Assessment of dietary intake of fluoride and maximum limits for fluoride in food supplements

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

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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 three VKM members of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy and a project leader from the VKM secretariat. The VKM Panel on Nutrition, Dietetic Products, Novel Food and Allergy evaluated and approved the final opinion drafted by the project group.

Authors of the opinion

Members of the project group that contributed to the drafting of the opinion (in alphabetical order after chair of the project group):

Martinus Løvik – Chair of the project group and member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) Norwegian University of Science and Technology (NTNU), Department of Clinical and Molecular Medicine, Trondheim.

Lisbeth Dahl – Member of the project group and member Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) Institute of Marine Research (IMR), Bergen.

Bente Mangschou - VKM secretariat, leader of the project. Affiliation: VKM.

Stine Marie Ulven – Member of the project group and member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) University of Oslo, Department of Nutrition, Institute of Basic Medical sciences.

Members of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy that contributed to the assessment and approval of the opinion (in alphabetical order before vice-chair of the Panel):

In addition to Martinus Løvik, Lisbeth Dahl and Stine M. Ulven these were (in alphabetical order before chair of the Panel):

Lene Frost Andersen – Vice chair of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) University of Oslo, Department of Nutrition, Institute of Basic Medical sciences.

Knut Tomas Dalen – Member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) University of Oslo, Department of Nutrition, Institute of Basic Medical sciences.

Kristin Holvik – Member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health, Department of Chronic Diseases and Ageing, Oslo.

Christine Louise Parr – Member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) OsloMet–Oslo Metropolitan University, Faculty of Health Sciences, Department of Nursing and Health Promotion.

Tonje H. Stea – Member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) University of Agder, Department of Public Health, Sport and Nutrition.

Tor A. Strand – Chair of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) Centre for International Health, University of Bergen and Innlandet Hospital Trust, Department of Research, Lillehammer.

Acknowledgment

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.

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Summary

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet, NFSA), evaluated the intake of fluoride in the diet, together with intake of fluoride from dental hygiene and caries prevention products. VKM has also evaluated suggested maximum limits for fluoride in food supplements at 0.5, 1, 5 and 7 mg/day in relation to established tolerable upper intake levels (ULs). The former maximum limit for fluoride of 0.5 mg/day in food supplements was repealed 30 May 2017.

Fluorine is a gaseous halogen which occurs naturally only in anionic form as fluoride (F^-). Fluorides are ubiquitous in air, water and the lithosphere. Fluoride is found naturally in all water sources. The highest levels are found in groundwater. Surface water usually has lower concentrations of fluoride than groundwater, most often under 0.5 mg/L.

Major dietary fluoride sources are water and tea. An important non-dietary source is dental hygiene products such as toothpaste and tablets for caries prevention. There is no fluoridation of drinking water or salt in Norway.

Fluoride is not an essential nutrient. Caries is not a fluoride deficiency disease. However, because of the beneficial effects for caries prevention, an adequate intake (AI) of 0.05 mg per kg body weight per day has been set for fluoride by the European Food Safety Authority (EFSA).

Readily soluble fluorides (sodium- and potassium fluoride) are rapidly and almost completely absorbed by passive diffusion in the stomach and the small intestine. Absorption is influenced by acidity and concomitant food intake.

Absorbed fluoride is rapidly distributed in blood plasma, but is retained only in calcified tissues, that are bones and teeth. Consequently, 99% of the total fluoride content of the body is found in bone and teeth. Absorbed fluoride which is not deposited in calcified tissues is excreted almost exclusively via the kidneys.

Whereas skeletal bone and dentine accumulate fluoride throughout life, enamel of teeth incorporate fluoride only at the time of tooth formation. Fluoride substitutes for hydroxyl groups in the apatite, increasing the resistance to caries. In permanent teeth enamel maturation is completed at the age of seven to eight years, except in the third molars. Post-eruptive fluoride uptake by enamel occurs only in the outer layer and depends on local oral fluoride levels. A linear relationship between fluoride exposure and caries resistance has been demonstrated. Over the years, the view has shifted from systemic fluoride being most effective for caries prevention to local oral exposure being most important.

Acute toxic effects may be provoked by fluoride, and deaths have been reported after intake of very large doses from fluoride tablets. The main adverse outcomes from intake of excess

doses of fluoride over time, are enamel fluorosis in children up to eight years of age, and bone fluorosis in older children and adults. Dental fluorosis causing mottled teeth is largely a cosmetic effect, whereas bone fluorosis causes stiff joints and a greater tendency to fractures. Tolerable upper intake levels (UL) for fluoride have been set by the American Institute of Medicine (IOM) and by the European Food Safety Authority (EFSA). In this report, we relate estimated fluoride intakes to the upper level set by EFSA.

Intakes of the main dietary fluoride sources, water and tea, in different age groups were obtained from Norwegian dietary surveys. High fluoride intakes were estimated by applying the 95 percentile of fluoride concentrations in water obtained from 2001 fluoride analyses from Norwegian waterworks in the period between 2010 and 2018 and in tea obtained from a Polish study to the daily volume consumed. Fluoride intakes from recommended use of dental hygiene and caries prevention products were then added, plus a small fixed value for undescribed sources. The estimated 95 percentile fluoride exposure calculated this way was compared to the upper level, and scenarios with additional fluoride supplementation of 0.5, 1, 5 or 7 mg/day were developed.

The estimated 95-percentile of fluoride exposure from water, tea and dental hygiene products alone (before fluoride from the suggested food supplement doses at 0.5, 1, and 7 mg/day were added) was found to exceed the upper level for 2-year old children and for adults.

VKM concludes that all the suggested food supplement doses considered will cause the tolerable upper intake level to be exceeded in all age groups, except for the supplement doses of 0.5 in 9- and 13-year olds and 1 mg/day in 9 year olds.

VKM emphasises that the current assessment of maximum limits for fluoride in food supplements is merely based on published reports concerning upper levels from the IOM (USA, 2001), Scientific Committee on Food (EU, 2003), Expert Group on Vitamins and Minerals (UK, 2003) and Nordic Nutrition Recommendations (Nordic Countries, 2012). VKM has not conducted any review of the literature for the current opinion, as this was outside the scope of the terms of reference from the NFSA.

Key words: VKM, risk assessment, Norwegian Scientific Committee for Food and Environment, fluoride, food supplements, safe upper level, guidance level, exposure.

Sammendrag på norsk

Vitenskapskomiteen for mat og miljø, VKM, har beregnet inntaket av fluorid fra kosten og inntak av fluorid fra kariesforebyggende tannpleieprodukter, på forespørsel fra Mattilsynet. VKM har videre vurdert hvorvidt et inntak av fluorid fra kosttilskudd på henholdsvis 0,5, 1, 5 eller 7 mg/dag i tillegg til inntak fra kost og tannpleieprodukter vil kunne føre til overskridelser av etablerte tolerable øvre inntaksnivåer (UL) for fluorid. Tidligere maksimumsgrense for fluorid i kosttilskudd var 0,5 mg/dag. Denne maksimumsgrensen ble opphevet 30. mai 2017.

Fluor er et halogen som naturlig kun forekommer i anionisk form som fluorid (F-). Fluorider finnes i luft, vann og litosfæren. Fluorid finnes naturlig i alle vannkilder. De høyeste nivåene finnes i grunnvann. Overflatevann har vanligvis lavere fluoridkonsentrasjoner enn grunnvann, oftest under 0,5 mg/L.

De viktigste kildene til fluorid i kosten er vann og te. En annen viktig fluoridkilde er kariesforebyggende tannpleieprodukter, som fluortabletter og tannpasta. Det er ikke tilsatt fluorid til hverken drikkevann eller salt i Norge.

Fluorid er ikke et essensielt næringsstoff, og karies forårsakes ikke av fluoridmangel. På grunn av at fluorid virker forebyggende på utviklingen av karies, har imidlertid European Food Safety Authority (EFSA) foreslått et adekvat inntak (AI) på 0,05 mg fluorid per kg kroppsvekt per dag.

Lettløselige fluorider (natrium- og kaliumfluorid) absorberes raskt og nesten fullstendig ved passiv diffusjon i magen og tynntarmen. Absorbsjonen påvirkes av surhetsnivå og samtidig inntak av mat.

Absorbert fluor transporteres raskt i blodplasma, men lagres kun i kalsifisert vev som bein og tenner. Derfor finnes 99 prosent av det totale fluorinnholdet i kroppen i bein og tenner. Absorbert fluor som ikke lagres i kalsifisert vev, skilles nesten utelukkende ut via nyrene.

Mens skjelettbein og tannbein (dentin) akkumulerer fluorid gjennom hele livet, bygges fluorid inn i tannemaljen bare under selve tanndannelsen. Fluorid erstatter hydroksylgrupper i apatitt, og øker motstanden mot karies. Permanent tannemalje er ferdig utviklet ved syv til åtte års alder, unntatt i de bakerste jekslene. Opptak av fluorid i tannemaljen etter tannens frambrudd forekommer kun i ytre lag og er avhengig av lokalt fluoridnivå i munnen. Forholdet mellom fluorideksponering og kariesmotstand er vist å være lineært. Mens man tidligere anså at systemisk fluoridbehandling var mest effektiv i forebygging av karies, anser man i dag lokal fluorid i munnen som viktigst.

