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Benefit and risk assessment of iodization of household salt and salt used in bread and bakery products

Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food and Environment

Report from the Norwegian Scientific Committee for Food and Environment (VKM) 2020:05
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Preparation of the opinion

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to answer the request from the Norwegian Food Safety Authority. The project group consisted of nine persons, including a project leader from the VKM secretariat. Two external referees commented on and reviewed the opinion. The VKM Panel on Nutrition, Dietetic Products, Novel Food and Allergy have discussed draft reports and evaluated and approved the final opinion drafted by the project group.

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Members of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy that contributed to the assessment and approval of the opinion. In addition to Sigrun Henjum, Kristin Holvik, Christine Louise Parr, Tonje H. Stea and Tor A. Strand, these were (in alphabetical order):

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Tim Korevaar for, Erasmus University Medical Center, for valuable inputs in the discussion of mild to moderate iodine deficiency, thyroid function and clinical relevance.
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Public Health) and Maria Andersson (Kinderspital Zurich, Eleonorenstiftung) for valuable reviewing and commenting on the manuscript.

Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

Table of Contents

Summary

Request from the Norwegian Food Safety Authority

Following a report from the National Nutrition Council calling for actions to secure adequate iodine intake in the population, the Norwegian Food Safety Authority requested the Norwegian Scientific Committee for Food and Environment (VKM) to conduct a benefit- and risk assessment of iodization of household salt and industrialised salt in bread.

VKM addressed the request

VKM appointed a project group consisting of members of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy and Panel on Contaminants to answer the request.

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy has reviewed and revised drafts prepared by the project group and finally approved the benefit- and risk assessment

This benefit and risk assessment is based on 1) established knowledge about health consequences from severe iodine deficiency, 2) systematic literature review of the evidence for health consequences of mild to moderate iodine deficiency, 3) literature review of studies on adverse health effects from excessive iodine intakes to re-evaluate existing tolerable upper intake levels (ULs), 4) evaluation of estimated iodine intake levels in different population groups in Norway compared to established dietary reference values, specifically estimated average requirement (EAR) and UL, and finally 5) an estimation of the effect of different scenarios of increasing iodization levels in household salt and salt in bread on iodine intake levels in different population groups compared to the established dietary reference values EAR and UL.

For the purpose of this benefit and risk assessment of iodization in household salt and salt in bread, *risk* may be understood as risk of adverse health effects related to too high or too low iodine intakes. *Benefit* may be understood as reduction or avoidance of adverse health effects related to too high or too low iodine intakes. For iodine, this is a challenging maneuver, as the gap between too low and too high intakes is narrow.

The project group conducted two systematic literature reviews. One was performed to evaluate the evidence for the impact of mild- to moderate iodine deficiency on neurodevelopment, thyroid function and birth outcomes, the other to evaluate the evidence for adverse health effects from excessive iodine intake to possibly re-evaluate the existing tolerable upper intake levels.

Current evidence for adverse health effects of iodine deficiency

Severe iodine deficiency resulting in hypothyroidism during foetal life, infancy, or early childhood may lead to permanent intellectual disability. Severe maternal iodine deficiency in pregnancy may also result in miscarriages, preterm delivery, stillbirth, and congenital

abnormalities. These effects are due to low levels of thyroid hormones affecting the developing tissues.

The health effects of severe iodine deficiency are well established, but for mild to moderate deficiency the effects are less known. After screening of more than 15 000 titles and abstracts and quality assessment of 131 full text scientific papers, 36 publications were included for the grading of evidence for consequences of mild to moderate iodine deficiency.

We used the criteria proposed by the World Cancer Research Fund for grading of evidence. Based on our systematic literature review, the evidence for adverse effects from mild to moderate iodine deficiency and neurodevelopment was judged to meet the criteria for *limited suggestive*. *Limited suggestive* means that the evidence is too limited to permit a probable or convincing causal judgement but shows a generally consistent direction of effect.

It was further concluded that there is *limited (no conclusion)* evidence to support that mild to moderate iodine deficiency causes thyroid dysfunction or has negative effects on birth outcomes. *Limited (no conclusion)* means that the evidence is so limited that no firm conclusion can be made.

Established reference values for iodine requirement

Several competent bodies have established dietary reference values for iodine. We have based this benefit and risk assessment on estimated average requirements (abbreviated EAR or AR) from the Nordic Nutrition Recommendations (2012) for adults, and from the Institute of Medicine (2001) for adolescents and children. Estimated average requirement is an iodine intake that is estimated to meet the requirement of half the healthy individuals in the population. The iodine intake is considered to be adequate if 97.5% of a population has a habitual intake above the estimated average requirement.

Re-evaluation of tolerable upper intake levels

As the evidence for health effects of excessive iodine intakes is far less comprehensive than for iodine deficiency, we did not aim at evaluating the literature for excess intakes with the same weight of evidence tools as for deficiency. We have only evaluated whether recent literature is in line with the existing tolerable upper intake levels or if it supports that tolerable upper intake levels should be changed. Generally, UL is the maximum level of total chronic daily intake judged to be unlikely to pose a risk of adverse health effects, and in the case of iodine the UL for adults is the maximum daily intake where changes in TSH are unlikely to occur (SCF, 2002).

After screening more than 2500 titles and abstracts, five studies fulfilled the inclusion criteria and were found relevant and included for evaluation of existing ULs. The existing ULs from the Scientific Committee on Food from 2001 is maintained. However, according to findings in new studies, the lowest-observed-adverse-effect levels (LOAEL) for excessive iodine intake may be lower than previously assumed, and the uncertainty factor inherent in the established ULs is reduced from three to 1.3 for adults. The findings also indicate a reduced

LOAEL for the existing ULs in children. Changes in thyroid stimulating hormone (TSH) without changes in thyroid hormones (T3 or T4), that is subclinical hypothyroidism, are observed in one randomised controlled dose-response study and four cross-sectional studies in children at iodine intakes close to the ULs. Subclinical hypothyroidism is not considered to be harmful, but may progress into overt hypothyroidism.

Iodine intake in Norwegian population groups and implications of salt iodization

Iodine intakes in adults are higher in men than in women and increase with increasing age for both sexes. Women of childbearing age and 13-year-old girls have the lowest estimated iodine intakes. 26% of the women of childbearing age have intakes below the estimated average requirement of 100 µg/day, and 38% of the 13-year-old girls have intakes below the estimated average requirement of 73 µg/day. The estimated iodine intakes in the 5th percentile of women of childbearing age and 13-year-olds is 70 and 38 µg/day, respectively. All adults and 13-, 9- and 4- year-olds have individual intakes below the tolerable upper intake levels.

The estimates for 2-year-olds show that 9% have intakes below the estimated average requirement, and 8% have intakes above the tolerable upper intake level. The estimated iodine intake in the 95th percentile is 215 µg/day, slightly above the tolerable upper intake level of 200 µg/day. The estimates for non-breastfed 1-year-olds show that 8% have intakes below the estimated average requirement, and 18% have intakes above the tolerable upper intake level. The estimated iodine intake in the 95th percentile for this group is 259 µg/day.

We present 12 scenario tables combining three scenarios (household salt alone, salt in bread alone and both household salt and salt in bread) with four iodization levels (15, 20, 25 and 50 mg iodine per kg salt). The percentages of the population groups with intakes above the estimated average requirement increases with increasing iodization levels, but so does the percentages with intakes above tolerable upper intake levels for some groups of the population.

The scenarios that seem to elevate iodine intakes in women of childbearing age and 13-year-olds up to adequate intakes, are iodization up to 15 or 20 mg iodine per kg salt, including iodization of salt in bread. Above these iodization levels, no increased benefit would be expected in women of childbearing age and 13-year-olds. For 1- and 2-year-olds all scenarios lead to an increase in the proportion of toddlers with estimated intakes above the tolerable upper intake level.

Benefit- and risk characterisation of iodization of household salt and industrialised salt in bread

Low estimated iodine intakes in adolescents (13-year-olds) and women of childbearing age (18-45 years) cannot be sufficiently corrected by the proposed increased iodization levels of salt and/or bread without imposing high iodine intakes in 1- and 2-year-old children.

VKM assumes that the women of childbearing age and 13-year-olds will benefit from increased iodization levels in salt and bread. This will also benefit other groups that, for various reasons, have few iodine-rich sources in their diet, e.g., people who do not eat lean fish or consume milk or other dairy products. The risk imposed on the youngest age groups is a higher proportion of the 1- and 2-year-olds with iodine intakes above the tolerable upper intake level.

Based on the scientific evidence and the data presented in this benefit and risk assessment it cannot be concluded that a specific iodization level benefits all age and gender groups without posing increased risk of harm to others or that the benefits in one population group outweighs the risks in others, or that the benefits in one group outweigh the risks in others.

It should be noted that recommendations for nutrients are set to secure adequate growth, development, maintenance of health, and to reduce the risk of chronic illnesses. Thus, iodine intakes below EAR or above UL will decrease the possibilities of achieving the beneficial effects of adequate intake. Current iodine intake in certain population groups is worryingly low, and trend studies indicate that consumption of milk and dairy products in Norway, the most significant iodine sources in the diet, is declining, especially among young women.

Several studies show that especially adolescents and women of childbearing age have insufficient iodine intakes, which may leave some at risk of severe iodine deficiency. There are, however, to our knowledge, no data on the prevalence of severe iodine deficiency in Norway. In other words, we do not know how many, if any, there are who have clinical consequences of inadequate iodine intakes.

The scenarios that seem to elevate iodine intakes in women of childbearing age and 13-year-olds (the groups at highest risk of low intakes) to adequate levels are iodization up to 15 or 20 mg iodine per kg salt, including iodization of salt in bread. Above these iodization levels, no increased benefit would be expected in women of childbearing age and 13-year-olds whereas several population groups will be at risk of exceeding UL, especially in 1- and 2-year-olds.

The WHO recommends salt as a vehicle for correcting iodine deficiency in a population, followed by a close monitoring of the iodization program.

Key words: VKM, benefit- and risk assessment, Norwegian Scientific Committee for Food and Environment, Norwegian Environment Agency, iodine

Sammendrag på norsk

Oppdraget fra Mattilsynet

På bakgrunn av en rapport fra Nasjonalt råd for ernæring som konkluderte med at det var behov for tiltak for å sikre økt jodinntak i den norske befolkningen, ba Mattilsynet Vitenskapskomiteen for mat og miljø (VKM) om å foreta en nytte- og risikovurdering av tilsetning av jod i husholdningssalt og industrisalt i brød.

Hvordan VKM har løst oppdraget

VKM utnevnte en prosjektgruppe bestående av medlemmer fra faggruppen for ernæring, dietetiske produkter, ny mat og allergi og et medlem fra faggruppen for forurensninger, naturlige toksiner og medisinrester for å utrede og besvare oppdraget.

Faggruppen for ernæring, dietetiske produkter, ny mat og allergi har gjennomgått og revidert flere utkast utarbeidet av prosjektgruppen, og godkjent den endelige nytte- og risikovurderingen.

Denne nytte- og risikovurderingen er basert på følgende elementer: 1) etablert kunnskap om helsemessige konsekvenser av alvorlig jodmangel, 2) en systematisk litteraturgjennomgang av kunnskapsgrunnlaget for helsemessige konsekvenser av mild til moderat jodmangel, 3) litteraturgjennomgang av studier om negative helseeffekter av høye jodinntak for eventuelt å revurdere eksisterende tolerable øvre inntaksnivåer (UL), 4), vurdering av beregnede estimater av inntak av jod i ulike befolkningsgrupper i Norge, og sammenlikning av disse estimatene opp mot såkalte referanseverdier for jod, nærmere bestemt det som på engelsk heter *estimated average requirement* (EAR), her oversatt til jodbehov og tolerable øvre inntaksnivåer (UL), og til slutt 5) vurdering av beregnet jodinntak ved ulike scenarier for økte nivåer av tilsetning av jod til husholdningssalt og industrisalt i brød og sammenlikning mot de etablerte referanseverdiene for jodbehov (EAR) og tolerabelt øvre inntaksnivå (UL).

I denne nytte- og risikovurderingen skal *risiko* forstås som risiko for negative helseeffekter relatert til for høye eller for lave inntak av jod. *Nytte* skal forstås som reduksjon eller fravær av negative helseeffekter relatert til for høye eller for lave inntak av jod. Dette er en utfordrende øvelse for næringsstoffet jod, fordi området mellom for lavt og for høyt jodinntak er smalt.

Prosjektgruppen gjennomførte to systematiske litteraturgjennomganger: én for å vurdere evidensen for negative effekter av mild til moderat jodmangel på nevroutvikling, skjoldbruskkjertelfunksjon, fødselsutfall og fertilitet, og én for å vurdere negative helseeffekter av høyt inntak av jod og hvorvidt det er grunnlag for å endre eksisterende tolerable øvre inntaksnivåer (UL).

Kunnskapsgrunnlag for negative helseeffekter av mild til moderat jodmangel

Alvorlig jodmangel i form av hypotyreose i fosterlivet, spedbarnsalder eller tidlig barndom, kan føre til permanent psykisk utviklingshemming. Alvorlig jodmangel i svangerskapet kan også føre til spontanaborter, for tidlig fødsel, dødfødsel og medfødte misdannelser. Alle disse negative helseeffektene skyldes endringer i nivå av skjoldbruskhormoner, som er svært viktige for vekst og utvikling.

Etter en screening av mer enn 15 000 titler og abstrakts og kvalitetsvurdering av 131 fulltekstartikler, ble 36 vitenskapelige artikler inkludert for evidensvurderingen av negative helseeffekter av mild til moderat jodmangel.

Vi benyttet vurderingskriterier lansert av World Cancer Research Fund. Basert på vår systematiske litteraturgjennomgang og bruk av World Cancer Research Funds retningslinjer for vurdering av evidens, ble evidensen for mild til moderat jodmangel og nevroutvikling vurdert å oppfylle kriteriene for *limited suggestive* – her oversatt til *begrenset antydende*. *Begrenset antydende* betyr at evidensen overordnet peker i en retning, men er for svak til å konkludere med at det er en sannsynlig eller overbevisende årsakssammenheng.

Det ble videre konkludert med at det er *limited (no conclusion)* evidens for at mild til moderat jodmangel forårsaker dysfunksjon i skjoldbruskkjertelen eller har negative effekter på fødselsutfall eller fertilitet (her oversatt til *begrenset (ikke konkluderende)*). *Begrenset (ikke konkluderende)* betyr at evidensen er for begrenset til det kan gis en sikker konklusjon.

Etablerte referanseverdier for jodbehov

Flere internasjonale organisasjoner har etablert såkalte referanseverdier for jod. Vi har basert denne nytte- og risikovurderingen på én type referanseverdi for jodbehov (forkortet EAR eller AR) fra de nordiske næringsstoffanbefalingene (2012) for voksne, og fra Institute of Medicine (2001) fra USA for barn og unge. Jodbehov (EAR eller AR) tilsvarer et daglig inntak av jod som anslås å dekke behovet hos halvparten av den friske befolkningen. Inntaket anses som adekvat hvis 97,5 % av befolkningen har et inntak over den fastsatte verdien for behov (EAR eller AR).

Re-evaluering av eksisterende tolerable øvre inntaksnivåer

Ettersom det er langt færre studier som har undersøkt hvordan høye inntak av jod påvirker helsen, var det ikke et mål å systematisk vurdere kunnskapsgrunnlaget for helseeffekter av høyt jodinntak etter samme metode som for mild til moderat jodmangel. Vi har kun vurdert om nyere litteratur støtter eksisterende tolerable øvre inntaksnivåer (UL), eller om det bør fastsettes nye nivåer.

Generelt er et tolerabelt øvre inntaksnivå (UL) det maksimale nivået av totalt kronisk daglig inntak som anses å ikke utgjøre en risiko for negative helseeffekter. For jod, er UL for voksne det maksimale daglige inntaket man kan ha uten sannsynlighet for at det fører til endringer i skjoldbruskstimulerende hormon (TSH) (SCF, 2002).

Etter screening av mer enn 2500 titler og abstrakts, ble fem nye studier funnet relevante og inkludert for vurdering av eksisterende UL. VKM foreslår etter gjennomgangen av studiene å opprettholde de allerede fastsatte tolerable øvre inntaksnivåene fra Den europeiske vitenskapskomiteen for mat (SCF) fra 2001.

Nyere studier tyder imidlertid på at den laveste dosen som har gitt negative helseeffekter ved høyt jodinntak (LOAEL) er lavere enn tidligere antatt, og den iboende usikkerhetsfaktoren i det tolerable øvre inntaksnivået er derfor redusert fra 3 til 1,3. Årsaken er at det er rapportert om endringer i skjoldbruskstimulerende hormon (TSH) uten endringer i skjoldbruskhormoner (T3 eller T4), altså såkalt subklinisk hypotyreose, i en randomisert kontrollert dose-responsstudie med voksne og i fire tverrsnittsstudier med barn ved jodinntak nært opptil disse tolerable øvre inntaksnivåene. Subklinisk hypotyreose anses ikke for å være skadelig, men kan utvikle seg til hypotyreose.

Inntak av jod i den norske befolkningen – inkludert scenarier ved økt tilsetning av jod til salt og brød

Jodinntaket hos voksne er høyere hos menn enn hos kvinner, og øker med alderen hos begge kjønn. Kvinner i fertil alder har det laveste estimerte jodinntaket blant voksne, og 26 % av kvinner i fertil alder har et jodinntak som ligger under jodbehovet (EAR eller AR). Jodbehovet (EAR) hos voksne er 100 mikrogram per dag. Jenter i 13 års alderen har det laveste jodinntaket, og 38 % av disse jentene har et inntak under jodbehovet (EAR eller AR) som er 73 mikrogram per dag for denne aldersgruppen. Det estimerte jodinntaket i den femte persentilen av kvinner i fertil alder og 13-åringer, er henholdsvis 70 og 38 mikrogram per dag. Alle voksne og 13-, 9- og 4- åringer har et beregnet jodinntak under de tolerable øvre inntaksnivåene.

Inntaksberegningene for 2 år gamle barn viser at 9 % har et jodinntak under jodbehovet (EAR eller AR), og 8 % har inntak over det tolerable øvre inntaksnivået. Det estimerte jodinntaket i 95-persentilen av 2-åringene er 215 mikrogram per dag, litt over det tolerable øvre inntaksnivået på 200 mikrogram per dag for denne aldersgruppen.

Inntaksberegningene for 1-åringer som ikke ammes, viser at 8 % har et jodinntak under jodbehovet (EAR eller AR), og 18 % har inntak over det tolerable øvre inntaksnivået på 200 mikrogram per dag. Det estimerte jodinntaket i 95-persentilen av 1-åringene som ikke ammes, er 259 mikrogram per dag.

Vi har presentert 12 scenariotabeller; tre scenarioer (bare husholdningssalt alene, bare salt i brød alene, samt både husholdningssalt og salt i brød) for fire nivåer av tilsetning av jod (15, 20, 25 og 50 mg jod per kg salt). Andelen av befolkningen med et jodinntak over behovet (EAR eller AR) øker med økt tilsetning av jod, men samtidig øker også andelen med et jodinntak over tolererbare øvre inntaksnivåer i noen grupper av befolkningen.

Scenarioene som ser ut til å øke jodinntaket hos kvinner i fertil alder og 13-åringer opp til et adekvat inntak, er tilsetning av jod opp til 15 eller 20 mg jod per kg salt, inkludert tilsetning av jod til salt i brød. Over disse berikningsnivåene forventes det ikke økte fordeler for kvinner

i fertil alder eller 13-åringer. For 1- og 2-åringer fører alle scenarioer til en økning i andelen småbarn med et beregnet jodinntak over det tolerable øvre inntaksnivået.

Nytte- og risikovurdering av tilsetning av jod til husholdningssalt og industrialisert salt i brød

De lave beregnede inntakene av jod hos ungdom (13-åringer) og kvinner i fertil alder (18-45 år) kan ikke korrigeres i tilstrekkelig grad av de foreslåtte økte tilsetningene av jod til husholdningssalt og/eller industrisalt i brød, uten at det medfører høye jodinntak hos 1- og 2-åringer.

VKM antar at kvinner i fertil alder og 13-åringer vil ha nytte av økt tilsetning av jod i salt og brød. Dette vil også være til fordel for andre grupper som av forskjellige årsaker har få matvarer som utgjør de viktigste kildene til jod i kostholdet, for eksempel mennesker som ikke spiser mager fisk eller bruker melk eller andre meieriprodukter. Risikoen dette medfører for de minste barna, er en høyere andel av 1- og 2-åringene som kommer over det tolerable øvre inntaksnivået. Basert på vitenskapelige studier/evidens og dataene som er presentert i denne nytte- og risikovurderingen, kan det derfor ikke konkluderes med at et spesifikt nivå av tilsetning av jod til salt og brød vil representere en nytte for alle populasjonsgrupper (alder og kjønn) uten at det samtidig utgjør en økt risiko for negative helseeffekter hos andre, eller at nytten i en populasjonsgruppe oppveier risikoen i en annen.

Det er viktig å understreke at anbefalinger for næringsstoffer er satt for å sikre tilstrekkelig vekst og utvikling, opprettholde god helse og redusere risikoen for kroniske sykdommer. Inntak av jod under EAR eller over UL reduserer mulighetene for å oppnå de gunstige effektene av tilstrekkelig inntak. Dagens jodinntak hos visse grupper er bekymringsfullt lavt, og trendstudier viser et synkende inntak av melk og meieriprodukter, de viktigste kildene til jod i det norske kostholdet, spesielt blant unge kvinner.

Flere studier viser at spesielt ungdom og kvinner i fertil alder har utilstrekkelig inntak av jod, noe som kan medføre at en rekke individer også har økt risiko for alvorlig jodmangel. Det er så vidt vi vet, ingen data om forekomst av alvorlig jodmangel i Norge. Med andre ord, vi vet ikke hvor mange, om noen, som har kliniske konsekvenser på grunn av for lavt jodinntak.

Scenarioene som ser ut til å øke jodinntaket til adekvat nivå hos kvinner i fertil alder og hos 13-åringer (gruppene som har høyest risiko for lavt inntak), er tilsetning av jod opp til 15 eller 20 mg jod per kg salt, inkludert salt i brød. Over disse nivåene forventes det ikke økt fordel for kvinner i fertil alder og 13-åringer, mens flere befolkningsgrupper vil ha en risiko for å overskride tolerabelt øvre inntaksnivå, og spesielt 1- og 2-åringer.

WHO anbefaler salt som kilde for jodtilsetning for å korrigere jodmangel i en populasjon, etterfulgt av en tett overvåking av joderingsprogrammet.

Abbreviations and definitions

Abbreviations

AI – adequate intake
AR – average requirement
bw – body weight
CI – confidence interval
Cr – creatinine
DRI – dietary reference intake
DRV – dietary reference value
EAR – estimated average requirement (IOM)
EFSA – European Food Safety Authority
EVM – Expert group on vitamins and minerals of the Food Standard Agency, UK
FFQ – food frequency questionnaire
fT3 – free triiodothyronine
fT4 – free thyroxine
ID – iodine deficiency
IDD – iodine deficiency disorders
IIH – iodine induced hyperthyroidism
IQR – interquartile range
IOM – Institute of Medicine, USA
KBS – kostberegningssystemet (Software system used to calculate dietary intake)
LOAEL – lowest observed adverse effect level
MCRA – Monte Carlo risk assessment
MoBa – the Norwegian Mother and Child Cohort
NFSA – Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NIS – Na^+/I^- symporter
NNR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
OIMs – observed individual means
PRI – population reference intakes
RDA – recommended dietary allowances
RI – recommended intake
SCF – Scientific Committee for Food
SGA – small for gestational age
SUL – safe upper intake level
T3 – triiodothyronine
T4 – thyroxine
TBG – thyroxin binding globulin
TDI – tolerable daily intake
Tg – thyroglobulin
TgAb – thyroglobulin antibody

TGR – total goiter rate
Thyroid nodules - abnormal growth of thyroid cells that forms a lump within the thyroid gland
TPOAb – thyroid peroxidase antibody
TRH – thyrotropin-releasing hormone
TSH – thyroid stimulating hormone also known as thyrotropin
Tvol – thyroid volume
UF – uncertainty factor
UIC – urinary iodine concentration
UL – tolerable upper intake level
VKM – Norwegian Scientific Committee for Food and Environment [*Norw.*: Vitenskapskomiteen for mat og miljø]

Definitions

Household salt: Salt (NaCl) for home cooking including table salt.

"Jod-Basedow effect"/syndrome: Iodine-induced hyperthyroidism is a rare cause of thyrotoxicosis seen typically after the administration of exogenous iodine. It appears to result from loss of the normal adaptation of the thyroid to iodide excess.

Mild iodine deficiency: In groups of children (> 6 years) and non-pregnant adults, iodine deficiency is characterised as mild when median urinary iodine concentration (UIC) is 50-99 µg/L (WHO, 2007; WHO, 2013). WHO defines median UIC<150 µg/L as insufficient and has no definition of mild iodine deficiency.

Moderate iodine deficiency: In groups of children (> 6 years) and non-pregnant adults, iodine deficiency is characterised as moderate when median UIC is 20-49 µg/L (WHO, 2007; WHO, 2013). In pregnant women, mild-to-moderate iodine deficiency is defined as median UIC in the range 50-149 µg/L (Zimmermann, 2007).

Percentile is a statistical measure indicating the value below which a given percentage of the observations fall. Percentiles can be reported as PX, i.e. that P5 indicates the level of a measurement for which 5% of the observations fall below. P50 is the same as median.

P5, P25, P50, P75 or P95-exposure is the calculated exposure at the 5, 25, 50, 75 or 95-percentile.

Severe iodine deficiency: In groups of children (> 6 years) and non-pregnant adults, iodine deficiency is characterised as severe when median UIC is < 20 µg/L (WHO, 2007; WHO, 2013). In pregnant women, severe iodine deficiency is defined as UIC <50 µg/L (Zimmermann, 2007).

"Wolff-Chaikoff effect": a description of the acute auto regulatory phenomenon, whereby the thyroid detects iodine excess and down-regulate the processes involved in thyroid hormone synthesis and secretion to protect against hyperthyroidism (Laurberg et al., 2010).

EFSA - Dietary Reference Values (DRVs) (EFSA, 2010c)

Average Requirement (AR) is the level of intake of a defined group of individuals estimated to meet the physiological requirement of metabolic demand, as defined by the specific criterion for adequacy for the nutrient, in half of the healthy individuals in a life stage or sex group, on the assumption that the supply of other nutrients and energy is adequate.

If an AR cannot be determined, then an Adequate Intake is used.

Adequate Intake (AI) is defined as the average (median) daily level of intake based on observed, or experimentally determined approximations or estimates of a nutrient intake, by a group (or groups) of apparently healthy people, and therefore assumed to be adequate. The practical implication of an AI is similar to that of a population reference intake, i.e. to describe the level of intake that is considered adequate for health reasons. The terminological distinction relates to the different ways in which these values are derived and to the resultant difference in the "firmness" of the value.

Population Reference Intake (PRI) is derived from AR of a defined group of individuals in an attempt to take into account the variation of requirements between individuals.

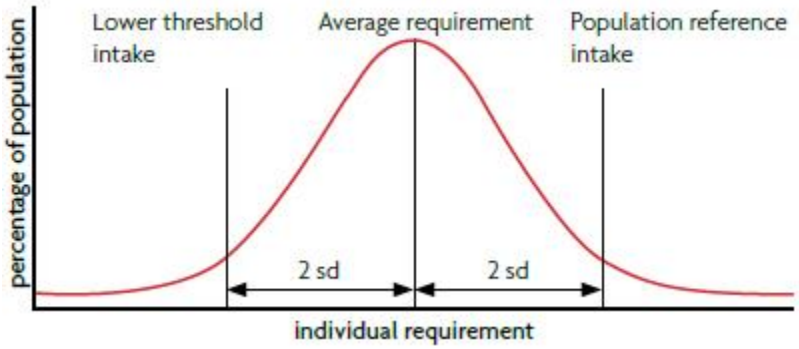

Figure 1 Population reference intake (PRI and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010b).

Lower Threshold Intake (LTI) is the lowest estimate of requirement from the normal distribution curve, and is generally calculated on the basis of the AR minus twice its SD. This will meet the requirement of only 2.5% of the individuals in the population.

Tolerable Upper Intake Level (UL) is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.

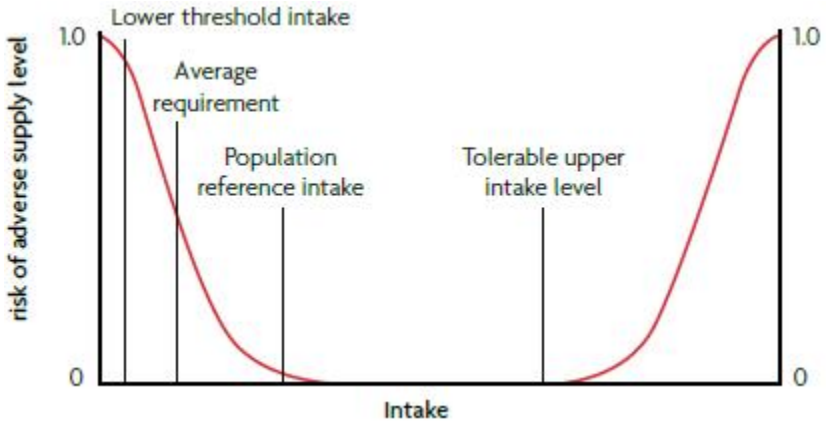

Figure 2 Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake.

IOM - Dietary Reference Intakes (DRIs) (IOM, 2000)

Estimated Average Requirement (EAR) is a nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a life stage and gender group.

Recommended Dietary Allowances (RDA) is the dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group. RDA = EAR + 2 SD_{EAR} or if insufficient data to calculate SD a factor of 1.2 is used to calculate RDA; RDA = 1.2*EAR

Adequate Intake (AI) is the recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people that are assumed to be adequate – used when an RDA cannot be determined

Tolerable Upper Intake Level (UL) is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population.

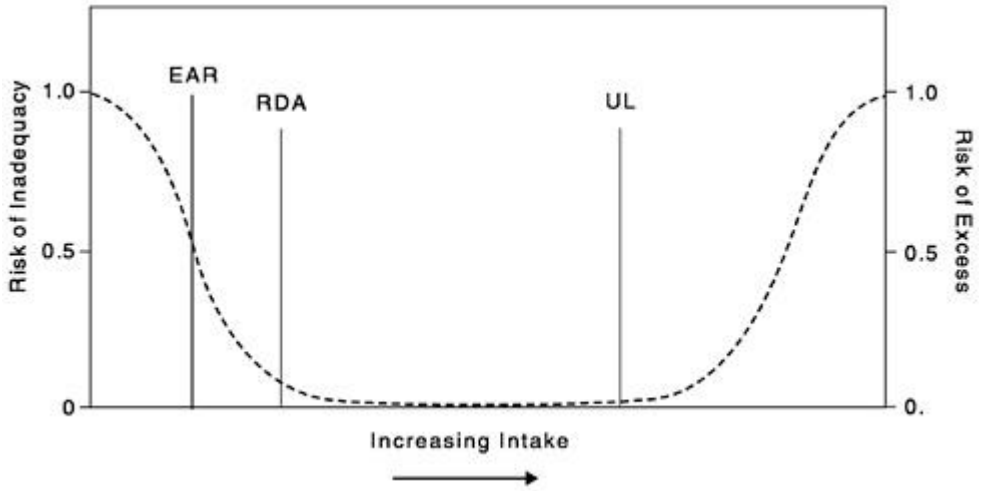

Figure 3 Dietary reference intakes.

NNR -Recommended Intake (NNR Project Group, 2012)

Average Requirement (AR) is defined as the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual i.e. the level of a nutrient that is sufficient to cover the requirement for half of a defined group of individuals provided that there is a normal distribution of the requirement.

$AR_{NNR} = EAR_{IOM} = AR_{EFSA}$

Recommended Intake (RI) is defined as the amount of a nutrient that meets the known requirement and maintains good nutritional status among practically all healthy individuals in a particular life stage or gender group. $RI = AR + 2SD_{AR.}$

$RI_{NNR} = RDA_{IOM} = PRI_{EFSA}$

Upper Intake Level (UL) is defined as the maximum level of long-term (months or years) daily nutrient intake that is unlikely to pose a risk of adverse health effects in humans.

$UL_{NNR} = UL_{IOM} = UL_{EFSA}$

The Lower Intake (LI) is defined as a cut-off intake value below which an intake could lead to clinical deficiency symptoms in most individuals. Same as LTI in EFSA's terminology.

World Health Organization (WHO, 2007)

Recommended nutrient intake (RNI), see RDA under Institute of Medicine above.

Background as provided by the Norwegian Food Safety Authority

Risk of iodine deficiency in Norway

Iodine is an essential nutrient required for the synthesis of the thyroid hormones triiodothyronine and thyroxine. These hormones help regulating key metabolic processes in every cell of the body and are particularly important for brain cell development. Both iodine deficiency and iodine excess increase the risk of thyroid disturbances.

In June of 2016, the National Nutrition Council in Norway published the report "Risk of iodine deficiency in Norway. Identifying an immediate need for action" (Nasjonalt råd for ernæring, 2016). The report shows insufficient iodine intake among fertile, pregnant and breastfeeding women. Iodine deficiency in pregnancy or during breastfeeding can impair the neurological development of the child. The World Health Organization (WHO) estimates that severe iodine deficiency is the leading cause of preventable brain damage in infants worldwide.

The main sources of iodine in the Norwegian diet are dairy products, eggs, fish and other seafood. Low iodine intake among Norwegian women is primarily caused by a decrease in the consumption of dairy products and fish. Other risk groups that may have too low iodine intake are vegans, individuals who are allergic to milk and fish and some ethnic minorities. According to the report from the National Nutrition Council, adult men and children aged 2 generally have adequate iodine intake. The recommended iodine intake for adults and children aged 10 and above is 150 µg of iodine daily.

An excessive iodine intake is associated with disruption of thyroid gland function. It may cause goiter, hypo- and hyperthyroidism as well as inflammation of the thyroid gland (thyroiditis). For adults, including pregnant and breastfeeding women, the tolerable upper intake level (UL) for iodine, that is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans, is set at 600 µg per day (NNR Project Group, 2012).

Iodized salt and other food items

Iodized household salt is available in Norway. Iodization of salt is currently not compulsory in Norway and only allowed in concentrations up to 5 µg of iodine per gram of salt. Some foods on the Norwegian market also contain iodized salt. These are primarily imported foods such as bread, baked goods, soups and sauces.

The report from the National Nutrition Council suggests various measures to increase iodine intake in the population, especially among women who are of childbearing age, pregnant or breastfeeding. The suggested measures include recalculating how much iodine should be added to salt, raising the upper limit for iodization of household salt and possibly enforcing

compulsory use of iodized salt in parts or all of the food industry. Iodine concentrations in salt vary across Europe, from 5 µg/g up to 75 µg/g. For example, Sweden and Finland have increased iodine intake in their population by using respectively 50 and 25 µg iodine per gram of salt. In Denmark, the salt iodization level required by the authorities of iodine in salt has been 13 µg/g but was increased to 20 µg/g from 1 July 2019. The order made by the Danish Ministry of the Environment and Food, applies to bread and general bakery.

The iodine compounds used for addition to foods are potassium iodide (KI), sodium iodide (NaI) and potassium iodate (KIO3).

Salt intake

The average salt intake in Norway is estimated to be about 10 grams per day for men and a little less for women. "The National action plan to reduce salt intake 2014-18" is based on the National Nutrition Council's Strategy for reducing salt intake in the population. The national action plan aims at reducing salt intake in the Norwegian population by 15 percent in 2018 and 30 percent by 2025.

Iodine in milk

The report also suggests regulating iodine content in Norwegian milk. Milk contains iodine which is added to cow feed in order to avoid iodine deficiency in cattle. Iodine fortification in animal feed is intended to cover the animal's needs rather than increasing iodine concentration in milk meant for human consumption. In recent years, the iodine concentration in milk has been stable in Norway (16 µg/100 g milk) and feed regulations remain difficult to alter. The possibility of reducing and/or standardising iodine concentration in milk was therefore not included in the terms of reference to VKM.

New data

The publication of the National Nutrition Council's report has been followed by the announcement of new data on iodine contents in foods as well as a new dietary survey carried out among children and adolescents (Ungkost 3). These new data offer an opportunity to adjust current estimates of iodine intake in the Norwegian population. New data on iodine intake among Norwegian women during pregnancy and breastfeeding have also been published.

In May 2018, the Norwegian Food Composition Table was published with updated iodine values for all foods, and the values for coffee and whey cheese was updated again in September 2019.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) hereby requests the Norwegian Scientific Committee on Food and Environment (VKM) to conduct a benefit-risk assessment of iodization of household salt and of industrial salt used in bread. The assessment should include subpopulations which are at risk of overly low or high intake of iodine, including women of childbearing age, women who are pregnant and breastfeeding, men and children. Other risk groups such as vegans, individuals suffering from allergy or intolerance to fish and dairy products, relevant ethnic minorities and individuals consuming iodine supplements should also be considered. Iodization of plant-based alternatives to cow milk products should also be considered. Imported foods that are fortified with iodine and sold on the Norwegian market should also be taken into account.

The aforementioned benefit-risk assessment should be executed in parallel with a separate assignment sent to VKM: establishing a new maximum limit for iodine in food supplements.

The benefit-risk assessment should cover the following:

1. What is the iodine intake in the general population and among identified risk groups? Risk groups meaning subpopulations at risk for overly low or high iodine intake.
2. What would the iodine intake in the general population and among identified risk groups (see above) be if household salt and industrial salt used in bread were to be iodized and if plant-based milks were to be fortified with iodine levels comparable to those in cow milk? Table 1 shows the iodization levels in salt for which the potential effect on iodine intake is to be estimated. The iodine intake resulting of the various scenarios should be estimated both with and without the added effect of iodine fortification of plant-based alternatives to dairy products (milk 16 µg/100 g). The estimates should also be considered in the context of the *Salt Strategy 2015* (governmental initiatives to reduce salt consumption).

Table 1 Requested scenarios.

Iodization levels	**Food items**	
20 mg iodine/kg	Household salt	
		Industrial salt used in bread
	Household salt +	Industrial salt used in bread
25 mg iodine/kg	Household salt	
		Industrial salt used in bread
	Household salt +	Industrial salt used in bread

Iodization levels	Food items	
50 mg iodine/kg	Household salt	
		Industrial salt used in bread
	Household salt +	Industrial salt used in bread

3. What potential health effects will the various iodization levels have for the general population and the identified risk groups (see above)?

NFSA requires that VKM estimates iodine intake based on data from the national dietary surveys among adults (Norkost 3; age 18-70 years) children and adolescents (Ungkost 3; ages 4-, 9- and 13-years), infants and children age 1 and 2 years (Spedkost and Småbarnskost), the Norwegian Mother and Child Cohort Study (MoBa) as well as other relevant dietary surveys and studies on iodine concentration in urine for other groups.

Assessment

1 Introduction

Iodine is an essential micronutrient required for synthesis of the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Through these hormones, iodine has an important role in energy-yielding metabolism and on the expression of genes that affect many physiological functions, including embryogenesis and growth, and the development of neurological and cognitive functions (Zimmermann et al., 2008).

Iodine deficiency has since the beginning of this century been recognised as a worldwide problem and is the most common preventable cause of brain damage (Hetzel, 2012). Although there has been remarkable progress in ameliorating iodine deficiency, it still remains a public health concern in many countries, including some European countries (Lazarus, 2014; WHO, 2007). Also, iodine deficiency in the population has re-emerged in some European countries previously considered iodine sufficient, including Norway. According to the report from the National Nutrition Council in Norway "Risk of iodine deficiency in Norway", iodine intake is particularly low among women of childbearing age including pregnant and breastfeeding women (Nasjonalt råd for ernæring, 2016).

A recent systematic review has confirmed that inadequate iodine intake is widespread in Norway among women of childbearing age, also pregnant and breastfeeding women, infants who are exclusively breastfed, elderly persons, vegans and Somali immigrants (Henjum et al., 2019). In particular, the authors of the review expressed concern regarding iodine status among women of childbearing age, as all included studies published after 2016 showed a median urinary iodine concentration (UIC) lower than the cut-off for adequate group median set by the WHO for this group (see Figure 1-1).

The need for action to secure adequate iodine intake in Norway, particularly in vulnerable groups is emphasised in the report from the Norwegian National Nutrition Council (Nasjonalt råd for ernæring, 2016). Increased iodization of salt and use of iodized salt in bread and bakery products were among the actions suggested in the report (Nasjonalt råd for ernæring, 2016).

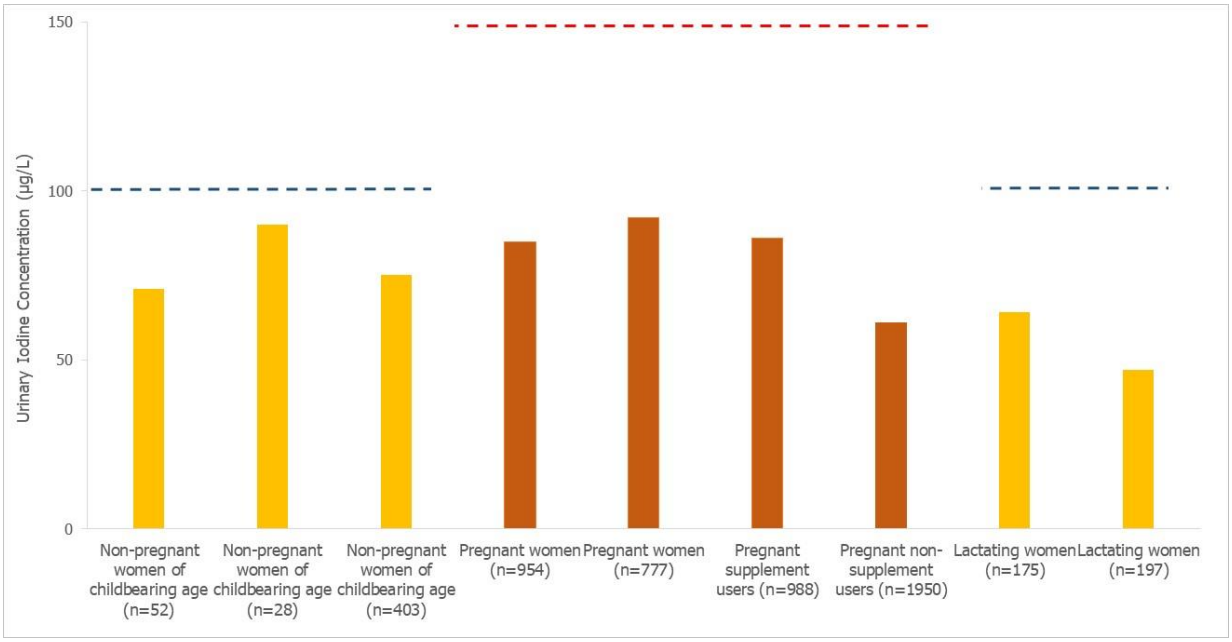

Figure 1-1 Median urinary iodine concentration (UIC) in Norwegian women of childbearing age. The dotted lines represent UIC cut-offs for insufficient iodine intake set by the WHO (median UIC<150 µg/L for pregnant women and median UIC<100 µg/L for non-pregnant) (WHO, 2007). The figure is based on eight Norwegian studies summarised by (Henjum et al., 2019).

1.1 Global recommendation for salt iodization

Iodization of salt (sodium chloride) has been recommended by the WHO as the preferred strategy for preventing iodine deficiency disorders in the global context (WHO, 2014), and is currently implemented in more than 120 countries worldwide. The recommendation was justified by a comprehensive systematic review and meta-analysis that provided a synthesis of available data comparing the effect of consumption of iodized salt on an array of health outcomes related to iodine deficiency, including goiter, cretinism, cognitive function, hypo- and hyperthyroidism. The authors concluded that iodized salt has a large effect on reducing the risk of iodine deficiency, goiter, cretinism and low cognitive function (Aburto et al., 2014). The authors also emphasised the importance of robust monitoring of salt iodization programmes to ensure safe and effective levels of iodine consumption, especially as countries implement programmes to reduce population salt intake.

According to the WHO, the reasons for salt being an appropriate vehicle for iodization include:

> "(i) it is widely consumed by virtually all population groups in all countries, with little seasonal variation in consumption patterns, and salt intake is proportional to energy intake/requirements; (ii) in many countries, salt production is limited to a few centres, facilitating quality control; (iii) the technology needed for salt iodization is well established, inexpensive and relatively easy to transfer to countries around the world; (iv) addition of iodate or iodide to salt does not affect the taste or smell of the salt or foods containing iodized salt, and therefore consumer acceptability is high; (v) iodine (mainly from iodate) remains in processed foods that contain salt as a main ingredient,

such as bouillon cubes, condiments and powder soups, and hence these products become sources of iodine; and (vi) iodization is inexpensive (the cost of salt iodization per year is estimated at US$ 0.02–0.05 per individual covered, and even less for established salt-iodization programmes)" (WHO, 2014).

WHO recommends salt as a vehicle for correcting iodine deficiency in a population, and furthermore, WHO recommends that iodization programs should be monitored (UNICEF, 2018; WHO, 2007).

The WHO report outlined the suggested iodization levels to account for recommended iodine intake (150 µg/day), losses before consumption (30%) and bioavailability (92%) at various salt consumption levels. At an estimated salt consumption of 10 g/day, the average suggested iodization level is 20 mg iodine per kg salt, while the suggested iodine concentration at an estimated salt consumption of 5 g/day is 39 mg per kg salt (WHO, 2014).

1.1.1 Current salt iodization in Norway

In Norway, most salt is currently not fortified with iodine. One type of household salt containing 5 mg added iodine per kg salt is available. Iodized salt is generally not used in the food industry, except that a few manufacturers have added iodized salt to selected products. At the current assumed intake level of 10 g salt per day, it would provide a maximum of 50 µg iodine per day if all salt was iodized at this level. Assuming a mean population salt intake of 5 grams per day, which is the long-term target in the governmental initiatives to reduce salt consumption, and that all salt used was iodized, salt would provide an average of 25 µg iodine per day with the current iodization level.

1.2 Methodology for this benefit and risk assessment

The overall aim of this report is to provide a benefit and risk assessment of the health impact related to current iodine intakes in the Norwegian population, and the health impact of increased iodization levels in household salt and salt in bread.

Established knowledge

In the first chapters; 2, 3 and 4 we describe what may be considered general and established knowledge about the physiology of iodine and health consequences of both low and high intakes. We also describe established dietary reference values e.g. recommended intakes, average requirement and tolerable upper intake levels based on values from other competent bodies.

Updated literature and evidence for health outcomes

In chapters 5 and 6, to identify the best available and updated evidence on the health effects of mild to moderate iodine deficiency and excessive iodine intakes, we review papers from systematic literature searches. For health effects related to mild to moderate iodine

deficiency, the literature was reviewed with a specific objective to identify all published scientific papers addressing how mild to moderate iodine deficiency affects health, and the literature was reviewed according to established methods for weight of evidence. As the evidence base for how excessive iodine affects health is far less comprehensive than for iodine deficiency, we did not aim at evaluating the literature for excess intakes with the same weight of evidence tools as for deficiency. We have only evaluated if new literature is in line with the existing tolerable upper intake levels or if new levels should be established.

Calculated iodine intakes – including the requested scenarios

In chapter 7 we calculate iodine intakes in the Norwegian population and compare the intakes to a selected set of the established dietary reference values described in chapter 4, and also calculate the requested scenario of increased iodization levels in household salt and salt in bread.

Bringing it all together

In the benefit and risk assessment in chapter 8, we bring together and discuss all relevant elements in the previous chapters and discuss and weigh the benefits from avoidance of iodine deficiency (or risks related to iodine deficiency), the risk related to excessive iodine intakes, and the impact of increased iodization levels in household salt and salt in bread.

Uncertainty, data gaps and conclusion

Finally, we describe the most evident uncertainties and data gaps and answere the questions in the terms of reference.

Iodine from food supplements

We have not taken into account intervention studies that have investigated effects of individual supplementation specifically. Furthermore, in the chapters describing and discussing the iodine exposure and the increased iodization scenarios, our conclusions are based upon calculations without iodine supplements. However, calculations for supplement users are presented in Appendix V.

In a separate assignment from the Norwegian Food Safety Authority, VKM is requested to evaluate the consequences of establishing maximum limits for iodine at 150, 250, 450, 600 or 1100 µg/day, as examples in food supplements, and to evaluate the total intakes of iodine in exposure scenarios including basic foods, iodized foods and food supplements, against tolerable upper intake levels. This assignment will be answered in a separate opinion.

2 Iodine physiology and metabolism

2.1 Chemistry

Nonradioactive iodine-127 is the most stable and common isotype of the 37 isotopes found in nature. Iodine belongs to the group of elements known as halogens. Due to its large atomic size, it is the least reactive of the halogens, but it can exist in different chemical states, including iodide (I^-), elemental iodine (I_2), iodate (IO_3^-) and periodate (IO_4^-). This redox sensitive chemical speciation makes the iodine cycle in the environment extremely complex. Approximately 70% of global iodine is present in marine systems. Iodine in the lithosphere and pedosphere is often limited, which causes iodine deficiency in some parts of world (Cox and Arai, 2014). Potassium iodide (KI) and potassium iodate (KIO_3) are often used for iodization of refined table salt. Iodate is less soluble and more stable than iodide. Foods contain iodine mainly as iodide (I-), but also as iodate (IO3-), or thyroxine.

2.2 Absorption, distribution, metabolism and excretion

Iodine is an essential micronutrient for humans. The human body possesses a number of mechanisms by which it can absorb, collect, concentrate and excrete iodine in the form of its monovalent anion iodide. This system encompasses several organ systems and different physiological processes, all to ensure strict control of iodine processing and utilisation.

Iodine in the form of inorganic iodide (I^-), is rapidly and nearly completely absorbed (>90%) in healthy adults (Nath et al., 1992; van der Reijden et al., 2019). Other chemical states of iodine, such as iodate and protein-bound iodine in foods, are reduced in the gastrointestinal tract to iodide prior to being absorbed. The sodium/iodide symporter (NIS), a transport protein of the apical surfaces of enterocytes, mediates active uptake of iodine from the stomach and small intestine (Nicola et al., 2009). NIS is also located on the basal membrane in thyroid follicular cells. As the activity of NIS is three to four times greater in the thyroid gland than in any other tissue in the body, it allows the gland to sequester iodide from the blood and accumulate iodine as a precursor for synthesis of thyroid hormones (T3 and T4) (Carrasco, 2003; Dohan and Carrasco, 2003).

The expression and function of NIS is under hormonal regulation by thyroid stimulating hormone (TSH) (Riedel et al., 2001). At low TSH levels, NIS transport activity is inhibited, while NIS is downregulated when the amount of iodide taken up from food increases (Callejas et al., 2016; Leoni et al., 2011; Nicola et al., 2012). Thus, the thyroid sequesters and accumulates iodide depending on iodine and thyroid hormone homeostasis (Doggui and El Atia, 2015; Portulano et al., 2014; Zimmermann, 2009).

A sudden excess of circulating iodide, as a consequence of high iodine intake, rapidly decreases iodine transfer into the thyroid, as well as production and release of thyroid hormones (Laurberg et al., 2010; Wolff and Chaikoff, 1949). This thyroid block, called the "Wolff-Chaikoff effect" is a mechanism to protect against hyperthyroidism. The effect is

transient and thyroid function returns to normal after a few days. In some individuals, the "Wolff-Chaikoff effect" does not occur and excess iodine leads to a sustained increase in hormone synthesis, resulting in iodine-induced hyperthyroidism, also known as the "Jod-Basedow effect". This effect is most frequently observed following iodine supplementation or fortification in areas with very low iodine intake (Delange et al., 1999).

A healthy adult body contains 15-20 mg of iodine, 70-80% of which is stored in the thyroid gland (Callejas et al., 2016). In chronic iodine deficiency, the iodine content of the thyroid may fall below 20 µg (Zimmermann, 2009). The thyroid takes up approximately 10% of the iodine from the circulation in an iodine-sufficient human, whereas in states of chronic iodine deficiency, the thyroid can take up more than 80% of the circulating iodine (DeGroot, 1966; Stanbury, 1954). During lactation, the mammary glands concentrate iodine and actively secrete it into milk for the infant. A few other tissues take up small amounts of iodine, including the salivary glands, gastric mucosa, and choroid plexus (Callejas et al., 2016).

When dietary iodine intake is abundant, absorbed iodide is distributed through the extracellular space with a half-life of approximately 10 h in the circulation. Approximately 90% of ingested iodine is excreted, mainly in urine and the remainder in feces (Callejas et al., 2016). In states of iodine deficiency, however, the half-life varies due to a more rapid thyroid uptake and increased glomerular filtration rate. Thus, losses via urine are regulated both through circulating levels (urine content is proportional to blood concentration) and the efficiency of tubular reabsorption (Kohlmeier, 2015).

2.3 Biomarkers of iodine status and thyroid function

Several different indicators are used to assess the iodine status and thyroid function in a population: urinary iodine concentration (UIC), serum thyroid stimulating hormone (TSH) or thyroid hormones (T3 and T4) concentrations, serum thyroglobulin (Tg), and thyroid volume (Tvol) by palpation and/or by ultrasonography. These indicators are complementary, in that UIC is a sensitive indicator of recent iodine intake (days), Tg is an indicator of intermediate response (weeks to months), whereas changes in Tvol and goiter rate reflect long-term iodine nutrition (months to years) (Zimmermann, 2008).

Figure 2.3-1 below illustrates a simplified model of human iodine and thyroid status at different stages (left to right) of decreasing iodine intake, published by (Zimmermann and Andersson, 2012). The three stages iodine sufficiency, iodine deficiency with increased thyroidal iodine clearance, and iodine deficiency leading to thyroid dysfunction, are separated by dashed vertical lines in Figure 2.3-1.

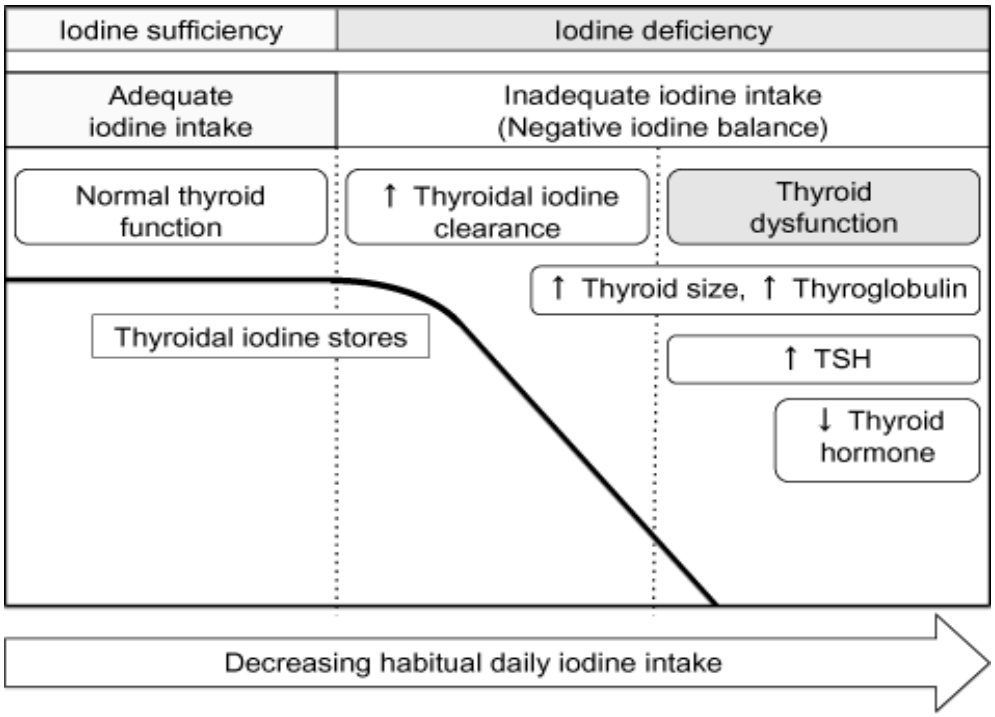

Figure 2.3-1 The physiological stages of iodine status (Source: Figure 5 (Zimmermann and Andersson, 2012).

According to Zimmermann, the scientific evidence is limited with regard to the absolute levels of habitual daily iodine intake at which thyroid stores decrease and thyroid dysfunction occurs. In addition, thyroid function is inhibited when iodine intake becomes too high (Laurberg et al., 2010). The biomarkers of iodine status are described in more details below.

Urinary iodine concentration (UIC)

Urinary iodine concentration (UIC) provides direct information about iodine intakes as ≥92% of dietary iodine is absorbed and, in healthy, iodine-replete adults >90% is excreted in the urine within 24-48 h (Callejas et al., 2016). Therefore, UIC is regarded as a reliable biomarker and the most commonly used indicator for assessing recent iodine intake at group level and to classify populations worldwide as iodine deficient, iodine sufficient or with excessive iodine intake (WHO, 2007; Zimmermann et al., 2008). Random spot urine samples are the most widely used specimen for biochemical measurement of UIC (Soldin, 2002) and has been recommended as an acceptable biomarker of short-term iodine intake at a population level (Rohner et al., 2014; WHO, 2014). The high day-to-day variability in the dietary iodine intake of individuals results in high day-to-day variation in UIC which limits the usefulness of this measure for assessing iodine status at an individual level (Andersen et al., 2008). It is therefore not correct to assume that all individuals with UIC<100 µg/L are iodine deficient, unless the UIC is based on several repeated measurements. According to one study, at least ten spot urine samples or 24-hour urine collections are needed to assess individual iodine status with 20% precision (Konig et al., 2011). Because the 24-h excretion of creatinine is constant over time within individuals, creatinine adjustment of UIC to correct

for urine volume has also been used for estimation of 24-h iodine excretion from spot urine samples (Pearce and Caldwell, 2016).

WHO has established criteria for assessing iodine status based on UIC. These criteria are presented in Table 2.3-1. A median urinary iodine concentration of 100 µg/L corresponds roughly to an average daily iodine intake of 150 µg (IOM, 2001).

Table 2.3-1 Epidemiological criteria for assessing iodine status in a population, based on median or range of urinary iodine concentrations, modified from (WHO, 2007).

MEDIAN UIC	IODINE INTAKE	IODINE STATUS
School-aged children (≥6 years) and non-pregnant adults		
<20 µg/L	Insufficient	Severe iodine deficiency
20–49 µg/L	Insufficient	Moderate iodine deficiency
50–99 µg/L	Insufficient	Mild iodine deficiency
100–199 µg/L	Adequate	Adequate iodine nutrition
200–299 µg/L	Above requirements	Likely to provide adequate intake for pregnant/lactating women, but may pose a slight risk of more than adequate intake in the overall population
≥300 µg/L	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism and autoimmune thyroid disease)
Pregnant women		
<150 µg/L	Insufficient	
150–249 µg/L	Adequate	
250–499 µg/L	Above requirements	
≥500 µg/L	Excessive	
Lactating women		
<100 µg/L	Insufficient	
≥100 µg/L	Adequate	
Children < 2 years of age		
<100 µg/L	Insufficient	
≥100 µg/L	Adequate	

Urinary iodine concentration (UIC) does not provide direct information on the effect of iodine intakes on thyroid function, but low UIC values reflect low iodine intakes and thereby suggest that populations have increased risk of developing thyroid disorders (Zimmermann, 2009).

Thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4)

Regardless of cause, serum thyroid stimulating hormone (TSH) is a sensitive early indicator of thyroid dysfunction (Spencer et al., 1990), and the thyroid gland secretes the thyroid hormones T3 and T4 in response to TSH, which is produced in the pituitary gland (Pearce and Caldwell, 2016).

The thyroid gland may adapt to iodine deficiency in several ways (Dayan and Panicker, 2009). Iodine deficiency will cause an increased avidity of the thyroid gland for available iodine, an increase in the ratio of T3 to T4 production (Stevenson et al., 1974), increased T4 to T3 conversion in peripheral tissues, and thyroid gland enlargement (Patel et al., 1973). In most populations with mild to moderate iodine deficiency, serum TSH, T3 and T4 are still in the normal range. An exception is shown in some areas of mild to moderate iodine deficiency, especially among elderly, in whom serum TSH values may be decreased due to the increased prevalence of hyperthyroidism from autonomously functioning nodular goiter (Knudsen et al., 2000).

In populations living in moderate to severe iodine-deficient areas, serum TSH levels may be elevated whereas T4 levels may be slightly low and T3 levels may be slightly high compared to those living in iodine-sufficient areas (Chopra et al., 1975). Changes in T3 and T4 concentration due to decreased iodine intakes can be explained by a preferential secretion of T3 by the thyroid which occurs because the activity of T3 is roughly four times that of T4, and T3 only needs 85% as much iodine for its synthesis (Callejas et al., 2016).

Likewise, studies show that excessively high iodine intakes can lead to thyroid dysfunction, which may result in slightly elevated serum TSH values (Laurberg et al., 2010; Meng et al., 2013). Although TSH may be slightly increased by mild to moderate iodine deficiency and excessive iodine exposure, values often remain within the reference range and TSH is an insensitive marker of iodine status and therefore a poor indicator of iodine status in older children and adults (Zimmermann, 2009; Zimmermann et al., 2008). However, a systematic review by (Zimmermann, 2008) concluded that in iodine deficient populations, TSH is a sensitive indicator of iodine status in newborns.

Thyroglobulin (Tg)

Thyroglobulin (Tg) is a protein synthesised and secreted by the thyroid gland. Serum Tg is widely used as a marker for monitoring thyroid cancer and also in the diagnosis of certain other thyroid diseases (Knudsen et al., 2001). Increased plasma Tg is seen both during iodine deficiency and iodine excess and is considered a sensitive marker for iodine status (Ma and Skeaff, 2014). For example, when iodine intakes decrease, an increase in Tg and thyroid volume will follow. Increased Tg or thyroid volume (Tvol) is as an early sign of increased thyroid activity and is not regarded as a clinically relevant endpoint for thyroid dysfunction if thyroid hormone production is still within the normal range.

In iodine sufficiency, small amounts of Tg are secreted from the thyroid into the circulation (Spencer and Wang, 1995). In iodine deficiency, serum Tg increases due to greater thyroid cell mass and TSH stimulation (Zimmermann, 2008). Studies have reported that serum Tg appears to be well correlated with the severity of iodine deficiency as measured by UIC and that Tg is a more sensitive indicator of iodine status than TSH or T4 (Bath et al., 2017; Benmiloud et al., 1994; Knudsen et al., 2001; Missler et al., 1994).

It is important to notice, however, that the validity of Tg as a measure of iodine deficiency is limited in people with detectable anti-thyroglobulin antibodies (TgAb), who comprise ~10% of the adult population (Hollowell et al., 2002; Spencer and Wang, 1995).

Furthermore, serum Tg levels are affected by the highly increased levels of human chorionic gonadotropin (hCG) during the first trimester of pregnancy, which stimulate thyroid function (Fantz et al., 1999). Some studies have therefore questioned whether Tg is a valid marker of iodine deficiency in pregnancy, at least in mildly iodine-deficient environments (Koukkou et al., 2016; Laurberg et al., 2007), whereas another study concluded that Tg shows promise as a long-term marker of iodine status in pregnant women (Bath et al., 2017).

Thus, researchers have suggested that future studies among pregnant women should consider measurement of Tg concentration concurrently with TgAb, in addition to urinary iodine-to-creatinine ratio and that validated assays with trimester-specific reference ranges may be needed when assessing the iodine status of pregnant women (Bath et al., 2017; Pearce and Caldwell, 2016).

Thyroid volume (Tvol)

Goiter, an enlarged thyroid gland, is the most visible effect of iodine deficiency. Correspondingly, large excesses of iodine inhibit thyroid hormone production, and may lead to increased TSH stimulation, thyroid growth and goiter (Farebrother et al., 2019a). Enlargement of the thyroid gland and prevalence of goiter is commonly measured by two different methods: neck inspection and palpation, and thyroid ultrasonography. In areas of mild to moderate iodine deficiency, the sensitivity and specificity of palpation are poor and measurement of thyroid size using ultrasound is preferable (WHO, 2007)

3 Health consequences of iodine deficiency or excessive iodine

Both severe iodine deficiency and excessive iodine intake can result in thyroid dysfunction. Iodine is essential for the synthesis of the thyroid hormones that are required for healthy development, growth, and metabolism (Zimmermann, 2011). Thyroid hormones are critically important for the foetus and young infant by affecting the development and maturation of the nervous system, skeletal muscles, and lungs. The health consequences of both deficiency and excess are accordingly mediated through altered thyroid function. This chapter describes the consequences of severe iodine deficiency and excess.

As discussed in chapter 2, there are substantial limitations in the iodine biomarkers. UIC is suitable to describe the status in populations but not in individuals. Severe iodine deficiency causes hypothyroidism. It is also prudent to assume that mild to moderate deficiency can have similar, but milder consequences. The limitations in defining iodine status in individuals, however, challenges the identification of a level at which adverse effects occur.

When the population median UIC is low, a higher proportion is likely to have severe deficiency compared to when the UIC is higher. Associations between UIC or iodine intake and thyroid-related health outcomes have been observed in populations with mild to moderate deficiency, however, whether these associations are due to consequences of mild to moderate or severe deficiency is not known.

The association between iodine intake and the occurrence of thyroid disorders in a population is U-shaped (Laurberg and Nohr, 2002) as illustrated in Figure 3-1.

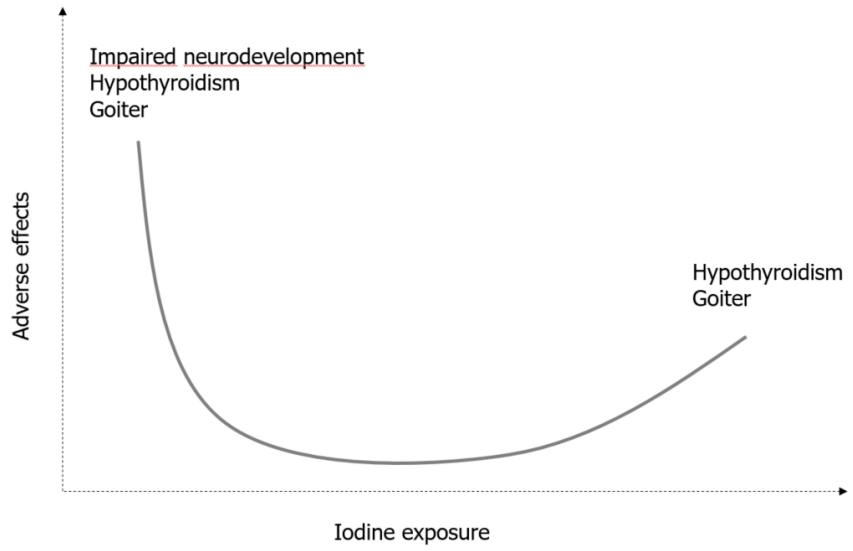

Figure 3-1 Adverse effects related to iodine deficiency and excess (Adapted from Laurberg, 2002).

3.1 Health consequences of iodine deficiency

The thyroid is estimated to use 60-80 µg of iodide daily to produce its customary output of thyroid hormones (Zimmermann, 2012). About a quarter of this is acquired from recycling endogenous iodide and the rest is acquired from the diet (Zimmermann et al., 2008).

3.1.1 Reduced thyroid function and goiter

When the availability of iodine decreases, various auto regulatory mechanisms are triggered to maintain normal thyroid function (euthyroidism). These include increased thyroid activity to maximise iodine uptake and preferential production of T3 to T4 to save one iodine atom per hormone molecule and secure availability of T3, the directly active form of thyroid hormone (Obregon et al., 2005). Therefore, many individuals in iodine deficient areas are clinically euthyroid and their TSH levels are not elevated because the level of circulating T3 is normal. Increased TSH production stimulates excessive growth of the thyroid gland, i.e. goiter, and occurs when thyroidal mechanisms are no longer sufficient to maintain normal T3 levels. Goiter may in the most severe form lead to mechanical difficulties such as difficulty in swallowing and breathing and may evolve into a life-threatening condition.

Hypothyroidism may also be caused by several other conditions than iodine deficiency. Common causes are autoimmune disease, such as Hashimoto's thyroiditis, surgical removal of the thyroid, and radiation treatment.

It has been reported that endemic goiter appears in populations where daily iodine intake is less than 50 µg/day (Hetzel, 1988; Stanbury and Hetzel, 1980), leading to a reduction in the iodine content of the thyroid gland. The most important functions of the thyroid hormones are regulation of metabolism, heart rate and organ development. Iodine deficiency may lead to several severe complications mediated through poor thyroid function, collectively termed iodine deficiency disorders (IDD). Iodine deficiency affects all populations at all stages of life, from the intrauterine stage to old age as shown in Table 3.1-1.

Table 3.1-1 Effects of severe iodine deficiency, by life stage (Source: Adapted from WHO, 2005).

Life stage	Effects
Foetus	Abortions Stillbirths Congenital anomalies Increased perinatal mortality Increased infant mortality Neurological cretinism: mental deficiency, deaf mutism, spastic diplegia and squint
Neonate	Neonatal goiter Neonatal hypothyroidism
Child and adolescent	Goiter Juvenile hypothyroidism

Life stage	Effects
	Impaired mental function Retarded physical development
Adult	Goiter with its complications Hypothyroidism Impaired mental function Iodine-induced hyperthyroidism

3.1.2 Neurodevelopmental outcomes

As thyroid hormones stimulate the metabolism in most body tissues, and are essential for brain development (Delange, 2001), poor iodine status may lead to poor development of foetuses, infants, and children.

The central nervous system grows rapidly during foetal life and into early childhood. The first 1000 days of life, counting from conception, are regarded as the most critical period for negative influences that may affect neurological development. The growth of the central nervous system is sequential, where the various steps may depend on each other, and each step may be particularly crucial for a distinct function. The severity and specific outcomes affected by negative influences are accordingly related to both the timing and magnitude of the exposure (Zoeller and Rovet, 2004). The different phases of brain development are depicted in Figure 3.1.2-1 below.

Thyroid hormone receptors are present in the foetal brain from around nine weeks after conception, and the foetal hormone production commences around week 14. However, little hormone synthesis occurs until the 18th to 20th week (Bernal, 2007). During this period, the foetus depends on maternal thyroid hormones, particularly T4, since T3 found in the foetal brain is predominantly derived locally from T4 (Obregon et al., 2005).

The thyroid hormones are required for neurogenesis, axon and dendrite growth, neuronal migration and differentiation of neural cells, for generating synapses, and for myelination of the central nervous system (Redman et al., 2016).

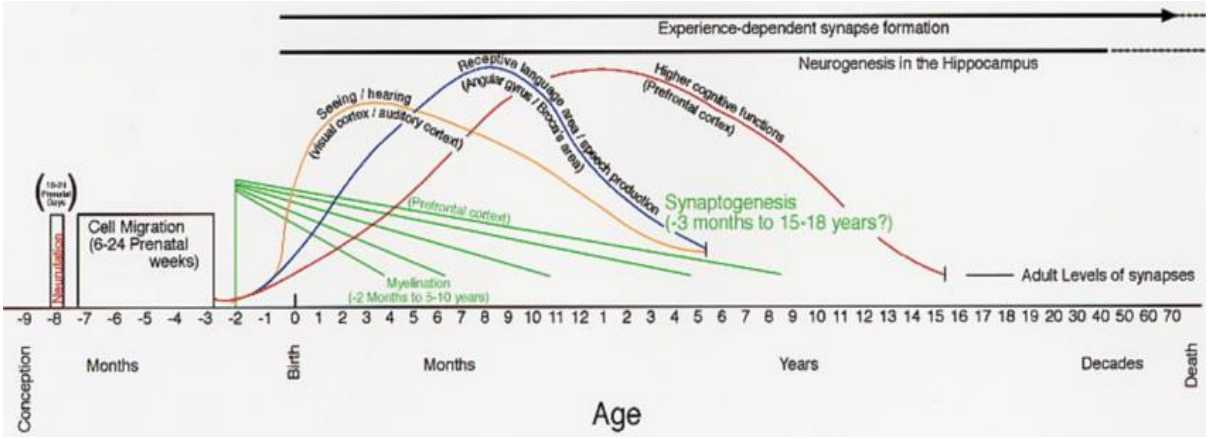

Figure 3.1.2-1 Human brain development (Source: adapted from (Thompson and Nelson, 2001). The x-axis is time from birth (conception = -9 months), y-axis is a relative scale indicating the magnitude of development of a particular neurodevelopmental function.

As illustrated in Figure 3.1.2-1, hypothyroidism due to iodine deficiency, occurring during certain sensitive periods of foetal life, infancy, or early childhood have the potential to hamper neurodevelopment and result in lasting suboptimal cognitive function. The impact and which functions that are affected, however, will depend on the timing and severity of deficiency. Severe iodine deficiency during these critical phases can lead to permanent intellectual disability, which in its most severe form is known as cretinism. This syndrome is characterised by permanent brain damage, mental retardation, deaf mutism, spasticity and stunting. Cretinism is currently hardly ever seen in Norway and most other affluent countries. While it is well documented that severe iodine deficiency during foetal life may cause impaired neurodevelopment in children, the potential adverse effects of mild to moderate deficiency are unclear (Zimmermann et al., 2008).

It should be noted that hypothyroidism is also a significant cause of infertility so that women with severe deficiency often fail to reproduce. Iodine deficiency is also a risk factor for thyroid cancer, particularly the more severe cancer forms (Zimmermann and Galetti, 2015).

3.1.3 Other health consequences of severe iodine deficiency

Severe maternal iodine deficiency in pregnancy may also result in miscarriages, preterm delivery, stillbirth, and congenital abnormalities. These effects are mediated through the action of thyroid hormones on the developing tissues as well as an indirect effect of decreased metabolism following reduced thyroid function (Zimmermann and Boelaert, 2015). Severe iodine deficiency in infancy increases neonatal and infant mortality (DeLong et al., 1997).

3.2 Health consequences of excessive iodine

In general, there have been more studies and reports of adverse health consequences of iodine deficiency than of iodine excess. However, it has been established that excessive iodine causes altered thyroid function and may lead to both increased (hyperthyroidism) and

decreased (hypothyroidism) thyroid hormone production (Burgi, 2010; Farebrother et al., 2019a; Katagiri et al., 2017; Laurberg et al., 2010).

Iodine-induced hyperthyroidism (IIH) may occur in individuals with thyroid nodular changes, as a side effect of iodine supplementation or in populations with increased iodine intake following recent iodine fortification (Delange et al., 1999; Stanbury et al., 1998). In this condition, excess iodine leads to a sustained increase in hormone synthesis ("Jod-Basedow effect)". IIH might be transient or permanent, and risk factors include thyroid diseases and chronic iodine deficiency (Laurberg et al., 2010; Pramyothin et al., 2011).

