown to provide similar taste enhancing properties that are only marginally lower than those obtained by the use of MSG, therefore maintaining food palatability without contributing to any dietary sodium intake.

A considerable number of studies have demonstrated that glutamates can help to reduce the use of salt in the diet by enhancing the palatability of different types of foods including soups, prepared dishes, processed meat and dairy products.

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The use of glutamate to replace salt in foods

In Japan, Yamaguchi investigated the palatability of Japanese clear soup containing varying amounts of NaCl with or without MSG (as shown in the Fig. 1). When the use of NaCl alone was reduced from its optimal level of about 0.92%, the palatability score of the soup decreased dramatically. However, by combining 0.38% MSG with 0.41% NaCl, the palatability rating of the soup recovered to the same level of pleasantness as was achieved by 0.92% NaCl alone. The sodium content of the soup with 0.92% NaCl was 0.36%, compared with 0.21% in the soup with 0.38% MSG and 0.41% NaCl, representing a 40% overall sodium reduction (Yamaguchi & Takahashi, 1984).

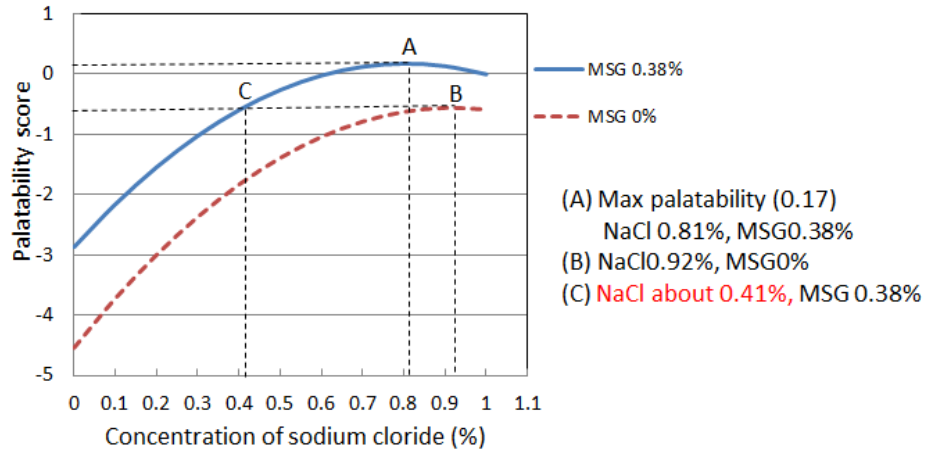

Fig 1. Palatability scores of clear soup at various concentrations of NaCl
(Created using the data by Yamaguchi and Takahashi, J. Food Sci. 49(1):82-85, 1984)

Research in the USA found that chicken broth containing 0.70% NaCl and 0.30% MSG had an equal palatability score when compared with a broth containing 0.84% NaCl and 0.19% MSG, representing a total sodium reduction of about 11% (Chi and Chen, 1992).

The effects of umami substances on the preferences on low-salt soups with 0.3% and 0.5% salt were assessed in Finland. The subjects consumed soup with or without umami (0.2% MSG, 0.05% disodium inosinate (IMP), disodium guanylate (GMP) during six sessions in five weeks. Ratings were higher in soup containing umami in both 0.3%- and 0.5%-salt groups. The authors concluded that the pleasantness ratings of reduced-salt foods could be increased by addition of umami substances such as MSG (Roininen *et al.*, 1996).

A group in Australia managed to reduce sodium content of a reference commercial pumpkin soup containing 150mM NaCl by substituting it with 50mM NaCl and 43mM MSG or CDG, while maintaining similarly acceptable taste characteristics. The level of sodium contained in a typical serving of the reference soup was estimated to contain 57 mmol of sodium. The soup prepared with the NaCl and CDG combination however contained only 33 mmol of sodium, representing a 40% reduction (Ball *et al.*, 2002).

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Another study in the USA by Carter et al. reported that CDG could partly replace NaCl at constant levels of liking and pleasantness (Carter *et al.*, 2011). They showed that pleasant and liking ratings of 0.85% NaCl chicken broths were not significantly different from that of 0.53% NaCl broths with 0.33% CDG. These data showed that sodium concentration of chicken broths could be reduced by 38% with CDG supplementation.

A Brazilian group evaluated the use of MSG together with KCl to replace 25% and 50% NaCl in varying proportions, which helped to maintain the sensory acceptability of a garlic seasoning salt formulation when applied to cooked rice (Rodrigues *et al.*, 2014).

In Malaysia, subjects were presented with local spicy soup dishes, such as curry chicken and chili chicken, containing varying amounts of NaCl and MSG. It was found that the optimal acceptance level of these dishes was 0.8% NaCl when used by itself. However, the partial replacement of NaCl with MSG in the ratio of 0.3% NaCl and 0.7% MSG achieved the same level of palatability. (Jinap *et al.*, 2016).

Similarly, the effects of sodium reduction and flavor enhancers such as MSG on the sensory profile of two types of hawker foods commonly consumed in Singapore, namely chicken rice and *mee soto* broth, were examined. Addition of 0.40% MSG into the 40% salt-reduced recipes resulted in a 22% sodium reduction in chicken rice and 29% in mee soto broth, respectively and the perception of saltiness of these recipes was maintained when compared with the control (Leong *et al.*, 2016).

Several groups also investigated the potential of glutamates to reduce salt in processed meat and dairy products. In France, Bellisle found that addition of MSG to meat *pâté* maintained its palatability even though NaCl content was reduced (Bellisle, 1998).

Elsewhere, CDG was used to improve palatability of salt-reduced sausage in a study conducted in Australia by using 0.12% NaCl and 0.10% CDG, which would be equivalent to a formulation with 0.69% NaCl (Woodward *et al.*, 2003).

In Brazil, the use of MSG in combination with other umami substances (IMPGMP) and amino acids (lysine, taurine) helped to reduce the negative sensory properties, such as bitter, astringent and metallic tastes, of using KCl to replace 50% and 75% of NaCl in cooked sausages (dos Santos *et al.*, 2014). In a separate study, MSG in combination with KCl was used in reduced sodium formulations of Mozzarella cheese, which helped to maintain acceptable sensory properties for formulations with up to 54% sodium reduction (Rodriguez, 2014). Quadros et al. also examined the acceptability of fish burgers containing various concentrations of NaCl and MSG, with the formulation containing 0.75% NaCl and 0.3% MSG scoring equally if not better than the formulation containing 1.5% NaCl only, therefore providing a 50% reduction (Quadros et al., 2015).

For the category of savoury snacks, a study in Denmark demonstrated that replacement of 30% of salt with MSG in potato chips remained acceptable to consumers (Sorensen et al., 2019). Similarly, Buechler et al. also demonstrated that MSG, in combination with IMP and GMP, was able to significantly reduce sodium in potato chips (up to 51%) and puffed rice snacks (up to 57%) (Buechler et al., 2019) without sacrificing palatability.

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Apart from sensory studies involving reduced-salt product formulations, a clinical study investigating the use of glutamate in the form of MDG as part of a low sodium diet and its effect on food intake and dietary sodium intake was undertaken by Kawano et al. For two weeks, a group of psychiatric patients in Japan were alternately provided with standard meals containing 3.28g sodium/day and low sodium meals with MDG containing 2.43g sodium/day. Their food intake was measured and was found not to be significantly different when provided with standard meals or low sodium meals containing MDG, indicating that palatability was not adversely affected for the latter. As a result, average daily sodium intake was found to have decreased by 0.85g sodium/day when consuming the low sodium meal with MDG (Kawano *et al.*, 2015).

Recognition of the role of glutamate in dietary salt reduction by authoritative public health bodies

In 2010, the Institute of Medicine (IOM) in the United States indicated that compounds imparting umami taste and flavour can be used to reduce the need for added salt. The IOM Report on Strategies to Reduce Sodium Intake in the United States stated that "It is possible to replace some of the salt in foods with other taste or flavor compounds. --- A prominent example of an added compound involves glutamic acid (an amino acid). Combining glutamic acid with sodium creates the well-known flavoring compound monosodium glutamate, or MSG. MSG imparts a savory taste (called "umami") as well as a salt taste to food. Some studies have shown that it is possible to maintain food palatability with a lowered overall sodium level in a food when MSG is substituted for some of the salt." (IOM, 2010)

In 2013, the Academy of Nutrition and Dietetics in the United States performed a systematic review to evaluate the effect of umami compounds (such as MSG) or foods rich in umami (such as soy sauce, fish sauce, etc.) on the sodium content in foods and/or sodium intake. Based on the evidence reviewed, it was concluded that "*the addition of umami compounds or foods rich in umami allows for reductions in sodium content of foods (reported as sodium chloride) without sacrificing taste, liking and pleasantness. However, the resulting reduction in sodium may vary depending on the type of food consumed as well as the amount and type of umami compounds present.*" (Academy of Nutrition and Dietetics, 2013)

Conclusion

The reduction of sodium intake is a major health concern worldwide. However, it is very difficult to develop sodium-reduced diets with an acceptable palatability, since salt taste is an important basic taste that significantly contributes to the palatability of food. Based on the wide body of evidence from studies conducted in various geographical regions, the addition of glutamate to different types of foods belonging to different cultural traditions, can allow for substantial reductions in sodium consumption without a significant deterioration in palatability. The proper use of glutamate should therefore be considered in the discussion on how to reduce population sodium intake.

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Survey response 4

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28th April 2023

Subject: Feedback on the WHO Draft Guideline on Reduced Sodium Salt Substitutes

COMMENTARY

Commentary on the appropriateness of the methods for the development of the World Health Organization Draft Guideline on Reduced Sodium Salts.

RESULTS Japan is an international NGO that aims to the world where all people, including those in low-income countries, can live healthy lives with smiles and dignity.
We commend the WHO for conducting a scoping review to summarize available studies on the association between low-sodium salt substitutes (LSSS) and health outcomes, using recent systematic reviews. However, we express concern that the literature covered only extends up to September 2021, potentially excluding valuable scientific papers published afterward. We would like to draw attention to the following post-2021 systematic reviews and original research articles:

1. Health outcomes related to LSSS

- Yin X et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. Heart. 2022 Sep 26;108(20):1608-1615.
- Yuan Y, et al. Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster randomised trial. Nature Medicine. 2023 April 14; NCT03290716.

2. New perspectives on LSSS (focusing on taste compensation)

- Umami: An Alternative Japanese Approach to Reducing Sodium While Enhancing Taste Desirability Shuhei Nomura, Aya Ishizuka, Shiori Tanaka, Daisuke Yoneoka, Hisayuki Uneyama, Kenji Shibuya. Health 2021: 13: 629-636 DOI: 10.4236/health.2021.136047

- Reducing salt intake with umami: A secondary analysis of data in the UK National Diet and Nutrition Survey. Haruyo Nakamura, Takayuki Kawashima, Lisa Yamasaki, Kaung Suu Lwin, Akifumi Eguchi, Hitomi Hayabuchi, Yuta Tanoe, Shiori Tanaka, Daisuke Yoneoka, Cyrus Ghaznavi, Hisayuki Uneyama, Kenji Shibuya, Shuhei Nomura Food Scie Nutri., 2022 12(2):872-882. doi: 10.1002/fsn3.3121.

- Salt intake reduction using umami substance-incorporated food: a secondary analysis of NHANES 2017-2018 data.
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- Modelling of salt intake reduction by incorporation of umami substances into Japanese foods: a cross-sectional study
Shiori Tanaka, Daisuke Yoneoka, Aya Ishizuka, Megumi Adachi, Hitomi Hayabuchi, Toshihide Nishimura, Yukari Takemi, Hisayuki Uneyama, Haruyo Nakamura, Kaung Suu Lwin, Kenji Shibuya, Shuhei Nomura. BMC Public Health1 ;23(1):516. doi: 10.1186/s12889-023-15322-6.

