



**FOOD** STANDARDS  
Australia New Zealand  
Te Mana Kounga Kai – Ahitereiria me Aotearoa

## **Systematic review of the evidence for a relationship between sodium and blood pressure**

**Prepared by: Food Standards Australia New Zealand**

**Review completed: August 2014**

# Executive Summary

<b><i>Does sodium / salt intake affect blood pressure?</i></b>	
<b>Food-health relationship</b>	Decreased sodium (or salt) intake reduces blood pressure
<b>Degree of certainty (GRADE rating)</b>	High ⊕⊕⊕⊕
<b>Component</b>	<b>Notes</b>
<b>Body of evidence</b>	A recent systematic review and meta-analysis of randomised controlled trials (RCTs) was updated. The findings are consistent with several recent systematic reviews with meta-analysis.
<b>Consistency</b>	The majority of RCTs, and the high quality RCTs, show decreased sodium intakes reduce blood pressure, irrespective of gender and ethnicity. The effect is present in both normotensive and hypertensive populations.
<b>Causality</b>	RCTs are a strong study design for causal evidence. In the He et al. 2013 systematic review, 32 of 34 trials found decreased sodium intake led to reduced blood pressure. The one new study identified in the FSANZ review also found the same effect and so strengthens the conclusion that there is a causal relationship between decreased sodium intake and reduced blood pressure.
<b>Plausibility</b>	The data from RCTs, in addition to laboratory evidence of effects on blood volume, the renin-angiotensin system and vasodilation, indicate a plausible relationship between sodium intake and blood pressure.
<b>Generalisability</b>	This relationship was assessed in 2005 as being applicable to Australia and New Zealand, and no evidence has emerged since then to challenge this conclusion.

In 2005 a health claims Scientific Advisory Group (SAG) established by FSANZ concluded the evidence was ‘convincing’ that decreased sodium (or salt) intake reduces blood pressure. The purpose of this review was to update the currency of scientific evidence underpinning this food-health relationship. To achieve this, FSANZ has critically appraised and updated a 2013 Cochrane review and meta-analysis on sodium/salt and blood pressure (He et al. 2013).

In performing this check for currency, FSANZ has followed the requirements for updates to existing systematic reviews, as set out in the *Application Handbook* and in Schedule 6 of Standard 1.2.7 – Nutrition, Health and Related Claims.

Thirty-four relevant RCTs were included in the He et al. (2013) review, with one additional study identified in the FSANZ update process. Results of the He et al. (2013) meta-analysis demonstrate decreased sodium intake reduced blood pressure in both normotensive and hypertensive populations. Sub-group analyses by ethnicity found the relationship was present in Caucasians and Asians as well as Africans. The additional study identified by FSANZ also showed a reduction in blood pressure with decreased sodium intake. The He et al. (2013) review concluded that there was ‘High’ quality evidence that decreased sodium intake leads to significant reductions in blood pressure. These conclusions are consistent with the 2005 SAG assessment of the relationship between sodium and blood pressure. FSANZ concludes that the new data do not change the high degree of certainty for the relationship.

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# 1 Introduction

In 2005 the FSANZ Scientific Advisory Group (SAG) for health claims agreed that the relationship between decreased sodium intake and reduced risk of high blood pressure was substantiated. To assist their considerations, a review of this relationship was prepared (subsequently released in a report by Samman, 2006<sup>1</sup>). FSANZ included the food-health relationship as a pre-approved high level health claim in Schedule 2 of Standard 1.2.7 – Nutrition, Health and Related Claims (See Table 1).

**Table 1** Pre-approved high level health claim for sodium or salt in Schedule 2 of Standard 1.2.7

Food or property of food	Specific health effect	Relevant population	Context claim statements	Conditions
Sodium or salt	Reduces blood pressure		Diet low in salt or sodium	The food must meet the conditions for making a nutrition content claim about low sodium or salt

The purpose of this paper is to evaluate the currency of evidence for the relationship between sodium or salt and blood pressure that underpins this high level health claim. This has been done by formally updating and critically appraising a recent, relevant systematic review (He et al. 2013).

## 1.1 Property of food – sodium or salt

Sodium is an electrolyte found in almost all foods. It has been estimated that only 10% of sodium intake in English subjects is derived from the sodium that occurs naturally in foods (James et al. 1987). Sodium chloride, also known as common salt or table salt (referred to in this document as salt), is an ionic compound with the chemical formula, NaCl. In water, NaCl dissociates to an equal number of sodium and chloride ions. Hence, based on the difference in molecular weight for sodium and chloride ions, salt contains approximately 390 mg of sodium per gram (or 17 mmol because 1 mmol sodium weighs 23 mg).

Processed foods may have high levels of salt, and sodium consumption in Australia and New Zealand may exceed the Upper Level of intake (2,300 mg/day for adults) recommended in the Nutrient Reference Values (<http://www.nrv.gov.au/nutrients/sodium.htm>). Data from the Australian Health Survey 2011-12 published by the Australian Bureau of Statistics (ABS) estimated the average sodium intake in Australians to be 2,400 mg/day (104 mmol/day). This estimate does not take account of discretionary salt added during home cooking or at the dining table. The average daily intake ranged from 1,400 to 3,100 mg in males and females >2 years of age (ABS 2014).

## 1.2 Health effect

Blood pressure is a measure of the force exerted on the vessel (typically artery) wall by blood as it is pumped around the body. It is measured in millimetres of mercury (mm Hg), and is usually reported as systolic blood pressure over diastolic blood pressure. Systolic blood pressure is the measure of force exerted on vessels immediately after the ventricles of the

<sup>1</sup> Report is available at <http://www.foodstandards.gov.au/consumer/labelling/nutrition/pages/reviewsforhighlevelc3090.aspx>

heart contract to eject blood from the heart, while diastolic blood pressure is the measure of force as the vessels relax while the heart refills with blood.

Blood pressure can be measured at rest or as ambulatory blood pressure. Measurement of ambulatory blood pressure involves a device that takes blood pressure measures repeatedly throughout a 24-hour period. Due to its more invasive nature it is less commonly measured than resting blood pressure. Both ambulatory and resting blood pressure measures are reliable and appropriate measures of blood pressure.

Elevated blood pressure is associated with increased risk of heart attack and stroke. As such, reductions in blood pressure or the maintenance of normal blood pressure (generally regarded to be <140/90 mm Hg<sup>2</sup>) are considered to be beneficial health effects. Specifically, sustained reductions in blood pressure are considered to be the beneficial health effect, rather than acute or transient effects that may occur with short-term interventions.

### **1.3 Proposed relationship**

The food-health relationship under review is the relationship that is currently included in Schedule 2 of Standard 1.2.7 – that foods carrying a claim about reducing blood pressure are required to meet the conditions for making a nutrition content claim about low sodium or salt.

## **2 Summary and critical appraisal of existing systematic review**

Searching for recent systematic reviews on this relationship identified four relevant reviews. The most recent was a Cochrane review published in 2013 by He et al. In 2012/13 the World Health Organization (WHO) published a systematic review in two forms to support the guidelines developed for sodium intake (Aburto et al. 2013; World Health Organization 2012). Two additional Cochrane reviews published between 2009 and 2011 were identified. The 2009 review focussed on trials of 6 months or longer duration, with the primary outcomes of mortality and morbidity, with blood pressure investigated as a secondary outcome (Hooper et al. 2009). The 2011 Cochrane review used broader eligibility criteria with no restriction on trial duration (Graudal et al. 2011).