Fluorid kan utløse akutte toksiske effekter, og det har blitt rapportert om dødsfall etter inntak av svært høye doser fra fluoridtabletter. De viktigste negative helseeffektene fra langvarig forhøyet inntak av fluorid er fluorose i tannemaljen hos barn opptil åtte år, og beinfluorose

hos eldre barn og voksne. Dental fluorose som gir flekkete tenner, er i hovedsak en kosmetisk effekt, mens beinfluorose gir stive ledd og kan gi økt tendens til beinbrudd. Både Institute of Medicine i USA og EFSA i EU har fastsatt tolerable øvre inntaksnivåer (UL) for fluorid. I denne rapporten vurderer vi de estimerte inntakene av fluorid opp mot UL fastsatt av EFSA.

Data for inntak av de viktigste fluoridkildene i kosten, vann og te, ble for denne rapporten hentet fra nasjonale kostholdsundersøkelser for ulike aldersgrupper i den norske befolkningen. I estimatene er 95 persentilen for fluoridkonsentrasjoner basert på 2001 vannanalyser fra norske vannverk i perioden 2010-2018 og te fra en studie fra Polen fra 2008. Deretter er inntak av fluorid fra anbefalt mengde kariesforebyggende tannpleieprodukter lagt til, samt en liten fast verdi for andre uspesifiserte kilder. Det estimerte inntaket av fluorid i 95 persentilen for fluorideksponering er sammenlignet med UL, og scenarier med ytterligere doser fluorid fra kosttilskudd på 0,5, 1, 5 eller 7 mg/dag er vurdert.

Estimatene for fluorideksponering i 95 persentilen fra vann, te og tannpleieprodukter alene viser et fluoridinntak som overstiger UL hos toårige barn og hos voksne (før fluoriddoser på 0,5, 1, 5 eller 7 mg/dag fra kosttilskudd ble lagt til).

VKM konkluderer med at alle de foreslåtte dosene for fluorid i kosttilskudd (0,5, 1, 5 og 7 mg/dag) vil føre til at UL overskrides i alle aldersgrupper, bortsett fra dosene på 0,5 for 9- og 13- åringer, og 1 mg/dag for 9-åringer.

VKM presiserer at denne vurderingen av maksimumsgrenser for fluorid i kosttilskudd er basert på publiserte rapporter om øvre inntaksnivåer fra Institute of Medicine (USA, 2000) og EFSA (EU, 2005). Ettersom mandatet i bestillingen fra Mattilsynet var å vurdere inntaket av fluorid basert på allerede eksisterende rapporter, har VKM ikke gjennomført et eget litteratursøk i denne vurderingen.

Nøkkelord: VKM, risikovurdering, Vitenskapskomiteen for mat og miljø, fluorid, kosttilskudd, eksponering.

Abbreviations and glossary

Abbreviations

AI — adequate intake
AR — average requirement
bw — body weight
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
GL — guidance level (for safe upper intake)
IOM — Institute of Medicine, USA
LOAEL — lowest observed adverse effect level
MoBa — Norwegian Mother and Child Cohort Study
NFSA — Norwegian Food Safety Authority [*Norw*.: Mattilsynet]
NNR — Nordic Nutrition Recommendations
NOAEL — no observed adverse effect level
PRI — population reference intake
RCT — randomised controlled trial
RDA — recommended dietary allowances
RI — recommended intake
SAE — serious adverse events
SCF — Scientific Committee for Food
SD — standard deviation
SUL — safe upper intake level
UF — uncertainty factor
UL — tolerable upper intake level
VKM — Norwegian Scientific Committee for Food and Environment [*Norw*.: Vitenskapskomiteen for mat og miljø]

Glossary

Saft: "Saft" is a traditional Norwegian product subject to national legislation, and cannot be translated directly into English. "Saft" is defined as a syrup or sweetened concentrate produced from fruit or berry juice that shall be diluted with water before drinking.

Percentile is a statistical measure indicating the value below which a given percentage of the observations fall. E.g. the 95-percentile is the value (or score) below which 95 percent of the observations are found.

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

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

Average Requirement (AR) is the level of intake of a defined group of individuals estimated to satisfy the physiological requirement of metabolic demand, as defined by the specific criterion for adequacy for the nutrient, in half of the heathy 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.
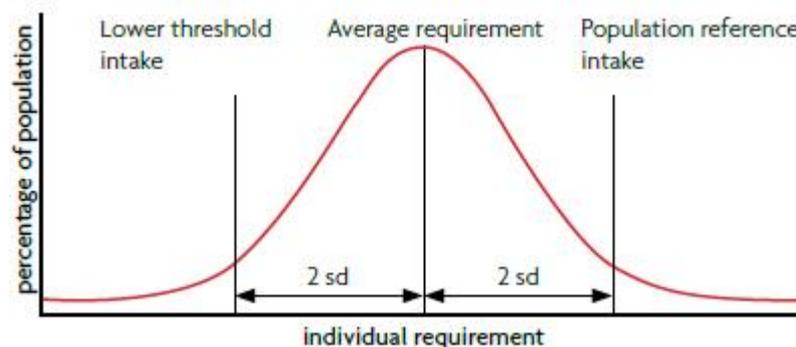
Figure 1: Population reference intake (PRI and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010).

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 standard deviation (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.
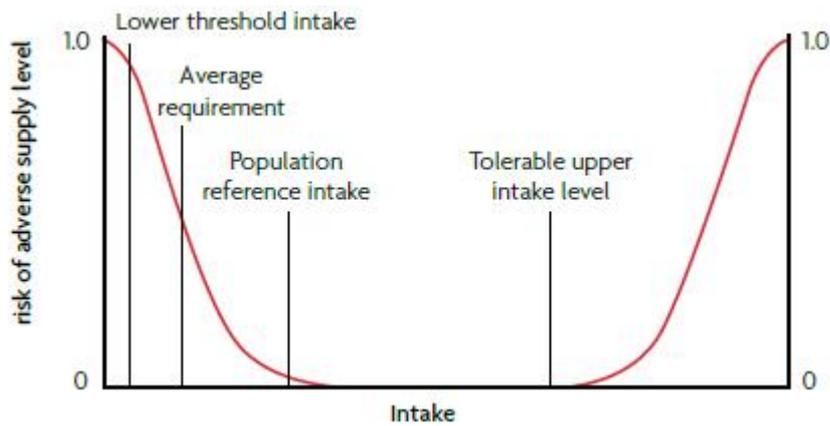
Figure 2: Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake using EFSA terminology.

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.
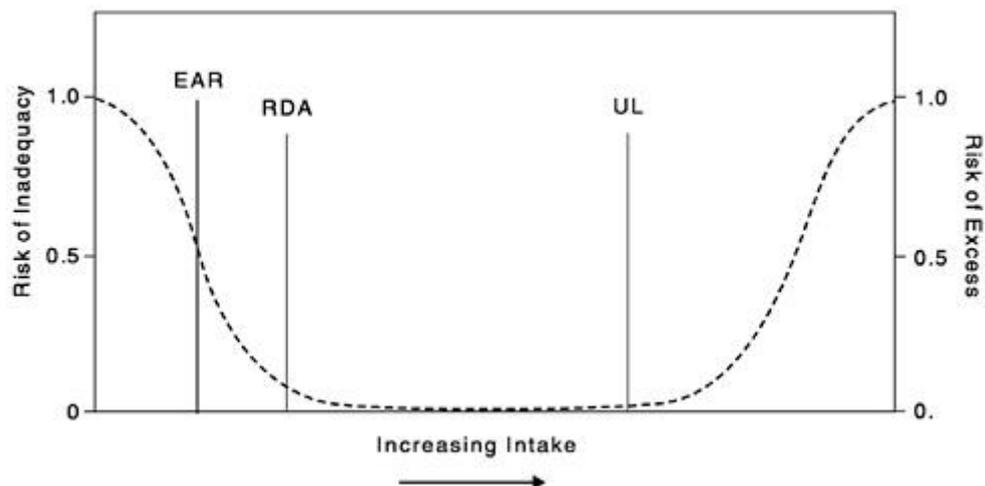
Figure 3: Dietary reference intakes using IOM terminology.

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.

$UL_{NNR} = UL_{IOM} = UL_{EFSA}$
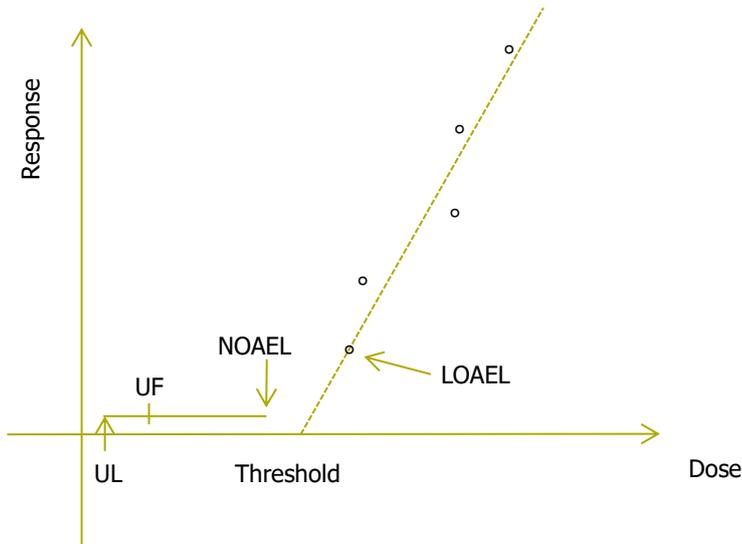
Figure 4: Derivation of Upper Intake Level (UL)
UF: Uncertainty factor

Expert group on vitamins and minerals (EVM), UK (EVM, 2003)

Safe Upper Intake Level (SUL): EVM used SUL instead of UL and defined SUL as the intake that can be consumed daily over a lifetime without significant risk to health on the basis of available evidence. The setting of these levels provided a framework within which the consumer could make an informed decision about intake, having confidence that harm should not ensue. The levels so set will therefore tend to be conservative.