In Kenya, where RESULTS Japan mainly implements the project, the problem of a double burden is already emerging, as the poor are severely undernourished while the wealthy are suffering from an increasing number of lifestyle-related diseases such as diabetes due to excessive salt intake. It is crucial to ensure that reduced-sodium products and recipes remain tasty to encourage widespread adoption. We believe that the combination of LSSS like KCl and other seasonings, such as umami and herbs, can provide a balanced, delicious flavor without compromising health benefits.
We urge the WHO to review and consider the findings from these post-2021 studies to properly inform the development of the LSSS guideline. Consumers need to understand that, except for those with specific health conditions, KCl does not pose cardiovascular toxicity risks at regular intake levels. Without this understanding, global salt reduction efforts may remain stagnant. We sincerely hope for accurate judgment and communication in this LSSS guideline.

Finally, while the pursuit of science is necessary, we must never forget that the psychological aspect of enjoying eating is also important for "eating well. RESULTS Japan hopes that the revised LSSS guidelines will include the perspective of enjoying eating.

Subject: Feedback on the WHO Draft Guideline on Reduced Sodium Salt Substitutes

COMMENTARY

Commentary on the appropriateness of the methods for the development of the World Health Organization Draft Guideline on Reduced Sodium Salts

RESULTS Japan is an international NGO that aims to the world where all people, including those in low-income countries, can live healthy lives with smiles and dignity.
We commend the WHO for conducting a scoping review to summarize available studies on the association between low-sodium salt substitutes (LSSS) and health outcomes, using recent systematic reviews. However, we express concern that the literature covered only extends up to September 2021, potentially excluding valuable scientific papers published afterward. We would like to draw attention to the following post-2021 systematic reviews and original research articles:

1. Health outcomes related to LSSS

- Yin X et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. Heart. 2022 Sep 26;108(20):1608-1615.
- Yuan Y, et al. Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster randomised trial. Nature Medicine. 2023 April 14; NCT03290716.

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We urge the WHO to review and consider the findings from these post-2021 studies to properly inform the development of the LSSS guideline. Consumers need to understand that, except for those with specific health conditions, KCl does not pose cardiovascular toxicity risks at regular intake levels. Without this understanding, global salt reduction efforts may remain stagnant. We sincerely hope for accurate judgment and communication in this LSSS guideline.

Finally, while the pursuit of science is necessary, we must never forget that the psychological aspect of enjoying eating is also important for "eating well. RESULTS Japan hopes that the revised LSSS guidelines will include the perspective of enjoying eating.

件名：WHO 低ナトリウム塩代替物（LSSS）に関するガイドライン案に対するフィードバック

コメント

世界保健機関（WHO）低ナトリウム塩代替物（LSSS）ガイドライン案の開発方法の適切性に関するコメント
日本リザルツは低所得国を含めた全ての人たちが健やかに笑顔に尊厳を持って暮らせる世界づくりを目指して、活動しています。
私たちは、WHO が最近のシステマティックレビューをもとに、低ナトリウム塩代替物（LSSS）摂取と健康転帰との関連を評価する利用可能な研究を要約するためにスコーピングレビューを実施したことを歓迎します。ただし、2021 年 9 月までの文献しかカバーしていないため、その後に公表された価値ある科学論文が除外される可能性があることを懸念しています。2021 年以降のシステマティックレビューおよび原著論文を以下のように紹介します。

❶ LSSS のヘルスアウトカムについて

- Yin X et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. Heart. 2022 Sep 26;108(20):1608-1615.
- Yuan Y, et al. Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster randomised trial. Nature Medicine. 2023 April 14; NCT03290716.

❷ LSSS の新しい視点について（味の補填の視点）
※ガイドライン案やスコーピングレビューでも指摘があるように、減塩を広く社会実装していくためには、おいしさを犠牲にしない、おいしい減塩のための新しい視点での“LSSS”の科学的妥当性を評価していくことが重要です。私たち NPO 法人、日本リザルツは主として低開発国の低所得者層の栄養と健康改善を行うべく活動を実施してきています。低開発国においても、栄養不足とともに、塩分過剰摂取が引き起こす健康課題は非常に大きな社会課題となっています。特に、低所得者層は栄養に乏しい超加工食品（食塩・砂糖・脂肪に偏った）や安価な食塩や砂糖を多量に使用した料理に起因すると考えられる非感染性疾患（NCD s ）が増えてきていることが危惧されています。これらの人々が自然に減塩製品や減塩調理を選択するためにはどうしても、おいしさの補填が重要となってきます。よく知られている通り、塩は安価で最良のおいしさを引き出す調味料のひとつであり、単純な LSSS による減塩はおいしさが低下し、継続施摂取につながりません。今回の LSSS ガイドラインの主たる内容は KC l 使用の科学的妥当性と理解していますが、KCl のみの使用では、最終

の減塩レシピ（減塩製品と健康な減塩メニューも含む）のおいしさを担保することは不可能であること食品関連者から説明を受けます。味の補填という視点で、私たちは 2021 年以降の下記の科学論文に注目しています。
LSSS として Umami 物質を活用した場合の日米英におけるポピュレーションレベルでの塩分摂取削減に関する推定研究です。これらの研究によれば、最大で、日本で 22%、英国で 19%、そして米国で 13%の味質を犠牲にしないおいしい減塩で塩分摂取量を削減できる可能性が示されています。

- Umami: An Alternative Japanese Approach to Reducing Sodium While Enhancing Taste Desirability
Shuhei Nomura, Aya Ishizuka, Shiori Tanaka, Daisuke Yoneoka, Hisayuki Uneyama, Kenji Shibuya.　Health 2021: 13: 629-636　DOI: 10.4236/health.2021.136047

- Reducing salt intake with umami: A secondary analysis of data in the UK National Diet and Nutrition Survey. Haruyo Nakamura, Takayuki Kawashima, Lisa Yamasaki, Kaung Suu Lwin, Akifumi Eguchi, Hitomi Hayabuchi, Yuta Tanoe, Shiori Tanaka, Daisuke Yoneoka, Cyrus Ghaznavi, Hisayuki Uneyama, Kenji Shibuya, Shuhei Nomura Food Scie Nutri., 2022 12(2):872-882. doi: 10.1002/fsn3.3121.

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私たちの組織が主に活動するケニアでは、貧困層では栄養不足が深刻である一方、富裕層では過剰な塩分摂取による糖尿病などの生活習慣病が増えていて二重負荷の問題がすでに出てきています。減塩製品と減塩レシピが美味しいままであることが、広範囲な普及を促進す

るために不可欠です。LSSS（例えば KCl）と他の調味料（ウマミやハーブなど）を組み合わせることで、健康効果を損なうことなくバランスの良い美味しい味を提供できると信じています。
WHO には、2021 年以降のこれらの研究結果をレビューし、LSSS ガイドラインの策定に適切に反映させるよう求めます。特定の健康状態を持つ人を除いて、KCl の循環器毒性に関して通常の摂取量では影響がないという科学的事実を、一般消費者が正しく理解することが重要です。この正しい理解がなければ、消費者は KCl を安心して受け入れることができず、過去 30 年以上進展が見られない世界的な減塩の取り組みは停滞したままとなるでしょう。今回の LSSS ガイドラインにおいて、正しい判断と情報提供が行われることを強く希望します。
世界中で味を犠牲にせず、おいしい減塩のための製品開発が行われています。その中核技術は、ここで検討されている LSSS としての KCl を使用し、ウマミやハーブなどの異なる調味料を組み合わせておいしさを維持するものです。KCl が優れた LSSS であることは多くの科学論文で示されていますが、一部の安全性に関する誤解が存在していることも事実です。WHO が提供する LSSS ガイドラインが、消費者に正しい情報を提供し、減塩の取り組みを成功させる一助となることを期待しています。今後とも、日本リザルツは発展途上国の低所得層の栄養と健康改善を目指して活動を続けます。減塩の普及と健康への配慮を踏まえた効果的な LSSS ガイドラインの策定に期待しています。

最後に科学の追究は必要ですが、「美味しく食べる」には、食べることを楽しむという心理的側面が重要であることを決して忘れてはいけません。日本リザルツとしては今回改定される LSSS ガイドラインに食べることを楽しむという視点を是非、入れていただきたいと考えています。

Survey response 5

Intersectoral Forum to Fight NCDs in Brazil - ForumDCNTs congratulates the World Health Organization (WHO) and contributes to the Draft WHO guideline: use of low-sodium salt substitutes

Since 2017, the Intersectoral Forum to Fight NCDs in Brazil (ForumDCNTs) unites organizations from the different sectors dedicated to policies and programs on NCDs prevention and care. It was planned from its conception to assist the country in achieving the SDG 3.4 through SDG 17. Nowadays, over a hundred and fifty organizations from the public, private and not-for-profit/civil society sectors join efforts in the key alliance for partnerships to fight NCDs that is the ForumDCNTs. It is worth mentioning that since 2019 PAHO and WHO have also joined the ForumDCNTs in several opportunities. Regarding the Public Consultation on the *Draft WHO guideline: use of low-sodium salt substitutes*, the ForumDCNTs and the institutions that comprise it - especially the ones co-signing below - share the following comments.

The WHO recommends a **reduction in sodium intake to <2 g/day sodium (5 g/day salt)**. (guidelines). Brazil has committed to achieving the global target of **reducing population salt intake by 30% by 2025** (1). As the Draft WHO guideline states, it is essential that this target is met in order to meet the overall goal of a 25% reduction in premature mortality from NCDs. In Brazil, the Strategic Action Plan for Tackling Chronic NCDs (2011-2022) included reducing salt intake and monitoring food intake using dietary surveys among its actions to reduce premature mortality from NCDs. **It is estimated that 15% of cardiovascular disease deaths could have been prevented if the average salt intake had been reduced to 5 g/d in Brazil, corresponding to 2000 mg of sodium/d** (2).

Mean salt intake from urinary sodium of **Brazilian adults** (2013 National Health Survey) was estimated at **9.34 g/day**. Male adults presented higher salt intake than women (9.63 g/day and 9.08 g/day, respectively) and only 2.4% of the national sample consumed less than 5 g/day of salt. Salt consumption varies little according to ethnicity and, although adults from 30 to 44 years of age consume the most salt (9.56 g/ day), even adults 60 years or older consume an average of 9.01 g/day (3).
Results of the National Health Survey (2014/2015) showed that 28.1% of adults had an

estimated salt intake greater than 10.56 g/day, as well as being positively associated with high salt intake and the presence of overweight, obesity and diabetes (4).

The Draft WHO Guideline is overall a well designed document, presenting a clear line-up of relevant evidence, the WHO Recommendations, as well as considerations for implementation, monitoring and evaluation and identification of research gaps. Considering the research gaps particularly in children and pregnant women which lead to a lack of evidence, we acknowledge WHO in not applying the current recommendation to these groups. Similarly, due to the limited data of the studies in adults, we agree that the WHO recommendation is a conditional recommendation, based on low certainty evidence.
The importance to develop studies addressing the research gaps is well-identified in the Draft WHO guideline**,** including in individuals who are normotensive. As the price of low-sodium salt substitutes (LSSS) is higher than the price of regular salt there is also an urgent need for studies that show the cost-effectiveness of them.

