



# Risk assessment of nitrate, nitrite and *N*-nitrosamines in food – Part 2

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Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics of the Norwegian Scientific Committee for Food and Environment

Nitrate and nitrite occur naturally in foods, particularly in vegetables, but are also used as food additives in certain products to inhibit bacterial growth. Nitrate can be converted to nitrite, and nitrite can be converted to *N*-nitrosamines, both in food and in the body. This assessment covers dietary exposure to nitrate, nitrite, and selected carcinogenic nitrosamines, as well as their endogenous formation, and evaluation of health risks in the Norwegian population.

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## Risk assessment of nitrate, nitrite and N-nitrosamines in food – Part 2

### *Preparation of the risk assessment*

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to draft the assessment. The project group comprised VKM members, external experts, and VKM staff. The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics assessed and approved the final opinion (VKM, 2024).

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The authors have contributed to the opinion in a way that fulfils the authorship principles of VKM (VKM, 2023). The principles reflect the collaborative nature of the work, and the authors have contributed as members of the project group and/or the VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics.

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### ***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 provisions on impartiality in the Norwegian Public Administration Act apply to all work carried out by VKM.

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## Summary

Nitrate and nitrite occur naturally in food, especially in vegetables, but are also used as food additives (E 249–252) in certain products to inhibit bacterial growth. Nitrate is permitted for use, for example, in some types of cheese, meat, and fish, while nitrite is permitted in certain processed meat products. Both nitrate and nitrite may also occur as contaminants, including in drinking water.

Nitrate can be converted to nitrite, and nitrite can react with naturally occurring amines to form nitrosamines, several of which are carcinogenic. Conversion of nitrate and nitrite can occur both in food and in the body (endogenous formation). VKM has assessed whether nitrate, nitrite, and nitrosamines exposure may pose a health risk to the Norwegian population. The assessment includes ten nitrosamines that have been detected in food and classified as carcinogenic. VKM estimated both the dietary intake of these substances and the contributing exposure from the formation of nitrite and nitrosamines in the body.

Exposure estimates are based on national dietary surveys and data on the occurrence of these substances in food. VKM used three intake levels: typical (median), average, and high intake (95th percentile). A typical intake reflects what is common in the population, while a high intake represents the top 5% of consumers.

Storage and processing can influence the conversion of nitrate to nitrite and nitrite to nitrosamines in food. Since most available occurrence data were from raw foods, VKM developed a model to estimate concentrations in ready-to-eat foods. The purpose was to provide a more realistic estimate of exposure than from estimates based on raw foods alone.

To estimate the total exposure to nitrite and nitrosamines, both from food and endogenous formation, VKM further developed mathematical models for endogenous formation. Since nitrate is converted to nitrite, which is responsible for the critical health effect, and this conversion was included in the total nitrite exposure, VKM did not perform a separate risk characterisation for nitrate.

VKM compared exposure levels with reference values established by the European Food Safety Authority (EFSA):

- For nitrite, EFSA has set an acceptable daily intake (ADI) of 0.07 mg/kg body weight per day, including a safety margin of 100, to protect against increased levels of methemoglobin in the blood, which can reduce oxygen transport. This condition is rare, it can be reversible but is potentially serious. The ADI is an estimate of the amount of a substance that can be consumed daily over a lifetime without appreciable health risk. For carcinogenic substances such as the nitrosamines in this risk assessment, health risk is assessed using the Margin of Exposure (MOE). This is defined as the ratio between the dose causing increased cancer risk in animal studies and the estimated human exposure. An MOE above 10,000 indicates low health concern.

Regarding exposure to nitrite and nitrosamines, VKM found the following:

- Typical and average dietary exposure to nitrite was below ADI for all age groups. High intake (P95) exceeded the ADI for 1- and 4-year-olds and adults, while it was below for 2-, 9-, and 13-year-olds.
- When endogenous formation was included, the total nitrite exposure in all age groups and intake levels exceeded the ADI (except typical intake in adults).
- The estimated nitrite exposure is at similar level to those of EFSA when endogenous production is included.
- MOE values for nitrosamines were below 10,000 for all intake levels and age groups.
- Nitrosamine exposure in Norway is similar to that observed in other European countries.
- The main source of exposure to nitrate was vegetables, while meat and meat products were the main sources of nitrite and nitrosamines. A major limitation of this assessment was the lack of data on nitrosamine levels in several food groups that are important contributors to nitrite exposure, particularly vegetables. This makes it difficult to assess whether, and to what extent, these food groups contribute to nitrosamine exposure.

To investigate how compliance with the Norwegian dietary guidelines may affect exposure to nitrites and nitrosamines, VKM developed two scenarios based on recommended intake levels. Scenario 1 represented the lower guidance intake (e.g. 500 g fruits and vegetables per day and no red meat), while Scenario 2 represented the upper guidance intake (e.g. 800 g fruits and vegetables and up to 50 g unprocessed red meat per day). Since these scenarios cover only part of the total diet, actual exposure may be higher or lower depending on other foods consumed. The exposure estimates were adjusted for energy intake to enable comparison with average intake in adults, as calculated from the national dietary survey Norkost 4.

Regarding how compliance with the dietary guidelines may affect exposure to nitrite and nitrosamines, VKM found the following:

- Both scenarios resulted in higher nitrate and nitrite intake compared to the intake in Norkost 4, mainly due to increased vegetable consumption.
- Nitrosamine exposure was lower in Scenario 1 and similar in Scenario 2. For the food groups included in the dietary guidelines, occurrence data were available for meat and cheese only.

**VKM concludes the following regarding the risk from nitrite exposure:**

- Total exposure, i.e. dietary and endogenous formation, exceeded the ADI at average and high (P95) intake levels in adults, and may therefore imply an increased risk of adverse health effects (methemoglobinemia).
- Typical and average exposure to nitrite from food alone was below the ADI for all age groups. The same applies to high intake (P95) for 2-, 9- and 13-year-olds. This indicates negligible risk of adverse health effects at these exposure levels. High intake (P95)

among 1- and 4-year-olds as well as adults exceeded the ADI and may therefore imply an increased risk of adverse health effects (methemoglobinemia) in these groups.

- In adults, the endogenous synthesis of nitrite from nitrate was up to five-fold higher than the estimated nitrite exposure from food (external exposure). Total exposure was not estimated for other age groups than adults, however, by assuming that endogenous formation is of the same order of magnitude across age groups, it cannot be excluded that total exposure at typical, average, and high (P95) intake levels also exceeds the ADI in these age groups. This may indicate an increased risk of adverse health effects (methemoglobinemia) across more exposure levels and age groups. There is greater uncertainty associated with total exposure than with exposure from food alone.

**VKM concludes the following regarding the risk from nitrosamine exposure:**

- MOE values were below 10,000 for all age groups at typical, average, and high intake levels. This implies that VKM cannot exclude an increased risk of cancer resulting from dietary exposure to nitrosamines in the Norwegian population.

## Sammendrag på norsk

Nitrat og nitritt forekommer naturlig i mat, særlig i grønnsaker, men brukes også som tilsetningsstoffer (E 249–252) for å hindre bakterievekst. Nitrat er tillatt å tilsette for eksempel i enkelte typer ost, kjøtt og fisk, mens nitritt er tillatt brukt i visse typer bearbeidet kjøtt. Både nitrat og nitritt kan også forekomme som forurensning, blant annet i drikkevann.

Nitrat kan omdannes til nitritt, og nitritt kan reagere med naturlig forekommende aminer og danne nitrosaminer, hvorav flere er kreftfremkallende. Omdanning av nitrat og nitritt kan skje både i maten og i kroppen. VKM har vurdert om eksponering for nitrat, nitritt og nitrosaminer kan innebære en helserisiko for den norske befolkningen. Vurderingen omfatter ti nitrosaminer som er påvist i mat og klassifisert som kreftfremkallende. VKM beregnet både hvor mye vi får i oss av de ulike stoffene fra maten og hvor mye som omdannes i kroppen av nitrat til nitritt og av nitritt til nitrosaminer.

Eksponeringsberegningene er basert på nasjonale kostholdsundersøkelser og data om forekomst av stoffene i mat. VKM har brukt tre ulike nivåer i beregningen av inntaket fra mat; vanlig (median), gjennomsnittlig og høyt inntak. Det vanlige inntaket beskriver hva som er typisk for befolkningen, mens det høye er nivået hos de 5 prosentene som får i seg mest.

Faktorer som lagring og prosessering påvirker omdannelsen av nitrat til nitritt, og nitritt til nitrosaminer i maten. Siden mesteparten av forekomstdataene VKM hadde tilgang til var analyser fra råvarer, ble det utviklet en modell for å beregne innholdet av de ulike stoffene i spiseklar mat. På denne måten kunne vi få et mer realistisk estimat av eksponering fra spiseklar mat enn fra estimater som kun var basert på nivåer målt i råvarer.

For å beregne den totale eksponeringen for nitritt og nitrosaminer både fra mat og det som dannes i kroppen, videreutviklet VKM matematiske modeller for å beregne mengden som dannes i kroppen. Siden nitrat omdannes til nitritt, som er ansvarlig for den kritiske helseeffekten, og omdanningen er inkludert i beregningen av den totale nitritteksponeringen, vurderte VKM at en separat risikokarakterisering for nitrat ikke var nødvendig.

VKM har sammenlignet eksponering for nitritt og nitrosaminer med referanseverdier som brukes for å vurdere helserisiko, fastsatt av EUs myndighet for næringsmiddeltrygghet (EFSA):

- For nitritt har EFSA fastsatt en grense for hvor mye som kan inntas daglig gjennom hele livet (akseptabelt daglig inntak, ADI) uten å føre til merkbare negative helseeffekter. Denne grensen på 0,07 mg/kg kroppsvekt per dag er satt for å beskytte mot økt nivå av methemoglobin i blodet, som kan redusere kroppens evne til å frakte oksygen. Methemoglobinemi er en sjelden, men alvorlig tilstand som også kan være reversibel. ADI-verdien inkluderer en sikkerhetsmargin på 100.
- For kreftfremkallende stoffer, som nitrosaminer i denne risikovurderingen, vurderes helserisiko ut fra størrelsen på forholdet (Margin of Exposure; MOE) mellom den dosen som har vist økt risiko for kreft (referansepunkt) i dyreforsøk og beregnet eksponering hos mennesker. Det er liten helsemessig bekymring knyttet til en MOE-verdi over 10 000.

VKM fant følgende om eksponering for nitritt og nitrosaminer:

- Vanlig og gjennomsnittlig eksponering for nitritt fra mat alene var lavere enn ADI for alle aldersgrupper. Hos 1- og 4-åringer, samt hos voksne, var det høye inntaket (P95) høyere enn ADI, mens det var lavere enn ADI hos 2-, 9- og 13-åringer.
- Når kroppens egen produksjon av nitritt ble inkludert, oversteg den totale eksponeringen ADI hos alle aldersgrupper og eksponeringsnivåer (unntatt vanlig inntak for voksne).
- VKMs estimater for nitritteksponering er på samme nivå som EFSA's når produksjonen i kroppen inkluderes.
- MOE var under 10 000 for vanlig, gjennomsnittlig og høy nitrosamineksponering hos alle aldersgrupper.
- Eksponeringen for nitrosaminer i den norske befolkningen er på samme nivå som i andre europeiske land.
- Den viktigste kilden til eksponering for nitrat var hovedsakelig grønnsaker, mens den for nitritt og nitrosaminer var kjøtt og kjøttprodukter. En viktig begrensning i denne vurderingen er at det mangler data om innholdet av nitrosaminer i flere matvaregrupper som er viktige kilder til nitritt, særlig grønnsaker. Dette gjør det vanskelig å vurdere om, og hvor mye, disse matvarene bidrar til eksponering for nitrosaminer.

For å undersøke hvordan etterlevelse av de nye norske kostrådene kan påvirke eksponeringen for nitritt og nitrosaminer, utarbeidet VKM to eksponeringsscenarier. Scenariene omfattet anbefalte mengder for matvarer inkludert i kostrådene: Scenario 1 dekket de nedre mengdene oppgitt i kostrådene (for eksempel 500 g grønnsaker, frukt og bær per dag og 0 g rødt kjøtt per dag), mens scenario 2 dekket de øvre mengdene (for eksempel 800 g grønnsaker, frukt og bær per dag og 50 g ikke-prosessert rødt kjøtt per dag). Siden scenariene kun dekker deler av kostholdet, kan den reelle eksponeringen både bli høyere og lavere, avhengig av den maten man spiser i tillegg til den som inngår i kostrådene. Eksponeringsberegningene ble justert for energiinntak for å muliggjøre sammenligning med gjennomsnittlig inntak hos voksne, slik det er beregnet fra kostholdsundersøkelsen Norkost 4.

VKM fant følgende om hvordan kostrådene kan påvirke eksponeringen for nitritt og nitrosaminer:

- Begge scenariene medførte høyere inntak av nitrat og nitritt sammenlignet med inntak beregnet fra Norkost 4, hovedsakelig fordi inntaket av grønnsaker vil være høyere når man følger kostrådene enn det som er rapportert i Norkost 4.
- Eksponeringen for nitrosaminer var lavere i scenario 1 og tilnærmet uendret i scenario 2. For matvaregrupper inkludert i kostrådene var det kun forekomstdata for kjøtt og ost tilgjengelig.

#### **VKM konkluderer følgende om risiko ved eksponering for nitritt**

- Den **totale eksponeringen** (inkluderer både det som dannes i kroppen og eksponering fra mat) overskred ADI ved gjennomsnittlig og høyt (P95) inntak hos voksne, og kan derfor innebære økt risiko for negative helseeffekter (methemoglobinemi).
- Eksponeringsverdier for nitritt **fra mat alene** var lavere enn ADI ved vanlig og gjennomsnittlig eksponering for alle aldersgrupper. Det var også det høye inntaket

(P95) for 2-, 9- og 13-åringer. Dette tilsier ubetydelig risiko for negative helseeffekter ved disse eksponeringsnivåene. Høyt inntak (P95) hos 1- og 4-åringer samt voksne overskred ADI, og kan derfor innebære økt risiko for negative helseeffekter (methemoglobinemi) i disse aldersgruppene.

- Mengden nitritt som dannes fra nitrat i kroppen bidrar opp til fem ganger mer til den totale eksponeringen hos voksne enn nitritt fra mat alene. Total eksponering er ikke beregnet for andre aldersgrupper enn voksne. Ved å anta at dannelsen i kroppen er av samme størrelsesorden for alle aldersgrupper, kan det ikke utelukkes at den totale eksponeringen ved vanlig, gjennomsnittlig og høyt (P95) inntak også overstiger ADI for de andre aldersgruppene. Dette kan innebære økt risiko for negative helseeffekter (methemoglobinemi) også for flere eksponeringsnivåer og aldersgrupper. Det er større usikkerhet knyttet til totaleksponering enn eksponering fra mat alene.

#### **VKM konkluderer følgende om risiko ved eksponering for nitrosaminer**

- MOE-verdiene var lavere enn 10 000 for alle aldersgrupper ved vanlig, gjennomsnittlig og høy eksponering. VKM kan derfor ikke utelukke økt risiko for kreft som følge av eksponering for nitrosaminer i kostholdet i den norske befolkningen.

## Abbreviations

ADME: Absorption, distribution, metabolism, excretion

ADI: Acceptable daily intake

BMD: Benchmark dose

BMDL: The lower bound of the benchmark dose

BMR: Benchmark response

bw: Body weight

DMA: Dimethylamine

GI: Gastrointestinal

FAIR: Findability, Accessibility, Interoperability, and Reusability

ICH: International Council for Harmonisation

ISO: International Organization for Standardization

LB: Lower bound

LM: Linear model

LOD: Limit of detection

LOQ: Limit of quantification

MB: Medium bound

N-NA: N-nitrosamines

NO<sub>3</sub><sup>-</sup>: Nitrate

NDBA: N-Nitrosodibutylamine

NDiBA: N-Nitrosodiisobutylamine

NDEA: N-Nitrosodiethylamine

NDMA: N-Nitrosodimethylamine

NDPA: N-Nitrosodipropylamine

NFSA: The Norwegian Food Safety Authority

NFC: NutriFoodCalc

NO<sub>2</sub><sup>-</sup>: Nitrite

LME: Linear mixed effects

NLP: Natural language processing

NMA: N-Nitrosomethylaniline

NMEA: N-Nitrosomethylethylamine

NMOR: N-Nitrosomorpholine

NPIP: N-Nitrosopiperidine

NPYR: N-Nitrosopyrrolidine

NSAR: N-Nitrososarcosine

OIM: Observed individual means

QA: Quality assurance

QC: Quality control

SR: Systematic review

TK: Toxicokinetic

UB: Upper bound

## Glossary

### Acceptable daily intake

The acceptable daily intake (ADI) is an estimate of the amount of a substance in food or drinking water that can be consumed daily over a lifetime without presenting an appreciable risk to health ([EFSA glossary](#)).

### Applicability domain

The applicability domain of a model is the suitability and performance of a model for a given question, and it defines the boundaries within which the model's predictions are considered reliable.

### Benchmark dose

The Benchmark dose (BMD) is the minimum exposure level or dose that of a substance that produces a clear, low-level health risk. The BMD is estimated from a mathematically fitted dose-response curve. The lower confidence bound of the BMD is the BMDL ([EFSA glossary](#)). BMDL<sub>10</sub> is the dose lower confidence limit at 10% response, representing the dose, with 95% confidence, that causes no more than a 10% increase in the adverse effect compared to control groups.

### **Benchmark response**

A Benchmark Response (BMR) is a predefined, acceptable change in the rate of an adverse effect (e.g., 5% or 10%) compared to a control group. It is used to calculate the Benchmark dose.

### **External exposure**

The quantity of a substance ingested via food and/or beverages.

### **FAIR**

Findability, Accessibility, Interoperability, and Reusability of data. “The principle emphasises machine-actionability (i.e., the capacity of computational systems to find, access, interoperate, and reuse data with none or minimal human intervention), because humans increasingly rely on computational support to deal with data as a result of the increase in volume, complexity, and creation speed of data” (<https://www.go-fair.org/fair-principles/>).

### **Food code**

A numerical identification code that is assigned to food items in the NutriFoodCalc database.

### **Foods**

The term “foods” includes both food items and beverages for human consumption.

### **FoodEx2**

A standardised system for classifying and describing food consisting of descriptions of many individual food items aggregated into food groups and broader food categories in a hierarchical parent-child relationship (EFSA, 2015). In its hierarchical structure, level 1 represents broad, main food categories (e.g. grains and grain-based products), while from level 2 and onwards the levels consist of more specific, aggregated terms and sub-groups, e.g. fine bakery ware. Lower levels (3-7) have more granular detail, such as cakes and types of cakes (EFSA, 2015).

### **Gastrointestinal (GI) exposure**

The quantity of a substance located in the gastrointestinal tract.

### **Lower bound estimate**

An estimate of the minimum exposure to a substance, where all analysis results below the limit of detection or quantification are treated as zero.

### **Margin of exposure (MOE)**

The ratio between a toxicological reference point (e.g. BMDL<sub>10</sub>) and the estimated exposure to a chemical substance. A MOE greater than 10,000 is considered to be of low concern (EFSA, 2005; EFSA, 2012).

### **Medium bound estimate**

An estimate of the exposure to a substance where all analysis results below the limit of detection or quantification are treated as LOD/2 or LOQ/2. This is an intermediate scenario between the lower bound and the upper bound scenarios.

### **Natural language processing (NLP)**

Natural language processing is a subfield of artificial intelligence that uses machine learning to enable computers to process human written and oral language.

### **NutriFoodCalc (NFC)**

The NutriFoodCalc is a food, energy and nutrient database and calculation system (originating from University of Oslo).

### **Observed individual means (OIMs)**

Observed individual means are exposure estimates calculated as the arithmetic mean for each individual across the days covered by a dietary survey. They are commonly used as proxies for an individual's chronic (long-term) dietary exposure.

### **Potency factor**

A potency factor is a numerical value used to express the relative toxic potency of a chemical compared with a reference substance.

### **Probabilistic approach for exposure estimation**

The probabilistic approach will provide characteristics for the variability and uncertainty in the estimates, and it may be useful for more detailed assessments (EPA, 2023). Probabilistic assessments use more complicated modelling approaches compared to the OIM approach and rely on existing distributions of data as inputs in place of point values for key parameters. This results in a distribution of possible exposure estimates. A probability distribution of concentration data is created by mathematical curve fitting (i.e. a curve is generated that best fits the data points).

### **R**

An open-source programming language and software environment designed specifically for statistical computing and graphics. R Core Team (2025). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>.

### **Toxicokinetic model**

A human toxicokinetic (TK) model is used to mathematically describe the fate of a chemical in the human body, as a function of dose and time, in terms of absorption, distribution, metabolism and excretion (ADME) (JRC, 2025):

- The rate of chemical absorption from the site of application into the blood stream
- The rate and extent of chemical movements out of blood into the tissue (distribution)
- The rate and extent of chemical biotransformation into metabolites (metabolism)
- The rate of chemical removal from the body (excretion)

### **TSD**

TSD (In Norwegian: Tjenester for Sensitive Data) is a secure IT platform in Norway designed for storing, processing, and analysing sensitive research data delivered by the University of Oslo.

**Upper bound estimate**

An estimate of the exposure to a substance for which all analysis results below the limit of detection (LOD) or quantification (LOQ) are assigned the value of the LOD or LOQ.