The WHO (2012) and He et al. (2013) reviews were most relevant to FSANZ as they specifically addressed the food-health relationship under review. Both reviews had similar inclusion and exclusion criteria, although the review by He et al. (2013) excluded trials in subjects with diseases such as diabetes and also trials that had used concomitant interventions. As the He et al. (2013) review literature searches were performed more recently it was selected to be formally updated in this report. However, consideration has been given to the conclusions of all four systematic reviews in FSANZ's assessment.

### **2.1 Methods used in the existing review**

The property of food (salt), the health effect (blood pressure measured in mm Hg using a sphygmomanometer) and the direction of effect investigated in the He et al. (2013) review are identical to those that FSANZ has specified above. Furthermore, we assumed that the property of the food was sodium because all the included studies measured urinary sodium. The diets were described as reduced salt intake, however, it is possible that other sources of

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<sup>2</sup> Australian Heart Foundation blood pressure classifications: normal <120/80 mm Hg, high-normal 120-139/80-89, hypertensive >140/90

sodium (e.g. sodium bicarbonate) were also restricted. However, given the predominance of salt as a source of sodium in the Western diet, trials achieving the level of sodium reduction described would have been predominantly achieved through reductions in sodium chloride (salt) intake.

He et al. originally published a systematic review assessing the effects of longer-term reductions in sodium intake<sup>3</sup> of 40-120 mmol/day on blood pressure in 2002, with a subsequent Cochrane review in 2004. This review was updated in 2005, 2006 and 2013, without substantial change to the conclusions of the review. The authors defined longer-term studies as those lasting 4 weeks or longer. Exclusion of studies with durations of less than 4 weeks is appropriate as this excludes acute effects of changes in sodium intake. Similarly, exclusion of studies which achieved reductions in sodium intake of more than 120 mmol/day is reasonable, and for FSANZ's purpose makes the review relevant to Australian and New Zealand populations as larger reductions would be difficult to achieve (see section 2.3).

The search strategy used by He et al. (2013) is detailed in Appendix 1. Searches were performed in the following databases from their commencement until the search dates, which were in December 2012:

- Ovid Medline
- Ovid EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Hypertension Group Special Register.

The basis for study selection, summarised under the PICOT headings, is in Table 2. For inclusion, studies must have had random allocation to control or experimental groups, with no concomitant interventions in either group. Included studies were performed in normotensive or hypertensive adults (including studies of essential hypertension) without other disease. Measures of 24-hour urinary sodium excretion were required, and the achieved reduction in sodium excretion in the intervention groups needed to be between 40-120 mmol sodium/day.<sup>4</sup> Measures of ambulatory or resting blood pressure were not distinguished.

**Table 2** PICOTS criteria for study selection in He et al. 2013 review

<b>Population</b>	Adults (≥18 years) With or without hypertension; if hypertensive, without medication Without other diseases (eg diabetes, heart failure)
<b>Intervention</b>	Reduced salt intake Reduction in sodium intake, measured as urinary sodium excretion of 40-120 mmol/day
<b>Comparator</b>	Usual salt intake measured by 24hr sodium excretion In blinded studies usual sodium intake was maintained through slow-release sodium tablets combined with reduced sodium diet
<b>Outcome</b>	Blood pressure (systolic, diastolic or both).
<b>Time</b>	≥4 weeks

Following selection of included studies, data were extracted by two of the review authors using a standard form. A random-effects meta-analysis with sub-group analyses, as well as meta-regression analyses, were performed using Review Manager 5.2 software and the Statistical Package for the Social Sciences (SPSS). Sub-groups for analysis were determined *a priori* and included:

<sup>3</sup> Sodium intake was measured as 24-hour urinary sodium excretion, which captures 85-90% of sodium intake. In this document values for sodium intake are taken from unadjusted measures of 24-hour urinary sodium excretion.

<sup>4</sup> 40-120 mmol sodium is approximately equivalent to 900-2,800 mg sodium, or 2,300-7,000 mg salt.

- blood pressure status
- ethnicity
- gender.

Risk of bias was assessed based on the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions 5.0.2* (The Cochrane Collaboration, 2009). The authors described their view of the quality of the body of evidence using the GRADE methodology (Guyatt *et al.*, 2008).

## 2.2 Summary of results

The search strategy identified 3,252 potentially relevant publications. Of these, 30 publications were included in the systematic review. Four of these publications included separate populations of normotensive and hypertensive individuals. These four publications were each counted as two separate trials, leading to 34 trials being included in the meta-analysis.

The main findings of the He *et al.* (2013) systematic review were that decreased salt intake/urinary sodium excretion was associated with decreased systolic and diastolic blood pressure in both normotensive and hypertensive populations. The meta-analysis results are presented in Table 3.

**Table 3** Main findings of He *et al.* (2013) systematic review and meta-analysis

Outcome		No. of studies (participants)	Mean difference mm Hg (95% CI)	GRADE rating	Comments
<b>Systolic blood pressure</b>		<b>33 (3206)</b>	<b>-4.18 [-5.18, -3.18]</b>	<b>High</b>	Mean reduction in salt intake equivalent to 4.4 g/day (1.7 g sodium/day)
BP Status	Normotensive	12 (2240)	-2.42 [-3.56, -1.29]	High	
	Hypertensive	21 (966)	-5.39 [-6.62, -4.15]	High	
<b>Diastolic blood pressure</b>		<b>34 (3230)</b>	<b>-2.06 [-2.67, -1.45]</b>	<b>High</b>	
BP Status	Normotensive	12 (2240)	-1.00 [-1.85, -0.15]	High	
	Hypertensive	22 (990)	-2.82 [-3.54, -2.11]	High	

CI: Confidence interval

The results of sub-group analyses also showed significant effects of reduced sodium intake on blood pressure in:

- normotensive men
- normotensive women
- hypertensive men
- hypertensive women
- normotensive Caucasians
- normotensive Africans
- hypertensive Caucasians
- hypertensive Asians (predominantly Indian)
- hypertensive Africans.

Effect estimates for systolic blood pressure ranged from -2.1 to -7.8 mm Hg, while effect estimates for diastolic blood pressure ranged from -0.9 to -4.1 mm Hg. All results were statistically significant, except for the change in diastolic blood pressure in the normotensive Africans sub-group. In this group, the change in 24-hour urinary sodium was not significant.

Meta-regression was used to explore sources of heterogeneity, as well as to determine whether a dose-response existed between the extent of sodium reduction and blood pressure change. Meta-regression results were reported in the text. The results indicated that age, ethnicity and extent of sodium reduction explained 51% of the heterogeneity between studies for systolic blood pressure. The linear meta-regression yielded a dose-response, with a 100 mmol reduction in 24-hour urinary sodium excretion associated with a reduction of 4.3 mm Hg (95% CI; 0.1, 8.5) in systolic blood pressure.

## **2.3 Critical appraisal of the existing review**

The primary objective of the systematic review was to *determine the effect of longer-term modest reductions in salt intake on blood pressure in hypertensive and normotensive individuals*. The authors defined modest salt reduction as a decrease of 2.3 to 7.0 g/day (40-120 mmol sodium). These reductions may be considered modest compared to some reductions of much greater magnitude. However, substantial dietary modification would be required for individuals to achieve the upper end of the reductions in daily sodium (as salt) intake in the Australian and New Zealand diet. Therefore the exclusion of studies testing larger sodium reductions is appropriate for investigating a relationship that is applicable in Australia and New Zealand.