Guidance Level (GL): For vitamins and minerals where a SUL could not be established due to insufficient data, EVM provided GL as an approximate indication of levels that would not be expected to cause adverse effects. As with SULs, the GLs are intended to represent the doses of vitamins and minerals that susceptible individuals could take daily on a life-long basis, without medical supervision. The EVM emphasised, however, that GLs should not be used as SULs, as they have been derived from limited data and are less secure than SULs.

Background as provided by the Norwegian Food Safety Authority

Directive 2002/46/EC on food supplements was implemented into Norwegian law in 2004 in Regulation 20 May 2004 No. 755 on food supplements. Pursuant to Directive 2002/46/EC, common maximum and minimum levels of vitamins and minerals in food supplements shall be set in the EU. The European Commission started to establish common limits in 2006, but the work was temporarily put on standstill in 2009. The time frame for the further work is not known.

National maximum limits for vitamins and minerals were established in the former vitamin and mineral supplements regulation from 1986 and were continued in the 2004 regulation.

The national maximum and minimum limits in the food supplement regulation were established a long time before the food supplement directive was adopted, and the limits were consequently not established in accordance with the criteria for limits set in the food supplement directive. Maximum limits for vitamins and minerals which were not already revised according to the criteria in article 5 in the food supplement directive, were therefore repealed from 30 May 2017.

- Maximum limits for levels of vitamins and minerals in food supplements shall be set on basis of the following criteria, pursuant to article 5 in Directive 2002/46/EC:
- Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups
- Intake of vitamins and minerals from other dietary sources

When the maximum levels are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

Pending establishment of common maximums limits in the EU, the Norwegian Food Safety Authority is evaluating the national maximum limits for vitamins and minerals in food supplements.

Norwegian authorities will as soon as possible, when it exists a scientific basis, and pending establishment of common maximums limits in the EU, establish new national maximum limits for those vitamins and minerals where limits were repealed 30 May 2017.

Assessment of fluoride

The Norwegian Food Safety Authority will consider establishing a new national maximum limit for fluoride in the food supplement regulation.

The former maximum limit for fluoride was 0.5 mg per daily dose, but this was repealed 30 May 2017. The minimum limit and permitted fluoride substances that may be used in the manufacture of food supplements, are listed in annex 1 and annex 2 in the food supplement regulation.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA, Mattilsynet) requests the Norwegian Scientific Committee for Food Safety (VKM) to assess the intake of fluoride from the diet including drinking water and beverages, in all age groups in the population above 1 year. Additionally, VKM is requested to assess the intake of fluoride from fluoride tablets and dental care products.

As there are no data on fluoride in the Norwegian food composition data base (KBS), VKM is requested to evaluate if other relevant intake data can be used - including the EFSA Scientific Opinion on Dietary Reference Values for fluoride (2013).

Furthermore, VKM is requested to evaluate the consequences of establishing a maximum limit for fluoride in food supplements of 0.5, 1, 5 or 7 mg per daily dose, and to evaluate these scenarios against existing tolerable upper intake levels.

1 Introduction

The mandate in this report is to evaluate intake scenarios against already established tolerable upper intake levels (ULs) for fluoride. This assessment is therefore based on previous reports on tolerable upper intake levels from national and international agencies, and no new literature search has been performed.

Chemistry

Fluorine is a gaseous halogen with an atomic mass of 18.998. Chemically, it is the most reactive and the most electronegative element, and therefore occurs naturally only in anionic form, i.e. as fluoride (F-), after reaction with metallic elements or hydrogen (EFSA, 2005). Fluorides are ubiquitous in air, water and the lithosphere, where they are the seventeenth in the order of occurrence, constituting 0.06-0.09% of the earth's crust (WHO, 1994). Most of the fluoride in rock and soil is firmly bound and not biologically available.

Fluoride is found naturally in all water sources, including fresh and sea water, and a concentration of fluoride in groundwater as high as 25 mg/L has been reported (EFSA, 2005). In Norway, the highest reported fluoride concentration found in groundwater from 201 waterworks was 4.0 mg/L (Abiyos, 2017). Another study reported 8.0 mg/L as the highest fluoride concentration in drinking water from western Norway (Bardsen et al., 1999). Surface water usually has lower concentrations of fluoride than groundwater, most often under 0.5 mg/L. Median fluoride concentration from 150 different waterworks in Norway was 0.05 mg/L (Abiyos, 2017). Sea water, for comparison, has a fluoride content between 1.2 and 1.5 mg/L (EFSA, 2005).

Fluoride also exists in the air in gaseous form or bound to particles, coming from soil, industry and burning of coal. However, in non-industrial areas the concentration is low (0.05-1.9 µg/m^3). EFSA (2005) states that for the purpose of setting an UL for oral intake of fluoride, exposure via inhalation is not relevant because of the low level and should therefore not be taken into account. The same applies to fluoride exposure via the skin.

Not an essential nutrient

Although fluoride is beneficial for caries prevention, caries is not a fluoride deficiency disease, and there is insufficient evidence that fluoride is necessary for human development and health. Fluoride deficiency conditions have not been identified in human or animal development and health studies. Consequently, the European Food Safety Authority (EFSA) concluded that fluoride is not an essential nutrient (EFSA, 2005). However, because of the ubiquity of fluoride, it is nearly impossible to create experimental situations with no fluoride intake.

Fluoride sources

Major dietary fluoride sources are water, tea, and albeit to a much smaller extent, marine fish, particularly if skin and bones are consumed. An important non-dietary source is dental hygiene products and tablets for caries prevention. The most important fluoride compounds for human use in a health context are sodium and potassium fluoride, which are highly soluble in water. They are added to foods (e.g. salt (not fluoridated in Norway)), dental hygiene products, and drinking water (no water fluoridation in Norway).

Absorption, distribution, metabolism an excretion

Readily soluble fluorides (sodium, potassium, hydrogen, fluorosilic, sodium monophosphate) are rapidly and almost completely absorbed. Absorption occurs by passive diffusion both in the stomach (20-25%) and in the small intestine. Higher acidity of the stomach increases absorption. The bioavailability of fluoride varies between food sources (EFSA, 2005; Trautner and Siebert, 1983), but on the average 80-90% of ingested fluoride is absorbed. Fluoride from toothpaste is also absorbed, but sodium monofluorophosphate from toothpaste needs dephosphorylation before absorption in the lower intestine. Sodium fluoride tablets given in water on an empty stomach were almost 100% absorbed. The same doses given with milk were 70% absorbed, and 60% absorbed when given with a meal (EFSA, 2005).

Absorbed fluoride is rapidly distributed in blood plasma to the extra- and intracellular fluids but is retained only in calcified tissues due to fluoride's high affinity for calcium. Consequently, 99% of the total fluoride content of the body is found in bone and teeth. In these tissues, fluoride substitutes for hydroxyl groups in the apatite. Body fluid and soft tissue fluoride concentrations are not under homeostatic control and reflect the recent intake. Apart from intake via water and diet, the fluoride concentration in saliva and dental plaque is dependent on topical fluoride application via dental care products (EFSA, 2005).

Absorbed fluoride which is not deposited in calcified tissues is excreted almost exclusively via the kidneys.

In contrast to skeletal bone and dentine which accumulate fluoride throughout life, enamel of teeth reflects the biologically available fluoride at the time of tooth formation (EFSA, 2005). Enamel maturation of deciduous teeth is completed between the age of two to 12 months. In permanent teeth enamel maturation is completed at the age of seven to eight years, except in the third molars in which it continues until the age of 12-16 years. Post-eruptive fluoride uptake by enamel occurs only in the outer layer and depends on fluoride in food, saliva, dental plaque and dental care products.

Caries prevention

As described in EFSA (2005) and EFSA (2013), the role of fluoride in the prevention of caries has been known for many years. Exposure to fluoride leads to incorporation into the hydroxyapatite of the developing tooth enamel and dentin. The resulting

fluorohydroxyapatite is more resistant to acids than hydroxyapatite, and teeth which contain fluoroapatite are less likely to develop caries. Apart from incorporation of fluoride into the dentin and enamel of teeth before eruption, the cariostatic effect from fluoride in children and adults is due to its effects on the dynamics of enamel surface layer de- and remineralisation during an acidogenic challenge (Marquis, 1995; Tatevossian, 1990, both cited in IOM, 1997). Further, fluoride interferes with the metabolism of oral microbial cells, by directly inhibiting, for example, glycolytic enzymes. Plaque fluoride concentrations are directly related to the fluoride concentrations in and frequencies of exposure to water, beverages, foods, and dental products.

Excess intakes and toxicity

Acute toxic effects may be provoked by ingestion of very high doses of fluoride and may be lethal (EFSA, 2005), as illustrated by some case reports. For example, a 3-year-old boy died after swallowing sodium fluoride tablets amounting to 16 mg fluoride per kg bodyweight (Eichler et al., 1982 cited in EFSA, 2005). Regarding chronic high intake, EFSA concluded that from the available data no increased risk of developing cancer at the observed fluoride dose levels could be deduced. Genotoxic effects associated with a high exposure to fluoride have been observed, predominantly in persons with clinically manifest symptoms of fluoride toxicity (skeletal fluorosis) (see below). Concerning reproductive effects, reports were not conclusive, and it remains unresolved if fluoride from drinking water may influence human fertility. Nephrotoxic effects of fluoride have not been reported. Regarding a claimed relationship between altered thyroid function, endemic goitre and fluoride exposure, alternative explanations have not been ruled out and are likely. Gastrointestinal symptoms like nausea, vomiting, anorexia, and diarrhoea were concluded by EFSA to occur with high fluoride intakes that also result in skeletal effects, i.e. with doses above 0.5 mg/kg bw/day.