## Background as provided by the Norwegian Food Safety Authority

Nitrate and nitrite can be converted into potentially carcinogenic substances, such as certain nitrosamines. These processes may occur both during the processing of products containing these substances and subsequently, within the digestive tract following intake. The European Food Safety Authority (EFSA) has established acceptable daily intakes (ADIs) for nitrate and nitrite. The intake of nitrate and nitrite among different population groups in Norway is unknown, and no records of nitrate- and nitrite-containing foods exist.

Nitrate and nitrite can both be added to or occur naturally in foods. For example, several types of meat products are added nitrate and/or nitrite for preservation. The substances inhibit the growth of bacteria, including *Clostridium botulinum*, which can form the toxic substance botulinum toxin. Several food plants have a natural content of nitrate.

The Nordic dietary guidelines ([NNR23](#)) and the current Norwegian dietary guidelines ([Helsedirektoratet 2024](#)) recommend a higher intake of fruit and vegetables than the previous Norwegian dietary guidelines from 2012. The Norwegian Food Safety Authority needs to know whether any future increases in the intake of fruit and vegetables in the Norwegian population may affect the intake of nitrate and nitrite.

An overview of which foods contain nitrate and nitrite, and what the population consumes, will give the Norwegian Food Safety Authority the opportunity to plan monitoring and control programs and be able to provide relevant advice to consumers.

## Terms of reference as provided by the Norwegian Food Safety Authority

With this assignment to the Norwegian Scientific Committee for Food and Environment (VKM), the Norwegian Food Safety Authority wants to ascertain whether exposure to nitrate and nitrite can pose a health risk to one or more groups in the Norwegian population. The Norwegian Food Safety Authority also aims to gain a comprehensive overview of which foods contain nitrate and nitrite.

The assignment is divided into two parts. The first part will contain an overview of foods that contain nitrate and nitrite. The Norwegian Food Safety Authority will use this overview to select which foods will be included in future monitoring and control programmes. The second part will address exposure estimations for nitrate and nitrite from food for different groups in the Norwegian population. The exposure estimations will provide the basis for health risk assessments in the population groups.

### Part 1

The Norwegian Food Safety Authority has requested VKM to compile an overview of foods containing nitrate and nitrite, both naturally occurring and from additives.

*This part was finalised in December 2024 (VKM et al., 2024a).*

### Part 2

The Norwegian Food Safety Authority has requested VKM to:

- Assess whether there is a need to update the Acceptable Daily Intakes (ADIs) for nitrate and nitrite.
- Calculate the dietary exposure to nitrate and nitrite in the Norwegian population.
- Include a scenario that reflects the recommendations in the Norwegian dietary guidelines from 2024.
- Assess the risk of negative health effects associated with nitrate and nitrite exposure.

## 1 Introduction

The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food and Environment (VKM; in Norwegian: *Vitenskapskomiteen for mat og miljø*), to perform an assessment of nitrate and nitrite intake from foods to determine whether such exposure constitutes a health risk. Since nitrite under certain circumstances can be a source of N-nitrosamines (N-NAs) in foods, the assessment also encompasses N-NAs. Furthermore, NFSA requested VKM to employ an exposure scenario based on the recommendations in the Norwegian dietary guidelines from 2024 (Norwegian Directorate of Health, 2024). In the current assessment, the term “foods” refers to food, beverages, and tap water (also termed “drinking water”). Nitrate and nitrite can be used as food additives, and as such, are included in this risk assessment. On the contrary, concurrent human N-NAs exposure from medicines and tobacco use is outside the scope of this risk assessment.

Plants require nitrogen as a component of essential macromolecules, including amino acids, nucleic acids, and chlorophyll. Nitrogen is taken up in plants from the soil in the form of nitrate ( $\text{NO}_3^-$ ) and ammonium ( $\text{NH}_4^+$ ). Nitrate is then metabolised and accumulated mainly in the leaf and stem tissues, and some is also stored in the root. Nitrate (oxidation state +5) can be reduced to nitrite ( $\text{NO}_2^-$ ; oxidation state +3); thus, both substances occur naturally in some plant foods, particularly in vegetables. The nitrate content of plants is influenced by environmental and agronomic factors. The photosynthetically active radiation (PAR) spectrum of solar radiation and heat generally reduce nitrate levels, while drought conditions and nitrogen fertilisation tend to increase them. Because greenhouse cultivation typically provides lower irradiance and total light dose (radiant exposure) combined with spectral changes compared with open-field conditions, plants grown in greenhouses typically accumulate higher nitrate concentrations (AGES, 2025; BfR, 2013; Sathee et al., 2025). Maximum levels of naturally occurring nitrate are set for specified foods in the Regulation (EC) No 2023/915 on maximum levels for certain contaminants in food (EU, 2023). Foods covered by this regulation are spinach (fresh, preserved, deep-frozen), fresh lettuce, iceberg-type lettuce, and processed cereal-based foods and baby foods for infants and young children.

Nitrate and nitrite are permitted preservatives to inhibit the growth of bacteria in some foods. One type of bacterium, namely the botulinum neurotoxin-producing *Clostridium botulinum* can be present in certain meat and fish products. Other types of *Clostridium spp.* can be present in cheese. The use of nitrates and nitrites as food additives is restricted by Regulation (EC) No 1333/2008 on food additives (Regulation (EC) No 1333/2008). The Regulation (EU) No 231/2012 (EU, 2012) lays down specifications for all food additives listed in Annexes II and III to Regulation (EC) No 1333/2008. Nitrate (E 251-252) can be added to selected cheese, meat, and fish products, while nitrite (E 249-250) can be added to selected meat products.

Nitrate and nitrite are water-soluble and are commonly present in drinking water supplies. The substances can occur naturally in small amounts, and occurrences are generally due to human activity, such as agriculture and sewage from domestic and industrial waste (Bekkelund et al., 2024). (AGES, 2025; BfR, 2013). Maximum levels are set for both nitrate and nitrite in Directive (EU) 2020/2184 on the quality of drinking water intended for human consumption (EU, 2020);

however, the directive is not yet implemented in Norwegian law, for which Directive 98/83/EC still applies (EU, 1998).

Nitrate and nitrite are oxidation products of nitrogen, of which nitrate is the more stable form. Being an intermediate form, nitrite is relatively unstable. Nitrate can be converted to nitrite in the body, e.g. by bacteria in the mouth. Nitrite can be further oxidised to nitrate or be reduced (Pauleta et al., 2019), e.g. in bacteria, to ammonium ( $\text{NH}_4^+$ ), nitrous oxide ( $\text{N}_2\text{O}$ ), nitric oxide (NO), or dinitrogen gas ( $\text{N}_2$ ) (WHO, 2016). Protein-rich foods contain amines that can react with nitrite to form N-NAs. Such amines can be primary, secondary and tertiary, of which the secondary amines generally are the most reactive (SCCS, 2012). The N-NA formation may occur in food products during e.g. storage, food preparation, and processing of nitrate- and nitrite-containing foods as well as endogenously in the gastrointestinal tract. The extent of N-NA formation depends on factors such as availability of amines, stomach acidity, and presence of antioxidants and nitrosamine inhibitors. The usually high level of antioxidants in vegetables is likely to prevent N-NA formation

About 20 different N-NAs have been identified so far in processed meat products. These N-NAs can be volatile (VNAs) or non-volatile (NVNAs) compounds (Niklas et al., 2022). Since VNAs evaporate easily, they often occur in food at low nanogram per gram (ng/g) levels, while NVNAs can reach concentrations in the microgram per gram ( $\mu\text{g/g}$ ) range (Mortensen et al., 2017). Some of the N-NAs are classified as group 2A (probably carcinogenic to humans) and 2B (possibly carcinogenic to humans) by The International Agency for Research on Cancer (IARC) (Niklas et al., 2022). The current risk assessment includes selected, potentially carcinogenic N-NAs occurring in foods (VKM et al., 2025).

The current risk assessment addresses the second part of the NFSA request. The first part involved compiling a database of foods on the Norwegian market that contains nitrate and nitrite. The conclusions from the first part were as follows: There were large differences in the amount of nitrate and nitrite between different food groups and between different food items within each food group. Concentration values were missing for some food groups, such as for food supplements (VKM et al., 2024). In the current risk assessment, the database has been updated to include N-NA concentration values in addition to recently published nitrate and nitrite concentration values. This expanded database is used for exposure estimations, alongside other information sources that complement it, in the current assessment, such as unpublished data from the ongoing NitRisk project (<https://animalia.no/no/ravare-og-foredling/foedling/nitrisk>), and unpublished water quality data from the Norwegian waterworks registry (VREG) (FHI, 2024).

To further accommodate the request from the NFSA to evaluate the health risk in the Norwegian population, intake data from age-specific national dietary surveys are used, as well as the NutriFoodCalc (NFC) system (University of Oslo, 2025) for identification of the food items reported to be consumed in the surveys. In addition, the EFSA-developed FoodEx2 system is used to categorise concentration data. In its hierarchical structure, level 1 represents broad, main food categories (e.g. grains and grain-based products), while from level 2 and onwards the levels consist of more specific, aggregated terms and sub-groups, e.g. fine bakery

ware. Lower levels (3-7) have more granular details, such as cakes and types of cakes (EFSA, 2015).

VKM employed mathematical and statistical models to account for concentration changes of nitrate, nitrite, and N-NAs in the transition from raw materials to ready-to-eat-foods and for the endogenous generation of nitrite and N-NAs. All R codes of the exposure modelling are published in open access repositories such as GitHub and archived on Zenodo (10.5281/zenodo.20495212).

Both a probabilistic approach and an observed individual means (OIM) approach are applied to estimate dietary (external) chronic exposures (Paoli et al., 2025). The grouping of foods for the exposure estimation is different for the two estimation approaches. For adults, a modelling approach is applied to estimate the total gastrointestinal exposure.

According to the protocol (VKM, 2025), two scenarios are designed to assess nitrate, nitrite, and nitrosamine exposure depicting a situation in which the Norwegian population follows the food-based dietary guidelines (Norwegian Directorate of Health, 2024). The scenarios represent the lower and upper intervals of the amounts of foods specified in the guidelines (Norwegian Directorate of Health, 2024), and the OIM approach is used to estimate the dietary exposures. The dietary guidelines include both general recommendations and recommendations specifying quantitative intakes for specific food groups. The scenarios are based only on the specified food group quantities provided in the guidelines (which do not cover all food groups). Consequently, only parts of the total diet are included in the dietary guideline scenarios. Notably, the scenario estimations are based on independent food group intakes; thus, they do not account for potential substitution effects, such as when a change in the consumption of one food group would naturally be balanced by adjustments of others. To meet the total energy requirement, it is possible to increase consumption of foods that either does or does not contain nitrate, nitrite, and nitrosamines.

To perform the risk assessment, the research questions shown in Table 1-1 will be assessed.

**Table 1-1.** Research questions to be answered in the risk assessment.

Part of the assessment	Research questions	Chapter
Conversion of nitrate, nitrite, and N-nitrosamines in foods	<ol style="list-style-type: none"> <li>1. What is the fraction of and conversion between nitrate, nitrite, and N-nitrosamines in different foods?</li> <li>2. Are there any existing models to predict conversion of nitrate to nitrite, and nitrite to N-nitrosamine in foods?</li> </ol>	2
Absorption, distribution, metabolism and excretion (ADME)	<ol style="list-style-type: none"> <li>3. What are the ADME characteristics of nitrate, nitrite, and N-nitrosamines in humans?</li> <li>4. What is the level of endogenous nitrite and N-nitrosamine production in the body?</li> <li>5. What is the fraction of and conversion between nitrate, nitrite, and N-nitrosamines in the body?</li> <li>6. Are the ADME characteristics of nitrate, nitrite, and N-nitrosamines in research animals similar to that in humans? If not, which adjustment factor should be applied?</li> </ol>	3

Part of the assessment	Research questions	Chapter
	7. Are there established models for nitrate, nitrite, and <i>N</i> -nitrosamine metabolism and conversion in humans?	
Hazard identification and characterisation	8. Should the ADI for nitrite be updated?	2
Exposure assessment	9. What are the concentrations of nitrate, nitrite, and <i>N</i> -nitrosamines in foods? 10. What is the consumption of nitrate, nitrite, and <i>N</i> -nitrosamine containing foods? 11. What are the nitrate, nitrite, and <i>N</i> -nitrosamine exposures in the Norwegian population? 12. What will the nitrate, nitrite, and <i>N</i> -nitrosamine exposures be if the Norwegian population follows the most recent national food-based dietary guidelines (Norwegian Directorate of Health, 2024)	3
Risk characterisation	13. Do the dietary exposures to nitrate, nitrite and <i>N</i> -nitrosamines represent risks for negative health effects for the Norwegian population?	4

## 2 Hazard assessment

A full hazard assessment for nitrate and N-NAs was not included in the current risk assessment (see Section 2.1). For the hazard assessment of nitrite, see Section 2.2.

### 2.1 Reference points for nitrate, nitrite, and N-NAs

Reference points for nitrate, nitrite, and N-NAs have been established by EFSA (EFSA et al., 2017a; EFSA et al., 2017b; EFSA et al., 2023). For nitrate and nitrite, acceptable daily intakes (ADIs) have been established (EFSA et al., 2017a; EFSA et al., 2017b). The reference point for N-NAs is the benchmark dose lower confidence limit at 10% response, (BMDL<sub>10</sub>), representing the dose, with 95% confidence, that causes no more than a 10% increase in the adverse effect compared to control groups (see Glossary). The ADI and the BMDL<sub>10</sub> are used to evaluate whether estimated chronic dietary exposures are compatible with long-term consumer safety. If estimated exposure is at or below the ADI, EFSA concludes that long-term intake does not raise a safety concern. In its 2005 opinion, EFSA's Scientific Committee expressed the view that in general a margin of exposure based on the BMDL from an animal study of 10,000 or higher, would be of low concern from a public health point of view (EFSA, 2005).

The ADI for nitrate is 3.7 mg/kg bw per day (EFSA et al., 2017a; JECFA, 2002; SCF, 1997). Elevated blood concentrations of methaemoglobin, resulting from nitrite formed through the reduction of nitrate in saliva (see Section 3.1), were identified as the critical effect for establishing the ADI (EFSA et al., 2017a).

For nitrite, the ADI is 0.07 mg/kg bw per day (EFSA, 2009; JECFA, 2002), and also for this substance, elevated blood methaemoglobin levels were considered the most relevant negative health effect for establishing the ADI (EFSA et al., 2017b). The ADI was based on benchmark dose (BMD) modelling of methaemoglobin formation in a 14-week drinking water study in rats (NTP, 2001). In this study, sodium nitrite induced a clear dose-response relationship for methaemoglobin formation, which was used as the critical endpoint. A BMR corresponding to a two-fold increase in methaemoglobin levels was selected, resulting in a BMDL of 9.63 mg/kg bw per day. Application of the default uncertainty factor of 100 gave an ADI of 0.1 mg sodium nitrite/kg bw per day, equivalent to 0.07 mg nitrite ion/kg bw per day.

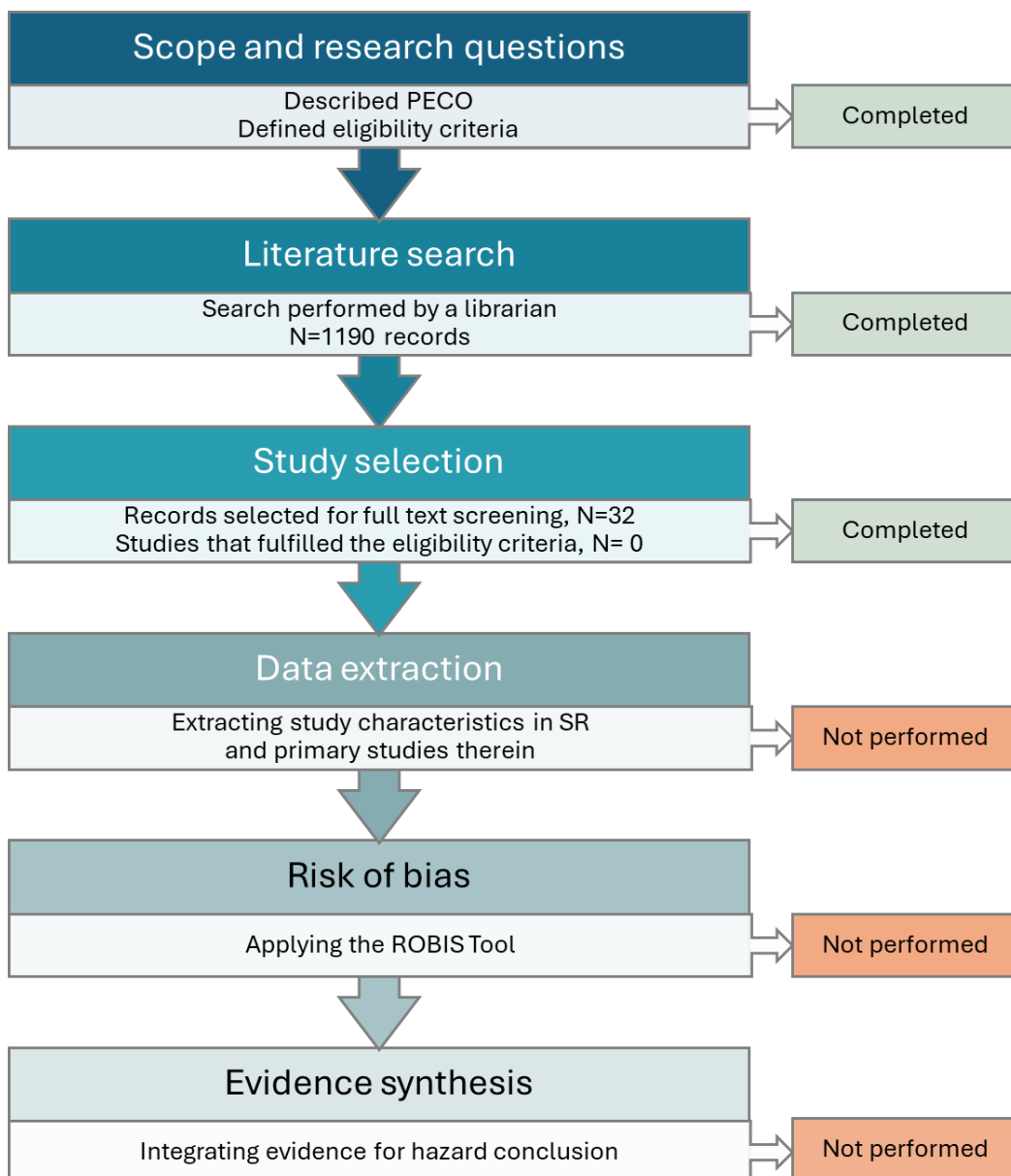
The BMDL<sub>10</sub> for N-NAs is 10 µg/kg bw per day, which is based on increased incidence of benign and malignant liver tumours in rodents caused by N-nitrosodiethylamine (NDEA) (EFSA et al., 2023). The main mode of action for the carcinogenic activity of N-NAs is genotoxicity. EFSA (2023) used the BMDL<sub>10</sub> for NDEA as reference point for 10 carcinogenic N-NAs occurring in food: N-nitrosodimethylamine (NDMA), N-nitrosomethylethylamine (NMEA), N-nitrosodiethylamine (NDEA), N-nitrosodipropylamine (NDPA), N-nitrosodibutylamine (NDBA), N-nitrosomethylaniline (NMA), N-nitrososarcosine (NSAR), N-nitrosomorpholine (NMOR), N-nitrosopiperidine (NPIP), and N-nitrosopyrrolidine (NPYR) in a margin of exposure (MOE) approach. This BMDL<sub>10</sub> is used in the risk characterisation step of the current risk assessment (see Chapter 4).

## 2.2 Hazard assessment of nitrite

VKM was asked by NFSA to evaluate whether the nitrite ADI should be updated (research question 8, “Should the ADI for nitrite be updated?” Table 1-1). According to the protocol (VKM et al., 2025), VKM would base the evaluation on previously summarised relevant evidence in an overview of systematic reviews (SR), rather than performing a full hazard assessment. The implementation was planned according to principles described for hazard identification and characterisation described in the Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration (NTP, 2019). To be relevant, the SR should report data on the association between nitrite intake and negative health effects per endpoint and study design, as well as on numerical data for nitrite exposure.

An overview of the performed and planned steps of the hazard assessment is depicted in Figure 2.2-1. The literature search, study selection, data extraction, and data management are described in Appendix 2.

Since none of the identified systematic reviews fulfilled the eligibility criteria for inclusion, VKM could not assess whether the ADI for nitrite should be updated. Consequently, the ADI for nitrite established by EFSA (0.07 mg/kg bw per day) was used for the risk characterisation (EFSA et al., 2017b).



**Figure 2.2-1.** An overview of the planned steps in the hazard assessment of nitrite and the status for each step. PECO: Population, Exposure, Comparator, and Outcome; SR: systematic review; ROBIS: a tool for assessing the risk of bias in systematic reviews.

### 3 Exposure assessment

A schematic overview of the stepwise approach for the estimation of dietary exposure (“external exposure”), gastrointestinal exposure (GI tract exposure), and systemic exposure (exposure following absorption) of nitrate, nitrite, and N-NAs is provided in Figure 3-1. By external exposure, we mean the quantity of a substance ingested via food and/or beverages. By gastrointestinal exposure, we mean the quantity of a substance in the gastrointestinal tract (dietary exposure and contributions from endogenous formation).