### **2.3.1 Study identification and selection**

The search strategy, selection criteria and method of study selection were appropriate for identifying studies useful in answering the research question. Searches of grey literature were not detailed, but funnel plot analyses indicated a low risk of publication bias. Given the large number of included studies and the consistency of results, it is unlikely that there would be sufficient unpublished data to alter the outcomes of the meta-analysis.

FSANZ cross-checked included studies with another recent systematic review (World Health Organization 2012). The WHO systematic review (World Health Organization, 2012) included more studies (36 compared to 33 in the He et al. (2013) review). Twenty-nine of these studies were included in both reviews. However, He et al. (2013) excluded studies in subjects with other diseases, such as diabetes, or with a concomitant intervention, whereas the WHO did not. Two recent studies were not in the He et al. (2013) table of excluded studies. This may be due to their publication during the review update period. Neither of these studies met the inclusion criteria for the He et al. (2013) review as they involved subjects with other diseases or concomitant interventions.

### **2.3.2 Assessment of bias**

The risk of bias for each included study was assessed by He et al. (2013). The majority of studies had a low risk of selection, attrition and reporting bias. In all but one small study the outcome assessor was blinded to the intervention, or the blood pressure device was automated. However, in 25% of included studies the investigator was not blinded, and in approximately 35% of studies the participants were not blinded to the intervention. The limitations of this were acknowledged by the review authors. It should be noted that in 24 of the included studies all subjects followed a low sodium diet, with different sodium intakes achieved through randomisation to either placebo or slow-release sodium chloride tablets.

Publication bias was assessed by funnel plot, with asymmetry evident for studies of systolic blood pressure. This was attributed to the inclusion of large trials which achieved reductions in sodium intake at the lower end of the required range. It is unclear whether the authors searched for unpublished studies. However, given the strength of the relationship and number of included studies, there would need to be a large number of unpublished studies of

similar size with either no effect or a negative effect for the conclusions of the review to be altered.

### **2.3.3 Data extraction and analysis**

Data extraction processes and statistical analyses were appropriate. A treatment effect was calculated for each trial. The difference in blood pressure between intervention arms was used for parallel studies. For cross-over studies the difference in blood pressure between the ends of each intervention phase was used. Sub-groups for meta-analysis were pre-specified. Meta-regression was performed to determine sources of heterogeneity, as well as to identify any dose-response relationships.

To assess accuracy of data extraction, reported data were cross-checked with another recent systematic review and meta-analysis (World Health Organization, 2012). Despite an apparently large difference in the number of participants included in the WHO and He et al. (2013) meta-analyses, this discrepancy is methodological as the WHO reports subjects participating in cross-over studies twice. The majority of values for change in systolic blood pressure in the He et al. (2013) meta-analysis match the mean differences in the WHO report. Some discrepancies arose due to methodological differences, for example splitting trials on blood pressure status or gender (for example Cappuccio et al. 1997 and Nestel et al. 1993), or inclusion of unpublished data by He et al. (2013) (for example Swift et al. 2005). For one study there was a large discrepancy in the extracted data in the two reviews (Silman et al. 1983). The difference arose as the WHO compared end of trial measures between the control and intervention group, whereas He et al. (2013) calculated the difference in the change in blood pressure between baseline and end of the trial between the control and intervention arm. Both methods are valid, and in the He et al. (2013) meta-analysis this approach has been consistently applied. Therefore, this apparent discrepancy does not raise concern for the methodology of either review.

The main findings of the He et al (2013) meta-analysis show a clear relationship between decreased sodium intake and reduced blood pressure in both normotensive and hypertensive populations (see Table 3). The relationship remained after subgroup analyses of gender and ethnicity. These results were consistent with the WHO systematic review and meta-analysis, despite the WHO review having wider inclusion criteria. Ethnicity was not assessed in the sub-group analyses performed by the WHO.

As discussed in Section 2.3.2, participants in 35% of trials were not blinded to the intervention. It is possible that this may affect trial outcomes and blinded trials are generally considered to be of higher quality than those that are not blinded. The reason why some trials could be blinded was that all subjects were given a low sodium diet and were randomised to salt or placebo. The un-blinded studies compared usual and low sodium diets and may have differed on more components than sodium. Therefore, FSANZ performed an analysis using StatsDirect statistical software (England: StatsDirect Ltd. 2008) to determine if there was a difference in treatment effect between blinded and non-blinded studies. As detailed in Table 4, these analyses demonstrate that the effect estimates were similar between trials that were blinded and those that were not. This analysis also provides further evidence that it is the reduction in sodium intake, and not other dietary changes that occur when consuming a low sodium diet, that are responsible for the reductions in blood pressure.

**Table 4** FSANZ's sub-group analysis based on blinding of participants included in He et al. (2013)

Systolic blood pressure	N Studies* (N participants)	Mean Difference (mmHg)	Lower 95% CI	Upper 95% CI	p-value
All trials	33 (3206)	-4.18	-5.18	-3.18	p<0.0001
Blinded trials	24 (923)	-4.26	-5.42	-3.10	p<0.0001
Not-blinded trials	11 (2283)	-3.92	-5.96	-1.89	p=0.0002

CI Confidence interval

\*Number of blinded and non-blinded trials does not add up to the total number of trials as two trials were split into separate trials on hypertensive status in the He et al. (2013) review

### 2.3.4 Interpretation

He et al. (2013) used the GRADE system to rate the quality of the evidence. In the summary of findings table, the relationship was rated as being supported by 'High' quality evidence for both systolic and diastolic blood pressure. The 'High' rating was given for all trials together, as well as to trials in normotensive and hypertensive populations.

In the systematic review, there is no discussion of how the rating was decided. In the GRADE system, 'High' is the starting point for systematic reviews of RCTs. The use of this rating indicates that the authors did not consider there was significant:

- risk of bias
- inconsistency between studies
- indirectness
- imprecision
- publication bias.

## 2.4 Comments on validity and strength of evidence

Overall, the He et al. (2013) systematic review and meta-analysis is of high quality. It concludes that there is 'High' quality evidence supporting the food-health relationship that decreased sodium intake reduces blood pressure. These conclusions are consistent with three other recent systematic reviews of sodium and blood pressure (Graudal et al. 2011; Hooper et al. 2009; World Health Organization 2012). In addition, FSANZ's sub-group analysis based on blinding of studies demonstrates that the risk of performance bias did not have a major impact on effect estimates. Together, these systematic reviews suggest that critical trials have not been overlooked and provide a high quality evidence base.

## 3 Evaluation of new evidence

In this section the He et al. (2013) review is updated to determine whether any new studies meeting the eligibility criteria will alter the conclusions of the review.

### 3.1 Methods

#### 3.1.1 Search strategy

Searches were performed in PubMed and Cochrane Central Register of Controlled Trials using the search terms used by He et al. (2013) (see Appendix 1). PubMed searches the Medline database and contains more recent publications than Medline and EMBASE. For

this reason the updated searches did not include an update to the EMBASE search. Reference lists of articles screened at full-text were scanned for relevant publications.