Excess intake of fluoride over time may cause dental (enamel) and bone fluorosis. Dental fluorosis is characterised by increased porosity of the enamel due to subsurface hypomineralisation with a loss of enamel translucency and increased opacity. On a population basis there is a positive correlation between fluoride intake and severity of dental fluorosis. However, due both to genetic and environmental factors, severity of dental fluorosis varies individually at the same level of intake. In a WHO report, it is stated that it may not be possible to achieve effective fluoride-based caries prevention without some degree of dental fluorosis, regardless of what methods are chosen to maintain a certain level of fluoride in the mouth (Petersen, 2003). Mild and moderate forms of dental fluorosis are of aesthetic concern only, while in severe cases the teeth are stained brown, show enamel defects, are pitted and fragile, and may be deformed or break.

Skeletal fluorosis occurs after many years of excessively high fluoride intake. Bones become denser but more brittle, and the risk of bone fractures is increased. Joint stiffness is another symptom of skeletal fluorosis. Severe skeletal fluorosis is practically unknown in Europe (EFSA, 2013). Skeletal fluorosis may be assessed radiographically, or clinically in terms of bone fractures.

2 Recommendations and tolerable upper intake levels

2.1 Recommendations

2.1.1 Institute of Medicine (1997), USA

Institute of Medicine (IOM) considered that because data were not available to determine an Estimated Average Requirement (EAR), the reference value to be used for fluoride was the Adequate Intake (AI) (IOM, 1997). According to IOM, the cariostatic effect of fluoride is a strong indicator for an AI of the fluoride ion. Based on part of the evidence also cited by EFSA (2013), an AI for fluoride from all sources of 0.05 mg/kg/day was set by IOM for males and females of all age groups, including pregnant and lactating women.

2.1.2 Nordic Nutrition Recommendations (2012)

No recommendation for daily fluoride intake was given, because fluoride is not considered an essential trace element (NNR Project Group, 2012).

2.1.3 European Food Safety Authority (2013)

EFSA did not consider fluoride to be an essential nutrient. Therefore, Average Requirement (AR) for the performance of essential physiological functions was not defined. Because of the beneficial effect of dietary fluoride on prevention and severity of caries, EFSA found that the setting of an AI is appropriate (EFSA, 2013).

For infants and children, EFSA considered that data on the dose-response relationship between caries incidence and consumption of drinking water with different fluoride concentrations (Dean, 1942; Dean and Elvove, 1937), which were confirmed by more recent data on total fluoride intake in the US (for references see EFSA (2013)), were sufficient to set an AI of 0.05 mg/kg body weight per day. The AI covers fluoride intake from all sources, including non-dietary sources.

For adults, EFSA considered that no data were available to define a dose-response relationship between fluoride intake and caries. Reliable and representative data on the total fluoride intake of the European population were not available. The available data on fluoride intake were variable, but generally were found to indicate an intake at or below 0.05 mg/kg body weight per day. EFSA considered that the AI for children of 0.05 mg/kg body weight per day can also be applied to adults, including pregnant and lactating women.

Table 2.1.3-1: Adequate Intakes (AI) from all sources for fluoride in different age groups (Source: EFSA, 2013).

Age	AI, Males (mg/day)	Reference weight, males (kg)	AI, Females (mg/day)	Reference weight, females (kg)
1-3 years	0.6	12.2	0.6	11.5
4-6 years	1.0	19.2	0.9	18.7
7-10 years	1.5	29.0	1.4	28.4
11-14 years	2.2	44.0	2.3	45.1
15-17 years	3.2	64.1	2.8	56.4
≥ 18 years	3.4	68.1	2.9	58.5

2.2 Tolerable upper intake levels

2.2.1 Institute of Medicine (1997), USA

IOM considered that the primary adverse effects associated with chronic, excess fluoride intake are enamel and skeletal fluorosis (IOM, 1997).

Adverse cosmetic effects for ages one to eight years: Enamel fluorosis

IOM states that enamel fluorosis is a dose-response effect caused by fluoride ingestion during the pre-eruptive development of the teeth. The pre-eruptive maturation of the crowns of the anterior permanent teeth is complete, and the risk of fluorosis is over by eight years of age (Fejerskov et al., 1977).

Because the cosmetic effects of the milder forms of enamel fluorosis are not readily apparent, moderate enamel fluorosis was selected by IOM as the critical adverse effect for susceptible age groups (infants, toddlers, and children through the age of eight years).

Dose-response assessment for enamel fluorosis (up to age eight years)

IOM considered that the most appropriate data available for identifying a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) were provided by two studies evaluating the severity of enamel fluorosis in children (Dean, 1942; Dean and Elvove, 1937). In these early studies, fluoride intake was almost exclusively from the diet (water) and not confounded by intake from dental products.

Based on the epidemiological data described above, IOM found that an average, chronic daily fluoride intake of 0.10 mg/kg bw appears to be the threshold beyond which moderate enamel fluorosis appears in some children. Consequently, a fluoride intake of 0.10 mg/kg bw/day was identified by IOM as a LOAEL for moderate enamel fluorosis in children from

birth through the age of eight years, at which age the risk of developing fluorosis of the anterior teeth is over.

The relationship between fluoride intake and enamel fluorosis was based on results from human studies, and enamel fluorosis is considered a cosmetic effect rather than an adverse functional effect. Therefore, an uncertainty factor (UF) of 1 was selected by IOM.

Based on a LOAEL of 0.10 mg/kg/day for moderate enamel fluorosis and a UF of 1, a Tolerable Upper Intake Level (UL) of 0.10 mg/kg/day was established by IOM for infants, toddlers, and children through eight years of age. This translates to a dose of 1.3 mg/day for children ages one through three years (reference weight of 13 kg). For children ages four through eight years with a reference weight of 22 kg, the UL is 2.2 mg/day.

Adverse functional effect age eight years and older: Skeletal fluorosis

IOM (1997) mentions three reviews of the literature that attempted to identify adverse functional effects of fluoride ingestion in adults (Kaminsky et al., 1990; NRC, 1993; USPHS, 1991). These reviews were found to indicate that the primary functional adverse effect associated with excess fluoride intake in children above eight years of age and in adults is skeletal fluorosis.

According to IOM, crippling skeletal fluorosis was extremely rare in the United States (only 5 cases had been confirmed during the last 35 years), even though for many generations there had been communities with drinking water fluoride concentrations in excess of those that have resulted in the condition in other countries (Singh and Jolly, 1970). This puzzling geographic distribution has, according to IOM, usually been attributed to unidentified metabolic or dietary factors that rendered the skeleton more or less susceptible.

Dose-response assessment of skeletal fluorosis (children from age eight years and adults)

At high, chronic intake levels greater than 10 mg/day of fluoride for 10 or more years (Kaminsky et al., 1990; NRC, 1993; USPHS, 1991), the risk of skeletal changes consistent with preclinical or stage 1 skeletal fluorosis were found to increase. Therefore, IOM states, the data deemed most appropriate for identifying a NOAEL (or LOAEL) for older children and adults are provided by studies on skeletal fluorosis.

Based on the available studies addressing the association between fluoride intake and skeletal fluorosis in North America, to a large extent determined radiographically, a NOAEL of 10 mg/day of fluoride was identified by IOM.

Because the NOAEL is derived from human studies and there is a lack of evidence for symptomatic skeletal fluorosis observed at this level of fluoride intake, a UF of 1 was selected by IOM. According to IOM, data from studies of fluoride exposure from dietary sources or work environments (Hodge and Smith, 1977) indicate that a dose of 10 mg/day

for 10 or more years carries only a small risk for an individual to develop preclinical or Stage 1 skeletal fluorosis.

An UL of 10 mg/day was established for children older than eight years and for adults.

No data indicated an increased susceptibility to fluorosis during pregnancy. Therefore, the UL for adults of 10 mg/day was also established for pregnant women. An UL of 10 mg/day was also established for lactation. Because only an extremely small proportion of fluoride is transferred to the breast milk it is unlikely that the child will be exposed to fluoride (Ekstrand et al., 1981; Ekstrand et al., 1984; Esala et al., 1982; Spak et al., 1982).

Exposure scenario

IOM states that prior to the 1960s, the diet, including water, was the only significant source of fluoride. Since then, fluoride ingestion resulting from the use of dental products and fluoride supplements had increased the risk of enamel fluorosis in children. Recommendations have been made to reduce fluoride intake from non-dietary sources (NRC, 1993; USPHS, 1991).

Risk characterisation

The IOM concluded that although the prevalence of enamel fluorosis in both fluoridated and non-fluoridated communities in the United States and Canada was substantially higher than it was when the original epidemiological studies were done some 60 years earlier, the severity remained largely limited to the very mild and mild categories.

The virtual absence of evidence of skeletal changes consistent with a diagnosis of skeletal fluorosis indicated, according to IOM, that the UL for older children and adults was not being exceeded in the United States or Canada.

2.2.2 Expert Group on Vitamins and Minerals (EVM, 2003), UK

No safe upper level was set for fluoride by the UK expert group.

2.2.3 European Food Safety Authority (EFSA, 2005), EU

The EFSA Panel identified different critical endpoints for the derivation of an UL of oral fluoride intake for the age from one to eight years (moderate dental (enamel) fluorosis) and for all ages above eight years (bone fracture). Different ULs were set for these groups. Bone fractures were used as one important measure of fluorosis.