The chronic exposure assessment was performed using three different approaches: a “traditional” observed individual means (OIM) approach, a probabilistic approach, and a modelling approach. The OIM approach was applied for all age groups included in the current assessment, the probabilistic assessment was applied to all age groups except 1- and 2-year-olds, and the modelling approach was only applied to adults. The OIM and the probabilistic approaches were applied to estimate dietary exposure, whereas the modelling approach was applied to estimate total gastrointestinal exposure. The main reasons for not applying all approaches to all age groups were the extent of the overall workload and the limited time available for the assessment. For these newer methods, we specifically wanted to test them on a subset of the data, rather than the entire dataset, to better evaluate their application and to observe the variability in estimates produced by different approaches.

An important distinction between the approaches is that the OIM approach uses one concentration value for each food item or food group, whereas in the probabilistic approach, all available concentration values were included to generate a distribution. Concentration values were then drawn randomly from this distribution, thereby capturing the full range of variation within the concentration values for a food item/food group.

The modelled exposure approach used both OIM and probabilistic estimates from dietary exposure as a starting point, but additionally included the modelled endogenously synthesized substances, thereby providing a more comprehensive estimate of total exposure.

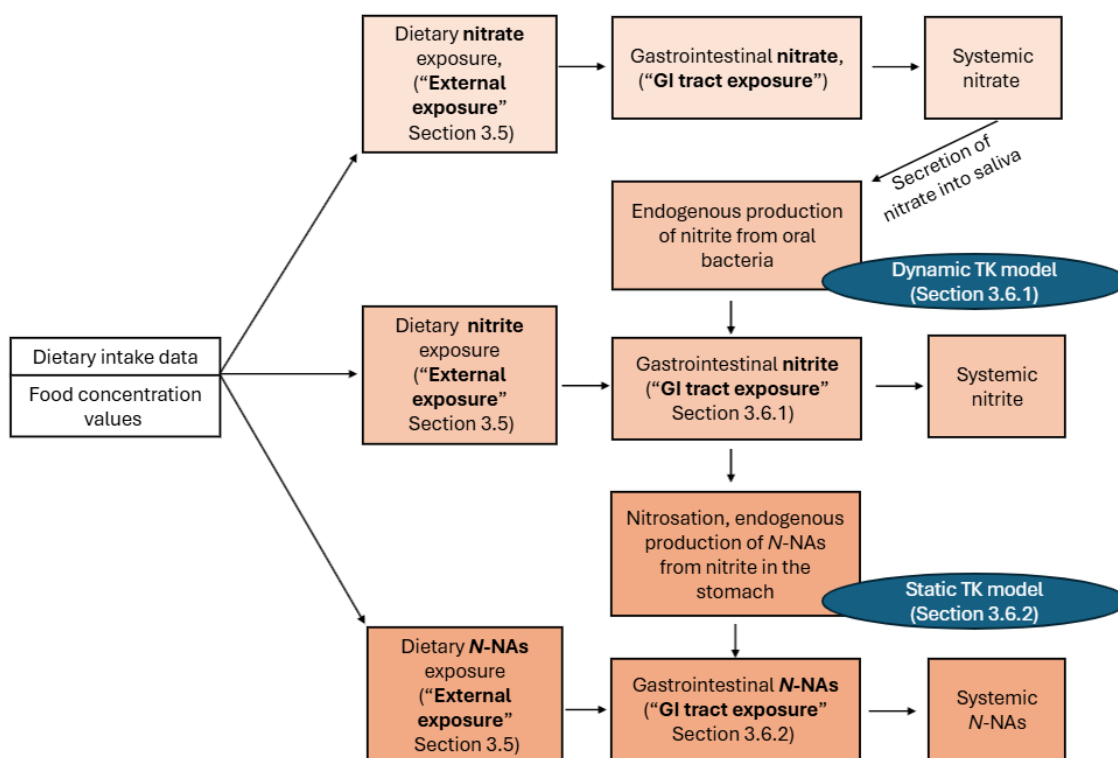
VKM considered it appropriate to apply the OIM approach to all age groups since this is regarded as the traditional method.

The starting point for the exposure assessment is data on concentrations of nitrate, nitrite, and N-NAs in foods (Section 3.2) and dietary intake data (Section 3.3). The methods and results for estimating dietary exposure and gastrointestinal exposure, are presented in Sections 3.5 and 3.6, respectively.

The following should be noted:

- N-NA exposure is the total N-NA exposure to all included carcinogenic N-NAs for which food concentration values were available.
- “Systemic” refers to the fraction of a substance that is absorbed from the gastrointestinal tract into the bloodstream and becomes available for distribution throughout the body.

- Exposure scenarios based on the Norwegian dietary guidelines are described in Section 3.7 (not shown in Figure 3-1).

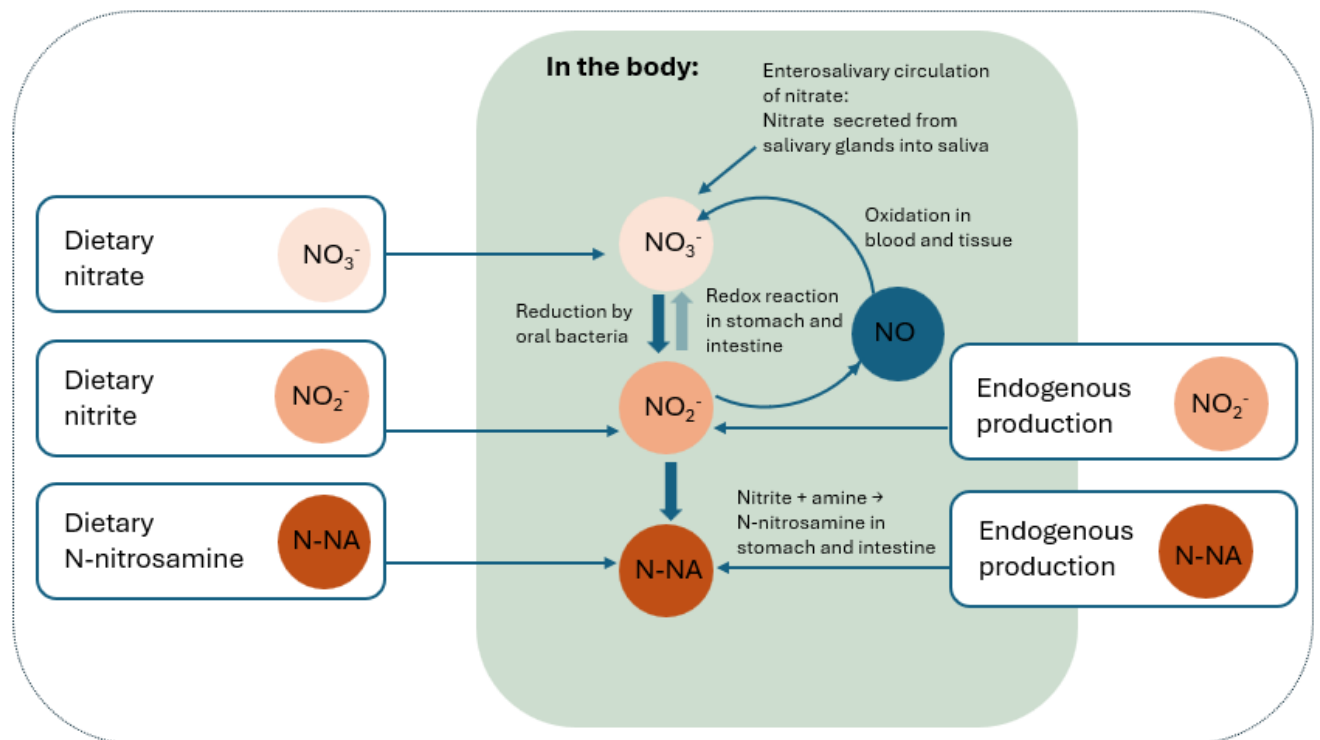


**Figure 3-1.** The stepwise approach for the estimation of dietary exposure (“external exposure”), gastrointestinal exposure (GI tract exposure), and systemic exposure (exposure following absorption) of nitrate, nitrite, and N-NAs. References to the sections describing each step are included in parentheses. TK: Toxicokinetic. “Systemic”: the fraction of the substance in question that is absorbed from the gastrointestinal tract into the bloodstream. A more detailed overview of the metabolism of nitrate, nitrite, and N-nitrosamines is provided in Figure 3.1-1.

### 3.1 ADME characteristics of nitrate, nitrite, and N-NAs

The total systemic exposure of nitrates, nitrites, and N-NAs arises from both dietary intake and endogenous formation within the body. Toxicokinetic (TK) models (Section 3.6) will be used to estimate combined exposure from ingested and endogenously generated nitrite and N-NAs. To support the exposure assessment using both dynamic and static models, the ADME characteristics of nitrates, nitrites, and nitrosamines are outlined below.

An overview of dietary sources and metabolism of nitrate, nitrite, and N-NAs in the human body is presented in Figure 3.1-1. Detailed descriptions are given in Sections 3.1.1 and 3.1.2.



**Figure 3.1-1.** Simplified schematic overview of dietary sources and formation of nitrate, nitrite, and N-nitrosamines in the human body. NO: Nitric oxide;  $\text{NO}_3^-$ : Nitrate;  $\text{NO}_2^-$ : Nitrite; N-NA: N-nitrosamines.

### 3.1.1 Nitrate

The ADME characteristics of nitrate in humans are described in detail in the re-evaluation of sodium nitrate (E 251) and potassium nitrate (E 252) as food additives by EFSA et al. (2017a). In short, dietary nitrate is rapidly and extensively absorbed through the gastrointestinal tract. A human dietary study demonstrated that the systemic availability was approximately 100% (70–116%). The calculated volume of distribution was between 18 and 32 L, which is lower than the body water content and higher than the blood volume, indicating that nitrate is distributed throughout the body. Nitrate is mainly converted reversibly to nitrite in a specific mechanism in which nitrate is secreted into saliva (20–25% of the dose) and converted to nitrite by bacterial metabolism in the mouth (5–36%) (Lin et al., 2020b; Zeilmaker et al., 2010). In the gastrointestinal tract, nitrite is absorbed and thereafter enters the general circulation where it can be oxidised by oxyhaemoglobin to form nitrate and methaemoglobin. The biotransformation of nitrate occurs in a dynamic equilibrium and comprises nitrate reduction, nitrite formation, nitrite reoxidation to nitrate, and formation of methaemoglobin or nitric oxide (NO). Most nitrate is excreted into the urine, up to 100%, but the amounts vary between 50% and 100%. EFSA et al. (2017a) calculated a total clearance (dose/AUC) of 38 and 54 mL/min from two human studies.

### 3.1.2 Nitrite

The ADME characteristics of nitrite in humans are described in detail in the re-evaluation of potassium nitrite (E 249) and sodium nitrite (E 250) as food additives by (EFSA et al., 2017b). In

short, the systemic availability of nitrite when given in solution is approximately 100%. The volume of distribution is larger than the body water content, indicating that nitrite is distributed at higher concentrations in some tissues compared to in the blood. The calculated distribution volume was between 64 and 124 L. Most of the nitrite is converted to nitrate, which is then excreted in the urine. Further metabolites of nitrite are nitric oxide and reactive oxygen species formed during the conversion of nitrite to minor metabolites. Small amounts of nitrite are found in the urine (0.02% of a dose).

Endogenous nitrite production in humans is primarily attributed to the enterosalivary circulation of dietary nitrate, which undergoes microbial reduction to nitrite by nitrate-reducing bacteria at the base of the tongue (EFSA et al., 2017b). The reported ratio of the nitrite to nitrate concentration in saliva varies across different studies and within individuals; between 5% and 36% of the nitrate secreted into the saliva is converted to nitrite by the oral bacterial metabolism. Physiologically based pharmacokinetic (PBPK) models (Lin et al., 2020a; Zeilmaker et al., 2010) suggest that on average, adults exposed to single or repeated doses of nitrate of 0-3.7 mg/kg bw per day would receive approximately 0.27-0.36 mg nitrite/kg bw per day. According to JECFA (2003), 31-41% of this nitrite exposure is derived from endogenous synthesis.

Nitrite can react with secondary amines to form *N*-NAs, this process occurs primarily in the stomach, but it can also take place in the colon.

### 3.1.3 *N*-NAs

The ADME characteristics of *N*-NAs in humans are discussed by EFSA in the risk assessment of *N*-NAs in food (EFSA et al., 2023). ADME data for *N*-NAs in humans are scarce, and their toxicokinetic behaviour remains poorly characterised. Most available information concerns NDMA.

Humans are exposed to *N*-NAs both from external sources such as diet and from endogenous formation. Although quantitative human absorption data are lacking, *N*-NAs appear to be rapidly and extensively absorbed, with NDMA showing high first-pass metabolism and an estimated hepatic extraction ratio of ~ 90% (EFSA et al., 2023). In the current exposure assessment, complete absorption (100%) after oral intake is assumed.

Endogenous formation occurs mainly in the stomach and colon and depends on nitrite availability, presence of nitrosatable secondary amines, nitrosation rate, gastric pH, contact time, and nitrosation inhibitors such as ascorbic acid (EFSA et al., 2017b; EFSA et al., 2023; Kobayashi, 2018; Ohshima and Bartsch, 1981; Tricker, 1997). Secondary amines (e.g. dimethylamine, diethylamine, pyrrolidine, piperidine) are naturally present in foods and determine which *N*-NA species may be formed (EFSA, 2023).

Among the *N*-NAs considered in this report, evidence of human endogenous formation exists only for NDMA, demonstrated in a crossover study combining nitrate and a diet rich in amines (Vermeer et al. 1998). Endogenous formation of other *N*-NAs is theoretically possible when the relevant amines are present. Formation of *N*-nitrosoproline (NPRO) in humans has also been demonstrated experimentally, confirming that nitrosation reactions occur in vivo (Ohshima and Bartsch, 1981). According to Tricker et al. (1997), the crude mass balance between

exogenous exposure and excretion in urine and faeces indicated that 45-75% of the total human exposure to N-nitroso compounds results through endogenous formation.

### 3.2 Concentration values for nitrate, nitrite, and N-NAs in foods

Concentration values for nitrate and nitrite in foods were compiled in the database prepared in Part 1 of the assignment. In Part 2, additional (new) concentration values for nitrate and nitrite, and concentration values for N-NAs were included. An overview of the data sources used is provided in Table 3.2-1.

**Table 3.2-1.** Report titles and extracted data from references containing concentration values used in the exposure assessment.

Report	Extracted data	Reference
Analyser av næringsstoffer i norske og importerte grønnsaker. Kartlegging av tungmetaller, nitrat, nitritt og per- og polyfluor alkylstoffer ( <i>in Norwegian</i> ). [English translation: Analyses of nutrients in Norwegian and imported vegetables. Mapping of heavy metals, nitrate, nitrite and per- and polyfluoroalkyl substances].  Two reports with the same title.	Analytical data on nitrates and nitrites in Norwegian and imported vegetables.	NFSA (2024)
		NFSA (2025)
Norwegian registry of drinking water supplies (unpublished data)	Analytical data on nitrates and nitrites in drinking water.	FHI (2024)
Risk assessment of N-nitrosamines in food	Analytical data on N-nitrosamines in food.	EFSA et al. (2023)
Re-evaluation of sodium nitrate (E 251) and potassium nitrate (E 252) as food additives	Summary data of analytical results of food additive nitrates (E251-252) and nitrates from other sources (natural presence or contamination), reported by the member states in the EU.  Summary of the reported use levels of food additive nitrates (E251-252) provided by industry.	EFSA et al. (2017a)
Re-evaluation of potassium nitrite (E 249) and sodium nitrite (E 250) as food additives	Summary data of analytical results of food additive nitrites (E249–250) and nitrates from other sources (natural presence or contamination), reported by the member states in the EU.  Summary of the reported use levels of food additive nitrites (E 249–250) provided by industry.	EFSA et al. (2017b)

Report	Extracted data	Reference
Nitrate in vegetables. Scientific Opinion of the Panel on Contaminants in the Food chain	Summary data of analytical results of food additive nitrate (E 249-250) provided by member states in the EU.	EFSA (2008)
The NitRisk project (unpublished data)	Analytical data on nitrates, nitrites and N-nitrosamines in selected meat products.	Animalia (2026)

### 3.2.1 Systematic literature search for concentration values for N-NAs in selected foods

#### 3.2.1.1 Literature search and study selection

In addition to the search for documentation of food concentration values listed above (3.2), relevant literature databases were searched for concentration values for selected N-NAs in selected foods for which EFSA et al. (2023) identified lack of data. To mitigate the workload, VKM determined to focus the search on the more data-poor N-NAs, and NDMA, for which there most data were available, was therefore not included in the search. The N-NAs included were NDEA, NDPA, NMEA, NDBA, NDIBA, NMA, NSAR, NMOR, NPIP, and NPYR. The food categories included were “fruit and fruit products”, “fruit and vegetable juices and nectars (including concentrates)”, “grains and grain-based products”, “legumes, nuts, oilseeds and spices”, “milk and dairy products”, “starchy roots or tubers and products thereof, sugar plants”, “vegetables and vegetable products”, and “water and water-based beverages”. A research librarian performed literature searches in the electronic databases Ovid MEDLINE(R), Embase, CAB Abstracts, Web of Science Core Collection, and Scopus. The search terms and strategy are included in Appendix 3.

The study selection followed the predefined eligibility criteria (Table 3.2.1.1-1 and the protocol (VKM et al., 2025)). For the eligibility criterion “Concentration values for N-nitrosamines in foods”, studies were included if they reported quantitative concentration data for the N-NAs listed in Table 3.2.1.1-1 for foods in the categories “fruit and fruit products”, “fruit and vegetable juices and nectars (including concentrates)”, “grains and grain-based products”, “legumes, nuts, oilseeds and spices”, “milk and dairy products”, “starchy roots or tubers and products thereof, sugar plants”, “vegetables and vegetable products”, and “water and water-based beverages”. In total, 3431 records were retrieved from searches conducted across the five databases. The records were imported into EndNote (Thomson Reuters, version X9), deduplicated, and the unique records were imported into Rayyan (Ouzzani et al., 2016) for title and abstract screening for relevance. The screening was performed independently by pairs of reviewers. To ensure consistency across reviewers, all reviewers screened a set of 100 titles and abstracts; discrepancies were discussed and resolved during a calibration meeting.

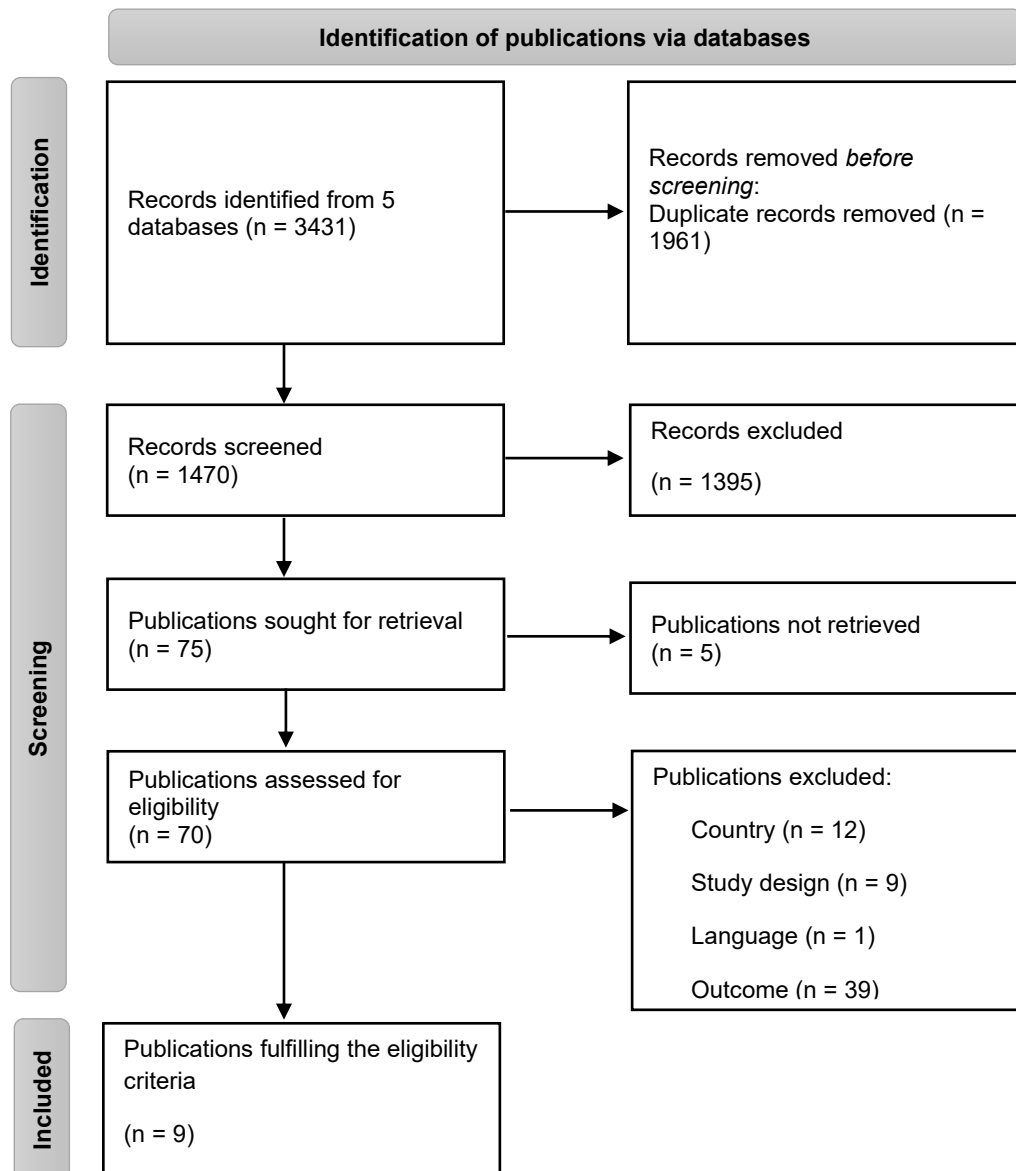
Of the records screened, 75 were selected for full-text assessment. Seventy full-text publications were successfully retrieved and evaluated independently by reviewer pairs using

the same software. Sixty-one publications were excluded at this stage because they (i) contained data collected from non-European countries (n = 12), (ii) reported concentration data for food items that were not intended for human consumption (n = 9), (iii) were written in a language not included in the eligibility criteria (n = 1), or (iv) did not address the selected N-NAs and/or selected food items (n = 39). Detailed reasons for exclusion are provided in Appendix 3.