We appreciated **the exclusion of individuals with contraindications to higher potassium intakes from this guideline,** as it is known that an increased intake of potassium could cause harm in them. These individuals include those with clinically diagnosed kidney disease or evidence of impaired renal function, clinically diagnosed or self-reported type 1 or type 2 diabetes, or taking potassium-sparing medications. We believe that **caution is necessary when using this guideline by government officials** as a help in the development, design and implementation of policies and programmes **in public health in low and middle income countries like Brazil since**, as the guideline states, **in some low resource settings, there may be a considerable proportion of the population who may not be aware of having the conditions mentioned.**

The recommendation on the Draft WHO guideline relates to **"discretionary use"** (salt that an individual adds to foods, including at home when preparing personal or family meal) **of LSSS and does not pertain to use of LSSS in manufactured food product**s or foods sold in markets, restaurants, cafeterias, and street vendors. Although we understand the reasons behind this, as the majority of trials investigated the implementation of LSSS as a discretionary intervention and the impossibility of drawing firm conclusions about non-discretionary LSSS implementations, we believe that it is important to mention that **recently the U.S. Food and Drug Administration (FDA)** proposed changes to the standards of identity (SOIs) for foods that include salt to **permit the use of safe and suitable salt substitutes.** The proposed rule does not list permitted salt substitutes but defines them as safe and suitable ingredients used to replace some or all of the added sodium chloride and that serve the functions of salt in food (5,6).

In Brazil, unlike many high-income countries like the USA with "Western" type diets, only about 35% of Brazilians' dietary sodium comes from industrialized foods and salt-based condiments, whereas over 55% comes from added table salt (7-10). Even though packaged food products are not the main source of sodium in the population's diet, **reducing sodium in processed foods is also needed** (1,11). A 2021 study found that the application of the Brazilian voluntary sodium targets for packaged foods between 2013 and 2032 could CVD prevent or postpone approximately 110,000 cardiovascular disease (CVD) cases among men and 70,000 cases among women, and also prevent or postpone approximately 2600 CVD deaths, 55% in men (7).

It is of fundamental importance the **implementation of frontal food labeling** to make more visible the disclosure of ingredients that may represent a health risk, establishing front-of-pack labeling requirements for food and beverages with high quantities of sodium, and others. In Brazil, the Brazilian Health Regulatory Agency (ANVISA) issued RDC Resolution n. 429/2020 and Normative Instruction n. 75/2020 on nutrition labeling requirements. The application of the front-of-pack labeling is expected when sodium ≥ 600 mg per 100 g, or ≥300 mg per 100 mL (1).

We sum our voices with the message that the **priority public health message is to reduce discretionary salt use**, which is especially important for countries where discretionary use is a major source of sodium intake like Brazil. The literature reinforces the need to support campaigns focused on homemade preparations and bakery foods (which are broadly consumed by the population and the major contributors of sodium) to have a greater impact on sodium intake and improve CVD outcomes more effectively (1). The use of LSSS is only one of many means in an overall strategy to reduce sodium intake as this guideline states.

The references to the percentage of iodized LSSS (under half of the LSSS available globally) and that action is required to ensure iodization of LSSS where this aligns with national policies on salt iodization in the Draft WHO guideline are remarkable. The addition of iodine to edible salt has been one of the most important public health successes of the past half century, enabling most countries to achieve optimal iodine intake and protect the brains of unborn children from the adverse consequences of iodine deficiency (12).

Among the draft guideline, we appreciated the reference to the **implementation of the recommendation** which will likely require consumer education and public health communications, some or all of which can be incorporated into existing public health nutrition education campaigns and other existing nutrition programmes **at the global, regional, national and subnational levels.**

We cordially acknowledge WHO's attention and the opportunity for this contribution, and put ourselves at its disposal to assist in global and regional recommendations, as well as to collaborate for their implementation in Brazil.

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Survey response 6

Notes for submission: 'Comments on the World Health Organization Draft Guideline on Reduced Sodium Salt Substitutes'

Umami Information Center
https://www.umamiinfo.com/
Vice Managing Director
Professor
Toshihide Nisimura, Ph.D.

COMMENTARY

Commentary on the appropriateness of the methods for the development of the World Health Organization Draft Guideline on Reduced Sodium Salt Substitutes
We appreciate that the WHO has conducted a scoping review to summarize the available studies assessing the association between low-sodium salt substitutes (LSSS) intake and health outcomes through the review and evaluation of recent systematic reviews. However, we are concerned that the scoping review covers literature up to September 2021, which may exclude valuable scientific papers published afterwards. Notable papers published after 2021 include:

Papers on health outcomes of LSSS:

- Yin X et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. Heart. 2022 Sep 26;108(20):1608-1615.
- Yuan Y, et al. Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster randomised trial. Nature Medicine. 2023 April 14; NCT03290716.

Papers on new perspectives of LSSS:

- Umami: An Alternative Japanese Approach to Reducing Sodium While Enhancing Taste Desirability
Shuhei Nomura, Aya Ishizuka, Shiori Tanaka, Daisuke Yoneoka, Hisayuki Uneyama,

Kenji Shibuya. Health 2021: 13: 629-636 DOI: 10.4236/health.2021.136047

- Reducing salt intake with umami: A secondary analysis of data in the UK National Diet and Nutrition Survey. Haruyo Nakamura, Takayuki Kawashima, Lisa Yamasaki, Kaung Suu Lwin, Akifumi Eguchi, Hitomi Hayabuchi, Yuta Tanoe, Shiori Tanaka, Daisuke Yoneoka, Cyrus Ghaznavi, Hisayuki Uneyama, Kenji Shibuya, Shuhei Nomura Food Scie Nutri., 2022 12(2):872-882. doi: 10.1002/fsn3.3121.

- Salt intake reduction using umami substance-incorporated food: a secondary analysis of NHANES 2017-2018 data.
Nomura S, Tanaka S, Eguchi A, Kawashima T, Nakamura H, Lwin KS, Yamasaki L, Yoneoka D, Tanoe Y, Adachi M, Hayabuchi H, Koganemaru S, Nishimura T, Sigel B, Uneyama H, Shibuya K.
Public Health Nutr. 2022: 1:1-8. doi: 10.1017/S136898002200249X. Online ahead of print.
PMID: 36453137
- Modelling of salt intake reduction by incorporation of umami substances into Japanese foods: a cross-sectional study
Shiori Tanaka, Daisuke Yoneoka, Aya Ishizuka, Megumi Adachi, Hitomi Hayabuchi, Toshihide Nishimura, Yukari Takemi, Hisayuki Uneyama, Haruyo Nakamura, Kaung Suu Lwin, Kenji Shibuya, Shuhei Nomura. BMC Public Health1 ;23(1):516. doi: 10.1186/s12889-023-15322-6.

Considering these post-2021 scientific papers, we hope that the WHO will review and consider these analysis results in addition to the commissioned Cochrane review. In particular, the development of reduced-sodium products without sacrificing taste is currently being pursued worldwide, with the core technologies being the validity of using KCl as an LSSS and taste compensation techniques when using KCl for salt reduction. It is necessary for general consumers to properly understand that there is no impact on cardiovascular toxicity of KCl at regular intake levels. Without this correct understanding, the global salt reduction efforts, which have not progressed for more than 30 years, may continue to stagnate. We sincerely hope for appropriate judgment and information provision in this LSSS guideline.

Survey response 7

COMMENTARY to 'THE CONSULTATION ON WORLD HEALTH ORGANIZATION DRAFT GUIDELINE ON REDUCED SODIUM SALT SUBSTITUTES (Version 1 dated 14th April 2023)'

Part I: Commentary on the WHO commissioned Cochrane systematic review

Authors' conclusions: When compared to regular salt, LSSS probably reduce blood pressure, non-fatal cardiovascular events and cardiovascular mortality slightly in adults. However, LSSS also probably increase blood potassium slightly in adults. These small effects may be important when LSSS interventions are implemented at the population level. Evidence is limited for adults without elevated blood pressure, and there is a lack of evidence in pregnant women and people in whom an increased potassium intake is known to be potentially harmful, limiting conclusions on the safety of LSSS in the general population. We also cannot draw firm conclusions about effects of non-discretionary LSSS implementations. The evidence is very uncertain about the effects of LSSS on blood pressure in children.

Commentary:

No.1 After viewing the review with scrutiny, we found that the commissioned Cochrane systematic review has many flaws in their analysis that minimized the pooled health effect size of salt substitute. Our judgment is based on the following observations:

1) The systematic review used effect estimates that were unfavorable to salt substitute when multiple estimates were available. For example, in the China Salt Substitute Study (CSSS), the first LSSS trial in China, due to the investigators' inexperience the salt already in use in the families were not sealed, the effect on blood pressure appeared a significant time trend with the effect the largest at the end of 1-year intervention. However, the authors selected the mean blood pressure between 3 months to 12 months, which was significantly smaller.

2) The systematic review selected effect estimates from subpopulation of a study that theoretically would have a lower effect. For example, the CSSS-2 study (Hu's) was a randomized trial with the main study on patients with hypertension (index patients) and ancillary study on the index patients' family members. The authors only select results from the ancillary study on family members that included many people with normal blood pressure. The CSSS-2 study was actually the first study trying to understand the effect of LSSS on blood pressure of adults with normal blood pressure and found a much smaller and statistical insignificant difference. Thus, the pooling analysis of results from studies in patients with high blood pressure and those with normal blood pressure would significantly biased the effect estimate for LSSS.

3) The systematic review included studies that used health education involving social marketing of salt substitute as the LSSS intervention. For example, the China Rural Health Initiative Sodium Reduction Study (CRHI-SRS) was trying to test if a population salt reduction strategy with intensive community health education plus introducing salt substitute into village shops for sale would effectively reduce sodium intake and blood pressure at population level. Although social marketing of salt substitute was included as part of the study intervention, the intervention was not salt substitute alone. And not all villagers were provided salt substitute for use in the intervention villages. The no effect of the salt reduction on blood pressure observed in the CRHI study should not be considered the results of salt substitute

replacing regular salt. In fact, the results from the CRHI demonstrated that promoting salt substitute in general population could be a more feasible and effective strategy for population salt reduction than distributing health knowledge among villagers. Thus, CRHI study should not be included in the meta-analysis on the effect of salt substitute.

4) The uncertainty of evidence in the systematic review was introduced by the authors themselves. As they admitted "The proportion of sodium chloride replacement in the LSSS interventions varied from approximately 3% to 77%. The majority of trials (23/26) investigated LSSS where potassium-containing salts were used to substitute sodium. In most trials, LSSS implementation was discretionary (22/26). Trial duration ranged from two months to nearly five years." The review should exclude those studies using salt substitute with small proportion of NaCl replaced. In fact, a regular salt could contain about 10% impurity substances. A product with less than 20 % NaCl replaced should not be defined as a salt substitute. Those studies using salt substitute not containing KCl should probably excluded too, not only because potassium intake reduce blood pressure but also because KCl proved the salty taste. Without keeping the taste unchanged, using a salt substitute with small proportion of NaCl is actually ineffective. People would intake the same amount of sodium simply by adding more of it to keep the taste unchanged. Likewise, those studies with salt substitute use not as the only discretionary salt use should be excluded. By our understanding, the definition of 'discretionary use' here in this WHO guidelines means to replace regular salt in preparation of all foods in all meals for the specified duration, not just replacing regular salt in some food items such as bread only.

The studies that should be excluded are the following:

a) The Omvik's study. The intervention in Omvik' study was mainly "a salt restricted diet (120mmol Na/24 h) for 6 months". On top of that, the participants were randomised in a double-blind manner to receive either Pansalt (P-group) or standard NaCl (S-group) as table salt in small amounts. This was a small study and the salt substitute was used only as for the table salt and in small amount.

b) The Suppa's study used the salt substitute only as table salt for the intervention.

c) The three studies using so-called salt substitute that contained no KCl. For example, Allaert's study used a LSSS containing 97% NaCl +3% Chitosan. That is not a salt substitute!

d) Toft's study used salt substitute only in breads and one of the two intervention arms also used counselling to further reduce sodium intake. The study could only demonstrate that their delivery method of salt substitute, not the salt substitute its self, was ineffective.

5) The systematic review did not conduct analysis and draw conclusions based on the original studies with high quality and did not differentiate the efficacy studies with effectiveness studies. Usually, the effect size in efficacy studies should be higher than that in effectiveness studies and should large in studies with higher compliance to the intervention. Those conducted in collective living environment should have much better adherence to the intervention and larger effect size than those among free living individuals.

