Sodium

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Related nutrients/biomarkers: potassium

Importance of sodium for health

Sodium is a nutrient essential for cellular homeostasis and regulation of fluid and electrolyte balance, and therefore blood pressure. Elevated sodium intakes are strongly linked to cardiovascular disease (CVD) and hypertension (1), which is a major risk factor for heart attacks and stroke. CVDs are the leading cause of death globally. WHO (https://www.who.int/elena/titles/sodium_cvd_adults/en/) estimated 17.6 million deaths were due to CVD in 2016, which is 32% of all deaths worldwide. The WHO Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013-2020 has identified, amongst other voluntary targets, a "30% relative reduction in mean population intake of salt/sodium" (2).

Dietary salt intakes can be monitored to assess the general population risk of CVD. Data can also be used to monitor trends in salt intake with time, for example, to assess the effectiveness of a public health intervention targeted at lowering salt intakes.

Deficiency of sodium occurs only in pathological conditions such as severe diarrhoea, uncontrollable vomiting and some kidney disease. It may be seen in relation to some tropical diseases such as cholera (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3761070/) (3). Under normal conditions, a deficiency in sodium is unlikely, due to the addition of salt (sodium chloride) to most pre-prepared foods, stocks, soups and bouillon cubes (4). The risk of excessive sodium intake is greater than the risk of a deficiency. An elevated sodium intake is a recognised causative factor in CVD and hypertension (1).

Human biomarkers of population sodium intake and status

Dietary sodium intake is cumulative. Sodium is naturally present in most foods in their native state, and salt is often added during processing, cooking including the use of flavour enhancers and condiments, and before eating. Some sodium may be lost during cooking. Dietary sodium intake is therefore difficult to measure using dietary assessments and food recall questionnaires. Human biomarkers of salt intake such as sodium excretion in urine therefore provide a more efficient and accurate intake assessment.

The main route by which sodium is eliminated from the body is via the urine, and about 90% of total daily sodium intake is excreted in this way (5). Urinary sodium, as opposed to serum/plasma sodium measurements should therefore be used when assessing population sodium consumption. Sodium is also lost in sweat; losses in sweat can increase when exposed to extreme heat conditions or a high sweat production due to intense physical activity, however acclimatisation to these conditions by the body is rapid (6).

Conversion of sodium to salt

The term “salt” (sodium chloride) is not synonymous with the term “sodium”.

To convert mmol to mg of sodium, chloride, or sodium chloride, multiply mmol by 23, 35.5, or 58.5 (the molecular weights of sodium, chloride, and sodium chloride), respectively (7).

Sodium in urine is typically measured in mmol. To convert mmol of sodium to salt equivalent:

1 mmol sodium = 23 mg sodium = 57.5 mg or 0.0575 g salt

104 mmol sodium = 2,400 mg sodium = 6000 mg or 6 g salt (~ 1 teaspoon)

Methods

Note: the following methods detail recommendations for population biomarker assessment and are not suitable for use to assess individuals or in an individual clinical setting.

Sodium excretion in 24 h urine samples

The **gold standard** for population sodium intake assessment is the measurement of sodium excreted in a 24 h urine sample (5). They are widely accepted as being the most reliable and practical method for assessing estimated population salt intakes.

The measurement of 24 h urine sodium excretion is a surrogate for 24 h sodium intake. The concentration of sodium in a 24 h collection, usually measured in mmol/L, can be multiplied by the volume in litres of urine collected to give mmol sodium excreted in 24 h (mmol/24 h) and subsequent conversion to salt equivalent.

Completeness of 24 h urine samples should be assessed. Incomplete and/or under-collection of urine due to missed urine voids can result in falsely low 24-hour sodium and potassium excretion. Over-collection, beyond 24 hours, can skew results in the opposite direction (8).

Several methods are available to assess the completeness of 24 h urine collections:

- *p*-aminobenzoic acid (PABA) recovery (9);
- Urinary creatinine concentration correction (10, 11).
- Questionnaire.

PABA: PABA is a non-toxic B-complex vitamin that is thought to be fully absorbed and is readily analysed (8). PABA is an accepted measure to assess the completeness of 24 h urine collection (12). It involves the concomitant administration of 80 mg PABA tablets usually with main meals (12). The use of PABA in national surveys has been reported in the National Diet and Nutrition Survey: assessment of dietary sodium in adults 19-64 years in England (2014) (page 15, section 2.6) (13).

Though used as an objective measure of urine collection completeness, the use of PABA is not without issue due to potential variation in excretion rate with age, non-adherence to the dosage regimen and potential interaction with medication although this is less of a problem when PABA is measured by HPLC (12, 14).

Example of a 24 h urine collection protocol for study participants using concomitant PABA administration to assess urine collection completeness, from UK National Diet and Nutrition Survey: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/509424/Appendix_D_field_documents.pdf

Method: SOP for PABA analysis by HPLC (See link on https://www.open-global.kcl.ac.uk/sodium/)

Creatinine: Creatinine correction is an alternative method for 24 h urine collection completeness assessment. Creatinine values should be interpreted dependent on sex, protein intake, muscle mass, degree of malnutrition and ethnicity (10, 11). Since standard cut-offs do not widely exist, creatinine should be used with caution. For guidance on creatinine measurement, see the OpeN-Global page on Common methods, https://www.open-global.kcl.ac.uk/common-methods/.

Questionnaire: Use of a questionnaire to assess 24 h urine collection completeness is reported in the US NHANES surveys (see link below). However, standardised procedures across study fieldworkers is paramount to reduce operator variation, and rigorous and intensive protocols are recommended to uphold data quality, including supervised urine collection (15).