The other harmful consequence of iodine excess is hypothyroidism. In order to protect against hyperthyroidism due to excess iodine, the normal physiological response is to block iodine transport into the thyroid, thereby inhibiting the production and release of thyroid hormones. This is called the "Wolff-Chaikoff effect" (Wolff and Chaikoff, 1949). Typically, thyroid hormone levels return to normal after a few days of this effect, termed the "escape" or "adaption" from the "Wolff-Chaikoff effect" (Eng et al., 1999). Failure to adapt and return to normal thyroid hormone production is considered to play a role in the development of clinical or subclinical hypothyroidism (Katagiri et al., 2017). Risk factors for iodine-induced hypothyroidism include previous iodine deficiency, underlying thyroid autoimmunity for which Caucasian populations may have a genetic predisposition (Laurberg et al., 2010), or a history of partial thyroidectomy.

Reviews of the epidemiological evidence on excess iodine in relation to thyroid function suggest that high iodine intake is associated with subclinical hypothyroidism more often than hyperthyroidism. The evidence is more limited in children than in adults.

The clinical consequence of excessive intakes in young children is uncertain, and the studies found adequate for comparison with the existing UL (chapter 6.2.2) only include children at or above the age of 6 years. However, a recent non-systematic review study of iodine excess and thyroid function highlights three publications that include children aged 6-24 months from areas of Africa, Asia, or Europe (Croatia only). The overall conclusion was that "…long term effects of chronic excessive iodine on thyroid function and somatic growth and development in infants and young children remain uncertain" (Farebrother et al., 2019a).

One of the studies included in this review assessed thyroid function and Tg concentrations in 6-24 month-old infants from several countries and observed an increase in Tg in infants with estimated habitual iodine intakes >230 µg/day. The authors concluded that "The association between UIC and Tg concentration follows the same U-shaped association in 6-24 months weaning infants as in other population groups. However, our data suggest the optimal intake range is narrower than in older children or adults» (Farebrother et al., 2019b). The two other studies were carried out in groups with more extreme iodine intakes (median UIC > 400 µg/L) and reported an increased prevalence of subclinical hypothyroidism (Aakre et al., 2016; Nepal et al., 2015). Whether these findings have clinical or developmental consequences is uncertain, but subclinical hypothyroidism may in some cases progress to overt hypothyroidism (Cooper and Biondi, 2012).

Iodine excess may be particularly harmful in certain life-stages and population groups, notably pregnant women, infants, and toddlers (Leung and Braverman, 2014). For this reason, high doses of iodine are contraindicated during pregnancy (Carswell et al., 1970; Frey, 1971). It has been pointed out that infants and children have a higher turnover of thyroid hormones than adults and that changes in thyroid physiology during infancy could increase the vulnerability of infants to extremes of iodine intake (Farebrother et al., 2019a). Whether excessive iodine exposure, acute or chronic, is a significant cause of poor neurodevelopment or other adverse health outcomes is still a matter of debate. Developmental brain damage due to excess iodine has only been demonstrated in animal models for extremely high doses.

3.3 Thyroid cancer

Both low and high iodine intakes may contribute to the development of thyroid cancer (Zimmermann and Galetti, 2015). The cited reviews are all found in the literature search, even though thyroid cancer was not included in the search terms, and the summary in this chapter is not systematic.

A comprehensive review including both animal and human studies, assessed the relationship between iodine intake and risk of thyroid cancer (Zimmermann and Galetti, 2015). Animal studies indicate that iodine deficiency is a strong promoter of thyroid cancer, mainly of the follicular, more malignant type. The proposed mechanism for the effects of iodine deficiency is chronic elevation of TSH that stimulates thyrocyte proliferation and increases the likelihood of mutagenesis. However, the relevance of these findings from animal studies to humans are uncertain (Zimmermann and Galetti, 2015).

Over the past two to three decades, there has been a clear temporal relationship in many countries between introduction of iodized salt and an increase in incidence of papillary thyroid cancer which is a mild form of thyroid cancer. However, at the same time, several countries that have stable or decreasing iodine intakes, including Australia, the U.S. and Switzerland have also experienced an increase in this cancer type. Although a causal role of iodine intake in the etiology of papillary thyroid cancer cannot be ruled out, a more likely explanation for the increasing incidence of papillary thyroid cancer worldwide is the introduction and wider use of improved thyroid diagnostics (Zimmermann and Galetti, 2015). The overall incidence of thyroid cancer in populations does not appear to be influenced by the usual range of iodine intakes from dietary sources. Data from countries before and after iodine prophylaxis have demonstrated a change in the distribution to less malignant subtypes, which is in line with the findings from animal studies. Thus, evidence from animal and ecological studies indicate that iodized salt programs might be contributing to the decrease in thyroid cancer mortality seen in many countries (Wiltshire et al., 2016).

3.4 Vulnerable groups for iodine deficiency and excessive iodine

In the following, vulnerable groups refer to populations that for biological reasons are especially vulnerable to low or high iodine intakes. Populations at particular risk of low or high iodine intakes are described in chapter 7.3.3.

Due to the massive and stepwise growth of the central nervous system in early life, foetuses, infants and toddlers face the most severe consequences of iodine deficiency and inadequate thyroid hormone production (Zoeller and Rovet, 2004). Even small impairments during this period may have severe and irreversible consequences for later life particularly for delicate systems such as the brain. Therefore, an adequate iodine intake is especially important in women of childbearing age and children.

Both inadequate and excess iodine intake lead to insufficient production of thyroid hormones and subsequent health consequences. Pregnant women, their foetuses, and young children are therefore also vulnerable to excessive iodine intakes. Some observational studies indicate that even a small abrupt increase in iodine intake in pregnant women with previous low iodine intake, e.g. from initiation of iodine supplement use, may result in "thyroid stunning", similar to the "Wolff-Chaikoff effect" (Moleti et al., 2011). This effect supports the importance of adequate iodine intake and maximised thyroidal iodine stores prior to conception (Bath, 2019).

Individuals with previous or ongoing thyroid dysfunction or those who have suffered from iodine deficiency for a long time are also at risk of disturbances in thyroid hormone status resulting from sudden increase or excess iodine intake.

Elderly women are susceptible to nodular goiter. An increased incidence of nodular goiter has been described in some populations after introduction of salt fortification, mainly seen in older women (Krejbjerg et al., 2014). However, this effect usually disappears when the overall iodine status in the population improves. Furthermore, the observed increased incidence of noduli is not associated with other clinical consequences, or increased use of thyroxine (T4) medication.

Dermatitis herpetiformis is an autoimmune blistering skin disease associated with gluten intolerance and celiac illness. Individuals with dermatitis herpetiformis may experience flare-ups when exposed to iodine in food or directly on the skin. Small amounts of iodine around the recommended daily requirements are not of concern (Nicolas et al., 2003).

3.5 Summary of health consequences of iodine deficiency and excessive iodine

Iodine deficiency and iodine excess both impair the production of thyroid hormones. Severe iodine deficiency will impair growth and neurodevelopment through lower production of thyroid hormones. The most severe effect is damage to the foetus resulting in irreversible brain damage. To ensure an adequate iodine intake is therefore especially important in

women of childbearing age. It is, however, less clear to which degree mild to moderate iodine deficiency may affect growth and development in infancy and childhood. The extent to which there is a dose-response relationship between iodine status and health outcomes in the mild to moderate deficiency range has not been well described.

Excessive iodine may lead to both increased (hyperthyroidism) and decreased (hypothyroidism) thyroid hormone production. Iodine-induced hyperthyroidism after excessive iodine intakes may be transient or permanent, and the risk is increased in persons with thyroid disease or chronic iodine deficiency. The observed health consequences of excess iodine are less severe than those of severe iodine deficiency.

4 Dietary reference values for iodine

Dietary reference values (DRVs) is an umbrella term for a set of nutrient reference values that includes the average requirement (AR), the population reference intake (PRI), the adequate intake (AI) and the reference intake range for macronutrients (RI). These values guide professionals on the amount of a nutrient needed to maintain health in an otherwise healthy individual or group of people. DRVs also include the tolerable upper intake level (UL), which is the maximum amount of a nutrient that can be consumed safely over a long period of time. These terms are described in detail in the chapter listing Abbreviations and definitions.

4.1 Iodine requirement and recommended intakes

4.1.1 Institute of Medicine, USA (2001)

In 2001, the US Institute of Medicine established a recommended dietary allowance (RDA) for iodine at 150 µg/day for adults. Thyroid iodine accumulation and turnover were used to set the estimated average requirement (EAR). The US Institute of Medicine (IOM) has recently been renamed and incorporated into the National Academies of Science, Engineering and Medicine (NASEM). Thus, all DRI reports through 2011 were published by IOM, while all subsequent reports are published by NASEM.

IOM (2001) proposed the following equation to calculate daily iodine intake from UIC:

Daily iodine intake = UIC (µg/L) × 0.0235 × bodyweight (kg)

The equation assumes that 92% of dietary iodine is absorbed. Although body weight is poorly correlated with urine volume in adults, the equation is a good approximation considering an average 24-h urine volume of 1.5 L/day in adults. Alternatively, daily iodine intake can be estimated from UICs by estimating the daily urinary iodine excretion by means of the urinary creatinine concentration.

The EAR for adolescents ≥14 years and adults was set to be 95 µg/day, assuming a coefficient of variation of 40%. The EAR for pregnant and lactating women was set to be 160 and 209 µg/day, respectively, with a coefficient of variation of 20%. The EARs for children 1-8 years an 9-13 years were set to 65 and 73 µg/day, respectively. For children 1-8 years, the EAR is based on iodine balance studies in children (Malvaux, 1969; Ingenbleek and Malvaux, 1974 both cited in IOM, 2001). For adolescents aged 9-13 years, the EAR was extrapolated from adult EARs on a metabolic body weight basis allowing for growth needs ($kg^{0.75}$).

The RDA was defined as equal to the EAR plus twice the coefficient of variation to cover the needs of 97 to 98 percent of the individuals in the group. The calculated values for RDA were rounded up to the nearest 50 µg. The suggested RDA values for various age groups and pregnant and lactating women are provided in Table 4.1.1-1.

In collaboration with WHO and FAO, NASEM has proposed harmonised nutrient reference values for populations. Instead of the term EAR, AR should be used, and for iodine the harmonised AR (h-AR) is the previous EAR for all age groups (Allen et al., 2019).

Table 4.1.1-1 Suggested recommended dietary allowances (RDAs) for iodine from IOM, µg/day (2001).

	Adults	**Pregnant**	**Lactating**	**Children and adolescents**		
	≥19 y			1-8 y	9-13 y	14-18 y
Recommended dietary allowances (RDAs)	150	220	290	90	120	130
EAR*	95	160	209	65	73	95

*The definition of EAR by IOM corresponds to the term AR used by NNR and the updated proposed harmonised nutrient reference values from NASEM (previously IOM).

4.1.2 WHO (2005 and 2007)

Based on recommendations from the Food and Nutrition Board of the United States National Academy of Sciences from 1989 and previous WHO-reports, WHO (2005) recommended a daily iodine intake of 40 µg/day for young infants (0–6 months), 50 µg/day for older infants (7–12 months), 60–100 µg/day for children (1–10 years), and 150 µg/day for adolescents and adults (WHO, 2005). According to WHO, these recommended values will ensure normal T4 production without stressing the thyroid iodide trapping mechanism or raising TSH levels. The recommended nutrient intake (RNI) at 150 µg iodine/day for adolescents and adults is justified by the fact that it corresponds to the daily urinary excretion of iodine and to the iodine content of food in non-endemic areas (i.e. in areas where iodine intake is adequate). Furthermore, it represents the intake of iodine necessary to maintain the plasma iodide concentration above the critical limit of 0.10 µg/dL, which is the average level likely to be associated with the onset of goiter. Moreover, 150 µg iodine/day is required to maintain iodine stores in the thyroid above the critical threshold of 10 µg, to avoid disorders in the production of thyroid hormones (WHO, 2005).

In 2007, WHO/UNICEF/ICCIDD increased the recommended nutrient intake (RNI) for iodine during pregnancy and lactation from 200 to 250 µg/day (WHO, 2007). During lactation, thyroid hormone production and UIC return to normal, but iodine is concentrated in the mammary gland for excretion into breast milk. Thus, using the UIC to estimate intake may lead to an underestimate of requirements. To ensure sufficient iodine from breast milk to build reserves in the thyroid gland in the infant, WHO increased the RNI for iodine for lactating women to 250 µg/day. On the other hand, the rationale for increasing the RNI for pregnant women was not well described. The consensus reached by the WHO/UNICEF/ICCIDD in 2007 emphasised that in countries without universal salt iodization, women of childbearing age should be given oral iodine supplementation to ensure that the total iodine intake meets the recommendation of 150 µg iodine per day. However, pregnant women should not be recommended to take iodine-containing supplements if the population in general had been iodine sufficient for at least 2 years (Andersson et al., 2007).

Table 4.1.2-1 Recommended nutrient intakes (RNIs) of iodine from FAO/WHO (2005[1]and 2007[2]), µg/day.

	Adults[1]	Pregnant[2]	Lactating[2]	Children 1-10 y[1]
Recommended nutrient intake (RNI)	150	250	250	90-120

4.1.3 Nordic and Norwegian Nutrition recommendations (2012)

Prior to the 5th revision of the Nordic Nutrition recommendations (2012), an expert group conducted a systematic literature review aiming to summarise the scientific basis for the previous iodine recommendation in the Nordic countries (Gunnarsdottir and Dahl, 2012). The recommended intake of iodine from 2004 remained unchanged for adults and children because no new data supported any changes in the 2012 revision. The iodine requirement to prevent goiter was estimated to be 50-75 µg/day for adult women and men, and the AR was estimated to be 100 µg/day, an intake level at which the iodine concentration in the thyroid gland reaches a plateau. The recommended intake (RI) for adults and adolescents therefore remained 150 µg/day and this amount includes a safety margin for goitrogenic substances (foods containing substances interfering with uptake of iodine in the thyroid gland, e.g. soy and cabbage).

The NNR expert group also evaluated the scientific rationale for the recommended increased iodine intake during pregnancy and lactation from WHO (Gunnarsdottir and Dahl, 2012). In pregnancy, a higher iodine intake is recommended to cover for the higher thyroid hormone production and simultaneously increased excretion in the urine (Andersen and Laurberg, 2016). A higher iodine intake is also recommended during lactation to ensure sufficient iodine in the breast milk. Although WHO decided to increase the recommended intake of iodine for pregnant and lactating women from 200 to 250 µg/day in 2007, these changes were not adopted in NNR (2012). The experts responsible for NNR (2012) based this decision on lack of new data to support changes in recommended iodine intake for this particular group, and that women in the Nordic countries were considered iodine replete before pregnancy and having easy access to iodine rich food, such as milk, seafood, and dietary supplements. The Norwegian recommendations were based on the Nordic recommendations, and the Nordic and Norwegian recommendations for intake of iodine in various age groups and pregnant and lactating women are shown in Table 4.1.3-1.

Table 4.1.3-1 Nordic and Norwegian dietary reference values for iodine, µg/day (NNR Project Group, 2012).

	≥ 10 years and adults	Pregnant	Lactating	Children		
				12-23 mo	2-5 y	6-9 y
Recommended intake (RI)	150	175	200	70	90	120
Average requirement (AR)*	100					

	≥ 10 years and adults	Pregnant	Lactating	Children		
				12-23 mo	2-5 y	6-9 y
Lower intake level (LI)	70					

*the definition of AR corresponds to the term EAR used by IOM (USA).

4.1.4 Dietary Reference Values from EFSA (2014)

The most recent dietary reference values (DRVs) for iodine were set by EFSA in 2014. The EFSA Panel concluded that there was insufficient evidence to derive an average requirement (AR) or a population reference intake (PRI) for iodine and decided to set an adequate intake (AI). The AIs from EFSA were based on studies exploring the relationship between iodine intake/status and thyroid gland volumes/prevalence of goiter as markers of mid to long-term iodine intakes (EFSA, 2014).

For adults and children, the AI was based on iodine intakes ensuring a UIC which had been associated with the lowest prevalence of goiter in school-aged children (≥100 µg/L). An UIC of 100 µg/L corresponds to an approximate daily intake of 150 µg iodine in older adolescents and adults. An average urinary volume of 1.5 L/day in adults derived from the water intake recommendations, was used to estimate the intake based on UIC at 100 µg/day.

For infants and young children the proposed AI was also based on the UIC, which had been associated with the lowest prevalence of goiter in school-aged children. For children, age-specific urinary volumes and absorption efficiency of dietary iodine were taken into account to calculate the AI.

For pregnant women, iodine intake was assumed to be adequate before conception. The AI for pregnant women at 200 µg/day takes into account the additional needs because of increased thyroid hormone production, and iodine uptake by the foetus, placenta and amniotic fluid accounting for an additional iodine requirement of 50 µg/day.

The proposed AI for lactating women of 200 µg/day takes into account the existence of large iodine stores in conditions of adequate iodine status before pregnancy and considers that a full compensation of the transitory loss of iodine secreted in breast milk is not justified for the derivation of an increased AI for iodine for lactating women. Thus, the same AI was set for pregnant and lactating women.

Table 4.1.4-1 Adequate intakes (AIs) for iodine from EFSA (2014), µg/day.

	Adults	Pregnant	Lactating	Children and adolescents		
	≥18 y			1-10 y	11-14 y	15-17 y
Adequate Intakes (AI)	150	200	200	90	120	130

4.1.5 Overview of dietary reference values from previous reports

Table 4.1.5-1 gives an overview of the recommended dietary iodine intake in adults, whereas Table 4.1.5-2 gives reference values for recommended iodine intake in pregnant and lactating women.

Table 4.1.5-1 Overview of dietary reference values for iodine in adults.

Authority	µg/day	Critical endpoint
EFSA, 2014	AI[1]=150	Thyroid volume enlargement
NNR, 2012	RI[2]=150	Thyroid volume enlargement
WHO, 2005	RNI[3]=150	Maintain normal T4 production and prevention of goiter
IOM, 2001/ NASEM (Allen et al., 2019)	RDA[4]=150	Thyroid iodine accumulation and turnover

[1]AI=Adequate Intake, [2]RI=Recommended intake, [3]RNI=Recommended nutrient intake, [4]RDA=Recommended Dietary Allowances.

Table 4.1.5-2 Overview of DRVs for iodine in pregnant and lactating women and the rationale for higher recommendations than in non-pregnant adults.

Authority	Pregnant µg/day	Lactating µg/day	Rationale for higher intakes than adults
EFSA, 2014	AI[1]=200	AI=200	*Pregnancy*: Increased thyroid hormone production, iodine uptake by foetus, placenta and amniotic fluid. Additional need approx. 50 µg/day, assuming adequate intakes before pregnancy. *Lactation*: Daily iodine losses in breast milk= 60-90 µg. However, to further increase iodine intake to cover full compensation for iodine losses in breast milk were not considered justified.
NNR, 2012	RI[2]=175	RI=200	*Pregnancy:* To cover the needs of the foetus and to maintain maternal thyroid gland function. Assuming adequate intakes before pregnancy. *Lactation*: To provide sufficient iodine in the breast milk.
WHO, 2007	RNI[3]=250	RNI=250	*Pregnancy:* Increased glomerular filtration in pregnant women. *Lactation*: To ensure sufficient iodine from breast milk to build reserves in the thyroid gland in the infant.
IOM, 2001	RDA[4]=220	RDA=290	*Pregnancy*: Thyroid iodine uptake by the foetus approx 75 µg/day *Lactation*: Average daily loss of iodine in breast milk approx 114 µg.

[1]AI=Adequate Intake, [2]RI=Recommended intake, [3]RNI=Recommended nutrient intake, [4]RDA=Recommended Dietary Allowances.

4.2 Tolerable upper intake levels (UL) for iodine

Institute of Medicine (IOM) in US established ULs for iodine in 2001, and Scientific Committee on Food (SCF) in EU established ULs for iodine in 2002. The Expert Group on Vitamins and Minerals (EVM) in Great Britain suggested safe upper level (SUL) for iodine in 2003, as did Nordic Nutrition Recommendations in 2012.

4.2.1 Institute of Medicine, US (2001)

The IOM stated that there is little uncertainty regarding the range of iodine intakes that are likely to induce elevated TSH concentrations. A lowest observed adverse effect level (LOAEL) of 1700 µg iodine per day and a no observed adverse effect level (NOAEL) of 1000 to 1200 µg iodine per day were estimated for adults (based on Gardener et al. (1988) and Paul et al. (1988) cited in IOM, 2001) (IOM, 2001). The IOM chose an uncertainty factor (UF) of 1.5 to derive a NOAEL from a LOAEL. A higher uncertainty factor was not considered necessary because of the mild, reversible nature of elevated TSH over baseline.

The LOAEL of 1700 µg/day was divided by a UF of 1.5 to obtain a UL of 1133 µg/day of iodine, which was rounded down to 1100 µg/day.

Table 4.2.1-1 Tolerable upper intake levels for iodine in different age groups adjusted by body weight suggested by the Institute of Medicine (2001).

Age (years)	UL µg/day
1-3	200
4-8	300
9-13	600
14-18	900*
19 and older	1100*

*Including during pregnancy and lactation.

In a proposed update from National Academies of Science, Engineering and Medicine (NASEM), the harmonised UL (h-UL) is reduced to 200-500 µg/day for children and 600 µg/day for adults (Allen et al., 2019).

4.2.2 Scientific Committee on Food, EU (2002)

The Scientific Committee on Food (SCF) also established an UL based on changes in TSH levels and the TSH response to thyrotropin-releasing hormone (TRH) administration (SCF, 2002). The changes were all considered to be of a biochemical nature and not associated with any clinical adverse effects. The elevated serum levels of TSH were regarded as indicators of an existing risk of induced hypothyroidism. Even though it was recognised that the changes were not associated with any clinical adverse effects at estimated intakes of 1700 and 1800 µg/day, the SCF used 1800 µg/day as a LOAEL. Most of the studies (also including Gardener (1988) and Paul (1988)) were characterised by short duration, few participants and low precision of the actual total dietary intakes. The results were, however, supported by a study covering a 5-year exposure to dietary iodide levels of approximately 30

µg/kg bw per day (equivalent to approximately 1800 µg iodide/day) in which no clinical thyroid pathology occurred. An UF of 3 was considered adequate and provided an UL for adults of 600 µg/day. An UL of 600 µg/day was also considered acceptable for pregnant and lactating women based on evidence of lack of adverse effects at exposures significantly in excess of this level. Since there is no evidence of increased susceptibility to excess iodine intake in children, the ULs for children were derived by adjustment of the adult UL based on body surface area (body weight 0.75).

Table 4.2-2 Tolerable upper intake levels for iodine for different age groups adjusted for body surface area (body weight$^{0.75}$) suggested by the Scientific Committee for Food (2002).

Age (years)	UL µg/day
1-3	200
4-6	250
7-10	300
11-14	450
15-17	500
Adults	600*

*Acceptable also for pregnant and lactating women.

4.2.3 Expert Group on Vitamins and Minerals, Great Britain (2003)

The Expert Group on Vitamins and Minerals (EVM) in UK concluded that there were insufficient data from human or animal studies to establish a Safe Upper Level for iodine. They cited some of the same studies as IOM, but interpreted the increase in TSH differently (EVM, 2003):

"A few studies (Paul et al., 1988; Chow et al., 1991; Gardner et al., 1988) have reported that supplemental doses of 0.5 to 1.5 mg iodine/day produced small changes in the levels of thyroid hormones. Other studies (Saxena et al., 1962; Freund et al., 1966) indicate that supplemental doses of 2 mg/day, in addition to the iodine present in the diet, result in the blockage of further iodine uptake. Although 0.5 mg supplemental iodine/day has been reported to alter thyroid parameters in some studies, the changes are likely to represent normal feedback processes rather than adverse effects."

For guidance purposes only, EVM suggested that a supplemental intake of 0.5 mg/day (equivalent to 0.003 mg/kg bw in a 60 kg adult), in addition to dietary iodine would not give significant adverse effects in adults. No uncertainty factors were applied as the data were considered to be derived from a number of well-designed, controlled human studies.

Assuming an intake of iodine from the diet of 0.43 mg/day, this equated to a total intake of 0.94 mg/day (equivalent to 0.015 mg/kg bw/day in a 60 kg adult), which was expected to be without adverse effects. The EVM commented that some consumers might have higher dietary iodine intakes, particularly children, but that compensatory mechanisms exist.

4.2.4 Nordic Nutrition Recommendations (2012)

NNR Project Group (2012) refers to tolerable upper intake levels for iodine established by SCF (2002) (described above) and mentions one additional study among children. This additional study is also included our own literature search described in chapter 5. Therefore, results from this particular study will not be further elaborated in this section.

4.2.5 Overview ULs from previous reports

Table 4.2.5-1 gives an overview of the conclusions for ULs/GL for iodine in adults in previous reports.

Table 4.2.5-1 Overview of the conclusions for ULs/GL for iodine in adults in previous reports.

	UL/GL µg/day	Endpoint	Based on	NOAEL	LOAEL (µg/day)	UF
IOM, 2002	1100	Elevated TSH-levels	Human studies, intravenous exposure TRH	-	1700	1.5
SCF, 2002	600	Elevated TSH-levels	Human studies, intravenous exposure TRH	-	1800	3
EVM, 2003	GL:500 µg/day from supplemental iodine					
NNR, 2012	600		SCF, 2000			

4.3 Summary of dietary reference values and discussion of use of reference values for comparison

IOM/NASEM, WHO, NNR and EFSA have all established dietary reference values for iodine, and they have all agreed upon a recommended daily iodine intake of 150 µg/day for adults. However, based on various arguments, the recommendations for pregnant women vary between 175 (NNR Project Group, 2012) and 250 (WHO, 2007) µg/day and for lactating women between 200 (EFSA, 2014; NNR Project Group, 2012) and 290 (IOM, 2001) µg/day. The recommendations for children and adolescents are in the range between 90 and 120 µg/day depending on age. In addition to recommended intakes, average requirements (AR or EAR), intake values that are estimated to meet the requirement of half the healthy individuals in a population, are established. In (NNR Project Group, 2012) the AR for adults was set to 100 µg iodine per day, but no values were set for children or adolescents. The IOM (2001) set the estimated average requirement for children and adolescents between 65 to 95 µg/day for children aged 1 to 18 years. The EFSA Panel (2014) concluded that there was insufficient evidence to derive an average requirement (AR).

The VKM project group responsible for the present report discussed which of the dietary reference values that is most appropriate for the purpose of comparison with the levels of iodine exposure described in chapter 6, including which of the datasets for intakes in the low range that holds a similar likelihood of inadequacy (and risks related to inadequacy) as does the UL and a likelihood of excessive intakes (and risks related to excess). The project group decided to use EAR and UL as comparison values, and this is in line with the recent proposal for harmonised dietary reference values from WHO, FAO, NASEM where AR and UL are considered the core values for evaluating population intakes (Allen et al., 2019).

The AR/EAR is the primary reference value for evaluation of nutrient intakes, and the RI, LI and UL can be used as complementary values (NNR Project Group, 2012). Comparison of population intakes with RI would give an overestimate of inadequacy as the RI is set to cover almost all individuals.

EAR is defined as an intake that is estimated to meet the requirement of approximately half of the healthy individuals in a life stage and gender group (i.e., median requirement). RI is derived by adding two standard deviations to EAR and is defined as the *average* long-term intake level of a nutrient that is estimated to meet the requirement of and maintain good nutritional status in almost all healthy individuals in a group. The range of optimal iodine intake is small. Using EAR rather than RI as the lower cut-off for acceptable iodine intake in the iodization scenarios will accommodate a higher flexibility, achieving a distribution of iodine intake levels that prevent deficiency without pushing the intake distribution to the higher end and thus increasing the probability of exceeding UL.

A simplified approach referred to as the EAR cut-point method can under certain assumptions, be used to estimate the prevalence of inadequate intake directly as the proportion with intake below the EAR (IOM, 2001). This method does not rely on a known requirement distribution, but the distribution should be symmetrical around the EAR, the variance of intake should be greater than the variance in requirements, and the intake and requirement should be independent (i.e. have a low correlation) implying that individuals with high requirements do not tend to have higher intakes. Assumptions related to requirements are in practice difficult to verify, but we have not come across literature or data to indicate that these assumptions do not hold for iodine.

In the iodization scenarios, the prevalence of inadequate iodine intake considered acceptable is ultimately a matter of judgment, but 2 to 3 percent has been used when planning diets for groups. According to the EAR cut-point method, 2.5% of the population will then have intakes below the EAR, and intake will be adequate for >97.5% of the population with intakes >EAR (IOM, 2003). While we present percentages > EAR in text and tables in this benefit and risk assessment, it should be kept in mind that the uncertainty in the estimated iodization scenarios is likely to be higher than a few percentages.

Generally, UL is the maximum level of total chronic daily intake judged to be unlikely to pose a risk of adverse health effects, and in the case of iodine the UL for adults is the maximum daily intake where changes in TSH are unlikely to occur (SCF, 2002).

Derived from the arguments above, the project group decided to compare the exposures in chapter 6 with the AR/EAR for adults from NNR (2012) and EAR for children and adolescents from IOM (2001) and the ULs established by the SCF (2002) as the cut-off for acceptable intake in the lower end and UL as the cut-off in the upper end of iodine intakes. Even though these cut-offs are not fully comparable, they were considered to be the most appropriate dietary reference values for comparison with the exposures for iodine. The health consequences from having intakes below EAR or above UL is elaborated on in the following chapters (5, 6, 8 and 10).

Table 4.3-1 Overview of values for comparison used to evaluate the iodine intake estimates in chapter 7.

EAR/AR	Adults (18-70 years)	13-year-olds	9-year-olds	4-year-olds	2-year-olds	1-year-olds
EAR/AR	100	73	73	65	65	65
UL	600	450	300	250	200	200

A review of new literature after year 2002 to re-evaluate the existing ULs is given in chapter 6 and discussed and summarised in section 6.2.3.

5 Systematic literature review and grading of evidence on the health effects of mild to moderate iodine deficiency

Systematic literature searches were conducted to retrieve the best available evidence on health effects of mild to moderate iodine deficiency to respond to the question concerning potential health effects of the various iodization levels suggested in the terms of reference for the general population and relevant risk groups. It is well recognised that severe iodine deficiency has severe health implications, but knowledge about possible adverse health effects of mild or moderate iodine deficiency is less established. The objective of the systematic literature search was therefore to identify all published scientific papers addressing how mild to moderate iodine deficiency might affect health. Based on knowledge about health outcomes related to severe iodine deficiency, expert judgement and test searches, we included search terms for neurodevelopment, thyroid function and birth outcomes and fertility.

Chapter 5 is divided into the following sections; a presentation of the literature search (5.1) (the search terms, databases and inclusion/exclusion criteria, publication selection and data extraction of all the included studies are described in detail in Appendix I, and therefore only briefly described here), methodological consideration of the included publications (5.2), a presentation of the guidelines for grading evidence (5.3) and results from the literature search (5.4) on neurodevelopment (5.4.1), thyroid function (5.4.2) and fertility and birth outcomes (5.4.3) and an evidence table with the grading of health effects related to mild to moderate iodine deficiency (5.5).

5.1 Systematic literature review concerning adverse health effects of mild to moderate iodine deficiency

Literature searches for studies investigating health outcomes related to mild to moderate iodine deficiency were performed in MEDLINE, EMBASE, Web of Science and PsycINFO, with no lower limit for publication year. The first literature search, performed in July 2018, resulted in 13 399 records after automatic and manual duplicate removal. It should, however, be noted that due to the vast number of articles, a large number of duplicates remained. The number of unique original records in this search is, therefore, lower than 13 399. The updated literature search, performed 14th May 2019, resulted in 899 records, and the latest update 18 November 2019 resulted in 622 records. Both the updated searches contained articles that were also found in the previous search. Consequently, the number of

articles could not be summarised. Details about the search strategy and publication selection are given in Appendix I.

To assess the evidence for a causal relationship between mild to moderate iodine deficiency and the health outcomes covered by the systematic literature review, we have used the guide for conducting systematic literature reviews updated version for the 5th edition of the Nordic Nutrition Recommendations (NNR5 working group, 2011; Shea et al., 2007), slightly modified for our purpose. Each individual study is rated with an A, B or C-category. The rating criteria are given in Appendix VI. Only studies categorised as A or B are included in the results. Studies categorised as A or B are listed in Appendix IIa. Each study with an A or B rating has been summarised in Summary Tables (Appendix III) and are described in chapter 5.4. Studies categorised as C are listed in Appendix IIb where also the most common reasons for grading/rating as category C are mentioned.

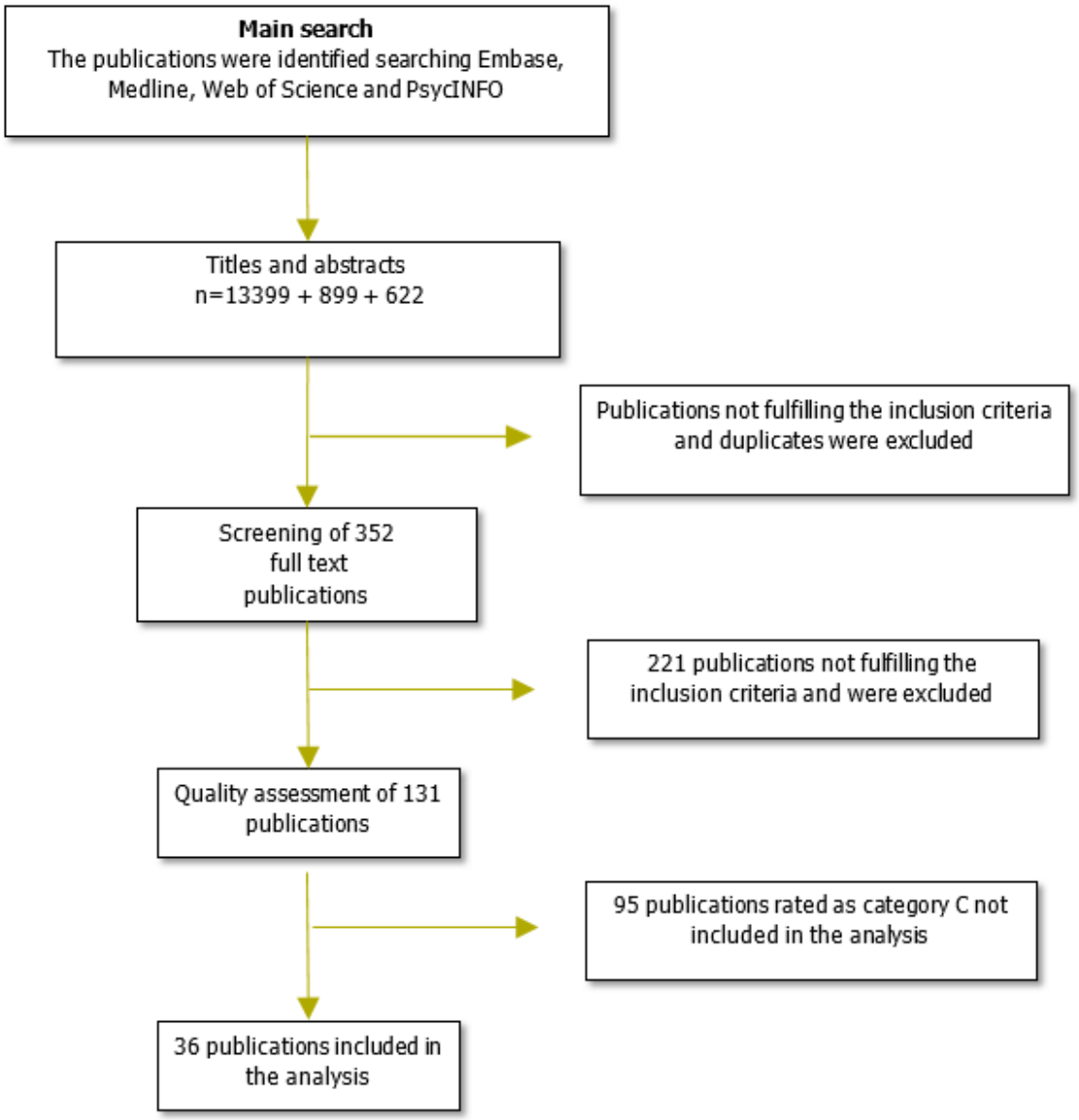

Figure 5.1-1 Flow chart for publication selection for literature concerning adverse health effects of mild to moderate iodine deficiency.

The systematic literature searches on mild to moderate iodine deficiency resulted in 131 studies, which were rated for quality (A-B-C). Of these, 1 study was categorised as A, while 35 studies qualified for category B, and 95 category C. The category C-studies were not considered further. Figure 5.1-1 shows a flow chart for the literature search and selection process for health outcomes related to mild to moderate iodine deficiency.

5.2 Methodological considerations of the included publications

5.2.1 Sample size and study design

The sample size varied substantially across the 36 publications included in the systematic literature review on health consequences of mild to moderate iodine deficiency, from large cohort studies with up to 39 471 participants to small studies with as few as 54 participants.

The included studies used different study designs, including RCTs, prospective cohort studies and cross-sectional studies. RCTs, if adequately designed and conducted, provide the best evidence for a causal relationship between an exposure and an outcome. Well-designed RCTs investigating health effects of iodine supplementation in populations with mild to moderate iodine deficiency, can provide evidence about the relationship between mild to moderate iodine deficiency and health outcomes. However, it is important that iodine status and intake at baseline is appropriately quantified and that the intervention is well-defined, such as a fixed daily dose of iodine as monotherapy, and a comparison group receiving placebo. In our literature search, five RCTs were identified that met these inclusion criteria investigating neurodevelopment in relation to thyroid function in various population groups.

Among the observational studies, the prospective cohort is generally regarded superior to case-control and cross-sectional studies. The majority of studies on mild to moderate iodine deficiency in the systematic literature review were prospective cohort studies. In a cohort design, a population is followed over time and disease and health outcomes that occur are registered prospectively. Concerning the influence of iodine status in pregnancy, several large-scale mother-and-child cohorts have been established that provide data about the associations between iodine intake/status prior to or during pregnancy and birth outcomes and developmental outcomes in the offspring. These include the Australian Gestational Iodine Cohort; the Norwegian Mother; Father and Child Cohort Study (MoBa); the Little in Norway (LiN) study; the Dutch Generation R study; the Southampton Women's Survey; the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC); the European Longitudinal Study of Pregnancy and Childhood (ELSPAC); and the Infancia y Medio Ambiente; Environment and Childhood (INMA) cohort in Spain. In these cohorts, data have been collected on maternal diet through FFQs, and/or stored biological samples that have been used to assess iodine status and/or markers of thyroid function in pregnancy.

While cross-sectional studies are pertinent for describing the prevalence of iodine deficiency, they are less suitable to investigate causal associations between iodine intakes or iodine status and health outcomes, since the exposure and the outcome are measured at the same point in time. Nevertheless, cross-sectional studies are frequently used for that purpose,

since they are feasible and require a relatively shorter time commitment and fewer resources to conduct. Evidence from studies with cross-sectional design alone is not sufficient to infer evidence for a causal effect between an exposure and an outcome, not even "limited – suggestive", but they add to the information from studies with RCT and cohort designs. For the current purpose, cross-sectional studies were considered if they addressed an association with a health outcome that could reasonably represent a potential causal relationship. Cross-sectional studies assessing the association between iodine status and parameters of thyroid function, were included if they had sufficient quality. Cross-sectional studies constituted the majority of the publications forming the basis for the conclusions concerning thyroid function. Cross-sectional studies aiming to assess cognitive development could not be considered to be reliable due to the limitations of the design.

5.2.2 Measures of iodine status and exposure

The methods used for examining iodine exposure in the reviewed literature included both measures of UIC and calculated iodine intake based on dietary data, mainly FFQ.

As described in section 2.3, WHO recommends UIC as a suitable indicator of iodine status at the group level. However, UIC should not be used for the purposes of individual diagnosis and treatment as it only reflects the short term iodine intake. Although UIC is not a good measure of iodine status at the individual level, lack of other easily available measures of individual iodine staus has resulted in widespread use of UIC in observational studies examining associations between iodine status and health outcomes.

Creatinine adjustment is often applied to remove variation in UIC due to hydration status. There is inter-individual variation in creatinine excretion, and including creatinine in the exposure variable provides an exposure measurement which is specific for the studied population as it is typically associated with participant characteristics such as age, gender, body mass index, life stage, and muscle mass. These are potential predictors of the outcome and it has therefore been advised against standardising for creatinine (Zimmermann and Andersson, 2012).

Even though dietary data are prone to measurement errors, calculating iodine intake using validated dietary assessment methods may provide a better and more reliable measure of habitual intake than UIC (Rohner et al., 2014). FFQs assess habitual consumption frequency and portion size over a predefined period. The applicability of dietary assessment of habitual iodine intake is generally considered to be high in populations where the iodine concentration in drinking water is low and the use of iodized salt is negligible, such as in Norway. Studies in Norway have shown moderate to high correlations (range 0.3-0.8) between calculated iodine intake and 24-hour urine collections or UIC, respectively (Brantsaeter et al., 2008; Brantsaeter et al., 2018; Henjum et al., 2018a).

In the reviewed cohort studies concerning the association of mild to moderate iodine deficiency and neurodevelopmental outcomes in children, the timing of iodine status assessment varied from before pregnancy, during pregnancy, and up to school age. It is important to consider the underlying distribution of iodine status of the studied population

when interpreting the results of the observational studies. In a population defined as being mildly to moderately iodine deficient, a proportion might have severe deficiency. For example, in populations with lower median UIC, a higher proportion of the population is expected to have iodine status in the moderate to severe deficiency range, and less likely to have sufficient thyroidal stores to maintain thyroid hormone production and ensure a sufficient supply to the foetus. On the other hand, in populations where median UIC is in the mild deficiency range, but close to the cut-off for adequate iodine intake (150 µg/L in pregnant women), it is likely that most participants have sufficient thyroidal stores to maintain sufficient thyroid hormone production.

5.3 Grading the evidence - guidelines

For appraising the evidence for a causal relationship between mild to moderate iodine deficiency and the health outcomes covered by the systematic literature review, we have used the guide for conducting systematic literature reviews updated version for the 5th edition of the Nordic Nutrition Recommendations (NNR). The NNR guide is based on other handbooks and guides, and has adopted a three-category quality grading system (AMSTAR) from Agency for Healthcare Research and Quality of each individual study that fulfills the literature inclusion criteria (NNR5 working group, 2011) and a grading system developed by the World Cancer Research Fund; WCRF (WCRF, 2018). This grading system is especially developed for a situation where observational studies form the bulk of the evidence.

In order to assess the quality of the included studies, Quality Assessment Tool tables (QATs) are available for different study designs, and for this benefit and risk assessment we have used the QATs for RCTs, prospective cohorts and cross-sectional studies (the forms are shown in Appendix VI). Each individual study is rated with an A, B or C-category by two independent reviewers. The criteria for each category are listed in Box 1 (from (NNR5 working group, 2011)). The grading criteria from WCRF are listed in Box 2 (WCRF, 2018).

In this benefit and risk assessment 131 papers investigating mild or moderate iodine deficiency were quality assessed. To save time, the reviewers did not fill out all the questions in the QATs if it was evident that a paper was categorised as C. All references for A, B or C studies are listed in Appendix II. For all the studies categorised as A or B, data was extracted in Summary Tables (listed in Appendix III). Category C-studies were not considered to have sufficiently good quality and were therefore excluded from further evaluation and not included in the results.

Box 1 Criteria for assessing the methodological quality of the studies: The three category quality grading system. The studies should be evaluated and graded within their own design strata.

A The results from studies that have an acceptably low level of bias are considered valid. These studies adhere mostly to the commonly held concepts of high quality including the following: a comprehensive study design; clear description of the participants, setting, interventions, and control group(s); appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; less than 30% percent dropout (depending on the length of the study see the QAT for clinical studies) or over 50% participation rate for prospective cohort studies; clear reporting of dropouts; and no obvious bias. Where appropriate, studies must provide a valid estimation of nutrient exposure, from dietary assessments and/or biomarkers with a reasonable range of measurement error, and justification for approaches to control for confounding in the design and analyses.

B Studies may have some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category "A", they have some deficiencies but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; there are large amounts of missing information, or discrepancies in reporting.

The next step after quality assessment and data extraction of each study, is a judgment of the total evidence base for each health outcome. Evidence is classified as convincing (strong evidence), probable (strong evidence), limited – suggestive and limited – no conclusion depending on the number and quality of supporting, non-supporting and contradicting studies. In addition, the WCRF lists special upgrading factors that may upgrade the reached judgement of the evidence. The evidence should be robust enough to be unlikely to be modified in the near future as new evidence accumulates. Box 2 lists the criteria from the WCRF cancer report (WCRF, 2018). The grading of each health outcome for mild to moderate iodine deficiency is given in sections 5.4.1-5.4.3 and 5.5.

Box 2 lists the criteria used in the WCRF cancer report (2018). The grades shown here are 'convincing', 'probable', 'limited — suggestive', 'limited — no conclusion'.

Convincing (strong evidence)
Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce risk of cancer. The evidence is robust enough to be unlikely to be modified in the forseeable future as new evidence accumulates. All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

Probable (strong evidence)
Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer. All the following criteria are generally required:

- Evidence from at least two independent cohort studies, or at least five case-control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Evidence for biological plausibility.

Limited — suggestive
Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws but shows a generally consistent direction of effect. This judgement is broad, and includes associations where the evidence falls only slightly below that required to infer a probably causal association through those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification. All the following criteria are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

Limited — no conclusion
Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but

where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited — no conclusion' for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of adjustment for known confounders), or by any combination of these factors.

When an exposure is graded 'limited — no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect of risk unlikely'

Special upgrading factors
These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a 'limited – suggestive' causal factor in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated. Factors may include the following:

- Presence of a plausible biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomized trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanism actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

5.4 Studies concerning mild to moderate iodine deficiency

5.4.1 Neurodevelopment

Sixteen studies of different study design (three RCTs and 13 prospective cohort studies) on different population groups (women prior to conception, pregnant women and schoolchildren) are included in this benefit- and risk assessment, all categorised as B.

In regard to neurodevelopment, during the first years of life, rapid and dynamic changes in brain development happens and neurodevelopmental tests are therefore less reliable in early age than at later ages and hence have poorer predictive value for future cognitive performance (Mansson et al., 2019). In appraising the evidence, one could argue that more weight should be given to studies that assessed neurodevelopmental outcomes in children at age 3 years or later than studies that assessed neurodevelopmental outcomes at earlier ages.

An overview of available neurodevelopment instruments highlight that different tests are needed for the assessment of different age groups and cognitive domains (Isaacs and Oates, 2008). There is limited guidance in the literature on which cognitive domains to assess in nutrition studies, and a common approach is to include a battery of tests that covers a variety of these. The Bayley Scales of Infant and Toddler Development is one of the most widely used test in infants and toddlers. The latest version of the Bayley (Bayley-III) covers three major areas of development assessed through direct administration with the child: cognitive, language (receptive and expressive) and motor (fine and gross) (Weiss et al., 2010). Thorough training and standardisation procedures with the study staff in the administration of the test are prerequisites (Isaacs and Oates, 2008). In older children, the variety of available neurodevelopment tests is larger. Although effects will be more pronounced in children with severe neurological disorders than in the general population, several validated tests are suitable to assess more subtle changes in performance (Isaacs and Oates, 2008).

The included studies had outcomes that reflected various aspects of neurodevelopment; such as early child development (cognitive, language and gross/fine motor skills and motor milestones), general ability scores (i.e. total IQ, verbal IQ and performance IQ), executive functioning, school performance (language, reading and writing skills, mathematics, special education), behaviour problems, ADHD diagnosis/ADHD symptom scores and auditory and short term visual memory outcomes. In some of the studies, neurodevelopmental outcomes were assessed using parental questionnaires that included questions from validated instruments or questions about teacher reports (e.g. MoBa), while in other studies trained study staff performed the outcome measurements directly with the study children (e.g. ALSPAC, INMA and the "Little in Norway" study). Moreover, the age at assessment vary from 6 months up to 15 years. The included studies on neurodevelopmental outcomes also differed in terms of population, sample size, iodine status, measurement of iodine exposure (UIC, creatinine-corrected UIC, or dietary intake), modelling of the iodine exposure (continuous or categorical) and how iodine from dietary supplements was treated in the statistical analysis. Consequently, there was heterogeneity in the type of effect estimates reported and their magnitude. However, the magnitude of the associations and their potential public health relevance were considered for all included studies.

5.4.1.1 Iodine status before conception and during pregnancy and neurodevelopmental outcomes

We identified a total of 14 studies, one RCT and thirteen prospective studies that examined the association between mild or moderate iodine deficiency before conception or during pregnancy, and neurodevelopmental outcomes in the offspring.

In a RCT of 832 pregnant women (median UIC at baseline 136 µg/L) in India (median UIC 188 µg/L) and Thailand (median UIC 112 µg/L) (Gowachirapant et al., 2017) 200 µg iodine or placebo were given daily throughout pregnancy. The primary endpoint was child neurodevelopment at 5-6 years assessed by three outcomes; verbal IQ and performance IQ by the Wechsler Preschool and Primary Scale of Intelligence (WPSSI-III), and global

executive composite score by the Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P). Secondary outcomes assessed at 5-6 years were externalising and internalising behaviour problems assessed by the Strengths and Difficulties Questionnaire (SDQ), auditory tests, anthropometrics (weight and length), and thyroid function parameters (TSH and T4). Moreover, several outcomes were assessed before the children were 24 months (Neonatal Behavioral Assessment Scales (NBAS) at age 6 weeks, the Bayley Scales of Infant Development 3rd edition (Bayley-III) at 1 and 2 years, pregnancy outcomes and maternal and infant thyroid volume and thyroid function parameters). There were no differences between the groups receiving supplement and placebo for the primary outcomes at age 5-6 years. Moreover, except for a higher score on expressive language in favour of placebo at 1 year, there were no differences in any of the secondary outcomes at age 5-6 years or at earlier ages.

The Norwegian Mother, Father and Child Cohort Study (MoBa) (Abel et al., 2019), measured UIC (n=2001) and iodine intake in pregnancy and neurodevelopment through maternal report in children at age 8 (n=39 471). The neurodevelopmental outcomes were maternal reported child language skills (The Children's communication checklist-Short (CCC-S)), reading skills (3 items selected from a sub-scale of Vineland Adaptive Behaviour Scale-II), writing skills (2 items selected from a sub-scale of Vineland Adaptive Behaviour Scale-II), school performance on reading and mathematics (mandatory mapping tests, teacher reports), and whether or not the child was granted special education in school due to disabilities or learning difficulties (extra educational services). The median UIC in gestational week 18 was 67 µg/L and the median iodine intake was 122 µg iodine per day. Habitual iodine intake was assessed by a food frequency questionnaire (FFQ) that covered food intake during the first half of pregnancy. The associations between iodine intake and the outcomes were modelled using iodine intake as a continuous variable. The curve-shaped associations indicated that habitual iodine intake from food lower than approximately 150 µg/day was associated with poorer skills in language, reading and writing, and increased likelihood low scores on school receiving special education, and lower score on school mapping test in reading, but not mathematics. Point estimates using the EAR of 160 µg/day as reference showed that intakes at or below 100 µg/day were associated with the child having 0.05-0.10 SD (standardised z-score) poorer skills in language, reading, and writing, 9-43% increased likelihood of scoring low on mapping test in reading, 6-13% increased risk of scoring low on mapping test in mathematics (non-significant), and a 10-29% increased likelihood of the child receiving special education services. Maternal UIC in mid pregnancy (n=2001) was not associated with any of the neurodevelopmental outcomes. There were no associations between maternal use of iodine-containing supplements and the child outcomes, irrespectible of when in pregnancy the iodine supplement use was initiated.

In the Little in Norway Cohort Study (Markhus et al., 2018) the median UIC in pregnancy was 78 µg/L (n=851). Five developmental outcomes (Bayley-III cognitive, receptive language, expressive language, and fine- and gross motor skills) were measured by trained research assistants at age 6 and 12 months by a shorter screening version, and at 18 months by the full version. The associations between iodine intake and the outcomes were modelled using UIC as a continuous variable. Each outcome was modelled as repeated

measures to take into account change over time. These associations showed a curvilinear pattern, which indicates that the negative associations of UIC with receptive and expressive language scores starts from an UIC of 100 µg/L or lower. A lower UIC was associated with lower standardised receptive language scores (difference between values above 100 µg/L and lowest values: -0.2 SD) and a lower expressive language score (difference between values above 100 µg/L and lowest values: -0.3 SD), but there was no association with cognitive score, fine motor skills, or gross motor skills. Maternal use of iodine-containing supplements was associated with lower gross motor skills (-0.18 SD), but not with other outcome measures.

In a cohort from Spain (Murcia et al., 2018), the median UIC in pregnant women was 123 µg/L (n=1803). Maternal iodine intake including the consumption of iodised salt (yes/no) was measured at 10-13 weeks and 28-32 weeks pregnancy by FFQ. Cognitive and motor development in children 4-5 years were measured by the McCarthy Scales of Children's Abilities (MSCA) (both the general cognitive scale and the motor scale) adapted to the Spanish population. Maternal iodine intake from food during pregnancy was not associated with scores on the general cognitive scale but was unexpectedly inversely associated with scores on the motor scale, a 100 µg/day increase was associated with a 2.4 point decrease (95% CI −3.98 to –0.85). UIC was associated with general cognitive, but not with motor development. After adjusting for creatinine (Cr) by the residual method, children of women with UIC~ Cr <100 µg/L had ~4 points lower general cognitive scores (beta: -3.93, 95% CI: -6.18, -1.69) than children in the reference group (150–249 µg/L), the corresponding decrease when adjusting for creatinine by the ratio method was beta -4.26 (95%CI: -6.57, -1.96) points. The coefficients were strongly attenuated by multiple imputation of missing creatinine values in sensitivity analyses. There were no associations with the motor scores. Neither use of iodine-containing supplements nor iodized salt during pregnancy appeared to improve children's neurodevelopment at 4–5 years.

In a cohort from the UK (n=654) (Robinson et al., 2018), maternal UIC (median 108 µg/L) and iodine intake were measured before conception and in early and late pregnancy. Offspring cognitive ability was measured by four outcomes at age 6-7 years. Full-scale IQ was assessed by two subtests of the Wechsler Abbreviated Scale of Intelligence (WASI). Executive functioning was measured by three subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB); two memory tests – the Delayed Matching to Subject (DMS) and the Spatial Span (SSP), and the Intra-Extra Dimensional Set Shift (IED) test assessing the ability of goal-directed action. Maternal IQ was also assessed using WASI. Data was analysed with linear regression using z-scores of the respective outcome measures as dependent variables and maternal preconception iodine status (iodine:creatinine ratio) as independent variable. There was a statistically significant positive linear association between preconception UIC (I/Cr ratio) and offspring full-scale IQ in adjusted models. In comparison with children of women with an I/Cr ≥150 µg/g, children of women with preconception urinary I/Cr <50 µg/g (moderate iodine pre-pregnant iodine deficiency) had 0.49 (95% CI: 0.79, 0.18) SD lower IQ, which is equivalent to a difference of 7.5 IQ points. The maternal I/Cr ratio was not associated with any of the three executive function outcomes (CANTAB).

In a prospective mother-child cohort from Australia (n=699) (Zhou et al., 2019), maternal UIC (median 186 µg/L) and iodine intake from food and supplements (mean 309 µg/day) was assessed at <20 weeks` gestation and at 28 weeks' gestation. The Bayley Scale of Infant Development 3. ed (Bayley-III) cognitive, language and motor composites were measured in the offspring at age 18 months. In this study, iodine intake included intakes from both food and supplements (initiated in pregnancy), and intake data from study entry (<20 weeks) and 28 weeks were averaged and used as primary exposure ranked into quartiles. Children of mothers with iodine intakes in the lowest quartile <220 µg/day (and those of mothers in the highest quartile (≥391 µg/day) in pregnancy had lower cognitive, language and motor scores. In comparison to children born to mothers in the second quartile (reference group, intakes 220-316 µg/day) those in the lowest quartile had 4.3 points lower scores on cognitive and 6.3 points lower scores on language. The corresponding odds of low scores (Bayley III-scores<85) was 2.8 (95%CI 1.3, 5-7) for cognitive, 2.4 (95%CI 0.9, 5.8) for language and 2.2 (95%CI: 0.9, 5.2) for motor in this iodine-sufficient population. There were no associations between UIC in pregnancy and the Bayley-III outcomes.

In a second publication from the MoBa cohort study (n=27 945) (Abel et al., 2017a), maternal iodine intake from food during pregnancy (median 122 µg iodine/day) and iodine supplement use were assessed in children at 3 years of age. Outcomes measured were language delay (classified according to 6 different categories from severe language delay to normal language development assessed by the Dale & Bishop language scale), communication skills (six items from the Ages and Stages Questionnaire, 2nd ed (ASQ-2)), motor milestones (the age at start walking), motor skills (4 items from the ASQ-2) and externalising and internalising behaviour at 3 years of age (Child Behaviour Check List). Iodine intake was modelled as a continuous exposure and the EAR value of 160 µg/day was set as the reference value. The results demonstrated a non-linear dose-response between habitual iodine intake from food during pregnancy and neurodevelopmental outcomes at intakes lower than approximately 150 µg/day. Iodine intakes lower than 100 µg/day were estimated to account for;12% (95% CI:22%, 23%) of cases of language delay; 31% (95% CI: 5%, 50%) of cases of severe language delay; 24% (95% CI: 17%, 31%) of cases of externalising behaviour problems >1.5 SD; and 24% (95% CI: 17%, 31%) of cases of internalising behaviour problems >1.5 SD in children at age 3 years, but not with of gross motor development or age at first steps unaided. There was no indication of any benefit of iodine supplement use during pregnancy, and some indication of an adverse association between uses of iodine supplements in mothers with low iodine intake from food and the behavioural outcomes.

The third publication from the MoBa cohort study (Abel et al., 2017b) examined associations between maternal iodine intake (median 121 µg/day) and ~~the~~ ADHD-diagnosis and maternal reported ADHD symptoms in children at 8 years of age. For the child ADHD-diagnosis outcome, the study population included 77 364 mother-child pairs, and for maternally reported ADHD symptoms at child age 8 years, the study population included 27 945 mother-child pairs. UIC was measured in a subsample (n=2938), the median was 68 µg/L in all, 61 µg/L in non-supplements users and 86 µg/L in iodine-supplement users. Child ADHD diagnosis was obtained by linkage to the Norwegian Patient Registry and child ADHD

symptoms were assessed in the eight-year-old questionnaire from MoBa on a four-point Likert scale (never/rarely, sometimes, often, or very often) covering inattention problems (nine items) and hyperactivity/impulsivity (nine items) from the ADHD Rating Scale. Among the non-supplement users, maternal iodine intake of less than 200 µg/day was associated with higher maternally reported child ADHD symptom scores at eight years of age (adjusted difference in score up to 0.08 SD). There were no association between maternal iodine intake and the risk of having received an ADHD diagnosis. There was no indication of a benefit of maternal iodine-containing supplement use on child ADHD diagnosis or symptom score, but an increased risk for both outcomes when iodine supplement use was initiated in gestational weeks 0-12. In participants with low iodine intakes from food, iodine supplement use initiated in gestational week 0-12 was associated with a ~29% increased risk of ADHD diagnosis (95%CI: 0%, 67%) and a 0.06 SD higher average score on ADHD symptoms at eight years of age (95% CI: 0.01, 0.11).

In a prospective study in 228 Australian pregnant women (Hynes et al., 2013), maternal UIC (median 81 µg/L) and its associations with standardised school tests (spelling, grammar, reading, writing and numeracy scores on the National Assessment Program – Literacy and Numeracy (NAPLAN) and English-literacy and mathematics-numeracy score on the Student Assessment and reporting information system (SARIS)) in 9 year old children were examined. There was a significant association between UIC (categorised at 150 µg/L) and spelling (NAPLAN) and borderline associations with grammar (NAPLAN) and English-literacy scores (SARIS), but not with reading, writing or numeracy scores. In comparison with children whose mothers had UIC≥150 µg/L, children whose mothers had UIC<150 µg/L had 10% reduction in spelling (-38; 95%CI: -65.5, -11.5, p=0.005), 7% reduction in grammar (-29.1; 95%CI; -59.9, -1.8, p=0.065), and 5% reduction in English grammar (-0.30; 95%CI: -0.62, 0.01, p=0.059).

A follow-up study was conducted when the children were 14-15 years old to examine whether the effects seen at age 9 continued into adolescence (Hynes et al., 2017). The main outcomes were longitudinal follow up of the standardized school tests in spelling, grammar, reading, writing and numeracy (NAPLAN) available for n=266 mother-offspring pairs with outcomes assessed at 4 time points (grade 3: age 8-9 years, grade 5: age 10-11 years, grade 7: age 12-13 years, and grade 9: age 14-15 years). The NAPLAN results at 8-9 years are the same as in (Hynes et al., 2013), but in the 2017 study these results are included in a mixed model with NAPLAN results at three subsequent ages. Two additional outcomes were obtained in a small subsample (n=45) adolescents at age 14-15 years by instruments to assess specific delays in language development (Comprehensive Evaluation of Language Fundamentals» (CELF-4)) and deficits in hearing and/or central auditory processing disorder (Central Auditory Processing Disorder (CAPD)). The NAPLAN results (repeated measures) showed that the difference in spelling scores between the <150 and ≥150 µg/L group in year 3, age 8-9 years (10%, -41.4 points, 95% CI -65.1, -17.6) persisted up to year 9, age 14-15 years (5.6%, -31.6 points 95% CI; -57.0, -6.2), even after full adjustment for confounders (including UIC in the child at the age of the test). For grammar and reading, differences at year 3 continued into year 5 but not until year 9 (an initial 6.5% difference in grammar reduced to 2.8% by year 9 and a 7.1% difference in reading reduced to 2.5% by

year 7). At age 14-15 years, there were no significant differences in CELF-4 (language development) or CAPD (hearing/auditory processing) scores although all CELF-4 measures were lower for offspring of mothers with UIC<150 µg/L than for those of mothers with UIC≥150 µg/L. The statistical power was extremely low as the groups included only 15 and 30 participants respectively.

In a Dutch multiethnic birth cohort (Ghassabian et al., 2014), maternal UIC (median UIC 230 µg/L) and its association with children's cognition was examined in 1525 mother–child pairs. Non-verbal IQ and language comprehension were assessed when the children were 6 years using validated Dutch test batteries (two subtests of the snijders-Oomen Niet-verbale intelligentie Test-Revisie and the receptive subtest of the Taaltest voor Kinderen). In total, 188 (12%) pregnant women had UIC<150 µg/g creatinine, with a median UIC equal to 119 µg/g creatinine. Non-verbal IQ and language comprehension scores were compared between children of mothers with UIC<15 µg/g and those of mothers with UIC≥150 µg/g as continuous scores and as the likelihood of having suboptimal scores (lowest quartile, i.e. scores <93 for non-verbal IQ and <0.77 for language comprehension). After adjustment for confounders, maternal low UIC was not associated with children's non-verbal IQ or language comprehension at 6 years. For non-verbal IQ, the likelihood (OR) of having suboptimal scores in the low maternal iodine group was 1.33 (95%CI: 0.92, 1.92) and for language comprehension the likelihood of suboptimal scores in the low maternal iodine group was 0.82 (95% CI: 0.56, 1.19).

In a prospective cohort study from UK in pregnant women that included 958 mother-child pairs (Bath et al., 2013), maternal UIC (median 91 µg/L) was measured at median 10 weeks pregnancy and neurodevelopment in the offspring at 8 years (IQ through an abbreviated form of the Weschler Intelligence Scale for Children IIIuk) and 9 years (reading speed, accuracy and comprehension through the Neale Analyses of Reading Ability). Low maternal iodine status (iodine:creatinine ratio <150 µg/g) was associated with an increased risk of suboptimum scores on verbal IQ at age 8 years (OR: 1.58; 95%CI: 1.09, 2.30) but not performance IQ, and with reading accuracy at age 9 years (OR:1.69; 95%CI: 1.15, 2.49) and reading comprehension at age 9 years (OR: 1.54; 95% CI: 1.06, 2.23), but not with words read per minute or reading score. The results were adjusted for a number of potential confounders. Furthermore, stratification of the low-iodine mothers showed that children in the group with urinary iodine (<50 µg/g) had lower scores than those from the group with iodine 50–150 µg/g, suggestion a worsening trend (dose-response) in cognitive outcomes with decreasing maternal iodine status (Bath et al., 2013).

In a prospective mother-child multi-centre cohort from Spain (INMA) (Murcia et al., 2011), the effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year (range of 11-16 months) of age was measured in one of four sub-cohorts using the Bayley Scales of Infant Development 2nd ed, Mental Development Index (MDI) and Psychomotor Development Index (PDI). The study population included 691 mother-child pairs. Maternal UIC, maternal iodized salt consumption or dietary intake of iodine rich foods, were not associated with infant neurodevelopment. However, maternal intake of 150 µg/day or more of iodine from iodine-containing supplements was associated with a 5.2-point decrease in

PDI scores and a 1.8 fold increased risk of having PDI scores <85 (-1 SD from mean). This association differed by sex, the OR of having PDI <85 was 4.0 (95%CI: 1.4, 11.4) in girls and 1.1 (95% CI: 0.5, 2.2) in boys (Murcia et al., 2011).

In 2013, the same study was performed in the other three sub-cohorts in other regions of Spain (Rebagliato et al., 2013). Maternal UIC (median 125 µg/L) and iodine intake from diet (median 162 µg/day) and iodine supplement use were assessed in 1519 pregnant women. Child development was measured using the Bayley Scales of Infant Development, 2nd ed, when the children were 16 months and mental development and psychomotor development scores were standardised and harmonised to a mean of 100 and a SD of 15. Maternal UIC, iodized salt consumption, and dietary iodine intake during pregnancy were not associated with neuropsychological development. Maternal consumption of 150 µg/day or more of iodine from supplements was associated with a non-significant decrease of 1.8 (95% CI: −5.6, 2.0) in mental scores and of 0.9 points (95% CI: −6.9, 5.0) in psychomotor scores. The corresponding risks of low mental and psychomotor scores (<85) when compared with supplemental iodine <100 µg/day were 1.7 (95% CI: 0.9, 3.0) for mental scores and 1.5 (95% CI: 0.8, 2.9) for psychomotor scores.

All the included papers for prenatal iodine status or iodine intakes and neurodevelopmental outcomes are summarised in Tables 5.4.1.1-1 (RCT) and 5.4.1.1-2 (cohorts).

Table 5.4.1.1-1 Overview of one randomised double-blind placebo-controlled trial (RCT) for assessment of iodine supplementation in pregnancy in a population of mildly to moderately iodine deficient women on neurodevelopmental outcomes in infancy and childhood.

Reference, Country, Summary Table (ST) number	Exposure/ iodine status during pregnancy, time of measurement (when in pregnancy)	Number of children	Neurodevelopmental outcome measures in child, age at time of measurement	Main findings
Gowachirapant et al., 2017 Thailand and India ST12	Intervention with 200 µg iodine or placebo daily from first trimester (mean 10.7 gw) throughout pregnancy. Baseline median UIC: 131 µg/L in all (188 µg/L in India and 112 µg/L in Thailand).	Baseline: n=832 pregnant women. Primary outcomes available for n=330 children at age 5-6y.	3 primary outcomes at age 5-6 y: verbal IQ and performance IQ by the Wechsler Preschool and Primary Scale of Intelligence (WPSSI-III), and global executive composite score by the Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P). Secondary outcomes at age 5-6 y: externalising and internalising behaviour problems by the Strengths and Difficulties Questionnaire (SDQ) and auditory tests. Secondary outcomes at earlier ages: child neurodevelopment at 6 weeks by the Neonatal Behavioral Assessment Scales (NBAS) and at 1 and 2y using the Bayley Scales of Infant Development (BSID)-III.	There were no differences between the groups receiving supplement and placebo for the primary outcomes at age 5-6y. Moreover, except for a higher score on expressive language in favour of placebo at 1y, there were no differences in any of the secondary outcomes at age 5-6y or at earlier ages.

Table 5.4.1.1-2 Overview of prospective cohort studies included for assessment of mild to moderate iodine deficiency and a range of neurodevelopmental outcomes in infancy and childhood (sorted by publication year and author).

Reference, Country, Summary Table (ST) number	Exposure/ iodine status during pregnancy, time of measurement (when in pregnancy)	Number of children	Neurodevelopmental outcome measures in child, age at time of measurement	Main findings
Abel et al., 2019 Norway, ST1	Food and supplement use assessed by FFQ in pregnancy. Calculated median iodine intake from food was 122 µg/d. The median UIC was 67 µg/L (mean gestational week 18.5).	Total n=39471 mother-child pairs. Subsample with UIC: n=2001.	6 outcomes at 8y: Language, reading and writing skills from subscales in the Children's communication checklist-Short (CCC-S), school performance on reading and mathematics (mandatory mapping tests, teacher reports), and whether the child received special educational services (all outcomes are maternally reported).	Maternal habitual iodine intake from food < ~ 150 µg/d from food was associated with poorer skills in language, reading and writing, and also increased likelihood of the child receiving special educational services at age 8 y. Poorer outcome was found for all outcomes except mapping tests for mathematics. In the subsample with maternal UIC there were no associations with the outcomes. In the whole study population, there were no associations between the use of iodine-containing supplements and the outcomes and no indication of adverse effects of iodine-containing supplement use.
Markhus et al., 2018 Norway, ST17	The median UIC in pregnancy (mean gestational week 23.7) was 78 µg/L. Questions on supplement use were embedded in a short web-based FFQ.	Total n=851 mother-child pairs.	5 outcomes: Bayley–III screening at 6 and 12 mo and Bayley-III full at 18mo. Three subscales: cognitive, language (receptive and expressive), and motor (gross and fine motor) skills. Each outcome was modelled as repeated measures to take into account change over time.	Children born to mothers with UIC below ~100 µg/L had reduced receptive and expressive language scores. For receptive and expressive language skills, the results showed a curvilinear dose-response association with UIC. There was no association with cognitive or motor skills. Maternal use of iodine-containing supplements was associated with lower gross motor skills, but not with other outcome measures.
Murcia et al., 2018 Spain, ST21	Median UIC in pregnant women (mean gestational week 13.5) was 123 µg/L. Median UIC adjusted for creatinine (by the residual method; UIC~Cr) was 125 µg/L.	Total n=1803 mother-child pairs.	2 outcomes at 4-5y: McCarthy Scales of Children's Abilities; general cognitive and motor scale.	No associations between use of iodized salt or the use of iodine containing supplements and the outcomes. For UIC, there were no associations without adjusting for creatinine. Children of mothers with UIC~Cr <100 µg/L had poorer cognitive, but not fine motor scores at age 4-5y. Dietary iodine intake was inversely associated with motor development, but not with the other neurodevelopmental outcomes. No indication of benefit or of maternal use of iodine containing supplements iodized salt in in pregnancy.

Reference, Country, Summary Table (ST) number	Exposure/ iodine status during pregnancy, time of measurement (when in pregnancy)	Number of children	Neurodevelopmental outcome measures in child, age at time of measurement	Main findings
Robinson et al., 2018 United Kingdom, ST27	Median maternal preconception (median 3.3y prior to conception) UIC was 108 µg/L and median I/Cr was 114 µg/g. FFQ before conception and in early and late pregnancy, included information on supplement use.	Total n=654 mother-child pairs.	4 outcomes at 6-7y: WASI full scale IQ, 3 CANTAB executive functioning tests (Delayed Matching to Subject, Spatial Span and Intra-Extra Dimensional Set Shift).	Preconception I/Cr ratio was positively associated with child IQ. Standardised beta-coefficient was 0.13 (95% CI 0.04, 0.21) SD higher IQ z-score per z-score higher I/Cr. Compared women with an I/Cr ≥150 µg/g, children of women with preconception urinary I/Cr <50 µg/g (moderate iodine pre-pregnant iodine deficiency) had 0.49 (95% CI: 0.79, 0.18) SD lower IQ, which is equivalent to a difference of 7.5 IQ points. Preconception I/Cr was not associated with any of the executive function outcomes.
Zhou et al., 2019 Australia, ST35	Median UIC was 186 µg/L at study entry (<20 gestational weeks). Total mean (SD) iodine intake was 309 (127) µg/d at study entry. FFQ answered twice in pregnancy.	N=699 mother-child pairs.	3 outcomes at 18mo: Cognitive, language and motor skills by Bayley-III.	Both low and high iodine intakes in pregnancy (food and supplements combined) were associated with poorer childhood neurodevelopment in this iodine-sufficient population. There were no association between UIC and the cognitive outcomes.
Abel et al., 2017a Norway, ST3	Iodine intake calculated by a validated FFQ: The calculated median iodine intake from food during pregnancy was 122 µg/d.	Total n=48 297 mother-child pairs in analyses of iodine supplement use and n=33 047 mother-child pairs in the analysis in non-supplement users only.	5 outcomes at child age 3 years: Language delay (a six-point ordinal language grammar rating scale developed by Dale & Bishop), communication skills (Ages and Stages Questionnaire, ASQ), motor milestone (ASQ), motor skills (AAQ) and behaviour problems (Child Behaviour Check List/ 11/2-5/LDS). All outcomes were maternally reported.	Maternal iodine intake <160 µg/d was associated with child language delay, more externalising and internalising behaviour problems, and lower fine motor skills in children at age 3 years. No associations with gross motor skills or the likelihood of not walking unaided at age 17 months.