No.2 The systematic review used inappropriate outcomes for the estimation of the salt substitute's health impact, that should either directly increase the statistical uncertainty or indirectly give readers an impression of smaller effect on cardiovascular health.

1) Clinical outcomes of cardiovascular health. Major adverse cardiovascular events (MACE) is

universally accepted as the most important composite clinical outcome for the evaluation of interventions on cardiovascular health, including drugs and therapeutic lifestyle changes for blood pressure-lowering, lipids-lowering, and glucose-lowering. It usually included fatal and non-fatal stroke and MI and sometime total mortality. Compared with each single component of MACE, the composite outcome reflects more complete health impact of the intervention that may targeted on the cardiovascular system rather than an organ. It is a collective measurement of the intervention effect and have higher statistical power than its each component. However, the review gave up this widely accepted clinical outcome and pooled data to estimate the effects on each single component, without giving persuasive reasons.

2) Blood pressure – the most important surrogate outcome of cardiovascular health. There have been tremendous studies providing evidence that SBP is more strongly associated with subsequent development of cardiovascular disease and death from the disease. However, the review used DBP rather than SBP to be the primary study outcome, probably because the pooled estimate of the effect on DBP (-2.43 mmHg) looks significantly lower than that on SBP (-4.76 mmHg).

No. 3 On the safety of salt substitute, the systematic review ignored the most important safety outcome and used a clinically less meaningful outcome as the primary safety outcome -mean serum potassium level, which should amplify the risk of salt substitute and raise unnecessary worries among the public.

1) Total death is the widely accepted most important safety outcome for any intervention safety evaluation. In the analysis 1.49, the total mortality was lower with salt substitute use compared with regular salt use (RR 0.89, 95%CI 0.83 to 0.95) . However, this important result was not presented in the Abstract and the Conclusion.
2) Clinical diagnosed hyperkalemia and other hyperkalemia-related clinical outcomes such as severe arrhythmia are the second important safety outcomes for salt substitute, because it contains potassium and may increase the risk of hyperkalemia. So far, with large scale randomized trials including SSaSS and DECIDE-Salt, there is no evidence that using salt substitute increased the risk of clinical diagnosed hyperkalemia, neither for other clinical outcomes like arrhythmia and sudden deaths. In this systematic review, the pooled estimate of effect on risk of clinical hyperkalemia was insignificant (RR 1.04; 95%CI 0.46 to 2.38).
3) Chemical hyperkalemia. The recent DECIDE-Salt trial reported a significant increase in the risk of chemical hyperkalemia. However, the study confirmed the intra-individual variability of serum potassium measurement was very high and the chemical hyperkalemia were largely occasional and not associated with any clinical outcomes.
4) Serum potassium is clinically meaningless unless it becomes very high or very low. The systematic review found a mean increase in serum potassium of 0.12 mmol/L with salt substitute use (95%CI 0.07 to 0.18) . Compared with the population mean of serum potassium (usually about 4.5 mmol/L), this is only a change of 2.7%. If compared with the commonly used up limit of normal serum potassium (5.5 mmol/L), it is only a change of 2.2%. What risk this tiny increase in mean serum potassium would cause to the human health is highly questionable. Particularly when salt substitute was found also significantly

reduce the risk of chemical hypokalemia, which presents another risk to the human health. Paying too much attention on this clinically unimportant outcome without considering the benefits from the increase in serum potassium is to raise unnecessary worries in the public. That will only harm the global efforts to reduce sodium intake by employing this evidence-based strategy, but nothing helps to increase the safety of human beings.

No.4 The studies on salt substitute run a very long time period, it includes early studies on the efficacy and later studies in real world practices in different settings and in different study populations (patients with hypertension, patients with high CVD risk, general community population, general population living collectively, etc.), and some even should be considered as implementation trials. Some were conducted with high quality and some were not. Some studied salt substitute as a high risk strategy and some as a population strategy for prevention and control of cardiovascular disease. The heterogeneity among these studies is naturally existing and simple statistical synthesis of these data without the appropriate differentiation should lead to very biased results.

Due to the above considerations, we suggest the WHO not to just reply on this systematic review for drafting the guidelines on salt substitute. Other existing systematic reviews should be considered, or a new systematic review should be commissioned.

Part II. Commentary on the WHO guidelines' recommendation

WHO recommendation: WHO suggests the **limited use** of low-sodium salt substitutes as a replacement for **discretionary salt use** when it contributes to reducing sodium intake to below 2 g/day in adults (**conditional recommendation**1, based on **low certainty evidence**).

Our commentary and suggestions:

1. **On the 'low certainty evidence'.** The WHO's judgment should be mainly based on the commissioned Cochrane review, in which the authors stated "We are moderately confident in the evidence. Our confidence was lowered mainly because of concerns about how some trials were conducted, and whether the results apply to the general population."
   First, it is unclear why the certainty of evidence was further lowered from 'moderate' to 'low' by the WHO.
   Second, the commissioned Cochrane systematic review has many flaws and should not be relied on for a solid conclusion. The review tried every efforts to minimize the pooled health effect estimates of salt substitute, including 1) using effect estimate that was unfavorable to salt substitute when multiple estimates were available (CSSS); 2) selecting effect estimate from subpopulation of a study that theoretically would have a lower effect (Hu's); 3) including studies that used health education rather than salt substitute as the study intervention (CRHI); 4) including studies using so-called salt substitute that had very little proportion of NaCl replaced (3% only); 5) including studies using so-called salt substitute that had no KCl added; 6) including studies that used salt substitute only to

partially replace regular salt use, e.g. in bread only; but drawing the conclusion for discretion use. By our understanding, the definition of 'discretionary use' here in this WHO guidelines means to replace regular salt in preparation of all foods in all meals for the specified duration, not just replacing regular salt in some food items such as bread only; and 7) not conduct analysis and draw conclusions based on those original studies with high quality.

Third, the above manipulates should also inappropriately increase the uncertainty of the summary estimates of the effects of salt substitute on health benefits outcomes. The review used separate single cardiovascular endpoints rather than their composite endpoint such as MACE to summarize the health effect of salt substitute, tentatively increased the statistical uncertainty. In addition, the review included studies with significant heterogeneity. It included studies with the proportion of sodium chloride replacement in the LSSS interventions varied from 3% to 77%, including products with and without KCl, either used discretionarily or not. Trial duration ranged from two months to nearly five years. However, the review did not analyzed data separately and draw its conclusion based on mixed data. The uncertainty was introduced by the authors, not by the original studies.

Thus, the WHO should not develop the guidelines on salt substitute use based on this systematic review. Other systematic reviews should be considered or a new systematic review should be done, which should be done by a more professional team with real experts in salt substitute studies. We believe the WHO has capacity and appeal to call for a better systematic review and meta-analysis with pooling data from all previous studies.

2. There have been many other systematic reviews on salt substitute and health outcomes published on peer-reviewed academic journals. The WHO commissioned a scoping review and concluded "Based on the result of the scoping review, it was concluded that there was not an existing systematic review that covered comprehensively the relevant studies, and that a new systematic review was needed to be able to develop a guideline for the use of LSSS as a replacement for regular salt." We believe the conclusion may be inappropriate. Before we have convinced the conclusion, the **WHO should clearly specify what have been lacking from the previous works and by what specific criteria the WHO drew the conclusion, to be transparent**.
3. **On the value of the so-called 'small effect' on blood pressure.** There are two equally important strategies for cardiovascular disease (actually all diseases) prevention and control, high risk strategy and population strategy. The former targeted on high-risk individuals such as those with hypertension, the later targeted on general population. Although the effect size on blood pressure of an intervention required for the later is much lower than that for the former, the effectiveness on prevention and control of major cardiovascular events and deaths is not less but often actually larger. This is because many more people will be affected by population strategy than by high-risk strategy. The theory on population strategy had been clearly illustrated by Jeffery Rose decades ago. For salt substitute, its effects in use as both a high-risk strategy (among patients with hypertension or high cardiovascular risk, CSSS, CSSS-2, CSSS-Tibet, and SSaSS) and a population strategy (among general population, DECIDE-Salt and study in Peru) have been extensively demonstrated with high quality randomized trials. All these studies

informed a large and significant health effect of salt substitute, indicating a huge potential as a population strategy for prevention and control of hypertension and its related diseases.

4. **On the definition of 'low-sodium salt substitute (LSSS)**'. LSSS in this recommendation refers to products where sodium chloride (NaCl) is partially replaced with potassium chloride (KCl) in varying amounts (i.e. 10 – 50% KCl). The effect of LSSS is coming from two mechanisms: lowering sodium intake and increasing potassium intake. With its flavor can be satisfied, the lower the sodium contained in the product the better its effect on blood pressure and health; the higher the potassium contained in the product also the better its effect on blood pressure and health. Thus, to guarantee its health effect, there should be a standard criterion requiring the upper limit of sodium chloride contained in these so-called LSSS. It is better also to require the lower limit of potassium contained in LSSS.
    a) Although the WHO defined in this guideline a lower limit of 10% KCl for a salt substitute, the commissioned Cochrane review included studies with no KCl.
    b) In fact, the regular salt is not necessarily 100% NaCl unless it is processed to be 'refined salt'. In many occasions, people use natural salt that may contain significant proportion of impurity substance. To guarantee the quality of products on the market, governments tried to regulate the products by issuing official production standard of edible salt. For example, in the Chinese National Standards on Edible Salt (GB/T 5461-2016) requires a product labeled as 'solar salt' could have as less as 91.2% NaCl (g/100g), the impurity substances could be as high as nearly 10%. To define a salt substitute, the least sufficient amount of NaCl should be replaced in the product without sacrificing the 'salty taste'. Otherwise it should be considered as a fake salt. We suggest at least 25% NaCl should be replaced with substances with salty taste such as KCl or other substances that provide a similar taste to NaCl. The Cochrane review included studies using a product with only 3% of NaCl replaced as a LSSS, that is completely wrong.
    c) BTW, it seems that the WHO's statement that there was no evidence for effect modification according to the percent of KCl replacing NaCl is correct, because there are no randomized controlled trials to compare LSSS with different dose head-to-head. But that was mainly due to no such a need to do, because there have been sufficient evidences that sodium intake is positively and potassium intake negatively associated with blood pressure, including many from randomized controlled trials.
5. **On the term of "Limited use".** The guideline explained that "Limited use" means LSSS being used at a reduced amount as compared to the amount at which regular salt would have been used. We believe the language use of the word 'limited use' is inappropriate here. Salt substitute may be appropriate to be limited to use among individuals with high risk of hyperkalemia such as those with chronic kidney disease. In common language, people rarely say something is limited to use without specifying to whom or what settings. For example, for an anti-hypertension medication with known adverse effects to increase the risk of hyponatremia among patients with hyponatremia, we can not say 'suggest the limited use of the drug, in general and without specifying the specific subpopulation to whom the extra risk from using the drug has been identified. Thus, we suggest the WHO

to specify in the recommendation to whom the salt substitute may be used in a limited way. It can not be a limited use or unlimited use to everyone.

6. **On the "Conditional"recommendation.** The guidelines state "The recommendation was assessed as conditional, because although there was consistent moderate-to-low certainty evidence of benefits to cardiovascular health, there is uncertainty about the balance between the benefits and potential harms, particularly in settings where a considerable proportion of the population may have undiagnosed conditions for which it would not be advisable to increase potassium intakes."

   As we commented earlier, the evidences up to date are sufficiently consistent to draw conclusions on the health benefit of salt substitute, particularly for blood pressure reduction and prevention of major adverse cardiovascular events including stroke and ACS. There may be not strong enough evidence on its safety before. However, the recent DECIDE-Salt study among older adults living in elderly care facilities that measured blood potassium multiple time and showed an ensured safety of salt substitute in older adults without excluding participants with high risk of hyperkalemia. The SSaSS study with 5 yeas use of salt substitute among 21 thousands participants also did not detect any difference in risk of clinical hyperkalemia. Further considering that salt substitutes have been on the global market for over 50 years and only few cases of clinical hyperkalemia with severe clinical manifestations were reported associated with the use of potassium-enriched salt substitute, it should be concluded that salt substitute is generally safe. The salt substitutes' health benefits are significantly large with clear certainty, its harms or risks are minimum with moderately certainty. If the word 'conditional' has to be used to salt substitute, it should be conditional to the small subgroups with clear high risk of hyperkalemia such as patients with severe chronic kidney disease, not to the general population of adults.