The nine publications that met all inclusion criteria were further assessed for methodological reliability and reporting quality (Section 3.2.1.2). The study selection is presented in Figure 3.2.1.1-1.

**Table 3.2.1.1-1.** Eligibility criteria for studies reporting food concentration values for N-nitrosamines.

<b>Substances</b>	<b>NDEA, NDPA, NMEA, NDBA, NDiBA, NMA, NSAR, NMOR, NPIP, and NPYR</b>
Study design	<ul style="list-style-type: none"> <li>• Analytical studies</li> <li>• Exposure studies</li> </ul> (reporting concentration values in foods and drinks)
Outcome of interest	Concentration values for N-nitrosamines in foods
Publication year	No restriction
Countries	Europe
Language	Danish, English, German, Norwegian, Polish, and Swedish



**Figure 3.2.1.1-1.** PRISMA flowchart for selection of studies reporting concentration values for the pre-defined N-nitrosamines in selected food items (from Moher et al. (2009)).

### 3.2.1.2 Evaluation of methodological reliability and reporting quality

The methodological reliability and reporting quality of the nine included studies were assessed according to the procedures described in the protocol (VKM et al., 2025). For a detailed description of the scoring, see Supplementary Materials 1. An overview of the results is shown in Table 3.2.1.2-1. Studies with a score range between 7 and 10 were assigned a “medium confidence level”. These studies show gaps but are overall considered to be reliable. Studies with a score range between 1 and 6 were assigned a “low confidence level” and were not included due to major deficiencies in method quality description, and studies with the score 0 were a priori excluded. None of the studies achieved a high confidence level (a score range between 11 and 14; meeting all or most criteria on all quality indicators). An overview of the

concentration values reported in Gavinelli et al. (1988), Kocak et al. (2012), and Mavelle et al. (1991) is available in Supplementary Materials 1.

**Table 3.2.1.2-1.** Assessment of methodological reliability and reporting quality. Confidence levels: low (score 1-6), medium (score 7-10), high (score 11-14).

Reference	Score	Confidence level
Kocak et al. (2012)	9	Medium
Mavelle et al. (1991)	9	Medium
Gavinelli et al. (1988)	8	Medium
Osterdahl (1988b)	6	Low
Stephany et al. (1978)	6	Low
Dressel (1976)	0	Inappropriate method is used, or method description is insufficient: A priori exclusion, study does not meet the minimum inclusion criteria
Smiechowska et al. (1994)	0	Inappropriate method is used, or method description is insufficient: A priori exclusion, study does not meet the minimum inclusion criteria
Terplan et al. (1980)	0	Inappropriate method is used, or method description is insufficient: A priori exclusion, study does not meet the minimum inclusion criteria
Terplan et al. (1978)	0	Inappropriate method is used, or method description is insufficient: A priori exclusion, study does not meet the minimum inclusion criteria

### 3.2.2 Predicting nitrate, nitrite, and N-NA concentrations in ready-to-eat foods

Changes in the concentrations of nitrate, nitrite, and N-nitrosamines in foods are influenced by storage conditions, processing methods (e.g. heating and freezing), and antioxidants (EFSA, 2008; EFSA et al., 2017a; EFSA et al., 2017b; EFSA et al., 2023). Consequently, concentration values obtained from analyses of nitrate, nitrite, and N-NAs in unprocessed food materials may not reflect the actual concentrations in consumed foods. Such discrepancies can lead to either overestimation or underestimation of dietary exposure. Since most concentration values available for the exposure assessment in the current risk assessment is from raw/unprocessed food materials, VKM considered it important to determine whether there are differences between nitrate, nitrite and N-NA concentrations in raw/unprocessed versus consumed foods. Such an analysis requires specifically defining the extent of these changes, the specific processing conditions and which food types are involved. To achieve this, detailed information on concentration changes and partition coefficients between these compounds must be collected. VKM searched for available models to estimate concentration changes, but none were identified.

Information on changes in the concentrations of the above-mentioned nitrogen compounds can be derived from paired measurements in the same food item, preferably collected before and after various types of processing (e.g. storage, cooking). The following investigations were performed to collect relevant information that contained detailed descriptions of the

processing conditions, including storage parameters, type of heat treatment, temperature, and duration:

- A search in the EFSA opinions ( (EFSA, 2008; EFSA et al., 2017a; EFSA et al., 2017b; EFSA et al., 2023) for concentration data on nitrate, nitrite, and N-NAs in the same food item before and after e.g. storage, freezing, or heat treatment (EFSA, 2008; EFSA et al., 2017a; EFSA et al., 2017b; EFSA et al., 2023).
- A call for data to the contact points in EU Member states, Iceland and Switzerland on concentration values for nitrate and/or nitrite and/or N-NAs analysed in the same food item.
- Exploratory, ad hoc literature searches, to identify concentration data for nitrate and/or nitrite and/or N-NAs in the same food item and concentration data for these substances before and after e.g. storage, freezing, or heat treatment.

Data from the following publications were identified and used in the conversion models for nitrate to nitrite and nitrite to N-NAs in food:

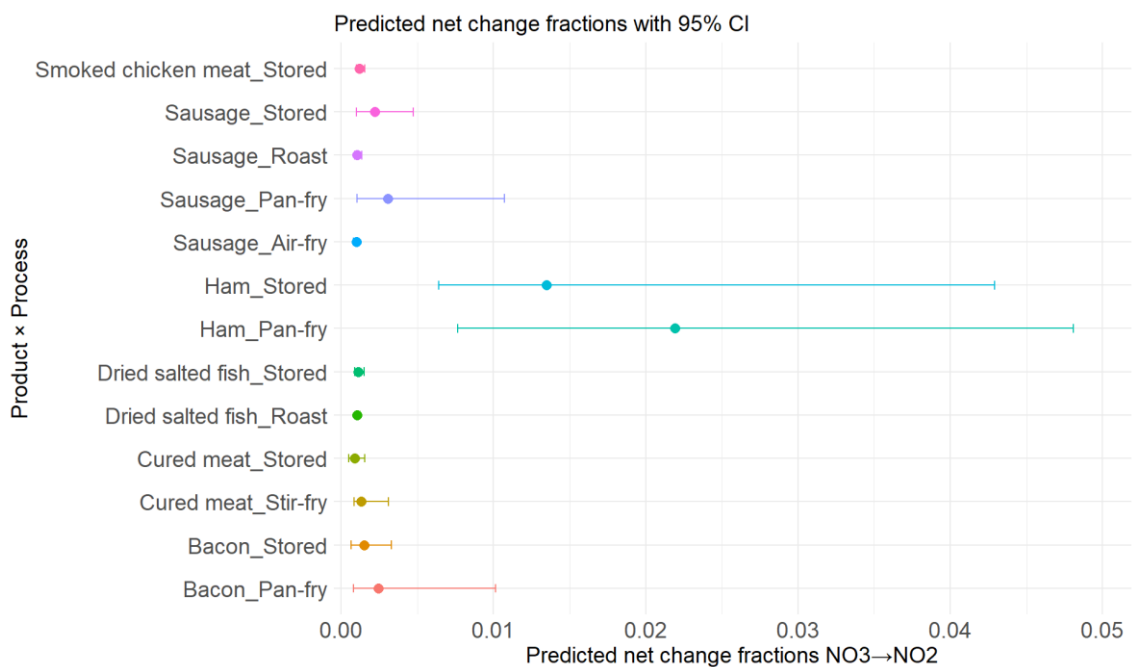
- Clayton-Cuch et al. (2025) presented the measurement of nine nitrate-accumulating leafy vegetables (e.g. rocket, spinach, Swiss chard, etc.) pureed (pre-processed), under defined storage conditions at different time points (e.g. 0 h, 3 h, etc.) and at temperatures of 5 °C, –20 °C, –80 °C.
- Chih et al. (2025) presented measurements of nitrate, nitrite, and N-NAs in 137 processed meat and fish products, including sausages, cured pork, ham, bacon, and pickled fish from the Taiwanese market, under defined storage (0, 3, and 7 days at 4 °C) and cooking conditions (both non-cooked and cooked foods; the cooking conditions were stir-fried, roasted, air-fried, and steamed).
- Zhou et al. (2025) presented measurements of nitrate, nitrite, and total N-NAs in a variety of commercially purchased Chinese food products, including processed meats (ham, sausage, bacon, cured pork), aquatic products (fish, shrimp), dairy products (milk, cheese), vegetables and cereals. The preparation conditions of the meat products were not described in detail. Concentration values for amines relevant for N-NA formation (e.g. dimethylamine, diethylamine, pyrrolidine, piperidine) were reported.
- Niklas et al. (2022) measured residual nitrate, nitrite and N-NAs in 100 Danish cured meat products. The preparation conditions of the cured meats and pre-processing conditions (e.g. temperature, curing duration, or spice additions), and amine content were not described in detail.
- Herrmann et al. (2015) analysed volatile and non-volatile N-NAs before and after heating (250 °C for 9 min) to assess the effect of heating on the formation of N-NAs in six Danish cured meat products (e.g. bacon, roast pork, meatloaf, Vienna sausage, salami, ham sausage). Concentrations of nitrate and nitrite were not reported.

Based on paired before–after measurements of nitrate, nitrite and N-NAs concentrations from Chih et al. (2025) and Clayton-Cuch et al. (2025), predicted net change (PNC) fractions were estimated using a linear mixed-effects (LME) model. The same modelling approach was applied separately to the nitrate→nitrite and nitrite→NAs equations, using logit-transformed PNC

fractions as the response variable. The model framework includes as fixed effects the processing conditions (process type, time, and temperature) and as random effects the variability between food types. This approach allows estimation of systematic trends in PNC fractions across experimental conditions, while preserving the data-driven nature of the paired measurements and explicitly accounting for uncertainty. See Appendix 1 for detailed descriptions.

The modelling framework was used to estimate PNC fractions, that is the observable change in nitrite and nitrosamine concentrations relative to initial levels under specific processing conditions (e.g. storage or heat treatment). These fractions do not represent true mechanistic conversion, but data-driven net concentration changes that incorporate simultaneous formation and degradation (e.g., loss, leaching, chemical reactions (oxidation, breakdown) processes. This allows initial occurrence concentrations to be adjusted in a consistent way while explicitly capturing variability introduced by processing, leading to more realistic exposure assessments for processed food scenarios.

The average PNC nitrite fractions ( $\text{NO}_3 \rightarrow \text{NO}_2$ ), estimated using the LME model for various fish and meat products under storage (refrigeration) and cooking conditions, together with their corresponding confidence intervals (CIs), are presented in Figure 3.2.2-1.



**Figure 3.2.2-1.** Predicted net change of nitrate to nitrite calculated by the LME model by food item and processing type with their corresponding confidence intervals (CIs). Air-fried: 165 °C; Non-cooked: refrigerated; Pan-fried: 200 °C; Reheated: 75 °C; Roasted: 180 °C; Stir-fried: 200 °C.

Based on the modelled PNC fractions ( $\text{NO}_3 \rightarrow \text{NO}_2$ ), the largest increases are observed for heat-treated ham (pan-frying) (PNC  $\approx 0.022$ ), followed by ham under storage conditions ( $\approx 0.014$ ), indicating that ham shows the strongest response among the evaluated foods. Moderate increases are observed for sausages during pan-frying ( $\approx 0.003$ ) and bacon during pan-frying ( $\approx 0.0025$ ), while storage of sausages ( $\approx 0.0022$ ) also shows a non-negligible effect. In contrast, cured meat, dried salted fish, smoked chicken meat, and most other cooking methods (e.g. roasting, air-frying) exhibit consistently low PNC fractions ( $\approx 0.001$ ), indicating limited changes.

For several food–process combinations, particularly those with higher mean values (e.g. ham), the confidence intervals are relatively wide, reflecting substantial variability and uncertainty in the underlying data. Overall, while cooking, especially pan-frying, tends to result in higher PNC fractions compared to storage, the magnitude and certainty of these effects vary considerably between food types.

Applying PNC fractions to estimate concentration values in processed food items provides a more realistic representation than using food concentrations before processing in exposure assessments. Nitrate and nitrite concentrations measured initially (“initial”, Time, h = 0) are used as the baseline. The concentration values for processed foods can be estimated using the following equations:

$$\text{Nitrite processed} \approx \text{initial nitrate} \times \text{PNC} + \text{initial nitrite} \quad (\text{Eq. 1})$$

$$\text{Nitrate processed} \approx \text{initial nitrate} \times (1 - \text{PNC}) \quad (\text{Eq. 2})$$

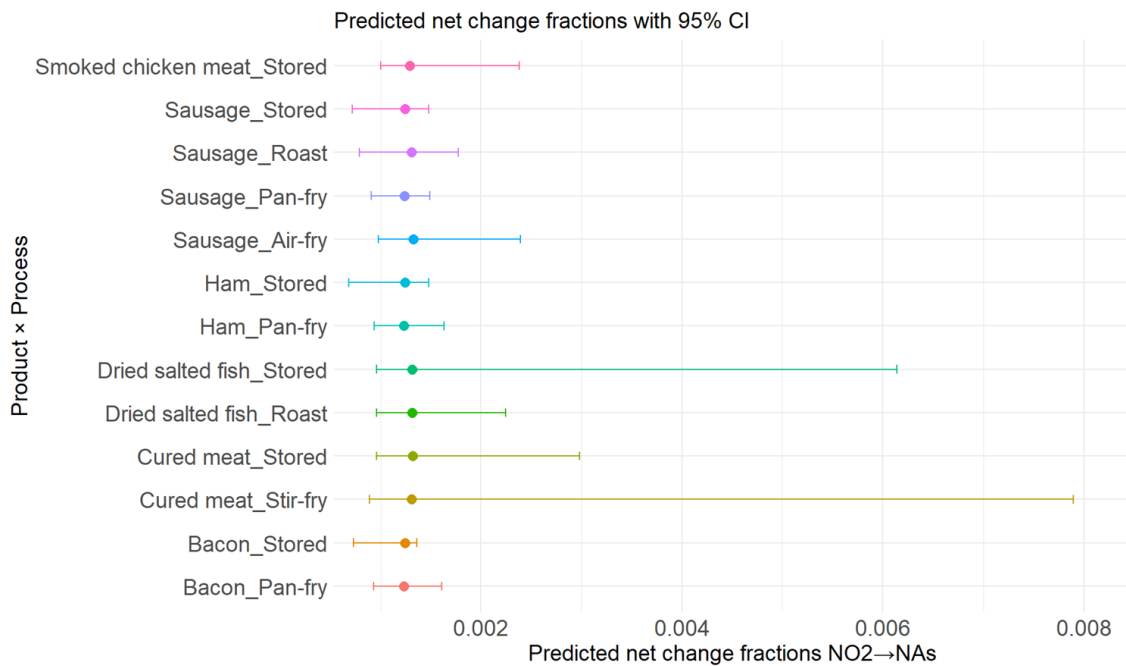
Equation (2) is an approximation as it assumes that the concentration change of nitrite is directly linked to a reduction in nitrate. This does not account for other pathways such as degradation, leaching, or alternative reactions. Conservatively, nitrate may also be assumed unchanged (i.e.  $\text{Nitrate}_{\text{processed}} \approx \text{initial nitrate}$ ) when no reliable data on nitrate loss are available, however Eq.2, is a good approximation. These equations represent net change effects; are data driven and do not imply mechanistic conversion. The CI bounds allow propagation of uncertainty. Some examples on how the food concentration values may be affected by refrigeration and heat treatment are shown below in Table 3.2.2-1.

**Table 3.2.2-1.** Examples on how the food concentration values from nitrate to nitrite may be affected by storage (refrigeration) and cooking in various ready to eat meats and how these values can be updated for realistic exposure estimates. PNC: Predicted net change.

Food_Process	Initial concentration (mg/kg)		PNC Fraction (95% CI) (%)	Final concentration (mg/kg)	
	Nitrate	Nitrite		Nitrate (95% CI)	Nitrite (95%CI)
Sausage_Pan fry	60.60	9.79	0.3% (0.1–1.1%)	60.42 (59.93–60.54)	9.97 (9.85–10.46)
Sausage_Air fry	60.60	9.79	0.1% (0.1–0.1%)	60.54 (60.53–60.55)	9.85 (9.84–8.86)
Cured meat_Stored	54.50	0.55	0.1% (0.04–0.1%)	54.45 (54.42–54.47)	0.60 (0.58–0.63)

The predicted processed concentrations and their bootstrap-derived confidence intervals (CIs) showed good agreement with the experimentally measured after-processing concentrations. Most measured values were contained within the predicted concentration ranges after accounting for limited analytical and processing variability.

The average PNC fractions ( $\text{NO}_2 \rightarrow \text{N-NAs}$ ), estimated using the LME model for various fish and meat products under storage (refrigeration) and cooking conditions, together with their corresponding confidence intervals (CIs), are presented in Figure 3.2.2-2.



**Figure 3.2.2-2.** Predicted net change of nitrite to *N*-NAs calculated by the LME model by food item and processing type with their corresponding confidence intervals (CIs). Air-fried: 165 °C; Non-cooked: refrigerated; Pan-fried: 200 °C; Reheated: 75 °C; Roasted: 180 °C; Stir-fried: 200 °C.

Across foods and processes, the PNC fractions are low (~0.0012–0.0013) with overlapping confidence intervals. This indicates weak separation between storage and cooking conditions for the  $\text{NO}_2 \rightarrow \text{N-NAs}$  pathway. Slightly higher effects are observed for sausage (air-fry) and cured meat (stir-fry), while bacon and ham under storage or pan-frying show slightly lower values; however, these differences are small.

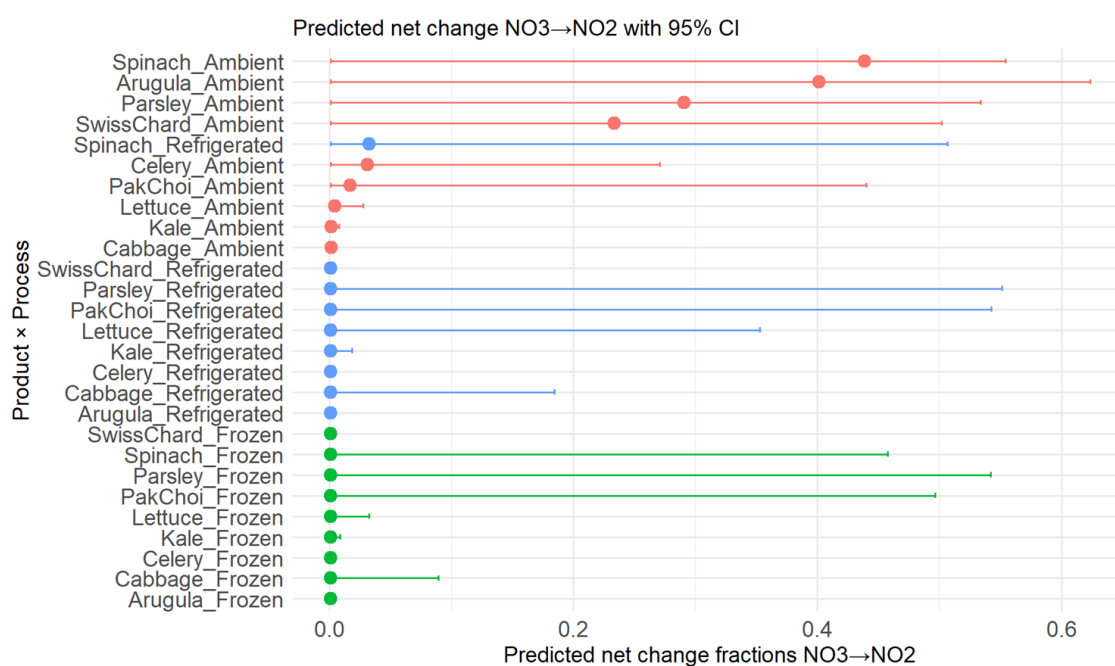
Applying PNC fractions taken from the model output for the  $\text{NO}_2 \rightarrow \text{N-NAs}$  pathway, *N*-NAs concentration values can be updated in processed foods. In this application, nitrite is treated conservatively as remaining approximately similar to the initial measured nitrite concentration, because the model output indicates only small and relatively uniform  $\text{NO}_2 \rightarrow \text{N-NAs}$  PNC fractions across foods and processes. The processed nitrosamine concentration is therefore estimated using adjusted Eq.1, as:  $\text{N-NAs}_{\text{processed}} = \text{initial N-NAs} + (\text{initial NO}_2 \times \text{PNC})$ .

Some examples of how the *N*-NAs concentration values may be affected by refrigeration and heat treatment are shown below in Table 3.2.2-2.