Reference, Country, Summary Table (ST) number	Exposure/ iodine status during pregnancy, time of measurement (when in pregnancy)	Number of children	Neurodevelopmental outcome measures in child, age at time of measurement	Main findings
Abel et al., 2017b Norway, ST4	Iodine intake calculated by a validated FFQ. Median iodine intake from food was 121 (IQR: 89-162) µg/d. Median UIC (mean 18.5 gw) was 61 (IQR: 32-104) µg/L in non-users of iodine supplements and 86 (IQR: 43-140) µg/L in iodine supplement users.	A total of n=77 164 mother-child pairs in the analysis of ADHD diagnosis, and n=27 945 mother-child pairs in the analysis of maternally reported ADHD symptom scores.	2 outcomes at 8y: ADHD diagnosis at any age until age 8y (Norwegian Patient Registry) and maternally reported ADHD symptom scores (a four-point Likert scale (never/rarely, sometimes, often, or very often) covering inattention problems (nine items) and hyperactivity/impulsivity (nine items) from the ADHD Rating Scale.).	No association between maternal iodine intake from food and risk of child ADHD diagnosis. Maternal iodine intake from food lower than ~200 µg/d) was associated with higher standardized child ADHD symptom scores (adjusted difference in score up to 0.08 SD. In participants with low iodine intakes from food, iodine supplement use initiated in GW 0-12 was associated with a ~29% increased risk of ADHD diagnosis (95%CI: 0%, 67%) and a 0.06 SD higher average score on ADHD symptoms at eight years of age (95% CI: 0.01, 0.11).
Hynes et al., 2017 Australia (Tasmania) ST13	Median UIC (mean of repeated UICs) was 83.2 µg/L in the 2017 study sample.	n=266 mother child pairs for the longitudinal analysis, of which 228 in the 2013 study sample. n=45 mother-child pairs in subsample for additional outcomes at 14-15y.	5 outcomes (spelling, grammar, reading, writing and numeracy) from the standardized school test in literacy and numeracy (NAPLAN in grades 3 (age 8/9y), 5 (10/11y), 7 (12/13y) and 9 (age 14/15y). 2 outcomes (incl. subscales) at 14/1y: language delay (CELF-4 test) and hearing deficits and/or a central auditory processing disorder (CAPD)	The longitudinal follow up study showed reductions in spelling in mothers with UIC < 150 µg/L, but not in the other outcomes. For grammar and reading, differences at year 3 continued into year 5 but not till year 9
Ghassabian et al. 2014, Netherland, ST10	Maternal UIC (mean 13.3 gestational weeks) was 230 µg/L (corresponding to 296.5 µg/g Cr).	n=1525 mother-child pairs.	2 outcomes at 6y: Non-verbal IQ and language comprehension by Validated Dutch test batteries: two subtests of the Snijders-Oomen Niet-verbale intelligentie Test-Revisie (SON-R 21/2–7) (Spatial visualization abilities and abstract reasoning abilities) converted to a non-verbal IQscore and the receptive subtest of the Taaltest voor Kinderen (TvK).	Children of mothers with UIC<150 µg/g Cr had lower non-verbal IQ in crude analysis, but no associations were seen for either non-verbal IQ or language comprehension in adjusted analyses.

Reference, Country, Summary Table (ST) number	Exposure/ iodine status during pregnancy, time of measurement (when in pregnancy)	Number of children	Neurodevelopmental outcome measures in child, age at time of measurement	Main findings
Bath et al., 2013 United Kingdom, ST6	Median UIC was 91.1 µg/L, equivalent to 110 µg I/g Cr.	Total n=958	7 outcomes at 8y or 9y: Abbreviated form of the Wechsler Intelligence Scale for Children (verbal, performance and total IQ) at 8 years. The Neale Analysis of Reading Ability (reading speed, accuracy, and comprehension) and words read per minute at age 9.	Children of mothers with inadequate iodine status (UIC<150 µg/g Cr) had lower verbal IQ, reading accuracy, and reading comprehension than children of mothers with UIC≥150 µg/g Cr in the fully adjusted models. Further stratification indicated a dose-response.
Hynes et al., 2013 Australia (Tasmania) ST14	Median UIC (mean of repeated UICs) was 81 µg/L in the 2013 study sample.	N=228 mother child pairs in the 2013 study sample.	7 outcomes at 9y: Australian National Assessment Program—Literacy and Numeracy (NAPLAN) tests of literacy (reading, writing, spelling, grammar) and numeracy in Australian children and Student Assessment and Reporting Information System (SARIS) scores of English-literacy and mathematics-numeracy in Tasmanian children).	This study showed reduced spelling, grammar and general English-literacy performance at age 9y in children of mothers with UIC<150 µg/L. No association was found for the other measures.
Rebagliato et al., 2013 Spain ST25	Median UIC was 125 µg/L. Median iodine intake from diet was 162 µg/d. Mean supplementary iodine intake was classified as a mean dose <100 µg/d, 100-149 µg/d, or ≥150 µg/d (range, 150-400 µg/d).	N=1519 mother-child pairs.	2 outcomes by Bayley 2nd ed at 16mo: standardised mental and psychomotor development scores.	Maternal UIC, iodized salt consumption, and dietary iodine intake during pregnancy were not associated with neuropsychological development.
Murcia et al., 2011 Spain ST22	Maternal iodine status (median UIC for group) not reported, but 55% of the women had UIC <150 µg/L.	N=691 mother-child pairs.	2 outcomes by Bayley at 12mo (range 11-16mo): Mental and psychomotor scores.	No association between UIC and infant neurodevelopment. However, maternal intake of 150 µg/d iodine supplement was associated decreased psychomotor development (PDI) in girls.

5.4.1.2 Grading of neurodevelopment – prenatal exposure

Our literature review included 14 studies that investigated associations between mild to moderate iodine deficiency (measured by UIC, iodine intake and/or iodine supplements) assessed prior to or during pregnancy and neurodevelopmental outcomes in children; one RCT and 13 prospective cohort studies (see Tables 5.4.1.1-1 and 5.4.1.1-2). Six of the 14 studies found an association between mild to moderate iodine deficiency (measured by UIC) and poorer neurodevelopmental outcomes, i.e. that children of mothers with UIC in the mild to moderate range had poorer neurodevelopmental outcomes. Four of the studies found an association between mild to moderate iodine deficiency (measured by iodine intake) and poorer neurodevelopmental outcomes, i.e. that children of mothers with iodine intakes in the lower range (<100-150 µg/day) had poorer neurodevelopmental outcomes. One study (Murcia et al., 2018) found an inverse association with mild to moderate iodine deficiency (measured by iodine intake), i.e. poorer neurodevelopmental outcomes with higher iodine intakes. Concerning iodine supplements, five of the 14 studies found that use of iodine-containing supplements in mild to moderate iodine deficient women was associated with poorer neurodevelopmental outcomes in the children.

The studies on iodine supplementation in pregnancy on neurodevelopment (Murcia et al., 2011; Rebagliato et al., 2013) showed that iodine supplementation did not improve infant neuropsychological development at 1 year of age but was inversely associated with Bayley II psychomotor scores. A sudden increase in iodine intake, although modest and within the recommendations, might also lead to a "stunning effect," with transient inhibition of maternal or fetal thyroid hormone production. In addition, the MoBa Study showed no protective effects of iodine supplementation during pregnancy on offspring neurodevelopment; there was also some suggestion of harmful effects of supplementation among women who had low dietary iodine intakes.

Fourteen studies investigated neurodevelopmental outcomes in children born to mothers with mild to moderate iodine deficiency prior to or during pregnancy, and 10 of these reported findings indicating an association between mild or moderate iodine status and various neurodevelopmental outcomes. However, the ten studies varied in study design, sample size, in neurodevelopmental domains, neurodevelopmental assessment tools, iodine status in the studied population and age of children at the time of outcome assessment (from 6 months to 15 years). Neurodevelopmental tests are less reliable in early age (<3 years) than at later ages and hence have poorer predictive value for future cognitive performance. Three of the 14 studies were performed in children less than 3 years old and more weight have been given to studies that assessed neurodevelopmental outcomes in children older than 3 years. However, the variation in neurodevelopmental domains and outcomes made it difficult to draw a clear conclusion.

The results from the included cohort studies on neurodevelopmental outcomes also differed in measurement of iodine exposure (UIC, creatinine-corrected UIC, dietary intake and supplements). Consequently, there was heterogeneity in the type of effect estimates reported and their magnitude.

Concerning iodine status, the studies which did not find associations between low UIC (or low iodine intake) and poorer neurodevelopmental outcomes generally included study populations having median UIC only slightly below WHO cut-off of 150 µg/L defining adequate iodine intake in pregnant women, i.e. in the upper end of the mild to moderate iodine deficiency range (50-149 µg/L). When a median UIC is above 100 µg/L, which is the cut-off for non-pregnant women, few women are truly iodine deficient. In the RCT (Gowachirapant et al., 2017), after the intervention, there was no difference in UIC between the pregnant women in the iodine supplementation group (intervention) and the placebo group. Median UIC at baseline (131 µg/L) (Gowachirapant et al., 2017), indicating mild iodine deficiency was considerable higher than median UIC in the observational studies from UK (mean 91 µg/L) (Bath et al., 2013) and from Australia (mean 82 µg/L) (Hynes et al., 2017; Hynes et al., 2013, where an association between UIC (or low iodine intake) and poorer neurodevelopmental outcomes were found. Median UIC was also < 100 µg/L in four studies from Norway included in the literature review for neurodevelopmental outcomes. Three were from the large population-based MoBa study (Abel et al. 2017, 2018, 2019) and one from the population-based Little in Norway study (Markhus et al. 2018). These studies reported subtle impairments in neurocognitive outcomes, including communication, behaviour and school performance spanning from age 18 months to age 8 years. Median UIC<100 µg/L has consistently been shown also in more recent status studies (or cross-sectional) studies in women of childbearing age as shown in Figure 1.1 (Henjum et al., 2019).

The quality of the included studies were evaluated, and one of the criteria for being categorised as a B article was that the associations had been adjusted for possible and relevant confounders. However, residual confounding can never be excluded in observational studies. Due to shortcoming of measuring individual iodine status, participants with a severe deficiency may have been misclassified as being mild to moderate deficient.

The biological mechanism for severe iodine deficiency and poorer neurodevelopmental outcomes is well known and presented in in chapter 3. The current understanding suggests that the effect of low iodine intake on child brain development is mediated by a combined impairment of maternal and fetal thyroid function, caused by inadequate levels of substrates for thyroid hormone synthesis. There is no clear distinction between moderate and severe iodine deficiency in pregnancy, and therefore, reason to assume that the adverse effect may appear along a continuum of decreasing long-term iodine intake and that the evidence for biological plausibility is strong.

The WCRF grading system includes factors (Box 2) that form part of the assessment of the evidence that, when present, can upgrade or strengthen the judgement reached. An exposure that might be judged as '*limited – suggestive*' in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one is present. Four of the included studies in the literature review on neurodevelopment showed a dose response in the association (Abel et al., 2017a; Abel et al., 2017b; Bath et al., 2013; Markhus et al., 2018).

Our literature review included 14 studies of which ten found poorer neurodevelopmental outcomes in children born to mothers with seemingly mild to moderate iodine deficiency. However, based on our systematic literature review and use of WCRF guidelines for grading of evidence, the evidence was not judged strong enough to meet the criteria for probable evidence. The three criteria for *limited suggestive* were met: 1) Evidence from at least two independent cohort studies or at least five case-control studies. 2) The direction of effect is generally consistent though some unexplained heterogeneity may be present. 3) Evidence for biological plausibility. It was therefore concluded that there is *limited suggestive* evidence for a causal relationship between mild to moderate iodine deficiency and poorer neurodevelopmental outcomes in children. Limited suggestive means that the evidence is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws but shows a generally consistent direction of effect.

5.4.1.3 Iodine status in schoolchildren and neurodevelopmental outcomes

For schoolchildren, two RCTs were identified on mild or moderate iodine deficiency and neurodevelopmental outcomes.

In a double-blind RCT from New Zealand (Gordon et al., 2009), 166 mildly iodine deficient (median UIC 63 µg/L) children aged 10-13 years were randomised into 2 groups; the intervention group receiving 150 µg supplemental iodine daily and a placebo group (duration 28 weeks). Cognitive performance was assessed by four tests from the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV): Picture concepts and Matrix reasoning (both assessing perceptual reasoning), Letter-number sequencing (working memory), and Symbol search (processing speed). Supplementation with 150 µg iodine per day corrected iodine deficiency by increasing median UIC from 66 to 145 µg/L and decreasing thyroglobulin from 16.5 to 8.5 µg/L. Iodine supplementation improved performance on the two tests of perceptual reasoning (picture concepts and matrix reasoning) compared to the placebo group. The overall cognitive score in the iodine supplementation group was 0.19 SDs higher than in the placebo group.

In a double-blind RCT from Albania (n=310) (Zimmermann et al., 2006) on schoolchildren 10-12 year old (median UIC 43 µg/L), the intervention group were provided with 400 µg iodine as iodized poppy seed oil capsule and the placebo group with sunflower-oil. Seven tests of cognitive and motor performance were performed by the children at baseline and after 24 weeks. These tests included; the Raven's Coloured Progressive Matrices (test of intelligence), Bead threading (fine motor), Rapid target marking, Digit span (short-term memory), Symbol search (visual perception and processing speed), Coding (short-term visual memory and processing speed), and Rapid object naming). The iodine intervention group significantly improved performance (adjusted treatment effect (95% CI)) on four of the seven tests; Raven's Coloured Progressive Matrices (4.7 (3.8, 5.8) points), Rapid target marking (2.8 (1.4, 4.0) points), Symbol search (2.8 (1.9, 3.6) points), and Rapid object naming (4.5 (2.3, 6.6) points). Results suggest that iodine supplementation for 24 weeks

improved information processing rates and the ability to reason and solve problems in these 10-12 year old schoolchildren.

Table 5.4.1.3-1 Iodine status in schoolchildren and neurodevelopmental outcomes.

Reference, Country, Summary Table (ST) number	Iodine status	Intervention	Number of children	Neurodevelopmental outcome measures in child, age at time of measurement	Main findings
Gordon et al., 2009 New Zealand ST11	Intervention study in children aged 10-13 years. Median UIC at baseline was 63 µg/L and 32% had UIC<50 µg/L.	Intervention with 150 µg supplemental I daily for 28 weeks.	N=166 children, 84 in the intervention group and 82 in the placebo group.	4 outcomes at 10-13y from the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV): Picture concepts, matrix reasoning, symbol search, letter-number sequencing and overall cognitive scores.	Supplementation with 150 µg I/day corrected iodine deficiency by increasing median UIC from 66 to 145 µg/L. Iodine supplementation improved performance on 2 of the 4 cognitive tests (picture concepts and matrix reasoning scores) relative to the placebo.
Zimmermann et al., 2006 Albania ST36	Intervention study in children aged 10-12 years. Median UIC at baseline was 43 µg/L.	Intervention with 400 µg iodine as iodized poppy seed oil capsule vs. placebo sunflower-oil capsules (swallowed with water under direct supervision).	N=310, 159 in the intervention group, 151 in the control group.	7 outcomes at 10-12y. Cognitive and motor performance tests at baseline and after 24 weeks: rapid target marking, symbol search (from WISC), rapid object naming, Raven's Coloured Progressive Matrices, Bead threading, Digit span (from WISC), and Coding (from WISC).	The intervention group significantly improved performance on 4 of the 7 tests; Raven's Coloured Progressive Matrices, Rapid target marking, Symbol search, and Rapid object naming.

5.4.1.4 Grading of neurodevelopment – schoolchildren

Our literature review included two RCTs on iodine supplementation in schoolchildren and neurodevelopment. Iodine supplementation in schoolchildren improved perceptual reasoning in mildly iodine-deficient children and improved information processing, fine motor skills, and visual problem solving in moderate iodine deficient children. However, both RCTs were conducted in areas with longstanding iodine deficiency and high goiter rates. The first criteria (evidence from at least two independent cohort studies), the second criteria (the direction of effect is generally consistent though some unexplained heterogeneity may be present) and the third criteria (evidence for biological plausibility) were met. The project group therefore concluded that the evidence is *limited suggestive* that mild to moderate iodine deficiency in schoolchildren is associated with poorer neurodevelopmental outcomes in schoolchildren.

5.4.2 Thyroid function

As described in chapter 3 and Figure 3-1, the association between iodine intake and thyroid function is U-shaped, with increased risk of altered thyroid function both at low and high iodine intakes (Laurberg and Nohr, 2002; Taylor et al., 2018). As an indicator of iodine intake, median UIC does not provide direct information about thyroid function. However, a low median UIC indicates that a population is at risk of developing thyroid disorders (WHO, 2007).

Fourteen studies of different study design (two RCTs, two prospective cohort studies and ten cross-sectional studies) in different population groups (non-pregnant adults, pregnant women and schoolchildren) were included. One RCT is categorised as A, and the other studies as category B.

Potential effects of mild to moderate iodine deficiency on thyroid hormones and thyroid function parameters are difficult to assess and are expected to differ across age and life stages. In populations with mild-to-moderate iodine deficiency, overall serum Tg concentrations are typically elevated and thyroid size is often increased, while TSH, T3, and T4 remain within the normal range (Zimmermann and Boelaert, 2015). Normal physiological changes in pregnancy (e.g. plasma volume expansion and increased thyroid hormone turnover) affect the concentrations of thyroid hormones and TSH. Consequently, it is difficult to distinguish between normal changes and changes that may result from mild or moderate iodine deficiency. Observational studies and experimental animal studies have shown that not only maternal hypothyroidism, but also that isolated hypothyroxinemia (low T4 and normal TSH) can adversely affect affects foetal neurodevelopment (Velasco et al., 2018). A recent meta-analysis of three European birth cohorts, demonstrated that low maternal T4 in the first half of pregnancy was associated with lower verbal and non-verbal child IQ (Levie et al., 2018). The results corroborate the findings of six observational studies (Haddow et al., 1999; Henrichs et al., 2010; Julvez et al., 2013; Korevaar et al., 2016; Pop et al., 2003; Roman et al., 2013) of which three were included in the meta-analysis. However, two randomised controlled trials of effects of levothyroxine (T4) treatment for women with subclinical hypothyroxinemia on child neurocognitive outcomes found no beneficial effects of T4 treatment initiated in mean gestational week (gw) 18 (range 8-20 gw) (Casey, 2017) or median gestational week 13 (range 12-20) (Lazarus et al., 2012). A possible explanation for the lack of treatment effect in these studies may be that treatment was initiated too late.

Auto-regulatory processes are initiated in the thyroid gland when the availability of iodine is reduced, resulting in preferential secretion of T3 over T4, in order to save one iodine atom per hormone produced. The fetus is especially vulnerable to maternal iodine deficiency in early pregnancy when the foetus depend on supply of maternal T4 (Bernal, 2007; Obregon et al., 2005).

Several papers included in the literature review on potential adverse effects of iodine deficiency on thyroid function parameters had cross-sectional design. Although cross-

sectional studies are generally not valid for causal inference, such studies were included due to the rapid response of the thyroid to increased iodine intakes (Zimmermann et al., 2013).

5.4.2.1 Iodine status in non-pregnant adults and thyroid function

For non-pregnant adults, seven studies have been identified on mild or moderate iodine deficiency and thyroid function; one RCT (categorised as A), two prospective studies, and four cross-sectional studies.

In a double blind placebo controlled RCT with factorial design from New Zealand (Thomson et al., 2009) men and women aged 60-80 years with median UIC 48 µg/L at baseline received iodine and selenium supplements (80 µg iodine/day) for three months. Thyroid stimulating hormone (TSH), free triiodothyronine (T3) and free thyroxine (fT4), thyroglobulin (Tg) and UIC were measured. Tg concentration decreased by 24% and 13% of baseline in the participants receiving iodine (iodine- and selenium plus iodine groups) in comparison with the placebo group. UIC increased from baseline only in the iodine group. No significant treatment effects were found for TSH, fT3, fT4, or ratio of T3 to T4. The authors concluded that iodine supplementation alleviated the moderate iodine deficiency and reduced elevated Tg concentrations (Thomson et al., 2009).

In a prospective cohort study from Denmark (DanThyr) (Krejbjerg et al., 2015) in women and men from a mild iodine deficient area (Copenhagen median UIC 61 µg/L) and a moderate iodine deficient area (Aalborg median UIC 45 µg/L), Tg was measured (at baseline in 1997-98 and at follow-up in 2008-10). After iodine fortification with 13 µg iodine/g salt in household salt and salt for the production of bread, there was no change in median Tg in adults living in Copenhagen, while Tg decreased significantly in adults living Aalborg. Regional differences in Tg evident before iodine fortification disappeared after iodine fortification. However, median Tg among non-users of iodine supplements were still higher than median Tg among iodine supplement users after iodine fortification. The authors raise the question whether the moderate level of iodine fortification of the salt was insufficient to secure adequate iodine intake in the entire study population (Krejbjerg et al., 2015).

In the same prospective cohort study as presented above, with men and women from Denmark (Rasmussen et al., 2002) on iodine status in two different areas (mild iodine status (Copenhagen, median UIC 61 µg/L) and moderate iodine status (Aalborg, median UIC 45 µg/L)), thyroid volume, thyroid enlargement, presence of thyroid nodules, serum Tg, TSH and thyroglobulin antibodies (TgAbs) were measured. A significant relation between iodine intake and thyroid volume was found. All measures of iodine intake, except iodine excretion measured as a urinary concentration, predicted thyroid volume (Rasmussen et al., 2002).

The associations between iodine status and thyroid antibodies were investigated in a cross-sectional study in 2808 adult men and women recruited in Shanghai, China, in 2016 (Wang et al., 2019). The median UIC was 165 µg/L. UIC was divided into four groups: UIC<100 µg/L (deficient), UIC 100-199.9 µg/L (adequate), UIC 200-299.9 µg/L (more than adequate), and UIC ≥ 300 µg/L (excess). UIC was not associated with TPOAb or TgAb positivity alone, but there was a U-shaped association between iodine status and thyroid

autoimmunity (TAI). The findings showed that the U-shaped relationships between iodine intake and TAI risk, and that both iodine deficiency and excessive iodine status were risk factors of TAI among adults.

A community-based cross-sectional study from eastern and central parts of China aimed at investigating the association between UIC and thyroglobulin antibodies (TgAbs) (Chen et al., 2018b). In men and women aged 15 years and older (mean age 45 years), UIC was measured in spot urine samples. Blood samples were drawn for measurement of TgAbs, TSH, TPOAbs in serum. FT4 and fT3 were measured only for those whose TSH levels were outside the reference range. Median UIC was 205 µg/L. A total of 2508 participants (17.6%) had UIC below 100 µg/L. The prevalence of isolated TgAb positivity decreased across increasing UIC categories (6.14%, 5.62%, 5.34%, and 5.15%). The same trend was not seen for the prevalence of isolated TPOAb positivity or TSH. Thus, the results showed that the prevalence of TgAb positivity was higher at UIC<100 µg/L in both men and women.

In a cross-sectional study from Tianjin, China (Fan et al., 2018), characteristics associated with the presence of thyroid nodules (TNs) were studied in adults. Median UIC was 134 µg/L and 35.6% had UIC below 100 µg/L. Prevalence of TNs was 25% when the UIC was in the range of 100-300 µg/L, and the prevalence of TNs was significantly decreased when the UIC was above 150 µg/L. A U-shaped association was observed between UIC and the prevalence of TN, with the highest prevalence at low (<100 µg/L) and very high UIC levels (>500 µg/L). The highest prevalence of TN of 30.7% was observed in the group with UIC levels 50-100 µg/L (183 out of 596). The prevalence of TN was 27.2% in those with UIC 100-150 µg/L (140 out of 515), 25.9% in those with UIC 150-200 µg/L (108 out of 417), 22.3% in those with UIC 200-250 µg/L (61 out of 273) and 22.4% in those with UIC 250-300 µg/L (34 out of 152 participants).

In another cross-sectional study from New Zealand (Thomson et al., 2001), men and women with mean UIC 59 µg/L were divided into three groups according to 24-hour iodine excretion (24 h urinary iodide excretion (<60, 60 ± 90; >90 µg iodide/day). Serum total T4, TSH and Tg as well as thyroid volumes were measured. Elevated Tg concentrations were found among participants with lower iodine status (<60 µg iodide/day). No associations with plasma TSH or T4 were observed. There was a significant difference in thyroid volume between the three groups, with larger thyroid volume at lower iodine status. No differences were observed when subjects were categorised according to UIC in µg/L.

5.4.2.2 Grading of thyroid function – non pregnant adults

Seven studies on iodine status and thyroid function were identified in the literature review; one RCT, two cohort studies and four cross-sectional studies. The studies showed an increase in either Tg or Tvol, however an increase in one of these markers without an accompanying change in thyroid hormone levels was not regarded as sufficient to indicate thyroid dysfunction. It is therefore concluded that the evidence is *limited (no conclusion)* that mild to moderate iodine deficiency in non-pregnant adults is associated with thyroid dysfunction. *Limited (no conclusive)* means that the evidence is so limited that no firm conclusion can be made. The evidence may be limited by the amount of evidence in terms of

the number of studies available, by inconsistency of direction of effect, by methodological flaws (lack of adjustment for known confounders).

5.4.2.3 Iodine status in pregnant women and thyroid function

For pregnant women, six studies have been identified on mild or moderate iodine deficiency and thyroid function; one RCT and five cross-sectional studies.

In a RCT on iodine supplementation (200 µg/day) in pregnant women from Denmark (duration up to 34 weeks), thyroid function was measured as serum TSH, Tg, T4, T3, fT4, ratio T4/T3 and thyroid volume (Pedersen et al., 1993). In women with median UIC at 51 and 55 µg/L, in control and intervention group, respectively, thyroid volume increased more in the control group than in the supplemented group during pregnancy. Maternal Tg values were significantly higher in controls at all-time points, except before initiation of iodine supplementation. In the control group, there was a significant increase in TSH during pregnancy. During the postpartum period, there was no significant difference in TSH between groups. No significant differences were found between the groups in the developments of T4, T3, ratio T4/T3 or fT4 during pregnancy or postpartum. The mild to moderate iodine deficient women in the control group had higher thyroid volume and Tg.

The associations of UIC with thyroid function and autoantibodies was investigated in 2009 pregnant women in the Swedish Environmental Longitudinal Mother and child Asthma and Allergy (SELMA) study (Levie et al., 2019). Data on UIC, creatinine and thyroid function parameters were collected at median gestation age 10 weeks (95% CI: 6-14 weeks). Median UIC was 90 (95%CI: 38, 439 µg/L) and when adjusted for creatinine the median was 85 (95%CI: 36, 386) µg/g. Gestational reference ranges for thyroid function tests did not differ substantially by iodine status. We show that a lower UIC/creatinine was associated with significantly lower TSH, higher TT4, and a higher risk of TPOAb positivity. A lower UIC/creatinine was also associated with a higher fT4, fT3, and TT3, but these associations did not reach statistical significance ($p < 0.10$). The fT4/fT3 and TT4/TT3 ratios were stable across the full range of UIC/creatinine.

A cross-sectional study in two Chinese cities examined the associations between iodine status and thyroid antibodies in 7073 pregnant women recruited in early pregnancy (gestational weeks 4-8) during 2012-2014 (Sun et al., 2019). The median UIC was 154 µg/L, indicating iodine sufficiency. Iodine deficiency (UIC < 100 µg/L) was associated with higher risks of TPOAb positivity and TgAb positivity. Women with isolated TPOAb positivity, isolated TgAb positivity, or both TPOAb and TgAb positivity increased risk of overt hypothyroidism, and increased risk of subclinical hypothyroidism. Moreover, the risks of overt and subclinical hypothyroidism in women with a high TPOAb were higher than in TPOAb-negative women. The risk of overt hypothyroidism in women with a high TgAb titer was higher than in TgAb-negative women.

In a cross-sectional study on mild to moderate iodine deficient pregnant women from Norway (Abel et al., 2018)) based on data from The Norwegian Mother and Child Cohort Study (MoBa), TSH, fT4, fT3, TPOAb and TgAb were measured in plasma samples from mid

pregnancy (mean gestational week 18.5). Median iodine intake from food was 121 µg/day and median UIC was 59 µg/L among those who did not use supplements at the time of sampling and 98 µg/L in the women taking supplements, indicating mild to moderate iodine deficiency in both groups. Habitual iodine intake from food calculated by the FFQ was not significantly associated with any of the outcome measures. UIC <100 µg/L (moderate iodine deficiency in pregnant women), was associated with an elevated fT3, and a higher UIC was associated with a slightly lowered fT4 concentration. In addition, introduction of iodine supplementation after gestational week 12 (i.e. period covering the time of sampling) was significantly associated with lower T4, but not T3.

In a cross-sectional national representative study on mild iodine deficient pregnant women from Belgium (Moreno-Reyes et al., 2013), the prevalence of thyroid disorders in 1st and 3rd trimesters based on maternal serum fT4, fT3, TSH, Tg, TPOAb, and TgAb, was measured. The prevalence of subclinical hypothyroidism and thyroid autoimmunity was increased among the pregnant women. Differences in Tg was only found between pregnant women with UIC/Cr=150–249 µg/g (adequate iodine status in pregnant women) and UIC/Cr ≤49 µg/g (severe iodine deficiency in pregnant women), with a significantly lower median Tg concentration in the group with adequate iodine status.

In a cross-sectional study on mildly iodine deficient pregnant women from Spain (Rebagliato et al., 2010), measuring TSH, fT4, urinary iodine and iodine intake, a higher TSH was found in women who consumed 200 µg or more of iodine supplements daily compared to those consuming less than 100 µg/day. The results showed no association between UIC and TSH levels.

5.4.2.4 Grading of thyroid function – pregnant women

Six studies on iodine status in pregnant women and thyroid function were identified in the literature review; one RCT and five cross-sectional studies. The studies showed that mild to moderate iodine deficiency might affect thyroid function negatively by increased Tvol and elevated Tg and free triiodothyronine (T3). However, elevated T3 was only found in one study. According to the WCRF grading system, the criteria for grading evidence as *limited suggestive*, findings from at least two independent cohort studies are required. It is therefore concluded that the evidence is *limited (no conclusion)* that mild to moderate iodine deficiency during pregnancy is associated with thyroid dysfunction.

5.4.2.5 Iodine status in schoolchildren and thyroid function

For schoolchildren, one study was identified on mild or moderate iodine deficiency and thyroid function.

In a cross-sectional study of schoolchildren from New Zealand (Skeaff et al., 2012), serum Tg, serum TSH, plasma fT4 and fT3 were measured. Tg was lower at UIC ≥100 µg/L (adequate UIC in children > 6 years) and higher at UIC <50 µg/L (moderate iodine deficiency in children > 6 years). Compared with children who had UIC ≥50 µg/L, those with UIC <50 µg/L had statistically significantly higher Tg and fT3, while TSH and fT4 did not

differ according to this cut-off. Correspondingly, compared with children who had UIC ≥100 µg/L, those with UIC <100 µg/L had statistically significantly higher Tg and fT3, while TSH and fT4 did not differ between the groups.

Overview of studies included for mild to moderate iodine deficiency and thyroid dysfunction in sections 5.4.2.1-5.4.2.5 are presented in Tables 5.4.2-1 to 5.4.2-3.

Table 5.4.2-1 Overview of RCTs included for assessment of mild to moderate iodine deficiency and a range of thyroid function parameters (sorted by publication year and author).

Reference, Country, Summary Table (ST) number	Iodine status/ exposure	Intervention	N, gender, age	Thyroid function measures	Main findings
Thomson et al., 2009 New Zealand ST31 Category A	Median UIC at baseline was 48 µg/L (IQR:31-79 µg/L).	A population with moderate iodine deficiency (median UIC 48 µg/L) received either 100 µg Se (selenium group), 80 µg I (iodine group), 100 µg Se + 80 µg I (selenium plus iodine group), or placebo daily for 3 months.	100 men and women aged 60-80y free of serious medical illness and without thyroid problems and not taking iodine or selenium supplements.	4 outcomes: TSH, fT3, T4 and Tg.	Tg concentration decreased by 24% and 13% of baseline in the iodine and selenium plus iodine groups in comparison with the placebo group (p=0.009 and p=0.108, respectively). No significant treatment effects were found for TSH, fT3, fT4, or ratio of T3 to T4.
Pedersen et al., 1993 Denmark ST23	Median (95% CI) for UIC spot urine in pregnant women at initial visit was 51 (32-58) µg/L in controls and 55 (30-73) µg/L in group that later received supplemental iodine.	200 µg/d supplemental iodine from weeks 17-18 of pregnancy to 12 months.	54 pregnant Caucasian women (49 women in the post partum period).	Maternal thyroid volume at gestational weeks 17-18, 28, 37; and 5 days, 26 wks, 52 wks after delivery Thyroid function in women: 5 outcomes in pregnant women: Serum TSH, T4, fT4, Tg and Tvol.	Thyroid volume was higher in the control than in the intervention group. There were no differences between the groups in the developments of T4, T3, ratio T4/T3 or fT4 during pregnancy or postpartum. Maternal Tg was significantly higher in controls at all time points, except before initiation of iodine supplementation. In the control group, TSH increased during pregnancy (p <0.01), but not in the intervention group. During the postpartum period, there was no difference in TSH between the groups.

Table 5.4.2-2 Overview of prospective cohort studies and included for assessment of mild to moderate iodine deficiency and a range of thyroid function parameters (sorted by publication year and author).

Reference, Country, Summary Table (ST) number	Iodine status/ exposure	Intervention	N, gender, age	Thyroid function measures	Main findings
Krejbjerg et al., 2015 Denmark ST15	Baseline (1997-98) median UIC in Copenhagen was 68 µg/L in supplement users and 61 µg/L in non-supplement users. Median UIC in Aalborg was 53 µg/L in supplement users and 45 µg/L in non-supplement users.	Participants were examined at baseline (1997-98) before the mandatory iodization (IF) (13 µg iodine/g salt in household salt and salt used in bread (2000), and at follow-up (2008-2010) after IF.	1417 women age range 18-65y and men 60-65y with no previous thyroid disease and without Tg-auto-antibodies.	1 outcome: Serum Tg was measured by immune-radiometric method.	During follow-up (mean 11y) period, there was no change in median Tg in Copenhagen while Tg decreased significantly in Aalborg. Regional differences in Tg before IF disappeared after IF. After IF, median Tg in non-users of iodine supplements was still higher than median Tg in iodine supplement users, indicating that the moderate IF might be insufficient to secure adequate iodine intake in the entire study population.
Rasmussen et al., 2002 Denmark ST24	Median spot urine UIC was 68 µg/L in Copenhagen and 53 µg/L in Aalborg. Median estimated 24-h iodine excretion was 111 µg/d in Copenhagen and 74 µg/d in Aalborg. Iodine intake from food and supplements was assessed by FFQ. Seven measures of iodine intake (based on UIC and FFQ) were evaluated for the two study cites combined.	None	4649 women age range 18-65y and men 60-65y with no previous thyroid disease and without Tg-auto-antibodies.	5 outcomes: Tvol, and occurrence of thyroid nodules, serum Tg, TSH and TgAb.	All measures of iodine intake except one (an iodine intake index) were inversely associated with the thyroid volume outcomes. Likewise, all measures of iodine intake were inversely associated with Tg concentration. The association between iodine intake and the occurrence of thyroid nodules was less clear. Iodine measures most consistently and inversely related to thyroid nodules were iodine intake from diet/kg bw, milk intake, and total iodine intake (diet and supplements). A low total iodine intake and a low milk intake were both risk factors for thyroid enlargement.

Table 5.4.2-3 Overview of prospective cross-sectional studies and included for assessment of mild to moderate iodine deficiency and a range of thyroid function parameters (sorted by publication year and author).

Reference, Country, Summary Table (ST) number	Iodine status/ exposure	N, gender, age	Thyroid function measures	Main findings
Chen et al., 2019 China ST8	Median UIC from spot urine was 205 µg/L. UIC was divided into four groups: UIC<100 µg/L, 100≤UIC<200 µg/L, 200≤UIC<300 µg/L and UIC≥300 µg/L.	14230 men and women ≥15y, mean 45y.	5 outcomes: TgAb, and additionally TSH, TPOAb, fT4 and fT3.	UIC was inversely associated with the prevalence of isolated TgAb positivity but not seen with the prevalence of isolated TPOAb positivity or TSH. Both males and females with UIC<100 µg/L were more prone to have positive TgAbs.
Levie et al., 2019 Sweden ST16	Median UIC was 90 µg/L (95%CI: 38, 439) µg/L, and when adjusted for creatinine the median was 85 µg/g (95%CI: 36, 386) µg/g.	2009 pregnant women in early pregnancy (median 10 gestational weeks, 95%CI: 6-14 weeks).	7 outcomes, of which 5 thyroid function parameters (TSH, fT4, TT4, fT3, TT3) and 2 thyroid autoantibody parameters: (TPOAb positivity and TgAb positivity)	Gestational reference ranges for thyroid function tests did not differ substantially by iodine status. We show that a lower UI/Creat was associated with significantly lower TSH, higher TT4, and a higher risk of TPOAb positivity. A lower UI/Creat was also associated with a higher fT4, fT3, and TT3, but these associations did not reach statistical significance. The fT4/fT3 and TT4/TT3 ratios were stable across the full range of UI/creatinine.
Sun et al., 2019 China ST30	Median UIC was 153.6 µg/L. UIC was categorised into 5 groups: <100 µg/L (deficient (20.8%)), 100-149.9 µg/L (borderline deficient (27.4%)), 150-249.9 µg/L (adequate (34.2%)), 250-500 µg/L (more than adequate (14.4%)), and UIC ≥ 500 µg/L (excessive (3.2%)).	7073 pregnant women in early pregnancy (4-8 gestational weeks, mean 7.2)	2 outcomes: TPOAb positivity and TgAb positivity.	Iodine deficiency (UIC < 100 µg/L) was associated with higher risks of TPOAb positivity and TgAb positivity. Women with isolated TPOAb positivity, isolated TgAb positivity, or both TPOAb and TgAb positivity increased risk of overt hypothyroidism, and increased risk of subclinical hypothyroidism. Moreover, the risks of overt and subclinical hypothyroidism in women with a high TPOAb were higher than in TPOAb-negative women. The risk of overt hypothyroidism in women with a high TgAb titer was higher than in TgAb-negative women.

Reference, Country, Summary Table (ST) number	Iodine status/ exposure	N, gender, age	Thyroid function measures	Main findings
Wang et al., 2019 China ST34	Median UIC was 164.5 µg/L. UIC was categorised into 4 groups: <100 µg/L (deficient (20.2%)), 100-199.9 µg/L (adequate (44.6%)), 200-299.9 µg/L (more than adequate (21.9%)), and UIC ≥ 300 µg/L (excessive (13.2%)).	2808 adult men and women	3 outcomes: TPOAb positivity, TgAb positivity, and TAI (defined as the presence of either TPOAb or TgAb or both)	The median UIC was 165 µg/L. UIC was divided into four groups: UIC<100 µg/L (deficient), UIC 100-199.9 µg/L (adequate), UIC 200-299.9 µg/L (more than adequate), and UIC ≥ 300 µg/L (excess). UIC was not associated with TPOAb or TgAb positivity alone, but there was a U-shaped association between iodine status and thyroid autoimmunity (TAI). The findings showed that the U-shaped relationships between iodine intake and TAI risk, and that both iodine deficiency and excessive iodine status were risk factors of TAI among adults.
Abel et al., 2018 Norway) ST2	Median UIC in spot urine was 59 µg/L in non-supplement users and 98 µg/L in supplements user at the time of urine sampling. FFQ: Median intake from food was 121 µg/d (IQR: 90-160 µg/d). 40% used iodine-containing supplements.	2910 pregnant women.	5 outcomes: TSH, fT4, fT3, TPOAb and TgAb were measured in plasma samples.	Iodine intake measured by FFQ was not associated with thyroid function while UIC was inversely associated with fT3 (p=0.002) and fT4 (p<0.001). Current iodine supplement use was not associated with the outcomes, but a recent initiation of iodine supplementation after GW 12 was significantly associated with lower mean fT4 (beta=-0.21) but not fT3 or TSH.
Fan et al., 2018 China ST9	Median UIC was 134 µg/L (IQR: 79-208 µg/L). There were 35.6% of the subjects whose UIC was lower than 100 µg, and 10.3% was higher than 300 µg/L.	2647 adult men(1352) and women (1295), aged 18y or older (mean age 43y).	5 outcomes: Presence of thyroid nodules (TNs). In addition, potential influencing factors on TNs including sex, age, iodine status, Tvol, TSH, TPOAb and TgAb.	In the range of urine iodine levels investigated, the relationship between UIC and the occurrence of TNs showed a U-shaped curve. Prevalence of TNs was 30.7% among subjects with UIC between 50 and 99 µg/L, and 25.3% among subjects with UIC in the range of 100-300 µg/L. The results showed that the prevalence of TNs was significantly decreased when the UIC was over 150 µg/L. There were no findings for the other measures.

Reference, Country, Summary Table (ST) number	Iodine status/ exposure	N, gender, age	Thyroid function measures	Main findings
Moreno-Reyes et al., 2013 Belgium ST20	Median UIC in 1st trimester was 117 g/L before and 103 µg/L after correction for Cr. Median UIC in 3rd trimester was 131 µg/L before and 138 µg/L after correction for Cr.	Of 1311 pregnant women, UIC was available for 550 healthy (negative for TPOAb and TgAb and no history of thyroid disease) women in 1st trimester and 616 women in 3rd trimester.	Prevalence of thyroid disorders in 1st and 3rd trimesters. 6 outcomes: maternal serum fT4, fT3, TSH, Tg, TPOAb, and TgAb.	UIC/Cr was inversely associated with Tg, but not with fT4, fT3, TSH, TPOAb, and TgAb.
Skeaff et al., 2012 New Zealand ST28	Median UIC spot urine was 68 (IQR: 50-95) µg/L.	1153 children 5-14y 611 boys 542 girls enrolled in 2002.	4 outcomes: Thyroid function defined by serum Tg, serum TSH, plasma fT4 and fT3.	UIC was inversely associated with Tg and fT3, but not with TSH and fT4. This was seen when groups were compared using a cut-off for UIC at 50 µg/L or a cut-off for UIC at 100 µg/L.
Rebagliato et al., 2010 Spain ST26	Median UIC in spot urine was 137 µg/L in all women. UIC was categorised as <50, 50-99, 100-149, 150-249, and 250+ µg/L in which 9, 23, 22, 25 and 21% belonged to the different categories, respectively. FFQ: 64% had iodine intake ≥160 µg/d. Iodine intake from supplements was categorised as 0-99, 100-199 and ≥200 µg/d, with 51, 16 and 33% in the respective categories.	1844 pregnant women enrolled 2004-2008 with singleton pregnancy and without thyroid pathology	2 outcomes: TSH and fT4	Consumption of ≥200 µg/d supplemental iodine was associated with higher TSH levels (β=0.090 (95% CI: 0.003, 0.177) and increased risk of hyperthyrotropinemia (TSH>3 µU/mL) compared to those consuming less than 100 µg/d (adjusted odds ratio=2.5 (95% CI; 1.2-5.4). The results showed no association between urinary iodine and TSH levels. Pregnant women from the area with the highest median iodine (168 µg/L) and highest supplement coverage (93%) had the lowest values of serum fT4 (geometric mean =10.09 pmol/L (95% CI: 9.98, 10.19).

Reference, Country, Summary Table (ST) number	Iodine status/ exposure	N, gender, age	Thyroid function measures	Main findings
Thomson et al., 2001 New Zealand ST32	Average of two separate 24-h urine collections: Mean UIC was 59 µg/L. Mean 24-h UIE was 86 µg/day. Mean I/Cr was 57 µg/g.	233 subjects, 114 men and 119 women, mean age 32y enrolled 1997-98.	4 outcomes: serum T4, TSH and Tg. Tvol by ultrasonography. The outcomes were analysed by three categories of I/Cr ratio divided according to the following cutoffs: Low (<40 µg/g Cr), medium (40-60 µg/g Cr) and high (>60 µg/g Cr) corresponding to adequate, low and marginal iodine status.	Tg concentrations and Tvols were higher in the low and marginal groups than in the adequate iodine status group, while serum TSH and T4 did not differ between groups.

5.4.2.6 Grading of thyroid function – schoolchildren

One cross-sectional study on iodine status and thyroid function in schoolchildren were identified. The study found elevated Tg and free triiodothyronine (T3) in schoolchildren with mild to moderate iodine deficiency. It is therefore concluded that the evidence is *limited (no conclusion)* that mild to moderate iodine deficiency in schoolchildren is associated with thyroid dysfunction.

5.4.3 Fertility and birth outcomes

Six prospective cohort studies measuring iodine status and fertility and birth outcomes were identified, all categorised as B.

In a prospective cohort study of pregnant women in US, the relationship between iodine status and pregnancy loss was measured in 329 women (Mills et al., 2019). The risk of loss was not elevated in the mildly, moderate or in the severe deficient group. Urinary iodine concentrations were in the deficiency range in 60% of the participants. The authors concluded that iodine deficiency at levels seen in many developed countries does not increase the risk of pregnancy loss.

A prospective study including 541 pregnant women was conducted in London, Leeds, and Manchester between 2004 and 2008 (Snart et al., 2019). The median UIC was 134 µg/L and was between 100 and 150 in all three cities. Less than 20% had UIC < 50 µg/L. UIC was not associated with pregnancy outcomes including birth weight, growth restriction (SGA) and spontaneous preterm birth.

In a prospective cohort study of women (n=501) planning a pregnancy in US (Mills et al., 2018), women with UIC <50 µg/L took significantly longer to become pregnant, experiencing a 46% decrease in probability of becoming pregnant over each cycle compared to women with UIC ≥100 µg/L (adequate iodine status in non-pregnant women). Women with UIC 50–99 µg/L (the mildly deficient range group) had a smaller, non-significant increase in time to conception, suggesting that the risk, if any, is modest in this group.

In a prospective cohort study from UK (Torlinska et al., 2018) on pregnant women with median UIC of 95 µg/L (moderate iodine deficiency in pregnant women) (n=3524), no associations were found between iodine status and seven different measures on adverse pregnancy outcomes including birth weight and preterm birth.

In a cohort study from Thailand (Charoenratana et al., 2016) in pregnant women (n=410), UIC<150 µg/L was associated with increased rate of preterm birth and low birth weight. In addition, women with a UIC <100 µg/L (moderate iodine deficiency in pregnant women) had a significantly higher rate of foetal growth restriction.

In a cohort study from Spain (Alvarez-Pedrerol et al., 2009) in pregnant women (n=657), higher birth weight and lower risk of having a small for gestational age (SGA) new-born was reported, in mothers with UIC between 100-149 µg/L (mild iodine deficiency in pregnant women), compared to mother with UIC<50 µg/L (severe iodine deficiency in pregnant women).

Table 5.4.3-1 Overview of six prospective cohort studies included for assessment of mild to moderate iodine deficiency in women and fertility and pregnancy/birth outcomes, all categorised as B (sorted by publication year and author).

Reference, Country, Summary Table (ST) number	Exposure/ iodine status	N, age	Fertility, pregnancy and birth outcome measures	Main findings
Mills et al., 2019, US ST18	Spot urine samples at the first in-home interview prior to conception. Median UIC 170 µg/d. Iodine was measured as µg/L and creatinine was used either as an independent variable or to use the ratio of iodine to creatinine (µg/g creatinine). The exposure was grouped into normal status (≥150 µg/L, n=133 (40%)), mild deficiency (100-149 µg/L, n=52 (16%)), moderate deficiency (50-99 µg/L, n=74 (22.5%)) and severe deficiency (<50 µg/L, n=70 (21%)).	Of 501 women, 329 women became pregnant and were included in the analyses.	1 outcome: Pregnancy loss. Pregnancy was assessed by the Clearblue fertility monitor. Pregnancy was identified by a positive test and pregnancy loss identified by conversion to a negative test.	The women with UIC in the deficiency range did not have a different loss rate than those in the sufficient group. Results were consistent in sensitivity analyses including creatinine adjustment or exclusion of women being treated for thyroid disease.
Snart et al., 2019 UK ST29	Urinary iodine concentration was measured in two spot urines, one in 15 gw and one in 20 gw. The mean UIC of both time points were the main exposure. Median UIC was 134 µg/L, (139 µg/L in Manchester, 130 µg/L in London and 116 µg/L in Leeds.	541 pregnant women.	4 outcomes: Birth weight, birth weight centile (primary outcome), small for gestational age (SGA) and spontaneous preterm birth.	No evidence of an association between UIC and birth weight centile, nor with odds of spontaneous preterm birth or SGA. Sensitivity analyses gave similar results (using creatinine adjusted UIC, µg/g Cr) and assessing iodine at the individual time points.
Mills et al., 2018, US ST19	Spot urine samples from 467 women as UIC and I/Cr-ratio. Iodine status was sufficient (UIC≥100 µg/L) in 260 (55.7%), mildly deficient (50–99 µg/L) in 102 (21.8%), moderately deficient (20–49 µg/L) in 97 (20.8%) and severely deficient (<20µg/l) in 8 (1.7%). Median UIC was 112.8 µg/L in the entire population, 114.1 µg/L in those who became pregnant, 97.2 µg/L in those who did not become pregnant, and 113.6 µg/L in those who withdrew.	501 women planning pregnancy, 18-40y, enrolled 2005-09.	1 outcome: Time to get pregnant. Fertility monitoring, home digital pregnancy test.	For women UIC in the moderate to severe deficiency range, it took significantly longer time to become pregnant, and they had a 46% decrease in probability of becoming pregnant over each cycle compared to women who were iodine sufficient. The mildly deficient range group had a smaller, non-significant increase in time to conception, suggesting that the risk, if any, is modest in this group.

Reference, Country, Summary Table (ST) number	Exposure/ iodine status	N, age	Fertility, pregnancy and birth outcome measures	Main findings
Torlinska et al., 2018, UK, ST33	Median UIC was 95 µg/L and median I/CR was 124 µg/g.	3140 women enrolled 1991-92 with child alive at 1y+42 women with pregnancy/ infant loss, median age 29y	7 adverse pregnancy outcomes: (i) hypertensive disorders in pregnancy; (ii) glucose derangement; (iii) anaemia; (iv) post-partum haemorrhage; (v) preterm birth; (vi) mode of delivery; and (vii) birthweight	No associations were found between iodine status and adverse pregnancy outcomes.
Charoenrata na et al., 2016, Thailand, ST7	Repeated urine samples, UIC in 1st (n=384), 2nd (n=325) and 3rd (n=221) trimesters. Median UIC 151 µg/L. The mean UIC of repeated measurements were categorised into ≥150 µg/L and <150 µg/L. The study also report the findings on foetal growth restriction using a cut-off of 100 µg/L.	410 pregnant women enrolled in 2013-2014, complete data for 390.	Gestational length/preterm birth, birth weight, foetal growth restriction, Apgar score at 1 and 5 min, antepartum haemorrhage, pregnancy hypertension, gestational diabetes, caesarean delivery.	UIC <150 µg/L was associated with increased risk of preterm birth and low birth weight. UIC <100 µg/L was associated with higher risk of foetal growth restriction. No association with the other outcomes.
Alvarez-Pederol et al., 2009, Spain, ST5	Median UIC in the 1st trimester (n=251): 95 µg/L. Median UIC in the 3st trimester (n=528): 104 µg/L. UIC was categorised into five categories <50 µg/L, 50-99 µg/L, 100-149µg/L, 150-249 µg/L and >249 µg/L.	657 mother/ infant pairs, enrolled 2004-06	Birth weight (continuous) and adjusted SGA	Women with 3rd trimester UICs between 100-149 µg/L had lower risk of having an SGA newborn than women with UICs below 50 µg/L (aOR (95%CI): 0.15 (0.03, 0.76). The newborns in this group also had higher mean birth weights. Similar results were indicated for 1st trimester UICs, but did not reach statistical significance.

5.4.3.1 Grading of fertility and birth outcomes

Six cohort studies on fertility and birth outcomes were identified in the literature review. In four of the five studies on birth outcomes, no association between iodine status and birth outcomes were found. In one of the studies on birth outcomes, a higher prevalence of preterm birth and low birth weight was found in mild to moderate iodine deficient women. In one of the studies, lower birth weight and higher risk of having a small for gestational age (SGA) newborn was found in severe iodine deficient women. It is therefore concluded that the evidence is *limited (no conclusion)* that mild to moderate iodine deficiency prior to conception or during pregnancy is associated with negative birth outcomes.

5.5 Evidence table and grading of health effects related to mild to moderate iodine deficiency

The systematic literature searches for evidence on health effects associated with mild- and moderate iodine deficiency resulted in 131 studies. As a result of quality assessment, one of these studies were categorised as an A-study, a total of 35 studies were categorised as B-studies, whereas a total of 95 studies were categorised as C-studies. The category C-studies (lowest quality score) were not considered further. The following sections are organised according to the health outcomes graded, starting with neurodevelopment, followed by thyroid function and finally birth outcomes. The grading of evidence for the outcomes neurodevelopment, thyroid function and birth outcomes is finally summarised in the evidence Tables in 5.5-1 and 5.5-2.

Table 5.5-1 Evidence based on the systematic literature review of mild to moderate iodine deficiency graded as *limited – suggestive* for neurodevelopmental outcomes. Positive association: Exposure and outcomes have the same direction. Negative association: Exposure and outcomes have the opposite direction.

Author, year	**Study design, N and age**	**Median UIC** µg/L **Median iodine intake** µg/d	**Finding of total main outcomes measured**	**Outcomes measured. Findings in bold**	**Findings associated with UIC**	**Findings associated with iodine intake**	**Findings associated with iodine supplement use**
Prenatal exposure							
Gowachirapant, 2017	RCT, n=330, 5-6y	Baseline all 131 µg/L In India 112 µg/L In Thailand 181 µg/L	0 of 3	3 outcomes: Verbal and performance IQ and global executive composite score.	Primary outcome - no effect.	Effect in favor of placebo on expressive language at 12 months (secondary outcome)	
Abel, 2019	Cohort, n=39471, 8y	67 µg/L 122 µg/d	5 of 6	6 outcomes: **Language skills, reading skills, writing skills, mapping test reading**, mapping test mathematics and **special education**.	**No** association between UIC and school performance tests	**Pos**. association between iodine intake with language, reading, writing, school and spec. ed.	**No** association with supplement and neurodevelopment
Markhus, 2018	Cohort, n=851, 6, 12 and 18mo	78 µg/L	2 of 5	5 outcomes: Cognitive, **receptive communication, expressive communication**, gross motor and fine motor.	**Pos.** association between UIC <100 µg/L and language (expressive and receptive)		**Neg.** association with gross motor performance

Author, year	Study design, N and age	Median UIC µg/L Median iodine intake µg/d	Finding of total main outcomes measured	Outcomes measured. Findings in bold	Findings associated with UIC	Findings associated with iodine intake	Findings associated with iodine supplement use
Murcia, 2018	Cohort, n=1803, 4-5y	123 µg/L	1 of 2	2 outcomes: **Cognitive** and **motor function.**	**No** associations for raw UIC. After adj. for creatinine UIC < 150 µg/g Cr associated with reduced general cognitive score	**Neg**. association with scores on motor scale**, no** association with general cognitive score	**No** association with cognitive or motor scores
Robinson, 2018	Cohort, n=654, 6-7y	108 µg/L	1 of 4	4 outcomes: **Full scale IQ** and executive function (CANTAB DMS, CANTAB IED and CANTAB SSP).	**Pos.** association between preconception UIC and full-scale IQ		
Zhou, 2019	Cohort, n=699, 18mo	186 µg/L	3 of 3	3 outcomes: **Cognitive, language and motor**.	**No** associations with Bayley-III scores	**Pos.** associations with maternal intake (<220 µg/day) and (≥391 µg/day) on all 3 subscales and higher odds of developmental delays.	
Abel, 2017a	Cohort, n=33047, 3y	61 µg/L 122 µg/d	3 of 5	5 outcomes: **Language delay**, communication skills, motor milestone, **fine motor skills** and **behavior problems**.		**Pos.** association between iodine intake <160 µg/day and language, behaviour (ext/int) and fine motor skills.	**Neg.** association with internal behavior
Abel, 2017b	Cohort, n=27945, 8y	61 µg/L (in non suppl-users) 122 µg/d	1 of 2	2 outcomes: ADHD diagnosis **and maternally-reported child ADHD symptoms.**		**Pos.** association between maternal iodine intake <200 µg/day and maternal reported ADHD scores	**Neg.** association with ADHD symptoms and diagnoses
Hynes, 2017	Cohort, n=228, 15y	83 µg/L	1 of 4	4 outcomes: Reading, **spelling**, grammar and writing.	**Pos.** associations between UIC <150 µg/L and spelling		
Ghassabian, 2014	Cohort, n=1525, 6 y	296.5 µg/g creatinine	0 of 2	2 outcomes: Non-verbal IQ and language comprehension.	**No** associations		
Bath, 2013	Cohort, n=958, 8-9y	91 µg/L	3 of 7	7 outcomes: **Verbal** and performance IQ, total IQ, words read per minute, **reading accuracy, comprehension** and reading scores.	**Pos.** association between UIC<150 µg/L and verbal IQ, reading accuracy and comprehension		
Hynes, 2013	Cohort, n=228, 9y	81 µg/L	3 of 7	7 outcomes: Literacy (reading, **spelling, grammar**, writing,	**Pos.** association between UIC <150 µg/L and		

Author, year	Study design, N and age	Median UIC µg/L Median iodine intake µg/d	Finding of total main outcomes measured	Outcomes measured. Findings in bold	Findings associated with UIC	Findings associated with iodine intake	Findings associated with iodine supplement use
				numeracy, **English-literacy score** and mathematics-numeracy score.	spelling, grammar and English grammer		
Rebaglioto, 2013	Cohort, n=1519, 16mo	125 µg/L	0 of 2	2 outcomes: Cognitive and psychomotor development.			**Neg.** association with Bayley-II PDI in 1 of 3 regions, and overall when including data from Murcia 2011.
Murcia, 2011	Cohort, n=691, 1y	134 µg/L	0 of 2	2 outcomes: Mental and **psychomotor scales**.	**No** associations	**No** associations	**Neg.** association with Bayley-II PDI
Exposure in children							
Gordon, 2009	RCT, n=166, 10-13y	63 µg/L	2 of 4	4 outcomes: **Picture concepts, matrix reasoning**, symbol search, letter-number sequencing and overall cognitive.			**Pos.** associations with picture concepts, matrix reasoning
Zimmermann, 2006	RCT, n=310, 10-12y	43 µg/L	4 of 7	7 outcomes: **Rapid target marking, symbol search, rapid object naming, Raven's Coloured Progressive Matrices**, Bead threading, Digit span and Coding.			**Pos.** associations with rapid target marking, symbol search, rapid object naming, Raven's Coloured Progressive Matrices

Table 5.5-2 Evidence based on the literature review of mild to moderate iodine deficiency graded as *limited – no conclusion* for thyroid function and birth outcomes and fertility.

	Population group exposed	Author, year	Study design, N, age	Finding of total main outcomes measured	Median UIC Median iodine intake	Outcomes measured. Findings in bold
Thyroid function	Non-pregnant adults	Thomsen, 2009	RCT, n=100	1 of 4	48 µg/L	4 outcomes: TSH, fT3, fT4 and **Tg**.
		Chen, 2019	Cross-sectional, n=14230	1 of 5	205 µg/L	5 outcomes: **TgAbs**, serum TSH, TPOAbs, fT4 and fT3.

	Population group exposed	Author, year	Study design, N, age	Finding of total main outcomes measured	Median UIC Median iodine intake	Outcomes measured. Findings in bold
		Wang, 2019	Cross-sectional, n=2808	1 of 3	165 µg/L	3 outcomes: TPOAb positivity, TgAb positivity, **Thyroid autoimmunity (TAI)** defined as a combination of positivity for one or both of TPOAb or TgAb.
		Fan, 2018	Cross-sectional, n=2647	1 of 5	134 µg/L	5 outcomes: **Thyroid nodules**, Tvol, TSH, TPOAb and TGAb.
		Krejbjerg, 2015	Cohort, n=1417	1 of 1	61 µg/L (45)	1 outcome: Serum **Tg**.
		Rasmussen, 2002	Cohort, n=4649	2 of 5	68 (53) µg/L	5 outcomes: Tvol, nodularity, Tg, TSH and TgAbs.
		Thomson, 2001	Cross-sectional, n=233	2 of 4	54 µg/L	4 outcomes: Serum total T4, TSH, **Tg and Tvol**.
	Pregnant women	Pedersen, 1993	RCT, n=54	2 of 5	51 µg/L	5 outcomes: Serum TSH, T4, fT4, **Tg and Tvol**.
		Levie, 2019	Cross-sectional, n=2009	4 of 7	90 µg/L (1st trimester)	**TSH,** fT4, **TT4**, fT3, TT3, **TPOAb positivity, TgAb positivity**, borderline significant for the rest (0.05>p<0.1).
		Sun, 2019	Cross-sectional, n=7073	2 of 2	154 µg/L (1st trimester)	**TPOAb positivity**, **TgAb positivity.**
		Abel, 2018	Cross-sectional, n=2910	2 of 5	59 µg/L 121 µg/d	5 outcomes: TSH, fT4, **fT3**, TPOAb and TgAb.
		Moreno-Reyes, 2013	Cross-sectional, n=1311	1 of 6	117 µg/L (1st trimester)	6 outcomes: **Tg**, TSH, TPOAb, TgAb, fT3 and fT4.
		Rebagliato, 2010	Cross-sectional, n=1844	0 of 2	137 µg/L (1st trimester)	2 outcomes: fT4 and TSH.
	School children	Skeaff, 2012	Cross-sectional, n=1153, 5-14y	2 of 4	68 µg/L	4 outcomes: Serum **Tg**, serum TSH, plasma fT4 and **fT3**.
	Before conception/ Fertility	Mills, 2018	Cohort, n=501	1 of 1	113 µg/L	1 outcome: **Time to get pregnant**.
Birth outcomes/ fertility	During pregnancy/ Birth outcomes	Mills, 2019	Cohort, n=329	0 of 1	Not available	1 outcome: Pregnancy loss.
		Snart, 2019	Cohort, n=541	0 of 4	134 µg/L	4 outcomes: Birth weight, birth weight centile (primary outcome), small for gestational age (SGA) and spontaneous preterm birth.
		Torlinska, 2018	Cohort, n=3140	0 of 2	95 µg/L	2 outcomes: Pregnancy/infant loss, or with other adverse pregnancy outcomes.

	Population group exposed	Author, year	Study design, N, age	Finding of total main outcomes measured	Median UIC Median iodine intake	Outcomes measured. Findings in bold
		Charoenratana 2016	Cohort, n=410	3 of 12	151 µg/L	12 outcomes: Gestational week at birth, **birthweight**, stillbirth, **Intrauterine growth restriction, preterm birth**, LBW, Low Apgar score 1 min, Low Apgar score 5 min, antepartum haemorrhage, PIH, GDM and Caesarean delivery.
		Alvarez-Pederol 2009	Cohort, n=657	2 of 2	95 µg/L (1st trimester)	2 outcomes: **Birth weight and SGA**.

6 Best available evidence on the upper level (UL) of iodine intake

Several scientific bodies have established ULs for iodine (described in chapter 4.2), the latest thorough evaluation of UL was, however, published back in 2002/2003. The literature search for adverse health effects from excessive iodine intakes for this report aimed at retrieving new literature after the year 2000 to possibly re-evaluate the existing ULs.

The literature search, search terms, databases and inclusion/exclusion criteria, publication selection of the included studies for iodine excess is described in detail in Appendix I, and therefore only briefly described in this chapter.

6.1 Literature search concerning the upper level (UL) of iodine intake

Literature searches for studies investigating health outcomes related to excessive iodine intakes were performed in MEDLINE and EMBASE and aimed at retrieving publications on adverse effects caused by high intakes of iodine published after 1999 (meta-analyses and systematic reviews) or 2000 (original research articles) to re-evaluate the existing ULs described in chapter 4.2. Details about the search strategy and publication selection are given in Appendix I. Studies of chronic iodine exposure with a range that covered excess intake and that included at least one dose-response analysis with an health outcome, were considered suitable for investigating thresholds and for comparison with existing ULs. Studies with a prospective design were considered optimal, but cross-sectional studies were included if no prospective studies were found and the potential for reverse causation was considered limited.

The literature search for meta-analyses and systematic reviews was conducted on September 21st 2017, and the systematic search for original research articles was conducted on November 23rd 2017. An updated search was conducted in May 2019 covering 2017 and until May 14th 2019, and the latest update vas conducted November 18th 2019.

The literature search for single studies performed in November 2017 identified 2919 articles, and the updated searches performed in May 2019 identified 466 articles and November 2019 identified 234 articles. Both updated searches contained articles that were also found in the previous search. Consequently, the number of articles could not be summarised. Both human and animal studies were included in the search strategy, it was however, decided not to include animal studies, as iodine excess in animals may not be transferable to human experiments.

In total, 5 studies were found relevant and included for evaluation of existing ULs in this opinion. Figure 6.1-1 shows a flow chart for the literature search and selection process for adverse health effects from excessive iodine.

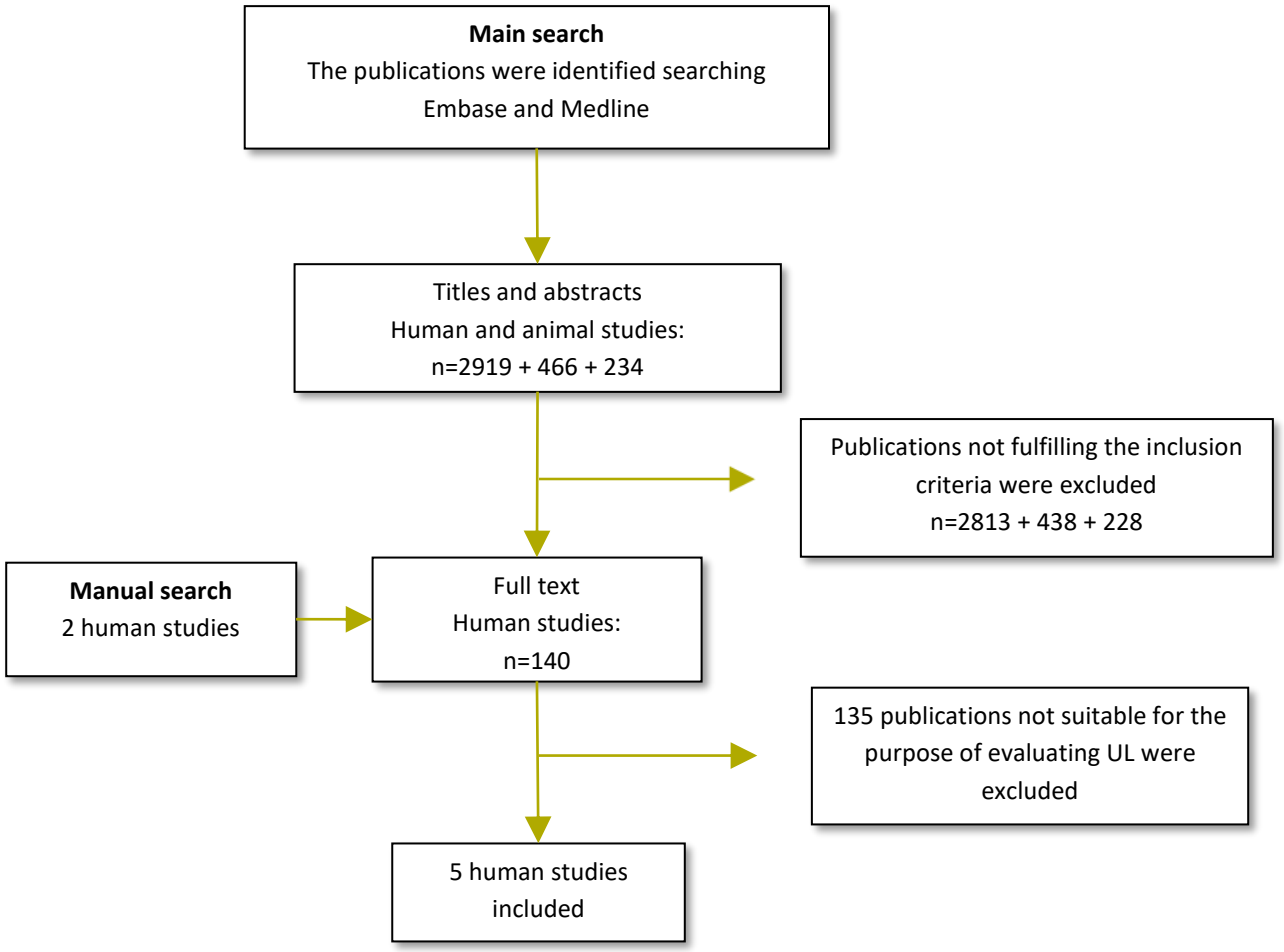

Figure 6.1-1 Flow chart for publication selection for literature concerning adverse health effects of excessive iodine intakes.

6.2 Included studies concerning the upper level (UL) of iodine intake

Few studies had a design suitable for investigating dose-response associations of chronic iodine intake in the excess range, with potential adverse health outcomes. Only five relevant human studies were identified and included from the literature search; one randomised, controlled dose response study in young adults and four cross-sectional studies in children and adolescents.

6.2.1 Study of upper level (UL) of iodine intake in adults

An overview of the RCT in adults is given in Table 6.2.1-1.

Table 6.2.1-1 An overview of the RCT investigating iodine and adverse health effects in adults.

Ref, country	Participant character-istics	Number in study groups		Doses	Measures	Duration of intervention	Conclusions
		phase 1	phase 2				
Sang, 2012 China	256 euthyroid adults, 19-24 years old	161 assigned to 1-7 groups: to 500-,750-, 1000-, 1250-, 1500-, 1750 and 2000	95 assigned to 1-5 groups: the 0-, 100-, 200-, 300-, and 400	0 to 2000 µg iodine/day	Serum concentrations of fT4, fT3, and TSH, TPOAb and TgAb, thyroid size (Tvol), and UIC measured in fasting blood and urine samples obtained in the morning at 0, 2, and 4 wk	4 weeks Follow-up in both phases was conducted after 1 and 3 mo.	Subclinical hypothyroidism appeared in the participants who took≥ 400-µg I supplement, which provided a total iodine intake of 800 µg/d or higher. Thus, the authors cautioned against a total daily iodine intake that exceeds 800 µg/d in China.

The objective of this randomised controlled dose-response study was to explore the safe upper level of total daily iodine intake from diet and supplements among adults in China (Sang et al., 2012). A 4-week, double blind, placebo-controlled, randomised trial was conducted in 256 euthyroid adults (19-24 years old). In phase 1, 161 euthyroid participants met the inclusion criteria and were included in 2004. In phase 2 of the study, an additional 115 participants were recruited in 2008 by using the same method, which resulted in 95 eligible participants. In 2004, in the phase 1 trial, the study participants were randomised to one of seven groups and received supplements of 500, 750, 1000, 1250, 1500, 1750, or 2000 µg iodine per day for 4 weeks. In 2008, phase 2 of the study was conducted, whereby 95 euthyroid participants were randomly assigned to one of the following five groups: 0, 100, 200, 300, or 400 µg iodine per day for 4 weeks. The 0 µg/day group was the control group and received a placebo. In total the participants were randomly assigned to 12 intervention groups with various iodine supplement doses ranging from 0 to 2000 µg/day. Fasting blood and urine samples were obtained in the morning at 0, 2, and 4 weeks. Follow-up in both phases was conducted after 1 and 3 months. Total iodine intake included iodine from both supplements and diet. Multiple outcome measures were used to evaluate possible adverse effects, including thyroid function (serum concentrations of fT4, fT3, and TSH, TPOAb and TgAb, thyroid size (Tvol), and UIC. The initial median UIC concentration was 291 µg/L (272 µg/L in phase 1 and 304 µg/L in phase 2), all of which were within the recommendations of the WHO/UNICEF/ICCIDD (200–299 µg/L). Before supplementation, the mean dietary iodine intakes from food and iodized salt of the participants were 105 (mean intake range of 93 to 117 µg/day between supplementation groups) and 258 µg/day (mean intake assigned to all groups), respectively. The contribution from drinking water was analysed and found to be small (9.9 µg/day) and therefore excluded from estimates of total iodine intake. The mean total iodine intake between supplementation groups ranged from 351 µg/day (placebo group) to 2375 µg/day (2000 µg supplement group). In comparison with the placebo group, all iodine supplemented groups responded with significant increases in median UICs ($p<0.05$) and in thyroid-stimulating hormone concentration ($p<0.05$). Thyroid volume decreased after 4 weeks in the high-iodine intervention groups (1500–2000 µg). Subclinical hypothyroidism (TSH >5 mIU/L and normal fT4) appeared in the groups that

received 400 µg iodine (5%) and 500–2000 µg iodine (15–47%). A small decrease from baseline (0 wk) was observed in the fT3 concentration in the 500–2000-µg intervention groups ($p < 0.05$), but it remained within the normal range. Similar changing patterns were observed for fT4. This study showed that subclinical hypothyroidism appeared in the participants who took the 400 µg iodine supplement, which provided a total iodine intake of 800 µg/day. Elevated TSH concentrations (TSH >5 mIU/L) remained in 5% of the participants who received 400 µg iodine per day 3 months after iodine withdrawal (Sang et al., 2012).

6.2.2 Studies of relevance to the upper level (UL) of iodine intake in children and adolescents

Four cross-sectional studies investigating health outcomes from excessive iodine in children and adolescents were included. An overview is given in Table 6.2.2-1.

Table 6.2.2-1 An overview of the four cross-sectional studies investigating iodine and adverse health effects in children and adolescents.

Reference, country	Study population	Basis for iodine intake estimate	Outcomes	Conclusion
Kang, 2018, Korea National Health and Nutrition Examination Surveys (KNHANES) VI	1288 children and adolescents, 6-19y, with median UIC 449 µg/L. Thyroid function test in sub-sample of 1000 children 10-19y.	Urinary iodine concentration (UIC) in one spot urine sample	TSH, fT4, thyro-peroxidase antibodies (TPOAb), subclinical hypothyroidism (SCH)	In euthyroid individuals 10-19y, there was a weak, positive correlation between UIC and TSH that was more prominent for UIC >1000 µg/L. The prevalence of SCH was significantly higher in the iodine-deficient and iodine-excessive groups compared to UIC of 100–299.9 µg/L. Excess iodine intake may be associated with SCH.
Chen, 2018 China, Shandong province	2224 children, 7-14y with adequate to excessive iodine concentrations in drinking water, median (IQR) 181 (67–402) µg/L.	Two 24-hour urine collections. Median (IQR) habitual iodine intake of 298 (186–437) µg/d	Thyroid volume (Tvol), total goiter rate (TGR), TSH, fT4, fT3, Tg, thyroid antibodies (TPOAb, TgAb)	The risk of total goiter significantly increased at iodine intakes ≥250–299 µg/day in children 7-10 years and at iodine intakes ≥300–399 µg/day in children 11-14 years. Similar to the publication in 2017, the authors recommended 250 and 300 µg/day as safe Tolerable Upper Intake Levels of iodine for children aged 7–10 years and 11–14 years, respectively.
Chen, 2017 China, Shandong province	2089 children, 7-14y with adequate to excessive iodine concentrations in drinking water, median (IQR) 183 (69–406) µg/L.	Two 24-hour urine collections. Median (IQR) habitual iodine intake of 298 (186–437) µg/d	Thyroid volume (Tvol) and total goiter rate (TGR)	Tvol began to increase in children with iodine intake ≥150 µg/d, and TGR exceeded 5% for daily iodine intake categories ≥250 µg/d in children 7-10 yrs, and ≥300 µg/d in children 11-14 yrs old. Authors conclude that 150-249 and 150-299 µg/d appears to be safe upper iodine intake ranges for children aged 7-10 and 11-14 yrs old, respectively.
Zimmermann, 2005 Multicenter: Bahrain, Japan, Peru, South Africa, Switzerland, United States	3319 children, 6-12y from areas with adequate to excessive iodine intake. Median UIC (µg/L) from 116 (Switzerland) to 728 (Coastal Hokkaido, Japan)	Urinary iodine concentration (UIC) in one spot urine sample	Thyroid volume (Tvol)	UIC concentrations ≥500 µg/L were associated with increasing Tvol, which may reflect adverse effects of chronic iodine excess.

