Joint Response from World Action on Salt and Health and Action on Salt to…

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

Action on Salt
Action on Salt (formerly Consensus Action on Salt & Health, CASH) is an organisation supported by 24 expert members and working to reduce the salt intake of the UK population to prevent deaths, and suffering, from heart disease, stroke, kidney disease, osteoporosis, stomach cancer and obesity.

For more information, please contact: Mhairi Brown, International Programme Lead
Mhairi.brown@qmul.ac.uk

Criteria (end points) on which to base Dietary Reference Values

Sodium Intake and Health Consequences

Lines 1483 – 1489 state:
"*Three categories of health outcomes were selected as the most suitable to inform the setting of DRVs: blood pressure, cardiovascular disease-related endpoints and bone health. They were selected on the basis of their biological relevance for the general healthy population, the biological plausibility of their relationship with sodium intake, and the type of evidence (i.e. RCTs and/or prospective observational studies) (see protocol, Annex A). Systematic reviews of the literature were conducted to characterise the relationship between sodium intake and these outcomes. The sub questions addressed by the systematic reviews are reported in Table 7.*

We are concerned that the narrow focus on blood pressure, cardiovascular disease-related endpoints and bone health underestimates the true impact of dietary salt on health.

A high salt intake has also been linked to chronic kidney disease and stomach cancer (with high biological plausibility), the evidence for which is briefly reviewed below. Due to these important omissions, we worry that the DRVs do not cover the whole of population health.

There is convincing evidence that salt intake is related to chronic kidney disease (Jones-Burton 2006). High salt intake is linked to many risk factors for the progression of the disease, such as raised blood pressure, fluid retention, proteinuria, inflammation, oxidative stress, and endothelial dysfunction (Al-Solaiman 2009; Ritz 2009). A recent Cochrane review has found consistent evidence that reducing salt intake in those with chronic kidney disease had health benefits beyond the lowering of blood pressure, such as a lower risk of proteinuria (McMahon, 2015).

The evidence has consistently shown a link between salt intake and stomach cancer for many years. High intra-gastric sodium cause mucosal damage and inflammation (Takahashi, 1985), which can increase cell proliferation and endogenous mutations (Furihata, 1996; Charnley, 1985). High salt intake can also change the viscosity of the protective mucous barrier (Tatematsu, 1975) and increase the colonization by H. pylori, which is a recognised risk factor for stomach cancer (Fox, 1999).

Furthermore, a more recent meta-analysis of 268,718 participants from 10 cohorts found an association between high salt intake and an increased risk of stomach cancer (d'Elia, 2012).

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- Charnley, G. and Tannenbaum, S.R., 1985. Flow cytometric analysis of the effect of sodium chloride on gastric cancer risk in the rat. Cancer research, 45(11 Part 2), pp.5608-5616
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- Fox, J.G., Dangler, C.A., Taylor, N.S., King, A., Koh, T.J. and Wang, T.C., 1999. High-salt diet induces gastric epithelial hyperplasia and parietal cell loss, and enhances Helicobacter pylori colonization in C57BL/6 mice. Cancer research, 59(19), pp.4823-4828
- Furihata, C., Ohta, H. and Katsuyama, T., 1996. Cause and effect between concentration-dependent tissue damage and temporary cell proliferation in rat stomach mucosa by NaCl, a stomach tumor promoter. Carcinogenesis, 17(3), pp.401-406
- Jones-Burton, C., Mishra, S.I., Fink, J.C., Brown, J., Gossa, W., Bakris, G.L. and Weir, M.R., 2006. An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. *American journal of nephrology*, *26*(3), pp.268-275.
- McMahon, E.J., Campbell, K.L., Bauer, J.D. and Mudge, D.W., 2015. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database of Systematic Reviews, (2)
- Takahashi, M. and Hasegawa, R., 1985. Enhancing effects of dietary salt on both initiation and promotion stages of rat gastric carcinogenesis. In Princess Takamatsu Symposia (Vol. 16, pp. 169-182)
- Tatematsu, M., Takahashi, M., Fukushima, S., Hananouchi, M. and Shirai, T., 1975. Effects in rats of sodium chloride on experimental gastric cancers induced by N-methyl-N'-nitro-N-nitrosoguanidine or 4-nitroquinoline-1-oxide. Journal of the National Cancer Institute, 55(1), pp.101-106
- Ritz, E., Koleganova, N. and Piecha, G., 2009. Role of sodium intake in the progression of chronic kidney disease. Journal of Renal Nutrition, 19(1), pp.61-62