**Table 3.2.2-2.** Examples on how the food concentration values from nitrite to *N*-NAs may be affected by storage (refrigeration) and cooking in various ready to eat meats and how these values can be updated for realistic exposure estimates. PNC: Predicted net change.

Food_Process	Initial concentration (mg/kg)		PNC fraction (95% CI) (%)	Final concentration (mg/kg)	
	Nitrite	N-NAs		Nitrite	N-NAs (95% CI)
Sausage_Air fry	9.79	0.00341	0.13% (0.10%-0.24%)	9.79	0.01639 (0.01298-0.02685)
Cured meat_Stir-fry	0.55	0.0411	0.13% (0.09%-0.79%)	0.55	0.04182 (0.04159-0.04544)
Bacon_Stored	9.3	0.000552	0.12% (0.07%-0.14%)	9.3	0.01214 (0.00734-0.01319)

The average PNC fractions (NO<sub>3</sub>→NO<sub>2</sub>), estimated using the LME model for various vegetable food types during ambient, refrigeration and frozen conditions with their corresponding confidence intervals (CIs), are presented in Figure 3.2.2-3.



**Figure 3.2.2-3.** Predicted net change of nitrate to nitrite calculated by the LME model by food item and processing type with their corresponding confidence intervals (CIs). Ambient: 20 °C; Refrigerated: 5 °C; Frozen: - 20 °C.

Based on the modelled predicted net change, the largest nitrite changes are observed for Spinach\_Ambient (PNC ≈ 0.439, 95% CI 0.001–0.554) and Rocket\_Ambient (PNC ≈ 0.401, 95% CI 0.001–0.624). These results indicate that under ambient conditions some vegetables can exhibit measurable net change. In contrast, most refrigerated and frozen vegetables show net changes close to 0.001, indicating essentially no detectable net nitrite formation. This occurs because many paired measurements show no increase or even a decrease in nitrite concentrations after storage (half LOD), and these cases were conservatively retained in the model. Consequently, many observations are producing very small predicted net changes. Storage at ambient temperature showing the strongest predicted net change, while refrigeration and freezing strongly suppress nitrite net change. The model responds correctly to the variability in the data, CIs for low-valued net changes are generally narrow around

~0.001, reflecting stable estimates of near-zero formation, whereas larger fractions show broader uncertainty due to stronger measurement variability.

Similarly, applying Eq.1 and Eq.2 and the corresponding PNC fractions the concentration values in processed vegetables can be updated. Some examples are given below in Table 3.2.2-3.

The PNC fractions quantify the relative processing-induced changes in nitrite and N-NAs concentrations with respect to the initial precursor concentrations under specific storage and heat-treatment conditions. Although the estimated PNC fractions were generally small, simple exposure examples, not presented here demonstrate that their application to foods, especially with elevated precursor concentrations may result in substantial increases in predicted processed nitrosamine concentrations and corresponding dietary exposure estimates. The highest predicted exposure increases were associated with thermal processing conditions, which generally produced the largest PNC estimates and processed nitrosamine concentration increases. This effect is particularly relevant because nitrite precursor concentrations are typically several orders of magnitude higher than nitrosamine concentrations, such that even small relative conversion fractions may translate into meaningful absolute increases in processed nitrosamine levels and exposure estimates. Storage and refrigeration conditions also showed measurable, although generally smaller, concentration increases. Even though, the paired before–after dataset is limited, the modelling framework provides indicative evidence that processing-related concentration updates may substantially influence exposure assessment and should therefore be considered in exposure-oriented evaluations of nitrate-, nitrite- and nitrosamine-containing foods.

**Table 3.2.2-3.** Examples of how the food concentration values from nitrate to nitrite may be affected by storage (ambient, refrigeration, frozen) conditions in various vegetables and how these values can be updated for realistic exposure estimates. PNC: Predicted net change.

Food_Process	Initial concentration (mg/kg)		PNC fraction (95% CI) (%)	Final concentration (mg/kg)	
	Nitrate	Nitrite		Nitrate (95% CI)	Nitrite (95% CI)
Rocket_Ambient	3816.00	0.06	40.1 (0.10-62.4)	2284.19 (1436.55-3812.15)	1531.87 (3.91-2379.51)
Celery_Ambient	579.00	0.06	3.1 (0.10-27.1)	560.86 (422.25-578.43)	18.20 (0.63-156.81)
Celery_Frozen	619.00	0.06	0.1 (0.10-0.1)	618.38 (618.08-618.39)	0.68 (0.67-0.98)

### 3.3 Dietary intake data for food containing nitrate, nitrite, and N-NAs

Intake data from the national dietary surveys Norkost 4 (Myhre et al., 2024), Ungkost 3 (Hansen et al., 2015), Småbarnskost 3 (Astrup et al., 2020), and Spedkost 3 (Myhre et al., 2020) were used in the exposure estimation. The food items reported as consumed in the national dietary surveys were identified using the NutriFoodCalc (NFC) system (University of Oslo). The

NFC system contains several databases, and different NFC databases are used depending on the survey. The main characteristics of the surveys are presented in Table 3.3-1.

**Table 3.3-1.** The Norwegian dietary surveys used for assessment of dietary exposure.

Dietary survey	NFC database	Year of data collection	Age groups (years)	Survey respondents (number)	Participation rate (%)	Method used	NFC database
Norkost 4	N4	2022 -2023	18-80	1964	40	Two 24-hour recalls, by telephone	Natural units (e.g. apples, eggs), household measures, or food portion photographs
Ungkost 3	AE14	2015	4	399	20	Four-days web-based food diary	
			9	636	55		
			13	687	53		
Småbarnskost 3	AE18	2019	2	1413	47	Semi-quantitative food frequency questionnaires <sup>1</sup>	Predefined household units (eggs, slice of bread, decilitres, etc.), or food portion photographs
Spedkost 3	AE18	2019	1	1957	66		

<sup>1</sup>The caretaker was instructed to consider the previous two weeks as a timeframe when completing the questionnaire.

### **3.4 Assigning concentration values to nitrate-, nitrite-, and N-NA-containing consumed foods**

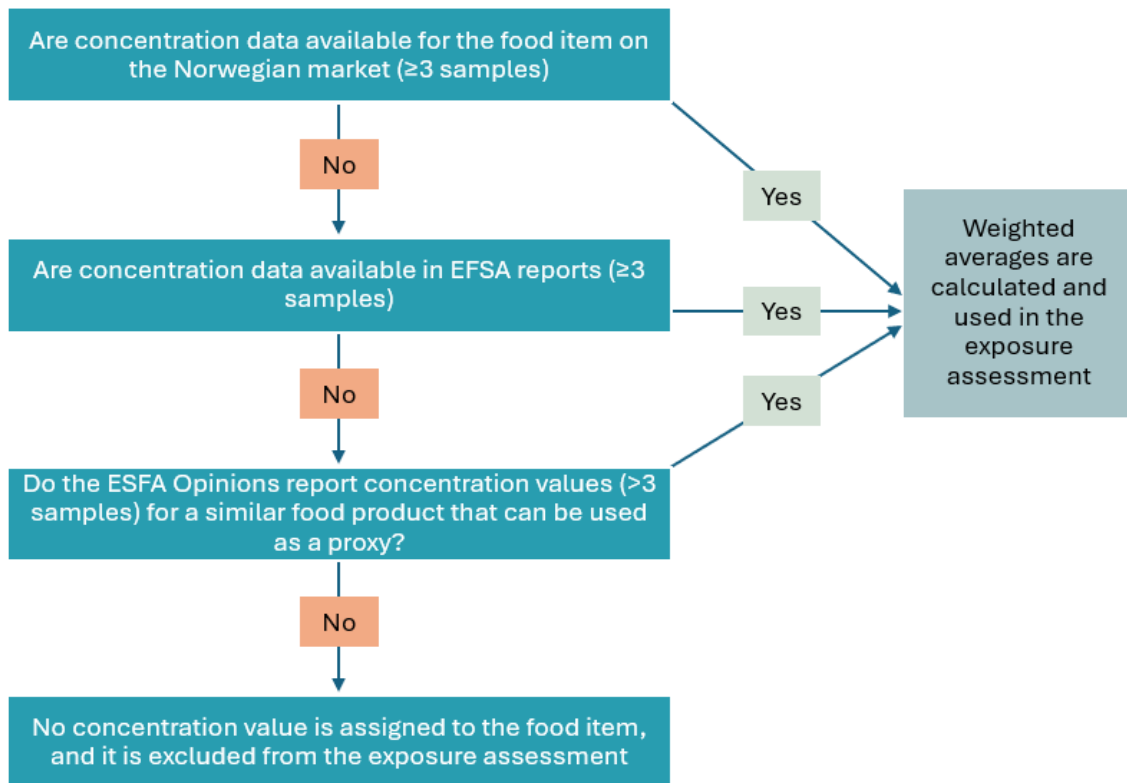
The main points of the procedures for assigning nitrate, nitrite, and N-NAs concentration values (Section 3.2) to foods to be used in the OIM (3.4.1) and probabilistic (3.4.2) exposure assessments (Section 3.5), are presented in this chapter. The foods are those recognised as 1) sources of nitrate, nitrite, or N-NAs (VKM et al., 2024a) and 2) reported as consumed in the national dietary surveys (Section 3.3).

#### *3.4.1 Assignment of concentration values (OIM approach)*

Assigning concentration values to nitrate-, nitrite- and/or N-NA-containing consumed foods for the OIM exposure assessment followed the established principles of traditional food composition work and the guidelines of Greenfield and Southgate (2003). The principles applied in the compilation process were the following:

- A minimum of three concentration values for a food item or food group was required for inclusion in the assessment.
- When multiple concentration values for a food item were available from both Norway and other countries, Norwegian concentration data were prioritised (NFSA, 2024; NFSA, 2025).
- When the opinions EFSA et al. (2017b), EFSA et al. (2017a), and EFSA et al. (2023) were the concentration data sources, VKM applied the median concentration from the medium-bound concentrations for nitrate and nitrite, while the mean was chosen for N-NAs.
- When several concentration values were available for a given food item or food group, weighted averages of the median from the medium bound concentration values based on the number of analyses were calculated.
- Due to the lack of specificity of the constituent food items, FoodEx2 Level 1 concentration values were deemed unsuitable for use.
- When concentration data for a specific food item were missing, concentration values from comparable food items were assigned when available.
- Concentrations for composite foods were based on recipes and ingredient composition in NFC.

The overall process is summarised in Figure 3.4.1-1. Further details are available in Appendix 4.



**Figure 3.4.1-1.** An overview of the process for assigning nitrate, nitrite, and N-NAs concentration values to a specific food item in the OIM exposure assessment.

### 3.4.2 Assignment of concentration values (probabilistic approach)

Concentration values from foods on the Norwegian market (Table 3.2-1) were limited when compared to the extensive data found in EFSA reports. Specifically, analyses of Norwegian foods rarely exceeded 100 samples and were often fewer than 10, whereas EFSA reports included between 100 to over 1000 analyses for various foods. Due to the scarcity of Norwegian concentration values, the main probabilistic exposure assessment relied exclusively on concentration values available in EFSA reports (EFSA, 2008; EFSA et al., 2017a; EFSA et al., 2017b; EFSA et al., 2023). The only exception was for Norwegian tap water, for which a high number of concentration data were available. To assess the influence of Norwegian concentration values on the exposure assessment, EFSA values were substituted with Norwegian data wherever the latter was available. A probabilistic exposure assessment was then conducted for adults using the Norkost 4 dataset. The results were evaluated to determine the effect of using Norwegian data in place of EFSA data when available.

Similar foods with diverse concentrations values (varying by more than one order of magnitude) were separated into groups of concentration values with the same order of magnitude. For example, rocket was not included in the food group “lettuce” for nitrate exposure, because rocket had a nitrate concentration of more than 4000 mg/kg, while lettuce had concentrations around 1000 mg/kg. In another example, processed meat with mean concentration of 20.70 mg/kg nitrite was separated from poultry with mean concentration of 12.00 mg/kg nitrite, and from beef with mean concentration of 4.99 mg/kg nitrite. This approach was applied to avoid individual food items with particularly high concentrations from

overly influencing the exposure estimates for an entire food group. Consequently, the groups contain a different number of food items, some include many different food items, whereas others are limited to a specific food item, and the grouping of food items differs for nitrates, nitrites, and *N*-NAs.

The nitrate and nitrite food concentration values from EFSA (EFSA et al., 2017a; EFSA et al., 2017b) were reported as summary statistics (minimum, mean, median, P95, and maximum) for the lower-bound (LB), middle-bound (MB), and upper-bound (UB) scenarios. In the EFSA LB scenario, all left-censored values were set to zero; in the MB scenario, they were assigned half the limit of detection (LOD) value; and in the UB scenario, they were assigned the full LOD value. EFSA also reported the number of analysed samples and the proportion of censored data. This information was used to simulate individual concentration values for each food item under the LB, MB and UB scenarios, according to the number of samples above the LOD.

To estimate values for the left-censored observations (below LOD), a Regression on Order Statistics (ROS, also called log-probit regression-LPR) model (EFSA, 2010), was applied using the R package NADA (Lee, 2025). Firstly, the number of detected values (calculated from the number of analyses and % left-censored data) were simulated based on the summary data for each food item throughout the dataset and assuming a log-normal distribution of the concentration data. Secondly, zeros corresponding to the proportion of non-detects were added to the simulated dataset. This dataset was used in R to impute the left-censored data for which the ROS method in the NADA package log-transformed all simulated detected values (not zeros) to approximate a log-normal distribution, and a regression line was fitted to these data. Parameters from this regression were then used to sample values representing the distribution of concentrations below the LOD. These imputed values replaced the initially added zeros, ensuring that the final dataset reflected both detected and censored observations. The complete dataset (detected and imputed values) was subsequently back-transformed to the original scale to obtain reconstructed individual-level concentrations for use in probabilistic exposure modelling. This imputation was done for the LB, MB and UB, and added to one dataset to avoid previous imputation to affect the concentration data.

The EFSA et al. (2008) Opinion did not include detailed summaries of the concentration values such as censoring percentages. Thus, imputation of non-detects was not possible for these data. The summary data reported in the EFSA et al. (2008) Opinion was used to simulate individual concentration data for each food item throughout the dataset.

For each food item, the number of analyses reported by EFSA (EFSA et al., 2017a; EFSA et al., 2017b) was used to determine how many individual values were to be simulated. Using this approach allowed food items with a higher number of analytical concentration values to receive more weight than food items with fewer values and enabled combination of concentration data from EFSA (2017a) and EFSA (2008) for the same food groups. New food-group summary statistics derived from the reconstructed datasets were then used in the probabilistic exposure modelling (Monte Carlo simulation in R).

Only mean LB, mean MB, and mean UB values for *N*-NAs were reported (EFSA et al., 2023). Because variability of data (e.g. standard deviation (SD), median, P95) was not reported, the full concentration distribution could not be simulated, and individual-level modelling was not

feasible. Instead, the mean MB value for each food item was aggregated to food group level and used to estimate a distribution to be used in the probabilistic exposure assessment. This approach is likely to underestimate the exposure (see Discussion). The external exposure was modelled for each of the N-NAs separately, giving an exposure distribution for each food group for each N-NA. The total exposure to all N-NAs was estimated by adding the exposure from each food group (the entire distribution) for each N-NA, after multiplying all exposure values for NDPA, NDBA, NMA, NPYR, NPIP, and NSAR with the potency factor 0.2 (EFSA et al., 2023). This potency factor was calculated by EFSA from the ratio between the lowest BMDL<sub>10</sub> of the N-NAs with the highest concern (0.010 mg/kg day for NDEA, NMEA, NDMA and NMOR) and the lowest BMDL<sub>10</sub> of the remaining N-NAs (0.062 mg/kg per day for NDPA, NDBA, NMA, NPYR, NPIP, NSAR) resulting in a potency factor of 0.2 (EFSA et al., 2023).

### 3.5 Estimation of dietary exposure of nitrate, nitrite, and N-NAs (external exposure)

The dietary exposure estimation of nitrate, nitrite, and N-NAs is based on food concentration data from scientific opinions, reports, and projects listed in Section 3.2 and food consumption data from the national dietary surveys (Section 3.3). It should be noted that the food groups used for the OIM and probabilistic exposure assessments may contain different food items despite having similar names. Therefore, overviews of the food groups are provided in Section 3.5.1 and 3.5.2.

#### 3.5.1 Dietary exposure estimation (OIM approach)

Table 3.5.1-1 shows an overview of the food groups and examples of the food items included for the OIM nitrate, nitrite, and N-NAs exposure estimation. The food grouping is not equal between the three databases that are used: AE14, AE18 and N4. The number of raw food codes is higher, and the number of indivisible dishes is lower in AE14 than in N4. This is shown when composite dishes in Norkost 4 are 119 g/day, while for Ungkost 3 (13-year-olds) the amount is 195 g/day. There are also differences between the three databases: AE14, AE18 and N4, specially for the food group composite dishes.

**Table 3.5.1-1.** An overview of the grouping of foods for the exposure assessment of nitrate, nitrite, and N-nitrosamines, and examples of food items included in each group.

Food categories	Food groups	Foods included in the exposure estimations		
		Nitrate	Nitrite	N-nitrosamines
Grain and grain products	Bread and cereals	Cereals, bread and bakery wares	NA	NA
Potatoes	Potatoes	All potatoes and potato-based foods like pommes frites and mashed potato	NA	NA

Food categories	Food groups	Foods included in the exposure estimations		
		Nitrate	Nitrite	N-nitrosamines
Vegetables - dishes and - products	Vegetables	Vegetables	Most vegetables, and vegetable products such as salads and vegetable stews	NA
	Legumes	Legumes, except fresh and frozen peas which is in the vegetable group	NA	NA
Fruit, berries, nuts, and seeds	Fruit, berries and juices	Fruit, berries and juices	NA	NA
Meat and meat products	Red meat and meat products	Red meat and meat products, including sausages and pâtés	All red meat and meat products, including sausages and pâtés	Meat products, breadspread and sausages
	White meat and meat products	White meat and products	White meat and products	White meat products
Fish, fish products and shellfish	Fish, fish products and shellfish	Fish, fish products, and shellfish	Most fish and some fish products	Smoked, processed and preserved
Egg	Egg	NA	NA	NA
Milk and dairy	Milk and dairy products	Milk and dairy products like yoghurt and cheese	All milk and dairy products like cheese and ice cream	Cheese
Margarine, oil, mayonnaise, dressing	Butter, margarine and oils	Butter, margarine and oils	NA	NA
Sugar and sweets	Sugar and sweets	Sugar, and chocolate	NA	NA
Beverages	Beverages, including drinking (tap) water and mineral water	Beverages, except juice and milk which are categorised in the groups "Fruit, berries, and juices" and "Milk and dairy products", respectively, and including tap water, wine and spirits	Beverages, except juice and milk which are categorised in the groups "Fruit, berries, and juices" and "Milk and dairy products", respectively, and including tap water, wine and spirits	Cocoa, beer, spirits

Food categories	Food groups	Foods included in the exposure estimations		
		Nitrate	Nitrite	N-nitrosamines
Infant food	Infant foods	Infant formula, baby porridge, and products made for young children	Infant formula, baby porridge, and products made for young children	NA
Diverse products	Composite dishes and products	Foods for which concentration data were available (EFSA et al., 2017b), but which were not covered by other predefined food groups in NFC.	Foods for which concentration data were available (EFSA et al., 2017b), but which were not covered by other predefined food groups in NFC.	NA

An overview of the estimated total daily exposures to nitrate, nitrite, and N-NAs is presented in Tables 3.5.1-2 and 3.5.1-3. The age group with the highest mean exposure per kg bw per day is 1-year-olds for nitrate and nitrite, and 4-year-olds for N-NAs. The age group with the lowest mean exposure per kg bw per day is 13-year-olds for nitrate, and adults for nitrite and N-NAs.

The share of food items lacking concentration values for nitrate, nitrite, and N-NAs varied between the different substances and across age groups. In general, concentration values were available for most food items reported eaten by 1-year-olds, whereas more food items consumed by the other age groups lacked concentration values and were therefore not included in the exposure estimation.

**Table 3.5.1-2.** OIM estimate of the external nitrate, nitrite and N-nitrosamine exposure for age groups included in the Norwegian national dietary surveys.

Age group, survey name	Nitrate (mg/day)			Nitrite (mg/day)			N-nitrosamines (ng/day)		
	Mean	Median	P95	Mean	Median	P95	Mean	Median	P95
18-80 years, Norkost 4	54.6	41.9	140	1.00	0.70	2.69	589	493	1463
13-year-olds, Ungkost 3	21.6	19.2	44.8	0.83	0.70	1.93	393	347	856
9-year-olds, Ungkost 3	19.3	17.6	36.2	0.66	0.57	1.49	335	283	757
4-year-olds, Ungkost 3	16.0	14.4	30.8	0.47	0.42	0.94	237	186	612
2-year-olds, Småbarnskost 3	17.1	15.5	31.6	0.41	0.38	0.70	155	140	312
1-year-olds, Spedkost 3, all	25.4	23.1	46.9	0.37	0.32	0.78	103	88.2	231

Age group, survey name	Nitrate (mg/day)			Nitrite (mg/day)			N-nitrosamines (ng/day)		
	Mean	Median	P95	Mean	Median	P95	Mean	Median	P95
1-year-olds, Spedkost 3, *not breastfed	29.2	27.3	49.9	0.40	0.35	0.82	110	95.9	245

\*Out of 1957 children, 1024 do not receive breast milk at the age of one, while 933 one-year-olds are breastfed.

