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

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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.

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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.

[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

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 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*	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

WHO sodium and potassium intake guidelines, composite cardiovascular disease was considered)	Sodium	RR 0.84 (0.57,1.23) – 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
	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