Lines 1493 – 1511 state:
"*Eligible study design included randomised controlled parallel (RCTs) or crossover trials (with a wash-out period of any duration) and prospective studies including cohort studies, nested case–control and case–cohort studies. Trials were eligible if the intervention consisted in a change in sodium intake compared with usual diet or placebo. In relation to blood pressure and CVD-related outcomes, trials with concomitant interventions deemed to affect the outcome of interest were excluded. For bone-related outcomes, trials in which the same concomitant intervention was applied to all study groups were included. On study duration, trials on blood pressure with a minimum duration of 4 weeks and trials on CVD outcomes with a minimum duration of 6 months were eligible. Trials on BMD or risk of osteoporotic fractures in adults had to last at least 1 year. On subject characteristics, eligible studies involved adults (≥ 18 years) and children (6 months to < 18 years) from the general population. Trials including diseased individuals, individuals on a therapeutic diet (including weight loss diet), hypertensive subjects on blood pressure-lowering medications, trials in pregnant women and trials with specialised exercise (e.g. athletes, militaries) and extreme environmental conditions (e.g. prolonged exposure to unusually high temperature) were excluded. Observational studies that did not explicitly exclude prevalent (i.e. pre-existing) cases of the outcome of interest at baseline were excluded. Studies were eligible if sodium intake was assessed based on urinary sodium excretion calculated from single or multiple 24-h urine collection(s). Other types of sodium intake measurements were excluded."*

The inclusion criteria are too stringent and exclude many valuable studies. F**ew RCTs have been designed and conducted specifically to examine the effect of salt reduction on health outcomes as appropriately designed and powered trials would be too expensive and potentially unethical, given the totality of evidence demonstrating the benefits of salt reduction. There are also** multiple methodological challenges, such as compliance with a lower salt intake over several years or cross-contamination between low- and high-salt groups.

Population studies provide valuable knowledge that cannot be obtained with other research design. This is because estimating the average salt intake of a population is far less subject to error than estimating salt intake at the individual level (Cogswell, 2016), which may explain why population-based studies are able to show a fall in cardiovascular mortality following a population salt reduction, while cohort studies based on spot urines either fail to find any significant association or produce J-shaped associations (i.e. both higher and lower salt intake being associated with an increased cardiovascular risk). When reviewing the effect of sodium on health, the totality of the evidence should be considered. Three countries have implemented and evaluated successful salt reduction strategies, including the UK, Finland and Japan. With the current selection criteria, several studies that looked at the impact of population-level salt-reduction interventions in these countries were excluded from the systematic review.

An evaluation of the UK's salt reduction programme (He, 2014) found that between 2003 and 2011, average population salt intake fell by 1.4g per day. This was accompanied by a fall in average blood pressure in the adult population in England by 3/1.4 mm Hg. Over the same period, mortality for stroke and ischemic heart disease decreased by 42% and 40%, respectively. An estimated 30% of the reduction in stroke deaths and 20% of the reduction in ischaemic heart disease deaths were attributable to the salt reduction. Cost-effectiveness analyses by the UK National Institute for Health and Care Excellence showed concordant results, estimating that the salt reduction programme prevents around 9000 deaths from stroke and ischaemic heart disease per year in the UK, thus saving around £1.5 billion in annual healthcare costs (National Institute for Health and Care Excellence, 2010).

A similar study in Japan (Sasaki, 1979) showed that a 4g reduction in average daily salt intake (18g to 14g) led to a fall in blood pressure and a reduction in stroke mortality of 80%.

Studies in Finland found that a reduction in average population salt intake from 14g per day in 1972 to 9g per day in 2002 (Laatikainen, 2006) was accompanied by a 10 mmHg fall in blood pressure and a reduction in CVD mortality by 75-80% (Karppanen, 2006).

- Cogswell, M.E., Mugavero, K., Bowman, B.A., Frieden, T.R., 2016. Dietary sodium and cardiovascular disease risk – measurement matters. N. Engl. J. Med. 375, 580–586. https://doi.org/10.1056/NEJMsb1607161.
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- Karppanen H. and Mervaala E., 2006. Sodium intake and hypertension. Prog. Cardiovasc. Dis. 49, 59–75.
- Laatikainen T., Pietinen P., Valsta L., Sundvall J., Reinivuo H., Tuomilehto J., 2006. Sodium in the Finnish diet: 20-year trends in urinary sodium excretion among the adult population. Eur. J. Clin. Nutr., 60, 965-970.
- National Institute for Health and Care Excellence, 2010. Cardiovascular disease prevention. Available at: https://www.nice.org.uk/guidance/ph25, Accessed 20 May 2019.
- Sasaki N., 1979. The salt factor in apoplexy and hypertension: epidemiological studies in Japan. In: Yamori, Y. (Ed.), Prophylactic Approach to Hypertensive Diseases. Raven Press, New York, pp. 467–474.