### **3.1.2 Inclusion and exclusion criteria**

The inclusion and exclusion criteria used by He et al. (2013) were applied (see Section 2.1), as they were relevant to assessing the food-health relationship.

### **3.1.3 Databases searched**

He et al. (2013) last updated their literature searches on 11/12/2012. PubMed was searched from 11/12/2012, while Cochrane CENTRAL was searched for all of 2012 and 2013, as searches cannot be restricted to specific dates in this database. Searches were conducted in:

- PubMed (22/8/13, 28 hits)
- Cochrane (21/8/13, 30 hits).

### **3.1.4 Unpublished material**

He et al. (2013) did not search for ongoing trials. For completeness, FSANZ searched the WHO International Clinical Trials Registry Platform (ICTRP) and PROSPERO for trials or reviews which may have been completed during 2013. The search terms used were: (blood pressure AND sodium) OR (blood pressure AND salt) OR (hypertension AND sodium) OR (hypertension AND salt).

### **3.1.5 Study selection, data extraction and analysis**

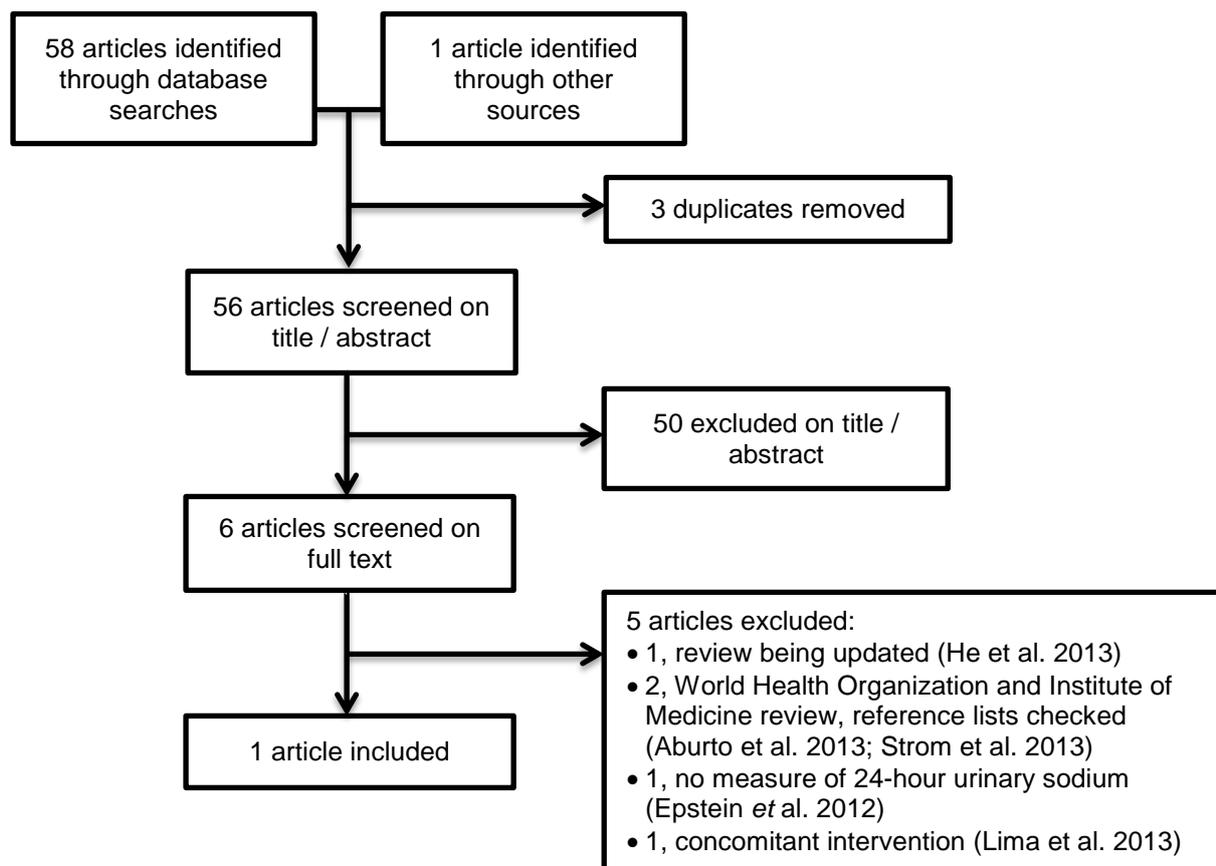
Records identified by the search strategy were imported into EPPI-Reviewer 4 (<http://eppi.ioe.ac.uk/cms/er4>). Following removal of duplicates, records were screened on title and abstract. Candidate full-text articles were retrieved and assessed against the selection criteria. Data were extracted using a standard form. Screening and data extraction was conducted by one investigator; data extraction was checked by a second person.

## **3.2 Results**

### **3.2.1 Search results**

The update to the search strategy yielded 58 records, with a further record identified through other sources. The screening of these results is detailed in Figure 1. Six articles were screened on full text, with only one study meeting the inclusion criteria. Scanning reference lists of these six studies did not yield any additional records for inclusion.

Searching the ICTRP identified four potentially relevant ongoing trials in hypertensive populations. The trials are being conducted in Australia, Korea, the Netherlands and Brazil. Given the consistency of results from other trials in hypertensive populations it is unlikely that the results of these trials would alter the conclusions of the He et al. (2013) review, even if the results were contradictory with earlier trials.



**Figure 1** PRISMA diagram for selection of studies in FSANZ update of the He et al. (2013) review

### 3.2.2 Included studies

One publication was identified as meeting the eligibility criteria (Jablonski et al. 2013). Briefly, the included trial was a randomised, placebo-controlled, double-blind cross-over trial conducted over 10 weeks. In both arms of the intervention dietary sodium intake was reduced, with participants then given either placebo to maintain low sodium intake, or NaCl supplementation to return dietary sodium intake to baseline levels.

### 3.2.3 Extracted data

Data were extracted by one investigator and are summarised in Table 5.

**Table 5** Jablonski et al. (2013) study details

<b>Reference</b>	Jablonski et al. 2013
<b>Study design</b>	Randomised, placebo-controlled, double-blind cross-over trial.
<b>Objectives</b>	The study sought to determine the effects of dietary sodium restriction on vascular endothelial dysfunction
<b>Sample size</b>	20 subjects enrolled, 3 withdrew, leaving 17 participants. Power calculations performed for flow mediated dilation outcome.
<b>Participants</b>	Adults (51-77 years old) with high normal blood pressure or stage I hypertension (systolic blood pressure of 130-159 mmHg, and diastolic blood pressure of <99 mm Hg).
<b>Interventions</b>	All subjects consumed a low sodium diet, and were given either a placebo or 100 mmol/day sodium as slow-release NaCl tablets for 5 weeks each
<b>Methods</b>	Sodium reduction achieved through dietary counselling. Resting systolic and diastolic blood pressure measured. 24-hour urinary sodium measured.