**Table 3.5.1-3.** OIM estimate of the external nitrate, nitrite and N-nitrosamine exposure for age groups included in the Norwegian national dietary surveys.

Age group, survey name	Nitrate (mg/kg bw/day)			Nitrite (mg/kg bw/day)			N-nitrosamines (ng/kg bw/day)		
	Mean	Median	P95	Mean	Median	P95	Mean	Median	P95
18-80 years, Norkost 4 <sup>a</sup>	0.74	0.55	1.90	0.010	0.010	0.040	7.68	6.44	18.8
13-year-olds, Ungkost 3 <sup>b</sup>	0.44	0.38	0.95	0.017	0.014	0.037	8.00	6.97	18.6
9-year-olds, Ungkost 3 <sup>c</sup>	0.60	0.54	1.17	0.021	0.017	0.046	10.4	8.57	24.1
4-year-olds, Ungkost 3 <sup>d</sup>	0.93	0.82	1.89	0.027	0.024	0.054	13.7	10.7	35.6
2-year-olds, Småbarnskost 3 <sup>e</sup>	1.34	1.22	2.49	0.032	0.030	0.056	12.2	11.0	24.1
1-year-olds, Spedkost 3 <sup>f</sup> , all	2.56	2.31	4.79	0.037	0.032	0.078	10.4	8.90	23.6
1-year-olds, Spedkost 3, not breastfed	2.92	2.83	5.16	0.093	0.035	0.084	10.9	9.31	24.0

<sup>a</sup>For adults there were 34 individuals who did not record their weight; for these, the average weight of 77.0 kg was imputed. <sup>b</sup>For 13-year-olds there were 22 individuals who did not record their weight; for these, the average weight of 50.3 kg was imputed. <sup>c</sup>For 9-year-olds there were 22 individuals who did not record their weight; for these, the average weight of 32.9 kg was imputed. <sup>d</sup>For 4-year-olds there were 17 individuals who did not record their weight; for these, the average weight of 17.4 kg was imputed. <sup>e</sup>For 2-year-olds there were 378 individuals who did not record their weight; for these, the average weight of 12.8 kg was imputed. <sup>f</sup>For 1-year-olds there were 174 individuals who did not record their weight; for these, the average weight of 10.0 kg was imputed.

As shown in Table 3.5.1-4, the food group “Vegetables” was the major contributor to the total mean nitrate exposure among adults (18-80 years), accounting for 67%. The food category “White meat and meat products” was the main contributor to the total mean nitrite (42%), and “Red meat and meat products” was the main contributor to the total mean N-NA exposure (60%).

For 13-year-olds, the food group “Composite dishes” was the major contributor to the total mean nitrate exposure, accounting for 29% (Table 3.5.1-5). “Red meat and meat products” was the main contributor to the total mean nitrite (26%) and N-NA (50%) exposure.

For 9-year-olds, the food group “Vegetables” was the major contributor to the total mean nitrate exposure, accounting for 25% (Table 3.5.1-6). “Red meat and meat products” were the main contributor to the total mean nitrite (29%) and *N*-NA (60%) exposure.

For 4-year-olds, the food group “Vegetables” was the major contributor to the total mean nitrate exposure, accounting for 29% (Table 3.5.1-7). The food category “Red meat and meat products” was the main contributor to the total mean nitrite exposure (26%) and the total mean *N*-NA exposure (68%).

For 2-year-olds, the food group “Vegetables” was the major contributor to the total mean nitrate exposure, accounting for 31% (Table 3.5.1-8). For nitrite and *N*-NAs, the food group “Red meat and meat products” was the main contributor to the total mean exposure (27% and 58%, respectively).

For 1-year-olds (Table 3.5.1-9), the food group “Baby food” was the major contributor to the total mean nitrate and nitrite exposure, accounting for 63% and 47% respectively. For *N*-NAs, the food group “Red meat and meat products” was the main contributor (57%).

**Table 3.5.1-4.** Contribution from different food groups to the total mean exposure of nitrate (54.6 mg/day), nitrite (1.0 mg/day), and *N*-nitrosamine (589 ng/day) exposure for the age group 18-80 years (Norkost 4, in mg/day and percent). NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure of each substance.

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			<i>N</i> -nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Bread and grain products	Bread and grain products	230	2.7	5.0	NA	NA	NA	NA	NA	NA
Potatoes	Potatoes	53	5.8	11	NA	NA	NA	NA	NA	NA
Vegetables -dishes and -products	Vegetables	178	36	67	178	0.11	11	NA	NA	NA
	Legumes	8	1.5	2.8	NA	NA	NA	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit, berries and juices	197	4.1	7.7	NA	NA	NA	NA	NA	NA
Meat and meat products	Red meat and meat products	104	1.46	2.7	104	0.27	27	104	347	60
	White meat and meat products	41	0.15	0.3	41	0.42	42	41	147	25
Fish, fish products and shellfish	Fish, shellfish and products	50	0.36	0.7	50	0.04	4.0	50	24.9	4.3
Milk and dairy	Milk and dairy	259	0.70	1.3	259	0.15	15	49	21.0	3.6
Margarine, oil, mayonnaise, dressing	Mayosalad	30	0.26	0.5	NA	NA	NA	NA	NA	NA
Chocolate, sweets, deserts, ice cream, sweet, breadspread	Sugar, honny, and sweets	26	0.03	0.1	NA	NA	NA	NA	NA	NA

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Beverages	Beverages, including drinking water	2133	0.46	0.9	2133	0.01	1.0	NA	NA	NA
	Beer, spirits	NA	NA	NA	NA	NA	NA	93	42.9	7.4
Composite dishes and products	Composite dishes and products, snacks, powder-bases	119	0.24	0.4	119	0.004	0.4	NA	NA	NA

**Table 3.5.1-5.** Contribution from different food groups to the total mean exposure of nitrate (21.6 mg/day), nitrite (0.83 mg/day), and N-nitrosamine (393 ng/day) exposure for the age group 13-year-olds years (Ungkost 3, in mg/day and percent). NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure of each substance.

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Grain and grain products	Bread and cereals	232	2.40	11	NA	NA	NA	NA	NA	NA
Potatoes	Potato	36	3.31	15	NA	NA	NA	NA	NA	NA
Vegetables -dishes and -products	Vegetables	37	4.45	20	37	0.021	2.5	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit and juice	192	2.65	12	192	0.010	1.2	NA	NA	NA

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Meat and meat products	Red meat and meat products	74	1.06	4.9	74	0.225	26	74	195	50
	White meat and meat products	8	0.12	0.6	8	0.090	11	8	30	7.7
Fish, fish products and shellfish	Fish, shellfish and products	27	0.17	0.8	27	0.024	2.8	27	3.1	0.8
Milk and dairy	Milk and dairy products (except cheese)	298	0.71	3.3	298	0.162	19	NA	NA	NA
	Cheese	26	0.40	1.8	26	0.100	12	26	10	2.6
Margarine, oil, mayonnaise, dressing	Butter, margarin, oil	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chocolate, sweets, deserts, ice cream, sweet, breadspread	Sugar and sweets	NA	NA	NA	NA	NA	NA	NA	NA	NA
Beverages	Beverages including drinking water	644	0.13	0.6	644	0.002	0.2	NA	NA	NA
Composite dishes and products	Composite dishes and products, snacks, powder-bases	195	6.40	29	195	0.220	26	176	153	39

**Table 3.5.1-6.** Contribution from different food groups to the total mean exposure of nitrate (19.3 mg/day), nitrite (0.66 mg/day), and N-nitrosamine (335 ng/day) exposure for the age group 9-year-olds (Ungkost 3, N=687, in mg/day and percent). NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure of each substance.

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Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Grain and grain products	Bread and cereals	238	2.53	13	NA	NA	NA	NA	NA	NA
Potatoes	Potato	32	2.92	15	NA	NA	NA	NA	NA	NA
Vegetables	Vegetables-dishes and -products	49	4.90	25	49	0.029	4.9	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit and juice	197	2.98	16	197	0.004	0.7	NA	NA	NA
Meat and meat products	Red meat and meat products	73	0.86	4.5	73	0.174	29	73	201	60
	White meat and meat products	6	0.09	0.5	6	0.068	12	6	23	6.9
Fish, fish products and shellfish	Fish, shellfish and products	26	0.17	0.9	26	0.021	3.5	26	5.0	1.5
Milk and dairy	Milk and dairy products (except cheese)	327	0.36	1.9	327	0.070	12	NA	NA	NA
	Cheese	26	0.41	2.1	26	0.101	17	26	10	3.0
Margarine, oil, mayonnaise, dressing	Butter, margarin, oil	10	0.02	0.1	NA	NA	NA	NA	NA	NA
Chocolate, sweets, deserts, ice cream, sweet, breadspread	Sugar and sweets	45	0.10	0.5	NA	NA	NA	NA	NA	NA
Beverages	Beverages, including drinking water	514	0.10	0.5	514	0.001	0.2	NA	NA	NA
Composite dishes and products	Composite dishes and products	143	3.83	20	143	0.125	21	143	95	28

**Table 3.5.1-7.** Contribution from different food groups to the total mean exposure of nitrate (16 mg/day), nitrite (0.47 mg/day), and N-nitrosamine (237 ng/day) exposure for the age group 4-year-olds (Ungkost 3, N=399, in mg/day and percent). NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure of each substance.

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Grain and grain products	Bread and cereals	208	2.2	14	NA	NA	NA	NA	NA	NA
Potatoes	Potato	18	1.6	10	NA	NA	NA	NA	NA	NA
Vegetables -dishes and -products	Vegetables	51	4.6	29	51	0.031	7.2	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit and juice	223	4.0	25	223	0.001	0.2	NA	NA	NA
Meat and meat products	Red meat and meat products	51	0.57	3.6	51	0.109	26	51	161	68
	White meat and meat products	4	0.06	0.4	4	0.040	9.3	4	17	7.0
Fish, fish products and shellfish	Fish, shellfish and products	34	0.21	1.3	34	0.018	4.2	34	10	4.4
Milk and dairy	Milk and dairy products (except cheese)	313	0.37	2.3	313	0.066	15	313	NA	NA
	Cheese	28	0.43	2.7	28	0.108	25	28	9.8	4.2
Margarine, oil, mayonnaise, dressing	Butter, margarin, oil	10	0.07	0.4	NA	NA	NA	NA	NA	NA

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Chocolate, sweets, deserts, ice cream, sweet, breadspread	Sugar and sweets	26	0.06	0.4	NA	NA	NA	NA	NA	NA
Beverages	Beverages, including drinking water	384	0.07	0.4	384	0.001	0.2	NA	NA	NA
Composite dishes and products	Composite dishes and products	79	1.7	11	79	0.054	13	79	38	16

**Table 3.5.1-8.** Contribution from different food groups to the total mean exposure of nitrate (17.1 mg/day), nitrite (0.41 mg/day), and N-nitrosamine (155 ng/day) exposure for the age group 2-year-olds (Småbarnskost 3, N=1413, in mg/day and percent). NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure of each substance.

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Grain and grain products	Bread and cereals	147	2.2	13	NA	NA	NA	NA	NA	NA
Potatoes	Potatoes	16	1.6	9.4	NA	NA	NA	NA	NA	NA
Vegetables -dishes and -products	Vegetables	86	5.2	31	86	0.07	17	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit, berries and juices	162	3.7	22	NA	NA	NA	NA	NA	NA

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Meat and meat products	Red meat and meat products	31	0.59	3.5	31	0.11	27	31	90.1	58
	White meat and meat products	6	0.07	0.4	6	0.04	9.7	6	38.1	25
Fish, fish products and shellfish	Fish, shellfish and products	28	0.17	1.0	28	0.01	2.4	28	20.2	13
Milk and dairy	Milk and dairy products (except cheese)	424	0.25	1.5	424	0.08	20	NA	NA	NA
	Cheese	21	0.26	1.5	21	0.08	20	21	6.10	3.9
Beverages	Beverages, including drinking water	563	0.07	0.4	563	0.001	0.2	NA	NA	NA
Infant food	Baby food	205	2.9	17	205	0.02	4.9	NA	NA	NA

**Table 3.5.1-9.** Contribution from different food groups to the total mean exposure of nitrate (25.4 mg/day), nitrite (0.37 mg/day), and N-nitrosamine (103 ng/day) exposure for the age group 1-year-olds (Spedkost 3, N=1957, in mg/day and percent). NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure of each substance.

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Grain and grain products	Bread and cereals	80	1.2	4.9	NA	NA	NA	NA	NA	NA

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	ng/day	%
Potatoes	Potatoes	16	1.6	6.1	NA	NA	NA	NA	NA	NA
Vegetables -dishes and -products	Vegetables	64	3.8	15	64	0.038	11	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit, berries and juices	77	1.8	7.3	NA	NA	NA	NA	NA	NA
Meat and meat products	Red meat and meat products	21	0.40	1.6	21	0.060	17	21	57	57
	White meat and meat products	5	0.05	0.2	5	0.034	9.4	5	27	26
Fish, fish products and shellfish	Fish, shellfish and products	18	0.12	0.5	18	0.004	1.1	18	14	14
Milk and dairy	Milk and dairy products (except cheese)	96	0.09	0.4	96	0.019	5.2	NA	NA	NA
	Cheese	10	0.11	0.4	10	0.037	10	10	3.1	3.1
Beverages	Beverages, including drinking water	284	0.04	0.2	284	0.001	0.3	NA	NA	NA
Infant food	Baby food	724	16	63	284	0.170	47	NA	NA	NA

### 3.5.2 Dietary exposure estimation (probabilistic approach)

An overview of the foods included in the probabilistic exposure estimations is shown in Table 3.5.2-1. It should be noted that a food group does not always contain the same food items for the nitrate, nitrite and N-NA estimations, which prevents these food groups from being compared directly. The grouping is guided by differences in concentration values, which will vary for both the substances and the food items (see explanation in Section 3.4.2).

**Table 3.5.2-1.** Foods in corresponding groups and categories containing nitrate, nitrite, and N-NAs included in the probabilistic exposure estimation. NA: Concentration values not available.

Food categories	Food groups	Foods included in the exposure estimations		
		Nitrate	Nitrite	N-nitrosamines
Grain and grain products	Grain	All baked goods (e.g. bread, cake, pastries, cookies), grains (e.g. oats, rye), flour, and cereals, excluding pasta and rice	NA	NA
	Pasta	Fresh pasta only (not dried pasta)	NA	NA
Vegetables -dishes and -products	Other, vegetables	All vegetables except beans, peas, lettuce, cabbage, root vegetables, rocket, and composite dishes	NA	NA
	Beans	Legumes, such as beans, lentils, and chickpeas	NA	NA
	Cabbage and root vegetables	Vegetables such as cabbage, Brussels sprouts, beets, swede, and celeriac	NA	NA
	Lettuce	All leafy vegetables (e.g. spinach, Romaine lettuce, lettuce), excluding rocket	All leafy vegetables (e.g. spinach, Romaine lettuce, lettuce), excluding rocket	NA
	Peas	Dried, fresh, and frozen peas	NA	NA
	Rocket	Lettuce with rocket as the major food item	NA	NA
Fruit, berries, nuts, and seeds	Fruit	All fruit and fruit juice	NA	NA
Meat and meat products	Meat	All types of meat, excluding meat in composite dishes	NA	All meat, excluding processed meat (salted and smoked), sausage, and meat in composite dishes
	Meat, other	NA	All meat other than pork, poultry, sausage or processed meat	NA
	Meat, processed	NA	Salted and smoked meat	Salted and smoked meat

Food categories	Food groups	Foods included in the exposure estimations		
		Nitrate	Nitrite	N-nitrosamines
	Bacon	NA	NA	Bacon only, excluding other salted and smoked meat
	Beef	NA	All meat from cattle, excluding salted and smoked meat	NA
	Pork	NA	All pork, excluding salted and smoked meat and pork in composite dishes	NA
	Poultry	NA	All poultry, excluding poultry in composite dishes	NA
	Sausage	NA	All sausages	All sausages
<b>Fish, fish products and shellfish</b>	Fish	All fish including salted and smoked fish, excluding composite foods containing fish	NA	NA
	Fish, processed	NA	NA	All salted and smoked fish, excluding fish in composite dishes
<b>Milk and dairy</b>	Cheese	All cheese, excluding whey cheese	All cheese, excluding whey cheese	NA
<b>Beverages</b>	Beverages	All drinks (e.g. soda, bottled water, coffee, tea), excluding tap water, fruit juice, and alcoholic drinks	NA	NA
	Alcohol	All alcoholic drinks, such as wine, beer, and strong liquor	NA	Alcoholic drinks (e.g. wine, strong liquor), excluding beer
	Beer	NA	NA	Beer
	Tap water	Water from the tap. Not bottled drinking water	Water from the tap. Not bottled drinking water	NA

An overview of the estimated total exposure to nitrate, nitrite, and *N*-NAs is presented in Tables 3.5.2-2 (expressed per day) and 3.5.2-3 (expressed per kg body weight per day). Adults had the highest mean *N*-NA exposure per kg bw per day, adults and 4-year-olds had the highest mean nitrite exposure, and 4-year-olds had the highest mean nitrate exposure per kg bw per day. The group with the lowest mean exposures to nitrate, nitrite, and *N*-NAs per kg bw per day was the 13-year-olds.

**Table 3.5.2-2.** Probabilistic estimates of the external exposure to nitrate (mg/day), nitrite (mg/day), and *N*-nitrosamines (ng/day) for all age groups included in the Norwegian national dietary surveys. Concentration values for tap water is from the Norwegian registry of drinking water supplies (VREG, 2024). All other concentration values are from EFSA et al., 2017a; EFSA et al., 2017b; EFSA et al., 2023.

Age group, survey name	Nitrate (mg/day)			Nitrite (mg/day)			<i>N</i> -nitrosamines (ng/day)		
	Mean	Median	P95	Mean	Median	P95	Mean	Median	P95
18-80 years, Norkost 4	105	59.8	328	1.58	0.70	5.62	631	478	1793
13-year-old, Ungkost 3	33.8	12.8	126	0.30	0.03	1.37	144	51.5	628
9-year-olds, Ungkost 3	32.6	13.0	119	0.37	0.05	1.55	144	61.5	568
4-year-olds, Ungkost 3	29.6	13.6	103	0.32	0.08	1.33	108	59.8	411

**Table 3.5.2-3.** Probabilistic estimates of the external exposure to nitrate (mg/kg bw per day), nitrite (mg/kg bw per day), and *N*-nitrosamines (ng/kg bw per day) for all age groups included in the Norwegian national dietary surveys. Concentration values for tap water is from the Norwegian registry of drinking water supplies (VREG, 2024). All other concentration values are from EFSA et al., 2017a; EFSA et al., 2017b; EFSA et al., 2023.

Age group, survey name	Nitrate (mg/kg bw/day)			Nitrite (mg/kg bw/day)			<i>N</i> -nitrosamines (ng/kg bw/day)		
	Mean	Median	P95	Mean	Median	P95	Mean	Median	P95
18-80 years, Norkost 4	1.40	0.79	4.45	0.02	0.01	0.08	8.26	6.26	23.5
13-year-olds, Ungkost 3	0.70	0.26	2.59	0.01	0.00	0.03	2.93	1.03	12.9
9-year-olds, Ungkost 3	1.02	0.40	3.73	0.01	0.00	0.05	4.50	1.86	17.9

Age group, survey name	Nitrate (mg/kg bw/day)			Nitrite (mg/kg bw/day)			N-nitrosamines (ng/kg bw/day)		
	Mean	Median	P95	Mean	Median	P95	Mean	Median	P95
4-year-olds, Ungkost 3	1.73	0.79	6.05	0.02	0.00	0.08	6.24	3.41	23.8

Using concentration data from EFSA, the food group “Other vegetables” was the major contributor to total mean nitrate exposure among adults (18-80 years), with a mean contribution of 38% (Table 3.5.2-4). For nitrite, the food group “Poultry” was the major contributor with a mean contribution of 29%. For N-NAs, the food group “Meat” was the major contributor with a mean contribution of 71%. When Norwegian nitrate concentration values were used for the food groups “Lettuce”, “Cabbage and root vegetables”, “Vegetables, other” and “Meat” instead of the concentrations reported by EFSA et al. (2017a), the total daily nitrate exposure increased from 105 mg/day (Table 3.5.2-2) to 140 mg/day (Table 3.5.2-5), and the total nitrite exposure was reduced from 1.58 mg/day (Table 5.3.2-2) to 1.45 mg/day (Table 3.5.2-5). “Vegetables, other” and “Poultry” remained the main sources for nitrate and nitrite exposure, respectively.

For children aged 13, 9, and 4 years, the food group “Vegetables, other” was the largest contributor to total nitrate exposure, with mean contributions of 38%, 45%, and 45%, respectively (Table 3.5.2-7). The food group “Cheese” contributed most to total nitrite exposure, accounting for 38%, 30%, and 32% of the mean intake in 13-, 9-, and 4-year-olds, respectively (Table 3.5.2-8). For N-NAs, the food group “Meat” was the predominant contributor, with mean contributions of 84%, 80%, and 78% for the same age groups, respectively (Table 3.5.2-9).

**Table 3.5.2-4.** Contribution from different food groups to the total mean nitrate (105 mg/day), nitrite (1.58 mg/day), and *N*-nitrosamine (631 ng/day) exposure for the age group 18-80 years (see Table 3.5.2-1). NA: Food group not included in the exposure assessment due to missing concentration values. -: Not relevant. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure.