7. **The current guidelines are contradictory to the existing WHO previous guidelines on sodium and potassium intake.**

   Both the sodium and potassium guidelines make strong overall recommendations, based on evidences significantly less than evidences available on LSSS. However, the current the guidelines on LSSS makes conditional recommendation for LSSS, which effectively combines the effects of lowering sodium intake while increasing potassium intake. It is an important change in the WHO position in recommendations on sodium and potassium intake. To be credible, the recommendations for the LSSS guideline must be consistent with the recommendations from other relevant guidelines.

8. **The recent published DECIDE-Salt trial provided important evidences on both efficacy and safety of salt substitute**, and demonstrated replacing regular salt with salt substitute was much more effective and acceptable than restriction of salt supply to the kitchens of elderly care facilities in China. The WHO guideline should consider to include results from this newly published study with a large sample size and long term use of salt substitute.

Reference: Yuan Y, Jin A, Neal B, et al. Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster-randomized trial. Nat Med. 2023;29(4):973-981. doi:10.1038/s41591-023-02286-8

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Survey response 8

SUBMISSION TO THE CONSULTATION ON DRAFT WORLD HEALTH ORGANIZATION GUIDELINE: USE OF LOW-SODIUM SALT SUBSTITUTES

BACKGROUND PERTINENT THIS SUBMISSION

Klinge Chemicals Ltd. has produced products directly related to this guideline for over 40 years and I am the Technical Sales and Marketing Director at Klinge Chemicals Ltd. While this company is owned by my father and uncle I have no investment interest in the company. My qualifications for being in this role is an education in Food Science and Biochemistry (BSc Hons) as well as having worked in the food industry for a number of years for various global companies. I think it important to highlight that while my main employment function is to drive the availability and uptake of the products that Klinge Chemicals Ltd. produces, I personally have a fundamental passion for improving public health, demonstrated by my creating the collaborative education initiative Season with Sense™[1] in 2021, designed to instigate behavioural change in relation to salt use.

Klinge Chemicals Ltd. produces 2 products:

- potassium chloride for use in various industries including food and pharma
- LoSalt®[2] a reduced sodium salt alternative (LSSS) launched in the UK in 1983 and now available in 25+ countries globally representing 5 continents

I have worked for the company for 17 years and feel that the contextual knowledge and insights I have gained in this time -particularly in relation to consumer behaviour, the commercial availability and uptake by manufacturers of LSSSs - has relevance in this consultation. I am grateful for the opportunity to share these through this response process.

SUBMISSION REASONING

Demonstrating strong consensus on sodium reduction as a life-saving strategy, all WHO member States (194) have committed to reducing population sodium intake by 30% by 2025, but current modelling shows that globally we are falling short of this target. In response, the recently published WHO Global Report On Sodium Intake Reduction[3] proposes that "countries may explore ways to increase the availability and use of potassium enriched low-sodium salt substitutes, particularly in populations that consume much of their sodium intake from salt added to food in cooking and/or at the table". Considering this, why then does this draft guideline conflict this by recommending **limited use of low-sodium salt substitutes**?

To drive positive change in public health there needs to be consistency of guidance and the recommendation proposed shows disparity to existing WHO recommendations for:

- a reduction in sodium intake to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults *(strong recommendation)*[4]
- an increase in potassium intake from food to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults *(strong recommendation)*[5]

With lower sodium and higher potassium levels than regular table, sea and rock salts, **low-sodium salt substitutes can be part of the solution to reduce incidence of hypertension** especially where discretionary salt use is high. I feel that the implied negative position the WHO seems to be taking on

LSSSs in this guidance is a missed opportunity for providing a tool to governmental policymakers when tackling NCD reduction, particularly in respect to the 'Best-Buy' of sodium/salt reduction.[6]

RELEVANT VIEWPOINTS AGAINST EVIDENCE TO RECOMMENDATIONS

I feel that the contextual factor narrative review[7] conducted was too abstracted from the marketplace to wholly inform the development of this guideline. My main comments to the information presented in the review and subsequently presented within the guideline as to whether the implementation of the intervention of LSSSs is feasible follow below.

1. **Cost of LSSSs to consumers**
   It is agreed that the cost of LSSS in comparison to regular, free-flow table/cooking salt is higher but when comparing price against the market sub-sectors of sea and rock salts which are growing in upper-middle-income countries (UMICs) and high-income countries (HICs), LSSs are in fact significantly lower in cost, therefore in such countries I feel cost is not a barrier to purchase. It is important to note that many UMICs and HICs have discretionary salt use levels in the region of 25-50% (see figs. 1 and 2 below).

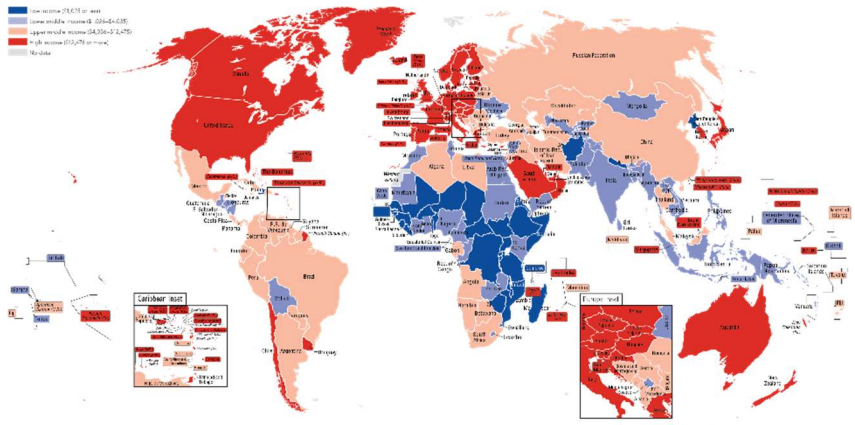

FIGURE 1: WLD Income Map

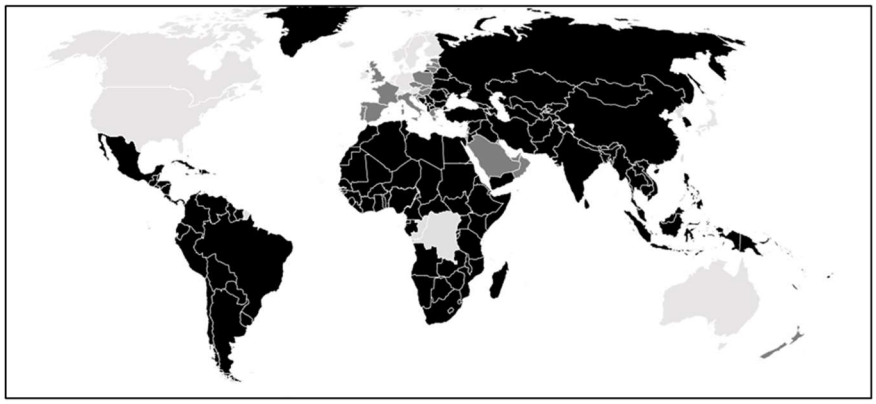

FIGURE 2: *from presentation*[8]

2. **Limited availability and low market share of LSSSs**
   In terms of retail availability, this is directly related to the decision of a buyer to stock an LSSS – a consumer can only buy an LSSS if they have access to it. LSSSs are poorly represented in the 'salt sets' of UMIC and HIC supermarkets; for example, currently in one major Australian retailer the salt offering is 47 products made up of 16 rock salts, 10 table/cooking salts, 10 sea salts, 10 flavour salts and only 1 LSSS. I would also comment that while sweeteners are commonplace alongside sugar in restaurants and food-2-go outlets, only rarely to you see a LSSS placed alongside salt sachets or cellars. Again this is a stockist issue rather than an availability issue. To my mind the barrier of LSSS implementation is not one of availability, moreover a lack of understanding on why a healthier alternative should be presented to the consumer.

3. **Acceptability of taste**
   In the consumer trials reviewed, bad taste was highlighted as a barrier to uptake of LSSSs, I would contend that this would be due to the formulation of LSSSs used in these trials. For our product (LoSalt®) research has shown an acceptability rate of 97%[9] and that there is a 94% likelihood of repeat purchase[9].

4. **Barriers for use of LSSSs in food manufacture**
   a. <u>Cost</u>
      As addressed earlier, LSSSs are more expensive than regular free-flow table and cooking salts. I would however contend that as salt constitutes such a small part of the ingredient costs of final product, the added cost is actually negligible
   b. <u>Taste</u>
      This area is slightly more nuanced than in the case of consumer acceptability. For food manufacturers maintaining consumer acceptability is understandably crucial and therefore NPD tasting is key in approving products reformulated for less sodium/salt. What has to be remembered is that the first round of taste-tests are usually performed by highly skilled individuals with palates trained to perceive any differences in flavour profile from the original. I would argue that were 1st round testing put to the public, such differences would be undetectable.
   c. <u>Labelling issues</u>
      I would agree with the view presented that referring to LSSSs on packaging labels as 'potassium salt" is preferable both to the manufacturer and un-informed consumer. My suggestion is that were the WHO to take a more positive stance in recommending LSSSs, then other governments would take the lead from USA in permitting such labelling.

   Under this heading I would like to highlight that without positive guidance on the use of LSSSs in reformulation I would contend that food manufacturers would have a reason to indefinitely stall their sodium/salt reduction programmes in favour of commercial gains.

It is highlighted that the primary goal and priority public health message should be to reduce discretionary salt intake – I believe that reconsideration has to be given to this long-standing belief. Taking the UK as an example which was pioneering in it's governmental salt reduction programme:

1. Our own consumer research shows us that:
   a. Salt is a home fixture
   b. Salt use is increasing out of home
   c. Salt use is intrinsic - 1 in 3 add salt instinctively to food without tasting
   d. Almost 1⁄4 people would continue using salt regardless of health advice

2. Salt market data (IRI and AC Nielsen*) shows us that we are buying the same amount of salt today as we were a decade ago, and during this time population salt intake has increased from 8.0g/day[10] to 8.4g/day[11]

In light of all these views I believe that the WHO should reconsider the recommendation in this guideline, positively promoting LSSSs for discretionary use, thereby giving:

1. those that will not give up salt a workable solution
2. buyers a reason to increase availability for consumers

While not being covered in the scope of this guideline I further believe that recommending an LSSS as a population sodium reduction tool will mean that

3. caterers would consider using an LSSS front and back of house (especially in institutional settings)
4. food manufacturers no longer have reason to stall their sodium reduction programmes

RELEVANT VIEWPOINTS AGAINST RECOMMENDATION AND SUPPORTING INFORMATION

I fully agree that there is poor global availability of iodized LSSSs. IT should be noted that the iodization of salt (be it a regular salt or a low-sodium salt) is an easy process. I concur that action be taken to where the iodization levels of LSSSs do not match those required for regular salt in any given country. Furthermore, due to the diversity of our global landscape I believe that both iodized and non-iodized LSSSs should be available in all markets.

OTHER COMMENTS

1. **Concerns about the safety of LSSSs in relation to hyperkalemia risk**
   Though out-with the scope of this recommendation, you have referenced the findings of the UK's joint Scientific Advisory Committee on Nutrition (SACN) and Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) assessment of the health benefits and risks of using potassium-based sodium replacers in foods in the UK[12] against the reported ineffectiveness that use of LSSSs in manufacturing does not reduce consumer preference for high-salt foods. I therefore feel that the conclusion of this assessment should be mentioned in relation to safety concerns:
   "Overall, at a population level, the potential benefits of using potassium-based sodium replacers to help reduce sodium in foods outweigh the potential risks… These beneficial effects at an individual level are likely to be small in size but would impact a large proportion of the population."