TSH=thyrotropin, fT4=free thyroxine, fT3=free triiodothyronine, TPOAb= thyroperoxidase antibodies, Tg, thyroglobulin, SCH=subclinical hypothyroidism.

6.2.2.1 Results based on changes in thyroid volume and risk of goiter

Two studies (three publications) examined threshold effects of habitual dietary iodine intake on thyroid volume and goiter (Chen et al., 2017; Chen et al., 2018a; Zimmermann et al., 2005).

In the publication from 2017 (Chen et al., 2017), children (n=2089, 49% boys) were selected randomly from 1 to 6 primary schools in each of two cities with varying drinking water iodine concentrations. After adjusting for age, sex, height, and body weight, the results suggested a positive, nonlinear relation of total estimated iodine intake with Tvol,

with an iodine intake threshold of 150 µg/day. The TGR exceeded 5% for total estimated iodine intake ≥ 250 µg/day in children aged 7-10 and ≥ 300 µg/day in children aged 11-14 years. Taken together the authors suggested safe, upper intake ranges of 150-249 µg/day for children aged 7-10 years and 150-299 µg/day for children aged 11-14 years.

In the publication from 2018 (Chen et al., 2018a), the children (n=2224, 49% boys) were selected from 4 areas. After adjusting for age, sex, BMI, TSH, and Tg, the risk of goiter significantly increased at total estimated iodine intakes ≥250–299 µg/day in children 7-10 years and at iodine intakes ≥300-399 µg/day in children 11-14 years. In line with the previous study (Chen et al., 2017), the authors recommended 250 and 300 µg/day as safe Tolerable Upper Intake Levels of iodine for Chinese children aged 7-10 years and 11–14 years, respectively.

A multi-center cross sectional study by (Zimmermann et al., 2005) examined the association between urinary iodine concentration (UIC) in spot urine and thyroid volume in a sample of school children aged 6-12 years (n=3319) from 5 continents (see Table 6.2.2-1) with iodine intakes ranging from adequate to excessive. The median (range) UIC was lowest in Switzerland (115 (2-450) µg/L) and highest in coastal Hokkaido, Japan (728 (28-11,000) µg/L). In the combined sample, after adjustment for age, sex, and body surface area, log(Tvol) began to rise at log(UIC)>2.7 corresponding to 500 µg/L. The authors concluded that UIC ≥500 µg/L are associated with increasing Tvol. There was no significant correlation between UIC and Tvol in any single study site with the exception of coastal Hokkaido (r=0.24, p<0.0001).

6.2.2.2 Results based on thyroid function

Two studies examined threshold effects of habitual dietary iodine intake on thyroid function (Chen et al., 2018a; Kang et al., 2018).

In (Chen et al., 2018a) the prevalence of hyperthyrotropinemia (defined as TSH >5.0 mIU/L with a normal fT4, reference range 13.4–20.6 pmol/L) was >10% in children at iodine intakes of 200–300 µg/day. However, there were no consistent differences in the risk of hyperthyrotropinemia with different iodine intakes over the range <100 µg/day to ≥ 600 µg/day. Adjusted TSH values were not significantly correlated with iodine intake. The authors concluded that thyroid volume and goiter appear to be more sensitive indicators of thyroid stress than TSH in children with long-term excess iodine intakes.

A study from the Korean National Health and Nutrition Examination Surveys (KNHANES) V (Kang et al., 2018) examined excessive iodine intake (based on the urinary iodine concentration (UIC) in spot urine) and subclinical hypothyroidism (SCH) in 1288 (55% male) euthyroid children. The median UIC was 449 µg/L (range 15-21,905 µg/L). Thyroid function tests were only performed on a sub-sample aged 10-19 years (n=1000, 56% male). SCH was defined as TSH >5.5 IU/mL with normal fT4 levels (0.89-1.76 ng/dL). The authors reported a positive, but weak correlation between UIC and TSH (r=0.09; p=0.004) that was more prominent for UIC >1000 µg/L. The prevalence of SCH was significantly higher in the

iodine-deficient group (8.5% for UIC <100 µg/L) and iodine-excessive groups (7-10% for UIC from 300-<600, 600-<1000, or ≥1000 µg/L) compared to 4% SCH in the group with an UIC of 100-299.9 µg/L. The authors conclude that excess iodine intake may be associated with SCH.

6.2.3 Discussion and summary of studies on excessive iodine intake and upper level

The results of the systematic literature search were used to evaluate established tolerable upper intake levels (ULs) of iodine (IOM, 2001; NNR Project Group, 2012; SCF, 2002) in light of new scientific evidence on health effects of excess iodine intake. UL has been defined as the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans (EFSA, 2010c). Existing UL values for iodine have predominantly been established based on changes in thyroid stimulating hormone (TSH) concentrations in studies of adults (Gardner (1988) and Paul (1988) cited in IOM, 2001 and SCF, 2002). Elevated TSH is considered to indicate an existing risk of induced hypothyroidism (SCF, 2002). ULs for children and adolescents have mainly been derived from adult values adjusted for body surface area.

The literature search identified five relevant publications with TSH and subclinical hypothyroidism, or goiter rate as outcome, but only one dose-response study. The dose-response study was limited to young adults from China (Sang et al., 2012) and had a short duration (4 weeks). Because dose-response studies in children are not available, four publications from three large, cross-sectional studies including populations from China, Korea, and Japan with high iodine exposures, were included (Chen et al., 2017; Chen et al., 2018a; Kang et al., 2018; Zimmermann et al., 2005).

In adults, the results from the dose-response study (Sang et al., 2012) were found to be in line with the UL of 600 µg/day in adults set by the SCF (2002) and later adopted by the NNR (2012). The study (Sang et al., 2012) included more participants (256 vs 20) with longer follow-up (4 vs 2 weeks) than previous studies underlying the current UL of 600 µg/day (Gardner (1988) and Paul (1988 cited in IOM, 2001 and SCF, 2002). This study showed that subclinical hypothyroidism appeared in the participants with a total iodine intake of 800 µg/day. The project group therefore considered that an UF of 1.3 was sufficient to apply to the UL of 800 µg/day of iodine suggested by the authors (800/1.3 = 600 µg/day).

In children, the cross-sectional studies were not considered sufficient to establish or re-evaluate existing ULs. Two studies assessed iodine exposure from UIC in a single spot sample (Kang et al., 2018; Zimmermann et al., 2005) which may not reflect chronic iodine intake in individuals. Most weight was placed on the studies by Chen et al. (2017 and 2018) where iodine exposure was assessed from UIC in two 24-hour urine collections in an area with high iodine concentrations in drinking water, which reflects long-term exposure to high iodine intakes with more certainty.

The studies by Chen et al. (2017 and 2018) suggested safe, tolerable upper intake levels of iodine of 250 µg/day for ages 7-10 years and 300 µg/day for ages 11-14 years based on increased goiter rate (> 5%) in Chinese children. One of the studies by Chen et al. (2018) and the study by Kang et al. (2018) measured TSH in children. Chen et al. (2018) reported that the prevalence of hyperthyrotropinemia exceeded 10% for iodine intakes ≥ 200 µg/day in children 7-10 and 11-14 years, but there was no dose-response relationship across intake categories up to ≥ 600 µg/day. Kang et al. (2018) reported a significantly higher prevalence of subclinical hypothyroidism in children aged 10-19 years in the iodine deficient and iodine excess groups (8-10%) compared to those in the UIC 100-299.9 µg/L group (4%). These results suggest that goiter rate and subclinical hypothyroidism and hyperthyrotropinemia, may increase in children with iodine intakes below existing UL values derived from studies in adults (SCF, 2002). However, given the uncertainties of these studies, the project group propose to keep the ULs for all age groups set by SCF in 2002.

7 Exposure assessment

In the terms of reference from the Norwegian Food Safety Authority, VKM is requested to estimate the iodine exposure in the general population and among specified potential risk groups. Imported foods that are fortified with iodine and sold on the Norwegian market should also be taken into account. In this benefit and risk assessment risk groups refer to subpopulations at risk for overly low or high iodine intakes, and include women of childbearing age, women who are pregnant and breastfeeding, men and children. Other risk groups such as vegans, individuals suffering from allergy to fish and dairy products, ethnic minorities which do not consume fish and dairy products, and individuals consuming iodine supplements are also requested to be included in the benefit and risk assessment of iodine, as is iodine fortified plant-based alternatives to cow's milk.

VKM is furthermore requested to estimate iodine exposures in the general population and among identified risk groups in scenarios according to graded concentrations of iodine added to household salt and industrial salt used in bread. The estimates are seen in conjunction with the Salt Strategy 2014-2018 (Helsedirektoratet, 2014).

The iodine exposure estimates are based on available food composition data updated for iodine (Carlsen et al., 2018) and consumption data from national dietary surveys. Estimated exposures to iodine in the Norwegian population are described below.

7.1 Food composition data

Intakes of iodine were computed using the Norwegian Food Composition Database and the software system KBS developed at the Institute of Basic Medical Sciences, Department of Nutrition, at the University of Oslo.

In 2017-2018, the Norwegian Food Composition Database was updated to include the iodine content of 3259 food items. The data were compiled using international guidelines and standards. Values were gathered from multiple sources, including analytical values, values from other food composition databases, estimated values, and values that were based on recipes (Carlsen et al., 2018). The KBS database version AE-18 (October 2019) containing the most recent iodine values for all foods were used.

In this assessment the point estimates of iodine content in each food are used. This do not take the variation of iodine content for all foods into consideration. An example is iodine content in Atlantic cod where the iodine variation was from 22 to 720 µg/100 g (Nerhus et al., 2018). However, the long term intake will most likely even out the large variations.

Mineral water has been analysed, and two brands had an iodine content of 30-40 µg/100 g. In the national surveys, the participants were not asked for brand name on mineral water, and these iodine values were therefore not included in the exposure calculations.

Foods from the marine environment, including some lean fish, seaweed, and sea salt have the highest content of iodine per 100 gram. In addition, Norwegian whey cheese have high iodine content.

In Norway, iodization of cow fodder has been mandatory since 1959 to protect the health of the animal. The maximum limit for iodine in cow fodder is set at 5 mg I/kg in Norway (Forskrift om fôrvarer, 2002: https://lovdata.no/dokument/LTI/forskrift/2002-11-07-1290) and in the EU. This results in increased iodine content in milk and dairy products.

Table 7.1-1 shows the average iodine content in selected foods in Norway.

Table 7.1-1 Average iodine content in selected foods, µg/100 g (KBS-database AE18).

Food	Mean µg/100g
Milk	15
Cheese	
Cheese, white (gauda type)	27
Cheese, whey, goat's milk	342
Cheese, whey, cow and goat milk	144
Cheese, whey, cow's milk	128
Fish	
Atlantic cod	279
Saithe	272
Salmon, farmed	5
Bread	2
Egg	34

7.2 Food consumption data

As VKM was requested to evaluate scenarios of potential iodine exposure according to different levels of iodization of household salt and/or bread, the relevant food consumption data variables were iodine from all sources in the diet, the "background level", household salt and salt in bread. The exposures to iodine were calculated using food consumption data from the national dietary surveys. Consumption data for the iodine exposure estimates were based on the national food consumption surveys listed below.

Norkost 3 was based on two 24-hour recalls by telephone at least one month apart. Food amounts were presented in household measures or estimated from photographs (Totland et al., 2012). The Norkost 3 study was carried out by the University of Oslo, Norwegian Food Safety Authority, Norwegian Directorate of Health and Norwegian Institute of Public Health in 2010/2011. A total of 1787 adults aged 18-70 years participated. The participation rate was 37%. No national dietary information among the older population (>70 years) exists in Norway.

Consumption data on bread from the Norwegian Mother and Child Cohort Study (MoBa) for pregnant women was considered. However, consumption data for bread in Norkost 3 were, considered to be more solid for the purpose of this benefit and risk assessment, as the consumption data in MoBa were based on a FFQ with relatively few questions related to bread consumption.

The exposures to iodine in 4-, 9- and 13-year-old children are calculated from the national food consumption survey Ungkost 3 (Hansen et al., 2017; Hansen et al., 2016). The Ungkost 3 study was carried out by the University of Oslo, Norwegian Food Safety Authority, Norwegian Directorate of Health and Norwegian Institute of Public Health in 2015 for 4th and 8th graders (8-9-year-olds and 12-13-year-olds), and in 2016 for 4-year-old children. The dietary assessment tool was a 4 days validated web-based food diary. A total of 399 4-year-old, 636 9-year-old and 687 13-year-old children participated.

The iodine exposures in 1-year-old children were estimated from the national food consumption survey Spedkost conducted in 2007 (Kristiansen et al., 2009), and the exposure in 2-year-olds were estimated from Småbarnskost 3, conducted in 2019 (Astrup et al., 2020). These food consumption surveys were based on semi-quantitative FFQs. The caretaker was asked to have the last two weeks in mind when answering the questionnaire. In addition to predefined household units, food amounts were also estimated from photographs. A total of 1635 1-year-olds, and 1413 2-year-olds participated. The participation rate was 56%, and 47% respectively.

Figure 7.2-1 illustrates mean contribution to the total iodine intake from different food groups (not including food supplements) in adults, 13-year-olds and 2-year-olds in percentage of the total iodine intake for each age group (not including iodine containing supplements).

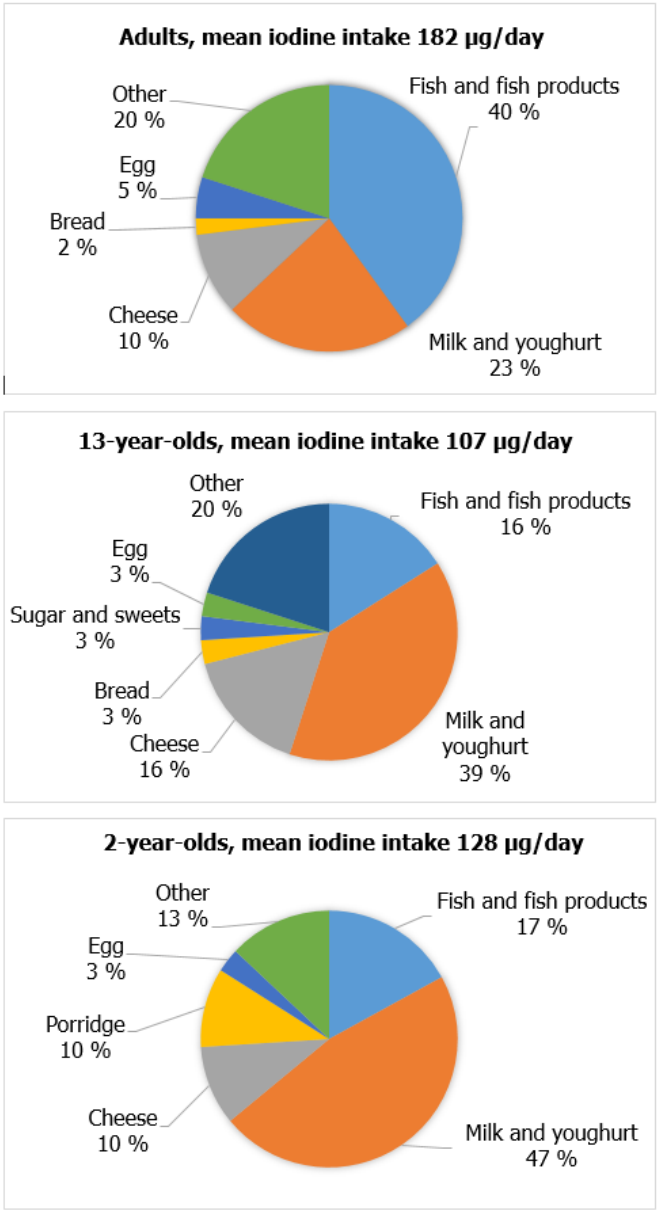

Figure 7.2-1 Contribution to the total mean iodine intake from the most significant food groups (not including supplements) in adults, 13-year-olds and 2-year-olds in % of the total mean iodine intake.

7.2.1 Consumption of total salt and household salt

Estimating salt (NaCl) intakes from dietary surveys has low validity due to a number of factors influencing the total salt intake. Processed foods may vary substantially in salt content. The same foods, e.g. cheese or bread, will differ in salt content depending on the producer. In addition, each producer will change recipes over time. Home cooked meals are prepared from a large variation of recipes, and both the recipes and the taste of the cook will influence how much salt was added. The individual amount of salt added to the food at the table varies depending on individual taste preferences. These variables are difficult to take into account in dietary surveys. Salt intake estimates from dietary surveys therefore

usually aim to cover salt added to processed foods, and standard amounts of salt added to home cooking. Use of household salt was not specifically asked for in the national dietary surveys.

The best method for measuring habitual salt intake is by measuring sodium from several 24-hour urine collections in the same person. The most recent sodium data from Norway are based on a single 24-hour urine collection in the seventh wave of the Tromsø study (Tromsø 7), carried out in 2015-16 (www.tromsostudy.com). The Tromsø Study is a population based longitudinal multi-purpose study focusing on lifestyle-related diseases and their risk factors (Jacobsen et al., 2012). All citizens aged 40 years and above (32 591) living in the municipality of Tromsø in northern Norway were invited, and a total of 21 083 people participated. 24-hour urine was collected from 496 participants aged 40-69 years and analysed for sodium, potassium, creatinine and iodine (Meyer et al., 2019). The total daily intake of NaCl (g) was calculated by multiplying daily sodium excretion with a factor of 2.54. Mean (SD) estimated daily salt intake was 10.4 (4.1) g in men and 7.6 (2.8) g in women.

There is a lack of knowledge about household salt use in the Norwegian population. Studies from England (Sanchez-Castillo et al., 1987), USA (Mattes and Donnelly, 1991), and Denmark (Andersen et al., 2009) have shown that household salt consumption is in the order of 10% of the total salt consumption. However, in studies from Italy (Leclercq and Ferroluzzi, 1991) household salt comprised close to 40% of total salt consumption. In addition to differences between countries, there is large individual variation.

In our exposure estimates we have assumed that the intake of household salt constitutes 10% of the total salt intake based on the Tromsø 7 study. In this assessment, the estimated daily intake of NaCl from Tromsø 7 was for men and women independently fitted with a log-normal distribution. These distributions represented, to our knowledge, the best available charaterisation of daily salt intake for adult Norwegians. To transform these daily intakes into chronic intakes (i.e. long-term average intakes) used in the probabilistic exposure assessment for each individual exposure, a mean of 365 randomly drawn daily salt intakes from the relevant distribution was calculated for each of the individuals used in the scenario calculations (see Appendix IV).

Data on salt consumption in Norwegian children or adolescents is, to our knowledge, lacking. In a study by Whelton et al. (2012) it was concluded that sodium intake was highly correlated with total energy intake, due to its inclusion in a wide variety of foods and meals (Whelton et al., 2012). To estimate salt intake in children and adolescents for our scenario estimates, we therefore have assumed that sodium intake scale linearly with energy intake across age classes. Sodium intake was scaled by calculating overall mean energy intakes for adults (Norkost 3)/ mean energy intakes children (2-, 4-, 9- and 13-year-olds) (Småbarnskost 3 and Ungkost 3), independently for boys and girls. Household salt is assumed to be 10% of total salt also in children and adolescents. The daily energy intakes used are means from the national dietary surveys, and are for men and boys 10.7 MJ (adults), 8.6 MJ (13 years), 7.8 MJ (9 years) and 6.1 MJ (4 years), 5.6 MJ (2 years), and for

women and girls 9.0 MJ (adults), 7.4 MJ (13 years), 6.9 MJ (9 years), 5.5 MJ (4 years), and 5.3 MJ (2 years).

The salt estimates used for the scenario calculations for adults, children and adolescents are given in Table 7.2.1-1. Daily salt intake for adults is assumed to follow a log-normal distribution (which means that the standard deviation of the log-normal distribution is the same for all groups within sexes). Parameters for the lognormal distributions of daily salt intake for adults are $\mu_{females}$ = log(7.1), $\sigma_{females}$ = 0.381 and μ_{males} = log(9.7), σ_{males}=0.395. The variation is assumed to represent variability between days. Reported below (7.2.1.-1) are the assumed long-term intakes of household salt (i.e. mean of 365 daily intakes, set to 10% of total salt intake). Note that for the scenario estimates, some variability in chronic salt intake is incorporated by sampling 365 'daily' intakes of salt for each individual (see Appendix IV).

One-year-olds consume less salt than adults, adolescents and children. The above assumption of a correlation between energy and salt intake was not presumed to be applicable for 1-year-olds, and no data on household salt are presented for this age group.

Table 7.2.1-1 Assumed household salt intakes in adults, children and adolescents (g/day), based on approximations from Tromsø 7. These are long-term mean intake (i.e. the mean of a log-normal distribution = $\exp(\mu + \sigma^2/2)$), see text for parameters.

	Adults (g/day)	**13 y (g/day)**	**9 y (g/day)**	**4 y (g/day)**	**2y (g/day)**
Males	1.0	0.8	0.8	0.6	0.5
Females	0.8	0.6	0.6	0.5	0.5

Present iodine fortification of household salt in Norway is 5 mg/kg salt, with both iodized and non-iodized salt are available in the Norwegian market. We do not have data on the iodized vs non-iodized salt consumption, and we assumed that the current intake of salt is only non-iodized salt.

7.2.2 Consumption of bread

VKM is requested to evaluate different iodization levels in industrialised salt used in bread production. We have categorised 'bread' as all whole grain and fine bread, rolls and baguettes, rusks, focaccia, crispbreads and other yeast bakings usually eaten with breadspreads, pizza or pie bottoms, tortilla wraps, naan, potato wraps ('lompe'), hot dog bread, and hamburger bun. It was assumed that all salt used for commercial bread production were iodized at the given levels. Not included in the category "bread" for the scenario estimates were sweet and salt biscuits, scones, taco shells, sweet yeast bakery wares, and cakes.

We do not have sales data regarding imported bread produce with iodized salt. If we assume that most of the imported bread is produced within Europe, the salt iodization levels could be as high as 75 mg iodine per kg salt. It should be noted that a noteworthy proportion of

bread products are imported, mostly as frozen breads, baguettes or rolls for home baking, or frozen doughs for in-store baking.

Imported bread with iodized salt is not included in our iodine exposure estimates neither in the estimates for current intake levels nor in the bread scenarios.

7.2.2.1 Salt content in bread

As bread consumption in Norway generally has been high, bread has been a significant contributor to the total salt intake in the Norwegian population. The Norwegian food industry and the health authorities collaborate to reduce salt in processed foods, including salt reduction in bread. In this context, salt was monitored in 29 breads at the Norwegian market in 2016, and these are the most recent analysis available of salt in bread in Norway. The analysis includes bread and crispbreads, but not rolls or baguettes. The mean salt content in bread in these analyses, was 1.1 g salt per 100 g bread (NIFES, 2017) and unpublished analyses from 2018-2019. In the present assessment, 1.1 g salt per 100 g bread was used for all bread in the intake modelling of daily individual intakes of "salt in bread".

7.2.3 Consumption of food supplements with iodine

The iodine content in regular food supplements used in Norkost 3 range from 25 to 150 µg per dose, but most iodine supplements contain 150 µg iodine per recommended daily dose. In Norkost 3, 16% (n=145) of the women reported use of iodine supplements with a mean iodine contribution of 95 µg/day. Among women between 18-45 years of age, a total of 17% (n=77) reported use of iodine supplements, with at mean iodine contribution of 96 µg/day. Similarly, 11% (n=92) of the men reported use of iodine supplements with a mean iodine contribution of 117 µg/day. Iodine exposures including food supplement (users only) are presented in Appendix V.

In 13-year-olds in Ungkost 3, 4% of the girls (n=14) and 3% (n=9) of the boys reported to use iodine supplements. In 9-year-olds, 4% of the girls (n=13) and 2% (n=6) of the boys reported to use iodine supplements. In 4-year-olds, 4% of the girls (n=8) and 5% (n=12) of the boys reported to use iodine supplements. In Småbarnskost 3, 10% of the 2-year-olds reported to use iodine supplements with at mean iodine contribution of 96 µg/day. In Spedkost-07 there were no reported use of iodine supplements among the 1-year-old infants.

Kelp- and seaweed-based products and supplements may contain high concentrations of iodine. Duinker et al. at Institute of Marine Research has analysed 125 kelp and seaweed samples for iodine (personal communication Arne Duinker and (NIFES, 2016). The iodine content varies from 525 mg iodine per kg dry weight to 10094 mg iodine per kg dry weight. (Gundersen and Olsen, 2018) collected 40 different dried kelp products from shops in Norway, and also from internet sites. The highest iodine content was measured in a kelp product with 5500 mg iodine per kg dry weight, while the lowest content was measured to 14 mg iodine per kg dry weight.

Consumption of kelp- and seaweed-based products and supplements may result in iodine intakes above UL. Vegetarians and vegans recruited to a study in the Oslo-area in 2014-2015 showed excessively high UIC (>1000 µg/L) in three individuals who used kelp-supplements (Brantsaeter et al., 2013). Thyrotoxicosis due to ingestion of kelp has been widely reported (Leung and Braverman, 2014).

Pregnant women participating in the Norwegian Mother and Child Cohort Study (MoBa) during years 1999-2008 provided information about dietary supplement use. The results showed that ~10% of the women initiated iodine-supplement use prior to conception and ~9% initiated iodine-supplement use in the first trimester (Abel et al., 2019). Overall, 32-37% of the women used iodine-containing supplements at some time during the first half of pregnancy (Abel et al., 2017a; Brantsaeter et al., 2013). The median amount of iodine intake from supplements (in iodine-supplement users) was 107 µg/day (Abel et al., 2017a; Brantsaeter et al., 2013). Information about consumption of kelp or kelp supplements is not available in MoBa.

In a study among 804 pregnant women, 32.7% of the participants reported using iodine-containing supplements (Henjum et al., 2018a). In a study in 175 lactating women 29% reported habitual iodine supplement use, whereas only 17.7% had actually consumed an iodine-containing supplement during the last 24-hours (Henjum et al., 2017). In a study in 403 women of childbearing age 9.4% reported habitual intake of an iodine-containing supplement (Henjum et al., 2018b). In this study, the median amount of iodine contributed by the supplements was 129 µg/day, the mean (SD) contribution was 106±60 µg/day, and the median adjusted increase in UIC associated with iodine supplement use was 70 µg/L.

7.3 Iodine exposure estimates

Chapter 7.3 responds to the following question in the terms of reference: What is the iodine intake in the general population and among identified risk groups? Risk groups meaning subpopulations at risk for overly low or high iodine intake.

The iodine exposure for the general population was estimated based on data from Norkost 3 (adults), Ungkost 3 (4-, 9- and 13-year-olds), Småbarnskost 3 (2-year-olds) and Spedkost (1-year-olds). For Norkost 3 and Ungkost 3 data the estimates for iodine exposure have been calculated using two different approaches and statistical tools. Since the iodine exposure estimates are based on data from different dietary survey methods, they are presented in different sections or tables or at least separated with thick lines if presented in the same tables.

Direct comparison between different dietary assessment methods in different age groups are challenging to interpret without validation and calibration studies. There is a tendency for FFQ (used for the 2-year-olds) to overreport the energy intake, and for recording methods (used for the other age groups) to underreport the energy intake (Andersen et al., 2004; Burrows et al., 2010; Medin et al., 2017a; Medin et al., 2017b).

1. Exposure calculations based on means of survey days. Two survey days for adults, and four survey days for adolescents and children (13-, 9- and 4-year-olds). This is generally referred to as *observed individual means* (OIMs). For 1- and 2-year-olds the reported intakes from the FFQs were also expressed as intake per day.
2. Exposure modelling using Bayesian generalised linear mixed models. Models were developed and fitted to daily intakes of iodine and salt and used to simulate long-term exposures. The models were used to correct for unrepresentativeness in the surveys on both sex-ratio, age and level of education for adults, and only sex-ratio for 13-, 9- and 4-year-olds. This was applied in the statistical environment *R*, using the Bayesian package MCMCglmm (Hadfield, 2010). These mixed models are in structure very similar to the *Monte Carlo Risk Assessment Tool* (MCRA), available from RIVM (van der Voet et al., 2015), and a preliminary comparison of the tailor-made scripts and models in *R* with MCRA was performed showing very similar results (see Appendix IV). However, as MCRA does not allow for estimation of variance between individuals (nor covariance between two intake variables, iodine and bread), MCRA was not used for the full assessment. Appendix IV detail the modelling approach. We refer to results from this modelling approach as *mixed models* (MM).

Exposure estimates based on OIMs (presented in Appendix V) can overestimate the variance in intake between individuals and lead to *bias* in the estimator, due to the low number of sampled days in the original survey as well as the degree of unrepresentativeness in survey respondents. The approach is particularly prone to overestimates of the tails of an intake distribution due to low number of sampled days. In general, the standard error of a mean decreases with the inverse of the square root of number of days (~1/sqrt(n_days)), which implies that using the mean of two (or 4) daily intakes as a long-term intake for each individual, is an estimate with a substantial standard error. When the population distribution then consists of a number of individual means with high standard error, the variance of long-term intakes at the level of the population is overestimated. In an attempt to alleviate this problem, we apply statistical models through which we can directly estimate and account for different levels of variability.

For long-term exposure, we wish to remove the day-to-day variability *within* individuals (to get long-term exposures at the individual level), but to correctly characterise the variability *between* individuals (accounting for the fact that individuals have different diets). One appropriate statistical framework for such an analysis is mixed models. A mixed model approach estimates the linear (fixed) effects of explanatory variables (sex, age, level of education) on daily iodine intake, but the variation in daily intakes is decomposed into *within*- and *between*-individual variability. This is possible when there are multiple 'observations', in our case several days of iodine intake. For all individuals we also fitted multivariate models, i.e. for each individual and day we have calculated iodine intakes and intakes of salt from bread, and explicitly incorporated how individuals covary in their iodine and bread intake.

Fitted models are able to simulate daily exposures, and averaging over many such daily simulated intakes predict chronic exposures. When simulating exposures, we also corrected for fixed effects (sex, age, level of education). For adults in the Norkost 3 survey we use age-distributions from the Norwegian population from (StatisticsNorway, 2018) and not the study population, thus partially correcting for unrepresentativeness in age among respondents. We also corrected for the over-representation of highly educated individuals. For 4-, 9, and 13- year-olds we present simulated exposure for each sex, and no fixed effect besides sex was included in the models. A more thorough introduction to this modelling approach and the details of the models developed for this project is presented in Appendix IV.

Simulated exposures of iodine are drawn together with simulated intake of salt from bread consumption and are then used to perform scenario analyses. The approach allows for direct analysis of correlation between intake of iodine and salt from bread, and scenarios incorporate this covariation, for each sex independently. This covariance is positive for males and females in all surveys modelled, except for 4-year-old boys. This implies that individuals that have an iodine intake above the population mean also have a bread intake above the population mean. For each scenario we also quantify the proportion of the (sub-) populations predicted to be below or above the estimated average requirements and tolerable upper intake levels.

The impact of MM-approach on the exposure estimates would typically be a reduction in the tails, i.e. a narrower distribution of chronic intake, compared to OIMs or daily intakes. Furthermore, a reduction in the mean intake is expected, as the daily intake distributions are skewed and an increase in the number of days will reduce the impact of rare days of very high intake (i.e. the upper tail).

Norkost 3, Ungkost 3, and Småbarnskost 3/Spedkost 07 have used different dietary assessment methods. Norkost 3 and Ungkost 3 have used recall and record methods that collect the food intake day by day for two non-consecutive days and four consecutive days respectively. The 2x24-hour recall method used in Norkost 3, and the 4-day precoded web-based food diary used in Ungkost 3 are both methods that can give detailed information about the food intake over a short period of time. These methods aim to identify the food actually eaten, and do not ask the participant to do estimations on long term intakes. The FFQs that were used for 1- and 2-year-olds asked the caretaker to make estimates about foods usually eaten, and the frequencies range from per day to per month. The caretaker was also asked to have the last two weeks in mind when answering the questionnaire. In toddlers, food habits change relatively quickly compared to older children and adults, and the changes are especially rapid around 1 year of age. The FFQs ask for the caretaker to estimate an average intake, whereas in the recall and record methods, mean intake can be calculated as OIMs, or modelled with MM-method. Because we have different approaches to the calculations for adults, for 13-, 9-, 4-year-olds, and for the 2-year-olds, we present the data in separated chapters, and have marked the tables with thicker lines to visualise that the data arrive from different food survey methods and statistics.

Also, the number of foods reported used illustrate the differences between the methods in detail level. In Norkost 3 approximately 1800 different food codes were reported eaten with the 24-hour recalls. In Ungkost 3, approximately 800 food codes were used in the precoded food diary. In the FFQs for 1- and 2-year-olds the number of food codes used is approximately 180.

As the three different methods have used different questions to assess dietary intake, the answers will also differ. Both the number of registration days, number of food items and level of details in the questions differ between methods used. Thus, comparison of iodine intakes based on data from the three different methods has methodological limitations.

Only the estimates for intakes without iodine supplements have been described and commented in the text below. The project group considers that it is appropriate to base the evaluation of the scenarios with increasing iodization levels in household salt and bread on intakes without food supplements. However, iodine exposure including iodine from supplements are presented in some of the tables and in Appendix V.

The project group decided to compare the iodine exposure estimates in the following sections with the AR/EAR for adults from NNR (2012) and EAR for children and adolescents from IOM (2001) and the ULs established by the SCF (2002). The rationale for this choice of dietary reference values for comparison with exposure estimates is given in section 4.3.

7.3.1 Exposures in adults, 13-, 9- and 4-year-olds

7.3.1.1 Model-based iodine exposure estimates

The MM iodine exposures are presented in Table 7.3.1.1-1. For each survey, models of daily (log) iodine intake were fitted together with daily (log) salt intake from bread. For Norkost models, fixed effects were included for age, sex and level of education. The simulated exposures were corrected for these biases by sampling age and level of education from Statistics Norway (SSB). For Ungkost data, only sex was used as fixed effect. For all models, individual level variance was implemented independently for each sex, and covariance between intake of salt from bread and iodine was explicitly modelled (this is used for scenario analyses, see section 6.5). Day-to-day variance was also estimated independently for each sex, but without explicit covariance. Values in the table are long-term exposures (mean of 365 simulated days) for 100 000 simulated individuals. In addition to summary statistics on the simulated population we also report the percentage of the groups that are simulated to have intake above EAR and below UL.

Table 7.3.1.1-1 MM iodine exposure estimates in adults and 13-, 9- and 4-year-olds, presented as mean and percentiles (µg/day) and percentages of population above the estimated average requirement (EAR) and under tolerable upper intake levels (UL). All groups are presented with or without supplement use when calculating all the daily intakes for all individuals. For each group, 100 000 individuals were simulated.

Survey	Group	Suppl	Mean	P05	P50	P95	Percent > EAR	Percent < UL
Norkost 3	Men, 18-70y	Wo	202	88	183	377	91	100
	Women, 18-70y	Wo	147	72	137	259	79	100
	Women, 18-45y	Wo	137	68	128	240	74	100
	Men, 18-70y	W	215	88	192	419	91	99
	Women, 18-70y	W	163	79	151	288	85	100
	Women, 18-45y	W	152	75	141	266	81	100
Ungkost 3	Boys 13y	Wo	124	48	110	248	79	100
	Girls 13y	Wo	95	38	85	187	62	100
	Boys 9y	Wo	118	64	111	193	89	100
Ungkost 3	Girls 9y	Wo	100	44	91	188	70	100
	Boys 4y	Wo	110	62	105	177	93	100
	Girls 4y	Wo	102	52	95	175	85	100
	Boys 13y	W	126	49	111	252	80	100
	Girls 13y	W	98	39	87	195	64	100
	Boys 9y	W	120	64	113	198	90	100
	Girls 9y	W	103	44	93	196	70	99
	Boys 4y	W	114	62	108	188	93	99
	Girls 4y	W	105	52	98	182	86	99

Wo=without iodine supplements, W=with iodine supplements.
EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day (Source: SCF, 2002).

The mean and median iodine intake in men is above the recommended intake of 150 µg/day, and 91% of the men have intakes above the EAR of 100 µg/day. In women, the

mean and median intakes are below the recommended intake. 74-79% of women have intakes above the EAR, and women of childbearing age have the lowest intakes among adults.

The mean and median iodine intakes in 13-year-old boys and girls are below the recommended intake of 150 µg/day, and the intakes in the girls are low; mean (median) intake is 95 (85) µg/day. Only 79% of the 13-year-old boys and 62% of the girls have intakes above the EAR of 73 µg/day.

The mean and median iodine intakes in 9-year-old boys and girls are below the recommended intake of 120 µg/day. The iodine intake is lower in girls than in boys, and 89% of the 9-year-old boys and 70% of the girls have intakes above the EAR of 73 µg/day.

The mean and median iodine intakes in 4-year-old boys and girls are above the recommended intake of 90 µg/day. 93% of the 4-year-old boys and 85% of the girls have intakes above the EAR of 65 µg/day.

Almost all (99-100%) of adults and 13-, 9- and 4- year-olds have intakes below the UL.

The dietary assessment methods used in Norkost 3 and Ungkost 3 tend to underestimate the energy intake, and the tendency differ between the age groups. Based on the method proposed by (Black, 2000), Norkost 3 reports that there is a high probability that participants with a ratio for energy intake:basal metabolic rate (EI:BMR) below 0.96 underreport their true energy intakes. The proportion who underreported energy intake was 16% in Norkost 3, and similar in men and women (Totland et al., 2012). In Ungkost 3, the proportion who underreported energy intake was 33% in the 13-year-olds, 12% in the 9-year-olds and 5% in the 4-year-olds (Hansen et al., 2017; Hansen et al., 2016), whereas the proportions for overreporting was 1%, 2% and 2% in the same age groups (EI:BMR > 2.49). Inaccurate estimates of energy intake can to some extent be a proxy for inaccuracy in the estimated intake of nutrients. In Norkost 3 and Ungkost 3, energy and iodine intakes were medium correlated (correlation coefficients in the range of 0.3-0.5 in some tested groups). The explanation may be that only a few food sources have high content of iodine whereas the energy intake will be affected by all foods with energy. However, due to the relatively high proportion of underreporters of energy intake in adults and 13-year-old (16 and 33%, respectively), it is reasonable to assume that our estimated iodine intakes in adults and especially in the 13-year-olds are somewhat lower than true intakes. It should be noted that under- and overreporting of energy intake was not accounted for in the MM-modelling of the iodine exposure estimates.

7.3.2 Exposures in 1- and 2- year-olds

Iodine exposure estimates for 1-year-olds are based on FFQ and collected in 2007. The differences in iodine intakes between boys and girls are small, and the intakes are given for boys and girls together. It should be noted that for breastfed infants, the iodine intake from breast milk consumption is not included in the estimates. New data for 1-year-olds will be

available in 2020. If the new data for the 1-year-olds differs substantially from the ones presented here for iodine, we will supplement this benefit and risk assessment with updated exposure estimates.

Table 7.3.2-1 Iodine exposure estimates for 1- and 2-year-olds based on food frequency questionnaire, presented as mean and percentiles (µg/day) and percentages of population above the estimated average requirement (EAR) or under the tolerable upper intake level (UL). 2-year-olds are presented with or without supplement use when calculating all the daily intakes for all individuals.

	Mean	P5	P50	P95	SD	Percent > EAR	Percent < UL
Boys (n=720), 2y, w	139	58	128	262	64	93	87
Girls (n=693), 2y, w	137	57	129	244	59	92	87
Boys (n=720), 2y, wo	129	56	122	215	52	92	92
Girls (n=693), 2y, wo	128	56	122	214	50	91	92
1y, both sexes, breastfed, n=722*	100	28	84	227	66	65	93
1y, both sexes, non-breastfed, n=881	147	54	139	259	69	92	82

Wo=without iodine supplements.
W=with iodine supplements.
EAR: 1- and 2-year-olds=65 µg/day (Source: IOM, 2001).
UL: 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).
*iodine from breastmilk is not included.

The estimates for 1- and 2- year-olds show mean and median intakes well above the recommended intakes of 70 µg/day in 1-year-olds and 90 µg/day in 2-year-olds. 91-93% of the 2-year-olds have intakes above the EAR, and 65% of breastfed 1-year-olds and 92% of non-breastfed have intakes above the EAR of 65 µg/day.

87-92% of 2-year-olds, and 93% of breastfed 1-year-olds and 82% of non-breastfed 1-year-olds have intakes below the UL, i.e., 8-13% of the 2-year-olds who do not use iodine supplements exceed the UL.

The iodine estimates for 1- and 2-year-olds are based on data from FFQ, and cannot be modelled as the estimates for adults and 13-, 9- and 4-year-olds have been done. Our iodine exposure estimates for non-breastfed 1-year-olds and the 2-year-olds, are higher than for the 4-year-olds also when comparing the mean intakes. To explore the differences between the dietary assessment methods used in 1-/2- and 4-year-old children, a comparison of energy intake was performed. The proportion of underreporters of energy intake in the 4-year-olds is 5% (Totland et al., 2012). According to NNR (2012), energy requirement increases approximately 25% in children from 2 to 4 years of age. However, the increase in energy between 2-year-olds (Småbarnskost 3) and 4-year-olds (Ungkost 3) is only 4 and 9% in girls and boys, respectively. The calculated mean energy intake in the 4-year-olds in Ungkost 3 is in line with the estimated daily energy requirements given in Table 8.6 in NNR (2012), whereas the calculated energy intake in 2-year-olds in Småbarnskost 3 exceeds the daily energy requirements for this age group. E.g. for 2-year-old girls the estimated

requirement is 4.14 MJ/day and the intake in Småbarnskost 3 is 5.3 MJ/day, which indicate an overreporting of energy intakes in the 2-year-olds. We cannot conclude that the observed overreporting of energy also applies to iodine. Nevertheless, the mean iodine intake among the 2-year-olds is approximately 20% higher than in the 4-year-olds. Altogether it is therefore reasonable to assume that the estimated iodine intakes in the 2-year-olds are higher than the true intakes.

7.3.3 Groups at risk of too low or high intakes

In the terms of reference, VKM is requested to identify groups/subpopulations at risk for low or overly high iodine intake. According to the benefit and risk assessment, these include vegans, individuals suffering from allergy to fish and dairy products, ethnic minorities which do not consume fish and dairy products and individuals consuming iodine supplements.

Norkost 3 and the other national dietary surveys do not provide data to calculate iodine intake estimates for vegans, ethnic minorities, persons with milk or fish allergies. Our intake estimates show that iodine at the 5th percentile is 88 µg/day in men, 72 µg/day in women and 68 µg/day in women of childbearing age (Table 7.3.1.1-1), and population groups that for various reasons have diets with low consumption of food sources rich in iodine are at risk of having intakes far below recommended intake. This also applies to the younger age groups, and especially 13-year-old boys with intake in the 5th percentile at 48 µg/day and girls at 38 µg/day. 13-year-olds have the same recommendations for intake as adults i.e. 150 µg/day (Table 7.3.1.1-1).

Studies of iodine intake and UIC consistently show that women have lower iodine intake than men, a difference that is apparent from adolescence onwards and may be explained by differences in food habits and total energy intake (Brantsaeter et al., 2018; Henjum et al., 2019).

In a Norwegian study, the median UIC was 46 µg/L and the median calculated iodine intake was 31 µg/day in 19 vegans and the median UIC was 105 µg/L and the calculated iodine intake was 116 µg/day in 25 vegetarians (Brantsaeter et al., 2018). Milk and dairy products were the main iodine source in the vegetarians.

Vegans are recommended to use iodine containing dietary supplements, and it should be noted that some of the vegans in the study had UIC above the UL due to use of a kelp-supplement (Brantsaeter et al., 2018).

Studies in women of non-Norwegian ethnic origin living in Oslo did not reveal lower iodine status in in these women than in women of Norwegian origin, although iodine status was generally low in all the women (Henjum et al., 2018b; Henjum et al., 2017).

As showed in Table 7.3.1.1-1 very few adults and adolescents have iodine intakes that exceed UL, even in those who use regular iodine supplements. However, kelp- and seaweed-based supplements, and also other foods made with kelp and seaweed may contain high

concentrations of iodine, and people who use these ingredients or supplements may be at risk of overly high iodine intakes. Consumption of kelp- and seaweed-based ingredients have not been reported in the national dietary surveys.

Table 7.3.2-1 show that high intakes and exceedance of UL is most frequent in 1- and 2-year-olds, and the iodine intake in the 95th percentile 2-year-olds without iodine supplements is 215 µg/day and in non-breastfed 1-year-olds 259 µg/day. The UL for this age group is 200 µg/day.

7.3.4 Plant-based alternatives to cow's milk

In the terms of reference, VKM is requested to evaluate what the iodine intake in the general population and among the specified potential risk groups (of both low and high iodine intakes) would be if plant-based milks were to be fortified with iodine levels comparable to those in cow's milk i.e. 15 µg per 100 g. Plant-based milks may be produced from e.g. oat, rice, soy or almond.

The national dietary surveys have not registered use of plant-based milk alternatives. The project group has, due to lack of intake data, assumed that consumption of plant-based milk alternatives replaces consumption of cow's milk, and that consumption of plant-based alternatives have similar individual variations as for cow's milk. The tables presenting iodine exposure in chapter 6.3 and 6.4 are therefore applicable for both cow's milk users and users of the plant-based alternatives given that all plant based alternatives have the same iodine content and bioavailability as cow's milk. Iodization of plant-based alternatives may contribute to increased iodine intake in vegans. Individuals with low consumption of plant-based alternatives will receive only small amounts of iodine from this source, whereas high-consumers will receive larger amounts. The risks related to high iodine intakes from iodized plant-based alternatives are not considered to be any larger than risks related to milk consumption in any age groups. Goitrogens in e.g. soy-milk may reduce the bioavailability of iodine, but the impact is considered to be low (Otun et al., 2019).

7.4 Scenarios with different iodization levels

Chapter 7.4 responds to the following question in the terms of reference: What would the iodine intake in the general population and among identified risk groups be if household salt and industrial salt used in bread were to be iodized and if plant-based milks were to be fortified with iodine levels comparable to those in cow milk? Table 7.4-1 shows the iodization levels in salt for which the potential effect on iodine intake is to be estimated. The iodine intake resulting of the various scenarios should be estimated both with and without the added effect of iodine fortification of plant-based alternatives to dairy products (milk 16 µg/100 g). The estimates should also be considered in the context of the *Salt Strategy 2015* (governmental initiatives to reduce salt consumption). In addition to the requested scenarios from the NFSA, we have also made scenario estimates for iodization level at 15 mg iodine per kg salt.

Table 7.4-1 The estimated scenarios with increased iodization levels.

Iodization levels	Food items		Abbreviation
15 mg iodine/kg	Household salt		Salt15-scenario
		Industrial salt used in bread	Bread15-scenario
	Household salt +	Industrial salt used in bread	Salt+bread15-scenario
20 mg iodine/kg	Household salt		Salt20-scenario
		Industrial salt used in bread	Bread20-scenario
	Household salt +	Industrial salt used in bread	Salt+bread20-scenario
25 mg iodine/kg	Household salt		Salt25-scenario
		Industrial salt used in bread	Bread25-scenario
	Household salt +	Industrial salt used in bread	Salt+bread25-scenario
50 mg iodine/kg	Household salt		Salt50-scenario
		Industrial salt used in bread	Bread50-scenario
	Household salt +	Industrial salt used in bread	Salt+bread50-scenario

In Table 7.4-2 we have presented these iodization levels as iodine per 100 g bread if the salt concentration in bread is 1.1 g salt per 100 g bread (the salt concentration used in our exposure estimates) and if the salt concentration is reduced to 0.9 g salt per 100 g bread (goal in the salt strategy).

Table 7.4-2 Iodine in bread at different iodization levels and different salt concentrations in bread.

Iodization level in salt in bread	Iodine (µg) per 100 g bread if bread contains 1.1 g salt per 100 g	Iodine (µg) per 100 g bread if bread contains 0.9 g salt per 100 g (aim in the salt strategy)
15 mg iodine/kg salt	16.5	13.5
20 mg iodine/kg salt	22	18
25 mg iodine/kg salt	27.5	22.5
50 mg iodine/kg salt	55	45

Model-based scenarios were conducted to estimate what the iodine intake would be if household salt and industrial salt used in bread were iodized up to 15 or 20 or 25 or 50 mg iodine per kg salt. The method for the scenario estimates for adults and 13-, 9- and 4-year-olds are based on the MM-method described in section 7.3.1 and Appendix IV. However, the scenarios for 1- and 2- year-olds are not based on the MM-method, as data for these age groups are based on FFQ.

The scenario estimates for the different iodization levels (scenarios), age groups and gender are presented in Tables 7.4-3 – 7.4-14. The scenario estimates in the tables are presented as mean, median, 5th and 95th percentiles, and as percent of the population estimated intakes above the estimated average requirements (EARs) and percent of the population with estimated intakes below the tolerable upper intake levels (ULs) (given in chapter 4).

The intake estimates presented below do not include iodine supplements. Scenarios including supplements (users only) indicate that these are not at high risk of exceeding the UL in adults and adolescent. 2-year-old iodine supplement users are at high risk of exceeding the UL. Full results for supplement users are presented in Appendix V.

The 1-year-olds are not included in the scenarios for household salt. The intake of household salt in 1-year-olds is assumed to be low, and consequently the impact of increased iodization in household salt on the total intake of iodine in 1-year-olds is assumed to be low.

Table 7.4-3 Estimated iodine exposures in adults, 13-, 9-, 4-and 2-year-olds if household salt contain 15 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Iodized household salt 15 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	218	104	199	396	96	100
Women, 18-70y	159	83	148	270	87	100
Women, 18-45y	149	79	139	253	83	100
Boys, 13y	137	61	122	261	88	100
Girls, 13y	105	48	94	196	72	100
Boys, 9y	129	76	123	205	96	100
Girls, 9y	109	53	100	197	79	100
Boys, 4y	119	71	114	186	97	100
Girls, 4y	109	59	102	182	91	99
Boys (n=720), 2y	138	65	131	224	95	89
Girls (n=693), 2y	135	63	130	221	95	91

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).

In the scenario where only household salt is iodized, at the iodization level of 15 mg iodine per kg salt (salt15-scenario), the mean and median iodine intake in men and women varies between slightly below or well above recommended intake. 96% of the men and 83-87% of the women have intakes above the EAR in the salt15-scenario, and women of childbearing age have the lowest intakes among adults.

In the salt15-scenario, the mean and median iodine intakes in 13-year-old boys and girls are below the recommended intake. The intakes in the girls are very low; mean (median) intake is 105 (94) µg/day. 88% of the 13-year-old boys and 72% of the girls have intakes above the EAR.

Mean and median iodine intakes in 9-year-old boys and girls are at or below the recommended intake. The iodine intake is lower in girls than in boys, and 96% of the 9-year-old boys and 79% of the girls have intakes above the EAR in the salt15-scenario.

In the salt15-scenario, the mean and median iodine intakes in 4-year-old boys and girls are above the recommended intake. 97% of the 4-year-old boys and 91% of the girls have intakes above the EAR.

Mean and median iodine intakes in 2-year-old boys and girls are well above the recommended intake. The iodine intake is similar in boys and girls, and 95% of the 2-year-olds have intakes above the EAR in the salt15-scenario.

All adults and 13- and 9- year-olds in the salt15-scenario have intakes below the UL. 4-year-olds have individuals (1%) that exceed the UL in this scenario, whereas in 2-year-olds, 9-11% have iodine intakes above UL.

Table 7.4-4 Estimated iodine exposures in all age groups if salt in bread contains 15 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Iodized salt in bread 15 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	243	119	223	430	98	99
Women, 18-70y	173	90	162	294	91	100
Women, 18-45y	165	86	155	279	89	100
Boys, 13y	158	75	144	291	96	100
Girls, 13y	123	61	112	221	87	100
Boys, 9y	148	88	142	232	99	99
Girls, 9y	126	65	117	220	90	99
Boys, 4y	133	81	127	202	99	99
Girls, 4y	122	67	115	201	96	99
Boys (n=720), 2y	149	73	142	243	97	85
Girls (n=693), 2y	146	73	143	242	97	86
Boys and girls, 1y, breastfed (n=722)*	117	32	98	265	74	89
Boys and girls, 1y, non-breastfed (n=881)	172	63	162	302	95	68

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).
*Iodine from breastmilk is not included.

In the scenario where only salt in bread is iodized, at the iodization level of 15 mg iodine per kg salt (bread15-scenario), the mean and median iodine intake in both men and women are above recommended intake. 98% of the men and 89-91% of women have intakes above the EAR.

In the bread15-scenario, the mean and median iodine intakes in 13-year-old boys are above or just slightly below the recommended intake, whereas the intake in girls is still well below. 96% of the 13-year-old boys and 87% of the girls have intakes above the EAR.

The mean and median iodine intakes in 9-year-old boys and girls are at or above the recommended intake. 96% of the 9-year-old boys and 87% of the girls have intakes above the EAR in the bread15-scenario.

In the bread15-scenario, the mean and median iodine intakes in 4-year-old boys and girls are close to the recommended intake. 99% of the 4-year-old boys and 96% of the girls have intakes above the EAR.

The mean and median iodine intakes in 1- and 2-year-olds are above the recommended intake. 97% of the 2-year-olds and 74/95% of the breastfed/ non-breastfed 1-year-olds have intakes above the EAR in the bread15-scenario.

All adults and 13-year-olds in the bread15-scenario have intakes below the UL. Among 9-year-olds (boys and girls) and 4-year-old boys there are individuals (1%) that exceed the UL in this scenario. In 2-year-olds 14-15% exceed the UL. In 1-year-olds 11-32% exceed the UL.

Table 7.4-5 Estimated iodine exposures in adults, 13-, 9-, 4- and 2-year-olds if both household salt and salt in bread contain 15 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Both household salt and salt in bread iodized 15 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	258	135	239	446	99	99
Women, 18-70y	185	101	173	306	95	100
Women, 18-45y	176	97	166	291	94	100
Boys, 13y	171	87	157	304	99	99
Girls, 13y	132	70	122	230	93	100
Boys, 9y	160	99	153	243	100	99
Girls, 9y	135	73	126	228	95	99
Boys, 4y	142	90	136	211	100	99
Girls, 4y	129	74	122	208	98	99
Boys (n=720), 2y	158	82	151	252	98	81
Girls (n=693), 2y	154	80	150	250	98	84

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).

In the scenario where both household salt and salt in bread is iodized, at the iodization level of 15 mg iodine per kg salt (salt+bread15-scenario), the mean and median iodine intake in both men and women are above recommended intake. 99% of the men and 94-95% of women have intakes above the EAR.

In the salt+bread15-scenario, the mean and median iodine intakes in 13-year-old boys are above the recommended intake, whereas the intake in the girls are still is below. 99% of the 13-year-old boys and 93% of the girls have intakes above the EAR.

The mean and median iodine intakes in 9-year-old boys and girls are above the recommended intake. All the 9-year-old boys and 95% of the girls have intakes above the EAR in the salt+bread15-scenario.

In the salt+bread15-scenario, the mean and median iodine intakes in 4-year-old boys and girls are well above the recommended intake. All the 4-year-old boys and 98% of the girls have intakes above the EAR.

The mean and median iodine intakes in 2-year-old boys and girls are well above the recommended intake. 98% of the 2-year-olds have intakes above the EAR in the salt+bread15-scenario.

All women and 13-year-old girls in the salt+bread15-scenario have intakes below the UL. Men, 13-year-old boys and 9-year-olds and 4-year-olds have individuals (1%) that exceed the UL in this scenario. In 2-year olds, 16-19% exceed the UL.

Table 7.4-6 Estimated iodine exposures in adults, 13-, 9-, 4-and 2-year-olds if household salt contain 20 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Iodized household salt 20 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	223	109	204	398	97	100
Women, 18-70y	163	87	152	275	89	100
Women, 18-45y	153	83	143	255	86	100
Boys, 13y	141	65	126	265	91	100
Girls, 13y	108	51	97	199	76	100
Boys, 9y	133	79	126	209	97	100
Girls, 9y	112	56	103	200	82	100
Boys, 4y	122	74	117	189	98	99
Girls, 4y	111	61	105	185	93	99
Boys (n=720), 2y	141	68	134	227	96	88
Girls (n=693), 2y	138	66	132	224	96	91

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).

In the scenario where only household salt is iodized, at the iodization level of 20 mg iodine per kg salt (salt20-scenario), the mean and median iodine intake in both men and women are approximately at or above recommended intake. 97% of the men and 86-89% of the women have intakes above the EAR in the salt20-scenario, and women of childbearing age have the lowest intakes among adults.

In the salt20-scenario, the mean and median iodine intakes in 13-year-old boys and girls are still below the recommended intake. The intakes in the girls are very low; mean (median) intake is 108 (97) µg/day. 91% of the 13-year-old boys and 76% of the girls have intakes above the EAR.

Mean and median iodine intakes in 9-year-old boys and girls are at or slightly below the recommended intake. The iodine intake is lower in girls than in boys, and 97% of the 9-year-old boys and 82% of the girls have intakes above the EAR in the salt20-scenario.

In the salt20-scenario, the mean and median iodine intakes in 4-year-old boys and girls are above the recommended intake. 98% of the 4-year-old boys and 93% of the girls have intakes above the EAR.

Mean and median iodine intakes in 2-year-old boys and girls are well above the recommended intake. The iodine intake is similar in boys and girls, and 96% of the 2-year-olds have intakes above the EAR in the salt20-scenario.

All adults and 13- and 9- year-olds in the salt20-scenario have intakes below the UL. 4-year-olds have individuals (1%) that exceed the UL in this scenario, whereas in 2-year-olds, 9-12% have iodine intakes above UL.

Table 7.4-7 Estimated iodine exposures in all age groups if salt in bread contains 20 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Iodized salt in bread 20 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	256	129	237	446	99	99
Women, 18-70y	182	95	170	306	93	100
Women, 18-45y	174	92	164	292	92	100
Boys, 13y	170	83	155	306	98	99
Girls, 13y	132	67	121	232	92	100
Boys, 9y	159	95	152	246	99	99
Girls, 9y	135	71	126	231	94	99
Boys, 4y	140	88	135	210	100	99
Girls, 4y	129	72	122	210	97	98
Boys (n=720), 2y	155	80	148	251	97	81
Girls (n=693), 2y	152	77	149	249	98	84
Boys and girls, 1y, breastfed (n=722)*	122	34	102	277	77	87
Boys and girls, 1y, non-breastfed (n=881)	180	66	169	316	95	64

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).
*Iodine from breastmilk is not included.

In the scenario where only salt in bread is iodized, at the iodization level of 20 mg iodine per kg salt (bread20-scenario), the mean and median iodine intake in both men and women are above recommended intake. 99% of the men and 92-93% of women have intakes above the EAR.

In the bread20-scenario, the mean and median iodine intakes in 13-year-old boys are above the recommended intake, whereas the intake in girls is still below. 98% of the 13-year-old boys and 92% of the girls have intakes above the EAR.

The mean and median iodine intakes in 9-year-old boys and girls are above the recommended intake. 99% of the 9-year-old boys and 94% of the girls have intakes above the EAR in the bread20-scenario.

In the bread20-scenario, the mean and median iodine intakes in 4-year-old boys and girls are well above the recommended intake. All the 4-year-old boys and 97% of the girls have intakes above the EAR.

The mean and median iodine intakes in 1- and 2-year-olds are above the recommended intake. 97-98% of the 2-year-olds and 77/95% of the breastfed/ non-breastfed 1-year-olds have intakes above the EAR in the bread20-scenario.

All women and 13-year-old girls in the bread20-scenario have intakes below the UL. Men, 13-year-old boys, 9-year-olds (boys and girls) and 4-year-old boys have individuals (1%) that exceed the UL in this scenario. In 4-year-old girls, 2% exceed the UL, and in 2-year-olds 16-19% exceed the UL. In 1-year-olds 13-36% exceed the UL.

Table 7.4-8 Estimated iodine exposures in adults, 13-, 9-, 4- and 2-year-olds if both household salt and salt in bread contain 20 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Both household salt and salt in bread iodized 20 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	277	150	258	467	100	99
Women, 18-70y	197	111	186	321	98	100
Women, 18-45y	189	107	179	307	97	100
Boys, 13y	187	100	172	323	100	99
Girls, 13y	145	80	134	244	97	100
Boys, 9y	174	110	167	261	100	98
Girls, 9y	147	82	138	243	98	99
Boys, 4y	152	100	147	222	100	98
Girls, 4y	138	81	131	219	99	98
Boys (n=693), 2y	167	92	160	263	99	77
Girls (n=720), 2y	162	87	159	259	99	79

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).

In the scenario where both household salt and salt in bread is iodized, at the iodization level of 20 mg iodine per kg salt (salt+bread20-scenario), the mean and median iodine intake in both men and women are above recommended intake. All the men and 97-98% of women have intakes above the EAR.

In the salt+bread20-scenario, the mean and median iodine intakes in 13-year-old boys are above the recommended intake, whereas the intake in the girls still is slightly below. All the 13-year-old boys and 97% of the girls have intakes above the EAR.

The mean and median iodine intakes in 9-year-old boys and girls are above the recommended intake. All the 9-year-old boys and 98% of the girls have intakes above the EAR in the salt+bread20-scenario.

In the salt+bread20-scenario, the mean and median iodine intakes in 4-year-old boys and girls are well above the recommended intake. All the 4-year-old boys and 99% of the girls have intakes above the EAR.

The mean and median iodine intakes in 2-year-old boys and girls are well above the recommended intake. 99% of the 2-year-olds have intakes above the EAR in the salt+bread20-scenario.

All women and 13-year-old girls in the salt+bread20-scenario have intakes below the UL. Men, 13-year-old boys and 9-year-old girls have individuals (1%) that exceed the UL in this scenario. In 9-year-old boys and 4-year-old boys and girls, 2% exceed the UL. In 2-year olds, 21-23% exceed the UL.

Table 7.4-9 Estimated iodine exposures in adults, 13-, 9-, 4- and 2-year-olds if household salt contains 25 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Iodized household salt 25 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	228	114	209	404	98	100
Women, 18-70y	166	91	156	278	91	100
Women, 18-45y	157	87	147	259	88	100
Boys, 13y	145	69	131	269	93	100
Girls, 13y	111	54	100	202	79	100
Boys, 9y	137	83	130	213	98	100
Girls, 9y	115	59	106	203	85	100
Boys, 4y	125	77	120	191	99	99
Girls, 4y	114	63	107	187	94	99
Boys (n=720), 2y	144	71	137	230	97	87
Girls (n=693), 2y	140	68	135	226	97	90

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).

In the scenario where only household salt is iodized, at the iodization level of 25 mg iodine per kg salt (salt25-scenario), the mean and median iodine intake in both men and women are approximately at or above recommended intake. 98% of the men and 88-91% of women have intakes above the EAR in the salt25-scenario, and women of childbearing age have the lowest intakes among adults.

In the salt25-scenario, the mean and median iodine intakes in 13-year-old boys and girls are still below the recommended intake, and the intakes in the girls are very low; mean (median) intake is 111 (100) µg/day. 93% of the 13-year-old boys and 79% of the girls have intakes above the EAR in the salt25-scenario.

The mean and median iodine intakes in 9-year-old boys and girls are at or slightly below the recommended intake. The iodine intake is lower in girls than in boys, and 98% of the 9-year-old boys and 85% of the girls have intakes above the EAR in the salt25-scenario.

In the salt25-scenario, the mean and median iodine intakes in 4-year-old boys and girls are above the recommended intake. 99% of the 4-year-old boys and 94% of the girls have intakes above the EAR.

The mean and median iodine intakes in 2-year-old boys and girls are well above the recommended intake, and 97% of the 2-year-olds have intakes above the EAR in the salt25-scenario.

All adults and 13- and 9- year-olds in the salt25-scenario have intakes below the UL. 4-year-olds have individuals (1%) that exceed the UL in this scenario. In 2-year-olds, 10-13% exceed the UL.

Table 7.4-10 Estimated iodine exposures in all age groups if salt in bread contains 25 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Iodized salt in bread 25 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	269	138	250	465	99	99
Women, 18-70y	190	101	179	319	95	100
Women, 18-45y	183	98	172	306	94	100
Boys, 13y	181	91	167	321	99	99
Girls, 13y	141	74	131	244	95	100
Boys, 9y	169	102	162	260	100	98
Girls, 9y	144	76	134	242	96	99
Boys, 4y	148	94	143	219	100	98
Girls, 4y	136	77	129	219	98	98
Boys (n=720), 2y	162	85	155	258	98	79
Girls (n=693), 2y	159	80	155	258	98	81
Boys and girls, 1y, breastfed (n=722)*	128	35	107	290	79	85
Boys and girls, 1y, non-breastfed (n=881)	188	69	177	330	96	62

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).
*Iodine from breastmilk is not included.

In the scenario where only salt in bread is iodized, at the iodization level of 25 mg iodine per kg salt (bread25-scenario), the mean and median iodine intake in both men and women are

above recommended intake. 99% of the men and 94-95% of women have intakes above the EAR in the bread25-scenario.

In the bread25-scenario, the mean and median iodine intakes in 13-year-old boys are above the recommended intake, whereas the intake in girls still is slightly below. 99% of the 13-year-old boys and 95% of the girls have intakes above the EAR.

The mean and median iodine intakes in 9-year-old boys and girls are above the recommended intake. All the 9-year-old boys and 96% of the girls have intakes above the EAR in the bread25-scenario.

In the bread25-scenario, the mean and median iodine intakes in 4-year-old boys and girls are well above the recommended intake. All the 4-year-old boys and 98% of the girls have intakes above the EAR.

The mean and median iodine intakes in 1- and 2-year-olds are above the recommended intake. 98% of the 2-year-olds and 79/96% of the breastfed/non-breastfed 1-year-olds have intakes above the EAR in the bread25-scenario.

All women and 13-year-old girls in the bread25-scenario have intakes below the UL. Men, 13-year-old boys, 9-year-old girls) have individuals (1%) that exceed the UL. In 9-year-old boys and 4-year-old boys and girls, 2% exceed the UL, and in 2-year-olds 19-21% exceed the UL. In 1-year-olds 15-38% exceed the UL.

Table 7.4-11 Estimated iodine exposures in adults, 13-, 9-, 4- and 2-year-olds if both household salt and salt in bread contain 25 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Both household salt and salt in bread iodized 25 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	296	164	277	491	100	99
Women, 18-70y	209	120	198	338	99	100
Women, 18-45y	202	117	191	325	99	100
Boys, 13y	202	112	188	342	100	99
Girls, 13y	157	90	146	259	99	100
Boys, 9y	188	121	181	279	100	97
Girls, 9y	158	91	149	257	99	98
Boys, 4y	163	109	158	234	100	97
Girls, 4y	147	88	140	230	100	97
Boys (n=720), 2y	177	100	170	273	100	70
Girls (n=693), 2y	171	92	167	271	100	75

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).

In the scenario where both household salt and salt in bread is iodized, at the iodization level of 25 mg iodine per kg salt (salt+bread25-scenario), the mean and median iodine intake in both men and women are well above recommended intake. All the men and 99% of women have intakes above the EAR.

In the salt+bread25-scenario, the mean and median iodine intakes in 13-year-old boys and girls are at or above the recommended intake. All the 13-year-old boys and 99% of the girls have intakes above the EAR.

The mean and median iodine intakes in 9-year-old boys and girls are above the recommended intake. All the 9-year-old boys and 99% of the girls have intakes above the EAR in the salt+bread25-scenario.

In the salt+bread25-scenario, the mean and median iodine intakes in 4-year-old boys and girls are well above the recommended intake. All the 4-year-old boys and girls have intakes above the EAR.

The mean and median iodine intakes in 2-year-old boys and girls are well above the recommended intake. All the 2-year-olds have intakes above the EAR in the salt+bread25-scenario.

All women and 13-year-old girls in the salt+bread25-scenario have intakes below the UL. Men and 13-year-old boys have individuals (1%) that exceed the UL. In 9-year-old girls, 2% exceed the UL, whereas in 9-year-old boys and in 4-year-old boys and girls, 3% exceed the UL. In 2-year-olds, 25-30% have intakes that exceed the UL.

Table 7.4-12 Estimated iodine exposures in adults, 13-, 9-, 4- and 2-year-olds if household salt contains 50 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Iodized household salt 50 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	254	141	235	430	100	99
Women, 18-70y	185	110	175	298	98	100
Women, 18-45y	176	106	166	278	97	100
Boys, 13y	166	90	152	290	99	100
Girls, 13y	127	70	116	218	93	100
Boys, 9y	156	102	149	232	100	99
Girls, 9y	130	74	120	217	95	99
Boys, 4y	140	91	135	206	100	99
Girls, 4y	125	75	119	199	99	99
Boys (n=720), 2y	159	86	152	245	99	82
Girls (n=693), 2y	153	81	147	239	99	85

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).

In the scenario where only household salt is iodized, at the iodization level of 50 mg iodine per kg salt (salt50-scenario), the mean and median iodine intake in both men and women are above recommended intake. All the men and 97-98% of women have intakes above the EAR.

In the salt50-scenario, the mean and median iodine intakes in 13-year-old boys are above, and the intakes in girls are still below the recommended intake. 99% of the 13-year-old boys and 93% of the girls have intakes above the EAR.

The mean and median iodine intakes in 9-year-old boys and girls are at or above the recommended intake. The iodine intake is lower in girls than in boys, and all the 9-year-old boys and 95% of the girls have intakes above the EAR in the salt50-scenario.

In the salt50-scenario, the mean and median iodine intakes in 4-year-old boys and girls are above the recommended intake. All the 4-year-old boys and 99% of the girls have intakes above the EAR.

The mean and median iodine intakes in 2-year-old boys and girls are well above the recommended intake, and 99% of the 2-year-olds have intakes above the EAR in the salt50-scenario.

Women and 13-year-olds in the salt50-scenario have intakes below the UL. Men and 9- and 4-year-olds have individuals (1%) that exceed the UL in this scenario. In 2-year-olds, 15-18% have intakes that exceed the UL.

Table 7.4-13 Estimated iodine exposures in all age groups if salt in bread contains 50 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Iodized salt in bread 50 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	337	181	317	561	100	97
Women, 18-70y	233	126	220	385	99	100
Women, 18-45y	229	124	216	378	99	100
Boys, 13y	239	128	224	401	100	97
Girls, 13y	188	106	176	305	100	100
Boys, 9y	220	134	212	335	100	89
Girls, 9y	187	104	177	305	100	94
Boys, 4y	185	122	180	267	100	92
Girls, 4y	169	99	162	265	100	93
Boys (n=720), 2y	195	107	189	305	100	57
Girls (n=693), 2y	189	102	184	301	100	62
Boys and girls, 1y, breastfed (n=722)*	155	43	130	353	86	74
Boys and girls, 1y, non-breastfed (n=881)	228	84	215	401	98	44

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-

year-olds=200 µg/day (Source: SCF, 2002).
*Iodine from breastmilk is not included.

In the scenario where only salt in bread is iodized, at the iodization level of 50 mg iodine per kg salt (bread50-scenario), the mean and median iodine intake in both men and women are well above recommended intake All the men and 99% of women have intakes above the EAR.

In the bread50-scenario, the mean and median iodine intakes in 13-year-old boys and girls are above the recommended intake. All the 13-year-old boys and girls have intakes above the EAR.

The mean and median iodine intakes in both 9- and 4- year-old boys and girls are well above the recommended intake. All the 4-year-olds (boys and girls) and all 9-year-old boys and 96% of the girls have intakes above the EAR in the bread50-scenario.

The mean and median iodine intakes in 1- and 2-year-olds are also above the recommended intake. All the 2-year-olds and 86/98% of the breastfed/non-breastfed 1-year-olds have intakes above the EAR in the bread50-scenario.

All women and 13-year-old girls in the bread50-scenario have intakes below the UL. In men and 13-year-old boys, 3% exceed the UL, whereas 7-8% of the 4-year-old boys and girls and 11% of the 9-year-old boys exceed the UL. In 2-year-olds, 38-43% have intakes above UL in this scenario. In 1-year-olds 26-56% exceed the UL.

Table 7.4-14 Estimated iodine exposures in adults, 13-, 9-, 4- and 2-year-olds if both household salt and salt in bread contain 50 mg iodine per kg salt (µg/day). For the age groups 4-70 years, 100 000 individuals were simulated.

Both household salt and salt in bread iodized 50 mg/kg	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent > EAR	Percent < UL
Men, 18-70y	389	233	369	614	100	94
Women, 18-70y	271	164	258	423	100	100
Women, 18-45y	267	162	254	416	100	100
Boys, 13y	281	170	266	443	100	95
Girls, 13y	219	138	208	337	100	99
Boys, 9y	259	173	250	373	100	78
Girls, 9y	216	133	206	334	100	90
Boys, 4y	215	152	210	297	100	80
Girls, 4y	193	123	185	288	100	87
Boys (n=720), 2y	225	137	219	335	100	37
Girls (n=693), 2y	214	127	209	326	100	43

EAR adults=100 µg/day (Source: NNR, 2012), EAR 9- and 13-year-olds=73 µg/day, 1-, 2- and 4-year-olds=65 µg/day (Source: IOM, 2001).
UL adults=600 µg/day, 13-year-olds=450 µg/day, 9-year-olds=300 µg/day, 4-year-olds=250 µg/day, 1- and 2-year-olds=200 µg/day (Source: SCF, 2002).

In the scenario where both household salt and salt in bread is iodized, at the iodization level of 50 mg iodine per kg salt (salt+bread50-scenario), the mean and median iodine intake in all adults, 13-, 9-, 4- and 2-year-olds are well above recommended intake, and all have intakes above the EAR.

All women in the salt+bread50-scenario have intakes below the UL. In the other groups, UL is exceeded in 1-20% with the highest exceedance percentage in the 9-year-old boys and 4-year-olds. However, in 2-year-olds 57-63% have intakes that exceed UL in this scenario.

We cannot calculate from the national dietary surveys how the different scenarios affect iodine intakes in other vulnerable groups mentioned in the assignment, such as persons with allergies or intolerance to fish or milk and dairy products, vegetarians, vegans or ethnic minorities. However, as salt consumption is assumed to be correlated with energy intake, the increase in iodine intake in the various scenarios with increased levels of iodine in salt may be the same in these potential risk groups as in the rest of the population, clearly with large individual variations within the different groups. Neither can we extract data on bread consumption among persons in these potential risk groups. The variation in bread consumption among persons with allergy or intolerance to fish, milk or dairy products, vegans, vegetarians and also some ethnic minorities might be similar to the variation in bread consumption in the rest of the population. Consequently, for persons with few iodine sources in the diet (vegans and people with allergy or intolerance), the increase in iodine intake from increased iodization of salt and bread may be the same as in the lower percentiles (e.g. the 5th percentiles) in the scenarios in Tables 7.4-3 - 7.4-14.