Other putative adverse outcomes, like bone mineral density, carcinogenicity, genotoxic and reproductive effects, nephrotoxic effects, effects on thyroid function and gastrointestinal effects were also considered during the evaluation.

Adverse cosmetic effect age one to eight years: Dental fluorosis

Several different recording systems have been employed for dental fluorosis, which often makes comparison between studies difficult. However, irrespective of scoring system, the development of tooth enamel fluorosis is dose dependent, but the sensitivity in both ends of the scoring scale will differ between systems.

Apparent from the epidemiological studies, according to EFSA, is that there is no real threshold value for a fluoride intake that is not associated with the occurrence of dental fluorosis in the population. While the intake of fluoride from water can be estimated with some certainty, the intake of fluoride from other sources is influenced by a wide variety of individual habits, and is therefore difficult to assess.

Dose-response assessment for dental fluorosis (up to age eight years)

EFSA based the assessment of dental fluorosis on the same studies as IOM. These studies from the late 1930ies and 1940ies, before fluoride was commonly added to oral hygiene products, found a linear relationship between fluoride content of drinking water and the prevalence of dental fluorosis (Dean, 1942; Dean et al., 1942; Dean et al., 1941). These findings were confirmed by two large studies in USA 25 and 40 years later (Butler et al., 1985; Fejerskov et al., 1996; Richards et al., 1967).

Similar dose-effect relationships to those with fluoride in water have been demonstrated between the fluoride intake from fluoride tablets and dental fluorosis. The EFSA report states that there is no reason to suppose that fluoride available from food, including fluorinated salt and beverages, and from toothpaste has a different effect on maturing enamel than fluoride from water and tablets, although no investigations of this relationship were available to EFSA.

From observational epidemiological studies EFSA concluded that among persons living permanently in communities with water fluoride concentrations of about 1 mg/L, 10 to 12% of the population was affected by mild forms of enamel fluorosis. The fluoride intake of children in these communities was calculated to be 0.02 to 0.1 mg/kg/day. At a fluoride intake at the higher end of this interval, 0.08-0.1 mg/kg/day, moderate (or worse) fluorosis was recorded in less than 5% of children. Very mild or mild fluorosis occurred in 48% of children with a calculated fluoride intake of 0.043 mg/kg/day.

EFSA concluded that a fluoride dose of 0.1 mg/kg bw/day has been described as a 'threshold' dose for the occurrence of less than 5% of moderate forms of dental fluorosis in a population for the ages from birth to eight years (Dean, 1942; Fejerskov et al., 1996). An intake of 0.1 mg fluoride/kg bw/day in children up to the age of eight years can be considered as the dose below which no significant occurrence of moderate forms of fluorosis in permanent teeth will occur.

EFSA states that no uncertainty factor was deemed necessary to derive an UL from this intake, because it is derived from population studies in the susceptible group.

Mild fluorosis is generally considered to be acceptable on a population basis, in view of the concomitant beneficial effect of fluoride in the prevention of caries.

For children up to the age of eight years, the intake level of 0.1 mg/kg bw/day was proposed as the UL. Based on body weight, the UL for children aged one to three years old and four to eight years old was 1.5 mg/day and 2.5 mg/day, respectively.

The ULs apply to intake from water, beverages, foodstuffs, including fluorinated salts, dental health products and fluoride tablets for caries prevention.

Adverse functional effect in children age eight years and older, and adults: Skeletal fluorosis

All studies on the relationship between fluoride in drinking water and bone density or risk of bone fracture suffer from imprecise exposure assessment. Although fluoride increases bone mineral density, there is a corresponding decrease in elasticity and strength of bone tissue. Consequently, according to EFSA, an increase in fluoride content is accompanied by an increase in bone strength only up to a certain dose level, thereafter bone strength decreases.

Dose-response assessment of skeletal fluorosis (children from age eight years and adults)

EFSA (2005) found that data on fluoride content in bone with the asymptomatic stage of skeletal fluorosis as well as clinical stages I and II plus III are available, but there are no parallel data on the fluoride intake associated with the reported levels of fluoride in bone. In the few cases of clinical skeletal fluorosis in which the fluoride intake could be estimated, it ranged from 15 to 20 mg/day and the period of exposure was over 20 years. EFSA concluded that a more precise threshold dose for fluoride causing skeletal fluorosis could not be defined.

EFSA decided not to use the data on the relationship between fluoride intake via drinking water and radiographic skeletal changes for setting an UL because of insufficient exposure estimates and a lack of more recent radiographic investigations.

EFSA found the available data to be of uncertain relevance with regard to the risk for bone fractures. It is pointed to the observational study by Li et al. (2001) as evidence that an increased risk of bone fractures occurs at a total intake of 14 mg fluoride per day, and that there are data (although not statistically significant) suggestive of an increased risk of adverse bone effects at total intakes above about 6.5 mg/day of fluoride. An observational study from Finland by Kurttio et al. (1999) is considered as supportive to this conclusion (IPCS, 2002).

A number of therapeutic randomised controlled studies of postmenopausal women found no difference in the occurrence of adverse skeletal effects (vertebral and non-vertebral fractures and lower-limb pain presumably caused by microfractures) with fluoride doses of 4.5 to 26 mg/day (up to 0.4 mg/kg bw/day) (Haguenauer et al., 2000). A study by Riggs et al. (1994) found that the non-vertebral fracture rate in the treatment group on a daily dose of 0.56 mg fluoride per kg body weight after six years was three times higher than in the control group. Thus, from therapeutic studies, it appeared that side-effects in the form of lower-limb pain occurred in a significantly higher frequency when fluoride doses of more than 0.4 mg/kg body weight were administered, compared with the placebo group. Lower limb pain was considered as indicative of incomplete fractures of the bone, a critical outcome in relation to setting an UL. It should be kept in mind that the subjects in the therapeutic studies were mostly elderly (> 50 years), predominantly female and were selected because of already existing changes in bone mass or density and were with or without a history of vertebral fractures (EFSA, 2005).

The EFSA Panel concluded that therapeutic randomised controlled trials with fluoride in postmenopausal women suggest a significantly increased risk for skeletal fractures at or above fluoride intakes of 0.56 mg/kg body weight, rounded up to 0.6 mg/kg bw/day to allow for intakes from dietary sources. Observational epidemiological data that indicated a significantly increased risk for fractures at all sites associated with a long-term total daily intake of fluoride of 14 mg/day were considered as supportive evidence (EFSA, 2005).

The EFSA Panel decided to apply an uncertainty factor of 5 to the intake of 0.6 mg fluoride/kg bw per day, stating that: "although the adverse effects were detected in a sensitive group of elderly postmenopausal women, the study duration was relatively short and the studies were not designed to systematically define a LOAEL."

Accordingly, for children older than eight years and adults, an intake of 0.12 mg fluoride/kg bw/day was proposed as an UL. This translates on a body weight basis (60 kg) into an UL of 7 mg/day for adults, and for nine to 14-year olds into an UL of 5 mg/day (EFSA, 2005).

Exposure scenario and risk characterisation

Children will, according to EFSA, have fluoride intakes from food and water well below the UL provided that the fluoride content of their drinking water is not higher than 1.0 mg/L. An increase in the prevalence of mild dental fluorosis observed in some countries has been attributed to the inappropriate use of dental care products, particularly of fluoridated toothpaste.

For children older than eight years and adults, the probability of exceeding the UL of 5 and 7 mg fluoride/day, respectively, on a normal diet is estimated by EFSA to be low. However, consumption of water with a high fluoride content e.g. more than 2-3 mg/L predisposes to exceeding the UL.

Table 2.2.2-1: ULs set by EFSA (2005) for different age groups.

Age groups	UL (mg/day)
Children 1-3 years	1.5
Children 4-8 years	2.5
Adolescents 9-14 years	5
> 14 years and adults	7

2.2.4 Nordic Nutrition Recommendations (NNR, 2012)

The UL set by EFSA is cited, and some of the potential adverse effects other than enamel fluorosis are mentioned.

2.2.5 Summary of upper intake levels in adults

Conclusions concerning ULs from previous reports on DRVs for fluoride are shown in Table 2.2.5-1.

Table 2.2.5-1 Overview of existing tolerable upper intake levels (ULs) for fluoride for adults set by various authorities.

	UL	Based on	UF
IOM, 1997	10 mg/day	NOAEL/LOAEL from human studies	1
EFSA, 2005	7 mg/day	NOAEL/LOAEL from human studies	5
EVM, 2003	ND		
NNR, 2012	ND		

ND: Not determined.

3 Exposure assessment

In Norway, drinking water, tea, toothpaste and other caries prevention products are regarded as the main contributors to human fluoride intake. Fluoride content in food is generally low and Norwegian food composition data on fluoride, or data on habitual dietary fluoride intake in nationally representative samples of the population are not available. We estimated the fluoride intake by combining intake data from national dietary surveys for the most important sources of fluoride, which are tea and water, with available values for distribution of fluoride concentrations in drinking water from reports from Norwegian waterworks. The obtained data for fluoride concentrations in drinking water are generated from NSFAs website[1], and in tea based on the fluoride content in infusions of commercially available teas such as black, green, and white tea (Malinowska et al., 2008). We used the individual intake in combination with selected percentiles of concentration of fluoride in drinking water and tea (given in Table 3.1-1). In addition, we have estimated the fluoride intake from commonly used dental products. A fixed value was added to cover intake from minor and unspecified sources.

