15 May 2019

Dietary Reference Values for sodium and chloride

Web meeting with stakeholders

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efsa
European Food Safety Authority

EFSA participants

- **EFSA working group on DRVs for minerals**
- Androniki Naska, chair
- Peter Aggett, member

- **EFSA Nutrition Unit**
- Valeriu Curtui, Head of Unit **(moderator)**
- Agnès de Sesmaisons Lecarré, staff
- Silvia Valtueña Martinez, staff
- Laura Ciccolallo, staff

Agenda of the meeting

10:00 – 10:05	Welcome and introductory remarks
10:05 – 10:35	Part 1 • Scope and methodological framework • Identification of the criteria on which to base DRVs
10:35 – 10:50	Questions and Answers
10:50 – 11:20	Part 2 • Data on which to base DRVs • Conclusions for each population group
11:20 – 12:00	Questions and Answers
12:00 – 12:15	Part 3 • DRVs for chloride
12:15 – 12:30	Questions and Answers

Rules

- Please note that you will be muted during the whole meeting to avoid background noises

- How to ask questions
  - During the talks: in writing through the chat
  - During the Q&A sessions: send a message through the chat so that moderator gives you the floor (unmute)

- The meeting is recorded and will be published on the EFSA website

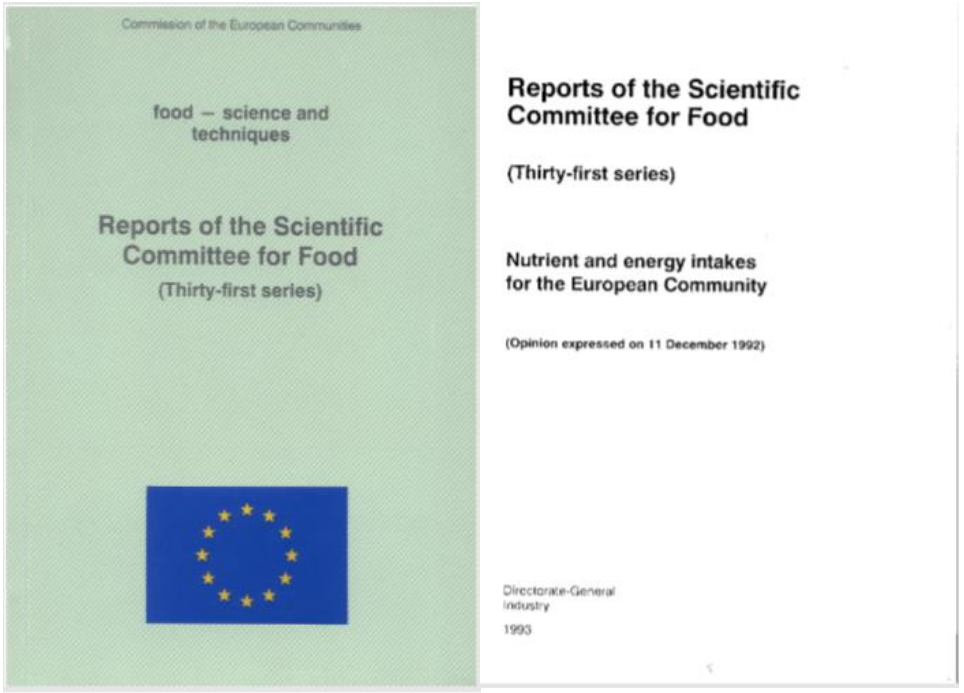
- Please note that you need to submit your comments by 22 May through the EFSA website for them to be considered

Part 1

- Scope and methodological framework
- Identification of the criteria on which to base DRVs

Mandate

- Request from the European Commission
- EFSA is asked to advise on population reference intakes of micronutrients in the diet
- To review and complete the SCF recommendations from 1993, in the light of new evidence



Process

2016	Task initiated
2017	Protocol for a systematic review Public consultation Protocol published Technical Report published
2018	Protocol implementation Completion of the draft Opinion
2019	Endorsement by the NDA Panel Public consultation Finalisation
July 2019	Adoption by the NDA Panel Opinion published Technical Report published

Contributors

- EFSA Working Group on DRVs for minerals
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  - Susan Fairweather-Tait
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  - Harry J McArdle
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  - Carmen Pelaez
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  - Alfonso Siani
  - Frank Thies
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  - Marco Vinceti

Methodological framework

1. Collection of relevant background information

2. Identification of the criteria on which to base DRVs
   - Including assessment of dose–response relationships

3. Integration of the available evidence and derivation of DRVs

Background information

- Sodium: functions, physiology and metabolism
- Interaction with other nutrients
- Biomarkers
- Effects of genotypes
- Dietary sources
- Dietary intake

Biomarker of intake

- On average, 93% of daily Na intake recovered in 24hr urine
- Reliability affected by variations over daily and weekly periods