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			<i>N</i> -nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%
Grain and grain products	Grain	200	3.15	3.0	NA	NA	NA	NA	NA	NA
	Pasta	12	0.79	0.8	NA	NA	NA	NA	NA	NA
Vegetables -dishes and -products	Vegetables, other	165	40.2	38	NA	NA	NA	NA	NA	NA
	Bean	5	1.77	1.7	NA	NA	NA	NA	NA	NA
	Cabbage and root vegetables	23	15.1	14	NA	NA	NA	NA	NA	NA
	Lettuce	13	16.3	16	17	0.02	1.3	NA	NA	NA
	Peas	2	0.08	0.1	NA	NA	NA	NA	NA	NA
	Rocket	1	3.78	3.6	NA	NA	NA	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit	111	4.66	4.5	NA	NA	NA	NA	NA	NA
Meat and meat products	Meat	147	5.40	5.2	-	-	-	-	-	-
	Meat, other	-	-	-	15	0.12	7.9	124	450	71
	Meat, processed	-	-	-	9	0.18	11	9	41.6	6.6
	Bacon	-	-	-	NA	NA	NA	3	7.2	1.2
	Beef	-	-	-	42	0.21	13	NA	NA	NA
	Pork	-	-	-	19	0.21	13	NA	NA	NA
	Poultry	-	-	-	38	0.45	29	NA	NA	NA
	Sausage	-	-	-	13	0.12	7.3	13	13.4	2.1

Food categories	Food groups	Food group contribution to the total exposure								
		Nitrate			Nitrite			N-nitrosamines		
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%
Fish, fish products and shellfish	Fish	43	0.50	0.5	NA	NA	NA	NA	NA	NA
	Fish, processed	NA	NA	NA	NA	NA	NA	14	26.8	4.2
Milk and dairy	Cheese	44	0.78	0.7	44	0.26	16	NA	NA	NA
Beverages	Beverages	834	10.7	10	NA	NA	NA	NA	NA	NA
	Tap water	1073	0.34	0.3	1073	0.01	0.8	NA	NA	NA
	Alcohol (not including beer for N-NAs)	121	1.16	1.1	NA	NA	NA	30	50.3	8.0
	Beer	NA	NA	NA	NA	NA	NA	91	41.8	6.6

**Table 3.5.2-5.** Comparison of the contribution from different food groups to the total nitrate exposure for the age group 18-80 years (Norkost 4), using either Norwegian or EFSA concentration values for the food groups “lettuce”, “cabbage and root vegetables”, “vegetables, other”, and “meat” (cells marked with orange). For the remaining food groups the same concentration values were used as in Table 3.5.2-1. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure.

Food categories	Food groups	Mean consumption g/day	Food group contribution to the total nitrate exposure			
			Total mean exposure: 105 mg/day EFSA concentration values for the food groups Meat, processed; Sausage		Total mean exposure: 140 mg/day Norwegian concentration values for the food groups Meat, processed; Sausage	
			mg/day	%	mg/day	%
Grain and grain products	Grain	200	3.15	3.0	3.15	2.3
	Pasta	12	0.79	0.8	0.79	0.6
Vegetables -dishes and -products	Vegetables, other	165	40.2	38	82.1	58.7
	Bean	5	1.77	1.7	1.77	1.3

Food categories	Food groups	Mean consumption g/day	Food group contribution to the total nitrate exposure			
			Total mean exposure: 105 mg/day EFSA concentration values for the food groups Meat, processed; Sausage		Total mean exposure: 140 mg/day Norwegian concentration values for the food groups Meat, processed; Sausage	
			mg/day	%	mg/day	%
	Cabbage and root vegetables	23	15.1	14	10.3	7.4
	Lettuce	13	16.3	16	19.7	14.1
	Peas	2	0.08	0.1	0.08	0.1
	Rocket	1	3.78	3.6	3.78	2.7
Fruit, berries, nuts, and seeds	Fruit	111	4.66	4.5	4.66	3.3
Meat and meat products	Meat	147	5.40	5.2	3.0	2.1
Fish, fish products and shellfish	Fish	43	0.50	0.5	0.50	0.4
Milk and dairy	Cheese	44	0.78	0.7	0.78	0.6
Beverages	Beverages	834	10.7	10	10.7	7.7
	Tap water	1073	0.34	0.3	0.34	0.2
	Alcohol	121	1.16	1.1	1.16	0.8

**Figure 3.5.2-6:** Comparison of the contribution from different food groups to the total nitrite exposure for the age group 18-80 years (Norkost 4), using either Norwegian or EFSA concentration values for the food groups sausage and meat, processed (cells marked with orange). For the remaining food groups the same concentration values were used as in Table 3.5.2-1. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure.

Food categories	Food groups	Mean consumption g/day	Food group contribution to the total nitrite exposure			
			Total mean exposure: 1.58 mg/day EFSA concentration values for the food groups Meat, processed; Sausage		Total mean exposure: 1.45 mg/day Norwegian concentration values for the food groups Meat, processed; Sausage	
			mg/day	%	mg/day	%
Vegetables -dishes and -products	Lettuce	17	0.02	1.3	0.02	1.4
Meat and meat products	Meat, other	15	0.12	7.6	0.12	8.3
	Meat, processed	9	0.18	11	0.08	5.5
	Beef	42	0.21	13	0.21	15
	Pork	19	0.21	13	0.21	15
	Poultry	38	0.45	29	0.45	31
	Sausage	13	0.12	7.6	0.09	6.2
Milk and dairy	Cheese	44	0.26	17	0.26	18
Beverages	Tap water	1073	0.01	0.6	0.01	0.7

**Table 3.5.2-7.** Contribution from different food groups to the total nitrate exposure for 13-year-olds (33.78 mg/day), 9-year-olds (32.6 mg/day), and 4-year-olds (29.6 mg/day) (see Table 3.5.2-1). NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure.

Food categories	Food groups	Mean consumption of nitrate-containing food (g/day)			Mean (mg/day) contribution to the total nitrate exposure			Mean (%) contribution to the total nitrate exposure		
		13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds
Grain and grain products	Grain	177	190	172	2.77	2.98	2.70	8.2	9.1	9.1
	Pasta	NA	0.01	NA	NA	0.00	NA	NA	0.0	NA
Vegetables -dishes and -products	Vegetables, other	53	61	55	12.9	14.8	13.5	38	45	45
	Bean	0.01	0.02	0.03	0.01	0.03	0.04	0.0	0.1	0.1

Food categories	Food groups	Mean consumption of nitrate-containing food (g/day)			Mean (mg/day) contribution to the total nitrate exposure			Mean (%) contribution to the total nitrate exposure		
		13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds
	Cabbage and root vegetables	3	4	5	2.08	2.79	3.52	6.2	8.5	12
	Lettuce	6	4	2	7.46	4.53	2.35	22	14	7.9
	Peas	0.3	0.3	0.4	0.01	0.01	0.01	0.0	0.0	0.0
	Rocket	0.03	0.01	0.01	0.14	0.06	0.05	0.4	0.2	0.2
Fruit, berries, nuts, and seeds	Fruit	48	67	110	2.00	2.79	4.61	5.9	8.5	16
Meat and meat products	Meat	44	45	34	1.60	1.64	1.24	4.7	5.0	4.2
Fish, fish products and shellfish	Fish	21	20	22	0.24	0.24	0.26	0.7	0.7	0.9
Milk and dairy	Cheese	20	19	18	0.35	0.34	0.31	1.0	1.0	1.1
Beverages	Beverages	320	182	75	4.08	2.32	0.96	12	7.1	3.2
	Tap water	410	356	342	0.13	0.11	0.11	0.4	0.4	0.4

**Table 3.5.2-8.** Contribution from different food groups to the total nitrite exposure for 13-year-olds (0.30 mg/day), 9-year-olds (0.37 mg/day), and 4-year-olds (0.32) (see Table 3.5.2-1).NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure.

Food categories	Food groups	Mean consumption of nitrite-containing food (g/day)			Mean (mg/day) contribution to the total nitrite exposure			Mean (%) contribution to the total nitrite exposure		
		13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds
Vegetables -dishes and -products	Lettuce	6	4	2	0.01	0.00	0.00	2.4	1.2	0.7
Meat and meat products	Meat, other	5	6	8	0.04	0.05	0.06	13	14	20

Food categories	Food groups	Mean consumption of nitrite-containing food (g/day)			Mean (mg/day) contribution to the total nitrite exposure			Mean (%) contribution to the total nitrite exposure		
		13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds
	Meat, processed	2	3	1	0.04	0.06	0.03	13	16	9.2
	Beef	3	5	3	0.02	0.02	0.01	5.2	6.8	4.4
	Pork	0.1	0.3	-	0.00	0.00	NA	0.5	0.7	NA
	Poultry	1	2	2	0.01	0.02	0.02	3.2	4.3	5.9
	Sausage	8	10	9	0.07	0.10	0.08	23	26	27
Milk and dairy	Cheese	20	19	18	0.11	0.11	0.10	38	30	32
Beverages	Tap water	378	337	321	0.01	0.00	0.00	1.5	1.1	0.0

**Table 3.5.2-9.** Contribution from different food groups to the total mean N-Nitrosamine exposure for 13-year-olds (144), 9-year-olds (144), and 4-year-olds (108) (see Table 3.5.2-1). NA: Food group not included in the exposure assessment due to missing concentration values. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure.

Food categories	Food groups	Mean consumption of N-Nitrosamine - containing food (g/day)			Mean (mg/day) contribution to the total N-Nitrosamine exposure			Mean (%) contribution to the total N-Nitrosamine exposure		
		13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds	13-year-olds	9-year-olds	4-year-olds
Meat and meat products	Meat	32	31	22	116	112	79.1	84	80	80
	Meat, processed	2	3	1	8.58	13.0	6.40	6.8	9.0	5.9
	Sausages	8	11	11	8.71	12.0	11.3	6.4	7.7	9.1
Fish, fish products and shellfish	Fish, processed	2	3	4	3.76	5.44	7.67	3.0	3.8	7.1

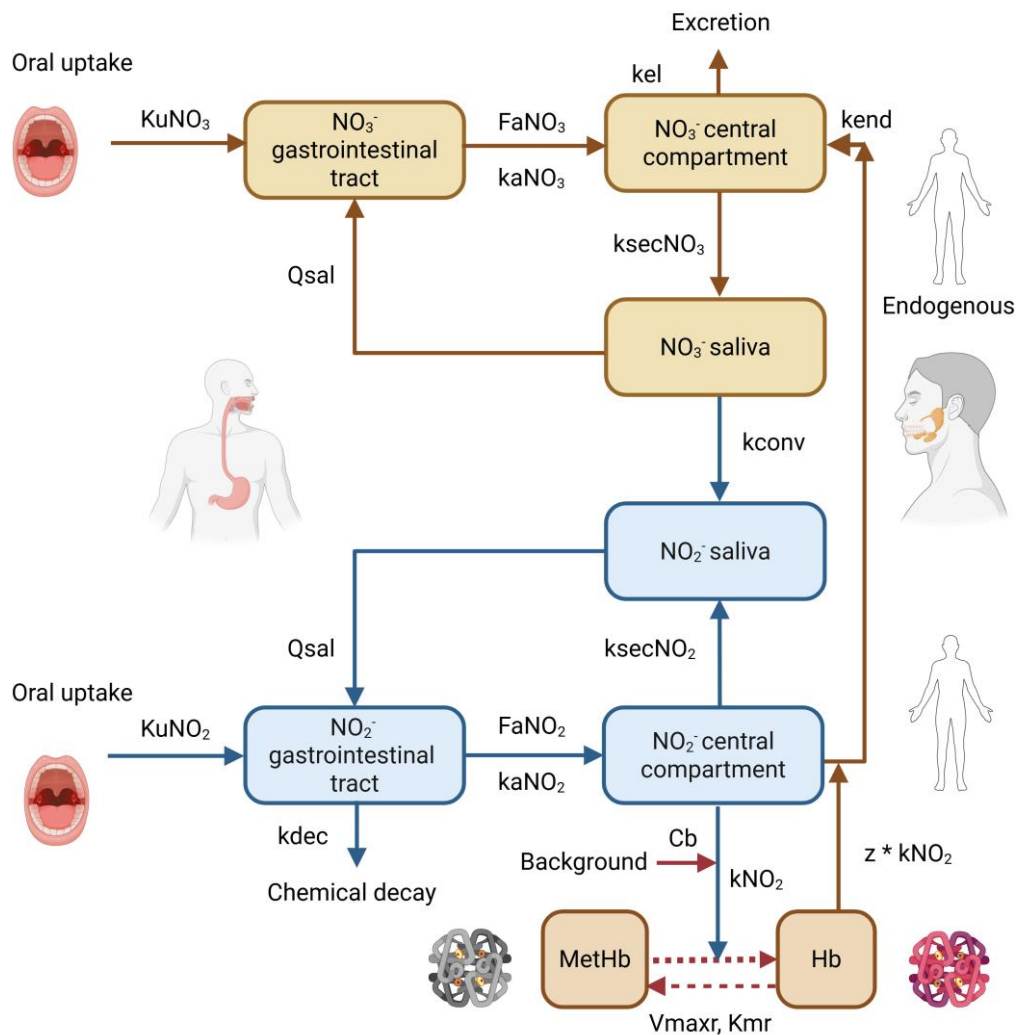
## 3.6 Gastrointestinal exposure

The gastrointestinal exposure, the sum of the external exposure (dietary exposure) and the endogenous formation, was only estimated for adults (18-80 years). We did not identify a model that estimated both endogenous nitrite formation and endogenous *N*-NA formation. However, one dynamic model describing the kinetics of nitrate and nitrite and a static model describing *N*-NA formation, both in humans, were identified from the *ad hoc* search (VKM et al., 2025) and were used to estimate the endogenous formation of nitrite and *N*-NA. The dynamic model and the estimated endogenous formation of nitrite are described in Section 3.6.1. The description and results of the static model for *N*-NA formation are presented in Section 3.6.2.

### 3.6.1 Method for estimating endogenous formation of nitrite

VKM identified a dynamic model for estimating endogenous nitrite formation and methaemoglobin generation (Lin et al., 2020a; Zeilmaker et al., 2010) which is incorporated in the currently described model. This model predicts oxygen transport capacity under different exposure conditions since nitrite in blood, can oxidise the ferrous ion ( $\text{Fe}^{2+}$ ) in oxyhaemoglobin to the ferric ion ( $\text{Fe}^{3+}$ ), resulting in methaemoglobin. This can occur as a result of genetic disposition (enzyme deficiency) or when the normal oxygen-carrying capacity of the blood is reduced due to exposure to oxidising agents (Chen and Nappe, 2026). This model consists of three main compartments: the absorption compartment (gastrointestinal tract), the central compartment (blood), and the saliva compartment. An overview of the model for estimating endogenous nitrite formation and methaemoglobin generation is shown in Figure 3.6.1-1.

The dynamic model by Zeilmaker et al. (2010) was extensively calibrated using human volunteer studies in which fasted participants were administered known quantities of nitrate or nitrite (in drinking water or food, either separately or combined), followed by measurements in blood, saliva, and urine. Lin et al. (2020) further refined and applied this model within a probabilistic framework to estimate gastrointestinal nitrate and nitrite doses from vegetable consumption across age groups. In this way, nitrite exposure in the gastrointestinal tract is modelled by incorporating endogenous nitrite formation from nitrate. The description of the parameters for the model is provided in Appendix 6.



**Figure 3.6.1-1.** Schematic presentation of the human toxicokinetic model for nitrate and nitrite following oral intake. This model structure was modified from Cheng et al. (2021), which was based on Lin et al. (2020a) and the model first published by Zeilmaker et al. (2010).  $KuNO_3$  /  $KuNO_2$ : dietary intake of  $NO_3^-$  /  $NO_2^-$ ;  $FaNO_3$  /  $FaNO_2$ : gastrointestinal absorption fraction for  $NO_3^-$  /  $NO_2^-$ ;  $kaNO_3$  /  $kaNO_2$ : gastrointestinal absorption rate constant for  $NO_3^-$  /  $NO_2^-$ ;  $ksecNO_3$  /  $ksecNO_2$ : blood-to-saliva secretion rate for  $NO_3^-$  /  $NO_2^-$ ;  $Q_{sal}$ : salivary flow rate;  $k_{el}$ : overall elimination rate constant of nitrate from the central compartment;  $k_{end}$ : rate constant of endogenous nitrate synthesis;  $k_{conv}$ : conversion rate of nitrate to nitrite in saliva;  $k_{dec}$ : rate constant of nitrite gastrointestinal decay to other;  $C_b$ : background concentration of haemoglobin oxidation;  $k_{NO_2}$ : nitrite reaction rate constant with haemoglobin;  $z$ : stoichiometric constant for regeneration of nitrate from methaemoglobin;  $V_{maxr}$ : methaemoglobin reductase maximum metabolic rate;  $K_{mr}$ : Michaelis-Menten constant of methaemoglobin reductase activity; Hb: haemoglobin; MetHb: methaemoglobin. Figure created with BioRender (<https://BioRender.com/4v84pep>).

### 3.6.2 Method for estimating endogenous formation of N-NAs

Health Canada proposed a simple static model describing endogenous formation of N-nitrosamines in the gastrointestinal tract (Health Canada, 2013). The model estimates nitrosamine formation as a function of gastric nitrite concentrations, availability of nitrosatable amines, and the nitrosation capacity of the gastric environment. EFSA used this model to

estimate the formation of N-nitrosodimethylamine (NDMA), which was used as a surrogate representing endogenous formation of carcinogenic N-NAs (EFSA et al., 2023).

In the present assessment, a similar modelling framework was adopted to estimate endogenous N-NAs formation. For this purpose, NDMA was selected as a surrogate marker due to its comparatively high carcinogenic potency and the availability of kinetic and toxicological data enabling parameterisation of the model. Minor adaptations to input parameters were introduced to improve physiological and exposure assumptions. The mathematical formulation of the model, parameter selection, and justification for these modifications are provided in Appendix 6.

### 3.6.3 Estimation of endogenous formation of nitrite and N-NAs

Gastrointestinal (GI) exposure to nitrite and N-NAs was modelled using external exposure estimates derived from both OIM and probabilistic assessments of nitrate and nitrite intake. To simulate nitrate concentrations in the GI tract, which we consider to be a relevant compartment, external nitrate exposure was administered to the model as a single oral dose at time zero. Nitrate levels in the GI compartment were then integrated over a 24-hour period using the dynamic model to estimate cumulative exposure of nitrate in the GI tract and the conversion of nitrate to nitrite (endogenous production). The exposure of nitrite in the GI tract was modelled by integrating nitrite formed endogenously via the reduction of ingested nitrate (Table 3.6.3-1). The total nitrite exposure in the GI tract was calculated by adding the endogenous production of nitrite to the dietary nitrite (external) exposure (see Table 3.8-2). The resulting nitrite (output from the dynamic model and external exposure) was subsequently used as input to a static model to estimate endogenous formation of N-NAs in the GI tract (Table 3.6.3-1). The endogenous N-NAs exposure was further added to the external N-NAs exposure from diet to estimate total N-NAs exposure (Table 3.8-2).

**Table 3.6.3-1.** Total GI tract exposure and modelled daily endogenous synthesis of nitrite (mg/kg bw/day) and N-nitrosamines (ng/kg bw per day) in the GI tract, for adults, from mean, P50 and P95 external exposure. (OIM): OIM estimates of external exposure used as input to the model; (P): Probabilistic estimates of external exposure used as input to the model. NA: not included.

Age group	Endogenous synthesis and total gastrointestinal exposure	Nitrite (mg/kg bw/day)			N-nitrosamines (ng/kg bw/day)		
		Mean	P50	P95	Mean	P50	P95
Adults, 18-80 years, Norkost 4 (OIM)	Endogenous synthesis	0.05	0.05	0.09	0.04	0.03	0.11
	Total gastrointestinal exposure (external exposure + endogenous synthesis)	0.07	NA	0.11	7.79	6.16	19.23
Adults, 18-80 years, Norkost 4 (P)	Endogenous synthesis	0.06	0.06	0.11	0.06	0.04	0.18
	Total gastrointestinal exposure (external exposure + endogenous synthesis)	0.08	NA	0.17	8.4	5.78	24

### 3.7 Exposure estimation scenarios based on the Norwegian dietary guidelines

The latest Norwegian national dietary guidelines were published 2024 (Norwegian Directorate of Health, 2024), with seven overall recommendations. With regard to nitrate, nitrite, and N-NAs, the recommendation of a maximum intake of 350 g red meat per week with as little as possible of processed meat, intake of fruit and vegetables with at least 500 to 800 g per day, and consumption of three portions of milk and dairy per day, will have an impact of the exposure. To explore how adherence to these guidelines might influence the population's exposure to nitrate, nitrite, and N-NAs, VKM developed two scenarios in which the dietary guidelines were applied strictly, meaning that the exact amounts stated were used without any adjustments. It should be noted that the dietary guideline scenarios do not represent total dietary intake; they include only the food groups explicitly covered by the guidelines with an amount in grams per day.

The two scenarios represent the lower and upper ends of the intake intervals specified in the guidelines (referred to as "scenario 1" and "scenario 2", respectively), e.g. red meat intake from 0 to 350 g per week and fruit and vegetable intake from 500 to 800 g per day (Table 3.7-1). In scenario 1, the lower recommended amounts from all food groups were used in the exposure estimations, whereas in scenario 2, the upper recommended amounts were applied. The amounts corresponding to those of the guideline food groups that have a single recommended amount (not a range), were used in both scenarios. For poultry, egg and potato, which are food groups without specified quantitative recommendations in the guidelines, the quantities applied were previously determined by VKM in consultation with the Norwegian Directorate of Health (VKM et al., 2024b).