<b>Confounders</b>	Controlled by cross-over design and restriction of both intervention and control subjects to the same diet
<b>Results</b>	Urinary sodium excretion (mmol/day): 153±27 (baseline), 151±37 (NaCl supplement) and 70±30 (sodium restricted). Systolic BP (mm Hg): 138±7 (baseline), 140±15 (NaCl supplement) and 128±10 (sodium restricted) Diastolic BP (mm Hg): 83±7 (baseline), 82±6 (NaCl supplement) and 79±6 /day (sodium restricted)
<b>Notes</b>	Reduced sodium intake improved endothelial function

### 3.2.4 Quality assessment (individual studies)

Jablonski et al. performed this trial to test the hypothesis that *dietary sodium restriction improves vascular endothelial dysfunction in middle-aged/older adults with moderately elevated systolic blood pressure by increasing nitric oxide and tetrahydrobiopterin bioavailability and reducing oxidative stress* (Jablonski et al. 2013). Resting blood pressure was also measured in the study subjects.

The risk of bias assessment is summarised in Table 6, with no risk of bias identified. The cross-over design minimised the effect of confounding. Subjects with high-normal blood pressure or stage I hypertension were selected as they are more likely to be salt-sensitive. While this does not introduce bias due to the study design, it may limit the generalisability of the results to the general population.

Power calculations were performed based on changes expected in flow-mediated dilation of the brachial artery. The number of subjects was approximately 3-times larger than that indicated by the power calculations, demonstrating that the study was adequately powered for this outcome.

### 3.2.5 Outcome data

Dietary sodium intake was significantly reduced by participants during both arms of the intervention, indicating compliance with the low sodium diet. Twenty-four-hour urinary sodium excretion remained relatively unchanged throughout the sodium chloride treatment (151±37 mmol/day), but was significantly reduced during the 5-week dietary sodium restriction-placebo intervention (70 ± 30 mmol/day). Dietary potassium intake and 24-hour urinary potassium excretion did not change throughout the 10-week intervention.

**Table 6** Risk of bias assessment in Jablonski et al. (2013)

Bias	Authors' judgement	Support for judgement
<b>Random sequence generation (selection bias)</b>	Unclear risk	Method for randomisation refers to methods of an earlier study (Cappuccio et al. 1997) which involved random-generated numbers
<b>Allocation concealment (selection bias)</b>	Unclear risk	As above, in Cappuccio's study randomisation and allocation was performed by researchers not involved in clinical assessments
<b>Blinding of participants and personnel (performance bias)</b>	Low risk	Participants and providers blinded
<b>Blinding of outcome assessment (detection bias)</b>	Low risk	Outcome assessors blinded
<b>Incomplete outcome data (attrition bias)</b>	Low risk	3 participants withdrew before first set of vascular measures
<b>Selective reporting (reporting bias)</b>	Low risk	Outcomes reported

Systolic blood pressure was on average 12 mm Hg lower after five weeks of low compared to normal sodium intake ( $p < 0.01$ ). Diastolic blood pressure was 3 mm Hg lower, but this change

was not significant. There was no significant difference in blood pressure between baseline and normal sodium intake achieved by reduced dietary sodium with NaCl supplementation.

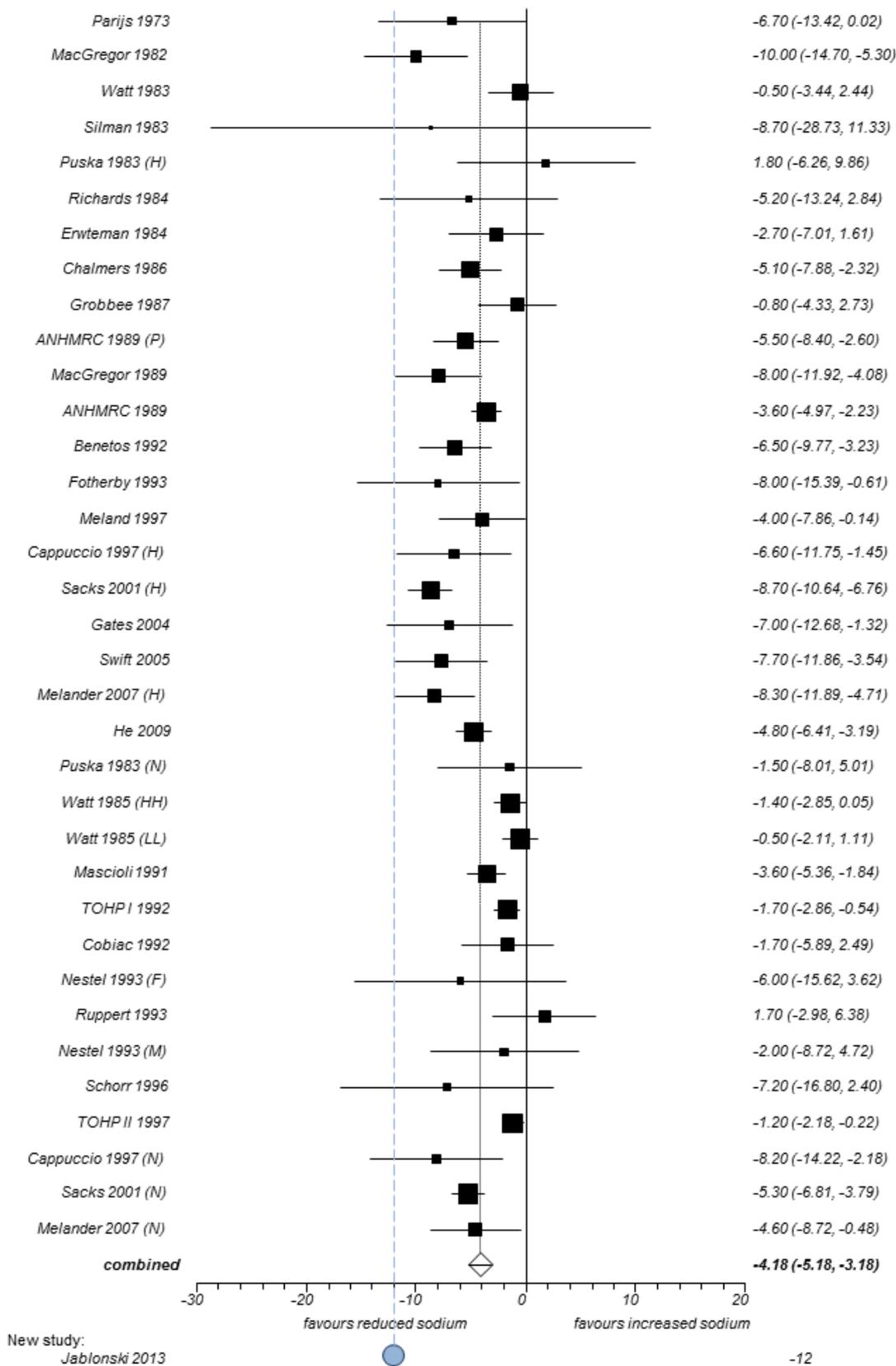
As the results of the one new study were more extreme than the overall meta-analysis result from He et al. (2013), the size of the overall effect would increase if it were added to the previous result. Therefore, the meta-analysis was not recalculated. Rather the results of the new study were plotted on the forest plot from the He et al. (2013) review (see Figure 2). Figure 3 shows the difference in urinary sodium excretion versus the difference in blood pressure for all trials including the new study.

Blood lipids, fasting glucose and circulating humoral factors were not significantly different following low and normal sodium intake. Flow-mediated dilation of the brachial artery was significantly increased by reduced sodium intake.