- 24–hour urine collections
  - Incomplete 24–hour urine collections can introduce errors in intake estimates
  - Na levels in 24-hour urine collections are variable
  - Single 24–hour urine collection
    - reliable estimate of average groups' intake
    - not a reliable measure of an individual's usual intake (random misclassification)
  - Multiple 24-hour urine collections per individual are preferred

- Casual/timed spot urine collections
  - Reliability affected by circadian variations
  - Estimates from predictive equations based on spot urine samples can be biased (ends of the distribution)

Identification of the criteria on which to base DRVs

1. Biomarkers as indicators of Na requirement
2. Balance studies
3. Sodium intake and health consequences

Biomarkers of status as indicators of Na requirement

- Findings
  - Homeostatic mechanisms maintain systemic distribution, acquisition and excretion of Na, including plasma Na concentration/activity, as a means of maintaining water homeostasis
  - Hyponatraemia and hypernatraemia related to disorders affecting water and electrolyte balance; seldom due to inappropriate Na intake
  - Plasma Na concentration does not accurately reflect Na body content

- Conclusion
  - No appropriate biomarkers of Na status that can be used for deriving DRVs for sodium

Balance studies

- Evidence
  - Several studies excluded because of methodological limitations
  - 3 studies in adults and 1 study in adolescents were thoroughly reviewed

- Findings
  - Balance maintained over a wide range of Na intake
    - Mean Na intake assessed in eligible balance studies ranged between 1.5 g and 4.9 g/day in adults and between 1.31 and 3.95 g/day in adolescents.
  - Rhythmical variations in the Na body pool independent of Na intake
  - Response of sympathetic nervous system and the renin–angiotensin–aldosterone system to conserve Na evident at excretion below 100mmol/24 hours

- Conclusion
  - Balance studies cannot be used to determine Na requirements
  - Can be used to inform about the levels of Na intake adequate to maintain a null balance.
  - Metabolic studies inform about systemic mechanisms to maintain a Na balance.

Sodium intake and health consequences

- Outcomes
  - Blood pressure and cardiovascular diseases
  - Bone health

- Selection criteria
  - Biological relevance for the general healthy population
  - Biological plausibility of their relationship with Na intake
  - Type of evidence (i.e. RCTs and/or prospective observational studies)

- Systematic reviews of the literature
  - Protocols published in PROSPERO and Zenodo