Figures 7.4-1-7.4-5 show the scenario estimates for iodization in males (blue lines) and females (red lines) in adults, 13-, 9-, 4- and 2-year-olds (dark red for females 18-45 and light red for all females in Figure 7.4.1). The three boxes in the top row show total iodine intake (µg/day) if household salt, bread and both household salt and bread are iodized (0-50 mg iodine per kg salt). The curves represent the intakes in the 5th percentiles (lower dashed lines), median (full lines) and 95th percentile (upper dashed lines). The horisontal lines represent the age specific EAR and UL given in Table 4.3-1. The three boxes in the middle row show percent of population group with iodine intakes above EAR (upper lines) and above UL (lower lines). The bottom boxes show percentage of males and females with intakes both above EAR and below UL, and thus represent the percentage of the target population deemed to be within the dietary reference values.

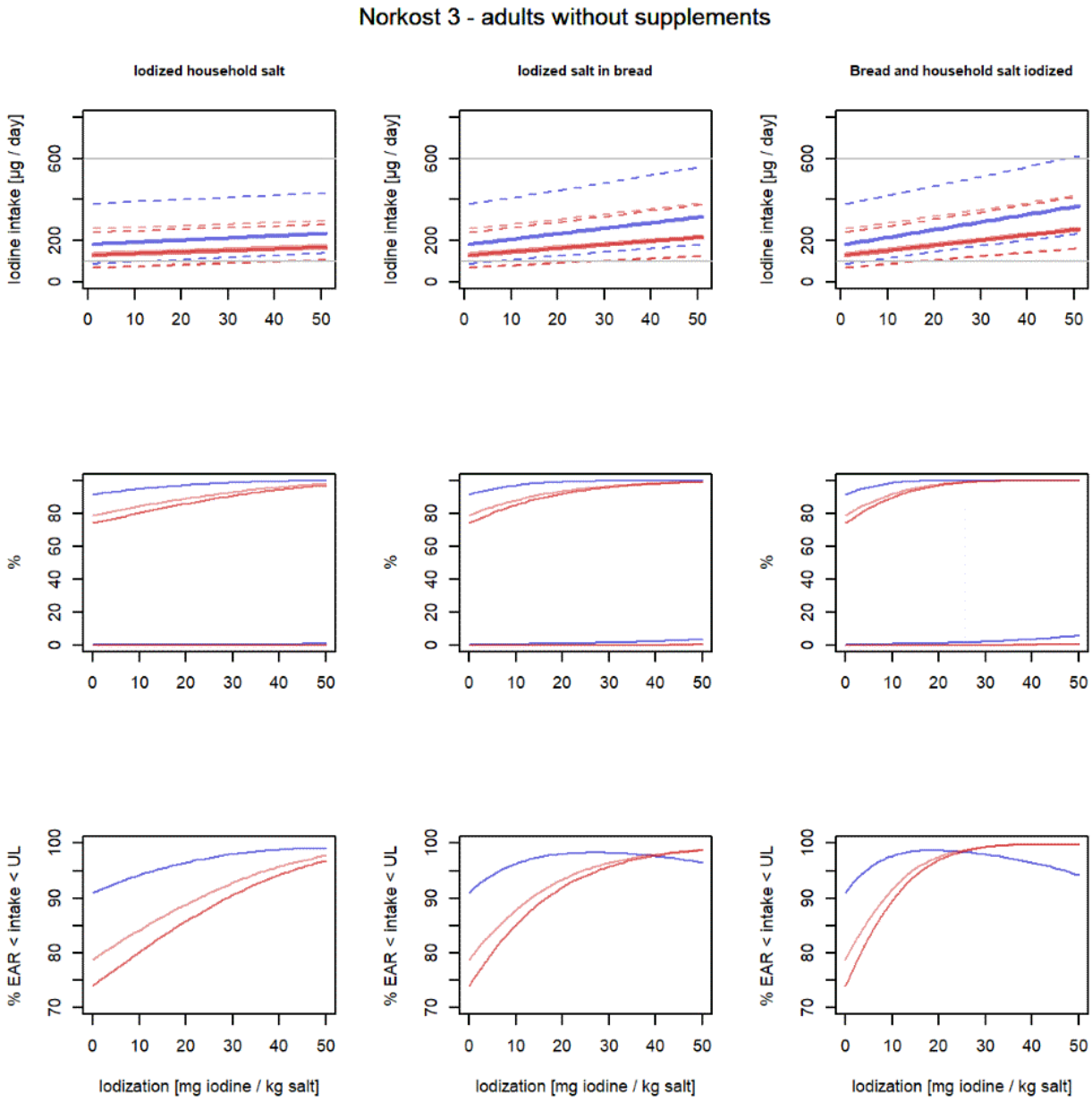

Figure 7.4-1 Scenario estimates for iodization in adult males (blue lines), females (light red lines) and females 18-45 years old. The three plots in the top row show total iodine intake (µg/day) if household salt, bread and both household salt and bread are iodized (0-50 mg iodine per kg salt). The curves represent the intakes in the 5th percentiles (lower dashed lines), median (full lines) and 95th percentile (upper dashed lines). The horisontal lines represent the age specific EAR (100 µg/day) and UL (600 µg/day) given in Table 4.3-1. The three plots in the middle row show percent of population group with iodine intakes above EAR (upper lines) and above UL (lower lines). The bottom plots show percentage of males and females with intakes both above EAR and below UL, and thus represent the percentage of the target population deemed to be within the dietary reference values.

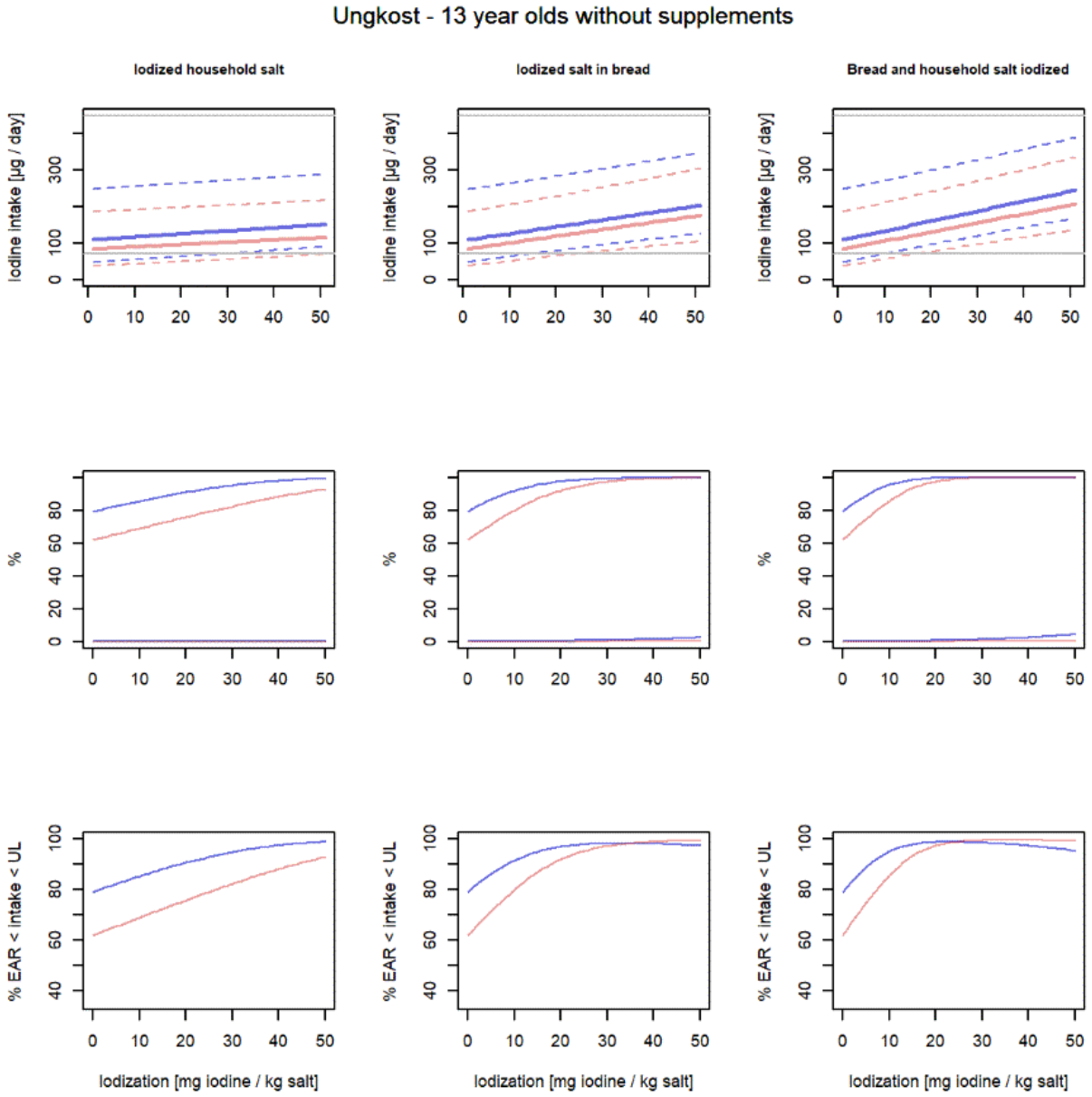

Figure 7.4-2 Scenario estimates for iodization in 13-year-olds boys (blue lines) and girls (red lines). The three plots in the top row show total iodine intake (µg/day) if household salt, bread and both household salt and bread are iodized (0-50 mg iodine per kg salt). The curves represent the intakes in the 5th percentiles (lower dashed lines), median (full lines) and 95th percentile (upper dashed lines). The horisontal lines represent the age specific EAR (73 µg/day) and UL (450 µg/day) given in Table 4.3-1. The three plots in the middle row show percent of population group with iodine intakes above EAR (upper lines) and above UL (lower lines). The bottom plots show percentages of boys and girls with intakes both above EAR and below UL, and thus represent the percentage of the target population deemed to be within the dietary reference values.

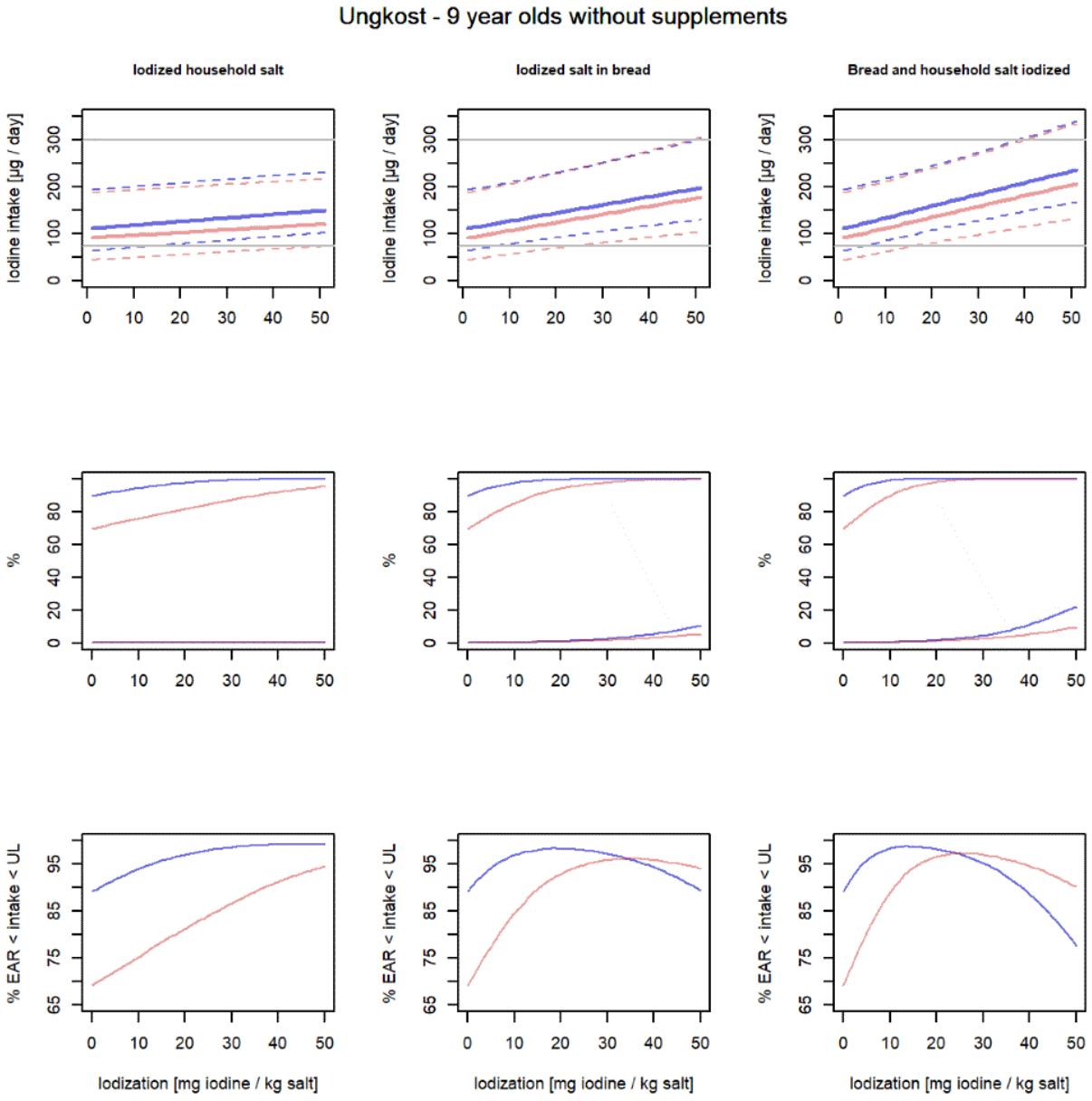

Figure 7.4-3 Scenario estimates for iodization in 9-year-olds boys (blue lines) and girls (red lines). The three plots in the top row show total iodine intake (µg/day) if household salt, bread and both household salt and bread are iodized (0-50 mg iodine per kg salt). The curves represent the intakes in the 5th percentiles (lower dashed lines), median (full lines) and 95th percentile (upper dashed lines). The horisontal lines represent the age specific EAR (73 µg/day) and UL (300 µg/day) given in Table 4.3-1. The three plots in the middle row show percent of population group with iodine intakes above EAR (upper lines) and above UL (lower lines). The bottom plots show percentage of boys and girls with intakes both above EAR and below UL, and thus represent the percentage of the target population deemed to be within the dietary reference values.

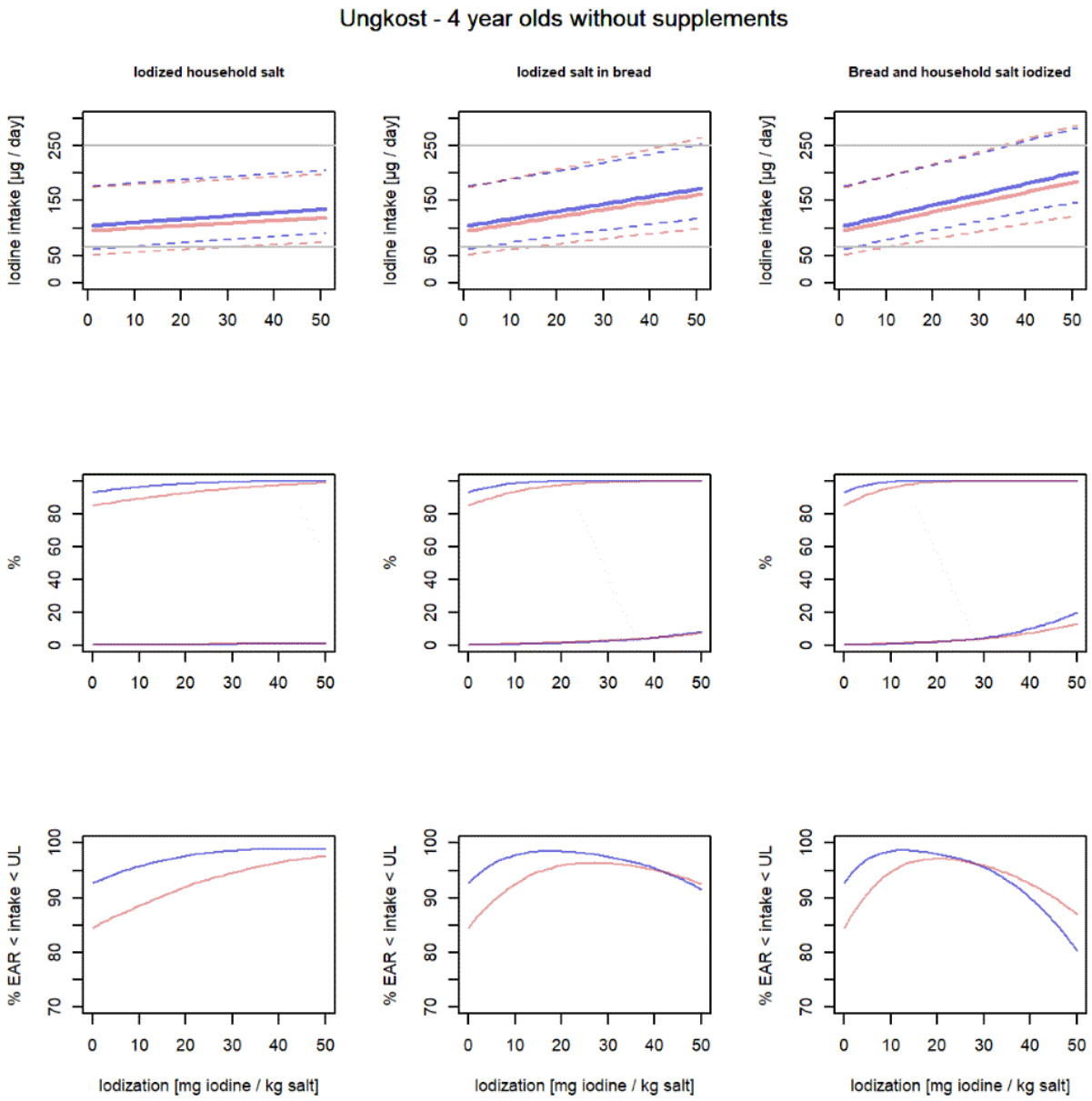

Figure 7.4-4 Scenario estimates for iodization in 4-year-olds boys (blue lines) and girls (red lines). The three plots in the top row show total iodine intake (µg/day) if household salt, bread and both household salt and bread are iodized (0-50 mg iodine per kg salt). The curves represent the intakes in the 5th percentiles (lower dashed lines), median (full lines) and 95th percentile (upper dashed lines). The horisontal lines represent the age specific EAR (65 µg/day) and UL (250 µg/day) given in Table 4.3-1. The three plots in the middle row show percent of population group with iodine intakes above EAR (upper lines) and above UL (lower lines). The bottom plots show percentage of boys and girls with intakes both above EAR and below UL, and thus represent the percentage of the target population deemed to be within the dietary reference values.

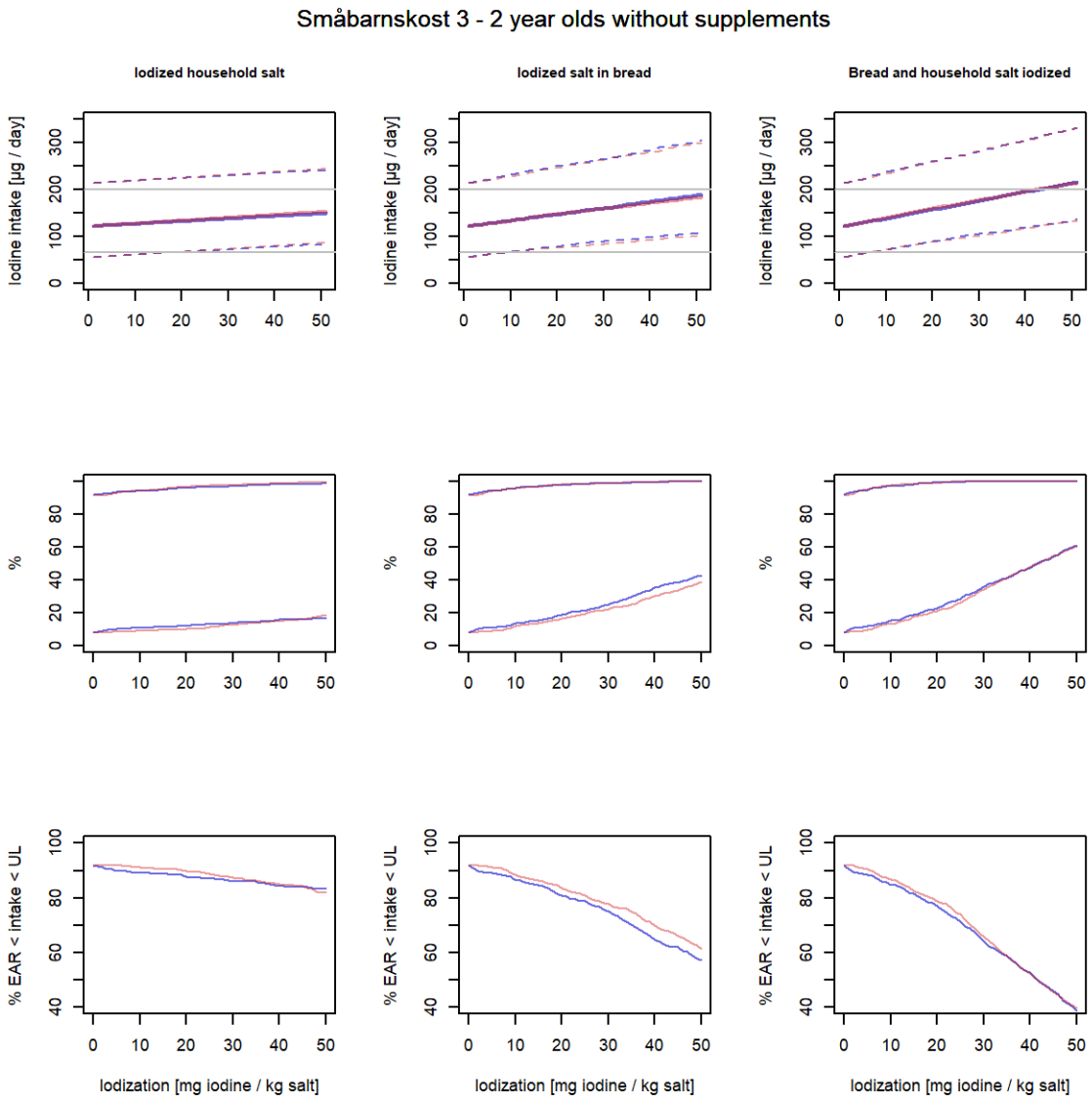

Figure 7.4-5 Scenario estimates for iodization in 2-year-olds boys (blue lines) and girls (red lines) (without supplements). The three plots in the top row show total iodine intake (µg/day) if household salt, bread and both household salt and bread are iodized (0-50 mg iodine per kg salt). The curves represent the intakes in the 5th percentiles (lower dashed lines), median (full lines) and 95th percentile (upper dashed lines). The horisontal lines represent the age specific EAR (65 µg/day) and UL (200 µg/day) given in Table 4.3-1. The three plots in the middle row show percent of population group with iodine intakes above EAR (upper lines) and above UL (lower lines). The bottom plots show percentage of boys and girls with intakes both above EAR and below UL, and thus represent the percentage of the target population deemed to be within the dietary reference values. Please note that these estimates are not modelled in the same manner as Norkost and Ungkost (Figures 7.4-1 through 7.4-5), due to the nature of the underlying data (FFQ).

7.4.1 Effect of potential salt reduction on the scenario estimates for iodine

This section responds to the following task in the terms of reference: The scenario estimates should also be considered in the context of the *Salt Strategy 2015* (governmental initiatives to reduce salt consumption).

The main goals in the Salt Strategy are 30% relative reduction in mean population intake of salt/sodium within year 2025 and a long-term target of mean salt consumption of 5 g/day. An intermediate objective is to reduce salt in bread to 0.9 g salt per 100 g bread. This corresponds to approximately 18% reduction in salt in bread compared to our scenario calculations.

A 30% reduction in salt consumption would imply a need for approximately 43% increased iodization levels to achieve the same levels of daily iodine intake as given in the scenario Tables 7.4-3-7.4-14 for all the age groups (1/(1-0.3) = 1.43). This estimate assumes a uniform 30% reduction, and no consideration is given to if the salt reduction is unevenly distributed between various food groups. Similarly, a reduction of salt in bread to 0.9 g salt per 100 g bread, would imply a need for approximately 22% increased iodization levels to achieve the same levels of daily iodine intake as given in the scenarios.

7.5 Discussion and summary of exposure/intake

Generally, in Norway, iodine intake estimates are considered to be reliable as few food products have been iodized and drinking water contains only small amounts of iodine. However, there are methodological concerns and limitations related to the various dietary survey methods for adults, adolescents and toddlers and infants.

Comparison of data from different dietary surveys

Norkost 3, Ungkost 3 and Småbarnskost 3/Spedkost 07 have all used different dietary assessment methods. Norkost 3 and Ungkost 3 have used recall and record methods that collect the food intake day by day, while FFQs were used in Småbarnskost 3/Spedkost-07. The iodine exposure estimates for 1- and 2-year-olds are based on individual intakes whereas the exposure estimates for adults, 13-, 9- and 4-year-olds are based on a mixed models (MM) method. Modelling to correct for day to day variation could not be carried out for iodine intakes in 1- and 2-year-olds, since the underlying data are based on FFQ. Day-to-day variation is partially accounted for in the FFQ method, as the dietary intakes estimated from an FFQ reflect habitual intakes over a longer period of time.

The impact of a mixed model approach on the exposure estimates is typically a reduction in the tails, i.e. a narrower distribution of chronic intake, compared to OIMs or daily intakes. Furthermore, a reduction in the mean intake is expected, as the daily intake distributions are skewed and an increase in the number of days will reduce the impact of rare days of very high intake (i.e. the upper tail).

The mean iodine intake estimates for 2-year-olds (Table 7.3.2-1) and non-breastfed 1-year-olds are higher than the mean iodine intake for 4-year-olds (Table 7.3.1-1), and it is therefore reasonable to assume that the estimated iodine intakes in the 2-year-olds are higher than the true intakes. Due to the relatively large proportion of underreporters of energy in adults and 13-year-old (16 and 33%, respectively), it is reasonable to assume that our estimated iodine intakes in adults and especially in the 13-year-olds are somewhat lower than true intakes. It should be noted that under- and overreporting of energy was not accounted for in the MM-modelling of the iodine exposure estimates.

The intake estimates and scenarios presented here in chapter 7 do not include intakes from food supplements. Scenarios including supplements (users only) are presented in Appendix V.

It has recently been proposed that comparison of population intakes with recommended intakes will yield an overestimate of inadequacy as the recommended intake is set to cover almost all individuals (Allen et al., 2019). We have commented on whether mean and median intakes are below or above the recommended intakes, but this information is not used to evaluate the adequacy of the intake in the benefit and risk characterisation.

Current iodine intake

Iodine intakes in adults are higher in men than in women and increase with age for both sexes. Women of childbearing age have the lowest estimated intakes among adults, and 74% have intakes above the EAR. 13-year-old girls have the lowest intake, and only 62% of these girls have intakes above the EAR. All adults and 13-, 9- and 4- year-olds have intakes below the UL (presented in Table 7.3.1-1).

The estimates for 1- and 2- year-olds show that 92% of the 2-year-old boys and 91% of the girls have intakes above the EAR, and 65% of breastfed 1-year-olds and 92% of non-breastfed have intakes above the EAR of 65 µg/day. The estimated iodine intake in the 95th percentile is 215 µg/day, slightly above the UL of 200 µg/day, and 8% of the 2-year-olds exceed the UL (presented in Table 7.3.2-1). However, excessive iodine intakes above the UL seem to be less frequent in the older age groups (from 4-years and older), and may therefore be described as transient.

The scenarios

Scenarios (presented in Tables 7.4-3 – 7.4-14) were conducted to estimate what the iodine intake would be if household salt and salt used in bread were iodized up to 15, 20, 25 or 50 µg iodine per kg salt.

The model-based scenarios in adults and 13-, 9- and 4-year-olds show impact at increasing iodization levels and naturally more impact if both household salt and salt in bread was iodized. We have presented 12 scenario tables, three scenarios (household salt alone, salt in bread alone and both household salt and salt in bread) for four iodization levels (15, 20, 25

and 50 mg iodine per kg salt). The percentages of the population groups with intakes above the EAR increases with increasing iodization levels, but so does the percentages with intakes above UL. In the scenario with both household salt and salt in bread at level 25 µg iodine per kg salt at least 99% of all the subjects in these age groups have iodine intakes above EAR and in all age groups the percentage of subjects exceeding UL is ≤ 3%.

For 2-year-olds all scenarios lead to an increase in both the proportion of toddlers with estimated intakes above EAR and intakes above UL. As increasing iodization levels of both household salt and bread elevates the children with low iodine intake above the EAR, a larger portion will have intakes exceeding the UL. At the iodization scenarios with 25 or 50 mg iodine per kg salt, including iodization of household salt and salt in bread, the proportion of 2-year-olds expected to exceed the UL rises to 30-63%.

Supplement use and population groups at risk of low or high intakes

Scenarios including supplements (users only) are presented in Appendix V. Adult and adolescent iodine supplement users (regular supplements – not seaweed and kelp based supplements) are not at special risk of high intakes, even in the scenarios with increased iodization levels, compared to the general population. 2-year-old supplement users are at high risk of exceeding UL. Kelp-, tare- and seaweed-based supplements may contain significantly higher concentrations of iodine than regular iodine supplement users.

A total of 16% of the women and 11% of the men participating in Norkost 3 reported use of supplements containing iodine, with a mean iodine contribution of 95 and 117 µg/day, respectively. In Småbarnskost 3, 10% of the 2-year-olds reported use of iodine-containing supplements with a mean iodine contribution of 96 µg/day. In MoBa, 32-37% of the pregnant women reported use of iodine-containing supplement during the first half of pregnancy (Brantsaeter et al., 2013). The median amount of iodine contributed by supplements was 107 µg/day in iodine-supplement users (Brantsaeter et al., 2013).

Individuals omitting all foods of animal origin receive very little iodine through their diet. Subjects with allergy to milk and/or fish-products and vegans are likely to have low iodine intakes. For persons with few iodine sources in the diet, the increase in iodine intake from increased iodization of salt and bread may be the same as for the lower percentiles (e.g. the 5th percentiles) in the scenarios in Tables 7.4-3 - 7.4-14. Vegans are recommended to use iodine-containing dietary supplements, and some vegans have iodine intakes above the UL due to use of a kelp-supplements.

Some ethnic minorities have been suggested to be at risk of low iodine intakes. However, a study on iodine status in women from the Oslo area, found no association between iodine status and ethnicity (Henjum et al., 2018a).

Effect of potential salt reduction on the scenario estimates for iodine

A uniform 30% reduction in average salt consumption implies a need for 43% increased iodization levels to achieve the same levels of daily iodine intake as given in the scenario Tables 7.4-3 -7.4-14 for all the age groups.

8 Benefit and risk assessment

This benefit and risk assessment is based on 1) established knowledge about health consequences from severe iodine deficiency, 2) evidence based systematic literature review of health consequences of mild to moderate iodine deficiency, 3) literature review of studies on adverse health effects from excessive iodine intakes to re-evaluate existing ULs, 4) evaluation of estimated iodine intake levels in different population groups in Norway compared to established dietary reference values, specifically estimated average requirement (EAR) and tolerable upper intake levels (UL), and finally 5) an estimation of the effect of different scenarios of increasing iodization levels in household salt and salt in bread on iodine intake levels in different population groups compared to the established dietary reference values.

This chapter attempts, in a systematic way, to bring all previous chapters and sections together to address possible benefits and risks from iodization of household salt and salt used in industrial bread and bakery products.

8.1 Benefit and risk assessment - guidelines

In 2010, the EFSA Scientific Committee developed "Guidance on human health risk-benefit assessment of foods" (EFSA, 2010a). EFSA recommended a stepwise approach for the risk- and benefit assessment, i.e. 1) an initial assessment, addressing the question whether the health risks clearly outweigh the health benefits or vice versa, 2) a refined assessment, aiming at providing semi-quantitative or quantitative estimates of risks and benefits at relevant exposure levels by using common metrics, and 3) a comparison of risks and benefits using a composite metric such as disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs) to express the outcome of the risk-benefit assessment as a single net health impact value. For the current assessment, step 3) was not employed.

8.2 Benefit and risk characterisation

The recommended daily iodine intake for adults is 150 µg/day, for pregnant women 175 µg/day and for lactating women 200 µg/day (NNR, 2012). The recommendations for children and adolescents are in the range between 90 and 120 µg/day depending on age. Estimated average requirement (EAR) for children ≥ 10 years and adults is 100 µg/day (NNR Project Group, 2012). In the Nordic Nutrition Recommendations 2012 (NNR) an EAR was not set for children < 10 years and adolescents. The US Institute of Medicine (IOM, 2001) set the EAR for children and adolescents (1 to 18 years) between 65 to 95 µg/day. The tolerable upper intake level (UL) set by the SCF (2002) for adults is 600 µg/day, 450 µg/day for 13-years-old and 200 µg/day for 2-years-old.

The project group decided to use EAR and UL as comparison values, and this is in line with the recent proposal for harmonised dietary reference values from WHO, FAO, and NASEM,

where AR and UL are considered the core values for evaluating population intakes (Allen et al., 2019). UL should by definition protect most of the population, whereas EAR is assumed to be sufficient for 50% of the population.

8.2.1 Groups at risk of low and high iodine intakes

VKM was requested to estimate iodine exposure from the diet in the general population and among specified risk groups at current intake level (no iodization).

VKM was furthermore requested to estimate iodine exposures in the general population and among specified risk groups in scenarios with graded levels of iodine added to household salt and industrial salt used in bread (20, 25 or 50 mg iodine per kg salt). In addition to the requested scenarios, we have estimated scenarios with 15 mg iodine per kg salt because according to national dietary surveys, 8% of 2-years-olds and 18% of non-breastfed 1-year-olds had iodine intakes above UL at current intake levels (no iodization). In the text below, we present the scenarios for iodine added to both household salt and industrial salt used in bread, since the scenarios with iodine added to household salt alone or industrial salt used in bread alone did not increase the estimated iodine intakes sufficiently in the groups at risk of low intakes.

The estimated effects of the different iodization levels and scenarioson iodine intakes in various age groups, are presented in Tables 7.4-3 - 7.4-14 and Figures 7.4-1 - 7.4-5. Scenarios for iodine-containing supplement users (users only) are presented in Appendix V Tables V-2 and V-3 and Figures V-1 and V-2.

It should be noted that the iodine intake estimates for 13-year-olds and women of childbearing age (18-45 years) are modelled using a mixed model approach (MM-approach), whereas the estimates for the 1- and 2-year-olds are based on reported intakes.

8.2.1.1 Groups at risk of low intakes – current level and scenarios

At current intake levels (no iodization), women of childbearing age (18-45 years) have the lowest estimated intakes among adults, and 26% have intakes below the EAR at 100 µg/day. The mean (median) iodine intake is 147 (128) µg/day for those who do not use iodine supplements, and the estimated intake in the 5th percentile is 68 µg/day. 13-year-old girls have the lowest estimated iodine intake, and 38% of these girls have intakes below the EAR at 73 µg/day. The mean (median) estimated iodine intake in 13-year-old girls is 95 (85) µg/day, and the estimated intake in the 5th percentile is 38 µg/day. It is reasonable to assume that our estimated iodine intakes in adults and especially in the 13-year-olds may be somewhat lower than true intakes. The rationale for this assumption is given in section 7.3.1.

The findings that especially young girls and women of childbearing age have low iodine intakes are in accordance with a recent review on iodine status in Norway, where all studies involving women in childbearing age, including pregnant and lactating women, found that

the median UIC was lower than the WHO cut-off for adequate iodine status (Henjum et al., 2019).

In Tables 8.2.1.1-1 and 8.2.1.1-2 we have presented how the estimated iodine intakes in the groups at risk of low intakes increase with the increasing iodization level scenarios. In the 13-year-olds, only the data for the girls are presented, as girls have lower intakes than boys. The estimates in these tables do not include contribution from iodine containing supplements.

In the with 15 mg iodine/kg added to both household salt and salt in bread (scenario salt+bread15), 94% of the women 18-45 years have iodine intakes above EAR and estimated mean (median) iodine intake is 176 (166) µg/day. The intake in the 5th percentile is 97 µg/day. In the scenario with 20 mg iodine/kg added to both household salt and salt in bread (salt+bread20), 97% have iodine intakes above EAR and estimated mean (median) iodine intake is 189 (179) µg/day. The intake in the 5th percentile is 107 µg/day. At the scenarios adding 25 or 50 mg iodine/kg (salt+bread25 and salt+bread50), 99-100% of the women 18-45 years have estimated iodine intakes above EAR, and estimated mean and median intakes are slightly below or above 200 µg/day.

The EAR in 13-year-olds is 73 µg/day. At scenario salt+bread 15, 93% have estimated iodine intakes above EAR and estimated mean (median) iodine intake is 132 (122) µg/day. The intake in the 5th percentile is 70 µg/day. At scenario salt+bread20, 97% are above EAR, and estimated mean (median) intake is 145 (134) µg/day. The intake in the 5th percentile is 80 µg/day. At scenario salt+bread25, the estimated intake in the 5th percentile has increased to 90 µg/day.

Table 8.2.1.1-1 Estimated iodine intakes in women 18-45 years in the different scenarios, sorted by mean intakes (increase from current intake levels in parentheses).

Scenarios	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent above EAR	Percent below UL
Current intake – no iodization	137	68	128	240	74	100
Salt15	149 (+12)	79 (+11)	139 (+11)	253 (+13)	83 (+9)	100
Salt20	153 (+16)	83 (+15)	143 (+15)	255 (+15)	86 (+12)	100
Salt25	157 (+20)	87 (+19)	147 (+19)	259 (+19)	88 (+14)	100
Bread15	165 (+28)	86 (+18)	155 (+27)	279 (+39)	89 (+15)	100
Bread20	174 (+37)	92 (+24)	164 (+36)	292 (+52)	92 (+18)	100
Salt+bread15	176 (+39)	97 (+29)	166 (+38)	291 (+51)	94 (+20)	100
Salt50	176 (+39)	106 (+38)	166 (+38)	278 (+38)	97 (+23)	100
Bread25	183 (+46)	98 (+30)	172 (+44)	306 (+66)	94 (+20)	100
Salt+bread20	189 (+52)	107 (+39)	179 (+49)	307 (+67)	97 (+23)	100
Salt+bread25	202 (+65)	117 (+49)	191 (+61)	325 (+85)	99 (+25)	100
Bread50	229 (+92)	124 (+56)	216 (+86)	378 (+138)	99 (+25)	100
Salt+bread50	267 (+130)	162 (+94)	254 (+124)	416 (+176)	100 (+26)	100

EAR adults=100 µg/day
UL adults=600 µg/day

Table 8.2.1.1-2 Estimated iodine intakes in 13-year-old girls in the different scenarios, sorted by mean intakes (increase from current intake levels in parentheses).

Scenarios	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent above EAR	Percent below UL
Current intake – no iodization	95	38	85	187	62	100
Salt15	105 (+10)	48 (+10)	94 (+9)	196 (+9)	72 (+10)	100
Salt20	108 (+13)	51 (+13)	97 (+12)	199 (+12)	76 (+14)	100
Salt25	111 (+16)	54 (+16)	100 (+15)	202 (+15)	79 (+17)	100
Bread15	123 (+28)	61 (+23)	112 (+27)	221 (+34)	87 (+25)	100
Salt50	127 (+32)	70 (+32)	116 (+31)	218 (+31)	93 (+31)	100
Bread20	132 (+37)	67 (+29)	121 (+36)	232 (+45)	92 (+30)	100
Salt+bread15	132 (+37)	70 (+32)	122 (+37)	230 (+43)	93 (+31)	100
Bread25	141 (+46)	74 (+36)	131 (+46)	244 (+57)	95 (+33)	100
Salt+bread20	145 (+50)	80 (+42)	134 (+49)	244 (+57)	97 (+35)	100
Salt+bread25	157 (+62)	90 (+52)	146 (+61)	259 (+72)	99 (+37)	100
Bread50	188 (+93)	106 (+68)	176 (+91)	305 (+118)	100 (+38)	100
Salt+bread50	219 (+124)	138 (+100)	208 (+123)	337 (+150)	100 (+38)	99 (-1)

EAR 13-year-olds=73 µg/day
UL 13-year-olds=450 µg/day

8.2.1.2 Groups at risk of high intakes – current level and scenarios

At current intake level (no iodization), almost all adults, adolescents and children above 2-years of age have individual iodine intakes below UL. Men and 4-year-olds are groups at risk of high intakes with increasing iodization levels, however, in all the 15, 20 and 25 mg iodine per kg salt scenarios, the percentage above UL is 1% at the most in the population groups above 2 years. In the scenarios with 50 mg iodine per kg salt scenarios including both household salt and bread (bread50 and salt+bread50), several population groups are at risk of intakes above UL.

In Tables 8.2.1.2-1 and 8.2.1.2-2 we have presented how the estimated iodine intakes in the groups at risk of high intakes increase with the increasing iodization level scenarios. The estimates in these tables and the text below do not include contribution from iodine containing supplements. It is reasonable to assume that the estimated iodine intakes in the 2-year-olds are higher than the true intakes. The rationale for this assumption is given in section 7.3.2.

The presentation of groups at risk of high estimated intakes is limited to the 1- and 2-year-olds. 18% of non-breastfed 1-year-olds and 8% of the 2-year-olds have iodine intakes above the UL of 200 µg/day at current intake level. The 95th percentile for iodine intake is 259 µg/day in non-breastfed 1-year-olds and 215 µg/day in 2-year-olds (UL in both 1- and 2-year-olds is 200 µg/day).

In 1-year-olds, only data for the non-breastfed are presented. We could not estimate iodine intake in breastfed infants as we do not have information about breast milk consumption, and therefore breastfed 1-year-olds are not included in this assessment. In the scenarios for

1-year-olds, only iodine in salt from bread has been estimated. Iodine in household salt was not included because salt consumption data in 1-year-olds were considered to be too uncertain. Furthermore, the general advice is to keep the salt intake in toddlers low, and to avoid adding extra salt to the food. It is reasonable to assume that consumption of household salt in 1-year-olds is low.

While currently available data on dietary intake in 1-year olds were collected in 2007, data from a new dietary survey in 1-year-olds are expected to be available before summer 2020. If the new upcoming data and new data differs substantially from the exposure estimates for 1-year-olds presented in chapter 7, this benefit and risk assessment will be supplemented with an updated evaluation for this group

In the 2-year-olds, only the data for the boys are presented, as the boys have slightly higher intakes than the girls. The group at absolutely highest risk of high intakes is 2-year-old iodine supplement users. Exposure estimates for this group is presented separately in Table V-3 in Appendix V.

In the scenarios (salt+bread15 or salt+bread20) that could elevate the estimated iodine intakes in the 5th percentile of women 18-45 years and 13-year-old girls up to the EAR or above the EAR, the proportion of 2-year-old boys exceeding the UL increases from 8% to 19 or 23%, respectively. In the salt+bread15-scenario, the estimated iodine intake in the 95th percentile of 2-year-old boys is 252 µg/day, and in the salt+bread20-scenario, the iodine intake in the 95th percentile of 2-year-old boys is 263 µg/day. At scenario salt+bread25, 30% exceeds UL and at scenario salt+bread50, 63% of the 2-years-old boys exceeds UL.

In the scenarios with 15 or 20 mg iodine per kg salt added to salt in bread alone (bread15 or bread20-scenario), the proportion of non-breastfed 1-year-olds exceeding the UL increases from 18% to 32 or 36%, respectively. In the bread15-scenario, the estimated iodine intake in the 95th percentile of 1-year-olds is 302 µg/day, and in the bread20-scenario, the iodine intake in the 95th percentile of 1-year-olds is 316 µg/day.

Few adults and adolescents have estimated iodine intakes that exceed UL, even in those who use regular iodine containing supplements. However, kelp- and seaweed-based supplements, and other foods made with kelp and seaweed may contain high concentrations of iodine. People who use these ingredients or supplements may be at risk of overly high iodine intakes at the estimated current intake level or in any given increased iodization level scenario. In the national dietary surveys, consumption of kelp- and seaweed-based ingredients has only been reported in the most recent dietary survey in 2-year-old children (Småbarnskost 3).

Table 8.2.1.2-1 Estimated iodine intakes in 2-year-old boys in the different scenarios, sorted by mean intakes (increase from current intake level in pharenteses).

Scenarios	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent above EAR	Percent above UL
Current intake – no iodization	129	56	122	215	92	8

Scenarios	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent above EAR	Percent above UL
Salt15	138 (+9)	65 (+9)	131 (+9)	224 (+9)	95 (+3)	11 (+3)
Salt20	141 (+12)	68 (+12)	134 (+12)	227 (+12)	96 (+4)	12 (+4)
Salt25	144 (+15)	71 (+15)	137 (+15)	230 (+15)	97 (+5)	13 (+5)
Bread15	149 (+20)	73 (+17)	142 (+20)	243 (+28)	97 (+5)	15 (+7)
Bread20	155 (+26)	80 (+24)	148 (+26)	251 (+36)	97 (+5)	19 (+11)
Salt+bread15	158 (+29)	82 (+26)	151 (+29)	252 (+37)	98 (+6)	19 (+11)
Salt50	159 (+30)	86 (+30)	152 (+30)	245 (+30)	99 (+7)	18 (+10)
Bread25	162 (+33)	85 (+29)	155 (+33)	258 (+43)	98 (+6)	21 (+13)
Salt+bread20	167 (+38)	92 (+36)	160 (+38)	263 (+48)	99 (+7)	23 (+15)
Salt+bread25	177 (+48)	100 (+42)	170 (+48)	273 (+58)	100 (+8)	30 (+22)
Bread50	195 (+66)	107 (+51)	189 (+67)	305 (+90)	100 (+8)	43 (+35)
Salt+bread50	225 (+96)	137 (+81)	219 (+97)	335 (+120)	100 (+8)	63 (+55)

EAR 2-year-olds=65 µg/day
UL 2-year-olds=200 µg/day

Table 8.2.1.2-2 Estimated iodine intakes in non-breastfed 1-year-olds in the different scenarios, sorted by mean intakes (increase from current intake level in parentheses).

Scenarios	Mean µg/day	P5 µg/day	P50 µg/day	P95 µg/day	Percent above EAR	Percent above UL
Current intake – no iodization	147	54	139	259	69	18
Bread15	172 (+25)	63 (+9)	162 (+23)	302 (+43)	95 (+26)	32 (+14)
Bread20	180 (+33)	66 (+12)	169 (+30)	316 (+57)	95 (+26)	36 (+18)
Bread25	188 (+41)	69 (+15)	177 (+38)	330 (+71)	96 (+27)	38 (+20)
Bread50	228 (+81)	84 (+30)	215 (+75)	401 (+142)	98 (+29)	56 (+38)

EAR 1-year-olds=65 µg/day
UL 1-year-olds=200 µg/day

8.2.2 Risk characterisation

For the purpose of this benefit and risk assessment of iodization in household salt and salt used in bread and bakery products, risk may be understood as risk of adverse health effects related to too high or too low iodine intakes.

8.2.2.1 Risks related to low iodine intakes

Women of childbearing age and 13-year-old girls have low iodine intakes. In addition, people who for various reasons include few iodine rich sources in their diet (e.g. people with allergies and intolerances to fish or milk/dairy products, vegans/vegetarians and certain ethnic minorities), have increased risk of low intakes.

Severe iodine deficiency during foetal life, infancy, or early childhood may lead to permanent intellectual disability. Severe maternal iodine deficiency in pregnancy may also result in miscarriages, preterm delivery, stillbirth, and congenital abnormalities. These effects are

mediated through the thyroid hormones on the developing tissues. For 13-year-old girls, an inadequate iodine intake might affect thyroid hormone production negatively. Severe iodine deficiency and reduced thyroid function during adolescence increase the risk of developing goiter, juvenile hypothyroidism, impaired mental function, and retarded physical development. Data for the prevalence of severe iodine deficiency or mild or moderate iodine deficiency in Norway are not available.

Several studies have found poorer neurodevelopmental outcomes in children born to mothers with seemingly mild to moderate iodine deficiency. However, based on our systematic literature review and use of WCRF's criteria for grading of evidence, the evidence was not judged strong enough to meet the criteria for probable evidence. We concluded that there is *limited suggestive* evidence to support that mild to moderate iodine deficiency prior to, or during pregnancy, causes poor neurodevelopment in children. *Limited suggestive* means that the evidence is too limited to permit a probable or convincing causal judgement but shows a generally consistent direction of effect.

After carefully reviewing the articles on the other outcomes relevant for women of childbearing age (thyroid function and birth outcomes), it was concluded that there is *limited (no conclusive)* evidence to support that mild to moderate iodine deficiency causes thyroid dysfunction or has negative effects on birth outcomes. *Limited (no conclusive)* means that the evidence is so limited that no firm conclusion can be made. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, and by methodological flaws (lack of adjustment for known confounders).

As for schoolchildren, it was also concluded that the evidence is *limited suggestive* that mild to moderate iodine deficiency in schoolchildren causes poor neurodevelopment. Only one study included in our systematic review investigated thyroid function, and no conclusion could be made.

For more detailed information about the grading of evidence from the systematic review on health effects related to mild to moderate iodine deficiency, see Tables 5.5-1 and 5.5-2.

Recommendations for nutrients are set to secure adequate growth, development, maintenance of health, and to reduce the risk of chronic illnesses. An adequate iodine intake is essential for synthesis of thyroid hormones and is critically important for the foetus and infant by affecting the development and maturation of the nervous system, skeletal muscles, and lungs. An adequate iodine intake is particularly important for women in childbearing age because their future children may be susceptible to the adverse effects of iodine deficiency. Women with intakes below EAR have a relatively high probability of inadequate iodine intakes and therefore a higher risk of adverse health effects from iodine deficiency. For 13-year-old girls iodine intake in the 5th percentile is 38 µg/day (EAR 73 µg/day) and for women of childbearing age 70 µg/day (EAR 100 µg/day).

Current iodine intake in certain population groups is worryingly low, and trend studies indicate that consumption of milk and dairy products in Norway, the most significant iodine

sources in the diet, is declining, especially among young women (Brantsaeter et al., 2013; Gunnarsdottir and Dahl, 2012).

8.2.2.2 ***Risks related to high iodine intakes***

The 2-year-olds are at risk of high iodine intakes, in addition to kelp or seaweed supplement users. Few studies with designs suited for risk assessment have investigated adverse health outcomes in relation to excessive iodine. However, excessive iodine intake has been associated with poor regulation of thyroid hormones and increased (hyperthyroidism) and decreased (hypothyroidism) thyroid hormone production. Whether excessive iodine exposure, acute or chronic, is a significant cause of poor neurodevelopment or other adverse health outcomes is still a matter of debate.

The clinical consequence of excessive intakes in young children is uncertain, and the studies found relevant for comparison with the existing UL (chapter 6.2.2) only include children at or above the age of 6 years. In our updated literature review, we included four publications from three large, cross-sectional studies including children from China, Korea, and Japan with high iodine exposures,

The prevalence of subclinical hypothyroidism in Chinese children (7-10 years old and 11-14 years old) was increased with iodine intakes ≥ 250 µg/day (Chen et al., 2017; Chen et al., 2018a). The ULs in these age groups are ranging from 300-450 µg/day. Kang et al. (2018) reported a significantly higher prevalence of subclinical hypothyroidism in Korean children aged 10-19 years in the group with UIC above 300 µg/L, corresponding to an estimated iodine intake of 333 µg/day. The ULs in this age groups are ranging from 450-600 µg/day. However, the study quality from these cross-sectional studies were not considered sufficient to establish new ULs. The project group therefore proposed to keep the existing ULs in children, including the UL of 200 µg/day for 1- and 2-year-olds, set by SCF in 2002.

A recent non-systematic review of iodine excess and thyroid function in children aged 6-24 months concluded that the long-term effects of chronic excessive iodine on thyroid function and somatic growth and development in infants and young children remain uncertain (Farebrother et al., 2019a). One of the studies included in this review assessed thyroid function and Tg concentrations in 6-24 month old infants, and observed an increase in Tg in infants consuming iodine above the UL (>230 µg/day) (Farebrother et al., 2019b). Two other studies were carried out in groups with higher iodine intakes (median UIC > 400 µg/L, corresponding to estimated iodine intake > 444 µg/day) and reported an increased prevalence of subclinical hypothyroidism (Aakre et al., 2016; Nepal et al., 2015).

In adults (19-24 years old), results from a randomised controlled dose-response study (12 intervention groups with various iodine supplement doses ranging from 0 to 2000 µg/day and total iodine intakes ranging from 351 µg/day (placebo group) to 2375 µg/day (2000 µg supplement group) (Sang et al., 2012) were found to be in line with the UL of 600 µg/day in adults set by the SCF (2002) and later adopted by the NNR (2012) and a recent proposal from NASEM (Allen et al., 2019). This study showed that subclinical hypothyroidism

appeared in participants with a total iodine intake of 800 µg/day (around 400 µg/day from food and 400 µg/day from supplements). No increase in TSH concentrations (TSH >5 mIU/L) or thyroid hormones appeared at lower intakes. However, according to findings in new studies, the lowest-observed-adverse-effect levels (LOAEL) for excessive iodine intake may be lower than previously assumed, and the uncertainty factor inherent in the established ULs is reduced from three to 1.3 for adults. It should be noted that elevated TSH concentrations (TSH >5 mIU/L) remained in 5% of the participants with a total intake of 800 µg iodine per day 3 months after iodine withdrawal (Sang et al., 2012).

It should be noted that in subclinical hypothyroidism, the production of the thyroid hormones T3 and T4 are within normal ranges, whether these findings have clinical or developmental consequences is uncertain, but subclinical hypothyroidism may progress to overt hypothyroidism (Cooper and Biondi, 2012).

In the salt+bread15 and salt+bread20-scenarios, 19 and 23% of the 2-year-olds have intakes above UL of 200 µg/day. The estimated intakes in the 95th percentiles are 252 and 263 µg/day, respectively. In the bread15- or bread20-scenario, the proportion of 1-year-olds exceeding the UL increases from 18% to 32% or 36%, respectively. In the bread15-scenario, the estimated iodine intake in the 95th percentile of 1-year-olds is 302 µg/day, and in the bread20-scenario, the iodine intake in the 95th percentile of 1-year-olds is 316 µg/day. These are intake levels that have been associated with an increase in TSH or Tg, without a change in the thyroid hormones T3 or T4.

According to the benefit and risk assessment, other groups at risk for overly high iodine intake are individuals consuming dried kelp or kelp supplements. In pregnant women, an abrupt moderate increase in iodine intake may cause transient thyroid dysfunction (Bath, 2019; Moleti et al., 2011). Data from the MoBa showed that the pregnant women were mildly to moderately iodine deficient. This might indicate that a high proportion of infants in Norway have been exposed to low iodine exposures during foetal life. From 4-6 months of age and through early childhood, the infants and toddlers probably increase their iodine intakes. Abrupt increase in iodine intakes in individuals with a previously mild to moderate iodine deficiency might disturb normal iodine metabolism and increase the risk of altered thyroid function.

8.2.3 Benefit characterisation

Benefit may be understood as reduction or avoidance of adverse health effects related to too high or too low iodine intakes. For iodine, this is a challenging maneuver, as the range between too low and too high intakes is narrow. The subjects with iodine intakes above EAR and below UL have less risk for developing iodine deficiency disorders or having excessive iodine intakes associated with thyroid dysfunction.

8.3 Summary of benefit and risk assessment

It is well established that severe iodine deficiency has adverse effects on thyroid function, neurodevelopment and birth outcomes. Several single studies described impaired neurodevelopmental outcomes related to mild to moderate iodine deficiency prenatally, during pregnancy and in schoolchildren. However, based on our systematic literature review and use of guidelines for grading of evidence, the project group concluded that there is *limited - suggestive* evidence for a causal relationship between mild to moderate iodine deficiency and adverse neurodevelopmental outcomes. The evidence was *limited (no conclusion)* that mild to moderate iodine deficiency causes thyroid dysfunction or affect fertility or birth outcomes.

At current intake level (no iodization), 26% of women 18-45 years of age and 38% of 13-year-olds girls have intakes below the estimated average requirement (EAR). It is, reasonable to assume that our estimated iodine intakes in adults and especially in the 13-year-olds are somewhat lower than the true intakes (section 7.3.1). The findings that especially young girls and women of childbearing age have low intakes are, however, in accordance with studies in Norway on iodine status in women of childbearing age (Henjum et al., 2019).

An adequate iodine intake is essential for synthesis of thyroid hormones and is critically important for the foetus and infant by affecting the development and maturation of the nervous system, skeletal muscles, and lungs. Subjects with intakes below EAR have a relatively higher probability of inadequate iodine intakes and therefore a higher risk of adverse health effects from severe iodine deficiency. An adequate iodine intake is particularly important for women in childbearing age because their future children may suffer adverse effects from iodine deficiency. The scenario (salt+bread 15 mg) that could adequately increase the iodine intakes of women 18-45 years and 13-year-old girls above EAR for 94%, put 19% of the 2-year-old boys at risk of intakes above UL.

Excessive iodine interferes with normal regulation of thyroid hormones and may lead to both increased (hyperthyroidism) and decreased (hypothyroidism) thyroid hormone production (Burgi, 2010; Farebrother et al., 2019a; Katagiri et al., 2017; Laurberg et al., 2010). However, the evidence for excessive iodine intakes leading to poorer neurodevelopmental outcomes is limited.

In regard to high iodine intakes, at estimated current intake level (no iodization), 8% of the 2-year-old children and 18% of the non-breastfed 1-year-olds exceed UL of 200 µg/day. With the intake scenarios of 15, 20 and 25 mg iodine per kg salt in household salt and bread, 19%, 23% and 30% of the 2-year-olds, respectively will exceed UL. It is, however, reasonable to assume that the estimated iodine intakes in the 2-year-olds are higher than the true intakes (section 7.3.2). Subclinical hypothyroidism (changes in TSH without changes in T3 or T4) have been reported in children with iodine intakes at or below the existing ULs. It should be noted that in subclinical hypothyroidism, the production of the thyroid hormones

T3 and T4 are within the normal range, and whether these findings have clinical or developmental consequences is uncertain, but subclinical hypothyroidism may progress to overt hypothyroidism (Cooper and Biondi, 2012).

The value for comparison in the upper intake range (UL) should by definition protect most of the population, whereas the chosen value for comparison in the lower intake range (EAR) is assumed sufficient for 50% of the population. It may therefore be argued that the chosen value for comparison in the upper intake range is more conservative than the chosen value for comparison in the lower intake range.

9 Uncertainties

9.1 Uncertainties related to the evidence for health impact of insufficient or excessive iodine intakes

The project group assessed the quality and risk of bias of all studies included in the literature reviews, but there will still be uncertainty related to the evidence. The uncertainties pertain to validity and precision of the exposure (iodine intake) and outcome measurements, as well as to the number and relevance of the available studies.

Table 9.1-1 Uncertainties related to the evidence for mild to moderate iodine deficiency and health outcomes.

Source of uncertainty	Consequences for our evaluation
Iodine status (UIC)	As an indicator of regular iodine intake in the diet, a single UIC measurement provides only a snapshot of recent intake. This measurement may provide information about median iodine intake in a population, while several repeated measurements are required to reliably estimate individual iodine status and to classify individuals as iodine deficient or sufficient. Yet, the classification of populations into subgroups of deficiency or sufficiency in most published studies are based on UIC in a single urine sample. This leads to a high degree of misclassification and incorrect estimates for: • the prevalence of iodine deficiency, insufficiency, sufficiency, and excess in individuals • the effect of mild and moderate iodine deficiency, or excess, on health outcomes in individuals
Neurodevelopmental outcomes and iodine deficiency	Neurodevelopmental tests might not capture the domain sensitive to iodine deficiency or excess. This might result in false negative results (type II errors).
	The results from neurodevelopmental tests in young children (i.e. early child development before approximately 3 years of age) are poor predictors for cognitive functions later. The reliability of the study results is poor which decreases the precision of the effect estimates.
	The results obtained from neurodevelopmental tests might be influenced by socioeconomic factors that increases the risk of confounding.
	The subjective nature of many of these tests increases the risk of both random and systematic errors.
Thyroid function and iodine deficiency	Although cross-sectional studies are generally not appropriate for causal inference, such studies were included due to the rapid response of the thyroid to increased iodine intakes

Source of uncertainty	Consequences for our evaluation
	Tg is a marker of iodine status rather than thyroid function. Increased Tg is an early sign of increased thyroid activity, but should not be regarded as a clinically relevant endpoint for thyroid dysfunction if thyroid hormone production is still within the normal range.
	Decreases in thyroid hormone concentrations and TSH occur during pregnancy as a consequence of the normal physiological changes in blood volume (hemodilution) in pregnancy. Consequently, it is difficult to distinguish between normal changes and changes that may result from mild or moderate iodine deficiency.
	Detecting effects of changing iodine intakes on thyroid function can be challenging since auto-regulatory processes are initiated in the thyroid gland, when the iodine intake increases or decreases, to maintain normal thyroid function.
EAR as reference value in this benefit and risk assessment	EAR in adults is based on studies of thyroid iodine accumulation and turnover in euthyroid adults, and supported by balance studies. There is more uncertainty related to EAR for children and for pregnant women, than for non-pregnant adults.
	Balance studies for deriving EAR have limitations, e.g. differences in long-term iodine intake prior to inclusion, iodine equilibrium relies on thyroidal store and not only intake and excretion, the studies were conducted at a time when key indicators such as serum TSH were not available.
	By definition, the iodine requirement is covered for only 50% of the population at EAR.
UL as reference value in this benefit and risk assessment	The UL from 2002 is based on small pharmacokinetic dose-response studies evaluating the effects of relatively short-term iodine exposures in euthyroid adults. Results from more recent studies suggest that the inherent uncertainty factor is lower for the existing UL in both adults, adolescents and children.
	UL is based on increase in TSH and later studies on subclinical hypothyroidism. There is uncertainty regarding the clinical relevance of changes in TSH and subclinical hypothyroidism.
	Only cross-sectional studies were available as a basis for appraising UL in children, which makes the uncertainty for the younger age groups even larger than for adults. This applies particularly for the extrapolation from adults to 1- and 2-year-olds.

9.2 Uncertainties related to iodine exposure

The main sources of uncertainty in the exposure estimates are presented in Table 9.2-1. The possible impact of the uncertainty on the exposure estimates was evaluated by expert judgement, and both the main sources to uncertainty and the possible effect on the exposure estimates are presented in the table.

Table 9.2-1 Main sources of uncertainties and the impact in the dietary exposure estimates of iodine, described by age and study population.

<table>
<tr><th>Source of uncertainty</th><th>Description</th><th>1-year-olds</th><th>2-year-olds</th><th>4-year-olds</th><th>9-year-olds</th><th>13-year-olds</th><th>Adult men</th><th>Adult women</th><th>Women 18-45-year-olds</th></tr>
<tr><td rowspan="3">Iodine concentration in food</td><td rowspan="2">Scenarios on brand loyal consumers are not included in this assessment.</td><td colspan="2">na[1]</td><td colspan="7">Two brands of mineral water were analysed to contain iodine between 30-40 µg/100g. For those who consume mineral water only from the brands with the highest iodine content, the exposure will be higher than estimated.</td></tr>
<tr><td colspan="9">Presented scenarios of salt in bread could be an underestimation of the variation iodine exposure.</td></tr>
<tr><td>Iodine concentrations in fish</td><td colspan="9">Iodine concentrations in white fish vary substantially. We have used one single mean concentrations from the Norwegian Food Composition Table. In a long term perspective this is not assumed to affect the iodine estimates in any specific direction.</td></tr>
<tr><td>Import of bread</td><td>Imported bread could include iodized salt, but was not taken into account.</td><td colspan="9">In the presented exposure estimates current intake could be underestimated.
Scenarios of salt in bread could be overestimated.</td></tr>
</table>

Source of uncertainty	Description	1-year-olds	2-year-olds	4-year-olds	9-year-olds	13-year-olds	Adult men	Adult women	Women 18-45-year-olds
Effect of cooking/processing	The effect of cooking/processing on iodine concentration in foods was not taken into account.	In the presented exposure estimates, sampled foods were assumed to represent consumed foods, which could lead to both over- and underestimation.							
Use of household salt	Gender- and energy-adjusted salt intake based on 10% of urinary iodine excretion data from Tromsø 7. The individual household salt consumption will differ between individuals, and will also correlate with intake of different types of foods. This correlation was not taken into account in this assessment, due to lack of data.	na[1]	Presented household salt scenarios will have a lower level of variation.						

Source of uncertainty	Description	1-year-olds	2-year-olds	4-year-olds	9-year-olds	13-year-olds	Adult men	Adult women	Women 18-45-year-olds
Different dietary assessment methods	Short period of food registration provides dietary data on group level, but can be inadequate for estimating individual intake.								
		Food frequency questionnaire will give an estimate with a higher degree of variance in both current intake and scenarios.		Four days web food diary; Iodine containing foods like milk and milk products, fish and for the scenarios bread consumption, are common food groups that is probably well captured by the survey. However, four days will not capture the impact of rarely eaten foods with high iodine concentrations.			Two recording days; some foods/food groups have high concentrations of iodine, and the long term consumption of these high iodine concentration products (e.g. brown weigh cheese, cod) will not be reflected in two days recalls for one person.		
Groups at risk	Subpopulations which are susceptible to overly low intake of iodine.						In the presented current intake and scenarios, persons not eating milk and/or fish will have an iodine intake in the lower percentiles. However, the largest uncertainty is lack of food intake data for these groups.		

[1]na – not applicable

9.2.1 Uncertainties related to the modelling method (Mixed Models approach)

Models in general have different *types* of uncertainties: data/input uncertainties (detailed above for the different surveys), structural uncertainties (do the parameters and structure of the model represent the true nature of the data), parametric uncertainties (are the parameters properly estimated, e.g. how iodine intake increases with age). Our MM-approach is Bayesian and all models were evaluated for convergence and stability of parameter estimates (by inspecting the effective sample sizes and plotting their trace and distribution), and therefore it is reasonable to assume that the parametric uncertainty is well captured by our approach.

The MM-methods applied here assume (for adults) that both iodine intake and bread consumption are linearly impacted by sex, age and level of education *on a logarithmic scale*. It is well known that intake distributions are often skewed (particularly since they are bounded by 0), and a log transformation is often performed. In our preliminary comparison with Monte Carlo Risk Assessment (MCRA) (see appendix IV) the log-transformation of iodine intake was favoured by the selection procedure within the MCRA software (which performs a comparison with various Box-Cox transformations), so the assumptions of normality on a log scale is probably justified.

The structural uncertainty in the MM-approach relates to whether or not the appropriate kinds of explanatory variables are included, and that the variance/covariance structure in the mixed model is justified. We did apply models using more covariates, including testing for sex-specific age-dependencies (i.e. that men and women differ in how age impacts the iodine intake in Norkost 3), and these models did not outperform the models with age-effect for both men and women. We also fitted models to several related, but slightly different data-sets (e.g. including and excluding supplements for all adults, as well as for users-only) and for ease of comparison between these, we assumed the same structure for them all. There are some indications that iodine intake is geographically structured in Norway (Medin et al., 2020), but we did not include this as a covariate.

For the iodine exposure estimates, including the scenarios, the combined uncertainty deriving from data and modelling the uncertainty is largest in the 2-year-olds (since no modelling was performed), substantially less for adults (Norkost 3), and thought to be even smaller for Ungkost 3 (4-, 9- and 13-year-olds), mostly due to the higher number of days (4 vs 2 in Norkost 3).

10 Answers to the terms of reference and concluding remark

The Norwegian Scientific Committee on Food and Environment (VKM) was requested by the Norwegian Food Safety Authority (NFSA) to conduct a benefit-risk assessment of iodization of household salt and industrial salt used in bread. The assessment should include subpopulations that are at risk of overly low or high intake of iodine, including women of childbearing age, women who are pregnant and breastfeeding, men and children. Other risk groups such as vegans, individuals suffering from allergy or intolerance to fish and dairy products, relevant ethnic minorities that do not consume fish and dairy products and individuals consuming iodine supplements should also be considered. Iodization of plant-based alternatives to cow milk products should also be considered. Imported foods that are fortified with iodine and sold on the Norwegian market should be taken into account.

The VKM Panel on Nutrition, Dietetic Products, Novel Food and Allergy has discussed several draft opinions and has evaluated and approved the final opinion drafted by the project group. The VKM Panel supports and agrees with the assumptions and conclusions drafted by the project group. The answers to the Terms of Reference from the VKM Panel are given below.

10.1 Current iodine intake

This section answers question 1 in the terms of reference: What is the iodine intake in the general population and among identified risk groups? Risk groups are subpopulations at risk for overly low or high iodine intake.

The four nationwide dietary surveys Norkost 3, Ungkost 3, Småbarnskost 3 and Spedkost-07, have used different dietary assessment methods; 2x24h-recall, 4 days web-based food diary and food frequency questionnaire (FFQ), respectively.

The iodine exposure estimates for adults, 13-, 9- and 4-year-olds are based on a mixed models (MM) method, whereas the exposure estimates for 1- and 2-year-olds are based on FFQ.

The impact of a mixed models approach on the exposure estimates is typically a reduction in the tails, i.e. a narrower distribution of chronic intake, compared to observed individual means or daily intakes.

It should be noted that it is reasonable to assume that our estimated iodine intakes in adults and especially in the 13-year-olds are lower than the true intakes, both at the current level and in the scenarios. The rationale for this assumption is given in section 7.3.1. Furthermore, it is reasonable to assume that our estimated iodine intakes in the 2-year-olds are higher

than the true intakes, both at the current level and in the scenarios, and the rationale for this assumption is given in section 7.3.2.

The iodine exposure estimates and the scenarios have been compared to the reference values EAR and UL. The rationale for this choice of reference values is given in section 4.3.

Current intakes in adults, 13-, 9- and 4-year-olds, the general population

The estimated iodine intakes in adults, 13-, 9- and 4-year-olds not using iodine-containing supplements are presented in Table 7.3.1.1-1.

91% of the men and 79% of the women have estimated intakes above the EAR of 100 µg/day. Estimated mean (median) intakes are 202 (183) µg/day and 147 (137) µg/day, in men and women, and the intakes in the 5th percentiles are 88 and 72 µg/day, respectively. In women of childbearing age, 74% have intakes above EAR and the estimated intake in the 5th percentile is 68 µg/day.

79% of the 13-year-old boys and 62% of the girls have estimated intakes above the EAR of 73 µg/day. The estimated mean (median) intakes in girls are 95 (85) µg/day, whereas the intake in the 5th percentile for girls is 38 µg/day.

89% of the 9-year-old boys and 70% of the girls have estimated intakes above the EAR of 73 µg/day. 93% of the 4-year-old boys and 85% of the girls have estimated intakes above the EAR of 65 µg/day.

All adults and 13-, 9- and 4- year-olds have estimated intakes below the UL at current intake level. The ULs for these age groups are 600, 450, 300 and 250 µg/day, respectively.

Estimated intake in adults including iodine containing supplements (users only) are presented in Table V-2 and Figure V-1 in Appendix V. In Norkost 3, 16% of the women and 11% of the men reported use of iodine supplements with a mean iodine contribution of 95 and 117 µg/day, respectively. In 4-, 9- and 13-year-olds, 2-5% reported use of iodine supplements.

Current intakes in 1- and 2-year-olds, the general population

The estimated iodine intakes in 1- and 2-year-olds are presented in Table 7.3.2-1.

91-92% of the 2-year-olds have estimated intakes above the EAR of 65 µg/day. The estimated mean (median) intakes are 128 (122) µg/day, whereas the intake in the 5th percentile is 56 µg/day. 92% of non-breastfed 1-year-olds have estimated intakes above the EAR of 65 µg/day.

8% of 2-year-olds, and 18% of non-breastfed 1-year-olds have estimated intakes above the UL of 200 µg/day. The estimated iodine intakes in the 95th percentile is 215 µg/day in 2-

year-olds and 259 µg/day in non-breastfed 1-year-olds. Excessive iodine intakes above the UL seem to be less frequent in the older age groups (from 4-years and older).

10% of the 2-year-olds have reported use of iodine containing supplements, and mean iodine contribution from supplements is 96 µg/day in users only. The estimated intakes in 2-year-old supplement users (users only) are presented in Table V-3 and Figure V-2 in Appendix V.

There is no reported use of iodine supplements in 1-year-olds.

Current intakes in groups at risk of low and high intakes

As presented above, 13-year-olds and women of childbearing age (18-45 years) are at particular risk of iodine intakes below EAR. One- and 2-year-olds are at special risk of intakes above UL. Norkost 3 and the other national dietary surveys do not provide enough data to calculate iodine intake estimates for vegetarians, vegans, ethnic minorities, and persons with milk or fish allergy or intolerance.

As shown in Table 7.3.1.1-1 very few adults and adolescents have estimated iodine intakes that exceed the UL, even in those who use regular iodine containing supplements (Table V-2 in Appendix V). However, kelp- and seaweed-based supplements, and other foods made with kelp and seaweed may contain high concentrations of iodine, and individuals who use these ingredients or supplements may be at risk of overly high iodine intakes. Consumption of kelp- and seaweed-based ingredients has not been reported in Norkost 3 or Ungkost 3, but five 2-year-olds reported use of kelp and seaweed in Småbarnskost 3.

10.2 The scenarios - the iodine intake if household salt and industrial salt used in bread were to be iodized

This section answers question 2 in the terms of reference: What would the iodine intake in the general population and among identified risk groups be if household salt and industrial salt used in bread were to be iodized and if plant-based milks were to be fortified with iodine levels comparable to those in cow's milk? The iodine intakes resulting from the various scenarios should be estimated both with and without the added effect of iodine fortification of plant-based alternatives to dairy products (milk 15 µg/100 g). The estimates should also be considered in the context of the *Salt Strategy 2015* (governmental initiatives to reduce salt consumption).

The scenario estimates for all age groups not using iodine containing supplements are presented in Tables 7.4-3 - 7.4-14.

We have presented 12 scenario tables, three scenarios (household salt alone, salt in bread alone and both household salt and salt in bread) for each iodization level (15, 20, 25 and 50 mg iodine per kg salt). In the text below, we present only the scenarios for iodine added to both household salt and industrial salt used in bread, since the scenarios with iodine only in

household salt or only in industrial salt used in bread do not increase the iodine intakes in the groups at risk of low intakes, sufficiently.