3.1 Concentrations of fluoride in relevant sources

Drinking water and tea

The registered waterworks in Norway supply approximately 90% of the population in Norway with water. Drinking water in Norway is obtained from two sources; surface water such as rivers and reservoirs, and groundwater. Of the registered waterworks, 90% use surface water sources. Additionally, small waterworks not registered in the Norwegian Waterworks Register supply approximately 600 000 persons in Norway (population approx. 5 mill). The majority of these persons have groundwater supply from private wells and small shared waterworks as their water source (Folkehelseinstituttet, 2016).

According to the regulation of water supply and drinking water in Norway[2], drinking water may contain a maximum of 1.5 mg fluoride per liter. The regulations are practically the same for tap water at home and bottled water as long as the bottled water is called "drinking water" or "mountain spring water" and is not added any flavor or other substances. "Natural

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[1]https://www.mattilsynet.no/mat_og_vann/vann/vannforsyningssystem/oversikt_over_vannforsynings system.1878

[2]Forskrift om vannforsyning og drikkevann; https://lovdata.no/dokument/LTI/forskrift/2016-12-22-1868.

mineral water", is subject to other regulations than drinking water, and may contain higher concentrations of fluoride compared to drinking water.

An overview of water quality analyses from registered waterworks in Norway is available on the website of NSFA. Results from fluoride concentration analyses is given for selected waterworks. 4666 fluoride analyses are reported for the period from 2010 until 2018 from 662 different waterworks. Most of the waterworks have reported only one analysis of fluoride (n=1530)[3].

We have excluded 13 analyses in the range between 120-3320 mg fluoride/L as these results were judged to be misreported.

The median fluoride concentration in the included analyses was 0.11 mg/L and the range was 0-47 mg/L. In a total of 2014 fluoride analyses, 33 reported values were >3.0 mg/L corresponding to 1.6% of the analyses. Nine of the analyses were >6.0 mg/L. 134 fluoride values were in the range of >0.5 -1.0 mg/L, 53 in the range >1.0 – 1.5 mg/L and 115 in the range >1.5 -3.0 mg/L. The majority (n= 1676) of the reported fluoride values were <0.5 mg/L corresponding to 83% of the values in the dataset.

According to Norwegian Geological Survey (NGU) the fluorine concentration in more than 15% of drinking water wells in solid rock in Norway is so high that water can damage teeth during formation, especially if children additionally receive fluoride tablets or use toothpaste added with fluoride[4].

The fluoride concentration in groundwater may be high. Figure 3.1-1 shows fluoride concentrations in various Norwegian groundwater wells in a study conducted in 2016 (Abiyos, 2017). Waterworks listed in the Norwegian Waterworks Register were invited, and 201 samples (one per waterwork) were analysed. Fluoride concentrations were above the maximum limit of 1.5 mg/L in the drinking water regulation at four of these waterworks.

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[3]https://www.mattilsynet.no/mat_og_vann/vann/vannforsyningssystem/oversikt_over_vannforsynings system.1878.

[4]https://www.ngu.no/grunnvanninorge/alt-om-grunnvann/grunnvannskvalitet/fluor.
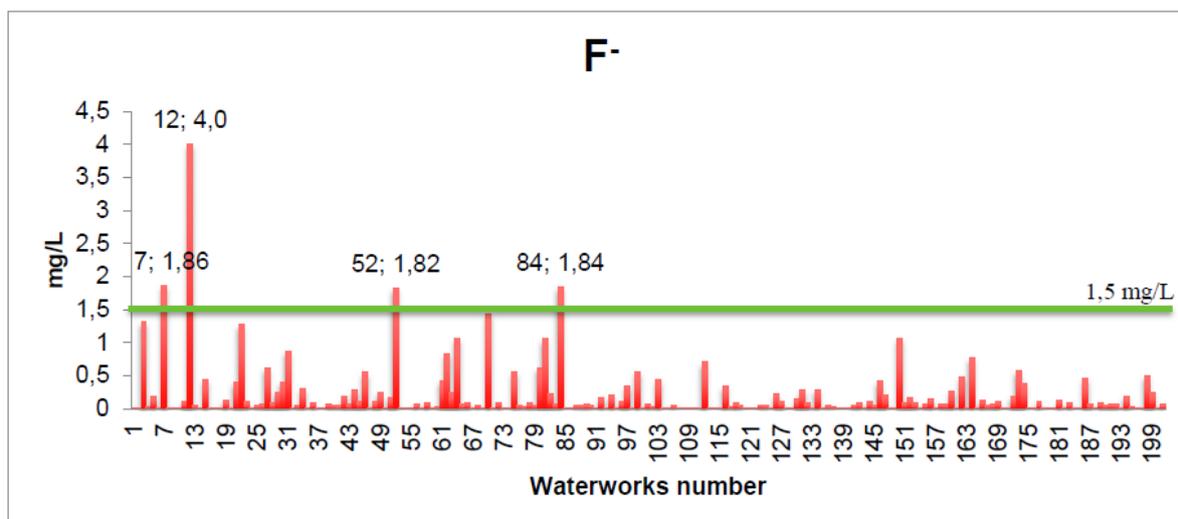
Figure 3.1-1. Analysed levels of fluoride (mg/L) in groundwater samples collected at 201 different waterworks in Norway in 2016. The green line indicates the Norwegian regulation upper limit of fluoride (1.5 mg/L) in water. Only one sample from each waterworks was available. Figure taken from Abiyos (2017).

Fluoride content in food is generally low (0.1-0.5 mg/kg), but tea is an exception. Tea may contain considerable amounts of fluoride (170-400 mg/kg dry weight in black and green teas made from young leaves and two to four times as much in brick tea made from mature leaves; whereas tea infusions may contain 0.34-5.2 mg fluoride per liter) (Chan and Koh, 1996; Schmidt and Funke, 1984; Wei et al., 1989), dependent on type of tea, brewing procedure and fluoride concentration of water. Some brands of instant teas can also be a significant source of fluoride intake (up to 6.5 mg/L when prepared with distilled water) (Whyte et al., 2005). In a paper from 2008, the fluoride concentration was measured in the water extracts of different types of tea (black, green, oolong, pu-erh, white) from several regions of the world, and in commercial blends, green tea with herbal additives, as well as in instant teas and soft ready-to-drink tea beverages using water from Poland (Malinowska et al., 2008). The fluoride concentration after 5 min of brewing ranged from 0.32-4.54 mg/L in black tea. The levels were higher in extracts prepared from granulated and powdered tea in bags, as compared to leaf tea. The fluoride levels also increased after 10 and 30 min of brewing. The average increase in fluoride content released into black tea infusions after 10 min of brewing was 21% (range 3.1-66%) and 37% (range 15-153%) after 30 min. In green tea, the concentration of fluoride ranged from 0.59-1.83 mg/L after 5 min of brewing. In green tea infusions with herbal additives the fluoride content ranged from 0.08-1.25 mg/L, and the amount of fluoride in white tea extracts was lower than that in other types of tea (0.37-0.54 mg/L) after 5 min of brewing. The herbal tea infusions such as rooibos Earl Grey was low after 5 min of brewing (0.02-0.09 mg/L). The mean fluoride levels in instant tea and ready-to-drink tea beverages were 0.07 mg/L (range 0.04-1.21 mg/L) and 1.23 mg/L (range 0.66-1.65 mg/L), respectively. In particular the intake of ready-to-drink tea can be a concern for those children who drink a lot of ice tea.

An overview of fluoride concentrations relevant for our exposure estimates are given in Table 3.1-1. The fluoride content in the water extracts of black and green tea is based on Malinowska et al. (2008), as they report the latest data from different types of commercially available teas around the world sold in a European country.

Table 3.1-1: Fluoride concentrations in drinking water, diluted syrup beverages (Norwegian "saft"), water in coffee and herb teas and fluoride concentrations in water extracts of black and green teas used in our fluoride exposure estimates (mg/L).

	Drinking water, "saft", water in coffee and herbal teas[1]	Black and green teas[2], 5 min brewing
Mean	0.43	1.38
Median	0.11	1.12
95th percentile	1.65	3.47
Max	47.00	4.54

[1]The fluoride concentration in water is based on analyses from 2001 samples from 662 different waterworks in Norway.
https://www.mattilsynet.no/mat_og_vann/vann/vannforsyningssystem/oversikt_over_vannforsyningssystem.1878
[2] Malinowska et al. (2008): The fluoride concentration is based on analyses of 20 different commercially available black teas and 11 different commercially available green teas.

Other dietary sources

Most foods contain only low amounts of fluoride. However, seafood is to some extent an exception. A study published in 1981 revealed a mean content of fluoride of 0.71 mg/kg (range 0.2-2.0 mg/kg) in a sample of edible fresh, frozen and smoked fish and marine products (Table 1 in Soevik and Braekkan (1981)). The lowest content was found in frozen saithe fillet, while the highest content was in salt cured herring fillet. Mean fluoride content in canned fish and marine products (Table 2 in Soevik and Braekkan (1981)) was 0.88 mg/kg (range 0.16-3.90 mg/kg). These products contain some bone and skin which may account for the elevated levels (Soevik and Breakkan 1979 cited in Soevik and Braekkan, 1981).

Vegetables and fruit, except when grown near fluoride-emitting industrial plants, contain between 0.02 and 0.2 mg/kg fresh weight, milk and dairy products 0.05-0.15 mg/kg, bread, cereals and cereal meals 0.1-0.29 mg/kg, meat and meat products 0.15-0.29 mg/kg, eggs 0.18 mg/kg (Bergmann, 1994; EVM,2001 both cited in EFSA, 2013).

In Norway, salt is not fluoridated, and therefore salt is not a source for fluoride in Norway.