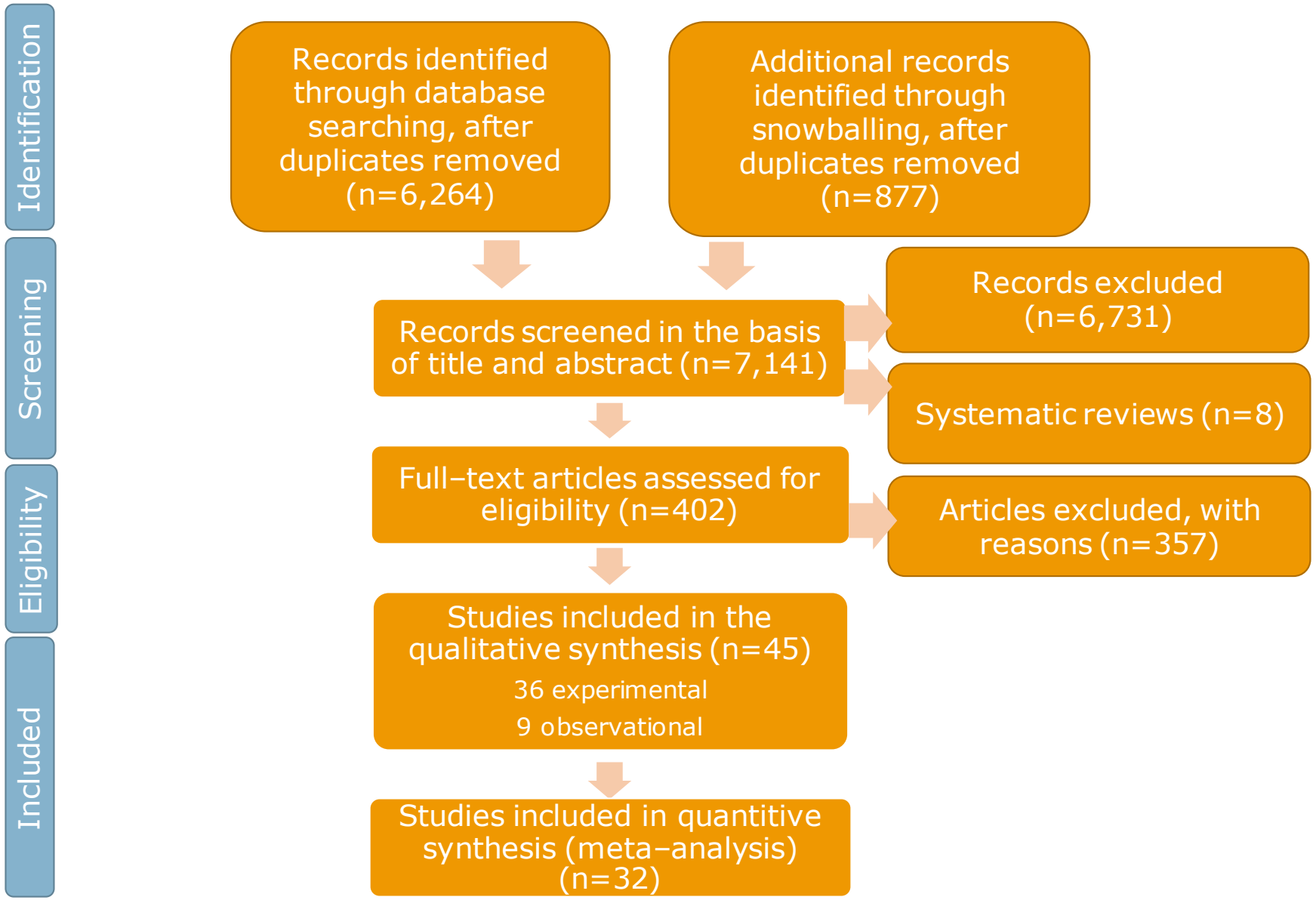
Protocol

- Eligibility criteria
  - Design: RCTs (parallel or crossover) and prospective studies
  - Duration :≥ 4 weeks for BP; ≥ 6 months for CVD outcomes; ≥ 1 year for BMD or risk of osteoporotic fractures in adults
  - Population: adults (≥ 18 years) and children (6 months to < 18 years) from the general population.
  - Na measurement: urinary Na excretion calculated from single or multiple 24–h urine collection(s).

- Risk of bias appraisal
  - OHAT–NTP tool
  - 3–tier classification: low, moderate or high risk of bias

Prisma chart

Blood pressure and cardiovascular diseases



Blood pressure in adults

- Evidence
  - 32 eligible RCTs
  - Random effect meta–analyses on the effect of Na reduction
  - Subgroup analyses to explore contextual and methodological sources of heterogeneity
  - Mixed–effects meta–regression models (dose–response)
  - Moderating effects of age and blood pressure status explored in stratified analyses

Blood pressure in adults

- Findings
  - Significant effects of Na reduction on SBP by –3.9 mmHg (95%CI: –5.1, –2.8 mmHg)
  - Significant effects of Na reduction on DBP by –2.0 mmHg (95%CI: –2.8, –1.2 mmHg)

  - Linear dose–response over the range of mean UNa observed (49 – 209 mmol/24 h (1.3 – 4.8 g/day))
  - Mean SBP increased by 5.3 mmHg (95% CI: 3.6, 6.9 mmHg) for each 100 mmol (2.3 g)/24–h increase in mean UNa
  - Mean DBP increased by 2.6 mmHg (95% 1674 CI: 1.6, 3.7 mmHg) for each 100 mmol (2.3 g)/24–h increase in mean UNa
  - Stronger association among hypertensive vs normotensive individuals and among subjects aged ≥50 years vs subjects <50 years

Blood pressure in adults

- Evidence
  - 1 prospective cohort study (moderate RoB) on the long–term relationship between UNa and blood pressure levels
  - 2 RCTs (low RoB) and 2 prospective observational studies (low and moderate RoB) on the relationship between UNa and risk of hypertension

- Findings
  - Support the positive relationship between UNa and blood pressure levels derived from RCTs

Blood pressure in children

- Evidence
  - 2 eligible RCTs (low and moderate RoB)
  - 1 prospective cohort study (PCS) (two publications) (low RoB)

- Findings
  - No evidence from RCTs for an effect of Na reduction on blood pressure in school–age children.
  - No significant association from PCS between UNa and blood pressure in pre–pubertal and pubertal children
  - Weak evidence from PCS for a positive association between UNa during adolescence and SBP in adulthood