Method: Details of a 24 h urine collection protocol for study participants using a questionnaire to assess urine collection completeness, from US CDC: https://www.cdc.gov/nchs/data/nhanes/nhanes_13_14/24_Hour_Urine_Study_Procedures_Manual.pdf

Sodium excretion in Spot urine samples

Where collection of 24 h urine samples is impossible, spot urine samples may be a valuable alternative. Further, since spot samples are often routinely used in other health surveys, e.g. measurement of urinary iodine, additional assay can be easily integrated into survey or research protocols. Spot samples also remove the need for multiple visits, and therefore may be a more efficient use of resources.

Sample size estimates may need adjustment to provide the correct power and precision, and other conversion or correction factors (e.g. measurement of urinary creatinine) may be needed (14).

Measurements of creatinine concentration and sodium concentration in a spot urine sample combined with details of the individual's sex, weight, height and age allow application of the Kawasaki formula which estimates 24 h urine excretion (16). It is recommended that this method, which is less accurate than using 24 h collections, can be used for population assessments provided that the sample size of the group is adequate.(5).

Review the Kawasaki method: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1440-1681.1993.tb01496.x?sid=nlm%3Apubmed

Laboratory methods

Note: urine is a potential biohazard, and safety precautions should be employed at all times whilst handling or manipulating urine samples.

Sample manipulation/processing and storage

Certain anticoagulants, preservatives, drugs and organophilic compounds may affect electrolyte determinations.

Visually turbid urine samples should be centrifuged prior to analysis. Urine samples should be transferred to the required storage receptacle, e.g. Eppendorf tubes, which should be clean and free of contamination. Samples should be frozen immediately if possible. If freezing is not possible, then refrigeration is preferred until the samples can be frozen.

Urine sample stability

- *Room temperature:* Sodium is stable in urine for ≤ 45 days (17), though this is not recommended due to bacterial growth in the urine, and operator comfort during analysis.
- *Frozen:* Sodium is stable indefinitely if stored frozen. Long-term storage for 20-25 years at -70 °C did not affect specimen desiccation (18).
- *Freeze-thaw cycles:* Up to 6 freeze-thaw cycles did not affect sodium concentrations (18).

OpeN-Global users should consult related SOPs for other planned analyses in collected urine samples to ensure all stability restrictions are considered.

Analytical methods

The gold standard method is **Inductively-Coupled Plasma Mass Spectrometry (ICP-MS)**, (https://www.nist.gov/sites/default/files/documents/srm/SP260-162-2.pdf , see p 7-1). This method can also be used on blood, serum and sweat.

The **Ion-selective electrode method (ISE)** method is also widely accepted and adopted for several electrolyte measurements, is accurate and precise and scalable for population studies e.g.US CDC NHANES surveys:

https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/labmethods/URLT_H_R_MET_Electrolytes.pdf

The classical method for sodium assessment in a clinical laboratory is by **Flame Atomic Emission Spectrometry (FAES) (also known as flame photometry)**, which is a selective method but not as easily automated nor as rapid. See page 3 of the OpeN-Global page on sodium https://open-global.kcl.ac.uk/sodium/ to access an example SOP.

Quality Control

ICP-MS and ISE: Standard Reference Materials (SRM) are available from the National Institute of Standards and Technology (NIST): SRM 2670a Toxic elements in urine (freeze-dried), level 1 (37.2 mmol/L) and level (41.0 mmol/L).

See https://www.nist.gov/sites/default/files/documents/srm/SP260-162-2.pdf p 7-2.
To order SRM from NIST: https://www-s.nist.gov/srmors/

ISE: CLINIQA standards used in the CDC NHANES method are available here:
http://www.cliniqa.com/Products/Details.aspx?ID=13

Confounding factors

The analysis of sodium can be biased by day-to-day intra-individual variations in sodium and fluid intake, physical activity, the environment and medication use, including antibiotics and diuretics that

can produce artificially high results, and corticosteroids and non-steroidal anti-inflammatory drugs e.g. ibuprofen that can produce artificially low results (7). Sodium is also lost in faeces and sweat, though in temperate climates this factor is negligible (5). In physically active persons or hot and humid climates, loss of sodium via the sweat and faeces may be >10% (14). Seasonal variability should be considered in such countries.

Accreditation schemes

For laboratory accreditation, validation and details on availability of proficiency testing, please see the OpeN-Global page on Laboratory accreditation: https://open-global.kcl.ac.uk/accreditation/

Technical assistance

Please contact the OpeN-Global team via www.open-global.kcl.ac.uk/contact/ or write to the NIHR BRC Nutritional Biomarker Laboratory, University of Cambridge: nbl@mrc-epid.cam.ac.uk

Useful links

CDC Sodium Reduction Toolkit (https://www.cdc.gov/salt/sodium_toolkit.htm)

National Academies Press, Dietary Reference Intakes for Water, Potassium, Sodium, Chloride and Sulfate (2005) https://www.nap.edu/read/10925/chapter/1

National Academies Press. Strategies to reduce sodium intake in the United States (010): https://www.nap.edu/read/12818/chapter/1

Institute of Medicine (2013) Sodium intake in populations: assessment of evidence. National Academies Press. https://doi.org/10.17226/18311
Available at: https://www.nap.edu/read/18311/chapter/1

UK National Diet and Nutrition Survey (NDNS) assessment of dietary sodium in adults in England, 2014 https://www.gov.uk/government/statistics/national-diet-and-nutrition-survey-assessment-of-dietary-sodium-in-adults-in-england-2014

WHO e-Library of Evidence for Nutrition Actions (eLENA) page: Reducing sodium intake to reduce blood pressure and risk of cardiovascular diseases in adults
http://www.who.int/elena/titles/sodium_cvd_adults/en/

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