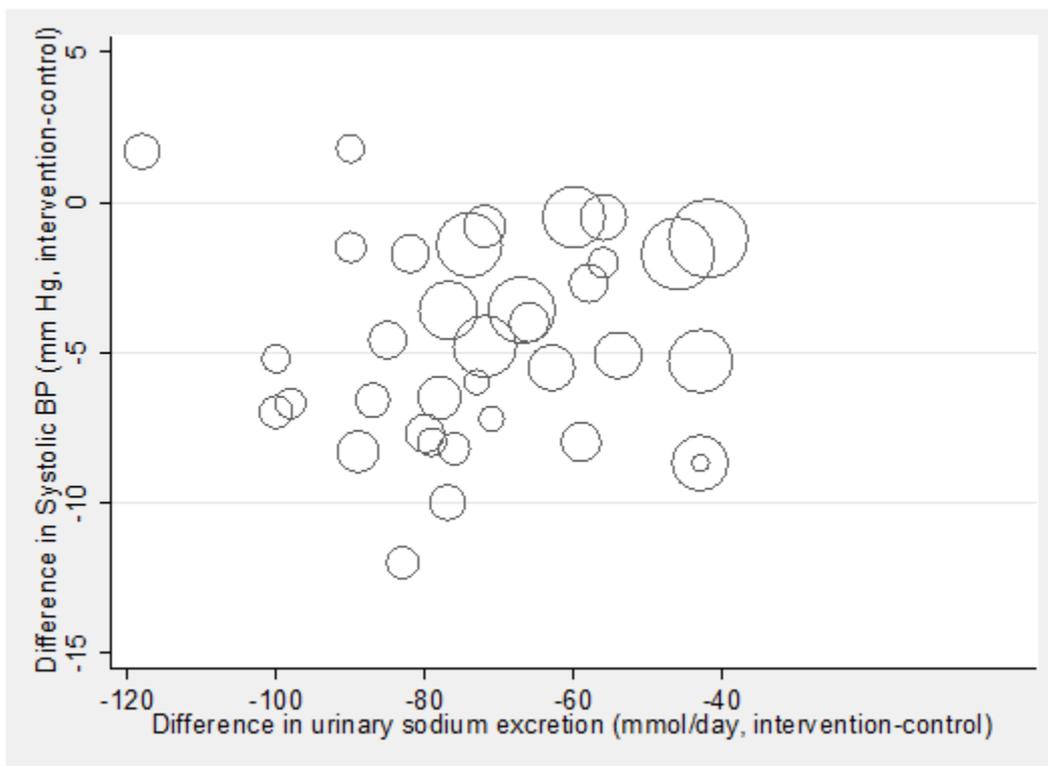
### **3.3 Summary of new evidence**

Fifty-nine potentially relevant articles were identified, of which one met the inclusion criteria. The Jablonski et al. trial of high-normal or early hypertensive subjects found a 12 mm Hg decrease in systolic blood pressure following dietary sodium restriction from 3,100 mg/day to 1,300 mg/day (equivalent to 7,900 mg/day and 3,300 mg/day salt respectively). The magnitude of the effect was greater than that estimated by the He et al. (2013) meta-analysis overall, or any specific study in the meta-analysis, but the direction was consistent and fell within the 95% CI for a number of the other trials (see Figure 2). This greater magnitude may be due to the selection of hypertensive participants who are more likely to be salt-sensitive. The inclusion of this study provides further evidence substantiating the relationship between sodium intake and blood pressure.

**Systolic blood pressure, all studies. Summary meta-analysis plot [random effects]**



**Figure 2** Overlay of Jablonski et al. (2013) results on forest plot from He et al. (2013) meta-analysis



**Figure 3** Scatterplot of the difference in systolic blood pressure versus the difference in urinary sodium excretion in the between the trial arms

(Negative values indicate that the intervention group had lower blood pressure or sodium excretion. The size of the circle for each study is related to the inverse of the variance used in weighting the meta-analysis)

As the new study tested a hypertensive population, it does not alter the effect reported by He et al. (2013) in the normotensive subgroup (see Table 3).

## 4 Weight of evidence

The food-health relationship between sodium and/or salt and blood pressure was included in Standard 1.2.7 when it was gazetted in 2013. As such, consideration has already been given to the plausibility of the relationship and applicability to the Australian and New Zealand context. The purpose of this report was to systematically review the scientific literature to determine whether recent studies will alter the conclusions made by the SAG in 2005.

### 4.1 Assessment of body of evidence

#### 4.1.1 Consistency and causality

Following the 2005 SAG review, two recent systematic reviews with meta-analyses have concluded that there is 'High' quality evidence supporting the relationship between decreased sodium intake and reduced blood pressure (using GRADE) (He et al. 2013; World Health Organization 2012). The relationship was found in studies of normotensive as well as hypertensive subjects. In two other systematic reviews the authors also concluded that reduced sodium intake decreased blood pressure (Graudal et al. 2011; Hooper et al. 2009). These four systematic reviews have reached consistent conclusions despite differences in eligibility criteria, for example exclusion of diabetic subjects or concomitant interventions, or different minimum trial durations. In this report, one study was identified for inclusion in the

update of the He et al. (2013) systematic review. The results of this study were consistent with the conclusions of He et al. (2013).

The systematic reviews included RCTs, which are a strong study design for detecting causal relationships. Therefore, these systematic reviews demonstrate a causal relationship between reducing sodium intake and decreasing blood pressure, which is consistent across high quality studies. In particular, the blinded studies provided the highest quality evidence for the causal relationship between sodium and blood pressure.

#### **4.1.2 Plausibility**

The weight of evidence from RCTs demonstrates that decreasing sodium and/or salt intake plausibly reduces blood pressure. Furthermore, the FSANZ sub-group analysis of trials in which the same low-salt diet was consumed with or without sodium chloride tablets demonstrates that it is the sodium that is responsible for the reduction in blood pressure associated with salt-restricted diets. In addition, experimental data demonstrate the effects of sodium on blood pressure include:

- changes in blood volume
- changes in the renin-angiotensin system
- changes in nitric oxide which affects vasodilation (reviewed in Meneton et al. 2005).

However, it should be noted that while some pathways of blood pressure regulation, and some individuals, are sensitive to salt/sodium, others are not (Meneton et al. 2005).

## **4.2 Applicability to Australia and New Zealand**

In 2005, the report commissioned by FSANZ<sup>5</sup> concluded that the relationship between sodium and blood pressure was both applicable and relevant to the Australian and New Zealand populations. Africans have a high incidence of salt-sensitive hypertension compared to other ethnicities and this has the potential to reduce the applicability of some studies to Australia and New Zealand. However, two of the identified systematic reviews assessed the relationship in ethnic subgroups. Both found the significant effect of salt restriction was present in studies of Caucasians and Asians (Graudal et al. 2011; He et al. 2013).

Therefore, the conclusions made by Samman (2006) are unchanged by this update to the review of scientific evidence. Moreover, the new study provides further weight to the evidence that the effect of reduced sodium intake on blood pressure is relevant to the Australian and New Zealand populations.