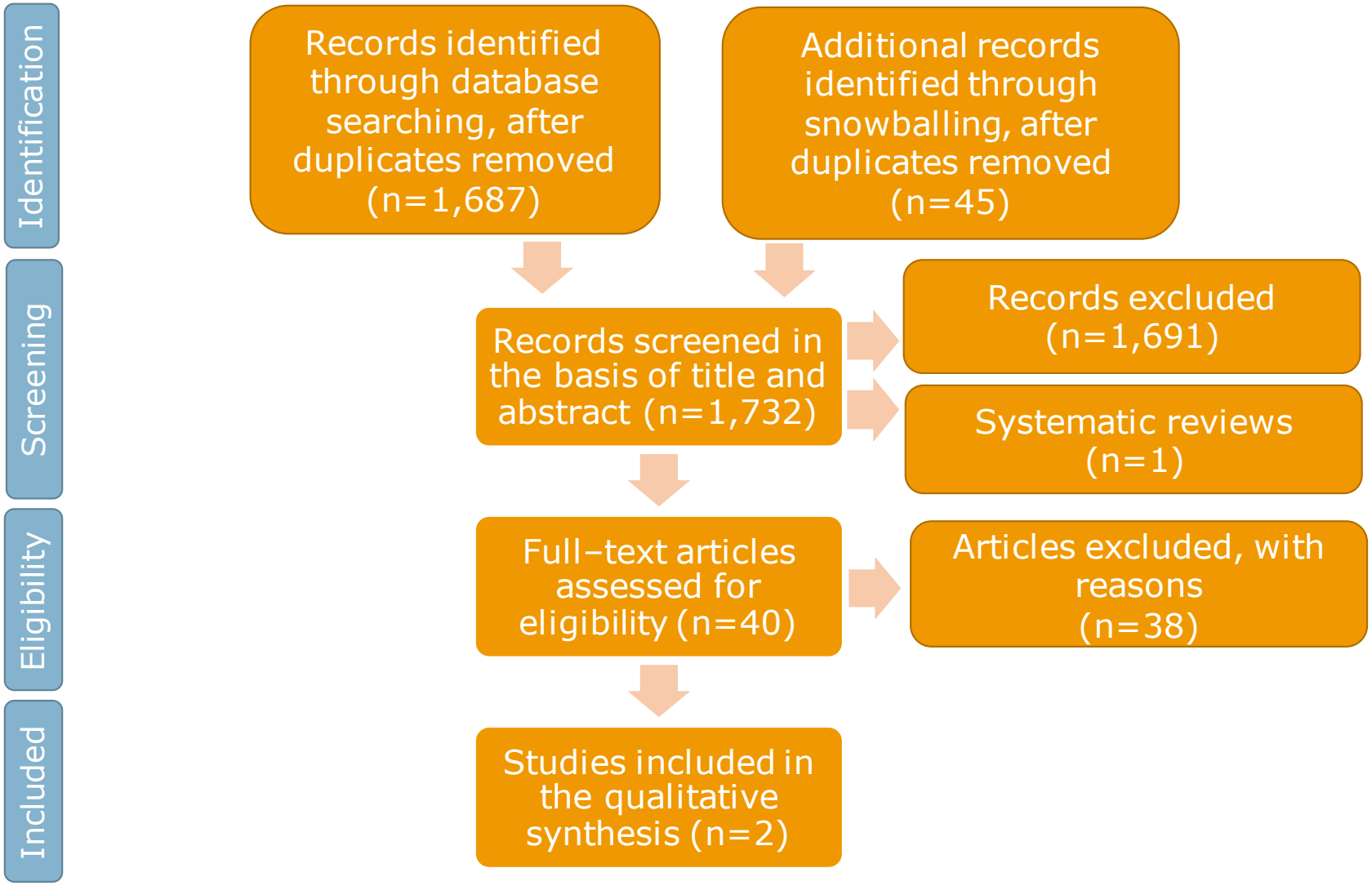
Cardiovascular diseases

- Evidence
  - No RCT eligible
  - Small number of PCS
    - 3 cohorts on the risk of stroke or on the risk of coronary heart disease
      PREVEND (low RoB); EPOGH/FLEMENGHO and the Finnish cohort (moderate RoB)
    - 3 cohorts on the risk of cardiovascular disease
      TOPHI/II (low RoB); EPOGH/FLEMENGHO and InCHIANTI (moderate RoB)
  - No quantitative analysis

- Findings
  - Limited conclusions
  - Risk of coronary heart disease: some evidence for a positive association
  - Risk of stroke: some evidence for a negative association
    - Small number of studies and mechanisms unclear
  - Risk of cardiovascular disease: some evidence for a positive association

Prisma chart

Bone Health



Bone health

- Evidence
  - 2 eligible papers

- Findings
  - Limited and inconsistent evidence for an association between Na intake and bone mineral density
  - Data cannot be used to set DRVs for Na

Questions & Answers

Part 2

- Data on which to base DRVs
- Conclusions for each population group

Relevant data and integration of the evidence

- An average requirement (AR) and a population reference intake (PRI) can NOT be established for Na, because the distribution of the requirement cannot be determined

- Data relevant to the setting of DRVs for sodium
  - Balance studies: levels of Na intake adequate to maintain a null balance
  - Relationship between Na and blood pressure or CVD risk: levels of Na associated with a reduced risk of chronic diseases

- Expert judgement, taking account of the associated uncertainties
- Use of a formal Expert Knowledge Elicitation (EKE) process