Conclusions

We are concerned that the inclusion of the Prevention of Renal and Vascular Endstage Disease (PREVEND) study has introduced uncertainty to the formation of the DRVs, particularly in respect to the effect of salt intake on stroke. This study, despite having been judged by the Panel to be at low risk of bias (tier 1), has important limitations. First is the oversampling of participants with elevated albuminuria at baseline (> 10 mg/L) (Joosten, 2014; Kieneker, 2018). In addition, we have concern over the possibility of under-collection of 24h urine samples in this study, which could have led two problematic findings, i.e. the inverse association between salt and risk for stroke (Kieneker, 2018),

and the unchanged risk for coronary heart disease up to 120 mmol/24h for women and 150 mmol/24h for men (Joosten, 2014).

Despite their biological implausibility, these findings were included as part of the expert group consensus on the lowest level of sodium intake at which the risk of stroke and coronary heart disease is minimised in the general population. This resulted in consensus that the range of 80 to 120 mmol/24 of urinary sodium was the most likely range to include the 'true' level of interest. This range corresponds to a salt intake of 4.9 to 7.4 grams per day, if we consider that 93% of the sodium we consume is excreted via the urine.

We contest this decision. There is strong evidence for a linear dose-response relationship of salt with blood pressure (He 2002, 2003), and also with cardiovascular events (Cook, 2014) and mortality (He, 2018), within the range of 3 to 12 grams of salt per day.

We would also like to highlight that, while the panel members include notable experts in nutrition generally, there appears to be a lack of experts in blood pressure, cardiovascular health or renal health. Input from these experts would have been beneficial in the formation of these crucial guidelines.

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- He, F.J., Campbell, N.R., Ma, Y., MacGregor, G.A., Cogswell, M.E. and Cook, N.R., 2018. Errors in estimating usual sodium intake by the Kawasaki formula alter its relationship with mortality: implications for public health. International journal of epidemiology, 47(6), pp.1784-1795.
- He, F.J., MacGregor, G.A., 2002. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. J. Hum. Hypertens. 16, 761–770.
- He, F.J., MacGregor, G.A., 2003. How far should salt intake be reduced?. Hypertension 42, 1093–1099.
- Joosten MM, Gansevoort RT, Mukamal KJ, Lambers Heerspink HJ, Geleijnse JM, Feskens EJ, Navis G, Bakker SJ and Group PS, 2014. Sodium excretion and risk of developing coronary heart disease. Circulation, 129, 1121–1128.
- Kieneker LM, Eisenga MF, Gansevoort RT, de Boer RA, Navis G, Dullaart RPF, Joosten MM and Bakker SJL, 2018. Association of low urinary sodium excretion with increased risk of stroke. Mayo Clin Proceedings, 93, 1803–1809.

Data on which to base Dietary Reference Values

Integration of the evidence and conclusions

Lines 2115-2116 state:
"Therefore, the Panel considers that 2.0 g of sodium per day is a safe and adequate intake for the general EU population of adults."

We disagree with the designation of a salt intake of 5 grams per day as 'safe'. In view of the problematic PREVEND study and the irrelevance of the sodium balance studies available when it comes to public health recommendations, we strongly encourage EFSA to revise its DRV for sodium. If communicated to the public as a 'safe' intake, the public may perceive this as a 'target' intake which may derail further necessary salt reduction work. Most people do not know how much salt they are eating, as in European diets most salt comes from processed, packaged food rather than salt which is added by the individual to food. Crucially, in relation to blood pressure, most people do not know they have high blood pressure and so reducing salt intake will benefit those without diagnosed hypertension. The DRV should reflect this to help protect population health.

It should be noted that organisations including the World Health Organization, the US National Academies of Sciences, Engineering, and Medicine and the UK National Institute for Clinical Care Excellence recommend a salt intake of **less** than 5 grams of salt per day (less than 5g, 3.75 g and 3g per day, respectively) (World Health Organization, 2012; Stallings, 2019; NICE, 2010).

Furthermore, although we recognise that EFSA is consulting on sodium and chloride separately, in light of the lack of evidence available for chloride to form independent DRVs, we strongly advise that EFSA communicate its recommendations in terms of salt instead of sodium to avoid confusion in the public. The major source of sodium in the diet is from sodium chloride (i.e. salt) and the majority of European countries refer to dietary salt as opposed to dietary sodium. In practice, any recommendation for sodium reduction translates into salt reduction.

- National Institute for Health and Care Excellence, 2010. PH25: Cardiovascular Disease Prevention https://www.nice.org.uk/guidance/PH25
- Stallings, V.A., Harrison, M., Oria, M., Committee to Review the Dietary Reference Intakes for Sodium and Potassium, Food and Nutrition Board, Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine, 2019. Dietary Reference Intakes for Sodium and Potassium, The National Academies Collection: Reports funded by National Institutes of Health. National Academies Press (US), Washington (DC).
- World Health Organization, 2012. Guideline: sodium intake for adults and children. World Health Organization, Department of Nutrition for Health and Development.