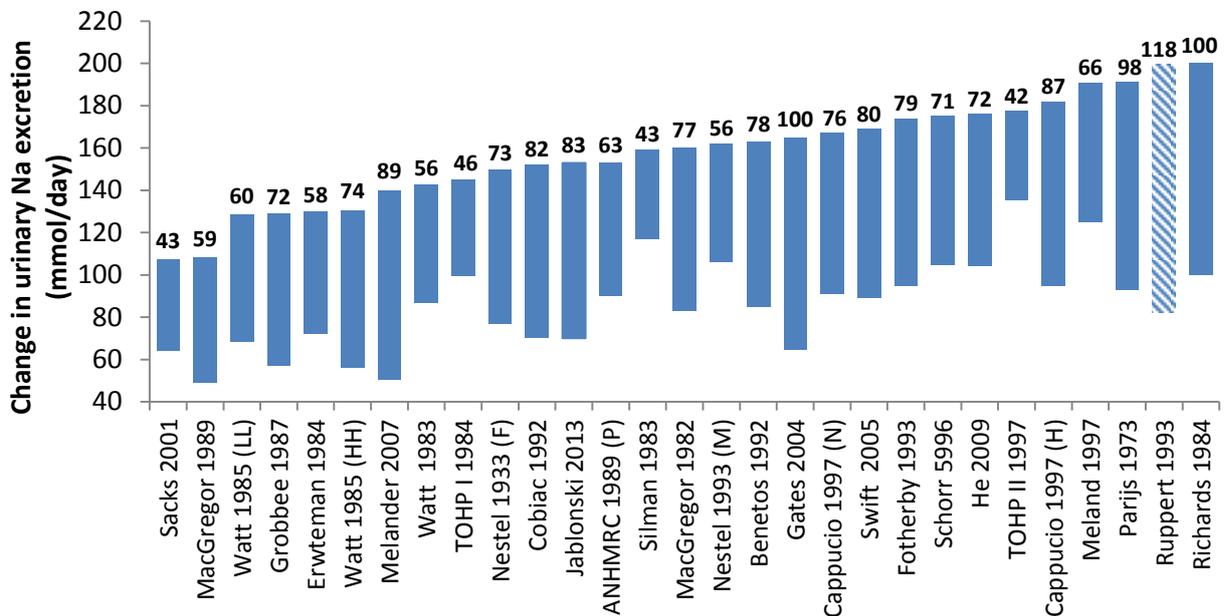
### **4.2.1 Sodium or salt intake reduction required for effect**

The studies included by He et al. (2013) achieved a mean reduction of 75 mmol/day urinary sodium excretion, and ranged from 42-118 mmol/day (970-2,700 mg/day). As illustrated in Figure 4, the included studies spanned a range of baseline or 'usual' sodium intakes that are consistent with current intakes in Australia and New Zealand (see Section 1.1), with reductions of variable magnitude achieved between studies. It is therefore important to note that the dose-response reported for a decrease of 100 mmol sodium intake per day by He et al. (2013) is an arbitrary unit of expressing the effect of sodium reduction from the meta-regression, and does not indicate that a minimum reduction of 100 mmol per day is required to achieve a beneficial effect on blood pressure outcomes. For studies that achieved similar

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<sup>5</sup> Report is available at <http://www.foodstandards.gov.au/consumer/labelling/nutrition/pages/reviewsforhighlevelc3090.aspx>

reductions in sodium intake, there was no evident pattern of baseline sodium intake on the magnitude of blood pressure outcomes achieved. Based on the available data it is evident that a 40 mmol (920 mg) reduction in sodium intake per day has beneficial effects on blood pressure outcomes, and that this reduction is achievable within the context of dietary intakes in Australia and New Zealand.



**Figure 4** Difference in baseline or ‘usual’ and end of intervention sodium intakes in trials of reduced sodium intake and blood pressure, ordered by increasing sodium intake in the control group (see He et al. (2013) for the reference list)

Quantification of the difference in sodium intake between control and intervention groups is reported above the bars. The hatched bar indicates the study that reported no reduction in blood pressure. Sodium data were generally reported for all arms in the trials together, hence Puska et al (1983) is shown as an overall reduction in blood pressure even though one arm in the trial had an increase (Figure 2)

It is possible that smaller reductions in sodium intake are also effective at reducing blood pressure. However, it is difficult to demonstrate small effects as large numbers of participants would be required. To see whether studies testing smaller differences were available, FSANZ retrieved the reports of trials excluded by He et al. (2013) and the WHO (2012) based on the achieved sodium reduction being less than 40 mmol/day urinary sodium excretion. In addition, FSANZ considered studies included in the Graudal et al. (2011) systematic review, but all included trials had a urinary sodium reduction of more than 40 mmol/day.

Seven trials were excluded from the He et al. (2013) systematic review on the basis of the achieved sodium reduction. Of these, three did not meet other inclusion criteria: one was not a trial (Logan, 1986), one did not measure blood pressure (Ireland et al. 2010), and the other only measured 8-hour urinary sodium excretion (Hypertension Prevention Trial Research Group 1990). In two of the other trials, there was no substantive reduction in urinary sodium excretion between the intervention and the control group (Alli et al. 1992; Cappuccio et al. 2006).

Two trials achieved reductions in urinary sodium excretion of less than 40 mmol/day (Morgan et al. 1978; Staessen et al. 1988). However, one was targeted at the population level, and individuals included in the baseline measures were excluded from the follow-up measurements (Staessen et al. 1988). Therefore, despite achieving an average decrease of 25 mmol urinary sodium excretion per day in women, this trial does not provide useful information on the effects of small decreases in sodium intake on blood pressure. The final trial supports an effect of small decreases in sodium intake being associated with reductions in blood pressure (Morgan et al. 1978). In this trial four groups of subjects with borderline hypertension were randomised to either no treatment, dietary sodium reduction or two drug treatments. Urinary sodium levels in the diet arm decreased by 38 mmol/day after 6 months, and remained at a similar level after this time. However, it should be noted that the collection of urinary sodium data was incomplete. Changes in standing blood pressure were approximately -8 and -10 mm Hg for systolic and diastolic blood pressure, respectively. In the control group there was no significant change in urinary sodium excretion or blood pressure. Due to the limitations in urinary sodium data collection caution is required in interpreting this data. However, the data suggest the relationship between sodium and blood pressure persists with smaller changes in sodium intake.

#### **4.2.2 Target population**

No specific target group was identified prior to the review. The results of the review do not suggest any restrictions on the relationship, beyond noting that only adults were included.

#### **4.2.3 Extrapolation from supplements**

The He et al. (2013) systematic review included trials of dietary intervention alone, or dietary intervention in all groups with sodium supplementation to 'usual' levels for the control group. Both types of trials achieved similar effects of blood pressure reduction. Furthermore, the supplement method trials provided a greater level of certainty that the change in sodium or salt intake was responsible for the reductions in blood pressure. Together, these high quality trials provide a strong body of evidence that decreases in dietary sodium or salt intake reduce blood pressure.

#### **4.2.4 Adverse effects**

The He et al. (2013) systematic review and meta-analysis considered whether longer-term reductions in salt intake might have adverse effects on specific biochemical parameters. No adverse effects were identified for the hormone or blood lipid levels examined. As only two of the trials were conducted for longer than 12 months, mortality and other disease outcomes could not be examined.