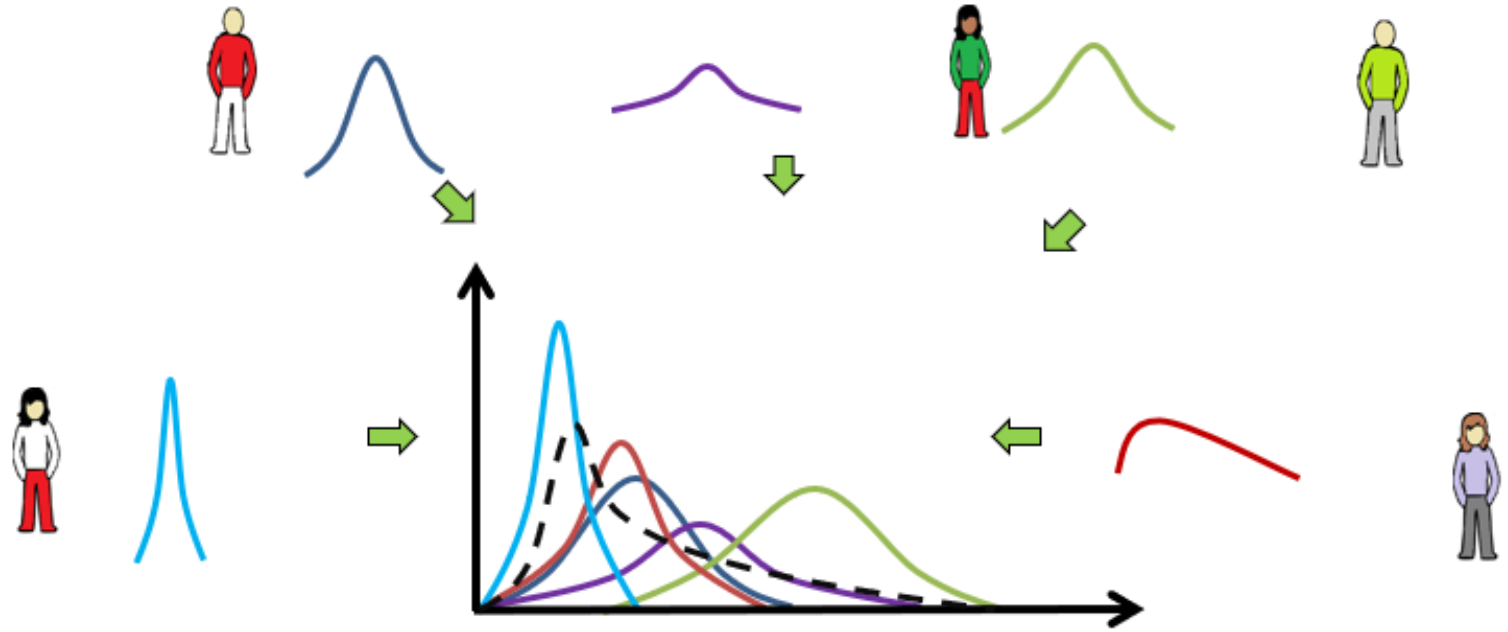
EKE method

- Formal Expert Knowledge Elicitation (EKE) (EFSA Guidance, 2014)
  - Evidence–based judgements about a quantity of interest
  - Judgements expressed about the range of possible values for the quantity of interest and their relative likelihood
  - Limits bias;
  - Structured process improves rigour of reasoning;
  - Clear and unambiguous expression of uncertainty;
  - Rationale documented.

- 'Sheffield' protocol
  - Method designed to elicit the knowledge of a group of experts in a face–to–face elicitation meeting
  - Result in an uncertainty probability distribution that represents the experts aggregated judgements achieved via discussion.
  - Presence of an elicitor essential.

EKE in practice

1. Collective review of the 'evidence dossier'
2. A separate distribution is elicited from each expert in parallel;
3. The individual judgements are shared and discussed;
4. A consensus distribution (dashed curve in graph) is elicited from the experts as a group.



EKE questions

- **Data on Na and blood pressure or CVD risks** could inform about the levels of sodium intake associated to a reduced risk of chronic diseases