2. **Population lack of awareness of LSSSs and associated health benefits**
   I would wholly agree that there is little public awareness of LSSSs in UMICs and HICs, let alone in lower income countries. This has to change if – as the WHO Global Report On Sodium Intake Reduction[3] proposes – countries should "explore ways to increase the availability and use of potassium enriched low-sodium salt substitutes". The WHO has already provided leadership in raising awareness of the huge, negative health impacts of excess salt consumption, which causes millions of unnecessary deaths globally each year. With this guideline the WHO has the opportunity to continue to strengthen this lead, offering a solution rather than suggesting limited use of LSSSs for discretionary salt use. Such a positive recommendation would strengthen the collaborative work we are doing in our behavioural change campaign, Season With Sense™ [1].

3. **Terminology**

   It was acknowledged in the contextual factor narrative review[7] that "low-sodium salt substitutes are considered to be formulations where sodium is reduced…". In the EU, the most widely available salt substitutes where sodium is reduced has to carry the product descriptor "reduced sodium salt"[13], a term omitted from the search string when reviewing available literature.

   To encourage consumer uptake, or at least meaningful discussion, there should be a uniformity in naming this product category and I feel that this is not addressed adequately in the guideline. Within the 'Executive Summary' the term low-sodium salt substitute is qualified as including "less sodium than regular salt and often add potassium chloride with or without other agents to achieve a flavor similar to regular salt." – I feel that for avoidance of doubt this statement should be detailed in the "Abbreviations and acronyms" section of the guideline.

   In my experience, "low in sodium" means "low in taste" both to consumer and manufacturer, should it therefore be the intention recommend the use of LSSSs (even as negatively outlined in the current draft guideline) I would recommend considering the renaming of the document to: "WHO Guideline: use of potassium-enriched salts", as referred to in various research publications[14] and public awareness drives[15]

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* this data only covers retail sales from leading retailers

Survey response 9

JOHNS HOPKINS
WELCH CENTER *for*
PREVENTION, EPIDEMIOLOGY
& CLINICAL RESEARCH

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Comments by the Johns Hopkins Resolve To Save Lives Team for Sodium Reduction on the Draft WHO guideline: Use of Low-Sodium Salt Substitutes

Based on available evidence, we urge replacement of the draft WHO recommendation with an alternative recommendation, as proposed below.

Draft WHO recommendation: WHO suggests the limited use of low-sodium salt substitutes as a replacement for discretionary salt use when it contributes to reducing sodium intake to below 2 g/day in adults (conditional recommendation, based on low certainty evidence).

Alternative recommendation: WHO recommends the use of low-sodium salt substitutes as a replacement for discretionary salt to reduce blood pressure and lower the risk of blood pressure-related CVD outcomes, consistent with prior WHO recommendations on reducing sodium and increasing potassium intake (conditional recommendation, based on moderate uncertainty for some safety outcomes).

In the sections that follow, we provide our rationale for this change in the recommendation. In addition, we highlight one other major concern at the end of this letter.

Understating the importance of the blood pressure reduction

The systematic review commissioned by WHO reported that LSSS, compared to regular salt, on average lowered systolic blood pressure (SBP) by 4.76 mmHg (95% confidence interval [CI]: 3.50-6.01; n = 21,414 participants) and diastolic blood pressure (DBP) by 2.43 mmHg (95% CI:1.36-3.50, n = 20,830 participants).[1] These effects are comparable to the effects of sodium reduction (SBP: 3.39 mmHg [95% CI: 2.46-4.31], n = 6,736 participants; DBP: 1.54 mmHg [95% CI: 0.98-2.11], n = 6,736 participants) and potassium supplementation (SBP: 3.06 mmHg [95% CI: 1.42-4.70] , n = 1,892 participants; DBP: 2.84 mmHg [95% CI: 1.01-4.66] , n = 1,857 participants) reported in WHO guidelines on sodium intake and potassium intake.[2, 3]

While the reported effects were similar, the interpretation of the effects differs greatly in the published sodium and potassium guidelines compared to the LSSS Draft Guidelines. The table below provides a summary of the sodium and potassium recommendations:

Sodium (2012 Guidance)	WHO recommends a reduction in sodium intake to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults (*strong recommendation*1). WHO recommends a reduction to <2 g/day sodium (5 g/day salt) in adults (*strong recommendation*).
Potassium (2012 Guidance)	WHO recommends an increase in potassium intake from food for reduction of blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults (strong recommendation). WHO suggests a potassium intake of at least 90 mmol/day (3510 mg/day) for adults (conditional recommendation).

The evidence of effects for sodium reduction and potassium supplementation were considered to be of "high quality" resulting in "strong recommendations" for reducing sodium intake and increasing potassium intake to lower blood pressure.[2, 3] The similar effects in the WHO-commissioned systematic review of LSSS are considered to be "small, important effects" of "moderate-certainty evidence" [1] and the Draft Guideline conclude that "the use of LSSS resulted in lower systolic and diastolic blood pressure (both moderate certainty evidence)".

Of note, the authors of the systematic review defined a threshold of clinically meaningful reduction in SBP as 10 mmHg and in DBP as 5 mmHg.[1] The selection of these threshold appears arbitrary, and it is unreasonable to expect any dietary intervention to result in an overall blood pressure reduction of this magnitude, and in fact, most classes of blood pressure lowering medications do not achieve this level of BP reduction.[4] A recent meta-analysis of sodium reduction trials reported a dose-response relationship between dietary sodium and SBP where 1 g/d reduction of sodium intake would lower blood pressure by 2.42 mmHg (95% CI: 1.97-2.87).[5] Thus, a 10-mmHg lowering of SBP would require a 4.1 g/d reduction in sodium intake. It is unlikely that WHO would require this magnitude of effect to consider a sodium reduction strategy meaningful.

A second issue is the inappropriate classification of the 'certainty of evidence' as moderate for the blood pressure lowering effects of LSS. The Cochrane review by Brand downgraded the evidence from strong to moderate based on 'substantial heterogeneity', not explained by subgroup analyses. Yet, heterogeneity is expected given the heterogeneity in the LSSS interventions and features of the study populations, including baseline blood pressure levels; further, heterogeneity will likely be unexplained in meta-analyses that do not have adequate data on factors that might explain the heterogeneity. Finally, it is noteworthy that such heterogeneity occurred in the meta-analyses conducted by Aburto et al. in support of the WHO potassium guidance, which nonetheless gave a 'strong' recommendation.[6]

From a public health perspective, blood pressure reductions of magnitudes comparable to the effect of LSSS trials are expected to have substantial impact on disease burden. For example, we recently estimated that an average SBP reduction by 4.65 mmHg in the adult population of India could avert around 350,000 cardiovascular deaths each year.[7] Empirical evidence also supports a substantial reduction of LSSS on cardiovascular outcomes and mortality. In the SSaSS trial, a mean SBP reduction of 3.3 mmHg was associated with a 14% reduction in strokes and 12% reduction in mortality,[8] effects which have clear public health relevance. For these reasons, we recommend that the 'clinically meaningful thresholds' of 10 mmHg for systolic BP and 5 mmHg for diastolic BP be dropped from this document and that recommendations for LSSS be aligned more closely with those of the WHO recommendations for sodium and potassium.

The proposed recommendation does not reflect the scientific evidence

The recommendation in the Draft Guidelines states "WHO suggests the limited use of low-sodium salt substitutes as a replacement for discretionary salt use when it contributes to reducing sodium intake to below 2 g/day in adults (conditional recommendation, based on low certainty evidence)." The recommendation is based on evidence of low certainty overall, with outcomes of interest listed as "effects on blood pressure, serum potassium (hyperkalaemia, hypokalaemia), stroke and cardiovascular events and mortality." This is not

consistent with the findings from the systematic review where the evidence for key outcomes, including blood pressure, fatal and non-fatal CVD, non-fatal stroke, serum potassium, and incident hyperkalemia was defined as moderate" (and which should be 'strong' for blood pressure, as documented in the above paragraph). Given that current WHO guidelines provide strong recommendations to reduce sodium intake and to increase potassium intake (based on less strong evidence), it is counterintuitive and confusing to the target audience that an intervention that effectively combines the two recommendations would be considered a conditional recommendation.

Chapter 8 'Developing recommendations' of the WHO handbook for guideline development states "A conditional recommendation is more likely if there is uncertainty about the balance of benefits versus harms or when there are only marginal net benefits, that is, when the anticipated net benefits are small". We have conducted modelling studies using the best available evidence to estimate potential benefits, harms, and net effects of nation-wide implementation of LSSS interventions in China and India.[7, 9] In these studies, we have adopted a cautious approach to avoid overestimating benefits and underestimating potential harms. However, in all modelled scenarios including a series of sensitivity analyses to assess the impact of alternative inputs and assumptions, we have consistently estimated substantial net benefits in the overall population, and importantly also net benefits in individuals at greatest risks of life-threatening hyperkalemia (i.e., individuals with advanced kidney disease).

There is very limited evidence to support potential harms of LSSS and the systematic review conclude that "LSSS interventions likely result in little to no difference in hyperkalaemia" of "moderate-certainty evidence". Small increases in serum potassium have been observed in both LSSS trials (mean increase: 0.12 mmol/l [95% CI: 0.07-0.18]) and potassium supplementation trials (mean increase: 0.14 mmol/L [95% CI: 0.09-0.19]).[1, 10] Such changes have limited clinical meaning if the increases occur within the normal range of serum potassium (i.e., 3.5-5.5 mmol/L). Thus, small changes in serum potassium are less suitable as safety outcomes compared to clinical hyperkalemia, arrhythmia, sudden cardiac death. Importantly, the systematic review and the Draft Guidelines did not consider two safety evaluations of LSSS (≤40% KCl) in elderly hospitalized patients [11] or heart failure patients,[12] or a recently published LSSS trial conducted in elderly care facilities,[13] which all reported no adverse clinical outcomes of LSSS use.

The Draft Guideline is not consistent with current guidelines on sodium and potassium intake

As mentioned above, there are important inconsistencies in how the evidence is synthesized and interpreted in the Draft Guidelines compared to the current guidelines for sodium and potassium intake.

- Current guidelines on sodium and potassium intake provide strong recommendations based on blood pressure effects comparable to those of LSSS, for which the draft recommendation is conditional.
- Furthermore, the sodium and potassium guidelines do not report any significant effects on cardiovascular disease outcomes based on evidence from randomized controlled trials (RCT), but instead report significant associations from observational cohort studies. Still, the recommendations regarding reduced sodium intake and increased potassium intake for cardiovascular disease prevention

in the guidelines are defined as strong, based on the known relationship between blood pressure and cardiovascular. For LSSS the evidence is based on findings from RCTs directly assessing the impact of LSSS on cardiovascular disease risk.
    - Also, the outcome definitions differ greatly between the current guidelines and the Draft Guidelines, where the former consider composite cardiovascular outcomes and the latter arbitrarily separate fatal and non-fatal events, reducing the statistical power to detect significant effects.
- Hypertension and blood pressure control were defined as outcomes when considering the overall recommendation for LSSS. Neither of these outcomes were considered in the guidelines for sodium and potassium.
- The current potassium guidelines provide strong recommendation to increase potassium intake among adults, without considering potential effects on serum potassium and hyperkalemia risk in the general population or in high-risk individuals. The Draft LSSS guideline considers effects on serum potassium, hyperkalemia, hypokalemia as primary outcomes, and refers to the uncertainties in these outcomes as a justification for the conditional recommendation.
- The Draft Guidelines states "… that while WHO recommends an increase in potassium intake from foods, increasing potassium intake should not be the purpose of using LSSS containing KCl.". However, the evidence underlying the WHO recommendation to increase potassium intake for blood pressure reduction was primarily based on trials using potassium supplementation (20 of 22 studies) and not dietary interventions.[6]

Hence, we recommend the WHO evaluate LSSS with the same standards used in support of prior WHO recommendations on sodium and potassium. The current recommendation and standards are inconsistent with the following statement (p13), "This guideline will be in line with other WHO guidelines and recommendations, including the WHO guidelines on sodium intake and potassium intake among others."