The percentages of the population groups with intakes above the EAR increase with increasing iodization levels, but so do also the percentages with intakes above the ULs for iodine.

The scenarios –adults, 13-, 9- and 4-year-olds, the general population

In Tables 8.2.1.1-1 and 8.2.1.1-2 we have presented how the estimated iodine intakes in the groups at risk of low intakes (women 18-45 years and 13-year-old girls) increase with the increasing iodization level scenarios.

The iodization option yielding the combined lowest proportions of the population below EAR and above UL, is the scenario of adding 15 µg iodine per kg salt to both household salt and salt in bread. At this iodization level, 93-100% of all adults and adolescents have iodine intakes above EAR and the proportion exceeding UL is ≤ 1%.

At this scenario, 94% of women 18-45 years have estimated iodine intakes above EAR. Estimated mean (median) intakes are 176 (166) µg/day, and the estimated iodine intake in the 5th percentile is 97 µg/day.

In the same scenario, 93% of the 13-year-old girls have estimated iodine intakes above EAR. Estimated mean (median) intakes are 132 (122) µg/day and the estimated intake in the 5th percentile is 70 µg/day.

At the scenario of adding 20 µg iodine per kg salt to both household salt and salt in bread, 97% of the women (18-45 years) and 13-year-old girls have estimated intake levels above EAR. The estimated mean intakes are 189 and 145 µg/day in women (18-45 years) and 13-year olds, respectively, and the intakes in the 5th percentiles are 107 and 80 µg/day.

At the scenario of adding 25 µg iodine per kg salt to both household salt and salt in bread, the estimated intake in the 5th percentile has increased to 90 µg/day in the 13-year-old girls.

At the scenario of adding 50 µg iodine per kg salt to both household salt and salt in bread, all age-groups have estimated iodine intakes above the EAR. All the women still have estimated intakes below the UL, however, 1-20% of the men and children are exceeding UL.

The scenario estimates for the different iodization levels in adults including iodine supplements (users only) are presented in Table V-2 in Appendix V.

The scenarios – 2-year-olds, the general population

For 2-year-olds, all scenarios lead to a decrease in the proportion of children expected to be within the acceptable range. While iodization of both household salt and bread lifts the children with low iodine intake over the EAR, a larger part will have intakes exceeding the

UL. At the highest iodization scenarios including iodization of salt in bread (salt+bread50), the proportion of children expected to exceed the UL rises to 63%.

At the scenario of adding 15 µg iodine per kg salt to both household salt and salt in bread, 17-19% of the 2-years-olds have iodine intakes exceeding UL, and the estimated iodine intake in the 95th percentile is 250 and 252 µg/day in girls and boys, respectively. At the scenario of adding 20 µg iodine per kg salt to both household salt and salt in bread, 21-23% of the 2-year-olds exceed UL, and the estimated iodine intake in the 95th percentile is 259 and 263 µg/day in girls and boys, respectively. At the scenario of adding 25 µg iodine per kg salt to both household salt and salt in bread, 25-30% of the 2-year-olds exceed UL, and the estimated iodine intake in the 95th percentile is 271 and 273 µg/day in the girls and boys, respectively. At the scenario of adding 50 µg iodine per kg salt to both household salt and salt in bread, 57-63% of the 2-year-olds exceed UL.

In the bread15 or bread20-scenario, the proportion of 1-year-olds exceeding the UL increases from 18% to 32 or 36%, respectively. In the bread15-scenario, the estimated iodine intake in the 95th percentile of 1-year-olds is 302 µg/day, and in the bread20-scenario, the iodine intake in the 95th percentile of 1-year-olds is 316 µg/day.

The scenarios – other specified risk groups of low and high iodine intakes.

There was no information available from the national dietary surveys to calculate the effect of the different iodization levels on the iodine intakes in the other specified groups at risk of low iodine intakes levels such as e.g. persons with allergy or intolerance to fish, milk or dairy products, vegans, vegetarians and some ethnic minorities. However, as salt consumption is assumed to be correlated with energy intake, the increase in iodine intake with increasing levels of iodized salt may be expected to be similar in these potential risk groups as in the rest of the population, although with large individual variations within the different groups. In addition, we do not have exact data on bread consumption among persons in these specified groups at risk. The variation in bread consumption among persons with allergy or intolerance to fish, milk or dairy products, vegans, vegetarians and some ethnic minorities may be assumed to be fairly similar to the variation in bread consumption in the general population. Consequently, for persons with few iodine sources in the diet (low milk in take), vegans and people with allergy or intolerance), the increase in iodine intake in these potential risk groups may be the same as the increase in the lower percentiles in the scenarios, e.g. the 5th percentiles in the scenarios in Tables 7.4-3 - 7.4-14.

Groups at risk of high iodine intake might be individuals consuming dried kelp or kelp supplements. In pregnant women, an abrupt moderate increase in iodine intake may cause a transient thyroid stunning effect, with a transient inhibition of maternal or fetal thyroid hormone production.

Plant-based alternatives to cow's milk

This section responds to the following in the terms of reference: The iodine intake resulting of the various scenarios should be estimated both with and without the added effect if plant-based alternatives were to be fortified with iodine levels comparable to those in cow's milk i.e. 15 µg per 100 g.

The suggested iodine level in plant-based alternatives to cow's milk corresponds to the concentration in cow's milk. The national dietary surveys have not collected information on use of plant-based milk alternatives. The project group has, due to lack of intake data, assumed that consumption of plant-based milk alternatives replaces consumption of cow's milk, and that consumption of plant-based alternatives have similar individual variations as for cow's milk. The tables presenting iodine exposure in sections 7.3 and 7.4 are therefore applicable for both cow's milk users and users of the plant-based alternatives given that all plant-based alternatives have the same iodine content and bioavailability as cow's milk. Iodization of plant-based alternatives may contribute to increased iodine intake in vegans. Individuals with low consumption of plant-based alternatives will receive only small amounts of iodine from this source, whereas high-consumers will receive larger amounts. The risks related to high iodine intakes from iodized plant-based alternatives are not considered to be any larger than risks related to milk consumption in any age groups.

Effect of potential salt reduction on the scenario estimates for iodine

This section responds to the following in the terms of reference: The iodine intake estimated should also be considered in the context of the *Salt Strategy 2015* (governmental initiatives to reduce salt consumption).

The main goals in the Salt Strategy are 30% relative reduction in mean population intake of salt/sodium within year 2025 and a long-term target of mean salt consumption of 5 g/day. An intermediate objective is to reduce salt in bread to 0.9 g salt per 100 g bread. This corresponds to approximately 18% reduction in salt in bread compared to our scenario calculations.

A 30% reduction in salt consumption would imply a need for approximately 40-45% increased iodization levels to achieve the same levels of daily iodine intake as given in the scenario Tables 7.4-3-7.4-14 for all the age groups (1/(1-0.3) = 1.43). This estimate assumes a uniform 30% reduction, and no consideration is given to whether the salt reduction is unevenly distributed between various food groups. Similarly, a reduction of salt in bread to 0.9 g salt per 100 g bread, would imply a need for approximately 22% increased iodization levels to achieve the same levels of daily iodine intake as given in the scenarios.

10.3 Health effects related to the various iodization levels

This section answers question 3 in the terms of reference: What potential health effects will the various iodization levels have for the general population and the identified risk groups?

We do not have enough dose-response data to evaluate the health effects for the various iodization levels. We have, however, evaluated possible health consequences of iodine intakes related to intakes below EAR and above UL in the various age-/ life stage-groups.

In addition, the systematic literature review on mild to moderate iodine deficiency in relation to neurodevelopment, thyroid function and birth outcomes provides support to this assessment. We have also reviewed the literature on excessive intakes of iodine and re-evaluated the existing UL.

Adequate iodine intake is essential for normal thyroid function. Thyroid hormones are crucial for the foetus and infant by affecting the development of the nervous system, skeletal muscles and lungs. Adequate iodine intake is especially important in women of childbearing age in order to secure optimal thyroid hormone production before pregnancy.

Severe iodine deficiency during foetal life, infancy, or early childhood may lead to permanent intellectual disability. Severe maternal iodine deficiency in pregnancy may also result in miscarriages, preterm delivery, stillbirth, and congenital abnormalities. All these effects are mediated through a lack of thyroid hormones. However, we do not know the prevalence of severe iodine deficiency in Norway.

The recommendations for vitamins and minerals generally aim to secure adequate growth and development and to maintain good health and prevent chronic illnesses. VKM generally assumes that intakes above EAR and below UL are beneficial to health, and that both too low and too high intakes, operationally defined as intakes below EAR and above UL in the current assessment, may entail increased risk of illness.

The recommendations for iodine are set to prevent goiter and to maintain normal thyroid function. Average requirements (AR or EAR) are intake levels that are estimated to meet the requirement of half the healthy individuals in a population.

Both too little and too much iodine can affect thyroid hormone production. Generally, UL is the maximum level of total chronic daily intake judged unlikely to pose any risk of adverse health effects. UL is derived from often sparsely available evidence of toxicity in humans or, if unavailable, in animals, by dividing the lowest-observed-adverse-effect level (LOAEL) by an uncertainty factor (UF). The choice of UF varies with the quality and relevance of the toxicity data, but it usually involves a several-fold safety margin between the intake levels potentially associated with health risks. In the case of iodine, the UL for adults is the maximum daily intake where changes in TSH are unlikely to occur, and the UL for iodine set by SCF in 2002 was based on a LOAEL for TSH alterations and used an uncertainty factor of three, resulting in an UL at 600 µg iodine/day. After reviewing new literature, VKM suggest to maintain this UL. However, a recent dose-response study in young adults showed that elevated TSH (subclinical hypothyroidism) appeared from a total iodine intake of 800 µg/day. Maintaining the UL at 600 µg/day therefore implies a reduction of the uncertainty factor to approximately 1.3, which is considered by the VKM to represent an acceptable safety margin due to a well-designed randomised controlled dose-response study. Furthermore, in the same RCT,

although a small decrease from baseline was observed in the fT3 concentration in the 500–2000-µg iodine from supplements-intervention groups, it remained within the normal range. Similar changing patterns were observed for fT4. It should be noted that in subclinical hypothyroidism, the production of the thyroid hormones T3 and T4 are within the normal range, whether these findings have clinical or developmental consequences is uncertain, but subclinical hypothyroidism may progress to overt hypothyroidism (Cooper and Biondi, 2012).

The actual comparison of estimated iodine intakes with EAR and UL is presented above in sections 10.1 and 10.2.

In addition to a comparison of intakes with the reference values, we performed a systematic literature review to summarise the evidence for effect of mild to moderate iodine deficiency and health outcomes specifically relevant for iodine. Many studies described a negative association between UIC and different adverse neurodevelopmental outcomes. Negative health outcomes of mild to moderate iodine deficiency cannot be excluded, but based on the existing literature and the use of guidelines for grading the evidence, the VKM Panel concludes that there is *limited suggestive* evidence to support that mild to moderate iodine deficiency prenatally or during pregnancy is associated with reduced neurodevelopment in children. The VKM Panel also concludes that there is *limited suggestive* evidence to support that mild to moderate iodine deficiency in schoolchildren is associated with poorer neurodevelopmental outcomes. Limited suggestive means that the evidence is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws but shows a generally consistent direction of effect. After carefully reviewing the articles on thyroid function and birth outcomes, the VKM Panel concludes that there is *limited – no conclusion* evidence to support that mild to moderate iodine deficiency is associated with thyroid dysfunction or has negative effects on birth outcomes. *Limited (no conclusion)* means that the evidence is so limited that no firm conclusion can be made. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (lack of adjustment for known confounders). For a detailed overview of the findings in the included articles, see Tables 5.5-1 and 5.5-2.

10.4 Concluding remarks

Low estimated iodine intakes in adolescents (13-year-olds) and women of childbearing age (18-45 years) i.e. intakes below EAR cannot be sufficiently corrected by the proposed increased iodization levels of salt and/or bread without imposing iodine intakes above UL in other population groups, particularly 1- and 2-year-old children.

Based on the scientific evidence and the data presented in this benefit and risk assessment it cannot be concluded that a specific iodization level benefits all age and gender groups without posing increased risk of harm to others or that the benefits in one population group outweigh the risks in others.

Several studies show that especially adolescents and women of childbearing age have insufficient iodine intakes, which may leave a number of individuals at risk of severe deficiency. There are, to our knowledge no data on the prevalence of severe iodine deficiency in Norway nor data on excessive iodine intakes. In other words, we do not know how many, if any, there are who may have clinical consequences due to inadequate or excessive iodine intakes.

Recommendations for daily intakes of nutrients are set to secure adequate growth, development, maintenance of health, and to reduce the risk of chronic illnesses. Thus, iodine intakes below EAR will decrease the possibilities of achieving the beneficial effects of adequate intake. It must be assumed that population groups with estimated iodine intakes below EAR, especially women of childbearing age and 13-year-olds, will benefit from increased iodine intakes. This will also benefit other groups that, for various reasons, have few iodine-rich sources in their diet, e.g., people who do not eat lean fish or consume milk or other dairy products. The scenarios that seem to raise the iodine intakes in women of childbearing age and 13-year-olds (the groups at highest risk of low intakes) to a sufficient intake level are iodization up to 15 or 20 mg iodine per kg salt, including iodization of salt in bread. Above these iodization levels, no increased benefit would be expected in women of childbearing age and 13-year-olds, whereas several population groups will be at risk of exceeding UL, and especially 1- and 2-year-olds.

The WHO recommends salt as a vehicle for correcting iodine deficiency in a population, followed by a close monitoring of the iodization program (UNICEF, 2018; WHO, 2007). Any increased iodization levels of household salt or salt in bread might lead to excessive intakes that may be associated with negative health effects in certain subgroups. It is therefore important that any increased levels of iodization are to be followed by a monitoring program to surveil both the benefits in the groups at risk of low intakes and the risks in groups with high intakes as recommended by WHO.

11 Data gaps

Iodine status

- Good biomarkers for iodine status: In the absence of a gold standard biomarker for iodine status, UIC is endorsed as the best available biomarker at group level. Due to its dependence on recent iodine and fluid intake, UIC has a high day-to-day variability and is accordingly not a good marker for long-term status. Other biomarkers such as thyroglobulin and breast milk iodine concentrations (BMIC) have been less used and have some of the same limitations as UIC.
- Data on iodine status in all age groups in Norway is lacking: Especially population groups at risk of low or high iodine intakes (e.g. adolescents, women of fertile age and infants and toddlers).
- Prevalence of iodine deficiency and excess in all age groups: We do not have good estimates of the prevalence of the different categories of iodine deficiency and excess in Norway.

Dietary food surveys and iodine intake

- Future dietary surveys should be designed to include participants from special groups at risk of low and high intakes of iodine; e.g. vegetarians, vegans, persons that do not eat milk/milk products and/or fish. Enough participants are needed from these groups to enable estimations of intake that are statistically robust.
- Similar dietary survey methods are needed to be able to compare intake, across age groups. In the age groups 1- and 2-year-olds, more detailed information at a day to day level are needed.
- To get a more precise estimate of iodine intake, brand specific information are needed for foods high in iodine

Dietary reference values

- Estimated average requirements for children and adolescents: The estimated average requirements for children and adolescents are interpolated from adults. This interpolation assumes a certain proportionality between the EAR and body weigh which might not be accurate.
- Updated ULs for all age groups: The UL for adults is well defined, but new evidence might be available after 2002. The values for other age- and life stage groups are also interpolated from the adult estimates.
- The clinical relevance of the thyroid "stunning effect": Some individuals are more sensitive to the "stunning effect" caused by high intakes of iodine. This has been demonstrated in those who have had thyroid disorders and those with poor iodine status.

Iodine intake and health outcomes – associations and dose-response

The knowledge about severe iodine deficiency as a cause of impaired neurodevelopment, thyroid dysfunction and adverse birth outcomes is well established. It is, however, lack of data on at what level of iodine status or iodine intake the various adverse effects occur:

- Consequences of mild to moderate iodine deficiency: Several observational studies suggest that mild to moderate iodine deficiency can result in various health outcomes related to poor thyroid functioning. However, the value of the evidence is limited due to the lack of good biomarkers of iodine status that can be used to define mild to moderate deficiency.
- Limitations in the assessment tools for neurodevelopment: Different aspects of neurodevelopment can be measured in various ways, and there is no consensus on the optimal measure.
- Timing of the exposure: Iodine deficiency, through impaired thyroid functioning, might have different consequences according to the timing and severity of the exposure.
- Reference values for thyroid hormones in different age groups and life stages: The consequences of very low or very high thyroid hormone levels are well described. The extent to which slightly elevated or lower levels of T3 and T4 have consequences in different populations is less certain. In other words, the reference limits for when thyroid function disturbances start to have consequences for human health in various populations is not well defined.
- Dose response studies for iodine intake and thyroid functioning: Iodine excess results in altered thyroid functioning. It is not clear, however, at which level of iodine intake adverse effects occur. Furthermore, it is also not known why the susceptibility to high doses of iodine varies between individuals. Evidence for excessive iodine intakes in children and adults, including during lactation and pregnancy is lacking.
- Health outcomes related to acute high intakes: E.g. kelp and seaweed based products.

Salt consumption

- There is limited information on total salt consumption in children and adults. This can be measured with sodium analyses of repeated 24 h urine in the different age groups.
- There is limited information from representative population studies on the consumption of household salt and the proportion of total salt consumption in children and adults that are from household salt. Household salt consumption is difficult to measure. If this is a priority for future RBA, designated studies with weighing of salt used in the household need to be designed. The number of participants need to be from different age groups, and large enough to be statistically robust.
- There were few analyses of salt content in different categories of bread and bakery products. A larger number of salt analyses in different bread and bakery categories will give more precise intake estimate for iodine.

- For the scenario estimates with iodized salt, we need updated data on the actual salt reduction resulting from the Salt Strategy.

Consumption of plant-based alternatives to cow's milk

- Data on consumption of plant-based alternatives to cow's milk in different population groups are lacking.

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Appendix I - Literature searches

a) Search strategy for health outcomes mild and moderate iodine deficiency

Searches for health outcomes related to mild and moderate iodine deficiency were conducted 4 July 2018 and updated 14 May and 18 November 2019.

#	Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946 to Present
1	Iodine/
2	("iodine" or "iodide").tw,kf.
3	Urine/
4	("urin*" or "status" or "intake*" or "deficiency" or "condition*" or "lack" or "concentration").tw,kf.
5	1 or 2
6	3 or 4
7	5 and 6
8	Goiter/
9	Goiter, endemic/
10	Goiter, nodular/
11	Hypothyroidism/
12	Thyrotropin/
13	exp Thyroid Diseases/
14	Thyroid Hormones/
15	Triiodothyronine/
16	Cognition/
17	Child development/
18	Cognitive dysfunction/
19	Developmental disabilities/
20	Child development deviations/
21	Brain injuries/
22	Neurocognitive disorders/
23	exp Neurodevelopmental disorders/
24	exp Autism Spectrum Disorder/
25	Intelligence/
26	Language Development Disorders/
27	Language Disorders/
28	Academic Performance/
29	Memory, Short-Term/
30	Memory Disorders/
31	Fertility/
32	Abortion, Spontaneous/
33	Birth Weight/
34	Infant, Premature/
35	Reproduction/
36	Pregnancy complications/
37	("goit*" or "idd" or "hypothyroidism?" or "thyroid stimulating hormone?" or "ths" or "thyroid-stimulating hormone?" or "thyroxin" or "triiodothyronine" or liothyronine or "thyrotropin" or "tri iodothyronine" or "tri iodo thyronine" or "triiodo l thyronine" or "lio thyronine" or "T3" or (("Thyroid*" or "thyreoid") adj2 ("function" or "disease?" or "dysfunction?" or "abnorm*" or "anomal*" or "disorder?" or "hormone?" or "agent?"))).tw,kf.

#	Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946 to Present
38	(("cognitive" adj3 ("function" or "decline" or "dysfunction" or "impairment" or "deterioration" or "Deficit*")) or (("child*" or "infant?" or "psychomotor*") adj3 "development*") or (("neurocognitive" or "neurodevelopmental" or "neurological") adj2 ("dysfunction?" or "disorder?" or "impact*")) or ("development*" adj3 ("deviation?" or "disorder?" or "disabili*")) or ("brain" adj2 ("damage?" or "injur*" or "development" or "disorder?")) or (("neurological" or "mental" or "intellectual" or "learning" or "memory") adj3 ("disorder?" or "retardation" or "disabilit*" or "disturbance?" or "impairment?" or "defianc*" or "short-term")) or "idiocy" or "IQ" or "intelligence deficit" or (("mental" or "intellectual") adj2 ("development" or "deficien*")) or "autism" or "autistic" or "kanner*" or "Asperger*" or "attention deficit" or "h#peractiv*" or "ADDH" or "ADHD").tw,kf.
39	("language" or "speech" or (("academic" or "school" or "educational") adj3 ("performance?" or "underachievement" or "adjustment" or "behavior*" or "behaviour*" or "score?")) or "fertility" or "fecund*" or ("abortion?" adj2 "spontaneous") or "miscarriage?" or (("birth" or "neonatal" or "newborn") adj2 "weight?") or "preterm" or "premature*" or "reproducti*" or "pregnancy complication?").tw,kf.
40	or/8-39
41	7 and 40

#	Database: Embase 1974 to dates for searches
1	Iodine/
2	("iodine" or "iodide").tw,kw.
3	urine/
4	("urin*" or "status" or "intake*" or "deficiency" or "condition*" or "lack" or "concentration").tw,kw.
5	1 or 2
6	3 or 4
7	5 and 6
8	iodine deficiency/
9	7 or 8
10	goiter/ or endemic goiter/ or nodular goiter/
11	hypothyroidism/
12	thyroid function/
13	thyroid disease/
14	thyroid hormone/
15	liothyronine/
16	Cognition/
17	Child development/
18	Cognitive dysfunction/
19	Developmental disorder/
20	cognitive development/
21	brain injury/
22	nervous system malformation/
23	intellectual impairment/
24	nervous system development/
25	attention deficit disorder/
26	brain development/
27	Intellectual disability/
28	Learning disorders/
29	working memory/
30	literacy/
31	exp Autism/
32	Asperger syndrome/
33	Intelligence/
34	developmental language disorder/
35	language disability/
36	academic achievement/
37	fertility/
38	spontaneous abortion/
39	birth weight/
40	prematurity/
41	pregnancy complication/
42	("goit*" or "idd" or "hypothyroidism?" or "thyroid stimulating hormone?" or "ths" or "thyroid-stimulating hormone?" or "thyroxin" or "triiodothyronine" or liothyronine or "thyrotropin" or "tri iodothyronine" or "tri iodo thyronine" or "triiodo l thyronine" or "lio thyronine" or "T3" or (("Thyroid*" or "thyreoid") adj2 ("function" or "disease?" or "dysfunction?" or "abnorm*" or "anomal*" or "disorder?" or "hormone?" or "agent?"))).tw,kw.
43	(("cognitive" adj3 ("function" or "decline" or "dysfunction" or "impairment" or "deterioration" or "Deficit*")) or (("child*" or "infant?" or "psychomotor*") adj3 "development*") or (("neurocognitive" or "neurodevelopmental" or "neurological") adj2 ("dysfunction?" or "disorder?" or "impact*")) or ("development*" adj3 ("deviation?" or "disorder?" or "disabili*")) or ("brain" adj2 ("damage?" or "injur*" or "development" or "disorder?")) or (("neurological" or "mental" or "intellectual" or "learning" or "memory") adj3 ("disorder?" or "retardation" or "disabilit*" or "disturbance?" or "impairment?" or "defianc*" or "short-term")) or "idiocy" or "IQ" or "intelligence deficit" or (("mental" or "intellectual") adj2 ("development" or "deficien*")) or "autism" or "autistic" or "kanner*" or "Asperger*" or "attention deficit" or "h#peractiv*" or "ADDH" or "ADHD").tw,kw.

#	Database: Embase 1974 to dates for searches
44	("language" or "speech" or (("academic" or "school" or "educational") adj3 ("performance?" or "underachievement" or "adjustment" or "behavior*" or "behaviour*" or "score?")) or "fertility" or "fecund*" or ("abortion?" adj2 "spontaneous") or "miscarriage?" or (("birth" or "neonatal" or "newborn") adj2 "weight?") or "preterm" or "premature*" or "reproducti*" or "pregnancy complication?").tw,kw.
45	reproduction/
46	or/10-45
47	9 and 46
48	limit 47 to (conference abstracts or embase)

	Database: PsycINFO 1806 to Year and week for searches
1	("iodine" or "iodide").tw.
2	Urine/
3	("urine*" or "status" or "intake*" or "deficiency" or "condition*" or "lack" or "concentration").tw.
4	2 or 3
5	1 and 4
6	exp Thyroid Disorders/
7	Thyrotropin/
8	thyroid hormones/ or triiodothyronine/
9	Cognition/
10	exp Cognitive Development/
11	Childhood Development/
12	Cognitive Impairment/
13	Developmental Disabilities/
14	Brain Damage/
15	Neurocognition/
16	Neurodevelopmental Disorders/
17	Autism Spectrum Disorders/
18	Intelligence/
19	Language Development/
20	Language Disorders/
21	Academic Achievement/
22	Short Term Memory/
23	Fertility/
24	Spontaneous Abortion/
25	Birth Weight/
26	Premature Birth/
27	("goit*" or "idd" or "hypothyroidism?" or "thyroid stimulating hormone?" or "ths" or "thyroid-stimulating hormone?" or "thyroxin" or "triiodothyronine" or liothyronine or "thyrotropin" or "tri iodothyronine" or "tri iodo thyronine" or "triiodo l thyronine" or "lio thyronine" or "T3" or (("Thyroid*" or "thyreoid") adj2 ("function" or "disease?" or "dysfunction?" or "abnorm*" or "anomal*" or "disorder?" or "hormone?" or "agent?"))).tw.
28	(("cognitive" adj3 ("function" or "decline" or "dysfunction" or "impairment" or "deterioration" or "Deficit*")) or (("child*" or "infant?" or "psychomotor*") adj3 "development*") or (("neurocognitive" or "neurodevelopmental" or "neurological") adj2 ("dysfunction?" or "disorder?" or "impact*")) or ("development*" adj3 ("deviation?" or "disorder?" or "disabili*")) or ("brain" adj2 ("damage?" or "injur*" or "development" or "disorder?")) or (("neurological" or "mental" or "intellectual" or "learning" or "memory") adj3 ("disorder?" or "retardation" or "disabilit*" or "disturbance?" or "impairment?" or "defianc*" or "short-term")) or "idiocy" or "IQ" or "intelligence deficit" or (("mental" or "intellectual") adj2 ("development" or "deficien*")) or "autism" or "autistic" or "kanner*" or "Asperger*" or "attention deficit" or "h#peractiv*" or "ADDH" or "ADHD").tw.
29	("language" or "speech" or (("academic" or "school" or "educational") adj3 ("performance?" or "underachievement" or "adjustment" or "behavior*" or "behaviour*" or "score?")) or "fertility" or "fecund*" or ("abortion?" adj2 "spontaneous") or "miscarriage?" or (("birth" or "neonatal" or "newborn") adj2 "weight?") or "preterm" or "premature*" or "reproducti*" or "pregnancy complication?").tw.
30	or/6-29
31	5 and 30

Database: Web of Science. Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI

((TOPIC: ("iodine" OR "iodide") AND TOPIC: ("urine*" OR "status") OR "intake*") OR "deficiency") OR "condition*") OR "lack") OR "concentration")) AND TOPIC: ("goit*" OR "idd") OR "hypothyroidism?") OR "thyroid stimulating hormone?") OR "ths") OR "thyroid-stimulating hormone?") OR "thyroxin") OR "triiodothyronine") OR liothyronine) OR "thyrotropin") OR "tri iodothyronine") OR "tri iodo thyronine") OR "triiodo l thyronine") OR "lio thyronine") OR "T3") OR (("Thyroid*" OR "thyrsoid") NEAR (((((("function" OR "disease?") OR "dysfunction?") OR "abnorm*") OR "anomal*") OR "disorder?") OR "hormone?") OR "agent?"))) OR ("cognitive" NEAR (((((("function" OR "decline") OR "dysfunction") OR "impairment") OR "deterioration") OR "Deficit*"))) OR ((("child*" OR "infant?") OR "psychomotor*") NEAR "development*")) OR ((("neurocognitive" OR "neurodevelopmental") OR "neurological") NEAR (("dysfunction?" OR "disorder?") OR "impact*"))) OR ("development*" NEAR (("deviation?" OR "disorder?") OR "disabili*"))) OR ("brain" NEAR ((("damage?" OR "injur*") OR "development") OR "disorder?"))) OR (((((("neurological" OR "mental") OR "intellectual") OR "learning") OR "memory") NEAR ((((((("disorder?" OR "retardation") OR "disabilit*") OR "disturbance?") OR "impairment?") OR "defianc*") OR "short-term"))) OR "idiocy") OR "IQ") OR "intelligence deficit") OR (("mental" OR "intellectual") NEAR ("development" OR "deficien*"))) OR "autism") OR "autistic") OR "kanner*") OR "Asperger*") OR "attention deficit") OR "h#peractiv*") OR "adds") OR "ADHD") OR "language") OR "speech") OR ((("academic" OR "school") OR "educational") NEAR (((((("performance?" OR "underachievement") OR "adjustment") OR "behavior*") OR "behaviour*") OR "score?"))) OR "fertility") OR "fecund*") OR ("abortion?" NEAR "spontaneous")) OR "miscarriage?") OR ((("birth" OR "neonatal") OR "newborn") NEAR "weight?")) OR "preterm") OR "premature*") OR "reproducti*") OR "pregnancy complication?"))

b) Search strategy for single studies excessive iodine

#	Database: Embase <1974 to 2017 November 22 and updated 14 May and 18 November 2019>, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946 to Present>
1	iodine*.ti.
2	high intak*.ti.
3	high iodine intake*.ti.
4	high iodine concentrat*.ti.
5	excess*.ti.
6	hypothyroidism*.tw.
7	thyroid volume.tw.
8	safe upper*.tw.
9	tolerable upper*.tw.
10	thyrotoxic*.tw.
11	iodized salt.tw.
12	iodised salt.tw.
13	seaweed.tw.
14	iodine-induc*.tw.
15	iodine induc*.tw.
16	risk*.ti.
17	safety*.ti.
18	side-effect*.ti,ab.
19	side effect*.ti,ab.
20	harm*.tw.
21	contraindicat*.ti,ab.
22	contra-indicat*.ti,ab.
23	toxic*.tw.
24	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25	1 and 24
26	limit 25 to yr=”2000 -Current”
27	remove duplicates from 26

c) Search strategy for meta-analyses and systematic reviews excessive iodine

Database: Embase <1974 to 2017 September 21>, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946 to Present>

1. "iodin*".m_titl. (47983)
2. limit 1 to human (28053)
3. limit 2 to yr="1999 -Current" (13592)
4. limit 3 to meta analysis (110)

Publication selection and data extraction

The search terms for defining health outcomes were predefined and based on knowledge about consequences of mild and moderate iodine deficiency (see chapter 3).

The literature searches were performed in the MEDLINE, Embase, Web of Science and PsycINFO databases in July 2018.

Updated search was conducted May 2019 covering 2018 and until 14 May 2019 and November, covering 14 May until 18 November 2019. The librarian had some difficulties in limiting the May update to specific dates, weeks or months, and consequently there was an overlap between these searches.

Publication selection and data extraction for articles relevant for iodine deficiency

The July 2018 search resulted in 13 399 records after automatical and manual duplicate removal. It should however be noted that due to the vast number of articles, a large number of duplicates remained. The number of original records in this search is therefore lower than 13 399. The May 2019 search resulted in 899 records, and the last update in November 2019 resulted in 622 records. Both the updated searches contained articles that were also found in the previous search. Consequently, the number of articles could not be summarised.

The titles and/or abstract of every record retrieved were screened independently in Rayyan QCRI by two reviewers to determine which studies required further assessment. Full text articles were retrieved when the information given in the titles and/or abstracts seemed to fulfil the inclusion criteria. If one of the two reviewers included the article, the paper was retrieved in full text. When there was any doubt regarding these criteria from screening the titles and abstracts, the full article was retrieved for clarification. Disagreements were resolved by discussion.

The criteria for inclusion were studies investigating mild or moderate iodine deficiency in combination with a predefined health outcome within the categories: thyroid function, neurodevelopment, and fertility and birth outcomes. The study types for inclusion in this opinion were human randomised controlled trials, prospective cohort studies presenting data for iodine intake or status in at least one subgroup, case-control studies and cross-sectional studies. An overview of the inclusion and exclusion criteria for studies with mild to moderate iodine deficiency is given in Table I-1.

Table I-1 Inclusion and exclusion criteria for publication selection iodine deficiency in this opinion.

Criteria for inclusion	• Studies investigating iodine status (mild or moderate deficiency) in relation to one or more health outcomes • RCTs, cohorts, cross-sectional and case-control studies
Criteria for exclusion	• Studies investigating iodine status or iodine intake without any relation to specific health outcomes • Studies in populations with severe iodine deficiency • Studies including other vitamins or minerals than iodine (if the effect from various nutrients could not be separated from each other) • Studies with iodine containing drugs/medications including iodine containing contrast medium • Studies with radioactive iodine • Studies investigating thyroid status and health outcomes if the thyroid status is not related to iodine status, e.g. studies investigating environmental contaminants • Studies investigating excessive iodine • Reviews and case histories • Animal model studies • *In vitro*-studies

Studies on iodine deficiency fulfilling the inclusion criteria were obtained and evaluated in full text by two reviewers.

To assess the relevance and quality of included studies a three-category (A-B-C) rating system based on the NNR5 AMSTAR Quality Assessment Tool (QAT) was applied (NNR5 working group, 2011; Shea et al., 2007), slightly modified for our purposes. By using QAT, the studies were rated according to study characteristics presented in the published papers. The rating system included questions for evaluating several aspects of a study, e.g. study design, population characteristics, assessment of dietary intervention, assessment of outcome, confounding factors, methods, results etc. Only studies categorised as A or B are included in the results. Studies categorised as A or B are listed in Appendix IIa. Each study with A or B rating has been summarised in a summary table (Appendix III) and are described in chapter 5.4. Studies categorised as C are listed in Appendix IIb were also the most common reasons for category C are mentioned.

The systematic literature searches on mild and moderate iodine deficiency resulted in 131 studies which were rated for quality (A-B-C). Of these, 1 study was categorised as A, while 35 studies qualified for category B, and 95 category C. The category C-studies were not considered further.

Publication selection and data extraction for articles relevant for iodine excess

Literature searches for studies investigating health outcomes related to excessive iodine intakes were performed in MEDLINE and EMBASE and aimed at retrieving publications on adverse effects caused by high intakes of iodine published after 1999 (meta-analysis and systematic reviews) or 2000 (original research articles). Both databases were searched to ensure comprehensive study retrieval. The literature search for meta-analysis and systematic reviews was conducted on 21 September 2017, and the search for original research articles was conducted on 23 November 2017. Updated search was conducted May 2019 covering 2017 and until 14 May 2019 and November 2019 covering 14 May and until 18 November 2019. Both the updated searches contained articles that were also found in the previous search. Consequently, the number of articles could not be summarised.

The titles and/or abstract of every record retrieved were screened independently by two reviewers to determine which studies required further assessment. The strategies for the searches are outlined in Appendix Ic.

Initially, to get an overview of the literature and relevant search terms, a literature search for meta-analysis and systematic reviews addressing health outcomes related to excessive iodine intakes was conducted. The literature search for excessive iodine intakes for this report aimed at retrieving new literature after year 2000 to re-evaluate the existing ULs. The literature search for single studies November 2017 identified 2919 articles, and the updated searches identified 466 articles in May 2019 and 234 articles in November 2019. Both human and animal studies were included in the search strategy, it was however decided not to include animal studies as human and animal iodine metabolism and thyroid hormone production may be difficult to compare. In the primary screening, titles and abstracts of all unique publications retrieved were independently screened against the inclusion criteria.

An overview of the inclusion and exclusion criteria for studies with excessive iodine intakes is given in Table I-2.

Table I-2 Inclusion and exclusion criteria for publication selection excessive iodine in this opinion.

Criteria for inclusion	• Chronic excess iodine exposure is addressed • Adverse effects from iodine are addressed • Route of exposure for humans is oral • Human studies are performed in apparently healthy individuals or patient groups assumed to have normal iodine absorption and metabolism
Criteria for exclusion	• In vitro studies • Animal studies • Cross-sectional studies unless no other evidence is available

Titles and abstracts that did not fulfil the inclusion criteria were excluded from further screening. The primary screening was performed by two persons.

The papers that passed the primary screening were reviewed in full text by one project member.

In the search aimed at retrieving original research articles, the primary screening of titles and abstracts resulted in 138 full-text articles fulfilling the inclusion criteria. In addition, 2 publications from manual search of relevant reference lists were identified and reviewed. From these 140 papers, 135 were not considered relevant for the purpose of assessing risk related to excessive iodine and evaluation of UL because of lack of dose-response analysis or focus on food survey methods or pathology, and not health effects. Thus, in total, 5 studies were found relevant and included for evaluation of existing ULs in this opinion.

Appendix II – List of papers categorised as A, B or C

a) List of papers categorised as A or B

The following 36 studies were categorised as A or B in accordance with the Quality Assessment Tool (QAT) tables adapted for variable study designs in A guide for conducting Systematic Literature Reviews for the 5th edition of the Nordic Nutrition Recommendations. Manuals for the QAT-tables for the various study designs are presented in Appendix VI.

Data from all A and B papers are extracted in Summary Tables 1-36 in Appendix III.

ST nr	Reference list for papers categorised as A or B	Category
1	Abel M.H., Brandlistuen R.E., Caspersen I.H., Aase H., Torheim L.E., Meltzer H.M., Brantsaeter A.L. (2019) Language delay and poorer school performance in children of mothers with inadequate iodine intake in pregnancy: results from follow-up at 8 years in the Norwegian Mother and Child Cohort Study. European Journal of Nutrition 12:12.	B
2	Abel M.H., Korevaar T.I.M., Erlund I., Villanger G.D., Caspersen I.H., Arohonka P., Alexander J., Meltzer H.M., Brantsaeter A.L. (2018) Iodine Intake is Associated with Thyroid Function in Mild to Moderately Iodine Deficient Pregnant Women. Thyroid 28:1359-1371. DOI:	B
3	Abel M.H., Caspersen I.H., Meltzer H.M., Haugen M., Brandlistuen R.E., Aase H., Alexander J., Torheim L.E., Brantsaeter A.L. (2017a) Suboptimal Maternal Iodine Intake Is Associated with Impaired Child Neurodevelopment at 3 Years of Age in the Norwegian Mother and Child Cohort Study. Journal of Nutrition 147:1314-1324.	B
4	Abel M.H., Ystrom E., Caspersen I.H., Meltzer H.M., Aase H., Torheim L.E., Askeland R.B., Reichborn-Kjennerud T., Brantsaeter A.L. (2017b) Maternal Iodine Intake and Offspring Attention-Deficit/Hyperactivity Disorder: Results from a Large Prospective Cohort Study. Nutrients 9:13.	B
5	Alvarez-Pedrerol M., Guxens M., Mendez M., Canet Y., Martorell R., Espada M., Plana E., Rebagliato M., Sunyer J. (2009) Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring. European Journal of Endocrinology 160:423-9.	B
6	Bath S.C., Steer C.D., Golding J., Emmett P., Rayman M.P. (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet 382:331-7.	B
7	Charoenratana C., Leelapat P., Traisrisilp K., Tongsong T. (2016) Maternal iodine insufficiency and adverse pregnancy outcomes. Maternal & Child Nutrition 12:680-7.	B

ST nr	Reference list for papers categorised as A or B	Category
8	Chen Y., Chen W., Du C., Fan L., Wang W., Gao M., Zhang Y., Cui T., Hao Y., Pearce E.N., Wang C., Zhang W. (2018) Iodine Nutrition and Thyroid Function in Pregnant Women Exposed to Different Iodine Sources. Biological Trace Element Research.	B
9	Fan L.L., Tan L., Chen Y.T., Du C., Zhu M., Wang K.L., Wei H.Y., Wang W., Gao M., Zhang Y.X., Cui T.K., Chen W., Shen J., Zhang W.Q. (2018) Investigation on the factors that influence the prevalence of thyroid nodules in adults in Tianjin, China. Journal of Trace Elements in Medicine and Biology 50:537-542.	B
10	Ghassabian A., Steenweg-de Graaff J., Peeters R.P., Ross H.A., Jaddoe V.W., Hofman A., Verhulst F.C., White T., Tiemeier H. (2014) Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area. Erratum appears in BMJ Open. 2017 Feb 8;7(2).	B
11	Gordon R.C., Rose M.C., Skeaff S.A., Gray A.R., Morgan K.M., Ruffman T. (2009) Iodine supplementation improves cognition in mildly iodine-deficient children. American Journal of Clinical Nutrition 90:1264-71.	B
12	Gowachirapant S., Jaiswal N., Melse-Boonstra A., Galetti V., Stinca S., Mackenzie I., Thomas S., Thomas T., Winichagoo P., Srinivasan K., Zimmermann M.B. (2017) Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes & Endocrinology 5:853-863.	B
13	Hynes K.L., Otahal P., Burgess J.R., Oddy W.H., Hay I. (2017) Reduced Educational Outcomes Persist into Adolescence Following Mild Iodine Deficiency in Utero, Despite Adequacy in Childhood: 15-Year Follow-Up of the Gestational Iodine Cohort Investigating Auditory Processing Speed and Working Memory. Nutrients 9:13.	B
14	Hynes K.L., Otahal P., Hay I., Burgess J.R. (2013) Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. Journal of Clinical Endocrinology & Metabolism 98:1954-62.	B
15	Krejbjerg A., Bjergved L., Pedersen I.B., Carle A., Knudsen N., Perrild H., Ovesen L., Rasmussen L.B., Laurberg P. (2015) Serum thyroglobulin before and after iodization of salt: an 11-year DanThyr follow-up study. European Journal of Endocrinology 173:573-81.	B
16	Levie D., Derakhshan A., Shu H., Broeren M.A.C., de Poortere R.A., Peeters R.P., Bornehag C.G., Demeneix B., Korevaar T.I.M. (2019) The Association of Maternal Iodine Status in Early Pregnancy with Thyroid Function in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy Study. Thyroid 29:1660-1668.	B

ST nr	Reference list for papers categorised as A or B	Category
17	Markhus M.W., Dahl L., Moe V., Abel M.H., Brantsaeter A.L., Oyen J., Meltzer H.M., Stormark K.M., Graff I.E., Smith L., Kjellevold M. (2018) Maternal Iodine Status is Associated with Offspring Language Skills in Infancy and Toddlerhood. Nutrients 10.	B
18	Mills J.L., Ali M., Louis G.M.B., Kannan K., Weck J., Wan Y.J., Maisog J., Giannakou A., Sundaram R. (2019) Pregnancy Loss and Iodine Status: The LIFE Prospective Cohort Study. Nutrients 11.	B
19	Mills J.L., Buck Louis G.M., Kannan K., Weck J., Wan Y., Maisog J., Giannakou A., Wu Q., Sundaram R. (2018) Delayed conception in women with low-urinary iodine concentrations: a population-based prospective cohort study. Human Reproduction 11:11.	B
20	Moreno-Reyes R., Glinoer D., Van Oyen H., Vandevijvere S. (2013) High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. Journal of Clinical Endocrinology & Metabolism 98:3694-701.	B
21	Murcia M., Espada M., Julvez J., Llop S., Lopez-Espinosa M.J., Vioque J., Basterrechea M., Riano I., Gonzalez L., Alvarez-Pedrerol M., Tardon A., Ibarluzea J., Rebagliato M. (2018) Iodine intake from supplements and diet during pregnancy and child cognitive and motor development: the INMA Mother and Child Cohort Study. Journal of Epidemiology & Community Health 72:216-222.	B
22	Murcia M., Rebagliato M., Iniguez C., Lopez-Espinosa M.J., Estarlich M., Plaza B., Barona-Vilar C., Espada M., Vioque J., Ballester F. (2011) Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. American Journal of Epidemiology 173:804-12.	B
23	Pedersen K.M., Laurberg P., Iversen E., Knudsen P.R., Gregersen H.E., Rasmussen O.S., Larsen K.R., Eriksen G.M., Johannesen P.L. (1993) Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. Journal of Clinical Endocrinology & Metabolism 77:1078-83.	B
24	Rasmussen L.B., Ovesen L., Bulow I., Jorgensen T., Knudsen N., Laurberg P., Perrild H. (2002) Relations between various measures of iodine intake and thyroid volume, thyroid nodularity, and serum thyroglobulin. American Journal of Clinical Nutrition 76:1069-76.	B
25	Rebagliato M., Murcia M., Alvarez-Pedrerol M., Espada M., Fernandez-Somoano A., Lertxundi N., Navarrete-Munoz E.M., Forns J., Aranbarri A., Llop S., Julvez J., Tardon A., Ballester F. (2013) Iodine Supplementation During Pregnancy and Infant Neuropsychological Development INMA Mother and Child Cohort Study. American Journal of Epidemiology 177:944-953.	B
26	Rebagliato M., Murcia M., Espada M., Alvarez-Pedrerol M., Bolumar F., Vioque J., Basterrechea M., Blarduni E., Ramon R., Guxens M., Foradada C.M., Ballester F., Ibarluzea J., Sunyer J. (2010) Iodine intake and maternal thyroid function during pregnancy. Epidemiology 21:62-9.	B

ST nr	Reference list for papers categorised as A or B	Category
27	Robinson S.M., Crozier S.R., Miles E.A., Gale C.R., Calder P.C., Cooper C., Inskip H.M., Godfrey K.M. (2018) Preconception Maternal Iodine Status Is Positively Associated with IQ but Not with Measures of Executive Function in Childhood. Journal of Nutrition 148:959-966.	B
28	Skeaff S.A., Thomson C.D., Wilson N., Parnell W.R. (2012) A comprehensive assessment of urinary iodine concentration and thyroid hormones in New Zealand schoolchildren: a cross-sectional study. Nutrition Journal 11:31.	B
29	Snart C.J.P., Keeble C., Taylor E., Cade J.E., Stewart P.M., Zimmermann M., Reid S., Threapleton D.E., Poston L., Myers J.E., Simpson N.A.B., Greenwood D.C., Hardie L.J. (2019) Maternal Iodine Status and Associations with Birth Outcomes in Three Major Cities in the United Kingdom. Nutrients 11.	B
30	Sun J., Teng D., Li C., Peng S., Mao J., Wang W., Xie X., Fan C., Li C., Meng T., Zhang S., Du J., Gao Z., Shan Z., Teng W. (2019) Association between iodine intake and thyroid autoantibodies: a cross-sectional study of 7073 early pregnant women in an iodine-adequate region. J Endocrinol Invest. DOI: 10.1007/s40618-019-01070-1.	B
31	Thomson C.D., Campbell J.M., Miller J., Skeaff S.A., Livingstone V. (2009) Selenium and iodine supplementation: effect on thyroid function of older New Zealanders. American Journal of Clinical Nutrition 90:1038-46.	B
32	Thomson C.D., Woodruffe S., Colls A.J., Joseph J., Doyle T.C. (2001) Urinary iodine and thyroid status of New Zealand residents. European Journal of Clinical Nutrition 55:387-92.	A
33	Torlinska B., Bath S.C., Janjua A., Boelaert K., Chan S.Y. (2018) Iodine Status during Pregnancy in a Region of Mild-to-Moderate Iodine Deficiency is not Associated with Adverse Obstetric Outcomes; Results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Nutrients 10:01.	B
34	Wang B., He W.W., Li Q., Jia X., Yao Q.M., Song R.H., Qin Q., Zhang J.A. (2019) U-shaped relationship between iodine status and thyroid autoimmunity risk in adults. European Journal of Endocrinology 181:255-266.	B
35	Zhou S.J., Condo D., Ryan P., Skeaff S.A., Howell S., Anderson P.J., McPhee A.J., Makrides M. (2019) Maternal iodine intake in pregnancy and childhood neurodevelopment at 18 months. Journal of Paediatrics and Child Health 55 (Supplement 1):55.	B
36	Zimmermann M.B., Connolly K., Bozo M., Bridson J., Rohner F., Grimci L. (2006) Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study. American Journal of Clinical Nutrition 83:108-14.	B

b) List of studies categorised as C

The following 95 studies were categorised as C in accordance with the Quality Assessment Tool (QAT) tables adapted for variable study designs in *A guide for conducting Systematic Literature Reviews* for the 5th edition of the Nordic Nutrition Recommendations. Manuals for the QAT-tables for the various study designs are presented in Appendix VI. Most of these articles were categorised as C because they provided inadequate statistical analysis for our purpose or was not designed to test our research hypothesis.

Reference list for articles categorised as C
Aghini Lombardi F., Pinchera A., Antonangeli L., Rago T., Chiovato L., Bargagna S., Bertucelli B., Ferretti G., Sbrana B., Marcheschi M., Vitti P. (1995) Mild iodine deficiency during fetal/neonatal life and neuropsychological impairment in Tuscany. Journal of Endocrinological Investigation 18:57-62.
Bienertova-Vasku J., Grulichova M., Mikes O., Zlamal F., Prusa T., Pohorala A., Andryskova L., Pikhart H. (2018) Estimated dietary iodine intake as a predictor of placental size: Evidence from the ELSPAC study. Nutrition and Metabolism 15 (1) (no pagination).
Blazewicz A., Makarewicz A., Korona-Glowniak I., Dolliver W., Kocjan R. (2016) Iodine in autism spectrum disorders. Journal of Trace Elements in Medicine & Biology 34:32-7.
Blumenthal N., Byth K., Eastman C.J. (2012) Iodine Intake and Thyroid Function in Pregnant Women in a Private Clinical Practice in Northwestern Sydney before Mandatory Fortification of Bread with Iodised Salt. Journal of Thyroid Research 2012:798963.
Brucker-Davis F., Ferrari P., Gal J., Berthier F., Fenichel P., Hieronimus S. (2012) Iodine status has no impact on thyroid function in early healthy pregnancy. Journal of Thyroid Research 2012:168764.
Caron P., Hoff M., Bazzi S., Dufor A., Faure G., Ghandour I., Lauzu P., Lucas Y., Maraval D., Mignot F., Ressigeac P., Vertongen F., Grange V. (1997) Urinary iodine excretion during normal pregnancy in healthy women living in the southwest of France: correlation with maternal thyroid parameters. Thyroid 7:749-54.
Casey B. (2017) Impact of iodine status in women with subclinical hypothyroidism or hypothyroxinemia on child neurodevelopment. American Journal of Obstetrics and Gynecology 216:S436-S437.
Censi S., Watutantrige-Fernando S., Groccia G., Manso J., Plebani M., Faggian D., Mion M.M., Venturini R., Andrisani A., Casaro A., Vita P., Avogadro A., Camilot M., Scaroni C., Bertazza L., Barollo S., Mian C. (2019) The Effects of Iodine Supplementation in Pregnancy on Iodine Status, Thyroglobulin Levels and Thyroid Function Parameters: Results from a Randomized Controlled Clinical Trial in a Mild-to-Moderate Iodine Deficiency Area. Nutrients 11.
Chan S.S.Y., Hams G., Wiley V., Wilcken B., McElduff A. (2003) Postpartum maternal iodine status and the relationship to neonatal thyroid function. Thyroid 13:873-876.
Eltom A., Elnagar B., Elbagir M., Gebre-Medhin M. (2000) Thyroglobulin in serum as an indicator of iodine status during pregnancy. Scandinavian Journal of Clinical & Laboratory Investigation 60:1-7.

Reference list for articles categorised as C
Etemadi A., Amouzegar A., Mehran L., Tohidi M., Azizi F., Moradi K., Delshad H. (2019) Isolated hypothyroxinemia in Iranian pregnant women, the role of iodine deficiency; a population based cross-sectional study. Thyroid. DOI: 10.1089/thy.2019.0047.
Farebrother J., Zimmermann M.B., Assey V., Castro M.C., Cherkaoui M., Fingerhut R., Jia Q., Jukic T., Makokha A., San Luis T.O., Wegmuller R., Andersson M. (2019b) Thyroglobulin Is Markedly Elevated in 6- to 24-Month-Old Infants at Both Low and High Iodine Intakes and Suggests a Narrow Optimal Iodine Intake Range. Thyroid 29:268-277.
Gebreegziabher T., Woltamo T., Thomas D.G., Kennedy T.S., Stoecker B.J. (2019) Iodine supplementation of lactating women and assessment of infant visual information processing and maternal and infant thyroid function: A randomized trial. PLoS One 14:e0223348.
Gerasimova L.I., Denisov M.S., Samoilova A.V., Gunin A.G., Denisova T.G. (2016) Role of iodine deficiency in the development of menstrual disorders in young females. Sovremennye Tehnologii v Medicine 8:104-106.
Gulaboglu M., Borekci B., Delibas I. (2010) Urine iodine levels in preeclamptic and normal pregnant women. Biological Trace Element Research 136:249-57.
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Appendix III – Summary Tables for papers categorised as A or B

Summary Tables 1-36

ST1 Summary table iodine

Reference details, first author, year, country	**Abel et al. (2019) Language delay and poorer school performance in children of mothers with inadequate iodine intake in pregnancy: results from follow-up at 8 years in the Norwegian Mother and Child Cohort Study, Norway**
Study design	Prospective cohort study
Population, subjects	This study is based on the Norwegian Mother and Child Cohort study (MoBa) in which women pregnant in their first trimester were recruited from all over Norway during the years 1999-2008. More than 99% of participants are of Caucasian origin. Pregnancy and birth records from the Medical Birth Registry of Norway are linked to the MoBa database. The women consented to participation in 41% of the pregnancies and the cohort now includes 114, 500 children, 95,200 mothers and 75,200 fathers. Exclusion criteria in the present study included; twins or triplets, maternal report of thyroid medication in pregnancy, missing food frequency questionnaire (FFQ), energy intake <4.5 or >20 MJ, or >3 blank FFQ pages and missing data on outcomes at child age 8 years.
Outcome measures	The questions about language and learning in the MoBa questionnaire at child 8 years was designed for the Language and Learning Sub-study (Språk og Læring Studien - SOL) within MoBa. The aim SOL is to provide the best possible knowledge base for the understanding of causes and developmental trajectories of language difficulties. Specific instruments answered by the mothers included *Child language difficulties from the Children's communication checklist-Short (CCC-S), *Reading and writing: 3 items selected from sub-scale of Vineland Adaptive Behaviour Scale-II, *Reading and mathematics: *Mandatory mapping tests (based on information from teachers on how the child had performed, and *whether the child received Special education due to language or learning difficulties (extra educational services).
Time between baseline exposure and outcome assessment	Eight years

Reference details, first author, year, country	**Abel et al. (2019) Language delay and poorer school performance in children of mothers with inadequate iodine intake in pregnancy: results from follow-up at 8 years in the Norwegian Mother and Child Cohort Study, Norway**
Exposure assessment/ Dietary assessment method	Maternal iodine intake was measured by 1) a food frequency questionnaire (FFQ) to capture dietary habits and use of dietary supplements during the first half of pregnancy, and 2) as iodine concentration in a spot urine sample (UIC) measured in gestational week 18.
No. of subjects analysed	The study sample for analysis includes 39,471 mother-child pairs enrolled in 2002-08.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	This study was based on information of maternal iodine intake from the first half of pregnancy and information of child language and learning at age 8 years. Based on the total number of participants in the MoBa-study the number of participants included in the present study (n=39,471) yielded a response rate was 35%.
Results	The calculated median iodine intake from food was 122 µg/day (IQR: 89-161 µg/day), and median UIC in gestational week 18 was 67 µg/L (n=2001). The children had adequate iodine status with median UIC of 110 µg/L in a subsample of 279 children at age 8 years). For all outcomes, maternal iodine intake was modelled flexibly (continuous variable). The curve-shaped associations indicated that habitual iodine intakes from food lower than approximately 150 µg/day were associated poorer outcomes. Point estimates using the EAR of 160 µg/day as reference showed that intakes at or below 100 µg/day were associated with the child having 0.05-0.10 SD (standardised z-score) poorer skills in language, reading, and writing, 9-43% increased likelihood of scoring low on mapping test in reading, 6-13% (non-significant) increased risk of scoring low on mapping test in mathematics, and a 10-29% increased likelihood of the child receiving special education services. The study showed no protective effect of supplemental iodine during pregnancy on neurodevelopment. The effect sizes were modest, but still relevant at the population level (public health effect) because the majority of mothers had low iodine intakes.
Comments	
Study quality, A-C	B

ST1 Dietary information*

SI	
Author, year, study name	Abel et al. (2019) Language delay and poorer school performance in children of mothers with inadequate iodine intake in pregnancy: results from follow-up at 8 years in the Norwegian Mother and Child Cohort Study, Norway.
Exposure	Iodine intake and UIC
Dietary assessment method**	A validated Food Frequency Questionnaire (FFQ) designed to capture intake of foods and dietary supplements during the first half of pregnancy.
Food composition database*** Definition of relevant nutrient****	The Norwegian food composition table
Internal calibration (or validity) of dietary assessment (y/n) - if yes - provide data	Yes. Previously, iodine has been validated separately and iodine intake by the FFQ, including supplemental iodine, agreed well with the reference methods 24-h UIE and 4 days weighed-food dairy, triangular validity coefficient for total iodine intake by the FFQ was 0.62 (95% CI: 0.46, 0.77).
Biomarker assay*****	Urinary iodine concentration (UIC)
Analytical validity of biomarker data reported? (y/n) – if yes – provide data	No
Time between biomarker sampling and analysis	No information provided
Season/ date when biomarker samples were drawn	No information provided
Background exposure data	

* write "nd" if there was no data reported. Please do not leave blank
** please refer to brief name indicated in dietary assessment method table. If other method was used, please describe the detail
*** specify database used to calculate nutrient intakes. Other nutrient analysis, please specify
**** E.g. are carbohydrates expressed as available carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical form of the nutrient
***** ONLY biomarker of interest for outcome

ST2 Summary table iodine

Reference details, first author, year, country	**Abel et al. (2018) Iodine Intake is Associated with Thyroid Function in Mild to Moderately Iodine Deficient Pregnant Women, Norway**
Study design	Cross-sectional study
Population, subjects	A population-based pregnancy cohort including pregnant women participating in The Norwegian Mother and Child Cohort Study.
Outcome measures	Plasma thyroid hormones and antibodies, i.e. thyroid stimulating hormone (TSH), free T4 (FT4), free T3 (FT3), thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb).
Time between baseline exposure and outcome assessment	NA
Exposure assessment/ Dietary assessment method	Maternal iodine intake was measured by 1) a food frequency questionnaire (FFQ), and 2) as iodine concentration in a spot urine sample.
No. of subjects analysed	A total of 2910 pregnant women.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	NA
Results	Median iodine intake from food was 121 µg/day (IQR: 90-160 µg/day), and 40% reported use of iodine-containing supplements in pregnancy. Median urinary iodine concentration (UIC) was 59 µg/L among those who did not use supplements and 98 µg/L in those reporting current use of iodine-containing supplements. Iodine intake measured by FFQ was not associated with the outcome measures, while UIC was inversely associated with fT3 ($p=0.002$) and fT4 ($p<0.001$). Current iodine supplement use was not associated with the outcomes, but a recent initiation of iodine supplementation after GW 12 was significantly associated with lower mean fT4 (beta=-0.21, $p=0.027$), but not fT3 or TSH.
Comments	
Study quality, A-C	B

ST2 Dietary information*

SI	
Author, year, study name	Abel et al. (2018) Iodine Intake is Associated with Thyroid Function in Mild to Moderately Iodine Deficient Pregnant Women, Norway
Exposure	Iodine intake and UIC
Dietary assessment method**	Food Frequency Questionnaire (FFQ).
Food composition database*** Definition of relevant nutrient****	The Norwegian food composition table.
Internal calibration (or validity) of dietary assessment (y/n) - if yes - provide data	Yes. Previously, iodine has been validated separately and iodine intake by the FFQ, including supplemental iodine, agreed well with the reference methods 24-h UIE and 4 days weighed-food dairy, triangular validity coefficient for total iodine intake by the FFQ was 0.62 (95% CI 0.46, 0.77).
Biomarker assay*****	TSH, free T4 (FT4), free T3 (FT3), thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb) were measured in plasma samples.
Analytical validity of biomarker data reported? (y/n) – if yes – provide data	Yes. The coefficient of variation (CV) of control samples for measuring UIC was 2.0-4.8%. The CV of control samples for measuring urinary creatinine was 1.4-1.7%. The CV of control samples for measuring plasma TSH, FT3, FT4, TPOAb, and TGAb was 1.8-8.5%. The CV of control samples for measuring plasma ferritin was 2.7-3.7%. The CV of control samples for measuring whole blood selenium was 1.5%.
Time between biomarker sampling and analysis	No information provided
Season/ date when biomarker samples were drawn	No information provided
Background exposure data	

* write "nd" if there was no data reported. Please do not leave blank
** please refer to brief name indicated in dietary assessment method table. If other method was used, please describe the detail
*** specify database used to calculate nutrient intakes. Other nutrient analysis, please specify
**** E.g. are carbohydrates expressed as available carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical form of the nutrient
***** ONLY biomarker of interest for outcome

ST3 Summary table iodine

Reference details, first author, year, country	**Abel et al. (2017a) Suboptimal Maternal Iodine Intake Is Associated with Impaired Child Neurodevelopment at 3 Years of Age in the Norwegian Mother and Child Cohort Study, Norway**
Study design	Prospective cohort study
Population, subjects	This study is based on the Norwegian Mother and Child Cohort study (MoBa) in which women pregnant in their first trimester were recruited from all over Norway during the years 1999-2008. More than 99% of participants are of Caucasian origin. Pregnancy and birth records from the Medical Birth Registry of Norway are linked to the MoBa database. The women consented to participation in 41% of the pregnancies and the cohort now includes 114, 500 children, 95,200 mothers and 75,200 fathers. Exclusion criteria in the present study included; multiple pregnancies, maternal report of thyroid medication in pregnancy, missing food frequency questionnaire(s) (FFQ) filled out around 1) week 17 (general questionnaire), 2) gestational week 22, and 3) when the child was 3 years of age, energy intake <4.5 or >20 MJ, or >3 blank FFQ pages and missing data on outcomes at child age 3 years.
Outcome measures	Child neurodevelopment at age 3 years. Language delay (a six-point ordinal language grammar rating scale developed by Dale & Bishop), communication skills (Ages and Stages Questionnaire, ASQ), motor milestones (ASO), motor skills (ASO) and behaviour problems at 3y (Child Behaviour Check List/ 11/2-5/LDS).
Time between baseline exposure and outcome assessment	Three years
Exposure assessment/ Dietary assessment method	A validated FFQ designed to capture dietary habits and use of dietary supplements during the first half of pregnancy.
No. of subjects analysed	A total of 48,297 mother-child pairs were included in this study. For the main analysis which excluded iodine supplement users, 33,047 mother-child pairs were included.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	This study was based on information of maternal iodine intake from the first half of pregnancy and information of child language and motor development and behaviour problems at age 3 years. Based on the total number of participants in the MoBa-study, the number of participants included in the present study (n=48,297) yielded a response rate was 42%.

Reference details, first author, year, country	Abel et al. (2017a) Suboptimal Maternal Iodine Intake Is Associated with Impaired Child Neurodevelopment at 3 Years of Age in the Norwegian Mother and Child Cohort Study, Norway
Results	The calculated median iodine intake from food was 122 µg/day (IQR: 89-161 µg/day). Maternal iodine intake was associated in a curvilinear dose-response with child language delay (p=0.024), externalising and internalising behaviour problems (both p<0.001), and fine motor skills (p=0.002) but not gross motor skills or the risk of not walking unaided at 17 mo of age. In the 74% of participants who did not use iodine-containing supplement and had an iodine intake <160 g/d (median: 105 mg/d; IQR: 80, 129 mg/d), intakes <100 µg/day were estimated to account for;12% (95% CI:22%, 23%) of cases of language delay; 31% (95% CI: 5%, 50%) of cases of severe language delay; 24% (95% CI: 17%, 31%) of cases of externalising behaviour problems >1.5 SD; and 24% (95% CI: 17%, 31%) of cases of internalising behaviour problems >1.5 SD in children at age 3 years. The results for iodine from food remained statistically significant after adjusting for multiple comparisons. There was no beneficial effect of iodine supplement use. When iodine supplement use was initiated in gestational weeks 0–12, supplement use was associated with an increased risk of externalising behaviour problems (adjusted OR of scoring >1.5 SD: 1.28; 95% CI: 1.09, 1.49), and initiation of supplement use in gestational week ≥13 was associated with an increased risk of internalising behaviour problems (adjusted OR of scoring >1.5 SD: 1.27; 95% CI: 1.10, 1.46). The results for supplement use did not remain statistically significant after adjusting for multiple comparisons.
Comments	
Study quality, A-C	B

ST3 Dietary information*

SI	
Author, year, study name	Abel et al. (2017a) Suboptimal Maternal Iodine Intake Is Associated with Impaired Child Neurodevelopment at 3 Years of Age in the Norwegian Mother and Child Cohort Study, Norway
Exposure	Iodine intake
Dietary assessment method**	Food Frequency Questionnaire (FFQ).
Food composition database*** Definition of relevant nutrient****	The Norwegian food composition table.
Internal calibration (or validity) of dietary assessment (y/n) - if yes - provide data	Yes. A validation study showed that relative to a dietary reference method (4-d weighed food diary) and several biological markers, the MoBa FFQ produces a realistic estimate of habitual intake and is a valid tool for ranking pregnant women according to high and low intakes of energy, nutrients, and foods. The relative validity of total iodine intake from food and supplements and the intake of specific food groups such as dairy products and seafood were evaluated separately. The total iodine intake calculated from the FFQ correlated well with the iodine intake reported from the 4-d food diaries at mid-pregnancy and with 24-h urinary iodine excretion data.
Biomarker assay*****	NA
Analytical validity of biomarker data reported? (y/n) – if yes – provide data	NA
Time between biomarker sampling and analysis	NA
Season/ date when biomarker samples were drawn	NA
Background exposure data	

* write "nd" if there was no data reported. Please do not leave blank
** please refer to brief name indicated in dietary assessment method table. If other method was used, please describe the detail
*** specify database used to calculate nutrient intakes. Other nutrient analysis, please specify
**** E.g. are carbohydrates expressed as available carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical

form of the nutrient
***** ONLY biomarker of interest for outcome

ST4 Summary table iodine

Reference details, first author, year, country	**Abel et al. (2017b) Maternal Iodine Intake and Offspring Attention-Deficit/Hyperactivity Disorder: Results from a Large Prospective Cohort Study, Norway**
Study design	Prospective cohort study
Population, subjects	This study is based on the Norwegian Mother and Child Cohort study (MoBa) in which women pregnant in their first trimester were recruited from all over Norway during the years 1999-2008. More than 99% of participants are of Caucasian origin. Pregnancy and birth records from the Medical Birth Registry of Norway are linked to the MoBa database. The women consented to participation in 41% of the pregnancies and the cohort now includes 114, 500 children, 95,200 mothers and 75,200 fathers. Exclusion criteria in the present study included; multiple pregnancies, maternal report of thyroid medication in pregnancy, missing food frequency questionnaire(s) (FFQ) filled out around 1) week 17 (general questionnaire), and 2) gestational week 22, energy intake <4.5 or >20 MJ, or >3 blank FFQ pages and missing data on outcomes at child age 8 years.
Outcome measures	Child attention-deficit/hyperactivity disorder (ADHD) diagnosis, registered in the Norwegian Patient Registry and maternally-reported child ADHD symptoms of eight years of age. Child ADHD symptoms were assessed in the eight-year-old questionnaire from MoBa on a four-point Likert scale (never/rarely, sometimes, often, or very often) covering inattention problems (nine items) and hyperactivity/impulsivity (nine items) from the ADHD Rating Scale.
Time between baseline exposure and outcome assessment	Eight years
Exposure assessment/ Dietary assessment method	Maternal iodine intake was measured by 1) a food frequency questionnaire (FFQ) to capture dietary habits and use of dietary supplements during the first half of pregnancy, and 2) as iodine concentration in a spot urine sample (UIC).
No. of subjects analysed	A total of 77,164 mother-child pairs were included in the study, and 27,945 participants reported ADHD scored when the child was aged eight years.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	This study was based on information of maternal iodine intake from the first half of pregnancy and information of child ADHD diagnosis at age 8 years. Based on the total number of participants in the MoBa-study the number of participants included in the present study (n=77,164) yielded a response rate was 67%.

Reference details, first author, year, country	Abel et al. (2017b) Maternal Iodine Intake and Offspring Attention-Deficit/Hyperactivity Disorder: Results from a Large Prospective Cohort Study, Norway
Results	Median iodine intake from food was 121 µg/day (IQR: 89-162 µg/day), and 31% reported use of iodine-containing supplements in pregnancy (median intake: 107 µg/day (IQR: 58-150 µg/day). Iodine intake from food did not differ between iodine supplement users and non-users. Median urinary iodine concentration (UIC) in non-users of iodine supplements and thyroid medication was 61 µg/L (IQR: 32-104 µg/L) and in iodine supplement users, the median UIC was 86 µg/L (IQR: 43-140 µg/L). In non-users of iodine supplements, the results showed no association between iodine intake from food and risk of child ADHD diagnosis, while low intake of iodine from food (<200 µg/day) was associated with higher child ADHD symptom scores (adjusted difference in score up to 0.08 standard deviation, p<0.001). In the total sample, there was no evidence of beneficial effects of maternal use of iodine-containing supplements on child ADHD diagnosis or symptom score. In participants with low iodine intakes from food, iodine supplement use initiated in GW 0-12 was associated with a ~29% increased risk of ADHD diagnosis (95%CI: 0%, 67%) and a 0.06 SD higher average score on ADHD symptoms at eight years of age (95% CI: 0.01, 0.11).
Comments	
Study quality, A-C	B

ST4 Dietary information

SI	
Author, year, study name	Abel et al. (2017b) Maternal Iodine Intake and Offspring Attention-Deficit/Hyperactivity Disorder: Results from a Large Prospective Cohort Study, Norway
Exposure	Iodine intake
Dietary assessment method**	Food Frequency Questionnaire (FFQ).
Food composition database*** Definition of relevant nutrient****	The Norwegian food composition table.
Internal calibration (or validity) of dietary assessment (y/n) - if yes - provide data	Yes. Previously, iodine has been validated separately and iodine intake by the FFQ, including supplemental iodine, agreed well with the reference methods 24-h UIE and 4 days weighed-food dairy, triangular validity coefficient for total iodine intake by the FFQ was 0.62 (95% CI 0.46, 0.77). Less than 5% were grossly misclassified.
Biomarker assay*****	NA
Analytical validity of biomarker data reported? (y/n) – if yes – provide data	NA
Time between biomarker sampling and analysis	NA
Season/ date when biomarker samples were drawn	NA
Background exposure data	

* write "nd" if there was no data reported. Please do not leave blank
** please refer to brief name indicated in dietary assessment method table. If another method was used, please describe the detail
*** specify database used to calculate nutrient intakes. Other nutrient analysis, please specify
**** E.g. are carbohydrates expressed as available carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical form of the nutrient
***** ONLY biomarker of interest for outcome

ST5 Summary table iodine

Reference details, first author, year, country	**Alvarez-Pederol et al. (2009) Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring, Sabadell, Spain**
Study design	Prospective study of maternal thyroid function (including UIC) measured in first and third trimester and birth weight in 657 mother infant pairs.
Population, subjects	Healthy pregnant women recruited in first trimester in a public health clinic in Sabadell. Of 657 recruited, 619 were followed until delivery and 568 remained after exclusion of women with thyroid disorders, preterm deliveries or missing data.
Outcome measures	Birth weight (continuous) and adjusted SGA. SGA was defined as i) birth weight <10th percentile birth weight distribution of the population based corresponding gestational age and as ii) <10th percentile weight according to a customised predicted birth weight accounting for maternal and newborn characteristics to better identify intrauterine growth restriction from constitutionally small infants. Only infants classified as SGA in both definitions were considered as SGA in the analyses.
Time between baseline exposure and outcome assessment	Analysis 1: First trimester to delivery Analysis 2: Third trimester to delivery
Exposure assessment/ Dietary assessment method	Median UIC in the 1st trimester: 95 µg/L. Free T_4 (fT4) and TSH was measured in 557 pregnant women. Median UIC in the 3st trimester: 104 µg/L. UIC was categorised into five categories <50 µg/L, 50-99 µg/L, 100-149µg/L, 150-249 µg/L and >249 µg/L.
No. of subjects analysed	N=251 mother had UIC measured in 1st trimester, n=528 had UIC measured in 3rd trimester and n=243 had both
Intervention	None
Follow-up period, drop-out rate	Follow up till delivery, no dropouts
Results	Women with 3rd trimester UICs between 100-149 µg/L had lower risk of having an SGA newborn than women with UICs below 50 µg/L (aOR (95%CI): 0.15 (0.03, 0.76). The newborns in this groups also had higher mean birth weights. Higher TSH levels were associated with higher risk of SGA and lower birth mean birth weight.
Comments	The lowest risk of SGA and highest mean birth weight was seen in mothers with UIC in the range 100-149 µg/L. The study has some limitations such as relatively low sample size and a large number of tests.
Study quality, A-C	B

ST6 Summary table iodine

Reference details, first author, year, country	**Bath et al. (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC), UK**
Study design	Prospective study of maternal iodine status in pregnancy and neurodevelopmental outcomes in children.
Population, subjects	Pregnant women and their children at age 8 years (n=1040 mother-child pairs) in the Avon Longitudinal Study of Parents and Children (ALSPAC). Inclusion criteria: first pregnancy, singleton delivery, availability of a urine sample from the first trimester, and a measure of intelligence quotient at 8 years.
Outcome measures	At age 8 years, IQ was assessed in the ALSPAC research clinic using an abbreviated form of the Weschler Intelligence Scale for Children IIIUK (WISC-IIIUK) and included verbal IQ, performance IQ and total IQ. At age 9 years, trained psychologist assessed children's reading by four outcomes: speed (words read per minute), accuracy, comprehension, and reading score.
Time between baseline exposure and outcome assessment	Baseline in first trimester (≤13 gw, median 10 gw), outcome assessment in children at 8 years (IQ) and 9 years (reading ability).
Exposure assessment/ Dietary assessment method	Maternal urinary iodine concentration (UIC) was analysed in spot urine samples and examined in all models as the ratio of iodine to creatinine (µg/g Cr). Median (IQR) UIC was 110 µg/g Cr (IQR 74-170), while the median unadjusted UIC was 91.1 µg/L (IQR: 53.8-143).
No. of subjects analysed	Total n=958
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Study sample only included mother-child pairs with available follow-up data.
Results	In statistical analyses, maternal UIC (iodine-to-creatinine-ration) was dichotomised into ≥150 µg/g (sufficient) or <150 µg/g (deficient). In additional analyses, the <150 µg/g category was divided onto <50 µg/g (severe) and 50-150 µg/g (mild-to-moderate). Seven associations were studied (3 for IQ, 4 for reading ability) using three regression models for each cognitive outcome to adjust for potential confounders. The second model included variables associated with at least one of the outcomes, while third model included variables that were potentially on the causal pathway. Irrespective of statistical testing, the results showed that children from the maternal low-iodine group (UIC<150 µg/g) were more likely to have scores in the lowest quartile for verbal IQ (OR: 1.58; 95%CI: 1.09, 2.30), reading accuracy (OR:1.69; 95%CI: 1.15, 2.49) and reading comprehension (OR: 1.54; 95%CI: 1.06, 2.23) than those from the sufficient group. Further stratification of the low-iodine mothers showed that children from the group with urinary iodine (<50 µg/g) had lower scores than those from the group with iodine 50–150 µg/g (dose-response).
Comments	The study provides evidence that mild-to-moderate iodine deficiency (inadequate iodine status during early pregnancy) is adversely associated with child cognitive development.