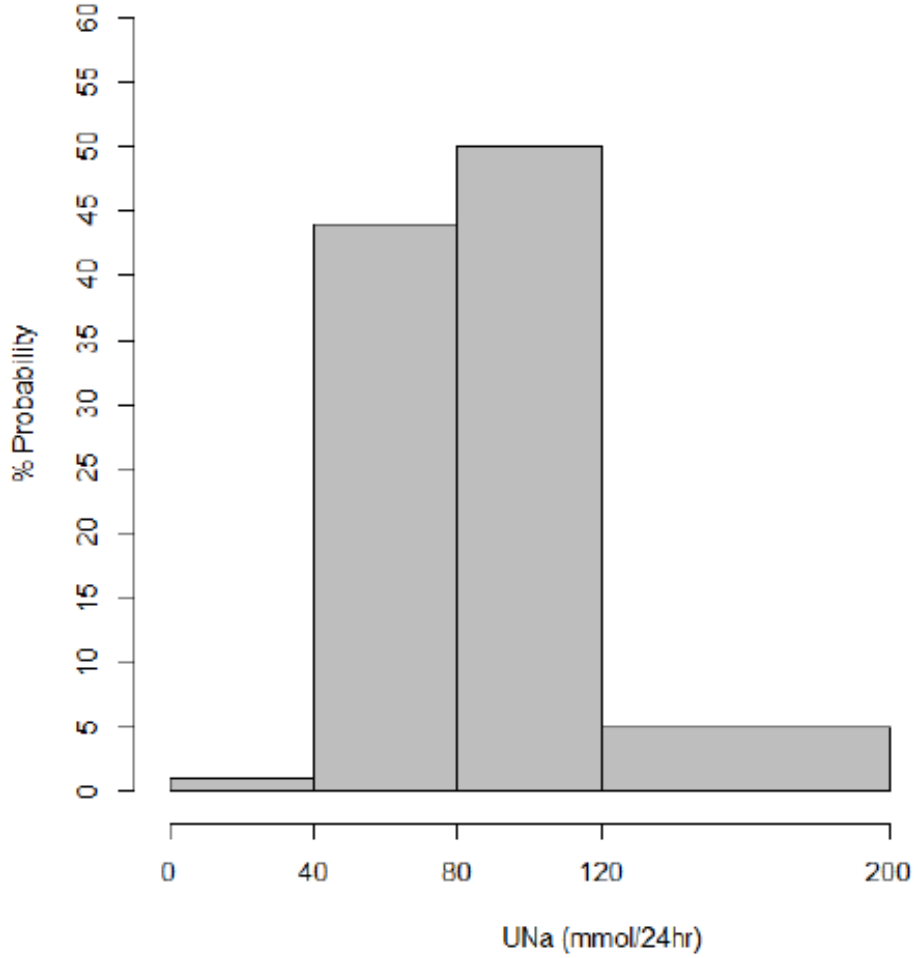
Question 1 What is the lowest level of sodium intake at which the risk of chronic disease (i.e. stroke, CHD) is minimised in the majority (≥ 97.5%) of the general population of adults?

- **Balance studies** could inform about the levels of sodium intake which are adequate to maintain a null sodium balance

Question 2 What is the lowest level of sodium intake which is adequate (i.e. amount which allows to maintain sodium balance) for the majority (≥ 97.5%) of the general population of adults?

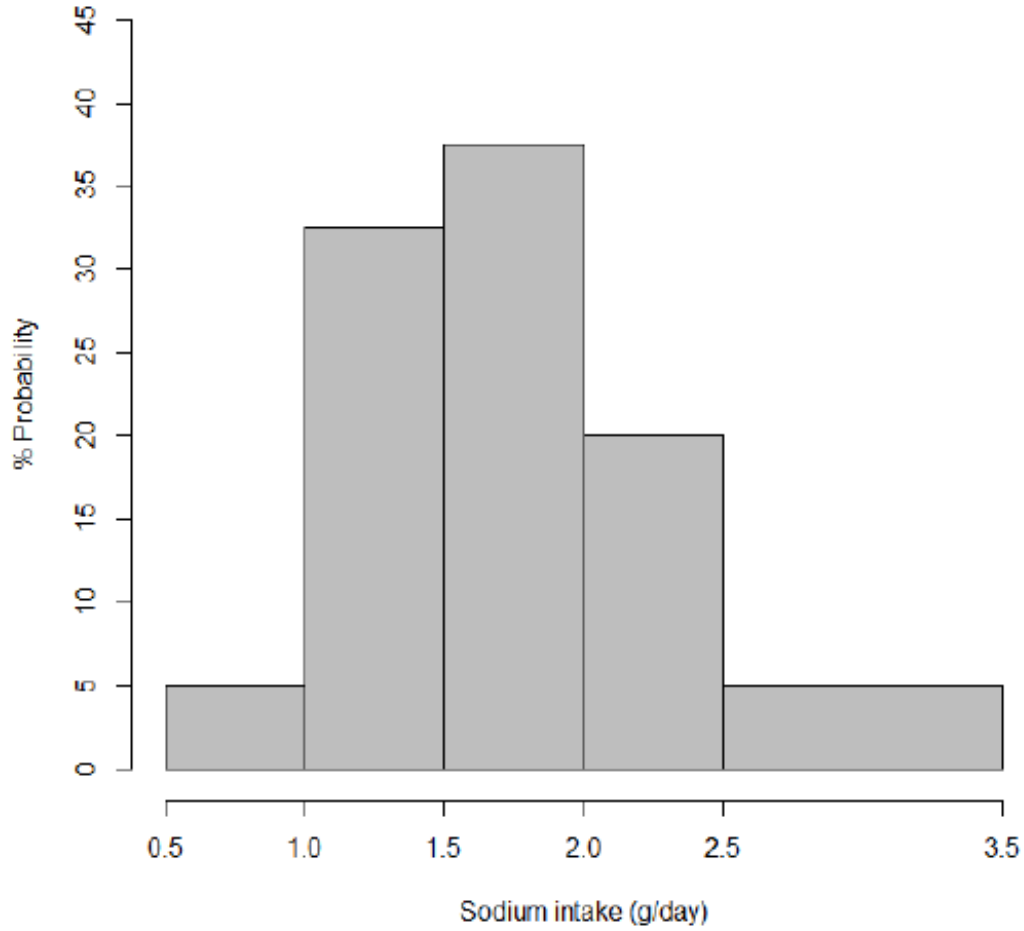
Group consensus uncertainty probability distribution I