Toothpaste and fluoride-containing dental products

Dental fluoride tablets and toothpaste contain various amounts of fluoride for different age groups. The most common fluoride concentrations in toothpaste in the Norwegian market is 1.0 mg/g (1000 ppm F⁻) for children (0-6 years) and 1.45 mg/g (1450 ppm F⁻) toothpaste for children above 6 years and adults. The fluoride concentrations are 0.25 mg and 0.5 mg per tablet for children above 3 years, and 0.75 mg per tablet for adults. The labelling states that if drinking water contains more than 0.25 mg/L, caution should be taken regarding use of dental fluoride tablets.

In addition to toothpaste and dental fluoride tablets, adolescents and adults may also be exposed to fluoride from mouthwashes and dental chewing gum. Fluoride concentrations in mouthwash products vary and may contain 0.1 - 1.0 mg/mL. Dental chewing gum may contain 0.14 mg fluoride per gum.

3.2 Consumption data for drinking water, tea, and fluoride containing dental products and other dietary sources in Norway

Consumption data are based on the national representative dietary surveys for different age groups; Norkost 3 for adults; Ungkost 3 for children and adolescents and Småbarnkost 2007 for young children.

Norkost 3 was based on two 24-hour recalls by telephone interview, performed at least one month apart. Food portions were presented in household measures or estimated from photographs. The study was conducted in 2010/2011, and 1787 adults (925 women and 862 men) aged 18-70 participated (Totland et al., 2012).

The exposures to fluoride in 4-, 9- and 13-year old children are calculated from the national dietary survey Ungkost 3. The Ungkost 3 study was a nationwide dietary assessment study conducted in 2015 (9- and 13-year olds) and 2016 (4-year olds). The dietary assessment method was a 4 days validated web-based food diary, and 399 4-year olds, 636 4th graders (8-9 years) and 687 8th graders (12-13 years) participated (Hansen et al., 2017; Hansen et al., 2016).

2-year-old children; Småbarnskost 2007 is based on a semi-quantitative food frequency questionnaire. In addition to predefined household units, food amounts were also estimated from photographs. The study was conducted in 2007, and a total of 1674 2-year-olds participated (Kristiansen et al., 2009).

For 2-, 4- and 9-year-olds the food category «drinks» include drinking water, juice, soda pop, and "saft". There were no reported intakes of tea or coffee in these age groups. For the older age groups "drinks" include drinking water, juice, soda pop, and "saft" and coffee and tea.

The consumption of "drinks" in the various age groups are given in Table 3.2-1.

Table 3.2-1: Consumption data for drinking water, juice, soda pops, "saft", coffee and tea in various age groups, g/day.

Age	Median	95 percentile	Mean	SD
2 years	399	988	465	280
4 years	463	863	486	190
9 years	575	1139	623	285
13 years	663	1550	760	480
Adults	1875	3462	1950	860

The consumption data for fluoride-containing dental products in our fluoride exposure estimates are based on use recommended by Norwegian health authorities in the different age groups. The Norwegian directorate of health advices children and adolescents to use toothpaste with fluoride twice a day. The recommended dose is low when the first tooth appears (0.1 ml toothpaste), and at the age of one year, the amount should be according to the size of the nail of the child. At the age of three years, the recommended amount is about 0.25 ml, and this amount increases when the child is five to six years old.

3.3 Fluoride exposure estimates

The exposure estimates for fluoride from food and drinks presented in this section and Appendix 1 are based on the statistical information about the fluoride concentrations in drinking water and green and black tea given in Table 3.1-1, combined with individual consumption data for drinking water and tea (see chapter 3.2). The drinking water estimates include several different drinks i.e. coffee, other teas than black or green tea, soda pops and "saft" as the water used for the preparation of these drinks will also contain fluoride. All the calculations are given in Appendix 1. In this chapter only the estimates based on the 95th percentile fluoride concentrations in water and black or green teas are presented.

The wide range of fluoride concentrations in water and tea poses a problem for exposure estimation. The fluoride concentrations in water and the fluoride fraction in tea due to extraction from the leaves will vary independently. There is no information available about fluoride concentrations that can be combined with intake data on the individual level to calculate observed fluoride intake levels. Our concern is to protect the population from high doses of fluoride that would cause adverse effects. Therefore, we use the 95 percentile of analysed fluoride concentrations for water and for tea to estimate potential high-level fluoride exposure. Further, we have used the 95 percentile of the resulting exposure estimates to assess the difference between high fluoride intakes and the ULs, and to describe the requested scenarios of adding specified amounts of fluoride supplementation. It should be emphasised that these exposure estimates based on combined high fluoride levels in tea and drinking water plus dental products represent a scenario of the highest potential

exposure levels, while they do not represent observed intakes or the intakes of the larger part of the population.

Based on food intake data among adults in Norkost 3, the mean intake of fish among men and women was 67 g/day, representing an intake of fluoride from fish based on highest concentration from Soevik and Braekkan (1981) to be 0.134 mg fluoride per day. Thus, seafood is not an important source of fluoride in Norway and is therefore not specified in the exposure estimates, nor are any other food groups.

The Norwegian directorate of health recommend children to use toothpaste with fluoride twice a day. When the first tooth appear, the dose is very low (0.1 mL toothpaste). At the age of 3 the amount is about 0.25 mL, corresponding to 250 mg toothpaste and 0.25 mg F-. The doses increases when the child get older (5-6 years). A child one to six years old using the age-specific recommended portion of toothpaste (0.25 mL) twice a day will be exposed to 0.25 mg fluoride under the assumption that 50% is swallowed (Birkeland et al., 2001). There is a large variation in how much toothpaste that is used among children (Birkeland et al., 2001). Based on the previous VKM report from 2006, the estimated use of toothpaste among adults was 480 mg/day (VKM, 2006). Since children above six years, adolecents and adults are not expected to swallow the toothpaste, the estimated intake of fluoride was 0.1224 mg/day (based on a retension factor of 0.17, and content of 1.5 mg/g fluoride in toothpaste) (VKM, 2006). In addition, if dental fluoride tablets are used, the dose of fluoride in fluoride tablets is 0.25 mg per day for children six months to three years, and 0.5 mg per day for children three to 12 years, and 1 mg per day for adolescents 12 to 18 years, and 1.5 mg per day for adults above 18 years.

Mouthwash products are primarily recommended for adolescents above 12 years and should not be swallowed. However, also children 6 to 12 years with high risk of caries can use mouthwash products. The recommended daily use is 10 mL 1-2 times daily and the daily amount of mouthwash used may contain between 1.0 to 20 mg fluoride per day. The fluoride exposure from mouthwash products will vary, and is dependent on how much is retained in the oral cavity and swallowed.

Dental chewing gum containing 0.14 mg fluoride per gum is only recommended for adults and children above 12 years of age.

In our exposure estimates, we have included dental fluoride tablets (not rinses and chewing gum) used according to health authority recommendations in the calculations, but not other use of fluoride containing food supplements. This will be addressed in the Answer to the terms of reference, as this is part of the mandate from the NFSA.

In our exposure estimates, we have assumed that the fluoride exposure from all other sources than drinking water (including coffee, other teas than black and green tea, soda pops, "saft" and juices), black or green tea, toothpaste and dental fluoride tablets is 0.2 mg/day in all age groups.

Fluoride exposure estimates in the 95 percentile based on 95 percentiles fluoride concentrations in water and black or green teas are given in Table 3.3-1 for adults, adolescents and children.

Table 3.3-1: 95 percentile exposure (mg/day) in the different age groups calculated using 95 percentile of fluoride concentrations in drinking water and black and green tea, and exposures from dental products and all other sources. Drinking water includes consumption of coffee, other teas than black or green tea, soda pops, juices and "saft". There are no data for coffee or tea consumption in the 2-, 4- or 9-years old.

Age	95P exposure with 95 percentile fluoride concentrations in water and black/green tea	Tooth-paste	Dental fluoride tablets	All other exposure	Total fluoride exposure
2 years	1.63	0.25	0.25	0.20	2.33
4 years	1.42	0.25	0.50	0.20	2.37
9 years	1.92	0.1224	0.50	0.20	2.74
13 years	2.73	0.1224	1.00	0.20	4.05
Adults	6.72	0.1224	1.50	0.20	8.54

4 Assessment of the suggested maximum limits

4.1 Selection of a Tolerable Upper Intake Level (UL)

ULs for fluoride have been set by EFSA and by IOM. For children up to eight years of age, the ULs set by IOM and by EFSA on a per kg basis are identical. The differences in ULs for the different age groups up to eight years of age are due to the use of different reference weights by IOM and EFSA. The ULs for older children and adults are based on different types of human studies for IOM and EFSA. IOM relies to a large extent on large radiographical studies. EFSA, in contrast, uses clinical data on fractures from smaller and somewhat diverse studies on fluoride treatment of osteoporosis. The study duration was relatively short and the studies were not designed to systematically define a LOAEL, which calls for the use of an uncertainty factor.

VKM decided in the present assessment of fluoride to employ the ULs derived by EFSA. The reasons were *i)* the EFSA assessment is the most recent and includes a number of studies published between the late 1990ies and up to 2005 that were not considered in the IOM report from 1996 *ii)* the EFSA report to a larger extent than the IOM document employs clinical outcomes (fractures) as critical outcomes.

Consequently, the ULs used by VKM in the assessment of the suggested maximum limits, are as follows: For children up to the age of eight years the UL is 0.1 mg/kg bw/day. Based on body weight, this translates for children age one to three years to an UL for fluoride of 1.5 mg/day, and for children age four to eight years to an UL of 2.5 mg/day. For children older than eight years and adults, including pregnant and lactating women, an intake of 0.12 mg fluoride/kg bw/day is used as an UL. This translates on a body weight basis (60 kg) into an UL of 7 mg/day for adults, and for nine to 14 year-olds into an UL of 5 mg/day.