Reference details, first author, year, country	Bath et al. (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC), UK
Study quality, A-C	B

ST7 Summary table iodine

Reference details, first author, year, country	**Charoenratana et al. (2016) Maternal iodine insufficiency and adverse pregnancy outcomes, Thailand**
Study design	Prospective cohort study: to compare the pregnancy outcomes between women with iodine insufficiency (UIC<150 µg/L) and iodine sufficiency (UIC ≥150 µg/L).
Population, subjects	410 pregnant Thai women with a median iodine concentration of 151 µg/L (across all three trimesters), complete data for 390.
Outcome measures	Pregnancy outcomes: Gestational week at birth, birth weight, stillbirth, intrauterine growth restriction, preterm birth, low birth weight, low Apgar score 1 min, Low Apgar score 5 min, antepartum haemorrhage, pregnancy induced hypertension, gestational diabetes, and Caesarean delivery. Adjusted analyses only reported for preterm birth and low birth weight.
Time between baseline exposure and outcome assessment	Exposures were measured during pregnancy and outcome at birth. I.e. duration of known pregnancy is maximum follow up time.
Exposure assessment/ Dietary assessment method	UIC in 1st (n=384), 2nd (n=325) and 3rd (n=221) trimesters. The mean UIC of repeated measures were categorised into ≥150 µg/L and <150 µg/L. They also report the findings on foetal growth restriction using a cut-off of 100 µg/L
No. of subjects analysed	The exposure was measured in n=384, n=325, and n=221 at different time points during pregnancy.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Follow up during antenatal visits in pregnancy to delivery, of 410 recruited, 390 had complete data on pregnancy outcomes.
Results	The duration of pregnancy was one week longer and birth weight was ·150g higher in the iodine sufficient group than in the group with UIC <150 µg/l. UIC < 150 µg/L was associated increased risk of preterm birth (adjusted OR 2.69, 95%CI: 1.38, 5.24) and increased risk of low birth weight (a OR 2.66; 95%CI: 1.40, 5.05). UIC<100 was associated with increased risk of intrauterine growth restriction.
Comments	The main finding was that insufficient iodine status (UIC<150 µg/L) was associated with increased rate of preterm birth and low birth weight. A weakness of this study is that it is not clear about the main objectives, the description of the statistics and rationale for adjustment is weak.
Study quality, A-C	B

ST8 Summary table iodine

Reference details, first author, year, country	**Chen et al. (2019) Iodine Nutrition and Thyroid Function in Pregnant Women Exposed to Different Iodine Sources, China**
Study design	Cross-sectional study
Population, subjects	This study included 15,008 adult men and women, aged 15 years or older (mean age 45 years) and was undertaken between 2011 and 2012 in 10 cities located in the eastern and central parts of China.
Outcome measures	Primary outcome: Presence of thyroglobulin antibodies (TgAbs). In addition, serum thyrothropin (TSH) and thyroid perioxidase antibodies (TPOAbs) were measured for each participant. If TSH was not within the reference range, free thyroxine (fT4) and free triiodothyronine (fT3) levels were measured.
Time between baseline exposure and outcome assessment	NA
Exposure assessment/ Dietary assessment method	Concentration of urinary iodine (UIC) from spot urine samples.
No. of subjects analysed	A total of 14,230 participants (6017 males and 8213 females) with complete data were enrolled in the final analyses.
Follow-up period, drop-out rate	NA
Results	Median UIC was 205 µg/L (5% and 95% percentiles: 66 and 538 µg/L). The participants were classified into four groups according to UIC level: UIC<100 µg/L, 100≤UIC<200 µg/L, 200≤UIC<300 µg/L and UIC≥300 µg/L. A total of 2508 participants (17.6%) had iodine deficiency (UIC<100 µg/L). The results showed that with the increase in UIC, the prevalence of isolated TgAb positivity decreased gradually (for TgAb: 6.14%, 5.62%, 5.34%, and 5.15%). The same trend was not seen with the prevalence of isolated TPOAb positivity or TSH. Thus, the result showed that both males and females with UIC<100 µg/L were more prone to have positive TgAbs.
Study quality and relevance, Comments A-C	B

ST9 Summary table iodine

Reference details, first author, year, country	**Fan et al. (2018) Investigation on the factors that influence the prevalence of thyroid nodules in adults in Tianjin, China.**
Study design	Cross-sectional study
Population, subjects	This study included 2647 adult men and women, aged 18 years or older (mean age 43 years), and was undertaken between March and October 2015 in Tianjin, China. Random cluster sampling was used to select one district in city and country respectively.
Outcome measures	Primary outcome: Presence of thyroid nodules (TNs), defined as areas of greatly reduced or absent echogenicity on thyroid ultrasonography. In addition, potential influencing factors on TNs including sex, age, iodine status, thyroid volume, thyroid hormone (TSH), thyroid antoantibody TPOAb, TgAb and living habits were analysed.
Time between baseline exposure and outcome assessment	NA
Exposure assessment/ Dietary assessment method	Concentration of urinary iodine (UIC) from spot urine samples.
No. of subjects analysed	A total of 2647 (1352 males and 1295 females) were enrolled in the final analyses.
Intervention Intervention/ exposure	
Follow-up period, drop-out rate	NA
Results	Median UIC was 134 µg/L (interquartile range 79-208 µg/L). There were 35.6% of the subjects whose UIC was lower than 100 µg, and 10.3% was higher than 300 µg/L. In the range of urine iodine levels investigated (10 levels: 0 µg/L ~, 50 µg/L ~, 100 µg/L ~, 150 µg/L ~, 200 µg/L ~, 250 µg/L ~, 300 µg/L ~, 350 µg/L ~, 400 µg/L ~, and 500 µg/L ~), the relationship between UIC and the occurrence of TNs showed a U-shaped curve. Prevalence of TNs was 30.7% among subjects with UIC between 50 and 99 µg/L, and 25.3% among subjects with UIC in the range of 100-300 µg/L. The results showed that the prevalence of TNs was significantly decreased when the UIC was over 150 µg/L.
Comments	
Study quality, A-C	B

ST10 Summary table iodine

Reference details, first author, year, country	**Ghassabian et al. (2014) Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area, Netherland**
Study design	Prospective study of maternal iodine status in pregnancy (UIC measured < 18 gestational weeks) and neurodevelopmental outcomes in children at age 6 years.
Population, subjects	Pregnant women and their children at age 6 years (n=1525 mother–child pairs) participating in Generation R, a multiethnic birth cohort in Rotterdam. The population was iodine sufficient with a median UIC of 296.5 µg/g creatinine (229.6 µg/L). Only 188 (12.3%) had UIC < 150 µg/g creatinine. Inclusion criteria: singleton live birth, data on UIC and on child cognitive measures at age 6 years.
Outcome measures	Non-verbal IQ and language comprehension were assessed during a visit to the research centre using Dutch test batteries when the children were 6 years.
Time between baseline exposure and outcome assessment	Baseline in first trimester (≤18 gw, median 10 gw), outcome assessment in children at 6 years.
Exposure assessment/ Dietary assessment method	Maternal iodine intake assessed by urinary iodine analysed in spot urine samples and modelled as the ratio of iodine to creatinine (µg/g Cr). Median UIC in all women: 296.5 µg/g creatinine (UIC=229.6 µg/L) and were iodine sufficient at the group level. UIC was dichotomised into <150 µg/g (n=188 (12.3%)) and ≥150 µg/g (n=1337 (87.7%)). Median UIC in the 188 women with UIC<150 µg/g was 119.3 µg/g creatinine.
No. of subjects analysed	Total n=1525
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Study sample only included mother-child pairs with available follow-up data.
Results	Children of mothers with UIC<150 µg/g had higher likelihood of suboptimum (lowest quartile, scores <93) non-verbal IQ in crude analysis (OR=1.44, 95% CI 1.02, 2.02), but no significant association for either non-verbal IQ or language comprehension in adjusted analyses (adj OR: 1.33 (95% CI: 0.92, 1.92) and adj OR 0.82 (95% CI: 0.56, 1.19), respectively).
Comments	The study included few women with low UIC.
Study quality, A-C	B

ST11 Summary table iodine

Reference details, first author, year, country	**Gordon et al. (2009) Iodine supplementation improves cognition in mildly iodine-deficient children, New Zealand**
Study design	Randomised double-blind placebo-controlled trial to determine the effect of iodine supplementation with 150 µg daily in mildly iodine deficient 10-13-year-old children. Median UIC in children at baseline was 63 µg/L and 32% had UIC<50 µg/L.
Population, subjects	Children (n=184) were recruited through schools and advertisement in 2007 and 2008. Inclusion criteria were: age 10-13 years, no known history of thyroid condition, and not taking iodine-containing dietary supplement.
Outcome measures	Primary outcome was a difference in cognitive test scores between the iodine and placebo groups. Cognitive performance was assessed by four tests from the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV): Picture concepts and Matrix reasoning (both assessing perceptual reasoning), Letter-number sequencing (working memory), and Symbol search (processing speed).
Time between baseline exposure and outcome assessment	28 weeks
Exposure assessment/ Dietary assessment method	The exposure was iodine-supplementation or placebo. At baseline, iodine intake from iodine rich foods, iodized salt and iodine-containing dietary supplements was assessed.
No. of subjects analysed	Total n=166
Intervention Intervention/ exposure	Intervention with 150 µg I daily (n=84) or placebo (n=82).
Follow-up period, drop-out rate	Follow up for 28 weeks (6 mo). Of 184 included in the study, 166 completed.
Results	In statistical analysis, the effect of supplementation was evaluated by using multiple linear regression for each of the 4 cognitive tests and biochemical indexes. Supplementation with 150 µg I/day corrected iodine deficiency by increasing median UIC from 66 to 145 µg/L and decreasing thyroglobulin from 16.5 to 8.5 µg/L. Iodine supplementation improved performance on 2 of the 4 cognitive tests relative to the placebo. The age standardised score obtained in picture concepts increased by 0.81 points (8.6%) and the score in matrix reasoning by 0.63 points (6.5%).
Comments	The study provides evidence that daily supplementation with 150 µg iodine improved perceptual reasoning, but not working memory or processing speed in mildly iodine deficient children. The study was limited by a small study population.
Study quality, A-C	B

ST12 Summary table iodine

Reference details, first author, year, country	**Gowachirapant et al. (2017) Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial, Thailand and India**
Study design	A randomised double-blind placebo-controlled trial with iodine supplementation in mild-to-moderate iodine deficient pregnant women and cognitive measures in their children. (Maternal Iodine Supplementation and Effects on Thyroid Function and Child Development, MITCH-trial).
Population, subjects	Pregnant women were recruited in Bangkok, Thailand and Bangalore, India. At each site, recruitment took place in a large, well-run antenatal clinic serving mainly middle-income families. To be included, women had to be 18-40 years, have singleton pregnancy less than or equal to 14 weeks of gestation, no thyroid disease or major illnesses, and not be taking iodine-containing dietary supplements. Median UIC in first trimester in all participants combined was 131 µg/L.
Outcome measures	Primary outcome: child neurodevelopment at age 5-6 years assessed by 3 outcomes; the Wechsler Preschool and Primary Scale of Intelligence (WPSSI-III) verbal IQ and performance IQ, and the Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) global executive composite score. Secondary outcomes at age 5-6 years: externalising and internalising behaviour problems assessed a by the Strengths and Difficulties Questionnaire (SDQ), auditory tests, anthropometrics (weight and length), and thyroid function parameters (TSH and T4). Secondary outcomes at earlier ages: child neurodevelopment assessed 6 weeks after birth using the Neonatal Behavioral Assessment Scales (NBAS) and at 1 and 2 years using the Bayley Scales of Infant Development (BSID)-III, pregnancy outcomes and maternal and infant thyroid volume and thyroid function parameters.
Time between baseline exposure and outcome assessment	From early pregnancy (≤14 gw) to children at age 5-6 years.
Exposure assessment/ Dietary assessment method	Intervention with 200 µg iodine or placebo daily throughout pregnancy.
No. of subjects analysed	In total n=832 women entered the trial, of which 412 were assigned to iodine and 420 assigned to placebo. Cognitive outcome measurements were available for 330 children at 5.4 years, 166 in the intervention group and 134 in the placebo group.
Intervention	Intervention with 200 µg iodine or placebo daily from first trimester (mean 10.7 gw) throughout pregnancy.
Follow-up period, drop-out rate	Follow up from pregnancy to age 5-6 years of children. Of the 832 women enrolled, 330 children (40%) were available at age 5-6.
Results	Statistical tests at 5-6 years for primary and secondary outcomes showed no differences between the groups receiving supplement and placebo for the primary outcomes at age 5-6 years. Moreover, except for a higher score on expressive language in favour of placebo at 1 year, there were no differences in any of the secondary outcomes at age 5-6 years or at earlier ages.

Reference details, first author, year, country	Gowachirapant et al. (2017) Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial, Thailand and India
Comments	Although women were mildly iodine deficient at baseline (median UIC 131 µg/L), women in India were iodine sufficient (UIC 188 µg/L) and only women in Thailand were deficient (UIC: 112 µg/L). Both study sites were in regions with reasonable coverage of iodized salt, and the UIC was sufficient in both the intervention and placebo group from 2. trimester onwards. Therefore, this study does not provide the evidence required to know whether mild-to-moderate iodine deficiency affects brain development and child cognition.
Study quality, A-C	B

ST13 Summary table iodine

Reference details, first author, year, country	**Hynes et al. (2017) Reduced Educational Outcomes Persist into Adolescence Following Mild Iodine Deficiency in Utero, Despite Adequacy in Childhood: 15-Year Follow-Up of the Gestational Iodine Cohort Investigating Auditory Processing Speed and Working Memory, Australia (Tasmania)**
Study design	Prospective cohort in pregnant women. Follow up of children in Hynes et al. 2013.
Population, subjects	Exposure (UIC) was measured in pregnancy during a period with moderate iodine deficiency in the population. The population iodine status substantially improved during the follow-up period of the study participants, thus this represent exposure to poor iodine status during early life only. In years 1999 to 2000, 449 pregnant women were recruited from antenatal clinics in Australia. Median UIC was 83 µg/L. The previous study (Hynes et al. 2013) examined associations between prenatal iodine and educational outcomes at 8-9 years, while this study examined associations between prenatal iodine and educational outcomes at later ages using mixed models of repeated NAPLAN-outcomes assessed in school year/grade 3 (i.e. 9 years of age), 5, 7 and 9 (i.e.15/6 year of age) years and gestational UIC as continuous variables, and in addition examined associations between gestational iodine and two outcomes (language delay and hearing/auditory processing) in a subsample of 45 participants at age 14-15 years.
Outcome measures	Standardised School tests (National Assessment Program—Literacy and Numeracy (NAPLAN) tests for spelling, grammar, reading, writing, numeracy) from grade 3 (age 9 y) up to and including grade 9 (15/16 y). In a subsample of adolescents at 14-15 years (n=45), additional outcomes included the "Comprehensive Evaluation of Language Fundamentals» (CELF-4) and A Central Auditory Processing Disorder (CAPD) assessment. These tests assess language development and hearing/auditory processing.
Time between baseline exposure and outcome assessment	14-15 years
Exposure assessment/ Dietary assessment method	None
No. of subjects analysed	266 children for mixed model analysis of repeated measures at grade 3 (8-9 years), grade 5, grade 7 and grade 9 (14-15 years), and 45 adolescents for two outcomes at 15 years.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Of 449 recruited, n=266 (59%) were included in the longitudinal analysis.

Reference details, first author, year, country	Hynes et al. (2017) Reduced Educational Outcomes Persist into Adolescence Following Mild Iodine Deficiency in Utero, Despite Adequacy in Childhood: 15-Year Follow-Up of the Gestational Iodine Cohort Investigating Auditory Processing Speed and Working Memory, Australia (Tasmania)
Results	The study showed that the association between UIC dichotomised at 150 µg/L and performance on standardised school test for spelling persisted to grade 9 (14-15 years). The outcomes were modelled using repeated measurements (NAPLAN measured in school years 3, 5, 7 and 9). In the fully adjusted model, children whose mothers had UIC < 150 µg/L exhibited persistent reductions in spelling from year 3, age 8-9 years (10%, -41.4 points (95% Confidence Interval -65.1 to -17.6, p = 0.001)) to year 9, age 14-15 years (5.6%, -31.6 (-57.0 to -6.2, p = 0.015)) compared to children whose mothers had UIC ≥150 µg/L. For grammar and reading, differences at year 3 continued into year 5 but decreased by year 9 (an initial 6.5% difference in grammar reduced to 2.8% by year 9 and a 7.1% difference in reading reduced to 2.5% by year 7). At age 15 years, there were no differences in CELF-4 (language development) or CAPD (hearing/auditory processing) scores. However, all CELF-4 measures were lower for offspring of mothers with UIC<150 µg/L than for those of mothers with UIC≥150 µg/L (not significant). The statistical power was extremely low as the groups that were compared had only 30 and 15 participants respectively.
Comments	This is a follow up study of maternal iodine status and educational outcomes in the same cohort as Hynes 2013 with repeated measures in the following years. The study population for the repeated measures (266 mother-child pairs) is about 50% of the original cohort. The study population for the two additional outcomes at 14-15 years of n=45 mother-child pairs is clearly underpowered.
Study quality, A-C	B

ST14 Summary table iodine

Reference details, first author, year, country	**Hynes et al. (2013) Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort, Australia (Tasmania)**
Study design	Prospective cohort study
Population, subjects	Exposure (UIC) was measured in pregnancy during a period with moderate iodine deficiency in the population. The population iodine status substantially improved during the follow-up period of the study participants, thus this represent exposure to poor iodine status during early life only. A total of 433 pregnant women were recruited between 1999 and 2000.
Outcome measures	Standardised School tests (Australian national curriculum and Tasmanian state curriculum educational assessment data for children) at 9 years. National Assessment Program—Literacy and Numeracy (NAPLAN) tests are standardised criteria-referenced measures of individual student's performance in literacy (reading, writing, and language conventions [spelling, grammar, and punctuation]) and numeracy. Student Assessment and Reporting Information System (SARIS) used by Tasmanian State Government schools to record individual student's academic achievement in assessments in English-literacy and Mathematics-numeracy.
Time between baseline exposure and outcome assessment	9-10 years
Exposure assessment/ Dietary assessment method	Some women but not all donated more than one UIC and the average value was assigned to those with more than one UIC. The median UIC was 81 µg/L. UIC was categorised into <150µg/L and ≥ 150 µg/L.
No. of subjects analysed	From the original cohort (n=433), 228 offspring were traced and linked to educational data at age 9 years.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	433 were included in the original cohort, and outcomes were available in 228 so almost 50% were lost during the follow-up period of nine year.
Results	There was a significant association between UIC (categorised at 150 µg/L) and spelling (NAPLAN) in the full model, and a borderline association between with grammar (NAPLAN) and English-literacy score (SARIS), but not with reading, writing or numeracy scores (NAPLAN). In comparison with children whose mothers had UIC≥150 µg/L, children whose mothers had UIC<150 µg/L had 10% reduction in spelling (-38; 95%CI: -65.5, -11.5, p=0.005), 7% reduction in grammar (-29.1; 95%CI; -59.9, -1.8, p=0.065), and 5% reduction in English grammar (-0.30; 95%CI: -0.62, 0.01, p=0.059). Significant effect sizes were also seen in the crude analyses and in the models with fewer (only biological, birth size, gestation age, sex etc.) variables.
Comments	There were significant and substantial associations in the crude analyses. Only one out of the 7 tests (spelling) remained statistically significant when all potential confounders were adjusted for, while two were borderline significant. The main weaknesses are the low sample size, too few adjustment variables, and high losses to follow-up.

Reference details, first author, year, country	Hynes et al. (2013) Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort, Australia (Tasmania)
Study quality, A-C	B

ST15 Summary table iodine

Reference details, first author, year, country	**Krejbjerg et al. (2015) Serum thyroglobulin before and after iodization of salt: an 11-year DanThyr follow-up study, Denmark**
Study design	A longitudinal population-based study (DanThyr) in two regions with different iodine intake at baseline: Aalborg (moderate iodine deficiency (ID) and Copenhagen (mild ID). Median UIC Aalborg: 45 g/L in non-supplement users and 53 µg/L in iodine-supplement users. Median UIC Copenhagen 61 µg/L in non-supplement users and 68 µg/L in iodine supplement users.
Population, subjects	Participants were chosen at random within specific age and sex groups using the Danish civil registration system: women aged 18–22 years, 25–30 years, 40–45 years and 60–65 years and men aged 60–65 years. A total of 4649 subjects participated (50% of the invited): 2429 participants in Copenhagen and 2220 participants in Aalborg. At follow-up, of the 4649 participants, 72 subjects had emigrated (out of the country) and 403 subjects deceased, allowing 4174 subjects to be invited for participation. 2465 subjects participated, corresponding to 59% of the invited, and 1417 participants with no previous thyroid disease and without Tg-autoantibodies were included in the analyses.
Outcome measures	Serum Tg was measured by immunoradiometric method. A daily intake of iodine from supplements in addition to iodine fortification (IF) was measured.
Time between baseline exposure and outcome assessment	Tg was assessed at baseline in 1997-1998 and at follow up in 2008-2010. The mean follow-up time was 11.2 years (range: 10.1–12.8 years).
Exposure assessment/ Dietary assessment method	Food frequency questionnaire was collected but not presented in this paper, only information about iodine supplements.
No. of subjects analysed	Total n=1417
Intervention Intervention/ exposure	Participants were examined at baseline (1997-98) before the mandatory IF of salt (2000), and again at follow-up (2008-2010) after IF. The IF was initiated in year 2000 and consisted of adding 13 µg iodine/g salt in household salt and into salt for the production of bread. The program was designed to increase the average daily iodine intake among adult Danes by 50 µg/day.
Follow-up period, drop-out rate	72 subjects had emigrated (out of the country) and 403 subjects deceased.
Results	Overall, the follow-up period saw no change in median Tg in Copenhagen (9.1/9.1 µg/L, p=0.67) while Tg decreased significantly in Aalborg (11.4/9.0 µg/L, p<0.001). Living in Aalborg (p<0.001) and not using iodine supplements at baseline (p<0.001) predicted a decrease in Tg whereas baseline thyroid enlargement (p<0.02) and multinodularity (p<0.01) were associated with an individual increase in Tg during follow-up.

Reference details, first author, year, country	**Krejbjerg et al. (2015) Serum thyroglobulin before and after iodization of salt: an 11-year DanThyr follow-up study, Denmark**
Comments	The iodization of salt initiated in 2000 (13 mg/g) was cautious in order to minimise side effects. The results raise the question if a moderate increase in the level of iodine added to the salt, bringing median urinary iodine values to a level around 100 mg/L as found in 2004–2005 could be beneficial for the Danish population and further increase the population iodine intake. This conclusion is in accordance with the results of urinary iodine measurements, indicating that at follow up in 2008–2010 the participants were in general suffering from mild ID.
Study quality, A-C	B

ST16 Summary table iodine

Reference details, first author, year, country	**Levie et al. (2019) The Association of Maternal Iodine Status in Early Pregnancy with Thyroid Function in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy Study, Sweden**
Study design	Cross-sectional study embedded within the Swedish Environmental Longitudinal Mother and child Asthma and Allergy (SELMA) study, aiming to investigate the association of maternal urinary iodine concentration with thyroid function and autoantibodies in a mild-to-moderate iodine deficient pregnant population.
Population, subjects	Pregnant Swedish women (n=2009) with data on UIC, creatinine and thyroid function parameters collected at median gestation age 10 weeks (95%CI: 6-14 weeks). Mean (SD) maternal age was 30 (5.2) years.
Outcome measures	Thyroid function: Thyrotropin (TSH), free thyroxine (fT4), free triiodothyronine (fT3), total T4 (TT4 and total T3 (TT3). Thyroid autoantibodies: positive test for thyroid peroxidase autoantibodies (TPOAb>34 IU/mL), positive test for Thyroglobulin autoantibodies (TgAb>115 IU/mL).
Time between baseline exposure and outcome assessment	None
Exposure assessment/ Dietary assessment method	The median UI/creat was 85 (95%CI: 36, 386) µg/g and UI/creat was <150 µg/g in 80.1% of women. Without correction for creatinine median UIC was 90 (38, 439 µg/L) and UIC was <150 µg/L in 78.6% of women.
No. of subjects analysed	N=2009
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	
Results	UI/Creat was modelled as a continuous variable and the results showed significant curvilinear associations of low UI/Creat (lower than ~100 µg/g) with lower TSH (p=0.027) and higher TT4 (p=0.032). There was also a trend toward an association of a lower UI/Creat with higher fT4 (p=0.081), fT3 (p=0.079), and TT3 (p=0.10), but no association of UI/Creat with the TT4/TT3 and fT4/fT3 ratios. In the whole study population, TPOAb positivity occurred more often in women with low or high UI/Creat; an increase of one unit in the natural logarithm of UI/Creat was associated with a 27% lower risk of TPOAb positivity (odds ratio (OR) 0.73; 95%CI: 0.56, 0.98, p=0.034), but not with TgAb positivity (OR 0.83; 95%CI 0.61, 1.14, p = 0.25). The results for thyroid function and autoantibodies were similar when examining UIC without adjusting for creatinine.

Reference details, first author, year, country	Levie et al. (2019) The Association of Maternal Iodine Status in Early Pregnancy with Thyroid Function in the Swedish Environmental Longitudinal, Mother and Child, Asthma and Allergy Study, Sweden
Comments	The analyses were adjusted for TPOAb, hCG, gestational age, maternal, age, maternal ethnicity, maternal education, parity, maternal BMI, smoking status based on the serum cotinine concentration, and child sex. The findings of lower TSH and higher TT4, and of (borderline) higher fT4, TT3 and fT3 were contra-intuitive to an expected increase in TSH and shift from T4 to T3, but is in line with results from other studies.
Study quality and relevance, Comments A-C	B

ST17 Summary table iodine

Reference details, first author, year, country	**Markhus et al. (2018) Maternal Iodine Status is Associated with Offspring Language Skills in Infancy and Toddlerhood, Norway**
Study design	A population-based prospective cohort.
Population, subjects	During 2011-2012, pregnant women were enrolled at nine public health clinics across all four Norwegian health regions. The clinics were chosen after considering demographic characteristics and size of the population to include participants from both cities and rural districts with a wide distribution of socioeconomic conditions. Midwives at the public health clinics approached pregnant women at 16–26 weeks gestation with an invitation to participate; however, some women were asked as late as weeks 31–34. Inclusion criteria for analysis in the present study were available data on UIC and on child development, singleton pregnancy, no thyroid medication in pregnancy, and no severe genetic disorder.
Outcome measures	Five developmental outcomes (domains) at 6, 12 and 18 months (Bayley Scales of Infant and Toddler Development, third). At six and 12 months, the screening version of the test was used measuring all five domains: cognitive, receptive communication, expressive communication, gross motor and fine motor. At 18 months, the full-scale version was used measuring cognitive and language skills. Health care nurses, trained under supervision of clinical psychologists specialised in infant and child development, administered the test at the public health clinics.
Time between baseline exposure and outcome assessment	NA
Exposure assessment/ Dietary assessment method	Maternal UIC was the main exposure. Questions on supplement use were embedded in a short web-based food frequency questionnaire explained elsewhere.
No. of subjects analysed	Total n=851 mother-child pairs
Intervention Intervention/ exposure	NA
Follow-up period, drop-out rate	Data collection up to age 18 months ended in November 2014. 1063 pregnant women included, 212 excluded due to multiple births, reported thyroid hormone drug therapy, Downs syndrome and missing data on the outcome or exposure variable.

Reference details, first author, year, country	Markhus et al. (2018) Maternal Iodine Status is Associated with Offspring Language Skills in Infancy and Toddlerhood, Norway
Results	The median UIC in pregnancy was 78 µg/L (IQR 46–130), classified as insufficient iodine intake according to the WHO. Eighteen percent reported use of iodine-containing multi supplements. A UIC below 100 was associated with reduced receptive (p = 0.025) and expressive language skills (p = 0.002), but not with reduced cognitive or fine- and gross motor skills. A lower UIC was associated with lower standardised receptive language scores (difference between values above 100 µg/L and lowest values: -0.2 SD) and a lower expressive language score (difference between values above 100 µg/L and lowest values: -0.3 SD), but there was no association with cognitive score, fine motor skills, or gross motor skills. These associations showed a curvilinear pattern, which indicates that the negative associations of UIC with receptive and expressive language scores starts to occur from a value of 100 µg/L or lower. Maternal use of iodine-containing supplements was associated with lower gross motor skills (b = -0.18, 95% CI = -0.33, -0.03, p = 0.02), but not with the other outcome measures.
Comments	An insufficient iodine intake in pregnancy, reflected in UIC below 100 µg/L, was associated with lower infant language skills measured at 6, 12 and 18 months (mixed model, repeated measure). Iodine-containing supplements was not associated with beneficial (protective) effects.
Study quality, A-C	B

ST18 Summary table iodine

Reference details, first author, year, country	**Mills et al. (2019) Pregnancy Loss and Iodine Status: The LIFE Prospective Cohort Study, USA**
Study design	A study of iodine status and pregnancy loss in women participating in a prospective population based study who had discontinued contraception within two months to become pregnant. Urinary iodine status was assessed at recruitment. The participants were followed up for 12 months and those who became pregnant were followed until the end of pregnancy.
Population, subjects	501 women/couples were recruited, of which 347 (69%) became pregnant. After exclusion of multiple births (n=3) and those with missing UIC (n=15), 329 women were included in the analyses. Of these, 196 (59.5%) had live births, 92 (28%) had pregnancy losses, and 41 (12.5%) withdrew or were lost to follow up.
Outcome measures	Pregnancy loss and time to pregnancy loss. Pregnancy was assessed by the Clearblue fertility monitor. Pregnancy was identified by a positive test and pregnancy loss identified by conversion to a negative test.
Time between baseline exposure and outcome assessment	From the time of positive pregnancy test to loss, delivery or withdrawal.
Exposure assessment/ Dietary assessment method	Spot urine samples at the first in-home interview prior to conception. Iodine was measured as µg/L and creatinine was used either as an independent variable or to use the ratio of iodine to creatinine (µg/g creatinine). The exposure was grouped into normal status (≥150 µg/L, n=133 (40%)), mild deficiency (100-149 µg/L, n=52 (16%)), moderate deficiency (50-99 µg/L, n=74 (22.5%)) and severe deficiency (<50 µg/L, n=70 (21%)).
No. of subjects analysed	N=329
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	From the time of positive pregnancy test to loss, delivery or withdrawal/drop out. Dropout rate: 12.5%
Results	The women with UIC in the deficiency range did not have a different loss rate than those in the sufficient group. The adjusted hazard ratio for pregnancy loss was 0.69 (95% CI 0.34, 1.38) in the mild iodine deficiency group, 0.81 (95% CI 0.43, 1.51) in the moderate deficiency group, and 0.69 (95% CI 0.32, 1.50) in the severe deficiency group. Results were consistent in sensitivity analyses including creatinine adjustment or exclusion of women being treated for thyroid disease.
Comments	The authors used weighted analysis to account for dropouts due to couples not getting pregnant, but the overall study sample was fairly small, and the majority of participants had UIC in the sufficient or mildly deficient range (56%). However, a major strength of this study is that the couples were recruited before conception making it possible to assess early pregnancy losses. This is not possible in pregnancy cohorts that usually recruit pregnant women well into pregnancy.

Reference details, first author, year, country	Mills et al. (2019) Pregnancy Loss and Iodine Status: The LIFE Prospective Cohort Study, USA
Study quality, A-C	B

ST19 Summary table iodine

Reference details, first author, year, country	**Mills et al (2018) Delayed conception in women with low-urinary iodine concentrations: a population-based prospective cohort study, USA**
Study design	The LIFE Study, a population-based prospective cohort study, enrolled women who had discontinued contraception within 2 months to become pregnant.
Population, subjects	501 couples were recruited from a defined area of 16 counties in Michigan and Texas. Couples planning a pregnancy were initially contacted by letter, then by a telephone screening interview. After obtaining full and informed consent, couples who wished to participate were seen at their homes for in depth interviews and training. Women were eligible if they were planning a pregnancy; were married or in a committed relationship; were between 18 and 40 years of age; had self-reported menstrual cycles ranging from 21 to 42 days; had not used injectable hormonal contraception in the past 12 months; were not off contraception for more than 2 months; were able to communicate in English or Spanish; and had a partner aged 18 or older. Of the 501 women enrolled, 467 (93%) had sufficient urine available for iodine analysis.
Outcome measures	Women reported on risk factors for infertility by interview then kept daily journals of relevant information. Women used fertility monitors to time intercourse relative to ovulation then used home digital pregnancy tests to identify pregnancies on the day of expected menstruation. Urine samples were obtained.
Time between baseline exposure and outcome assessment	12-month study period.
Exposure assessment/ Dietary assessment method	Spot urine samples from 467 women as UIC and I/Cr-ratio. Iodine status sufficient (UIC≥100 µg/L) in 260 (55.7%), mildly deficient (50–99 µg/L) in 102 (21.8%), moderately deficient (20–49 µg/L) in 97 (20.8%) and severely deficient (<20µg/L) in 8 (1.7%) samples. Median UIC was 112.8 (IQR 53.6-216.9) µg/L in the entire population, 114.1 (IQR 103.1-126.3) in those who became pregnant, 97.2 (IQR 73.5-128.5) µg/L in those who did not become pregnant, and 113.6 (IQR 92.9-138.9) µg/L in those who withdrew.
No. of subjects analysed	N=501
Intervention Intervention/ exposure	NA
Follow-up period, drop-out rate	332 (71%) became pregnant; 47 (10%) did not become pregnant and 88 (19%) withdrew or were lost to follow-up.
Results	The group whose iodine–creatinine ratios were below 50 µg/g (moderate to severe deficiency) had a 46% reduction in fecundity (p = 0.028) compared with the group whose iodine–creatinine ratios were in the adequate range: adjusted fecundability odds ratio of becoming pregnant per cycle, 0.54 (95% confidence interval 0.31–0.94).

Reference details, first author, year, country	**Mills et al (2018) Delayed conception in women with low-urinary iodine concentrations: a population-based prospective cohort study, USA**
Comments	Significant delays in becoming pregnant occur at iodine concentrations that are common in women in the USA and parts of Europe. Replicating these findings will be important to determine whether improving iodine status could be beneficial in improving fecundability. However, iodine concentrations vary within individuals over time, so the data must be interpreted by group as we have done; residual confounding is possible. The group between 50 and 100 µg/g or µg/L may be at risk, but if they are, the risk is much smaller.
Study quality, A-C	B

ST20 Summary table iodine

Reference details, first author, year, country	**Moreno-Reyes et al. (2013) High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study, Belgium**
Study design	Cross-sectional: national population-based survey of pregnant women, selected by a multistage stratified (by region: North vs South Belgium) and clustered sampling design, with the antenatal clinics as unit of cluster.
Population, subjects	Target population: all pregnant women in Belgium within the 1st and 3rd trimesters of pregnancy during survey period (between September 2010 and June 2011). National representative sample from 55 obstetric clinics. A random sample of 1311 women was included: 215 from Brussels, 641 from Flanders, and 455 from Wallonia. Mean (SD) age all participants from both trimesters (n=1311): 28.5 (5.1) yrs. Ethnicity (Caucasian, Asiatic, African, North African, and Hispanic) adjusted for in analysis, but % distribution not reported in paper.
Outcome measures	Prevalence of thyroid disorders in 1st and 3rd trimesters: maternal serum free T4 (fT4), free T3 (fT3), TSH, Tg, thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb).
Time between baseline exposure and outcome assessment	Cross-sectional. Not described in paper, but assumed that urine samples and blood samples were collected at the same time during visit to antenatal clinic in 1st or 3rd trimester.
Exposure assessment/ Dietary assessment method	Urinary iodine concentration before (UIC, ug/L) and after correction for creatinine (UIC/Cr, ug/g Cr) in 1st or 3rd trimester. Reported in paper that a questionnaire about sociodemographic and socioeconomic characteristics, smoking and alcohol drinking behavior, thyroid diseases, use of iodine-containing supplements and food consumption, and use of iodized household salt was completed face to face with the study nurse. But method/data not described.
No. of subjects analysed	A random sample of 1311 pregnant women was included. Urinary iodine concentration (UIC) available for n=550 women in 1st trimester and n=616 women in 3rd trimester who were negative for TPO-Ab and Tg-Ab and without known history of thyroid disease. Women positive for TPO-Ab, Tg-Ab, or with a history or thyroid disorder were n=130 (excluded in evaluation of serum Tg as a marker of iodine status).
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Cross-sectional study. No follow-up or drop out.

Reference details, first author, year, country	Moreno-Reyes et al. (2013) High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study, Belgium
Results	**Iodine status** Median (IQR) UIC in 1st trimester= 117 (70-189) ug/L before and 103 (71-172) after correction for Cr. (Median (IQR) UIC in 3rd trimester= 131 (74-239) ug/L before and 138 (81-234) after correction for Cr – increase form 1st trimester probably reflects intake of iodine supplements). **Multivariable linear regression analysis with log serum TSH and log serum Tg as outcomes** UIC/Cr was a significant predictor of Tg (β= - 0.134, P=0.001), but not TSH (β= - 0.038, P=0.57). Other predictors in models were gestational age, maternal age, ethnicity, and season (winter, spring, summer autumn). Analysis probably combines women in 1st and 3rd trimesters. Main finding highlighted by authors in Abstract is that women with an adequate iodine status (UIC/Cr=150–249 µg/g) had significantly lower median Tg concentration compared to moderately iodine deficient women (UIC/Cr <=49µug/g), 19 µg/L and 25 µg/L, respectively. But, these results are unadjusted for potential confounders.
Comments	Reported that most women, but not how many, started taking iodine supplements (approximately 150 µg/d) during pregnancy. So higher UIC in 3rd compared with 1st trimesters probably reflects supplement use. Different women were assessed in 1st and 3rd trimesters, so changes between trimesters also includes other inter-individual variations.
Study quality, A-C	B

ST20 Dietary information*

SI	
Author, year, study name	Moreno-Reyes et al. (2013) High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study, Belgium
Exposure	Urinary iodine concentration before (UIC, µg/L) and after correction for creatinine (UIC/Cr, µg/g Cr).
Dietary assessment method**	ND
Food composition database*** Definition of relevant nutrient****	ND
Internal calibration (or validity) of dietary assessment (y/n) - if yes - provide data	ND
Biomarker assay*****	UIC measured in duplicate by a modification of the Sandell-Kolthoff reaction using spectrophotometric detection.
Analytical validity of biomarker data reported? (y/n) – if yes – provide data	The sensitivity of UIC assay was 12 µg/L
Time between biomarker sampling and analysis	ND
Season/ date when biomarker samples were drawn	All seasons (winter, spring, summer autumn).
Background exposure data	

* write "nd" if there was no data reported. Please do not leave blank
** please refer to brief name indicated in dietary assessment method table. If other method was used, please describe the detail
*** specify database used to calculate nutrient intakes. Other nutrient analysis, please specify
**** E.g. are carbohydrates expressed as available carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical form of the nutrient
***** ONLY biomarker of interest for outcome

ST21 Summary table iodine

Reference details, first author, year, country	**Murcia et al. (2018) Iodine intake from supplements and diet during pregnancy and child cognitive and motor development: the INMA Mother and Child Cohort Study, Spain**
Study design	INMA (Infancia y Medio Ambiente (Environment and Childhood)) pregnancy cohort, multicentre, 4 regional centres
Population, subjects	2644 women enrolled between 2003 and 2008 after consecutive sampling at first routine specialised antenatal care visit in the geographical areas of Valencia, Sabadell, Asturias and Gipuzkoa. 2506 women (95%) delivered a live infant, and 2007 children (80%) were followed until the age of 4–5 years and tested between March 2009 and January 2013. The final study sample included 1803 children (72%) with valid neuropsychological assessment. No report of maternal age. Maternal country of birth (measure of ethnicity) included in analysis, but % distribution not reported.
Outcome measures	A version of the McCarthy Scales of Children's Abilities (MSCA) adapted to the Spanish population. The MSCA includes both a general cognitive scale (GCS) and the motor scale. The cognitive function included four additional subscales (verbal, perceptual-performance, quantitative and memory). The motor function was disaggregated into gross and fine motor subscales.
Time between baseline exposure and outcome assessment	3 maternal baseline exposures reflect different time points: 1) Spot urine (and blood samples) collected before 24 gestational weeks: mean (SD) 13.5 (2.0) weeks. 2) FFQ (intake of iodine, dairy and seafood) administered twice (11-13 wks and 28-32 wks gestation) and used to estimate average dietary intake from last menstrual period to 3rd trimester. 3) Iodine supplement intake estimated as mean of months used, but unclear timing in pregnancy (se Comments to Murcia et al 2011). Children were tested at mean (SD) age 4.8 (0.6) yrs (range 4.0-6.4 yrs).
Exposure assessment/ Dietary assessment method	Semi-quantitative FFQ (100 items) administered twice. Structured questionnaire for intake of iodised salt (no, yes) and iodine containing supplements (brand name, composition, daily dose, and timing of consumption. Mean calculated for months of consumption).
No. of subjects analysed	Final study sample included 1803 children (72% of births) with valid neuropsychological assessment. Maternal UIC reported for 1,526 women.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Children were followed for a mean (SD) period of 4.8 (0.6) yrs (range 4.0-6.4 yrs) after birth. 80% of live borne children were followed until the age of 4–5 years. Drop out (%) was 20%.

Results	**Iodine status in pregnancy (at mean (SD) 13.5 (2.0) weeks gestation** Median (IQR) UIC in pregnant women was 123 (73, 208) µg/L before correction for creatinine. **General cognitive score (GCS) as outcome (multivariable linear regression)** Iodine intake (dietary iodine g/day, salt use, or iodine supplementation) was not associated with GSC. Urinary iodine excretion was not associated with GCS before adjusting for creatinine, but after. After adjusting by the residual method, children of women with UIC~Cr <100 µg/L had lower GCS scores (beta:-3.93, 95% CI: −6.18 to −1.69) compared with the reference category (150–249 µg/L). Similarly, a UIC/Cr <100 µg/g creatinine was associated with a lower score (beta:- 4.26, 95% CI: −6.57 to −1.96) compared with 150–249 µg/g. By using the UIC/Cr ratio, the category 100–149 µg/g was also associated with reduced scores (beta: -5.28, 95% CI: -7.70 to -2.87). However, when missing creatinine values were imputed in sensitivity analysis, the associations with GCS lost significance (UIC~Cr <100 µg/L, beta=−1.85; 95% CI −3.78 to 0.08), or coefficients for the ratios UIC/Cr <100 µg/g and 100–149 µg/g were attenuated. **Motor development as outcome (multivariable linear regression)** Dietary iodine intake was inversely associated with motor development: a 100 µg/day increase was associated with a 2.41 decrease in score (beta: -2.41; 95% CI: −3.98 to −0.85). Dairy intake and, specifically, milk intake (not other dairy products or seafood) accounted for the association (beta: −1.36; 95% CI: −2.12 to −0.61; per one daily serving of milk). Urinary iodine excretion was not associated with motor skills, before or after adjustment for creatinine. All models were adjusted for psychologist, child's age at evaluation and gender, and maternal history of thyroid disorder and education. GCS models were additionally adjusted for birth order, main care provider at evaluation, occupational social class, paternal education, maternal intelligence proxy. No interaction was found between iodine from supplements and iodised salt use and iodine status from diet, or between child' gender and GCS or motor scores. **Number of tests:** A total of 8 maternal iodine exposures (UIC, UIC adjusted for creatinine by 2 methods, iodized salt intake, iodine supplementation, iodine intake, dairy intake, and seafood intake) were tested against two main scales; general cognitive scale (GCS) and the motor scale, and 4 subscales of GCS and 2 subscales of the motor scale (fine and gross). Without considering sub-scales, significant inverse associations were reported for two of eight iodine exposures with motor scores; iodine intake and dairy intake (due to milk when disaggregated).

Reference details, first author, year, country	Murcia et al. (2018) Iodine intake from supplements and diet during pregnancy and child cognitive and motor development: the INMA Mother and Child Cohort Study, Spain
	Without considering sub-scales, significant associations were reported for two of eight iodine exposures with cognitive scores; low UIC after adjustment for creatinine with either method, was associated with lower scores.
Comments	The sub-cohorts are from four iodine-sufficient or mildly iodine-deficient regions in Spain, according to paper. But it is not described which regions are considered deficient (or sufficient). Results could/should have been stratified or meta-analysed according to region/sub-cohort to account for differences in baseline status of iodine. Timing of iodine supplement use not clearly defined in this paper.
Study quality, A-C	B

ST22 Summary table iodine

Reference details, first author, year, country	**Murcia et al. (2011) Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age, Spain**
Study design	INMA (Infancia y Medio Ambiente (Environment and Childhood)) pregnancy cohort, multicentre, but only one centre included (Valencia) in current study. The study examined associations between maternal iodine nutrition and child neurodevelopmental outcomes using maternal UIC grouped into <100, 100-149, 150-249 and ≥250 µg/L, maternal use of iodized salt (yes/no), maternal intake of iodine rich foods by FFQ, and maternal iodine intake from supplements (µg/day) grouped into <100, 100-149 and ≥ 150 µg/day.
Population, subjects	855 women enrolled during first prenatal visit to Le Fe hospital in Valance before 13 wks gestation, of which 691 mother-child pairs with data on maternal UIC and child mental and motor development. Mean (SD) age of mothers: 30.1 (4.4) yrs Ethnicity of mothers: 83/691 (12%) had country of origin other than Spain.
Outcome measures	Bayley Scales of Infant Development tested at age 1 yr (range 11-16 mths). Only Mental Scale (163 items) and Motor Scale (81 items) used. Mental Development Index (MDI) and Psychomotor Development Index (PDI) obtained by adjusting raw scores for psychologist and child's age at testing. PDI score < 85 (No/Yes) – corresponds to PDI < 1 SD of mean (outcome for logistic regression).
Time between baseline exposure and outcome assessment	3 maternal baseline exposures at different time points: 1) Spot urine (and blood samples) taken at end of 1st trimester (mean week 12.4, SD=0.66). 2) FFQ intake (dairy and seafood) estimated twice (11-13 wks and 28-32 wks gestation) and used to estimate average intake from last menstrual period to 3rd trimester. 3) Iodine supplement use estimated as mean of months used, but unclear timing (se Comments further down). Outcome assessment 1 yr (11-16 mths) after birth.
Exposure assessment/ Dietary assessment method	Semi-quantitative FFQ (100 items, 11 dairy, 11 fish), adapted from Willett, translated and validated. Structured questionnaire for intake of iodised salt (no, yes) and iodine containing supplements (brand name, composition, daily dose, and timing of consumption. Mean calculated for months of consumption).
No. of subjects analysed	691 children included in regression models with MDI and PDI as outcomes, excluding children tested at older age (n=4), incomplete neuropsychological assessment (n=8), clinical conditions=5 (preterm=2, Down syndrome=1, epilepsy=1, autism=1). Note: 2 outliers for mental and 2 outliers for psychomotor scores (<4 SD or > 4SD from mean) excluded from analysis according to paper, but unclear if these exclusions overlap with other exclusion criteria (e.g. incomplete neuropsychological assessment og clinical conditions).

Reference details, first author, year, country	Murcia et al. (2011) Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age, Spain
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Follow-up: from 1st trimester of pregnancy (inclusion) to infant neurodevelopmental testing at 1 yr (11-16 mths). Drop out: from inclusion (n=855 mothers) to child testing at age 1 yr (n=708 children)=(855-708)/855=17%.
Results	**Statistically significant results related to maternal supplement intake, reported in Table 3:** Maternal intake of ≥150 µg/day, compared with <100 µg/day, of iodine from supplements associated with a 5.2-point decrease in PDI (β=-5.2, 95% CI: -8.1, -2.2, linear regression, F-test overall p-value 0.002) and 1.8-fold increase in odds of having a PDI <85 (OR=1.8, 95% CI: 1.0, 3.3, logistic regression, Likelihood ratio overall p-value 0.013). **Sig p-value for interaction between iodine supplements and child's sex of having PDI <85** (p=0.01). When stratified by sex, the association was intensified for girls, but not sig in boys: Girls (n=325): β=-8.7 95% CI: -13.0, -4.4, p<0.001 overall; OR=4.0, 95% CI: 1.4, 11.4, p=0.017 over all categories) Boys (n=357: β=-1.8, 95% CI: -6.0, 2.5, p=0.56 overall; OR=1.1, 95% CI: 0.5, 2.2, p=0.013 over all categories). Results on iodine supplements were adjusted for child's sex, maternal age, mother's cohabitant (father or other), social class, day-care attendance, and maternal history of thyroid disease. ORs also adjusted for country of origin. **No sig associations found for other exposures** (maternal UIC categories, intake of iodized salt, intake of dairy foods, or seafood) with PDI score. No sig associations found for any of the exposures (maternal UIC, iodine from supplements, intake of iodized salt, intake of dairy foods, and seafood) and MDI (Mental development index). Multivariable model results presented in Web Table 2. **Number of tests:** the main study objective was related to maternal iodine supplementation, but five maternal iodine exposures (UIC, iodized salt intake, iodine supplementation, dairy intake, and seafood intake) were tested against two outcomes in infants; the mental development index (MDI) and psychomotor development index (PDI). A statistically sig inverse association was reported for maternal iodine supplementation and PDI (lower PDI with higher supplement dose) regardless of scale (continuous or categorical) but was limited to girls. No other association reached statistical significance (p<0.05).

Reference details, first author, year, country	Murcia et al. (2011) Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age, Spain
Comments	Note: Valencia region described as iodine sufficient in later publication Murcia et al. 2018. Maternal iodine status (median UiC for group) not reported, but 55% of women had UIC <150 µg/L (Table 2). Main findings relate to iodine supplement intake, but unclear timing. Stated in paper that starting time of supplement intake (before or after the end of the first trimester of pregnancy) was not associated with neurodevelopment (data not shown). No estimate of dietary iodine. Typical iodine content of salt not reported. Strict cut-off value for sig statistical interactions ($p<0.05$). Interaction between iodine from reported main sources (supplements and salt) were tested for (reported in text) but not results found in paper so p-value was probably not statistically sig. Association maternal iodine supplement intake with infant neurodevelopment also investigated in remaining 3 study centres in separate publication: Rebagliato M et al. Am J Epidemiol 2013;177:944–53.
Study quality, A-C	B

ST23 Summary table iodine

Reference details, first author, year, country	**Pedersen et al. (1993) Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation, Denmark**
Study design	RCT of daily iodine supplementation (200 µg/day) in pregnant women from weeks 17-18 of pregnancy to 12 mths after delivery.
Population, subjects	Participants were normal pregnant Caucasian women attending the out-patient clinic of the Department of Obstetrics and Gynecology, Randers Centralsygehus, early in pregnancy as part of local routine. None had previous thyroid disease, and none took iodine supplementation or medication that could affect thyroid function. Of 74 women willing to participate, 20 left the study after first visit and 54/70=77% participated. Of the 54 women, 28 received iodine supplements and 26 were controls. The median age of women was 25.0 yrs in supplemented group and 26.3 yrs in control group.
Outcome measures	Maternal thyroid volume (ml - sonography) at gestational weeks 17-18, 28, 37; and 5 days, 26 wks, 52 wks after delivery. Thyroid function in women: serum TSH (mU/L), Tg (µg/L), T4 (nmol/L), T3 (nmol/L), free T4 (pmol/L), ratio T4/T3. Thyroid function in newborns (cord blood serum): TSH (mU/L), Tg (µg/L), T4 (nmol/L), T3 (nmol/L), free T4 (pmol/L). Iodine in morning spot urine samples. Urine sample at 52 weeks postpartum was taken after women had stopped taking iodine.
Time between baseline exposure and outcome assessment	Repeated measurements of the same women. Blood and urine samples were obtained at the time of measurement of thyroid volume and at 13 and 39 weeks after delivery.
Exposure assessment/ Dietary assessment method	None
No. of subjects analysed	Data available for 54 women during pregnancy and 49 women in the postpartum period.
Intervention Intervention/ exposure	Daily intake of 200 µg of iodine as 10 drops of KI solution from weeks 17-18 of pregnancy to 12 months after delivery. Probably no placebo control.
Follow-up period, drop-out rate	During the year after delivery, 5 women left the area (3 from the iodine supplementation group and 2 from the control group). They were excluded from the postpartum part of the investigation.

Reference details, first author, year, country	Pedersen et al. (1993) Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation, Denmark
Results	**Iodine status at baseline** Median (95% CI) for UIC in pregnant women at initial visit was 51 (32-58) µg/L in controls and 55 (30-73) µg/L in group that later received supplements. **Thyroid volume (Fig 3)** Thyroid volume increased more in controls than supplemented group during pregnancy ($p<0.05$). **T4, T3, T4/T3, free T4 in supplemented vs control group (Fig 1)** No significant differences were found between the control group than supplemented group in the developments of T4, T3, ratio T4/T3 or free T4 during pregnancy or postpartum. **Tg and TSH in supplemented vs control group (Fig 2)** Maternal Tg values were significantly higher in controls at all time points, except before initiation of iodine supplementation. Tg in cord blood was also sig higher in children of control mothers ($p=0.005$). In the control group, there was a sig increase in TSH during pregnancy ($P <0.01$), whereas no sig increase was found in the iodine supplemented group ($P = 0.29$, by Friedman's test). During the postpartum period, there was no significant difference in TSH between groups. **Authors' interpretation:** low iodine intake/status during pregnancy creates thyroidal stress (increases in thyroid size, higher Tg) which was ameliorated by iodine supplementation. Hormone levels did not change, suggesting that the thyroid gland was able to adapt under the (normal) circumstances in the study.
Comments	Unclear randomisation process, probably no placebo given to controls, relatively small but solid.
Study quality, A-C	B

ST24 Summary table iodine

Reference details, first author, year, country	**Rasmussen et al. (2002) Relations between various measures of iodine intake and thyroid volume, thyroid nodularity, and serum thyroglobulin, Denmark**
Study design	Study uses baseline data from the DanThyr (Danish Investigation of Iodine Intake and Thyroid Diseases) cohort study. Participants met for clinical examination at baseline. Inclusion period from 10 March 1997 to 1 June 1998.
Population, subjects	Recruitment from 2 cities: Aalborg and Copenhagen. Random samples drawn from civil registration system of all inhabitants of the regions around the 2 cities. Study population included women aged 18–22, 25–30, 40–45, and 60–65 y and men aged 60–65 y. Younger subjects and women were oversampled. Response rate (enrolled/invited) = 4649/9274= 50.1%. Of 4649 subjects studied at baseline, 62 (1.3 %) were pregnant and 85 (1.8 %) were lactating. Ethnicity not reported. Stated in paper that children were not included because unpublished observations did not show cases of goiter in schoolchildren.
Outcome measures	Thyroid volume (ultrasonography): calculated as the max length × width × depth × $\pi/6$ of each lobe. Thyroid enlargement (thyroid volume >18 mL for women and > 25 mL for men). Thyroid nodules (ultrasonography): presence of all solitary nodules > 5 mm against no nodules; all solitary nodules > 10 mm against no nodules; all multiple nodules > 5 mm against no nodules; multiple nodules > 10 mm against no nodules. Serum thyroglobulin (Tg) and thyroid stimulating hormone (TSH): immunoluminometric assays (Lumitest). Thyroglobulin antibodies: radioimmunoassay (DYNOtest) with a functional assay sensitivity < 20 kU/L.
Time between baseline exposure and outcome assessment	All data from clinical baseline examination. FFQ completed while waiting for examination. Not possible to determine time period covered by FFQ from paper. Supplement use appears to be current use.

Reference details, first author, year, country	Rasmussen et al. (2002) Relations between various measures of iodine intake and thyroid volume, thyroid nodularity, and serum thyroglobulin, Denmark
Exposure assessment/ Dietary assessment method	Iodine intake from foods: semi-quantitative, validated FFQ, 53 items, iodine rich foods, described more elsewhere (Rasmussen LB et al. Eur J Clin Nutr 2001;55:287–92). Iodine intake from supplements: subjects were asked to bring in all dietary supplements, and brand names, dosage, and frequency of use were recorded. If they forgot to bring the supplements (< 5% did so), they were interviewed about current supplement use. 7 measures/models of iodine intake were analysed 1. Iodine excretion, spot urine (µg/L): <20, 20–49.9, 50–99.9, >= 100 2. Estimated 24-h iodine excretion (µg/d): <50, 50-99.9, 100-149.9, >=150 3. Total iodine intake (from the diet plus supplements, µg/day, quintiles): <= 80, 81-126, 127-187, 188-256, >256 4. Iodine intake from the diet (ug/day, quintiles): <=70, 71-98, 99-130, 131-175, >175 5. Iodine intake from the diet/kg body wt (µg/kg): <=1.1, 1.1–1.4, 1.5-1.9, 2.0-2.5, > 2.5 6. Iodine intake index (low, medium, high) 7. Milk intake (glasses/day): 0–0.2, 0.3–1.0, 1.1–2.0, 2.1–3.0, >3.0 A low iodine intake index was < 75 g fish/wk and < one-half glass of milk/d and a high iodine intake index was > 200 g of fish/wk and ≥ 0.5 L milk/d. Medium iodine intake index presented in paper, but not defined. Note: Iodized salt was illegal in Denmark at the time the study took place. Note: All milk and milk products were included in milk intake according to Methods, but presented as glasses in Tables.
No. of subjects analysed	Multivariate models for Tvol and thyroid enlargement as outcome included around 4100-4300 participants, depending on iodine exposure. Multivariate models for nodules as outcome included from 3412 to 3819 participants, depending on iodine exposure and nodule outcome (all, multiple, or solitary nodules). Subjects being treated for thyroid disease (n = 77) were not included in the analysis. Subjects with thyroglobulin antibodies > 20 kU/L (n = 627) were excluded from the serum thyroglobulin analyses because of the risk of analytic interference.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Cross-sectional, no follow-up.

Results

Iodine status:
Median (IQR) UIC (spot urine) was 68 (38–112) µg/L in Copenhagen and 53 (30–90) µg/L in Aalborg.
Median (IQR) estimated 24-h iodine excretion was 111 (74–180) µg/d in Copenhagen and 74 (48–126) µg/d in Aalborg.

Results from 7 multivariable regression models (each iodine exposure) per outcome:
Notes regarding estimates: the paper reports estimates for 7 different iodine exposures (categorised) with each of 5 outcomes (mean Tvol; thyroid enlargement (no, yes); multiple nodules (no,yes), solitary nodules (no,yes), or mean Tg). Selected estimates (highest vs lowest) have been extracted for exposure models 1-3 which are considered most relevant (sport urine, estimated 24-h iodine excretion, and total iodine intake). Results are based on the two cities combined; Copenhagen with mild ID and Alborg with moderate ID. The reference categories (lowest) for odds ratios (ORs) are quite low (as specified under exposure models).

Log Tvol/geometric means (Table 2, linear reg) or thyroid enlargement (Table 3, logistic reg) as outcome: Significant (P<0.05) inverse relations with 4 of 7 iodine measures (24-h urinary iodine, total iodine intake from diet and supplements, iodine from diet/kg body wt, milk intake in glasses/day), but not urinary iodine excretion (µg/L), iodine from diet only (excl supplements), and iodine index. Risk estimates (ORs) for the highest categories of iodine from diet only, and the iodine index were significant although overall p-value was not.**Log serum Tg as outcome (Table 5):** All 7 iodine measures were significantly inversely related (p<=0.002) to log serum Tg concentration

Occurrence of thyroid nodules as outcome (Table 4, logistic reg): Results less clear than for Tvol and Tg. Iodine measures most strongly and inversely related to nodules were iodine intake from diet/kg body wt, milk intake, and total iodine intake (diet and supplements).

Models 1,2,3 **High-low effect estimates**	**Thyroid enlargement** **(>18 mL for W, > 25 mL for M)** **OR (95% CI)**	**Nodules, multiple or solitary** **OR (95% CI)**
Model 1: UIC spot urine **≥ 100 vs < 20 µg/L (ref)**	0.81 (0.61, 1.08) Non-sig	Reported as NS, multiple and solitary
Model 2: 24-h urinary iodine excr. ≥150 vs <50 µg/d (ref)	0.54 (0.41, 0.70)	Reported as NS for multiple.

<table>
<tr><td>Reference details, first author, year, country</td><td>Rasmussen et al. (2002) Relations between various measures of iodine intake and thyroid volume, thyroid nodularity, and serum thyroglobulin, Denmark</td></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>Solitary (all):

0.90 (0.66, 1.22)</td></tr>
<tr><td>Model 3: total iodine (diet + suppl) intake >256 vs. ≤ 80 µg/d (ref)</td><td>0.68 (0.51, 0.89)</td><td>Multiple (all): 0.64 (0.47, 0.88)

Solitary (all): 0.70 (0.51, 0.95)</td></tr>
</table>
<table>
<tr><th>Models 1,2,3

High-low effect estimates</th><th>Predicted geometric mean (95% CI),

Tvol, ml</th><th>Predicted geometric mean (95% CI),

serum Tg, µg/L</th></tr>
<tr><td>Model 1: UIC spot urine ≥ 100 vs < 20 µg/L</td><td>13.8 (13.4, 14.2) vs 14.0 (13.5, 14.6)</td><td>19.4 (17.0, 22.1) vs 29.0 (24.9, 33.6)</td></tr>
<tr><td>Model 2: 24-h urinary iodine excr. ≥150 vs <50 µg/d</td><td>13.3 (13.0, 13.7) vs 14.4 (13.9, 14.9)</td><td>18.9 (16.5, 21.6) vs 33.0 (28.7, 38.0)</td></tr>
<tr><td>Model 3: total iodine intake (diet + suppl) >256 vs. ≤ 80 µg/d</td><td>13.7 (13.3, 14.2) vs 14.7 (14.2, 15.2)</td><td>20.0 (17.4, 23.0) vs 29.2 (25.4, 33.6)</td></tr>
</table>
All models were adjusted for city, subject group (age and sex), smoking (daily smoker or not daily smoker), drinking (≥8 drinks/wk or < 8 drinks/wk), and thyroid disease in the family.</td></tr>
<tr><td>Comments</td><td>Statistical notes: Can’t tell which tests were used to calculate p-values. Total iodine intake (diet and supplements) more strongly associated with Tvol than iodine intake from diet adjusted for iodine supplement intake (Table 2 footnote).</td></tr>
<tr><td>Study quality, A-C</td><td>B. Some unclarities /missing information, but maybe available elsewhere</td></tr>
</table>

ST25 Summary table iodine

Reference details, first author, year, country	**Rebagliato et al. (2013) Iodine Supplementation During Pregnancy and Infant Neuropsychological Development INMA Mother and Child Cohort Study, Spain**
Study design	Prospective cohort study
Population, subjects	This multicentre mother and child cohort study was established in Spain between 2003 and 2008, and the present analyses is based on data from the regions of Sabadell (Catalonia), Asturias, and Gipuzkoa (Basque County). Women were enrolled during their first visit to the main public hospital or a regional health centre and were followed through pregnancy. A total of 1789 women agreed to participate and met the following inclusion criteria; ≥16 years of age, singleton pregnancy, intention to deliver at the reference hospital, no communication handicap, and no assisted conception. After excluding the women who withdrew from the study, were lost to follow-up, had induced or spontaneous abortions, or foetal deaths, the study sample comprised 1719 women who delivered a live infant between October 2004 and August 2008.
Outcome measures	Infant neuropsychological development. Cognitive and psychomotor development was assessed using the Bayley Scales of Infant Development in infants median age 16 mo.
Time between baseline exposure and outcome assessment	From enrolment of pregnant women during their first routine antenatal care visit and until outcome assessment at child age 1 year.
Exposure assessment/ Dietary assessment method	- A FFQ was administered twice, at 10-13 weeks and 28-32 weeks of gestation, to assess the usual dietary intake of 100 food items and beverages from the last menstrual period until the third trimester of pregnancy. - Information of the consumption of iodized salt and the use of specific potassium iodine supplements or vitamin/mineral preparations containing iodine was collected using a structured questionnaire. Iodine intake from supplements was estimated based on the supplement brand name and composition, daily dose, and timing of consumption. - Urinary iodine concentration (UIC) was measured in spot samples.
No. of subjects analysed	A total of 1532 (89%) participants were evaluated for neuropsychological development at 1 year of age.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	From baseline to follow-up at child age 1 year. Among the pregnant women who agreed to participate in the present study (n=1789), 89% of their children (n=1532) were evaluated or neuropsychological development at 1 year of age.

Reference details, first author, year, country	Rebagliato et al. (2013) Iodine Supplementation During Pregnancy and Infant Neuropsychological Development INMA Mother and Child Cohort Study, Spain
Results	Median iodine intake from diet was 162 µg/day (IQR:133-191 µg/day). Mean supplementary iodine intake during the months of consumption was classified as a mean dose <100 µg/day, 100-149 µg/day, or ≥150 µg/day (range, 150-400 µg/day). A total of 45, 15.2, and 39.8% of the participants belonged to the different categories, respectively. Median UIC was 125 µg/L (IQR:72-212 µg/L) in the total sample. Maternal consumption of 150 µg/day or more of iodine from supplements was associated with a non-significant decrease of 1.8 (95% CI: −5.6, 2.0) in mental scores and of 0.9 points (95% CI: −6.9, 5.0) in psychomotor scores. The corresponding risks of low mental and psychomotor scores (<85) when compared with supplemental iodine <100 µg/day was 1.7 (95% CI: 0.9, 3.0) for mental scores and 1.5 (95%CI: 0.8, 2.9) for psychomotor scores. However, these associations did not reach statistical significance. Findings previously reported in the Valencia cohort (Murcia et al. 2011) were only partially verified. However, when the results from Murcia et al. (2011) were included in a meta-analyses with results from the other three sub-cohorts, there was a 1.7-fold increase in the odds of a psychomotor score less than 85. In conclusion, maternal UIC, iodized salt consumption, and dietary iodine intake during pregnancy were not associated with neuropsychological development.
Comments	
Study quality, A-C	B

ST25 Dietary information*

SI	
Author, year, study name	Rebagliato et al. (2013) Iodine Supplementation During Pregnancy and Infant Neuropsychological Development INMA Mother and Child Cohort Study, Spain.
Exposure	Iodine intake
Dietary assessment method**	Food Frequency Questionnaire (FFQ)
Food composition database*** Definition of relevant nutrient****	The iodine contents of the food items were primarily obtained from food composition tables from the US Department of Agriculture and from additional information available for iodized salt in Spain.
Internal calibration (or validity) of dietary assessment (y/n) - if yes - provide data	The authors confirm that the questionnaire has previously been used and validated in the general population in Valencia, Spain.
Biomarker assay*****	Iodine in spot urine and serum thyroid hormones (TSH and free thyroxine).
Analytical validity of biomarker data reported? (y/n) – if yes – provide data	No
Time between biomarker sampling and analysis	No information provided.
Season/ date when biomarker samples were drawn	No information provided.
Background exposure data	

* write "nd" if there was no data reported. Please do not leave blank
** please refer to brief name indicated in dietary assessment method table. If other method was used, please describe the detail
*** specify database used to calculate nutrient intakes. Other nutrient analysis, please specify
**** E.g. are carbohydrates expressed as available carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical form of the nutrient
***** ONLY biomarker of interest for outcome

ST26 Summary table iodine

Reference details, first author, year, country	**Rebagliato et al. (2010) Iodine intake and maternal thyroid function during pregnancy, Spain**
Study design	Cross-sectional study
Population, subjects	Between 2004 and 2008, pregnant women were recruited at their first routine antenatal care visit in the main public hospital or health centre of reference in the regions of Sabadell (Catalonia) , Asturias, and Gipuzkoa (Basque County). A total of 2137 women agreed to participate and met the inclusion criteria. The study included participants being at least 16 years old, having a singleton pregnancy, and not following any program of assisted reproduction. In addition, only women providing a serum sample available for thyroid hormone testing and questionnaire data on iodine intake before 24 weeks of gestation were included in the study. Those who reported having been diagnosed with thyroid pathology, regardless of whether or not they continued in treatment, were excluded from the analyses.
Outcome measures	Thyroid hormones (TSH and free thyroxine).
Time between baseline exposure and outcome assessment	NA
Exposure assessment/ Dietary assessment method	- A FFQ was used to assess the usual dietary intake of 100 food items and beverages from the last menstrual period to the time of interview. - Iodine concentrations were measured in a spot urine sample.
No. of subjects analysed	The final analysis was based on 1844 pregnant women.
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	NA

Reference details, first author, year, country	Rebagliato et al. (2010) Iodine intake and maternal thyroid function during pregnancy, Spain
Results	In the total sample, 64% of the participants reported adequate iodine intake (≥160 µg/day) and 96% of the iodized salt consumers reported adequate iodine intake. Iodine intake from supplements was categorised as 0-99, 100-199 and ≥200 µg/day, in which 51, 16 and 33% of the total sample belonged to the different categories, respectively. Urinary iodine concentration was categorised as <50, 50-99, 100-149, 150-249, and 250+ µg/L in which 9, 23, 22, 25 and 21% of the total sample belonged to the different categories, respectively. Consumption of ≥200 µg/d supplemental iodine was associated with higher TSH levels (β=0.090 (95% CI: 0.003, 0.177) and increased risk of hyperthyrotropinemia (TSH>3 µU/mL) compared to those consuming less than 100 µg/d (adjusted odds ratio=2.5 (95% CI; 1.2-5.4). The results showed no association between urinary iodine and TSH levels. Pregnant women from the area with the highest median iodine (168 µg/L) and highest supplement coverage (93%) showed the lowest values of serum free thyroxine (geometric mean = 10.09 pmol/L (9.98-10.19).
Comments	
Study quality, A-C	B

ST26 Dietary information*

SI	
Author, year, study name	Rebagliato et al. (2010) Iodine intake and maternal thyroid function during pregnancy, Spain
Exposure	Iodine intake
Dietary assessment method**	Food Frequency Questionnaire (FFQ).
Food composition database*** Definition of relevant nutrient****	Iodine values were obtained primarily from food composition tables from the US Department of Agriculture and from additional information available for iodized salt in Spain.
Internal calibration (or validity) of dietary assessment (y/n) - if yes - provide data	The authors confirm that the questionnaire has previously been used and validated in the general population in Valencia, Spain.
Biomarker assay*****	Iodine in spot urine and serum thyroid hormones (TSH and free thyroxine).
Analytical validity of biomarker data reported? (y/n) – if yes – provide data	No
Time between biomarker sampling and analysis	No information provided.
Season/ date when biomarker samples were drawn	No information provided.
Background exposure data	

* write "nd" if there was no data reported. Please do not leave blank
** please refer to brief name indicated in dietary assessment method table. If other method was used, please describe the detail
*** specify database used to calculate nutrient intakes. Other nutrient analysis, please specify
**** E.g. are carbohydrates expressed as available carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical form of the nutrient
***** ONLY biomarker of interest for outcome

ST27 Summary table iodine

Reference details, first author, year, country	**Robinson et al. (2018) Preconception Maternal Iodine Status Is Positively Associated with IQ but Not with Measures of Executive Function in Childhood, UK**
Study design	Prospective mother-offspring cohort: The Southampton Women's Survey (SWS).
Population, subjects	A cohort of 12,583 non-pregnant women aged 20-34 were recruited through GPs in Southampton 1998-2002. These were interviewed at home by study nurses and provided blood and urine samples. The 3158 women who became pregnant within the study period and had a live singleton infant were followed up in pregnancy and their children have been assessed in ongoing follow-up studies. Ethnic background is not stated, but may be assumed to be predominantly Caucasian (Approximately 94% of the Southampton population are white according to the SWS Cohort profile paper (Inskip, 2006)).
Outcome measures	Offspring cognitive ability at age 6-7 was assessed by full scale IQ and executive function measured at home visit in 2010, supervised by educational psychologist. Full-scale IQ was assessed by the 2-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI). Executive function by three tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). To reduce the likelihood of chance findings only the following three subscores of CANTAB were applied: 1: Delayed Matching to Subject (DMS) memory test: total correct (12 s delay); 2: Spatial Span (SSP) memory test assessing working memory capacity: span length (longest sequence successfully recalled); 3: Intra-Extra Dimensional Set Shift (IED) test: total errors (adjusted for each stage not attempted due to failure). Maternal (full-scale IQ) was also assessed using WASI. Data was analysed with linear regression using standardised z-scores of the respective outcome measures as dependent variables and maternal preconception iodine status (iodine:creatinine ratio) as independent variable.
Time between exposure and outcome assessment	Exposure assessed median 3.3 years (interquartile range 2.2-4.7 years) before conception, outcome assessed in offspring at age 6-7 years.
Exposure assessment/ Dietary assessment method	Maternal preconception iodine status measured by iodine:creatinine ratio (I/Cr) in spot urine samples at enrolment Maternal diet was assessed by an administered FFQ before conception and in early and late pregnancy. Detailed information on supplement use was collected; supplementary iodine intakes were calculated with the use of manufacturers' composition data, together with participants' reported supplement frequency, dose, and duration of use. (The maternal iodine intake in pregnancy was included as a covariate in the main analysis to improve the accuracy of the model.)
No. of subjects analysed	Of the 942 children who had an assessment of cognitive function at age 6-7 years, 58 (6%) were preterm (born before gestation week 37) and 230 (24%) had no available maternal urine sample. Thus, 654 mother-child pairs were included.
Intervention Intervention/ exposure	None

Reference details, first author, year, country	Robinson et al. (2018) Preconception Maternal Iodine Status Is Positively Associated with IQ but Not with Measures of Executive Function in Childhood, UK
Results	Median maternal preconception UIC was 108 (IQR: 62-168) µg/L and median I/Cr was 114 (IQR: 76-164) µg/g. In statistical analysis, four different associations were studied, i.e. the associations of preconception urinary I/Cr ratio with the four respective outcome parameters in the offspring at age 6-7 years: IQ determined by WASI, and the executive function subtests DMS, SSP and IED determined by CANTAB. Altogether 16 statistical tests appear to have been performed, i.e. associations of urinary I/Cr ratio with the 4 outcome parameters x 2 analyses according to covariate adjustment (crude and adjusted) x 2 analyses according to the nature of the exposure variable (continuous and in categories according to predefined cutoffs). Corrections for multiple testing were not made. One statistically significant finding: There was a statistically significant positive linear association between preconception I/Cr and offspring IQ. Beta-coefficient 0.13 (95% CI 0.04, 0.21) SD (standardised z-score) higher IQ z score per z score higher I/Cr after adjustment for maternal IQ, maternal education, and maternal pre-pregnancy BMI, breastfeeding duration, smoking in pregnancy, sex, age, and maternal iodine intakes in pregnancy. In comparison with children of women with an I/Cr ≥150 µg/g, children of women with preconception urinary I/Cr <50 µg/g (moderate iodine pre-pregnant iodine deficiency) had 0.49 (95% CI: 0.79, 0.18) SD lower IQ, which is equivalent to a difference of 7.5 IQ points. Three null findings: Maternal I/Cr was not associated with any of the three executive function outcomes assessed using CANTAB.
Comments	
Study quality, A-C	B

ST28 Summary table iodine

Reference details, first author, year, country	**Skeaff et al. (2012) A comprehensive assessment of urinary iodine concentration and thyroid hormones in New Zealand schoolchildren: a cross-sectional study, New Zealand**
Study design	Cross-sectional
Population, subjects	"Children's Nutrition Survey"; cross-sectional survey of a nationally representative sample of New Zealand school children aged 5-14 years, carried out 2002. Two-stage school-based sampling frame with over-sampling of Māori and Pacific children to allow for ethnic specific analysis. Schools were randomly selected from the Ministry of Education rolls and children from these schools were randomly selected in proportion to the number of children on the school roll. Blood and urine samples were collected from a subset of children during school hours (urban schools only, to avoid long transport affecting stability). Of 200 invited schools, 172 schools (86%) agreed. Of 4728 invited children in the participating schools, 3275 (69%) participated. Urine was collected from 1796 children (55% of participants). Blood was collected from 1927 children (59% of participants). Finally, 1153 children had available measurement data for exposure and outcomes and were included in the analysis (35% of participants; 24% of the invited children in the schools that had agreed). 611 were boys and 542 were girls. Children were categorised into three ethnic groups based on parental report; Māori (n=338; 29%), Pacific (n=482; 42%), and New Zealand European & all Other ethnicities ("NZEO": n=333; 29%).
Outcome measures	Thyroid function defined by serum thyroglobulin (Tg), serum Thyroid Stimulating Hormone (TSH), plasma free thyroxine (fT4) and free triiodothyronine (fT3). Regression analysis was performed to estimate mean and 95 confidence intervals of the four blood biomarkers according to iodine status categories defined by UIC cutoffs of 50 µg/L and 100 µg/L, respectively. The data analysis took into account the clustering (school-based design), weighting (urban children and ethnic groups), socioeconomic status (based on deprivation index of residential address), age, sex and ethnicity.
Time between exposure and outcome assessment	Cross sectional design; the urine samples for exposure assessment (UIC) and the blood samples for outcome assessment (Tg, TSH, fT4 and fT3) were collected at the same time.
Exposure assessment/ Dietary assessment	Iodine status defined by urinary iodine concentration (UIC) in a spot urine sample (µg/L). A 24-hour diet recall was collected from participating children, but iodine intakes were not determined since the iodine content of foods was neither complete nor reliable in the New Zealand Food Composition Database.
No. of subjects analysed	n=1153 children
Follow-up, drop-out	See "population and subjects" for attendance rate.