- What is the lowest level of sodium intake at which the risk of chronic disease (i.e. stroke, CHD) is minimised in the majority (≥ 97.5%) of the general population of adults?



Group consensus uncertainty probability distribution II

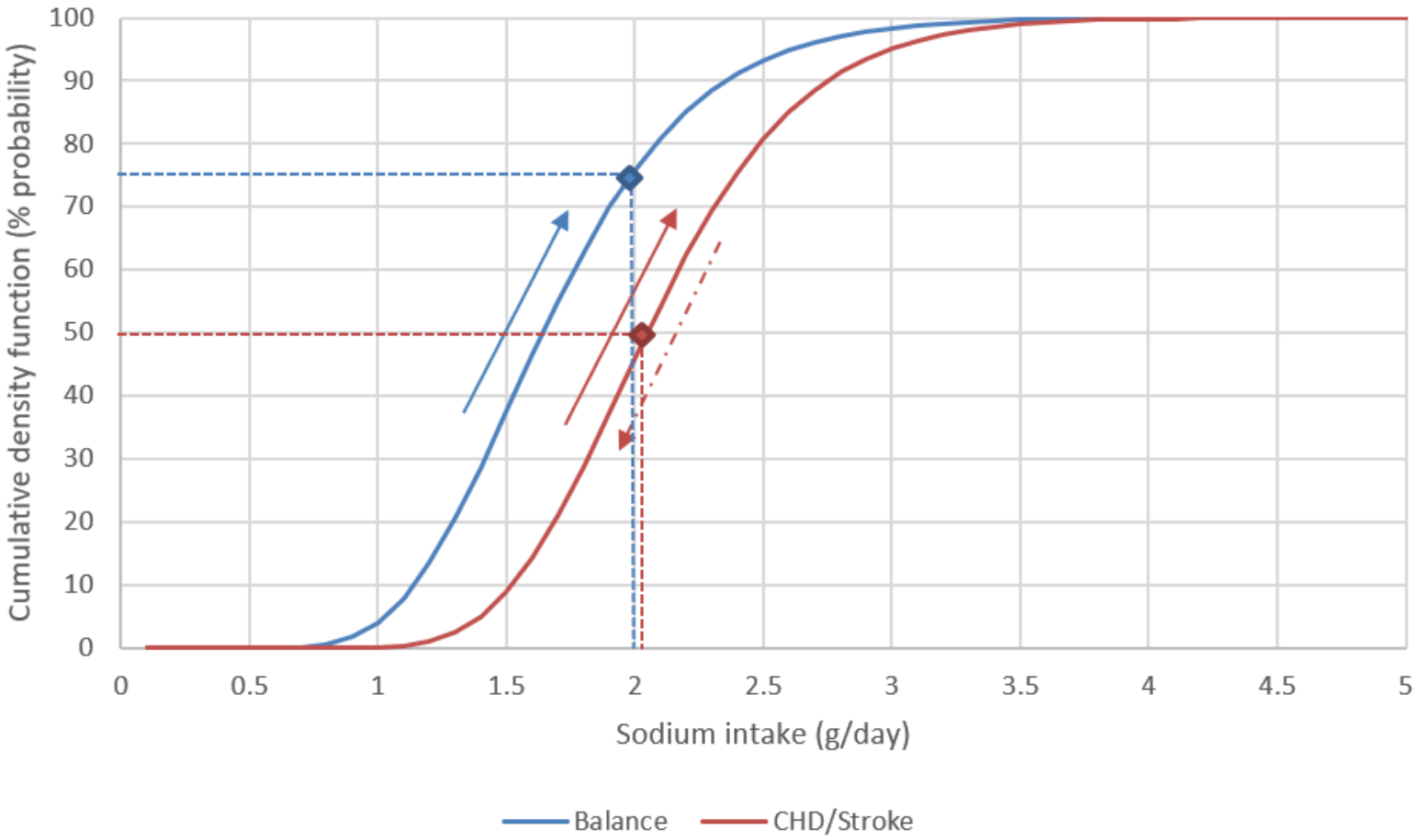
- What is the lowest level of sodium intake which is adequate (i.e. amount which allows to maintain sodium balance) for the majority (≥ 97.5%) of the general population of adults?