Other issue

Diabetes is not condition that requires restriction of dietary potassium intake. While persons with diabetes have a greater risk of hypertension and its complications including kidney disease, there is no evidence (or recommendation) that all persons with diabetes should restrict their potassium intake. Neither US nor European guidelines recommend restriction of potassium intake in persons with diabetes; neither of these documents expressed concern about hyperkalemia except for those persons with concomitant kidney disease.[14, 15] **Accordingly,** text that diabetes is a condition for which persons 'would be advised not to increase potassium intakes' should be removed from the document.

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Survey response 10

The launch, on 31 March 2023, of the WHO draft guideline on use of low-sodium salt substitutes was of great interest at a high level and we thank the WHO for this interesting and necessary initiative. The draft of the document is clear, comprehensive.

However, as pediatricians primarily interested in NCD prevention and health promotion, we believe a small but important clarification is in order.

No reference is made to the age group of infants in the text. We believe it is necessary to point out that the use of sodium chloride substitutes is absolutely NOT indicated in this age group.

In this range, the only intervention to be implemented, as already stated in various WHO documents, is the elimination of added salt for up to two years and subsequently its contribution contained within the recommended limits.

The use of potassium chloride could direct the families who use it as an adjuvant in reducing salt intake for reasons of already full-blown pathology of some of its adult members to consider it healthier than the sodium equivalent and direct them to indiscriminate use also for the feeding of infants.

Given the absence of certain data on the safety of its consumption, it is more prudent to specify the NOT use of the product in the first years of life.

Furthermore, potassium chloride can alter the taste of foods, giving them a certain bitter taste, or even to make naturally unbitter foods taste worse. This can negatively affect the development of healthy food habits and preferences, by making it more difficult to accept vegetables and other foods naturally tending to have a bitter taste.

For these reasons, we believe that in the final text of the guidelines on the use of salt substitutes it should be emphasized that these products should NOT be used in infants and toddlers.

We thank you for your attention to our comment and your precious work

Sincerely yours

Margherita Caroli MD PhD

Survey response 11

Response from World Action on Salt, Sugar and Health to *Public consultation: draft WHO guideline on use of low-sodium salt substitutes*

World Action On Salt, Sugar and Health (WASSH) is a global group with the mission to improve the health of populations throughout the world by achieving a gradual reduction in salt and sugar intakes. WASSH has expert members in 100 countries, all of whom are committed to salt and sugar reduction. We provide resources and advice to enable the development and implementation of salt and sugar reduction programmes worldwide.

We welcome the WHO's focus on low-sodium salt substitutes (LSSS), in line with wider work to reduce salt intakes and increase potassium intakes globally. We thank the WHO for the opportunity to respond to the draft LSSS guideline. However, **we have serious concerned by the conclusions reached** in this consultation, which we have outlined in detail below. We also **found the wording throughout the guideline confusing**, particularly the wording of the primary recommendation which on first reading appears to discourage the use of LSSS. The **use of 'limited' implies a negative stance on the use of LSSS** and could be interpreted that discretionary salt is better to consume instead. This **recommendation is also likely to be exploited by the food industry**, who may use this to refuse using LSSS in their food products, with an aim of undermining public health policies, furthering their commercial interests, and maintaining power within the global food system.

For more information on our response or our work, please contact Mhairi Brown, International Projects Lead Mhairi.brown@qmul.ac.uk

Consultation Questions

Summary of Evidence

Of great concern is the criteria set within the commissioned Cochrane review, of a clinically meaningful reduction in blood pressure being at least a 10mmHg reduction. This is a huge effect; from a clinical perspective, a 10mmHg fall is more than what is achieved with most blood pressure lowering drugs and, for example, twice the magnitude of the fall in blood pressure observed in a meta-analysis of trials of the antihypertensive drugs class ACE inhibitors (4 mmHg). This 4mmHg fall alone led to reductions in stroke (20%) heart failure (21%), acute coronary syndrome (13%) and major cardiovascular events (17%). From a public health perspective, experience from the UK's salt reduction programme shows that following a reduction in population salt intake (15%) between 2003 and 2011, there was a fall in blood pressure of 3.0±0.33 mmHg[1]. This was associated with a reduction in 18,000 stroke and heart attack events, 9000 of which would have been fatal, and resulted in savings to the UK economy of £1.5 billion annually. The 10mmHg benchmark represents a failure to understand the clinical and public importance of small reductions in blood pressure.

In the WHO-commissioned review, the interpretation of the effects of LSSS on blood pressure highlights the heterogeneity of effect sizes between studies but fails to acknowledge the reduction in blood pressure observed in all studies. Differences in the size of effect between studies are to be expected because studies included different populations and tested different LSSS. The important observation is that blood pressure reduction was achieved for all and would be expected in the long-term to reduce the risk of cardiovascular outcomes for all.

Despite being highlighted by the WHO as related guidelines, there is a lack of consistency between the outcomes reviewed - and the interpretations of evidence made - between the LSSS guideline and the WHO sodium and potassium intake guidelines. WHO's existing guidance is to reduce sodium intake "to

[1] He FJ, Pombo-Rodrigues S, MacGregor GASalt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortalityBMJ Open 2014;4:e004549

reduce blood pressure, stroke and coronary heart disease in adults (strong recommendation)", and "increase potassium intake from food to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease (strong recommendation)". This is inconsistent with the recommendation and rationale for LSSS, which combines these two effects. If all guidelines are aiming to achieve a goal of lowering excess salt intake – which we know are having a huge impact on individuals, communities, healthcare systems and economies globally – while increasing potassium intakes, then evidence should be interpreted in a consistent manner. Furthermore, different outcomes appear to have been evaluated between the supposedly complementary guidelines. For example, in the LSSS guideline, incidence of hypertension and blood pressure control rate was examined as an outcome, but neither hypertension nor blood pressure control were examined as outcomes for the WHO guideline on sodium intake or the WHO guideline on potassium intake. Similarly, the LSSS guideline examined change in blood potassium, hyperkalaemia and hypokalaemia as outcomes but these were not considered in WHO's guideline on potassium intake. The LSSS guideline focuses inappropriately on subgroups of cardiovascular events (fatal separate from non-fatal, no overall assessment of cardiovascular events) whilst the WHO guidelines on sodium intake and potassium intake both considered composite cardiovascular disease outcomes. The recommendations for the LSSS guideline must be consistent with the recommendations from other relevant guidelines to have credibility.

A comparison of the three guidelines is displayed in Table 1, prepared by The George Institute for Global Health.

Table 1. Comparison of WHO's draft guideline on low-sodium salt substitutes and WHO's published guidelines on sodium intake and potassium intake.

Outcomes	WHO Guideline	Effect	n*	Quality of evidence
Change in SBP (mmHg)	Low-sodium salt substitutes	MD 4.76 lower (6.01 to 3.5 lower)	21,414	Moderate
	Sodium	MD 3.39 lower (4.31 to 2.46 lower)	6,736	High
	Potassium	MD 3.06 lower (4.70 to 1.42 lower)	1,892	High
Change in DBP (mmHg)	Low-sodium salt substitutes	MD 2.43 lower (3.5 to 1.36 lower)	20,830	Moderate
	Sodium	MD 1.54 lower (2.11 to 0.98 lower)	6,736	High
	Potassium	MD 2.84 lower (4.66 to 1.01 lower)	1,892	High
Cardiovascular disease *(In the LSSS guideline, cardiovascular mortality and events were separate outcomes, whereas in the WHO sodium and potassium intake guidelines,*	Low-sodium salt substitutes	Rate ratio 0.77 (0.6 to 1.00) – reduced cardiovascular mortality with LSSS interventions	23,200	Moderate
		Rate ratio of 0.70 (0.52 to 0.94) – reduced non-fatal acute coronary syndrome events with LSSS interventions	20,995	Moderate
	Sodium	RR 0.84 (0.57,1.23) – decreased risk of composite cardiovascular disease with decreased sodium intake	720	Moderate

composite cardiovascular disease was considered)		RR 1.12 (0.93 to 1.34) – increased risk of composite cardiovascular disease with increased sodium intake	46,483 (from cohort studies)	Very low
	Potassium	RR 0.88 (0.7 to 1.11) – decreased risk of composite cardiovascular disease with increased potassium intake	29,067 (from cohort studies)	Very low
Stroke *(In the LSSS guideline, non-fatal stroke and stroke mortality were examined separately, whereas in the WHO sodium and potassium intake guidelines, overall stroke was considered)*	Low-sodium salt substitutes	RR 0.90 (0.80 to 1.01) for non-fatal stroke when comparing LSSS with regular salt	21,250	Moderate
		Rate ratio 0.64 (0.33 to 1.25) for stroke mortality	21,423	Very low
	Sodium	Only 1 inconclusive RCT. Based on cohort studies, there was an increased risk of **all** strokes (RR 1.24 (1.08 to 1.43)) with increased sodium intake	72,878 (from cohort studies)	Very low
	Potassium	Based on cohort studies, there was a decreased risk of stroke with increased potassium intake (RR 0.79 (0.68 to 0.93))	97,152 (from cohort studies)	Low

*Number of participants from randomised controlled trials unless otherwise specified

We further question the outcomes assessed within the summary of evidence. For large-scale trials and meta-analyses of interventions targeting cardiovascular outcomes through blood pressure lowering there are well established sets of outcomes for evaluation:

- primary clinical efficacy outcome would be total major cardiovascular events comprising cardiovascular death, non-fatal stroke and non-fatal acute coronary syndrome
- Secondary outcomes would typically be total stroke (fatal and non-fatal), total acute coronary syndrome (fatal and non-fatal), total heart failure (fatal and non-fatal) and cardiovascular death. Sudden deaths, arrhythmias, hospitalisations and procedures may also be reported.

Separate reporting of fatal and non-fatal events would usually be an exploratory analysis. In the WHO-commissioned review the interpretation of the effects on clinical outcomes is based primarily on separate review of subsets of fatal and non-fatal outcomes. This hugely impacts on the statistical power to detect effects and means the conclusions of benefit for clinical outcomes are deemed of lower quality evidence. Another systematic review that focuses on the most appropriate outcomes (total cardiovascular events, total stroke, total acute coronary syndrome) and fatal and non-fatal events combined identifies strong protective effects of LSSS on multiple clinical outcomes. This is directly at odds with the findings of the Cochrane review upon which the WHO draft guideline is based.

The key safety outcomes for the main risk selected for the WHO-commissioned review (hyperkalaemia) are also not well chosen – clinical hyperkalaemia, arrhythmia, sudden cardiac death (or sudden death) and total mortality would be more appropriate (and more patient-centred) than the blood potassium levels (which are irrelevant unless linked to negative health outcomes) and biochemical hyperkalaemia focused upon. The overview found evidence of a small increase in serum

potassium but no evidence of any other harm, which is a non-finding in the context of this guideline unless linked to a more positive recommendation. WHO have stated previously that global potassium intakes are lower than recommended – surely it should be positive that serum potassium levels rose? Indeed, the Cochrane review findings which indicate moderate quality evidence of a small clinically unimportant increase in blood potassium, moderate quality evidence of 'little to no difference in…hyperkalaemia" and very low quality evidence of no hypokalaemia events and adverse events when comparing LSSS with regular salt. The failure to specify appropriate outcomes for harms meant that safety in terms of moderate strength evidence of no effect on clinical hyperkalaemia events and no effect on sudden death were not appropriately identified and included in the assessment.