Reference details, first author, year, country	Skeaff et al. (2012) A comprehensive assessment of urinary iodine concentration and thyroid hormones in New Zealand schoolchildren: a cross-sectional study, New Zealand
Results	Median UIC was 68 (IQR: 50-95) µg/L. Tg was lower at UIC ≥100 µg/L (estimated mean 10.3 (95% CI 8.8, 12.1) µg/L) and higher at UIC <50 µg/L (estimated mean 15.6 (95% CI 14.0, 17.3) µg/L) while there were only minor differences in the other outcome parameters. Compared with children who had UIC ≥50 µg/L, those with UIC <50 µg/L had statistically significantly higher Tg (estimated mean 15.6 vs. 12.3 µg/L) and fT3 (estimated mean 6.1 vs. 5.9 pmol/L), while TSH and fT4 did not differ according to this cutoff. Correspondingly, compared with children who had UIC ≥100 µg/L, those with UIC <100 µg/L had statistically significantly higher Tg (estimated mean 13.9 vs. 10.3 µg/L) and fT3 (estimated mean 6.0 vs. 5.9 pmol/L), while TSH and fT4 did not differ between the groups.
Comments	
Study quality, A-C	B

ST29 Summary table iodine

Reference details, first author, year, country	**Snart et al. (2019) Maternal Iodine Status and Associations with Birth Outcomes in Three Major Cities in the United Kingdom, UK**
Study design	Data from pregnant women in London, Manchester and Leeds participating in the Screening for Pregnancy Endpoints (SCOPE) birth cohort (n=541) were used to assess prospective associations between maternal iodine status (UIC) in two spot urines (donated in gestational weeks 15 and 20) and birth outcomes.
Population, subjects	
Outcome measures	Pregnancy outcomes: primary outcome: birth weight and birth weight centile, secondary outcomes: birth weight, small for gestational age (SGA, defined as<10^{th} customised centile adjusted for maternal height, weight, parity, ethnicity, gestational age and sex), and spontaneous preterm birth (<37 completed weeks).
Time between baseline exposure and outcome assessment	15 gw to delivery
Exposure assessment/ Dietary assessment method	Urinary iodine concentration was measured in two spot urines, one in 15 gw and one in 20 gw. The mean UIC of both time points were the main exposure. Median UIC was 134 µg/L, (139 µg/L in Manchester, 130 µg/L in London and 116 µg/L in Leeds), and the proportion with UIC <50 µg/L was <20% in all three cities.
No. of subjects analysed	541
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	Follow up from recruitment (antenatal visit) in week 15 to delivery.
Results	No evidence of an association between UIC and birth weight centile (-0.2% per 50 µg/L increase in UIC), nor with odds of spontaneous preterm birth (odds ratio: 1.00; 95%CI: 0.84, 1.20) or SGA (odds ratio: 1.09,; 95%CI: 1.00, 1.20). Sensitivity analyses gave similar results (using creatinine adjusted UIC, µg/g Cr) and assessing iodine at the individual time points.
Comments	The study population was small and the participants were only mildly iodine deficient (median UIC was 134 µg/L and <20% had UIC below 50 µg/L). The participants were not sufficiently iodine deficient to detect associations.
Study quality, A-C	B

ST30 Summary table iodine

Reference details, first author, year, country	**Sun et al. (2019) Association between iodine intake and thyroid autoantibodies: a cross-sectional study of 7073 early pregnant women in an iodine-adequate region, China**
Study design	Cross-sectional study examining associations between UIC and thyroid autoantibodies in pregnant women in two Chinese cities.
Population, subjects	7073 pregnant women recruited in gestational weeks 4-8 (mean 7.2) in the cities Dalian and Shenyang in 2012-2014. Age range 19-40 years.
Outcome measures	Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) positivity defined by TPOAb > 34 IU/mL and TgAb > 115 IU/mL. The prevalence of TPOAb positivity was 8.8% and of TbAb was 12.2%. In total, 15.5% were positive to TPOAb, TgAb or both.
Time between baseline exposure and outcome assessment	None
Exposure assessment/ Dietary assessment method	Median UIC was 153.6 µg/L. UIC was categorised into five groups based on WHO criteria for pregnant women: UIC<100 µg/L (deficient), UIC 100-149.9 µg/L (borderline deficient), UIC 150-249.9 µg/L (adequate), 250-500 µg/L (more than adequate), and UIC ≥ 500 µg/L (excess). The distribution was 20.8% deficient, 27.4% borderline deficient, 34.2% adequate, 14.4% more than adequate, and 3.2% excessive.
No. of subjects analysed	N=7073
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	
Results	Low urinary iodine (UIC<100 µg/L) was significantly associated with higher TPOAb as well as TgAb positivity. The adequate iodine group had the lowest antibody rates. Compared to individuals with UIC in the adequate group (150-249.9 µg/L), the adjusted odds of TPOAb positivity in those with UIC <100 µg/L was 1.64 (95%CI 1.29, 2.08) and the aOR for TgAb was 1.44 (95%CI 1.16, 1.80). The associations were not significant for the other iodine groups.
Comments	The associations were adjusted for age, weeks of gestation, BMI and mutual adjustment for TPOAb positivity and TgAb positivity.
Study quality and relevance, Comments A-C	B

ST31 Summary table iodine

Reference details, first author, year, country	**Thomson et al. (2009) Selenium and iodine supplementation: effect on thyroid function of older New Zealanders, New Zealand**
Study design	Double-blind, randomised, placebo-controlled trial (RCT).
Population, subjects	This RCT was carried out with older male and female residents of Dunedin in the South Island of New Zealand from August to November 2005. Participants were aged between 60 and 80 y; noninstitutionalised, were free from serious medical illness such as cancer, diabetes, or cardiovascular disease; were not using medications form thyroid function or with any known thyroid problems and were not taking multivitamin-multimineral or other dietary supplements that contained selenium or iodine. Block randomisation with stratification for sex was used to assign 76 participants into 1 of 3 treatment groups.
Outcome measures	Thyroid-stimulating hormone (TSH), free triiodothyronine (T_3) free thyroxine (T_4), thyroglobulin, plasma selenium, whole-blood glutathione peroxidase (GPx) activity, and urinary iodine concentration (UICs) were measured.
Time between baseline exposure and outcome assessment	Three months
Exposure assessment/ Dietary assessment method	- Blood and urine samples were collected in order to examine plasma selenium concentrations and urinary iodine concentration (UIC). - For dietary assessment, participants also completed a brief questionnaire that included questions on dietary habits, supplements and medication use, and consumption of foods high in selenium or iodine such as seafood and Brazil nuts.
No. of subjects analysed	A total of 100 participants at baseline, and 97 participants who completed the trial.
Intervention Intervention/ exposure	A population with moderate iodine deficiency (median UIC 48 µg/L) received 100 µg Se/d, 80 µg I, 100 µg Se + 80 µg I, or placebo for 3 months.
Follow-up period, drop-out rate	From baseline to follow-up. Of the 102 participants initially randomly assigned to treatment groups, 1 participant was excluded from all analyses because her test indicated thyroid disease, 1 participant did not attend the baseline clinic, leaving 100 participants from whom baseline characteristics are reported. By week 12, a further 3 participants had dropped out, leaving 97 participant who completed the trial (23,25,24,25 in the placebo, selenium, iodine, and selenium plus iodine groups, respectively). A further 9 participants did not provide urine samples for reasons that include difficulty in passing urine or were unwilling to provide a sample. Compliance with supplement use was excellent with 90% of all participants consuming all supplements and 10% consuming between 97% and 99% of their supplements.

Reference details, first author, year, country	Thomson et al. (2009) Selenium and iodine supplementation: effect on thyroid function of older New Zealanders, New Zealand
Results	Median UIC at baseline was 48 µg/L (IQR:31-79 µg/L) in the total sample. Plasma selenium ($p<0.0001$) and whole-blood GPx activity ($p<0.0001$) increased from baseline to week 12 in the selenium and selenium plus iodine groups in comparison with the placebo group. UIC increased in the iodine and selenium plus iodine groups and was significant only form the iodine group ($p=0.0014$). Thyroglobulin concentration decreased by 24% and 13% of baseline in the iodine and selenium plus iodine groups in comparison with the placebo group ($p=0.009$ and $p=0.108$, respectively). No significant treatment effects were found for TSH, free T_3, free T_4, or ratio of T_3 to T_4.
Comments	
Study quality, A-C	A

ST32 Summary table iodine

Reference details, first author, year, country	**Thomson et al. (2001) Urinary iodine and thyroid status of New Zealand residents, New Zealand**
Study design	Cross-sectional
Population, subjects	Adult population in a low soil iodine area of the South Island of New Zealand. 350 Otago residents aged 18-49 years were recruited 1997-98. Initially recruitment was by random selection from the electoral roll and later by non-random selection from blood donors at the Dunedin Blood Bank. Of these, 233 subjects (114 men and 119 women, mean age 32 years) were recruited for assessment of thyroid hormone status in a blood sample and for thyroid volume by ultrasonography.
Outcome measures	Thyroid status determined from serum total thyroxine (T4), Thyroid Stimulating Hormone (TSH) and thyroglobulin (Tg), and thyroid volumes measured by ultrasonography. Thyroid hormone levels and thyroid volume of subjects were analysed according to three categories of I/Cr ratio divided according to the following cutoffs: Low (<40 µg/g Cr), medium (40-60 µg/g Cr) and high (>60 µg/g Cr). The cutoffs were chosen in order to give approximately equal numbers in each group, and were close to the criteria adapted from Clugston and Hetzel (1994) for adequate, low and marginal status. Comparisons of outcomes between the groups were done using multiple regression controlling for gender and weight.
Time between baseline exposure and outcome assessment	Cross sectional design; no time span between exposure and outcome measurements.
Exposure assessment/ Dietary assessment method	Iodine status measured by two 24-hour urine collections. Complete 24 h urine collections were done by all subjects on two occasions. An average of the two results was used to assess urinary iodine status. The following three measures are presented: 24 h urinary iodide excretion (µg/day), iodide/creatinine ratio (µg/g Cr) and urinary iodide concentration (µg/L). Diet was not assessed, but subjects completed a questionnaire on use of supplements and iodine-containing medications.
No. of subjects analysed	N=233 participants
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	-

Reference details, first author, year, country	Thomson et al. (2001) Urinary iodine and thyroid status of New Zealand residents, New Zealand
Results	Mean (SD) 24-h UIE was 86 (49) µg/day. Mean (SD) UIC was 59 (33) µg/L. Mean I/Cr was 57 (35) µg/g. Thyroid status: In multiple regression analysis of thyroglobulin controlling for gender and weight showed a significant difference among the three groups categorised according to 24-hour excretion (P=0.019) and I/Cr ratio. (P=0.005), with higher thyroglobulin concentrations at lower iodine status: Low (<40 µg I/g Cr): Mean 8.0 (95% CI 6.2, 9.8) ng/ml. Medium (40-60 µg I/g Cr): Mean 6.6 (95% CI 5.3, 7.9) ng/ml. High (>60 µg I/g Cr): Mean 6.2 (95% CI 4.8, 7.5) ng/ml. No associations with plasma TSH or T4 were observed. Thyroid volume: In multiple regression analysis controlling for gender and weight there was a significant difference in thyroid volume between the three groups when categorising according to 24-hour iodide excretion (P=0.029) and when categorising according to I/Cr ratio (P=0.035), with larger thyroid volume at lower iodine status. Low (<40 µg/g Cr): mean 16.7 (95% CI 15.0, 18.4) ml. Medium (40-60 µg/g Cr): mean 14.5 (95% CI 13.3, 15.8) ml. High (>60 µg/g Cr): mean 12.2 (95% CI 11.3, 14.2) ml. No differences were observed when subjects were categorised according to UIC in µg/L.
Comments	
Study quality, A-C	B

ST33 Summary table iodine

Reference details, first author, year, country	**Torlinska et al. (2018) Iodine Status during Pregnancy in a Region of Mild-to-Moderate Iodine Deficiency is not Associated with Adverse Obstetric Outcomes; Results from the Avon Longitudinal Study of Parents and Children (ALSPAC), UK**
Study design	Mother-and-child cohort
Population, subjects	ALSPAC recruited pregnant women from Avon county in South-Western UK, with expected dates of delivery April 1991 through December 1992. Of 14,541 women enrolled, 13,988 had offspring surviving for at least 12 months. The current study was based on 3524 women with a singleton pregnancy who had a urinary I/Cr measure during pregnancy (already available from ongoing substudies examining maternal iodine status and child IQ at age 8 years). In addition, 46 women who had experienced pregnancy/infant loss up to the age of 1 year and who had an available antenatal urine sample were selected. Women with excessively high UIC (>500 mg/L) and/or high I/Cr ratio (>700 mg/g) were excluded due to concern that the samples had been contaminated with iodine from urine test strips (child alive at 1 year: n=414, 11.7%; pregnancy/infant loss n=5, 10.9%). If a woman had a later urine sample (with result that could be considered uncontaminated) that was used to replace the contaminated result (child alive at 1 year n=50; pregnancy/infant loss n=1). Those using thyroid hormone medication during pregnancy were excluded (child alive at 1 year n=20, 0.5%; pregnancy/infant loss, n=0). The resulting sample included in the analysis was 3140 women with a child alive at 1 year, and 42 women with a pregnancy/infant loss. Median age was 29 years (interquartile range 26-32) and similar in the two groups. Mean BMI was 22 kg/m^2 and similar in the two groups. The distribution of ethnic background is not presented but it is stated with reference to the cohort profile paper (Fraser et al., *Int J Epidemiol* 2013) that the majority of ALSPAC participants were white and had indicators of high SES.
Outcome measures	Seven different adverse pregnancy outcomes: (i) hypertensive disorders in pregnancy; (ii) glucose derangement; (iii) anaemia; (iv) post-partum haemorrhage; (v) preterm birth; (vi) mode of delivery; and (vii) birthweight. Details of obstetric outcomes were extracted from hospital records following delivery. Associations between I/Cr grouped in four categories and odds of each pregnancy outcome was examined in logistic regression, with the highest I/Cr (150–249 µg/g) as reference category. Adjustment was made for pre-pregnancy BMI, age, parity, cigarette smoking in early pregnancy, and trimester of urine sample.
Time between exposure and outcome assessment	Exposure assessed in early pregnancy (see details in "Exposure"), outcomes assessed later in pregnancy or at birth.
Exposure assessment/ Dietary assessment	Iodine status measured in spot urine samples, reported both as UIC (µg/L) and I/Cr ratio (µg/g). I/Cr ratio was categorised into: <50 µg/g, 50-149.9 µg/g, 150-249.9 µg/g, and ≥250 µg/g, broadly speaking related to severely deficient, mildly-to-moderately deficient, sufficient, and more-than adequate iodine. For women with a repeat urine sample, the earliest available sample was used, as the authors postulated that impact of iodine status on pregnancy outcome is greatest in early pregnancy. Dietary data were not included.
No. of subjects analysed	n=3140 women with a child alive at 1 year, and n=42 women with a pregnancy/infant loss.

Reference details, first author, year, country	Torlinska et al. (2018) Iodine Status during Pregnancy in a Region of Mild-to-Moderate Iodine Deficiency is not Associated with Adverse Obstetric Outcomes; Results from the Avon Longitudinal Study of Parents and Children (ALSPAC), UK
Results	Median UIC was 95 (IQR 57-153) µg/L and median I/Cr was 124 (IQR 82-198) µg/g. No associations were found between iodine status and adverse pregnancy outcomes.
Comments	The study was underpowered to detect associations with rare outcomes (pregnancy and infant losses).
Study quality, A-C	B

ST34 Summary table iodine

Reference details, first author, year, country	**Wang et al. (2019) U-shaped relationship between iodine status and thyroid autoimmunity risk in adults, China**
Study design	Cross-sectional study examining associations between iodine status and thyroid antibodies in adults.
Population, subjects	2808 adult men and women recruited in Shanghai in 2016.
Outcome measures	Thyroid autoimmunity defined by the presence of positive thyroid peroxidase antibody (TPOAb) defined as TPOAb>34 IU/mL, or thyroglobulin antibody (TgAb) defined as TgAb>50 IU/mL, or thyroid autoimmunity (TAI) defined as a combination of positivity of one or both.
Time between baseline exposure and outcome assessment	None
Exposure assessment/ Dietary assessment method	Median UIC was 164.5 µg/L. UIC was divided into four groups: UIC<100 µg/L (deficient), UIC 100-199.9 µg/L (adequate), UIC 200-299.9 µg/L (more than adequate), and UIC ≥ 300 µg/L (excess). The distribution of the different categories was 20.2% deficient, 44.6% adequate, 21.9% more than adequate, and 13.2% excessive.
No. of subjects analysed	N=2808
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	
Results	No association for TPOAb or TgAb alone, but a U-shaped association between iodine status and TAI. Compared to individuals with UIC in the more than adequate range (200-299.9 µg/L), the adjusted odds of thyroid autoimmunity in those with UIC <100 µg/L was 1.50 (95%CI 1.03, 2.17). The corresponding aOR was 1.50 (95%CI 1.09-2.07) in those with UIC in the adequate range (100-199 µg/L) and 1.68 (95%CI 1.11-2.53) in those with excessive iodine (≥ 300 µg/L).
Comments	The associations were adjusted for age, sex, smoking, diabetes, BMI, hypertension and mutual adjustment for TPOAb and TgAb.
Study quality and relevance, Comments A-C	B

ST35 Summary table iodine

Reference details, first author, year, country	**Zhou et al. (2019) Maternal iodine intake in pregnancy and childhood neurodevelopment at 18 months, Australia**
Study design	Prospective cohort design
Population, subjects	Iodine intake (primary), UIC during pregnancy in 699 women with available data on outcome in children at 18 months in Adelaide, Australia. This population was categorised as mildly iodine deficient before mandatory bread- iodine fortification was implemented in 2009, but at the time of this study, the population was iodine sufficient (median UIC was 186 µg/l (IQR 108–308 µg/L). The pregnant women were included between 2011 and 2013.
Outcome measures	Cognitive, language and motor skills assessed by the Bayley Scale of Infant Development (BSID) III.
Time between baseline exposure and outcome assessment	Main exposures were measured at wk 20 and 28 of pregnancy. BSID was measured at 19.5 months of age. I.e. approximately 22-24 months between exposure and outcome
Exposure assessment/ Dietary assessment method	An iodine-specific FFQ measured twice in pregnancy (wk 20 and 28). Items with iodine 5% of the RDI were included. They also recorded table salt and iodine supplement use. Iodine from food and supplements were summed. The intake was averaged between the two time points and the difference in BSID scores were compared between the iodine intake quartiles. In addition, UIC was examined as the exposure.
No. of subjects analysed	699
Intervention Intervention/ exposure	None
Follow-up period, drop-out rate	24 months. > 90% of the mother-infant dyads could be included in the analyses.
Results	The relationship between iodine intake and BSID had an inverted U shape; those with the lowest and highest intakes had lower BSID scores and were at a higher risk of a BSID score of <85. In comparison to children born to mothers in the second quartile (reference group, intakes 220-316 µg/day), children of mothers with iodine intakes in the lowest quartile <220 µg/day had 4.3 points lower scores on cognitive, 6.3 points lower scores on language, and 3.5 lower scores on motor. The corresponding odds of low scores (Bayley III-scores<85) for children of mothers in the lowest quartile was 2.8 (95%CI 1.3, 5.7) for cognitive, 2.4 (95%CI 0.9, 5.8) for language and 2.2 (95%CI: 0.9, 5.2). There were no associations between UIC in pregnancy and the Bayley-III outcomes.
Comments	The study participants had in general adequate iodine intake and status. Several confounders were adjusted for including maternal IQ (WAIS), SES, Home stimulation environment, and pregnancy related factors.
Study quality, A-C	B

ST35 Dietary information*

SI	
Author, year, study name	Zhou et al. (2019) Maternal iodine intake in pregnancy and childhood neurodevelopment at 18 months, Australia.
Exposure	Iodine intake and UIC
Dietary assessment method**	A validated iodine food frequency questionnaire (I-FFQ) which included 44 food items and assessed intake over the previous month. The I-FFQ also asked participants whether they used salt in cooking or at the table and if the salt added was iodized salt. Iodine intake from supplements was calculated by multiplying the average daily number of tablets consumed and the level of iodine per tablet provided by the manufacturers. Iodine intake from foods and supplements was summed as iodine intake in pregnancy.
Food composition database*** Definition of relevant nutrient****	The most up-to-date Australian food composition database, NUTTAB 2010
Internal calibration (or validity) of dietary assessment (y/n) - if yes - provide data	A validation study that showed a moderate correlation in iodine intake assessed using the I-FFQ and a 4-day weighed food record, with good reproducibility and a fair agreement in classifying adequate or inadequate iodine intake.
Biomarker assay*****	NA
Analytical validity of biomarker data reported? (y/n) – if yes – provide data	NA
Time between biomarker sampling and analysis	NA
Season/ date when biomarker samples were drawn	NA
Background exposure data	

* write "nd" if there was no data reported. Please do not leave blank
** please refer to brief name indicated in dietary assessment method table. If other method was used, please describe the detail
*** specify database used to calculate nutrient intakes. Other nutrient analysis, please specify
**** E.g. are carbohydrates expressed as available carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical form of the nutrient
***** ONLY biomarker of interest for outcome

ST36 Summary table iodine

Reference details, first author, year, country	**Zimmermann et al. (2006) Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study, Albania**
Study design	A double-blind randomised controlled intervention trial with iodine versus placebo and follow up for 24 weeks.
Population, subjects	Children (10-12 years) recruited in primary schools in Albania in an area with severe iodine deficiency (87% had goiter). Intervention group n=159, placebo n=151. 166 boys and 144 girls. Median UIC indicated moderate iodine deficiency (43 µg/L) while 87% had goiter, and nearly one-third had low concentrations of circulating TT4.
Outcome measures	Cognitive and motor performance tests at baseline and after 24 weeks (Raven's Coloured Progressive Matrices (intelligence), Bead threading (fine motor), Rapid target marking, Digit span (short-term memory from WISC), Symbol search (visual from WISC), Coding (from WISC), and Rapid object naming (speed/time at which a child is able to name a series of familiar objects)).
Time between baseline exposure and outcome assessment	24 weeks
Exposure assessment/ Dietary assessment method	Urinary iodine concentration, thyroid volume, TSH, total thyroxine TT4 (hypothyroxinemia) measured at baseline and at the time of outcome.
No. of subjects analysed	159 in the intervention group, 151 in the control group.
Intervention	A 400 mg iodine as iodized poppy seed oil capsule vs. placebo sunflower-oil capsules (swallowed with water under direct supervision).
Follow-up period, drop-out rate	24 weeks, dropout: 6 children (1.9 %), 4 in the I group and 2 in the placebo group.
Results	The iodine intervention group significantly improved performance (adjusted treatment effect (95%CI)) on 4 of the 7 tests; Raven's Coloured Progressive Matrices (4.7 (95%CI: 3.8, 5.8) points), Rapid target marking (2.8 (95%CI: 1.4, 4.0) points), Symbol search (2.8 (95%CI: 1.9, 3.6) points), and Rapid object naming (4.5 (95%CI: 2.3, 6.6) points).
Comments	The results showed improvement on some cognitive tests, but no improvement on test relying on working memory.
Study quality, A-C	B

Appendix IV – Exposure – supplementary methodological information

This appendix describes the approaches to exposure estimates and scenarios presented in chapter 7. The mixed models approach for exposure estimates is detailed, and some simple comparisons between the three different methods for calculating exposure estimates; observed individual means (OIMs), mixed models approach (MM) and Monte Carlo risk assessment (MCRA) is presented.

Details about the MM-method

The main goal of a chronic intake calculation is to arrive at some characterisation of the long-term mean intake for many individuals. Classical approaches to intake analysis and exposure estimation usually consists of summary statistics (mean, percentiles, median etc.) on *observed individual means* (OIM); i.e. the means of intake for each individual in the survey. The standard error, i.e. a measure of the accuracy with which we can estimate all these individual means, is inversely related to the number of days from which we have intakes (se = sd/sqrt(n_days)). Firstly, this implies that, regardless of methodology, a lower number of days will lead to an overestimation of the variation *between* individuals, since there will be much more noise in the calculation of the means for each individual. Secondly, since most intake distributions have long upper tails (i.e. they are bounded by 0, and the distribution is highly skewed), using OIMs will particularly lead to an overestimation of the upper intake percentiles.

In this report we also apply generalised linear *mixed models* (MM) and use them to simulate long-term exposures and implement scenarios. In addition to directly addressing the problem with overestimation of outer (and particularly upper) percentiles compared to OIMs, there are several other benefits of using mixed models to analyse individual level exposures: 1) MM allows for a flexible decomposition of variance, 2) MM can take into account covariance of variables (e.g. for daily iodine intake and bread consumption) in a multivariate model, 3) MM can easily be used to correct for (part of) the bias in the survey. In our approach the data for the models is the individual level *daily* intakes of *iodine* and *bread*.

Flexible decomposition of variance – not all subgroups vary in the same way

In contrast to OIMs a statistical model of daily exposures can also decompose variability in selected subgroups. For instance, we can define the model structure such that males and females exhibit different levels of variability within individuals. This is of particular

importance when interested in the exposure of high-risk sub-groups; they might not only differ in the *mean* exposure compared to the whole population, but also exhibit a different level of variability. For iodine intake in the Norkost 3 survey this holds; women do not only get less iodine through their diet, but there is also a much lower level of variability between individual women. A mixed model is especially applicable for data with repeated observations, which survey data is. Explicitly estimating the between individual variability and the between day variability *within* individuals yields more robust inferences on the long-term exposures in which we wish to factor out daily variability, but keep variability between individuals.

Multivariate models – bread and iodine intake are correlated

In addition to decompose variability in a mixed model, a *multivariate* model can also be constructed - a model with more than one response variable. Such multivariate analyses is especially important for iodization of salt in bread, as there can be a correlation between iodine intake and bread consumption. In case of implementing measures it is of crucial importance to assess the degree to which a particular measure will reach the intended sub-group. In all surveys analysed in this benefit and risk assessment (except for 4-year-old boys), there is a positive correlation between intake of bread (and thus salt in bread) and intake of iodine. This means that individuals with low iodine levels also have a low intake of salt and thus the effect of iodization will to a large degree only increase intake in those with already high intakes of iodine. This positive correlation/covariance is exactly what we find in all our models and is accounted for in all MM scenarios. Without such accounting the effect of iodization of salt in bread would be overestimated.

Using a MM for exposures and scenarios - correcting for bias in survey respondents

When constructing the statistical models, we have included predictors (i.e. fixed effects) *sex*, *age* and *level of education* (for Norkost 3), and only sex (Ungkost 3: 4- ,9- and 13-year-olds). Therefore, we can also correct for some of the biases in the survey.

Exposure estimates are performed as simulations; essentially we draw a large number of 'individuals' of different ages, levels of education and sex, and for each of these individuals we draw a large number of individual days of intake of iodine (and bread). For each of these individuals we then calculate a mean iodine intake which, over many individuals, is our estimated population level exposure.

For Norkost 3 we directly estimated the effect of age on the intake of both iodine and bread. When simulating exposures we used a different age-distribution when sampling the population level exposure from the fitted model. In other words, instead of sampling the age of the focal individual from the Norkost 3 recipients, we sampled the age of this individual from the age-distribution of Norwegians in general. Our estimates are therefore more likely to fit the general population, rather than to describe the intake of the particular group that

was part of the survey. We also corrected for level of education in the Norkost 3 survey, which also has an effect on both bread consumption and iodine intake.

Our use of MM here consisted of two steps. First, we constructed a suitably parameterised model for the exposures and then we used *Monte Carlo* sampling/simulation to draw exposures from the fitted model. Assumptions on the intake of household salt enters when using the models to evaluate the scenarios. This is in principle similar to some of the parts of *MCRA* (Monte Carlo Risk Assessment-tool) from the Netherlands National Institute for Public Health and the Environment (RIVM) (van der Voet et al., 2015). However, the models in MCRA does not allow for the more complex nesting of individual level effects within sexes, i.e. allowing males to have a different level of variation than females. Nor does MCRA allow for multivariate analysis necessary for properly including correlation of iodine and salt intake. Results from MCRA is therefore only shown for Norkost 3, estimated iodine intake for women of childbearing age (18-45 years), see Table IV-1 and also for comparison of the three exposure methods used in this benefit and risk assessment.

Household salt consumption

None of the surveys have reliable data on use of household salt. We therefore estimated the long-term intake of salt based on data from Tromsø 7 (see section 7.2.1). For all the scenarios and for all simulated individuals we drew household salt consumption as detailed in Table 7.2.1-1. We do not have any information about the potential covariance between household salt usage and intake estimates and assume they are independent.

Model setup for iodine or bread/salt in bread intake

Data in this section refer to intakes (either iodine or bread/salt in bread) for a given individual for a given day. We have no individual level data for household salt intake.

For Norkost 3 we have 1767 individuals whose diet is coded for two days, giving multiple observations (one per day) for two variables (iodine intake and bread/ salt intake from bread). The fixed predictors included were *sex*, *level of education* (binary: more or less than 13 years of schooling) and *age*. The logarithm of exposure is denoted with y_{ij} (for individual i, on day j). Explanatory variables (sex, age, education) are denoted by x_{il}. Random effects are incorporated in a design matrix Z, where membership in the groups for which the random effects are calculated is coded. The exposure is log-transformed to improve the estimation of the parameters and since exposures are bounded by 0 (but the log is unbounded). In our case the link function is the identity. The basic model is

$$Y = X\beta + Zb + \varepsilon$$

Where Y, X and Z, is the matrices of exposures (composed of all y_{ij}'s), the fixed effects design matrix (composed of all x_{ij}'s) and the random effects design matrix (composed of coded membership in groups), respectively. The simplest mixed model would be one with no

predictors and only one group of random effects. In such a case the log exposures are modelled as

$$y_{ij} = \beta_1 + b_i + \varepsilon_j$$

Thus the observed log exposure y_{ij}, of individual *i* on day *j*, is a sum of the overall mean (β_1), this particular individual's deviation from the mean (b_i), and a residual term capturing the deviation for this particular day. All *b's* are assumed to come from a normal distribution with mean 0 and variance σ_1, and similarly all ε_j are assumed to come from a different normal distribution with mean 0 and variance σ_2.

To apply Monte Carlo sampling on such a model we would draw a 'new' individual level deviation (b_{new}) from *N(0,* σ_1*)*, and several (say 365), daily deviations (ε_j) from a *N(0,* σ_2*)*. Then we back-transform these 365 daily exposures to the original scale and calculate the mean. This is the long-term exposure from one unobserved individual. This is repeated a large number of times to get a distribution of exposures. If this is performed in a Bayesian setting then formally these posterior predictive numbers correspond to the estimated probability distribution of exposure in the population given the original data, the priors and the structure of the model.

For the models applied herein, both the random effects (i.e. *between-individual* variability) as well as the residuals (i.e. the *day-to-day* variation within individuals) were assumed different between the sexes. In other words, we directly estimated the degree to which males and females vary between days and between individuals independently. In multivariate models, where two or more intakes or exposures are modelled in concert, the covariance in the *between-individual* variability can be estimated independently for males and females. This captures the degree to which individuals with a high intake of iodine also have a high intake of salt from bread-products. Characterising this covariance is crucial for generating robust fortification scenarios. For all models, four different sets of priors were designed to test for prior-dependence, but both fitted parameters and simulated exposures were almost identical between priors, indicating strong signal from the data.

These mixed models were all implemented in the computing environment *R*, using the Bayesian MCMCglmm package (Hadfield, 2010). Code to conduct the analysis is available upon request

The model detailed above is in structure relatively similar to the main component of the MCRA tool developed by the Netherlands National Institute for Public Health and the Environment (RIVM) (van der Voet et al., 2015). However, more customisable approaches are readily available when using the R environment. For instance, a MM-model can easily be defined to estimate both individual differences and day-to-day difference in iodine exposure to be different for females and males.

We applied statistical modelling of iodine and salt from bread using data from Norkost 3 and Ungkost 3.

Models

For each survey we constructed eight models: iodine intakes with or without supplements combined with four different types of priors for the covariance structure to check for sensitivity of the prior. Priors for fixed effects were defaults (wide normal distributions centered on 0). All models response variables were iodine intake and salt from bread consumption (using 1.1 g salt per 100 g bread). Response variables were logged before analysis, and thus impacts are proportional.

Data

As detailed above, the raw data for these modelling exercises is the coded diets from the National Dietary Surveys listed above, together with the newly established concentrations of iodine in Norwegian Food Composition Table. For each individual-day in the surveys, the intake of iodine was calculated. Additionally, we extracted the consumption of bread-products and assumed an average salt concentration of bread product to be 1.1 g salt per 100 g bread. Covariates of sex, age and level of education were also extracted.

Software/ statistical environment

Performed using the MCMCglmm package (version 2.26) in Rstudio, running R version 3.5.2. Custom made functions were defined to simulate exposures.

Model results

Note that the intakes discussed here correspond to *daily* intakes. Long-term intakes are higher, since the day-to-day variability is modelled on the log-scale. Long-term intakes and scenarios are presented in the next section.

Norkost 3:

The four different priors for the variance components had negligible effects on parameter estimates and are not further discussed.

For daily intakes, men have approximately a 25% higher intake of iodine than women (impact of being male on a log scale: 0.25 (0.19-0.31, credibility interval)). Men have about 48% (42-53%) higher daily intake of salt from bread. While iodine intake increases with age for adults (0.7% increase per year, 0.5-0.9), salt intake from bread decreases (-0.6% per year, -0.7 to -0.3%). Individuals with low level of education (i.e. < 3 years of higher education), have a lower (but uncertain) daily intake of iodine (-4%, -12% - 1%), and a higher intake of salt through bread (6%, 0.1-10%). Men vary more between individuals in iodine intake but vary less in salt (on a log scale). Both men and women with high intake of iodine also have a higher intake of bread.

Ungkost 3:

4-year-old girls had about 10% (2-20%) lower daily iodine intake than boys, and about 20% (11-28%) lower intake of salt from bread. For 9-year-olds, girls had about 17% (9-27%) lower iodine intake and 20% (12-27%) lower salt intake from bread. 13-year-old girls had 17% lower daily intake of iodine (8-27%) and 24% (17-30%) lower intake of salt from bread. In general boys varied more between individuals, and for all except 4-year-old girls, there was a positive covariance between iodine intake and bread intake.

Model-based exposure (Monte Carlo Risk Assessment software)

The web-based Monte Carlo Risk Assessment software (MCRA 8.2) was employed to estimate the dietary exposure of iodine in food for women between the ages of 18 to 45 in Norway. MCRA was run on this population subsets with gender as cofactor and age as a covariate. A custom exposure model was fitted using logistic normal-normal with a logarithmic transformation. The MCRA was run using the earlier version of the AE database, for which the iodine concentrations in coffee and whey cheese were different, and the numbers are therefore not comparable to the ones presented in the main text in chapter 6. The reason for presenting them here is to show that the exposure estimates are almost identical between the MCRA model and our R based MM-method. The distribution of daily iodine exposures is presented in Figure IV-1, and the exposure estimates from MCRA are presented in Table IV-1 below.

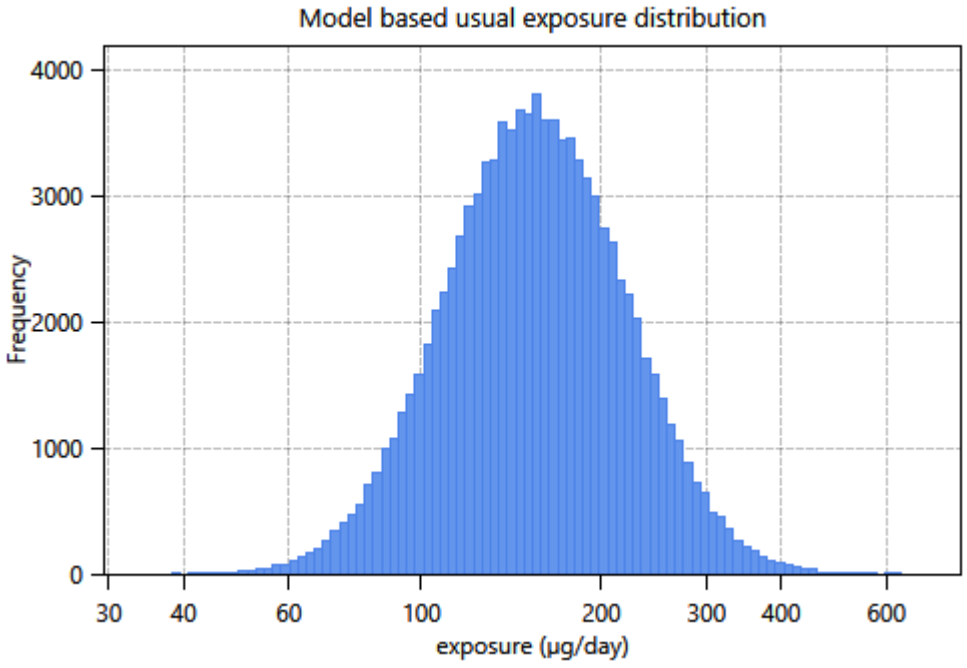

Figure IV-1 MCRA-model output showing frequency distribution of daily iodine exposures in women between the ages of 18 to 45 in Norway.

Comparing the estimates from OIMs, MM and MCRA

Exposure estimates for women of childbearing age (18-45 years) were performed using the MM-method, means of survey days (OIMs) and MCRA, and relevant statistics are presented in Table IV-1. As expected, both the lower and upper tails are less extreme with model-based estimates. The differences between MCRA estimates and MM estimates are minor, showing that the outcome of our tailor-made R models are in line with a more established software.

The comparisons below was using the early version of the AE database, for which the iodine concentrations in coffee and whey cheese were slightly different, and the numbers are therefore not identical or comparable to the ones presented in the main text in chapter 6. The reason for presenting them here is to show that the exposure estimates are almost identical between the MCRA model and our R based MM-method. Furthermore, we wanted to show the differences between these two models and the OIMs estimates.

Table IV-1 Iodine exposures in Norwegian women 18-45 years (n=466) based on tree different methods (OIMs, MM and MCRA 8.2 software,), using an earlier version of the AE database, µg/day.

Method	Mean	P5	P10	P20	P25	P30	P40	P50	P75	P95
OIM	164	48	59	78	86	95	111	129	207	415
MM	160	83	94	111	118	124	137	150	191	280
MCRA	164	87	99	116	122	129	142	155	195	273

Comparing MM-method with MCRA

The software MCRA was utilised for a preliminary comparison of our *mixed-model* (MM) approach with a more established model. The structure of the main modelling part in MCRA is also a mixed model, almost identical to the one we present in this report. However, the crucial difference is that MCRA does not allow for a *multivariate* analysis, i.e. fitting a model with both intake of iodine and bread (or salt in bread) as a function of age, sex etc. Additionally, MCRA does not allow for decomposing the variability between individuals and/or days to be different between the sexes.

Comparing OIMs with the model based approaches

Using two datapoints (i.e. the two days in Norkost) to estimate an individual mean will give an overestimation of the lower and upper percentiles across individuals, simply because the error with which we can estimate the 'true' mean intake for any given individual scales with the inverse square-root of the number of days. Figure IV-2 illustrates this by using the fitted model for Norkost 3. Using the MM-approach, we simulated iodine intake for 1, 2, 5, 10, 50

and 365 days, for 1787 individuals (corresponding to number of participants in Norkost 3). To chart the variability, for each number of days, one thousand replicates of these 1787 individuals were simulated. The main purpose of this exercise is to show that the MM-model generates data commensurate with the underlying daily intake data.

The shaded regions show the range of possible percentiles across these replicates and the cross indicates the percentile of the first day in Norkost or the OIMs of the two days. These simulations were not corrected for age, sex and education, so as to mimic the underlying data as much as possible. The upper most grey regions show the range of 95-percentiles using the model and the crosses indicate the 95-percentile of iodine intake for the first day (at *Days sampled* = 1) and the 95-percentile for the OIMs. The middle shaded regions denote the range of medians from the simulations, and the lower regions the 5-percentile. Simulating intakes for 1 and (mean of) 2 days generate exposure distributions that overlap with the observed data (crosses), except for a slight underestimation of the upper tail of the intakes for any single day. At 365 days the short horisontal black line indicate the percentile when sampling a very large (100 000) number of individuals.

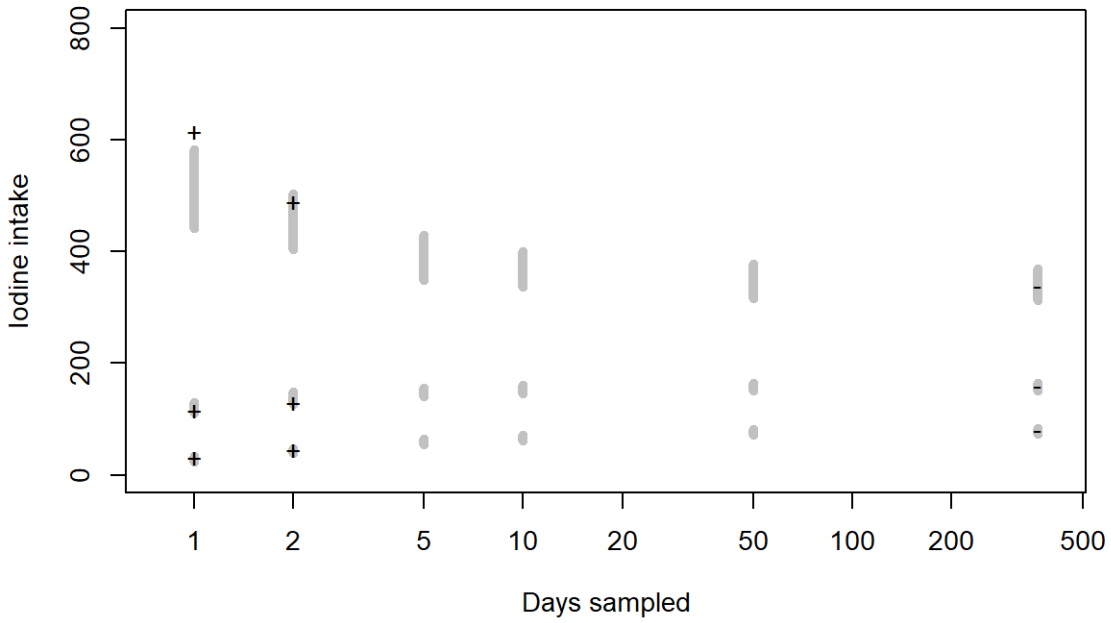

Figure IV-2 Simulated mean intakes over 1, 2, 4, 10, 50 and 365 days for 1787 individuals as in Norkost 3. The grey lines indicate the range of percentiles across 1000 replicated simulations, uppermost 95-percentile, mid – median and lower ones 5- percentiles. Black crosses indicate the 5, 50 and 95% persentiles for 1 day or the mean of the 2 days of Norkost. The range of the simulations for 1 and 2 days encompass the observed data, except for the 95-persentile for 1 day intake. The black lines at x=365 indicate the 5, 50 and 95-persentiles for the mean intake of 100 000 individuals over 365 simulated days.

Increasing the number of simulated days shows that the range of iodine intakes becomes narrower, as the upper percentiles are decreasing, and lower percentile increasing towards the right in Figure IV-2. This indicates that the primary reason for the difference between OIMs and MM-method exposure estimates is due to an appropriate decomposition of and correction of variability to suitably estimate usual intakes, and simulating intakes for much higher number of days and for a higher number of individuals, giving a simulation of long-term intake.

Appendix V – Exposure - additional estimates

In this appendix we have presented some data that are not presented in chapter 6. I.e. exposures based on observed means of survey days (OIMs) for adults and adolescents from Norkost 3 and Ungkost 3, and exposure estimates and scenarios for food supplement users (users only).

Exposures based on means of survey days (OIMs)

The iodine exposures based on means of survey days (OIMs) from Norkost 3 and Ungkost 3 are presented in Table V-1. Data for 1- and 2-year-olds are based on FFQ, and data are presented in Table 7.3.2-1.

Table V-1 Iodine exposures calculated from reported food intake (without iodine supplements) from means of survey days in the national dietary surveys in different age groups, mean and percentiles (µg/day), and percentage of participants over AR/EAR and under UL. Iodine intake (µg/day) – observed individual means (OIMs).

Survey	Group	Suppl	Mean	P5	P50	P95	SD	Percent > EAR	Percent < UL
Norkost 3	Men, 18-70y n=862	Without suppl	211	53	151	569	181	73	96
	Women, 18-70y n=925	Without suppl	154	40	108	421	126	55	99
	Women, 18-45y n=466	Without suppl	135	37	103	365	105	51	100
	Men, 18-70y n=862	With suppl	224	54	162	603	192	75	95
	Women, 18-70y n=925	With suppl	169	42	124	436	132	60	99
	Women, 18-45y n=466	With suppl	151	40	112	392	112	57	100
Ungkost 3	Boys, 13y n=332	Without suppl	117	34	100	256	72	71	100
	Girls,13y n=355	Without suppl	93	29	78	206	58	56	100
	Boys, 9y n=295	Without suppl	119	44	108	229	59	81	99
	Girls, 9y n=341	Without suppll	100	37	90	198	56	64	99
	Boys, 4y n=204	Without suppl	111	49	101	219	54	86	98

Survey	Group	Suppl	Mean	P5	P50	P95	SD	Percent > EAR	Percent < UL
	Girls, 4y n=195	Without suppl	101	42	94	188	45	76	100
	Boys, 13y n=332	With suppl	118	34	101	260	72	71	100
	Girls, 13y n=355	With suppl	96	30	80	213	61	58	100
	Boys, 9y n=295	With suppl	119	44	108	229	59	81	99
	Girls, 9y n=341	With suppl	100	37	90	198	56	64	99
	Boys, 4y n=204	With suppl	114	49	103	233,13	56	86	97
	Girls, 4y n=195	With suppl	103	43	95	193,49	47	78	100

[1] EAR depending on age group, see table 4.3-1.
[2] UL depending on age group, see table 4.3.1.

Exposures and scenarios for food supplement users (users only)

The iodine content in regular food supplements used in Norkost 3 range from 25 to 150 µg per dose, but most iodine supplements contain 150 µg iodine per recommended daily dose. In Norkost 3, 16% (n=145) of the women reported use of iodine supplements with a mean iodine contribution of 95 µg/day. Among women between 18-45 years of age, a total of 17% (n=77) reported use of iodine supplements, with at mean iodine contribution of 96 µg/day. Similarly, 11% (n=92) of the men reported use of iodine supplements with a mean iodine contribution of 117 µg/day.

In 13-year-olds in Ungkost 3, 4% of the girls (n=14) and 3% (n=9) of the boys reported to use iodine supplements. In 9-year-olds, 4% of the girls (n=13) and 2% (n=6) of the boys reported to use iodine supplements. In 4-year-olds, 4% of the girls (n=8) and 5% (n=12) of the boys reported to use iodine supplements.

In Småbarnskost 3, 10% of the 2-year-olds reported to use iodine supplements.

In Spedkost-07, there were no reported use of iodine supplements among the 1-year-old children.

Iodine exposure estimates for adult food supplements users and the scenarios are presented in Table V-2 and Figure V-1.

Tabel V-2 Iodine exposure estimates (current intake level and scenarios MM-method) for adults supplement users (users only).

Scenario	Group	Mean	P05	P50	P95	Percent > EAR	Percent < UL
No iodization	Men, 18-70y n=92	310	192	301	456	100	99
	Women, 18-70y n=145	249	183	245	326	100	100
	Women, 18-45y n=77	236	175	233	304	100	100
Salt15	Men, 18-70y	324	207	315	472	100	99
	Women, 18-70y	260	194	257	337	100	100
	Women, 18-45y	247	188	244	315	100	100
Bread 15	Men, 18-70y	347	224	338	502	100	98
	Women, 18-70y	274	203	270	355	100	100
	Women, 18-45y	261	197	258	335	100	100
Salt+ bread15	Men, 18-70y	363	240	354	518	100	98
	Women, 18-70y	285	215	281	366	100	100
	Women, 18-45y	273	209	270	347	100	100
Salt20	Men, 18-70y	330	212	322	477	100	99
	Women, 18-70y	264	199	260	341	100	100
	Women, 18-45y	251	191	248	319	100	100
Bread20	Men, 18-70y	362	234	352	519	100	98
	Women, 18-70y	282	211	278	366	100	100
	Women, 18-45y	270	203	267	347	100	100
Salt+ bread20	Men, 18-70y	383	255	373	540	100	98
	Women, 18-70y	297	226	293	382	100	100
	Women, 18-45y	285	218	282	363	100	100
Salt25	Men, 18-70y	336	218	327	482	100	99

Scenario	Group	Mean	P05	P50	P95	Percent > EAR	Percent < UL
	Women, 18-70y	268	203	264	345	100	100
	Women, 18-45y	255	195	252	323	100	100
Bread25	Men, 18-70y	375	244	365	537	100	98
	Women, 18-70y	290	216	286	377	100	100
	Women, 18-45y	279	209	275	360	100	100
Salt+ bread25	Men, 18-70y	401	270	391	563	100	97
	Women, 18-70y	309	236	305	396	100	100
	Women, 18-45y	298	228	294	379	100	100
Salt50	Men, 18-70y	362	244	353	509	100	98
	Women, 18-70y	287	222	283	364	100	100
	Women, 18-45y	274	214	271	342	100	100
Bread50	Men, 18-70y	440	288	427	633	100	93
	Women, 18-70y	332	245	326	438	100	100
	Women, 18-45y	322	238	316	425	100	100
Salt+ bread50	Men, 18-70y	492	341	480	686	100	87
	Women, 18-70y	370	283	364	476	100	100
	Women, 18-45y	360	276	354	463	100	100

Iodine exposure estimates for 2-year-olds food supplements users (users only) and the scenarios are presented in Table V-3 and Figure V-2.

Tabel V-3 Iodine exposure estimates (current intake level and scenarios) for 2-year-old supplement users (users only).

Scenario	Group	Mean	P05	P50	P95	Percent > EAR	Percent < UL
No iodization	Boys n=70	237	125	224	420	100	37
	Girls, n=69	221	99	219	365	100	38
Salt15	Boys n=70	246	134	233	429	100	34

Scenario	Group	Mean	P05	P50	P95	Percent > EAR	Percent < UL
	Girls, n=69	230	108	228	374	100	30
Bread15	Boys n=70	259	145	254	450	100	24
	Girls, n=69	240	120	235	392	100	29
Salt+ bread15	Boys n=70	268	154	263	459	100	21
	Girls, n=69	248	129	244	401	100	25
Salt20	Boys n=70	249	137	236	432	100	30
	Girls, n=69	233	111	231	377	100	29
Bread20	Boys n=70	266	150	263	460	100	23
	Girls, n=69	246	128	240	399	100	25
Salt+ bread20	Boys n=70	278	162	275	472	100	21
	Girls, n=69	258	140	252	411	100	20
Salt25	Boys n=70	252	140	239	435	100	29
	Girls, n=69	236	114	234	380	100	28
Bread25	Boys n=70	273	156	270	469	100	21
	Girls, n=69	252	137	245	407	100	23
Salt+ bread25	Boys n=70	288	171	285	484	100	16
	Girls, n=69	267	152	260	422	100	16
Salt50	Boys n=70	267	155	254	450	100	20
	Girls, n=69	251	129	249	395	100	22
Bread50	Boys n=70	310	183	300	498	100	10
	Girls, n=69	282	164	268	450	100	13
Salt+ bread50	Boys n=70	340	213	330	528	100	3
	Girls, n=69	312	194	298	480	100	6

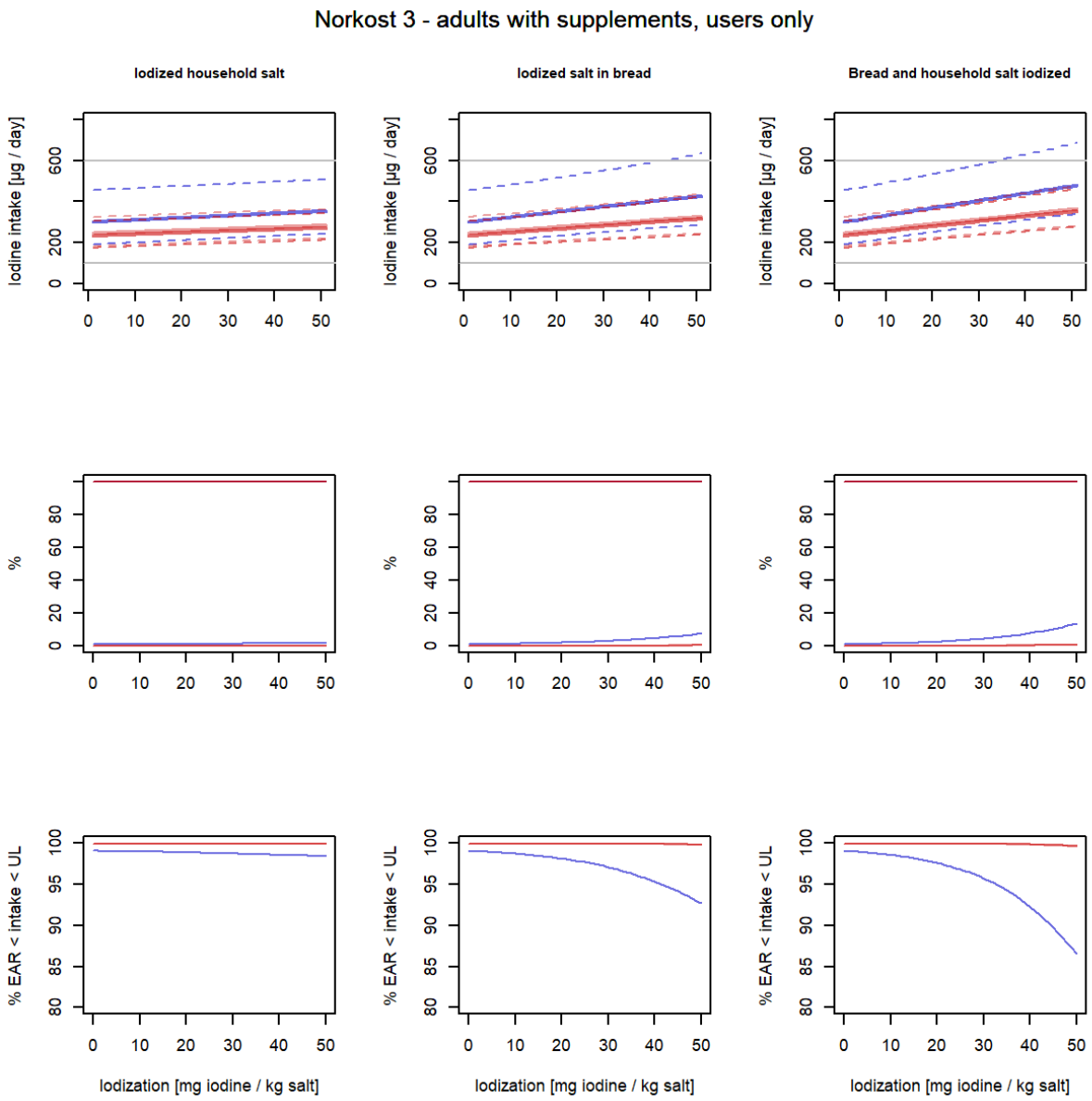

Figure V-1 Scenario estimates for iodization in adult males (blue lines), females (light red lines) and females 18-45 years old (dark red, almost indistinguishable from light red) when only using data for users of supplements. The three plots in the top row show total iodine intake (µg/day) if household salt, bread and both household salt and bread are iodized (0-50 mg iodine per kg salt). The curves represent the intakes in the 5th percentiles (lower dashed lines), median (full lines) and 95th percentile (upper dashed lines). The horisontal lines represent the age specific EAR (100 µg/day) and UL (600 µg/day) given in Table 4.3-1. The three plots in the middle row show percent of population group with iodine intakes above EAR (upper lines) and above UL (lower lines). The bottom plots show percentage of males and females with intakes both above EAR and below UL, and thus represent the percentage of the target population deemed to be within the dietary reference values.

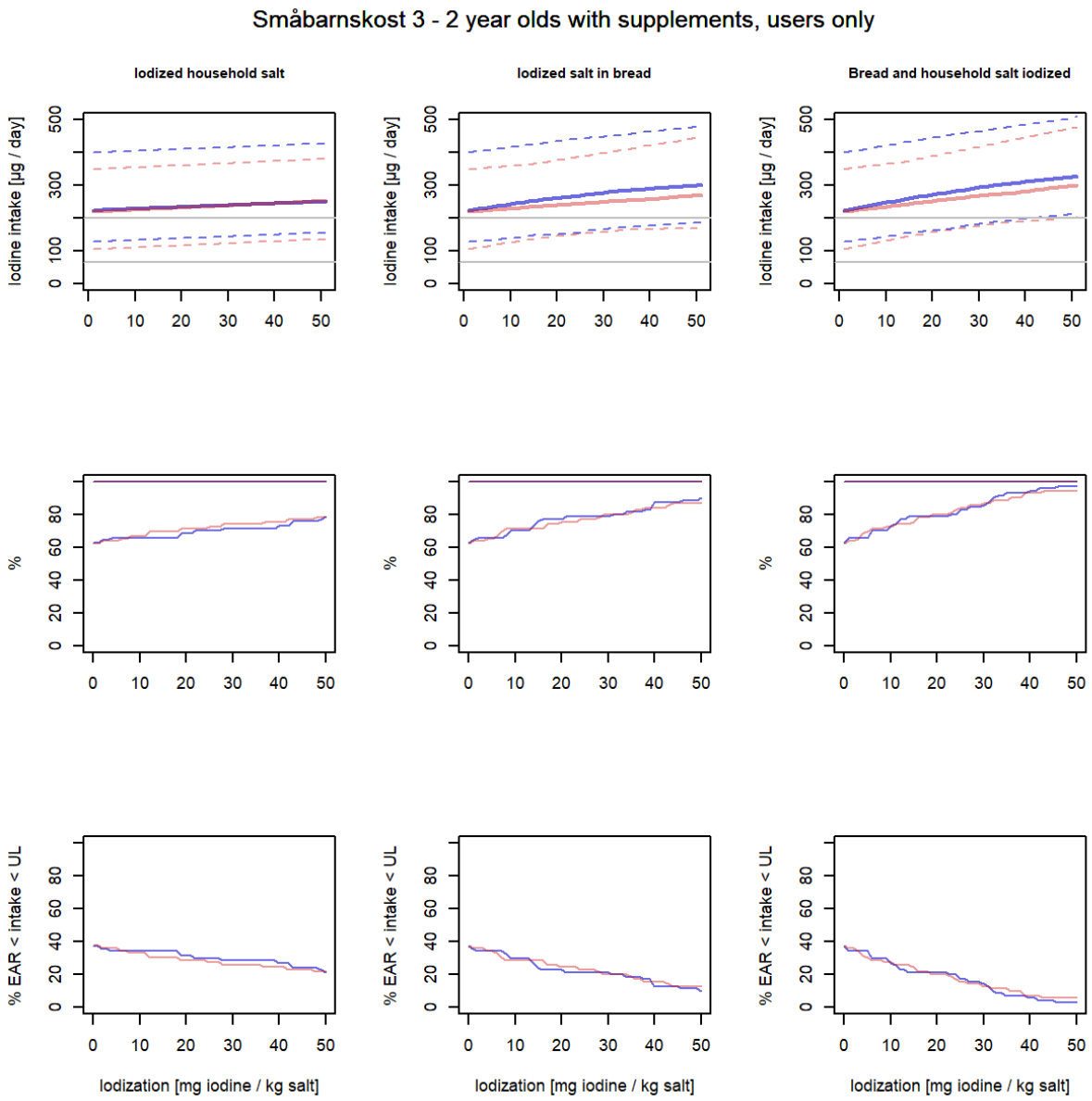

Figure V-2 Scenario estimates for iodization in 2-year-olds boys (blue lines) and girls (red lines) (with supplements – user only). The three plots in the top row show total iodine intake (µg/day) if household salt, bread and both household salt and bread are iodized (0-50 mg iodine per kg salt). The curves represent the intakes in the 5th percentiles (lower dashed lines), median (full lines) and 95th percentile (upper dashed lines). The horisontal lines represent the age specific EAR (65 µg/day) and UL (200 µg/day) given in Table 4.3-1. The three plots in the middle row show percent of population group with iodine intakes above EAR (upper lines) and above UL (lower lines). The bottom plots show percentage of boys and girls with intakes both above EAR and below UL, and thus represent the percentage of the target population deemed to be within the dietary reference values. Please note that these estimates are not modelled in the same manner as Norkost and Ungkost (Figures 7.4-1 through 7.4-5), due to the nature of the underlying data (FFQ).

Appendix VI - Manuals for the QAT-tables for the various study designs

Quality assessment tool for clinical studies

Article reference					Requires Yes for level A	B	C
1. General questions and study design							
a) Research question/hypothesis clearly formulated?	Yes	No	Can´t tell	NA	x	x	
b) Was the study design suited to test the research hypothesis?	Yes	No	Can´t tell	NA	x	x	
c) Was the duration of the study suited to test the research hypothesis?	Yes	No	Can´t tell	NA	x		
d) Sample size and power calculations reported/ considered (relevant for the main outcome variable)?	Yes	No	Can´t tell	NA	x		
2. Participants and compliance							
a) Population (target group) well described and relevant (for VKM)?	Yes	No	Can´t tell	NA	x	x	
b) Sample (possible participants) reqruited in an acceptable way?	Yes	No	Can´t tell	NA	x	x	
c) Criteria for inclusion/exclusion clearly formulated and acceptable?	Yes	No	Can´t tell	NA	x		
d) Actual participants comparable with the relevant (target) population?	Yes	No	Can´t tell	NA	x		
e) Method of randomisation allocation stated and appropriate?	Yes	No	Can´t tell	NA	x		
f) Was there an account of the comparability of groups with regard to relevant/ possible factors that might affect outcome?	Yes	No	Can´t tell	NA	x		
g) Compliance reported in an acceptable way? Compliance acceptable?	Yes	No	Can´t tell	NA	x		
h) Drop-out rate within an acceptable range? 6mo<30%, 12mo<40%, 24mo<50%	Yes	No	Can´t tell	NA	x		

Article reference					Requires Yes for level A B C
i) The drop-outs did not differ between the groups?	Yes	No	Can´t tell	NA	x
3. Dietary intervention and assessment					
a) Intervention diets clearly defined and characterised (foods and nutrients)?	Yes	No	Can´t tell	NA	x x
b) Method used for dietary assessment valid/ adequately validated?	Yes	No	Can´t tell	NA	x
c) Intervention diets consist of normal foods/ relevance to research question?	Yes	No	Can´t tell	NA	x
d) Measurement errors in dietary reporting considered?	Yes	No	Can´t tell	NA	x
e) Energy intake at credible level? Were the results adjusted for energy intake?	Yes	No	Can´t tell	NA	x x
c) Food composition database reported?	Yes	No	Can´t tell	NA	x
4. Outcome, results and analysis					
a) Acceptable and clear definition of the outcome/ endpoint?	Yes	No	Can´t tell	NA	x x
b) Biological mechanism for endpoint plausible?	Yes	No	Can´t tell	NA	x x
c) Results analysed blind?	Yes	No	Can´t tell	NA	
d) Attempts in the analysis phase made to adjust for imbalances between treatment arms with regard to important determinants for the outcome (e.g. through multivariate modelling)?	Yes	No	Can´t tell	NA	x
e) Valid biomarkers used to study compliance with the dietary exposure	Yes	No	Can´t tell	NA	x if relevant
f) Possible use of medication/ supplements taken into account?	Yes	No	Can´t tell	NA	x if relevant
g) Between measurement variation minimised/ standardised?	Yes	No	Can´t tell	NA	
h) Smallest effect clinically relevant/ reasonable?	Yes	No	Can´t tell	NA	
i) No possible conflicts of interest affecting the study quality?	Yes	No	Can´t tell	NA	x
9. Summary of the study quality	A	B	C		

Quality assessment tool for prospective cohort studies

Article reference					Requires Yes for level A	B	C
1. General questions and study design							
a) Research question clearly formulated?	Yes	No	Can´t tell	NA	x	x	
b) Outcome clearly defined?	Yes	No	Can´t tell	NA	x	x	
c) Was the study design suited to test the research hypothesis?	Yes	No	Can´t tell	NA	x	x	
2. Sampling (Ascertainment of cases and non-cases)							
a) Source population/study base well defined? Recruitment done in an acceptable way?	Yes	No	Can´t tell	NA	x	x	
b) Response rate reported and acceptable?	Yes	No	Can´t tell	NA	x		
c) Criteria for inclusion/exclusion clearly formulated and acceptable?	Yes	No	Can´t tell	NA	x	x	
d) Participants and non-participants comparable with Nordic population?	Yes	No	Can´t tell	NA	x		
e) Time period of baseline examinations clearly identified?	Yes	No	Can´t tell	NA	x		
f) Endpoint clearly ascertained and assessed in a valid way?	Yes	No	Can´t tell	NA	x	x	
g) Follow-up period clearly identified?	Yes	No	Can´t tell	NA	x		
h) Time-exposure-variable clearly defined (i.e., period non-cases being exposed)?	Yes	No	Can´t tell	NA	x		
i) Loss to follow up <20%?	Yes	No	Can´t tell	NA	x		
3. Dietary assessment							
a) Type of exposure (nutrients, food groups etc) reported in sufficient detail?	Yes	No	Can´t tell	NA	x	x	
b) Particulars of dietary assessment tool reported in sufficient detail?	Yes	No	Can´t tell	NA	x		
c) Food composition database reported?	Yes	No	Can´t tell	NA	x		
d) Concurrent validity (validation coefficients) of specific exposures reported?	Yes	No	Can´t tell	NA	x		
e) Associations between dietary exposures reported?	Yes	No	Can´t tell	NA	x		

Article reference					Requires Yes for level		
					A	B	C
f) Measurement errors in dietary reporting considered?	Yes	No	Can´t tell	NA	x	x	
g) Energy intake at credible level?	Yes	No	Can´t tell	NA	x	x	
h) Energy adjustment adequately done?	Yes	No	Can´t tell	NA	x		
i) Repeat assessment of diet during follow up?	Yes	No	Can´t tell	NA	x		
j) Use of dietary markers adequate? Details of assessment and handling reported? Valid biomarker assay?	Yes	No	Can´t tell	NA	x if relevant		
k) Time period between biomarker assessment and diagnosis acceptable?	Yes	No	Can´t tell	NA	x if relevant		
4. Anthropometry							
a) Assessment detailes clearly reported and assessment adequately performed?	Yes	No	Can´t tell	NA	x		
5. Physical activity							
a) Assessment detailes clearly reported and assessment adequately performed?	Yes	No	Can´t tell	NA	x		
6. Confounding							
a) Were important confounders identified/ascertained and considered by authors?	Yes	No	Can´t tell	NA	x	x	
b) The distribution of confounders similar in cases and non-cases?	Yes	No	Can´t tell	NA	x		
7. Statistical power							
a) Was the study power considered and sample size and power calculations reported?	Yes	No	Can´t tell	NA	X		
b) In view of multiple tests, were by chance findings considered?	Yes	No	Can´t tell	NA	x		
c) Sufficient size of study population and no. of outcomes/cases?	Yes	No	Can´t tell	NA	x		
8. Statistical analysis							
a) Appropriately handled?	Yes	No	Can´t tell	NA	x		

Article reference					Requires Yes for level A	B	C
b)) Relevant confounders adequately handled: Restriction, Stratified analysis, Multivariate modelling, Interaction tested?	Yes	No	Can´t tell	NA	x	x	
c) Ascertainment/detection bias considered (e.g. cases detected due to screening)?	Yes	No	Can´t tell	NA	x		
d) Cases detected early during the follow-up period removed?	Yes	No	Can´t tell	NA	x	x	
9. Summary of the study quality	A	B	C				

Quality assessment tool for cross-sectional studies

Article reference					Requires Yes for level A	B	C
1. General questions and study design							
a) Research question clearly formulated?	Yes	No	Can´t tell	NA	x	x	
b) Outcome clearly defined?	Yes	No	Can´t tell	NA	x	x	
2. Recruitment/ Participation							
a) Source population well defined and recruitment done in an acceptable way?	Yes	No	Can´t tell	NA	x		
b) Participation rate acceptable (>50%)?	Yes	No	Can´t tell	NA	x		
c) Criteria for inclusion/exclusion clearly formulated and acceptable?	Yes	No	Can´t tell	NA	x		
d) Were the participants with primary outcome adequately identified/diagnosed?	Yes	No	Can´t tell	NA	x		
e) Are the differences in outcome between groups relevant?	Yes	No	Can´t tell	NA	x		
f) Are the participants comparable with relevant (target) Nordic population?	Yes	No	Can´t tell	NA	x	x	
3. Dietary assessment							
a) Method used for dietary assessment adequate and valid?	Yes	No	Can´t tell	NA	x	x	
b) Diets/nutrients studied clearly defined and characterised?	Yes	No	Can´t tell	NA	x		
c) Energy intake at credible level?	Yes	No	Can´t tell	NA	x	x	
d) Energy adjustment adequately done?	Yes	No	Can´t tell	NA	x		
e) Use of biomarkers adequate?	Yes	No	Can´t tell	NA	x if relevant		
f) Results adjusted for mis/underreporting?	Yes	No	Can´t tell	NA	x	x	
g) Possible drug usage taken into account	Yes	No	Can´t tell	NA	x		
h) Food composition database reported	Yes	No	Can´t tell	NA	x		
4. Confounding							

Article reference					Requires Yes for level A	B	C
a) Were important confounders identified/ascertained and considered by authors?	Yes	No	Can´t tell	NA	x	x	
b) Relevant confounders adequately handled: restriction, stratified analyses, multivariate modelling, interaction tested?	Yes	No	Can´t tell	NA	x	x	
5. Anthropometry							
a) Assessment detailes clearly reported and assessment adequately performed?	Yes	No	Can´t tell	NA	x if relevant		
6. Physical activity							
a) Assessment detailes clearly reported and assessment adequately performed?	Yes	No	Can´t tell	NA	x if relevant		
7. Statistical power							
a) Was the study power considered and sample size and power calculations reported?	Yes	No	Can´t tell	NA	x		
8. Analysis							
a) Was the statistical method adequate	Yes	No	Can´t tell	NA	x	x	
b) No possible conflicts of interest affecting the study quality?	Yes	No	Can´t tell	NA	x		
9. Summary of the study quality	A	B	C				

A The results from studies that have an acceptably low level of bias are considered valid. These studies adhere mostly to the commonly held concepts of high quality including the following: a comprehensive study design; clear description of the participants, setting, interventions, and control group(s); appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; less than 30% percent dropout (depending on the length of the study see the QAT for clinical studies) or over 50% participation rate for prospective cohort studies; clear reporting of dropouts; and no obvious bias. Where appropriate, studies must provide a valid estimation of contaminant exposure, from assessments and/or biomarkers with a reasonable range of measurement error, and justification for approaches to control for confounding in the design and analyses.

B Studies may have some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category "A", they have some deficiencies but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; there are large amounts of missing information, or discrepancies in reporting.