## **5 Conclusion**

In 2005 the SAG concluded that there was 'convincing' evidence (in the terminology of the time<sup>6</sup>) to support the food-health relationship that decreased sodium or salt intake reduces blood pressure. In 2013, He et al. updated their earlier systematic review and meta-analysis and concluded that reductions in salt intake for greater than 4 weeks cause significant

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<sup>6</sup> The definition of 'convincing' evidence: there are consistent associations between the diet, food or component and the health effect, with little or no evidence to the contrary. There should be a substantial number of human studies of acceptable quality, preferably including both observational and experimental studies and preferably conducted in different population groups. Any intake-response relationships should be supportive of a causal relationship and the relationship should be biologically plausible. Supporting evidence sources should be consistent with the findings of human evidence.

reductions in blood pressure, irrespective of blood pressure status, gender and ethnicity. The quality of evidence for these relationships was rated as 'High'. In the current report, the He et al. (2013) literature searches were updated to August 2013, and one new study was identified. The results of this study were consistent with the conclusions of He et al. (2013). It is therefore evident that the conclusions of the SAG have retained their currency, and that the food-health relationship between sodium or salt and blood pressure is substantiated in both normotensive and hypertensive populations with a 'High' degree of certainty.

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# Appendix 1 – Search terms

## 1. Search terms used by He et al. 2013.

### **MEDLINE search strategy**

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update

Search Date: 11 December 2012

1 sodium chloride, dietary/

2 exp sodium, dietary/

3 diet, sodium-restricted/

4 ((sodium or salt) adj3 (restrict\$ or curb\$ or limit\$ or minimi\$ or low\$ or reduc\$ or intake or diet\$ or free)).tw.

5 or/1-4

6 randomised controlled trial.pt.

7 controlled clinical trial.pt.

8 randomised.ab.

9 placebo.ab.

10 clinical trials as topic/

11 randomly.ab.

12 trial.ti.

13 or/6-12

14 animals/ not (humans/ and animals/)

15 13 not 14

16 5 and 15

### **EMBASE search strategy**

Database: Embase <1974 to 2012 Week 49>

Search Date: 11 December 2012

1 sodium chloride, dietary/

2 sodium intake/

3 sodium restriction/

4 ((sodium or salt) adj3 (restrict\$ or curb\$ or limit\$ or minimi\$ or low\$ or reduc\$ or intake or diet\$ or free)).tw.

5 or/1-4

6 randomised controlled trial/

7 crossover procedure/

8 double-blind procedure/

9 random\$.tw.

10 (crossover\$ or cross-over\$).tw.

11 placebo\$.tw.

12 (doubl\$ adj blind\$).tw.

13 assign\$.tw.

14 allocat\$.tw.

15 or/6-14

16 (animal\$ not (human\$ and animal\$)).mp.

17 15 not 16

18 5 and 17

### **CENTRAL search strategy**

Database: Cochrane Central Register of Controlled Trials on Wiley <Issue 11, 2012>

Search Date: 11 December 2012

#1 MeSH descriptor: [Sodium Chloride, Dietary] this term only

#2 MeSH descriptor: [Sodium, Dietary] explode all trees

#3 MeSH descriptor: [Diet, Sodium-Restricted] this term only

#4 sodium near/3 (restrict\* or curb\* or limit\* or minimi\* or low\* or reduc\* or intake or diet\* or free):ti,ab in Trials

#5 salt near/3 (restrict\* or curb\* or limit\* or minimi\* or low\* or reduc\* or intake or diet\* or free):ti,ab in Trials

#6 #1 or #2 or #3 or #4 or #5 in Trials

## 2. Search terms used by FSANZ

### PubMed

Searched 22/8/13

Date restriction applied: from 11/12/2012

((((((((((randomised controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR randomised[Title/Abstract]) OR placebo[Title/Abstract]) OR clinical trial as topic[MeSH Terms]) OR randomly[Title/Abstract]) OR trial[Title])) NOT ((animals[MeSH Terms]) NOT ("humans"[MeSH Terms]) AND "animals"[MeSH Terms]))) AND (((sodium chloride, dietary[MeSH Terms]) OR sodium, dietary[MeSH Terms]) OR diet, sodium restricted[MeSH Terms]) OR (((sodium OR salt) AND n3 AND (restrict\* OR curb\* OR limit\* OR low\* OR reduc\* OR intake OR diet\* OR free)) AND Text Word))

### Cochrane

Searched 21/8/13

ID Search

#1 MeSH descriptor: [Sodium Chloride, Dietary] this term only

#2 MeSH descriptor: [Sodium, Dietary] explode all trees

#3 MeSH descriptor: [Diet, Sodium-Restricted] this term only

#4 sodium near/3 (restrict\* or curb\* or limit\* or minimi\* or low\* or reduc\* or intake or diet\* or free)

#5 salt near/3 (restrict\* or curb\* or limit\* or minimi\* or low\* or reduc\* or intake or diet\* or free)

#6 #1 or #2 or #3 or #4 or #5 in Trials

#7 #6 from 2012 to 2013

## Appendix 2 – GRADE summary of findings table

GRADE summary of findings table of FSANZ's updated systematic review (adapted from He et al. 2013)

Question: What is the effect of decreased sodium or salt intake relative to higher sodium or salt intake on blood pressure in adults (≥18 years of age)?

Source: He et al. (2013) Cochrane review (note: additional reference identified in update not included in effect estimate)

Quality Assessment of body of evidence							Participants		Effect	Quality (degree of certainty in relationship)
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Considerations	Parallel studies	Cross- over studies	Mean difference mmHg (95% CI)	
<b>Systolic blood pressure - all</b>										
33	RCTs	No serious risk <sup>1</sup>	No serious inconsistency	None	None	None <sup>2</sup>	2287	919	-4.18 (-5.18, -3.18)	⊕⊕⊕⊕ High
<b>Systolic blood pressure – studies in normotensive participants</b>										
12	RCTs	No serious risk	No serious inconsistency	None	None	None	1931	309	-2.42 (-3.56, -1.29)	⊕⊕⊕⊕ High
<b>Systolic blood pressure – studies in hypertensive participants</b>										
21	RCTs	No serious risk <sup>1</sup>	No serious inconsistency	None	None	None <sup>2</sup>	356	610	-5.39 (-6.62, -4.15)	⊕⊕⊕⊕ High
<b>Diastolic blood pressure – all</b>										
34	RCTs	No serious risk <sup>1</sup>	No serious inconsistency	None	None	None <sup>3</sup>	2311	919	-2.06 (-2.67, -1.45)	⊕⊕⊕⊕ High
<b>Diastolic blood pressure – studies in normotensive participants</b>										
12	RCTs	No serious risk	No serious inconsistency	None	None	None	1955	309	-1.00 (-1.85, -0.15)	⊕⊕⊕⊕ High
<b>Diastolic blood pressure – studies in hypertensive participants</b>										
22	RCTs	No serious risk <sup>1</sup>	No serious inconsistency	None	None	None <sup>3</sup>	356	610	-2.82 (-3.54, -2.11)	⊕⊕⊕⊕ High

<sup>1</sup>Removal of one study with high risk of bias did not significantly alter the effect estimate

<sup>2</sup>Results from additional study identified in update were stronger than the overall effect estimate for systolic blood pressure and so the mean results from the original systematic review were not re-calculated to include the additional study

<sup>3</sup>Results from additional study identified in update were stronger than the overall direction of effect estimate for diastolic blood pressure, although results in individual study were not significant, and so the mean results from the original systematic review were not re-calculated to include the additional study