Appropriate assessment of the right outcomes would have identified strong evidence of benefits for blood pressure and cardiovascular protection with moderate quality evidence for an absence of harms. Based on this evidence the recommendation for LSSS should, in the context of GRADE, be assessed as strong not weak.

The summary of evidence makes clear the characteristics of the systematic review, the primary/secondary outcomes and the WHO interpretation of the evidence. However, the evidence in question does not appear to be current. Research on low-sodium salt substitutes is a fast evolving area and it is likely that the WHO review of evidence was undertaken prior to there being comprehensive systematic reviews and meta-analyses published. We note the following examples, and strongly recommend a further review of evidence to ensure all relevant research is captured and considered, in addition to the commissioned Cochrane review:

- Yin X et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. Heart. 2022 Sep 26;108(20):1608-1615.
- Yuan Y, et al. Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster randomised trial. Nature Medicine. 2023 April 14; NCT03290716.

Evidence to Recommendations

The overall recommendation in the LSSS guideline is considered to be based upon 'evidence of *low* certainty overall'. This conclusion appears to be driven by a failure to understand the clinical and public health importance of the impact of LSSS on blood pressure, and conclusions of low certainty evidence about efficacy and safety.

The LSSS guideline should have a strong overall recommendation with areas of uncertainty identified through conditional recommendations for particular subgroups or settings.

Recommendations and Supporting Information

The WHO draft guideline concludes that LSSS compared to regular salt 'probably slightly reduces diastolic and systolic blood pressure'. This is incorrect, as the systematic review found 'small, important effects on DBP' and 'small, important effects on SBP', and should be amended for accuracy.

The LSSS guideline infers significant uncertainty about the likely overall balance of benefits and risks with use of LSSS. This is inconsistent with the data, which suggest blood pressure lowering benefits most of the population, with corresponding long-term reductions in cardiovascular risks for most. Additionally, the guideline fails to state that just 1% of the population are likely at risk of hyperkalaemia and the majority would be aware of their risk and have been advised to avoid salt and products with a high potassium content. Indeed, the guideline recommendation only considers the effect of LSSS on population sodium intake, but neglects the potential effect LSSS would have on population potassium intake. WHO recommends a minimum intake of 3510 mg of potassium for adults to protect health but

in many countries, intakes are much lower than this. LSSS could contribute to lowering sodium intake while increasing potassium intake.

We note the UK's joint Scientific Advisory Committee on Nutrition (SACN) and Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) benefit-risk assessment to consider the impact of substituting 15-25% of sodium in foods with potassium[2]. The modelling predicts that potassium intakes would increase by around 8–15 mmol/day (300–600 mg/day) for different UK population age groups, without taking intake above the reference nutrient intake. While this review relates to the replacement of sodium salts in food products which was not in scope of the WHO guideline, the SACN-COT report concluded that although there would be increases in population potassium intake, at a population level the potential benefits of using potassium-based sodium replacers to help reduce sodium in foods outweigh the potential risks. This is a key finding that should be considered by the WHO when weighing up the numerous, evidence-based benefits of LSSS use against any minor risks. We also highlight that around 80% of dietary salt intake in many countries comes from processed and prepared food. The guideline should be expanded in scope to incorporate the use of LSSS by the food industry to protect health.

Other Comments

The WHO has already provided leadership in raising awareness of the huge, negative health impacts of excess salt consumption, which causes millions of unnecessary deaths globally each year. In many countries, the majority of dietary salt comes from processed and prepared foods, but in several low- and middle-income countries (LMICs), discretionary salt is a leading source. LMIC populations are suffering disproportionately from the impact of excess salt intake, and healthcare systems are not equipped to handle the active response needed to an ever-growing problem. Research demonstrates that a 15% reduction in population salt in 23 LMICs could avert 8.5 million cardiovascular deaths over 10 years and result in major cost-savings to individuals, their families and the health services[3]. Indeed, such a modest reduction in salt intake is more, or at the very least, just as cost-effective as tobacco control in terms of reducing cardiovascular disease, the leading cause of death and disability worldwide. Prevention policies are urgently needed globally, with LSSS providing immediate benefits to population health, and LSSS use should be encouraged in line with the evidence.

[2] https://www.gov.uk/government/publications/sacn-cot-statements-on-potassium-based-sodium-replacers#:~:text=The%20joint%20SACN%2DCOT%20benefit,foods%20outweigh%20the%20potential%20risks.

[3] Asaria P, Chisolm D, Mathers C, Ezzati M, Beaglehole R (2007) Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. *Lancet* 370: 2044–53

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Comments on the Draft WHO Guideline on the use of Low-Sodium Salt Substitutes (LSSS)

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Research Director, Tokyo Foundation for Policy Research, Tokyo, Japan

I am grateful for the opportunity to provide feedback on the WHO draft guideline. Firstly, I would like to commend the WHO and its secretariat for undertaking this groundbreaking exercise, which holds the potential to benefit millions of individuals worldwide. It is crucial for the draft guideline to incorporate the latest evidence and focus on the population health impact at national, regional, and global levels to ensure its successful implementation. Please allow me to summarize several key technical issues and express my hope that the WHO addresses these concerns in an open and transparent manner.

1. The WHO should revise the systematic review based on the most recent evidence and update the recommendations. It has been a few years since the WHO's scoping review in September 2021, which identified the need for a comprehensive systematic review to develop a guideline for the use of LSSS as a substitute for regular salt. However, multiple systematic reviews and meta-analyses have since emerged in this field, and a significant new outcome trial was recently reported. These include:
    - Yin X, Rodgers A, Perkovic A, et al. Effects of salt substitutes on clinical outcomes: a systematic review and meta-analysis. Heart 2022;108:1608-1615.
    - Yuan Y, et al. Salt substitution and salt-supply restriction for lowering blood pressure in elderly care facilities: a cluster-randomized trial. Nature Medicine. 2023 April 14; NCT03290716.

Furthermore, there have been recent publications on low-sodium salt substitutes that I hope will be considered during the guideline revision:

- Nomura S, et al. Umami: An Alternative Japanese Approach to Reducing Sodium While Enhancing Taste Desirability. Health 2021: 13: 629-636. DOI: 10.4236/health.2021.136047
- Nakamura H, et al. Reducing salt intake with umami: A secondary analysis of data in the UK National Diet and Nutrition Survey. Food Sci Nutri., 2022 12(2):872-882. doi: 10.1002/fsn3.3121.
- Nomura S, et al. Salt intake reduction using umami substance-incorporated food: a secondary analysis of NHANES 2017-2018 data. Public Health Nutr. 2022: 1:1-8. doi: 10.1017/S136898002200249X. Online ahead of print. PMID: 36453137

- Tanaka S, et al. Modelling of salt intake reduction by incorporation of umami substances into Japanese foods: a cross-sectional study. BMC Public Health 2023;23(1):516. doi: 10.1186/s12889-023-15322-6.

2. **The WHO Draft Guideline should have a strong overall recommendation, with areas of uncertainty identified through conditional recommendations for subgroups or settings**. The overall recommendation in the Draft Guideline is based on "evidence of *low* certainty overall". However, there is compelling evidence of blood pressure reduction in all LSSS studies, and the wrong cardiovascular outcomes have been reported on in the systematic review. In addition, the conclusions about potential harms are not justified by the LSSS Systematic Review findings. There should be strong recommendations for LSSS use in general healthy adult populations and clinical settings, with a conditional recommendation for avoidance among population groups such as those with advanced kidney disease or in very remote settings where healthcare diagnostic facilities are absent.

3. **The Draft Guideline should state that the slight increase in blood potassium seen with LSSS compared to regular salt is not clinically important.** The draft states that 'the meta-analysis showed small, important effects on blood potassium on average between LSSS and regular salt groups (MD 0.12, 95%CI 0.07 to 0.18, I2 = 0%, 784 participants, 6 RCTs, moderate-certainty evidence)" (page 27). There is no justification provided in this paragraph for the clinical- or population-level importance attributed to this slight increase, in contrast to previous paragraphs about systolic and diastolic blood pressure, where the importance was illustrated through estimates of population impact. Further, in the LSSS Systematic Review, the conclusion explicitly states that "a small pooled mean difference in blood potassium between LSSS and regular salt indicated a small increase in this outcome for the LSSS group. This was not considered to be clinically important (moderate-certainty evidence) given its impact on the upper end of a 'normal' blood potassium level would not reach levels indicative of moderate hyperkalaemia."

   The pursuit of developing reduced-sodium products without compromising taste is a global endeavor. Key technologies involved in this pursuit include the utilization of potassium chloride (KCl) as a low-sodium salt substitute (LSSS) and the implementation of taste compensation techniques when reducing salt content using KCl. It is crucial for the general consumers to gain a comprehensive understanding that KCl, when consumed within normal intake levels, does not pose any cardiovascular toxicity risks. Without this accurate understanding, the ongoing global efforts to reduce salt intake, which have faced stagnation for over three decades, may persist in

a state of inertia. I earnestly hope for the dissemination of appropriate judgment and information through the WHO guideline.

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Dedicated to the Prevention and Control of Hypertension Globally
World Hypertension League
In official relations with the *International Society of Hypertension* and the *World Health Organization*

World Health Organization

Guideline on use of low-sodium salt substitutes (LSSS)

May 19, 2023

Re: Comment from the World Hypertension League (WHL) on the WHO guideline on use of low-sodium salt substitutes (LSSS)

Dear WHO Colleagues,

I am writing on behalf of the WHL Executive Committee and the WHL Publications and Presentations Committee with feedback on the draft WHO guideline on the use of LSSS.

The WHL congratulates the WHO guideline committee for their extensive work towards providing global guidance on the use of LSSS. The WHL is in strong support of this important initiative, and the draft document was read with great interest.

The comments below are made with collegial intent and are chiefly directed towards the guideline recommendation:

"WHO suggests the limited use of low-sodium salt substitutes as a replacement for discretionary salt use when it contributes to reducing sodium intake to below 2 g/day in adults (conditional recommendation1, based on low certainty evidence)."

Comment 1. The wording of any guideline recommendation must be clear and unequivocal. The WHL is concerned that the recommendation suggesting 'limited use' of LSSS as currently worded is potentially confusing. It is acknowledged that qualification as to the meaning of 'limited use' is provided in the document, but this is presented quite separately from the recommendation. Failure to qualify the meaning of 'limited use' within the recommendation itself potentially undermines clarity of the committee's position.

The WHL asks that the wording of the recommendation is modified for unequivocal clarity, including reference to what is meant by 'limited use.' For example:

"WHO suggests the limited use of low-sodium salt substitutes (LSSS) as a replacement for discretionary salt use when it contributes to reducing sodium intake to below 2 g/day in adults.

Use of LSSS should be limited to a reduced amount as compared to the amount at which regular salt would have been used (conditional recommendation1, based on low certainty evidence)."

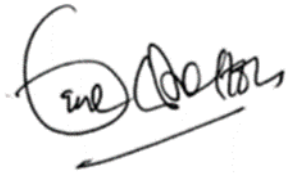
Comment 2. The WHL agrees with the importance of considering potential harms for people where potassium supplementation is contraindicated, and the particular risk for those who are undiagnosed and unaware of the need to avoid excessive potassium intake. This uncertainty has been weighted against consistent moderate certainty evidence of positive health outcomes from LSSS for adults without contra-indications to higher potassium intakes (lower systolic and diastolic blood pressure, reduced risk of non-fatal acute coronary syndromes, stroke and cardiovascular mortality).

The WHL asks the guideline committee to consider additional wording to distinguish the intended target population and provide more clarity on this nuanced aspect of the recommendation. For example:

"The use of potassium-based sodium substitutes for sodium can be recommended for adults in whom there is no history or evidence for chronic kidney disease or other clinical conditions where excessive intake of potassium should be avoided."

We appreciate your consideration of this feedback and look forward to your response.

Yours sincerely,



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