Conclusion – DRVs for adults

- A sodium intake of 2.0 g/day represents a level of sodium for which there is sufficient confidence in a reduced risk of CVD in the general adult population.
- A sodium intake of 2.0 g/day is likely to allow most of the general population to maintain sodium balance

- 2.0 g of sodium per day is a safe and adequate intake for the general EU population of adults



Terminology

- Safe:
  - The concept of a safe intake has been used when providing advice on a daily intake of a nutrient which does not give rise to concerns about adverse health effects, in case a tolerable upper intake level (UL) could not be established.
  - The reference value for Na is called 'safe' as the value proposed takes account of an increased risk of CVD at higher levels of Na intake and prolonged exposure.

- Adequate:
  - An adequate intake (AI) is the value estimated when a population reference intake (PRI) cannot be established because an average requirement (AR) cannot be determined.
  - It involves more expert judgement than is used for determining an AR or PRI.
  - An AI is similar to a PRI from a practical point of view. The distinction in the terms relates to the different strength of the scientific basis on which they rest.
  - The reference value for Na is called 'adequate' in line with this definition.

Conclusions – DRVs for pregnancy and lactation

- Requirement for the daily accretion rate of sodium in fetal and maternal tissues can be met by adaptive changes that maintain Na homeostasis during pregnancy
- No evidence that Na requirement of lactating women differs from the requirement of non–lactating women

- 2.0 g sodium per day is a safe and adequate intake for pregnant and lactating women

Conclusions – DRVs for infants

- Lack of data from which an AR could be derived for infants
- Upwards extrapolation from the estimated Na intake of fully breast–fed infants during the first 6 months of life (120 mg/day)

- Adequate Intake of 0.2 g/day proposed for infants aged 7–11 months

Conclusions – DRVs for children

- Lack of data from which an AR could be derived for children
- Downwards extrapolation from the reference value for adults, based on the AR for energy and including a growth factor

- $Value_{child} = Value_{adult} \times$ (AR for energy of children/AR for energy of adults aged 18–29 years) × (1 + growth factor)

DRVs for sodium

	Adequate Intake (g/day)
7–11 months	0.2

	Safe and Adequate Intake (g/day)
1–3 years	1.1
4–6 years	1.3
7–10 years	1.7
11–17 years	2.0
≥ 18 years	2.0

Recommendations for research

- Moderating effect of energy intake on the relationship between sodium intake and blood pressure
- Health effects of sodium and of the Na/K ratio at intakes approximating their respective DRVs
- Life course effects of Na intake on blood pressure, in particular the effect of Na intake on neurohormonal control during childhood (programming);
- Effect of prolonged exposure to 'low' Na on the effective functioning of its homeostatic regulation (i.e. SNS and RAAS)
- Effects of Na intake on bone health in growing and ageing populations
- Effects of Na intake on renal function in the general population
- Characterisation of genes involved in determining 'salt–sensitive' phenotypes and of moderating factors of 'salt sensitivity'

Questions & Answers

Part 3

- DRVs for chloride

Findings

- Kidney is the main route of excretion; excretion of Na and Cl in urine are closely related
- In Western diets, NaCl is the major source of Cl intake which is reflected in the similar levels of urinary excretion of Na and Cl, on a molar basis
- Close relationship between Na and Cl balances in the body

- Evidence that chloride can contribute to the effect of NaCl on blood pressure
- No studies on the association between Cl intake or urinary excretion and cardiovascular diseases

Conclusions

- No data that can be used to determine Average Requirements and Population Reference Intakes for Cl
- Reference values for Cl can be set at values equimolar to the reference values for Na for all life–stage groups
- Values proposed for chloride are considered to be safe and adequate intakes for the general EU population, under the consideration that the main dietary source of Cl is NaCl

DRVs for chloride

	Adequate Intake (g/day)
7–11 months	0.3

	Safe and Adequate Intake (g/day)
1–3 years	1.7
4–6 years	2.0
7–10 years	2.6
11–17 years	3.1
≥ 18 years	3.1

Recommendations for research

- As the proportion of NaCl substituted by other Cl salts increases in the diet, to investigate health effects of Cl intake, independent from that of Na

Questions & Answers

Have your say!

- Please submit your comments **by 22 May** through the EFSA website

- Na: https://www.efsa.europa.eu/en/consultations/call/190403
- Cl: https://www.efsa.europa.eu/en/consultations/call/190403–0

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