4.2 Risk characterisation

Regarding the fluoride intake from the diet and fluoride containing dental products, we chose to base our risk characterisation on the 95-percentile fluoride exposure from drinking water and of tea, the two main variable fluoride sources. The exposure estimates are based on 95 percentile fluoride concentrations in water and tea combined with individual intakes. As for fluoride containing dental tablets, we have used exposures from recommended use for each age groups. The daily fluoride exposure from toothpaste was set to 0.25 mg for children age 2-4 years and 0.1224 mg for older children, adolescents and adults. Additionally, a fixed value of 0.2 mg fluoride per day is added for all age groups to cover intakes from food, possible use of fluoridated mouth rinses, etc. The input to the total exposure is given in

Table 3.3-1. The differences between the total exposures and the upper levels in the various age groups are presented in Table 4.2-1.

Table 4.2-1: Differences between the estimated 95 percentile total fluoride exposure (mg/day) (see text), and the respective ULs for different age groups.

Age	Total from all included fluoride sources, 95P	UL	Difference between 95P exposure and UL
2 years	2.33	1.5	0.83
4 years	2.37	2.5	-0.13
9 years	2.74	5.0	-2.26
13 years	4.05	5.0	-0.95
Adults	8.54	7.0	1.54

In the exposure estimates, the upper level for fluoride is exceeded in 2- year olds and adults.

The total high intake as shown in Table 4.2-1 covers the adequate intake (AI) for all age groups (AI values from EFSA 2013).

5 Uncertainties

Inherent uncertainties in the studies employed when setting the UL for fluoride, e.g. lack of reliable individual exposure data.

Unexplained geographical differences in the occurrence of adverse effects from high levels of fluoride intake.

Influence of environmental factors and regional and individual dietary habits on the risk of adverse effects from fluoride.

Possible gender differences in fluoride requirements and toxicity.

Influence of changing trends in food and drink consumption (e.g. reduced use of milk and fish products in Norway) on the risk of adverse effects from fluoride (less calcium with meals may increase fluoride uptake).

Inherent uncertainties in the food dietary surveys.

How well the factor 0.2 mg fluoride introduced to cover 'other and unspecified sources' corresponds to real intakes.

Consumption of bottled ice tea may have increased much the latest years, in which case fluoride intakes will have increased.

Fluoride concentration in soda 'pops' included as water intake.

Fluoride concentrations in teas on the Norwegian market, and population use of teas with different fluoride contents.

Tea fluoride concentrations are based on 5 min brewing. Tea may often be brewed for a longer time, which will lead to an increased fluoride concentration.

Accuracy of data on fluoride concentrations in Norwegian drinking water, in relation to numbers of individuals supplied from the different waterworks i.e. how correct is the 95P fluoride concentration for drinking water.

Variation in fluoride content in the water used for making tea relative to the fluoride concentration in the water used for the laboratory studies on fluoride content in tea (will probably tend to underestimate fluoride exposure).

Amount of fluoride absorbed from the oral mucosa and ingested with the use of fluoridated toothpaste, as well as fluoridated mouth rinses and chewing gum in different age groups.

The amount of toothpaste used for children can be much larger than what is recommended by the health authorities, and thus lead to a larger intake of fluoride among the youngest children.

The extent to which the use of fluoride tablets, fluoridated toothpaste and mouth rinses is reduced as recommended by health authorities in areas with a high content of fluoride in the water, is unknown. The lack of correction for such reductions will tend to cause overestimation of fluoride intakes.

6 Answers to the terms of reference

The Norwegian Food Safety Authority (NFSA, Mattilsynet) has requested the Norwegian Scientific Committee for Food and Environment (VKM) to assess the intake of fluoride from the diet, including fortified products, in all age groups in the population above one year.

There are no data on fluoride in the Norwegian food composition data base, and VKM was requested to evaluate if other relevant intake data can be used.

Based on consumption data from Norwegian national dietary surveys, data on fluoride content in water from the Norwegian Waterworks Register and a Polish study of fluoride content of teas (see chapter 3), VKM found that the main sources of fluoride consumed by the Norwegian population are drinking water and tea, together with fluoridated toothpaste and dental fluoride tablets. The intake of fluoride from food is presumed to be low, and was therefore covered by setting a fixed overall value of 0.2 mg/day for all age groups for intakes from food and unspecified sources. The high fluoride exposure for the various age groups included in the assessment was estimated from individual consumption volumes and 95 percentile fluoride concentrations of water and included drinks. The 95-percentile of the exposure to fluoride thus calculated is given in Table 4.2-1. This table also shows the exposure estimates in relation to the UL for the respective age groups.

VKM was also requested to conduct scenario estimations to illustrate the consequences of establishing maximum limits for fluoride at 0.5, 1, 5 or 7 mg/day in food supplements. The consequences of establishing maximum limits for fluoride at 0.5, 1, 5 or 7 mg/day in food supplements, are shown in Table 6-1. The table shows the resulting total fluoride intakes in the different age groups, based on the values in Table 4.2-1. It should be noted that the amounts of fluoride from toothpaste and tablets recommended by national health authorities for the prevention of caries, are included in the basic intake data.

Table 6-1: The consequences for the total fluoride exposure of adding different amounts of fluoride in food supplements (doses 0.5, 1.0. 5.0 and 7.0 mg/day) to the 95th percentile fluoride exposures given in Table 4.2-1. Green colour indicating no exceedance of UL, and red indicating exceedance of UL.

Age	Dose 0.5 mg/day	Dose 1.0 mg/day	Dose 5.0 mg/day	Dose 7.0 mg/day	ULs mg/day
2 years	2.83	3.33	7.33	9.33	1.5
4 years	2.87	3.37	7.37	9.37	2.5
9 years	3.24	3.74	7.74	9.74	5.0
13 years	4.55	5.05	9.05	11.05	5.0
≤18 years and adults	9.04	9.54	13.54	15.54	7.0

VKM concludes that all the suggested food supplement doses will cause the UL to be exceeded in all age groups except for the supplemental doses at 0.5 in 9- and 13 years old and 1 mg/day in 9 year olds.

7   Data gaps

- Fluoride concentration in food products including soft drinks in Norway
- Fluoride concentrations in tea products for home tea brewing in Norway
- Complete and updated information about fluoride content in drinking water in Norway
- Updated information regarding consumption of tea-based soft drinks by adults and children in Norway
- Data on uptake of fluoride from fluoridated toothpaste, mouth rinses and chewing gum
- Data regarding gender differences in fluoride toxicity

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Appendix 1 additional exposure estimates

Fluoride exposure estimates from water and tea for different age groups, see chapter 3 for explanation.

2-year-olds

For 2-year-olds the food category «drinks» include drinking water, juice, soda pop, and "saft". There were no questions of tea in the food frequency questionnaire, and thereby no reported intake of tea.

Table 1: Fluoride exposures in 2-year-olds (mg/day).

	Mean[1]	Median[1]	95P[1]	Max[1]
Mean exposure	0.20	0.05	0.78	21.85
Median exposure	0.17	0.04	0.67	18.76
95P exposure	0.42	0.11	1.63	46.42
Max exposure	1.34	0.34	5.15	146.64

[1]The columns represent the different concentrations used for fluoride in drinks in the exposure estimates.

4-year-olds

For 4-year-olds the food category «drinks» include drinking water, juice, soda pop, and "saft".

Table 2: Fluoride exposures in 4-year-olds (mg/day).

	Mean[1]	Median[1]	95P[1]	Max[1]
Mean exposure	0.21	0.06	0.81	22.85
Median exposure	0.20	0.05	0.77	21.74
95P exposure	0.37	0.10	1.42	40.54
Max exposure	0.56	0.19	2.11	60.21

[1]The columns represent the different concentrations used for fluoride in drinks in the exposure estimates.

9-year-olds

For 9-year-olds the food category «drinks» include drinking water, juice, soda pop, and "saft".

Table 3: Fluoride exposures in 9-year-olds (mg/day).

	Mean[1]	Median[1]	95P[1]	Max[1]
Mean exposure	0.28	0.08	1.06	29.34
Median exposure	0.26	0.07	0.99	27.03
95P exposure	0.51	0.16	1.92	53.55
Max exposure	1.01	0.54	3.69	95.63

[1]The columns represent the different concentrations used for fluoride in drinks in the exposure estimates.

13-year-olds

For 13-year-olds the food category «drinks» include drinking water, juice, soda pop, "saft", and coffee.

Table 4: Fluoride exposures in 13-year-olds (mg/day).

	Mean[1]	Median[1]	95P[1]	Max[1]
Mean exposure	0.36	0.11	1.33	35.82
Median exposure	0.32	0.09	1.18	31.73
95P exposure	0.73	0.27	2.73	72.85
Max exposure	2.71	0.7	10.40	296.10

[1]The columns represent the different concentrations used for fluoride in drinks in the exposure estimates.

Adults 18-70 years

For adults the food category «drinks» include drinking water, juice, soda pop, "saft", and coffee.

Table 5: Fluoride exposures in adults 18-70 years (mg/day).

	Mean[1]	Median[1]	95P[1]	Max[1]
Mean exposure	1.05	0.39	3.76	92.35
Median exposure	0.97	0.29	3.56	88.95
95P exposure	1.99	1.03	6.72	163.45
Max exposure	4.69	3.35	12.89	323.08

[1]The columns represent the different concentrations used for fluoride in drinks in the exposure estimates.