Not all food groups in the dietary guideline scenarios (Table 3.7-1) were designated nitrate, nitrite, and N-NA concentration values. Food groups lacking any of these concentration values were excluded from the exposure estimations. For example, whole grains were included in the exposure estimation for nitrate because concentration values were available, whereas for nitrite and N-NAs no concentration data were available for this food group and it was, therefore, excluded from the exposure estimation. The situation was different for e.g. vegetables, for which extensive concentration data on both nitrate and nitrite were available, and for these food groups the food items selected in the scenarios corresponded to the proportions of foods reported as consumed in Norkost 4 (Myhre et al., 2024).

**Table 3.7-1.** Availability (yes/no) of concentration values for nitrite, nitrate, and *N*-nitrosamines in food groups included in exposure scenarios 1 and 2 representing the lower and upper ends of the intake intervals specified in the recommendations from the national dietary guidelines (Norwegian Directorate of Health, 2024).

Food group	Dietary guideline recommendations	Concentration data availability		
		Nitrate	Nitrite	<i>N</i> -nitrosamines
Vegetables	At least five and preferably eight 100 g-servings per day, including a maximum of 100 g fruit or vegetable juice. Scenario 1: 500 g per day (250 g fruit, 250 g vegetables) Scenario 2: 800 g per day (300 g fruit, 100 g fruit juice, and 400 g vegetables)	Yes	Yes	No
Fruits and berries		Yes	No	No
Juices		Yes	No	No
Whole grains	At least 90 g per day (dry weight). Scenario 1 and scenario 2: 90 g per day.	Yes	No	No
Milk and dairy products	Three portions of milk or dairy products daily (5 dl). Choose variants with less fat. Two servings should consist of milk, fermented milk or yogurt, and one serving of cheese (20 g) Scenario 1 and scenario 2: 350 g per day of milk and yoghurt. Scenario 1 and scenario 2: 20 g per day of cheese	Yes	Yes	Yes
Fish and fish products	From 300 to 450 g prepared fish per week of which. At least 200 grams should be fatty fish. Scenario 1: 43 g per day. Scenario 2: 64 g per day.	Yes	Yes	No
Red meat	Intake should be limited to 350 g prepared meat per week or less. Red meat includes non-processed meat from beef, pork, lamb, and goat. Intake of processed red-meat products should be kept to a minimum. Scenario 1: 0 g per day Scenario 2: 50 g per day	Yes	Yes	Yes
White meat	Intake of processed white-meat products should be kept to a minimum. Scenario 1: 23 g per day Scenario 2: 23 g per day	Yes	Yes	Yes
Legumes	Choose legumes such as beans, lentils, and peas for dinner at least once a week, and as a side dish or spread. Scenario 1 and scenario 2: 41 g per day.	Yes	No	No
Potatoes	Is part of a healthy and varied diet. Not included in the daily recommendation for vegetables.	Yes	No	No

Food group	Dietary guideline recommendations	Concentration data availability		
		Nitrate	Nitrite	N-nitrosamines
	Scenario 1 and scenario 2: 23 g per day.			
Nuts, unsalted	It is recommended to eat 20 to 30 g unsalted nuts daily. Scenario 1: 20 g per day Scenario 2: 30 g per day	No	No	No
Eggs	Egg day can be part of a healthy and varied diet. Scenario 1: 0 g per day Scenario 2: 60 g per day	No	No	No

It should be noted that the energy intake is lower in the scenarios compared to the intake reported in various dietary surveys. The scenarios are based on the specified food group quantities provided in the guidelines. Consequently, only parts of the total diet are included in the dietary guideline scenarios. Scenario 1 covers approximately half of total energy intake, while scenario 2 covers slightly more. To meet the total energy requirements, it is possible to both increase and decrease consumption of foods that contain nitrate, nitrite, and nitrosamines. The total nitrite, nitrate, and *N*-NA exposure from the dietary guideline scenarios 1 and 2 and the mean OIM exposure estimates based on Norkost 4 (18-80 years) is shown in Table 3.7-2. One should not expect that exposure estimates are identical, as they are based on concentration data from comparable food groups that may differ between the scenarios and the Norkost 4 dataset.

**Table 3.7-2.** Total mean energy intake and total mean nitrite, nitrate, and *N*-nitrosamine (*N*-NA) exposure from the dietary guideline scenarios 1 and 2 and the mean OIM exposure estimates based on Norkost 4 (18-80 years, see Table 3.5.1-2).

	Energy (kJ)	Nitrate			Nitrite			N-NA		
		mg/ day	mg/kg bw per day*	mg/kJ per day	mg/day	mg/kg bw per day*	mg/kJ per day	ng/day	ng/kg bw per day*	ng/kJ per day
Scenario 1, dietary guidelines	4669	115	1.49	0.025	0.9	0.011	0.0002	159	2.06	0.034
Scenario 2, dietary guidelines	5976	165	2.14	0.028	1.3	0.018	0.0002	424	5.51	0.071
Mean exposure, Norkost 4	9154	55	0.74	0.006	1.0	0.010	0.0001	589	7.68	0.064

\*For the scenarios, the mean bw from Norkost 4 (77 kg) is used.

**Table 3.7-3.** Contribution from different food groups to total nitrate exposure in the dietary guideline scenarios 1 and 2 (in mg/day and percent). NA: Not included in the scenario; No: No food concentration values available. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure. For Norkost 4, not all reported food groups are included (see Table 3.5.1-4).

Food categories	Food groups	Food group contribution to the total nitrate exposure									
		Scenario 1, total exposure: 115 mg/day			Scenario 2, total exposure: 165 mg/day			Norkost 4, total exposure: 55 mg/day			
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Food groups included in the assessment	Mean consumption g/day	mg/day	%
Grain and grain products	Whole grains	90	1.4	1.2	90	1.4	0.8	Bread and cereals	230	2.7	5.0
Potatoes	Potatoes	65	7.3	6.3	65	7.3	4.4	Potatoes	53	5.8	11
	Vegetables	250	78.2	68	400	123.6	75	Vegetables	178	36	67

Food categories	Food groups	Food group contribution to the total nitrate exposure									
		Scenario 1, total exposure: 115 mg/day			Scenario 2, total exposure: 165 mg/day			Norkost 4, total exposure: 55 mg/day			
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Food groups included in the assessment	Mean consumption g/day	mg/day	%
Vegetables -dishes and -products	Legumes	41	20.5	18	41	20.5	12	Legumes	8	1.5	2.8
Fruit, berries, nuts, and seeds	Fruit, berries and juices	250	6.3	5.5	400	9.0	5.4	Fruit. berries and juices	197	4.1	7.7
	Nuts	25	NA	NA	25	NA	NA	Nuts	7	NA	NA
Meat and meat products	Red meat and meat products, (red meat only in scenario 2)	0	No	No	50	1.47	0.9	Red meat and meat products	104	1.5	2.7
	White meat	23	0.53	0.5	23	0.53	0.3	White meat	41	0.2	0.3
Fish, fish products and shellfish	Fish and fish products	43	0.37	0.3	64	0.81	0.5	Fish. shellfish and products	50	0.4	0.7
Egg	Egg (Scenario 2 only)	0	No	No	60	No	No	Egg	27	No	No
Milk and dairy	Milk and dairy products	370	0.5	0.4	370	0.58	0.4	Milk and dairy products	259	0.7	1.3

**Table 3.7-4.** Contribution from different food groups to total nitrite exposure in dietary guideline scenarios 1 and 2 (in mg/day and percent). NA: Not included in the scenario; No: No food concentration values available. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure. For Norkost 4, not all reported food groups are included (see Table 3.5.1-4).

Food categories	Food groups	Food group contribution to the total nitrite exposure									
		Scenario 1, total exposure: 0.9 mg/day			Scenario 2, total exposure: 1.3 mg/day			Norkost 4, total exposure: 1.0 mg/day			
		Mean consumption g/day	mg/day	%	Mean consumption g/day	mg/day	%	Food groups included in the assessment	Mean consumption g/day	mg/day	%
Grain and grain products	Whole grains	90	No	No	90	No	No	Bread and cereals	NA	NA	NA
Potatoes	Potatoes	65	No	No	65	No	No	Potatoes	NA	NA	NA
Vegetables - dishes and - products	Vegetables	250	0.19	22	400	0.30	24	Vegetables	178	0.1	11
	Legumes	41	No	No	41	No	No	Legumes	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit, berries and juices	250	No	No	400	No	No	Fruit. berries and juices	NA	NA	NA
	Nuts	25	No	No	25	No	No	Nuts	NA	NA	NA
Meat and meat products	Red meat and meat products, (red meat only in scenario 2)	0	No	No	50	0.29	23	Red meat and meat products	104	0.3	27
	White meat	23	0.44	51	23	0.44	35	White meat	41	0.4	42
Fish, fish products and shellfish	Fish and fish products	43	0.09	10	64	0.09	7.1	Fish. shellfish and products	50	0.04	4.0
Egg	Egg (Scenario 2 only)	0	No	No	60	No	No	Egg	No	No	No
Milk and dairy	Milk and dairy products	370	0.15	17	370	0.15	12	Milk and dairy products	259	0.2	15

**Table 3.7-5.** Contribution from different food groups to total N-nitrosamine exposure in dietary guideline scenarios 1 and 2 (in ng/day and percent). NA: Not included in the scenario. The blue-, yellow-, and green-shaded cells represent the largest, second largest and third largest contributing source, respectively, to the total exposure. For Norkost 4, not all reported food groups are included (see Table 3.5.1-4).

Food categories	Food groups	Food group contribution to the total N-nitrosamine exposure									
		Scenario 1, total exposure: 159 ng/day			Scenario 2, total exposure: 424 ng/day			Norkost 4, total exposure: 589 ng/day			
		Mean consumption g/day	ng/day	%	Mean consumption g/day	ng/day	%	Food groups included in the assessment	Mean consumption g/day	ng/day	%
Grain and grain products	Whole grains	90	NA	NA	90	NA	NA	Bread and cereals	NA	NA	NA
Potatoes	Potatoes	65	NA	NA	65	NA	NA	Potatoes	NA	NA	NA
Vegetables -dishes and -products	Vegetables	250	NA	NA	400	NA	NA	Vegetables	NA	NA	NA
	Legumes	41	NA	NA	41	NA	NA	Legumes	NA	NA	NA
Fruit, berries, nuts, and seeds	Fruit, berries	250	NA	NA	300	NA	NA	Fruit, berries and juices	NA	NA	NA
	Juices	0	NA	NA	100	NA	NA	Juices	NA	NA	NA
	Nuts	25	NA	NA	25	NA	NA	Nuts	NA	NA	NA
Meat and meat products	Red meat and meat products (red meat only in scenario 2)	0	No	No	50	266	63	Red meat and meat products	104	347	60
	White meat	23	150	95	23	150	35	White meat and meat products	41	147	25

Food categories	Food groups	Food group contribution to the total N-nitrosamine exposure									
		Scenario 1, total exposure: 159 ng/day			Scenario 2, total exposure: 424 ng/day			Norkost 4, total exposure: 589 ng/day			
		Mean consumption g/day	ng/day	%	Mean consumption g/day	ng/day	%	Food groups included in the assessment	Mean consumption g/day	ng/day	%
Fish, fish products and shellfish	Fish and fish products	43	NA	NA	64	NA	NA	Fish, shellfish and products	50	25	4.3
Egg	Egg (Scenario 2 only)	0	No	No	60	NA	NA	Egg	NA	NA	NA
Milk and dairy	Milk and dairy products	350	NA	NA	350	NA	NA	Cheese	49	21	3.6
	Cheese	20	8.8	5.5	20	8.8	2.1				

### 3.8 Summary of the exposure assessment

Four national dietary surveys representing different age groups: Norkost 4 (adults 18–80 years), Ungkost 3 (children aged 4-, 9-, and 13-year-olds), Småbarnskost 3 (2-year-olds), and Spedkost 3 (1-year-olds) are used in the exposure assessment, and foods consumed were identified using the NutriFoodCalc system (Section 3.3). Food concentration values for nitrate, nitrite, and *N*-NAs were collected from EFSA and NFSA reports, and unpublished concentration values for Norwegian drinking water (Section 3.2). A systematic literature search was conducted to identify studies reporting concentration values for selected *N*-NAs in specific foods on the European market (Section 3.2.1). For further descriptions of the concentration data used for the OIM and probabilistic external exposure assessments, see Sections 3.4.1 and 3.4.2. Both OIM and probabilistic approaches were applied for the dietary exposure assessment (“external exposure”, Section 3.5). The gastrointestinal exposure (Section 3.6) included the modelled endogenous production of nitrite and *N*-NAs in addition to the dietary exposures. Overviews of the estimated total daily exposures are shown in Table 3.8-1 (external exposures per day) and Table 3.8-2 (external and gastrointestinal exposures per kg per day). For the modelled gastrointestinal exposures (Table 3.8-2), the endogenous production of nitrite is higher for nitrite and lower for *N*-NAs than the estimated dietary exposure.

**Table 3.8-1.** Estimated daily mean (P95) external exposure for each age group. OIM: Observed individual means; P: Probabilistic; NA: not included in the exposure assessment.

Age group, dietary survey	Nitrate (mg/day)		Nitrite (mg/day)		<i>N</i> -nitrosamines (ng/day)	
	OIM	P	OIM	P	OIM	P
18-80 years, Norkost 4	55 (140)	105 (328)	1.0 (2.7)	1.6 (5.6)	589 (1463)	631 (1793)
13-year-olds, Ungkost 3	22 (45)	34 (126)	0.8 (1.9)	0.3 (1.4)	393 (856)	144 (628)
9-year-olds, Ungkost 3	19 (36)	33 (119)	0.7 (1.5)	0.4 (1.6)	335 (757)	144 (568)
4-year-olds, Ungkost 3	16 (31)	30 (103)	0.5 (0.9)	0.3 (1.3)	237 (612)	108 (411)
2-year-olds, Småbarnskost 3	17 (32)	NA	0.4 (0.7)	NA	155 (312)	NA
1-year-olds, Spedkost 3	25 (47)	NA	0.4 (0.8)	NA	103 (231)	NA

**Table 3.8-2.** Estimated daily mean (P95) external and gastrointestinal exposure to nitrate (mg/kg bw per day), nitrite (mg/kg bw per day) and *N*-NAs (ng/kg bw per day) using different assessment methods. OIM: Observed individual means; (OIM): OIM external exposure assessment used as input in the model; E: External exposure; GI: Gastrointestinal exposure; M: Modelled; P: Probabilistic; (P): Probabilistic external exposure assessment used as input in the model; NA: not included in the exposure assessment.

Age group, dietary survey	Nitrate (mg/kg bw per day)				Nitrite (mg/kg bw per day)				<i>N</i> -nitrosamines (ng/kg bw per day)			
	E, OIM	E, P	GI, M(OIM)	GI, M(P)	E, OIM	E, P	GI, M(OIM)	GI, M(P)	E, OIM	E, P	GI, M(OIM)	GI, M(P)
<b>18-80 years, Norkost 4</b>	0.74 (1.9)	1.4 (4.5)	0.54 (0.78)	0.78 (1.1)	0.01 (0.04)	0.02 (0.08)	0.07 (0.11)	0.08 (0.17)	7.7 (19)	8.3 (24)	7.8 (19)	8.4 (24)
<b>13-year-olds, Ungkost 3</b>	0.44 (0.95)	0.70 (2.6)	NA	NA	0.02 (0.04)	0.01 (0.03)	NA	NA	8.0 (19)	2.9 (13)	NA	NA
<b>9-year-olds, Ungkost 3</b>	0.60 (1.17)	1.0 (3.7)	NA	NA	0.02 (0.05)	0.01 (0.05)	NA	NA	10 (24)	4.5 (18)	NA	NA
<b>4-year-olds, Ungkost 3</b>	0.93 (1.89)	1.7 (6.1)	NA	NA	0.03 (0.05)	0.02 (0.08)	NA	NA	14 (36)	6.2 (24)	NA	NA
<b>2-year-olds, Småbarnskost 3</b>	1.34 (2.49)	NA	NA	NA	0.03 (0.06)	NA	NA	NA	12 (24)	NA	NA	NA
<b>1-year-olds, Spedkost 3</b>	2.56 (4.79)	NA	NA	NA	0.04 (0.08)	NA	NA	NA	10 (24)	NA	NA	NA

To evaluate how adherence to the 2024 Norwegian dietary guidelines may influence exposure, two intake scenarios including the food groups included in the guidelines were developed (see Section 3.7). The dietary guideline scenarios do not represent total dietary intake. The estimated energy intakes for scenario 1 and scenario 2 were 4669 kJ and 5976 kJ, respectively, whereas the total mean daily energy intake for adults was 9154 kJ according to the dietary survey Norkost 4. When comparing the estimated daily nitrate exposure from the two scenarios with the mean adult exposure estimated from Norkost 4 (see Table 3.7-2), the exposure per kJ was 2 to 3 times higher in the scenarios. For nitrite, the estimated exposures in the two scenarios were about similar to the mean exposure estimated for adults. Nitrite exposure adjusted for energy intake was about 2-fold higher for the scenarios compared to the adult exposure estimated from Norkost 4. For *N*-NAs, the estimated exposure from Norkost 4 was 3.7-fold and 1.4-fold higher than for scenario 1 and scenario 2, respectively. *N*-NA exposure adjusted for energy intake was about half the mean exposure estimated for adults in the scenario 1, whereas it was about similar for scenario 2.

An overview of the food categories with the highest contribution to the total nitrate, nitrite, and *N*-NA exposure, for all age groups and both dietary guideline scenarios, is shown in Tables 3.8-3 to 3.8-5.

To increase the comparability between the OIM and probabilistic external exposure estimates, the contributions from the food groups “Beans”, “Cabbage and root vegetables”, “Lettuce”, “Vegetables, other”, “Peas”, and “Rucola” were combined into the aggregated food group “Vegetables.” Likewise, the contributions from “Alcohol” and “Beer” were combined into the aggregated food group “Alcoholic drinks”, the food groups “Fish” and “Fish, processed” were combined into “Fish and fish products”, and the food groups “Bacon”, “Beef”, “Meat”, “Meat, other”, “Pork”, “Poultry”, “Sausage”, and “Meat, processed” were combined into the aggregated food group “Meat and meat products.”

For the OIM exposure assessment, the food group “Composite dishes and products” included foods for which concentration data were available (EFSA et al., 2017b), but which were not covered by other predefined food groups.

**Table 3.8-3.** Food categories with the three highest contributions to the total external nitrate exposure (in %) depending on OIM or probabilistic estimations for two dietary guideline scenarios and all age groups. NA: Not included in the exposure estimations.

	Highest mean contribution to the total nitrate exposure (%)		Second highest mean contribution to the total nitrate exposure (%)		Third highest mean contribution to the total nitrate exposure (%)	
	OIM	Probabilistic	OIM	Probabilistic	OIM	Probabilistic
Scenario 2, dietary guidelines	Vegetables (75)	NA	Legumes (12)	NA	Fruit, berries and juices (5)	NA
Scenario 1, dietary guidelines	Vegetables (68)	NA	Legumes (18)	NA	Potatoes (6)	NA
18-80 years, Norkost 4	Vegetables (70)	Vegetables (74)	Potatoes (11)	Beverages (10)	Fruit, berries and juices (7)	Meat (5)
13-year-olds, Ungkost 3	Composite dishes (29)	Vegetables (67)	Vegetables (20)	Beverages (12)	Potato (15)	Grain and grain

	Highest mean contribution to the total nitrate exposure (%)		Second highest mean contribution to the total nitrate exposure (%)		Third highest mean contribution to the total nitrate exposure (%)	
	OIM	Probabilistic	OIM	Probabilistic	OIM	Probabilistic
						products (8)
9-year-olds, Ungkost 3	Vegetables (25)	Vegetables (68)	Composite dishes and products (20)	Grain (9)	Fruit and juice (16)	Fruit (8)
4-year-olds, Ungkost 3	Vegetables (29)	Vegetables (66)	Fruit and juice (25)	Fruit (16)	Grain and grain products (14)	Grain and grain products (9)
2-year-olds, Småbarnskost 3	Vegetables (31)	NA	Fruit, berries and juices (22)	NA	Baby food (17)	NA
1-year-olds, Spedkost 3	Baby food (63)	NA	Vegetables (15)	NA	Fruit, berries and juices (7)	NA

**Table 3.8-4.** Food categories with the three highest contributions to the total external nitrite exposure (in %) depending on OIM or probabilistic estimations for two dietary guideline scenarios and all age groups. NA: Not included in the exposure estimations.

	Highest mean contribution to the total nitrite exposure (%)		Second highest mean contribution to the total nitrite exposure (%)		Third highest mean contribution to the total nitrite exposure (%)	
	OIM	Probabilistic	OIM	Probabilistic	OIM	Probabilistic
Scenario 2, dietary guidelines	Meat and meat products (58)	NA	Vegetables (24)	NA	Milk and dairy products (12)	NA
Scenario 1, dietary guidelines	Meat and meat products (51)	NA	Vegetables (22)	NA	Milk and dairy products (17)	NA
18-80 years, Norkost 4	Meat and meat products (69)	Meat and meat products (82)	Milk and dairy products (15)	Cheese (16)	Vegetables (11)	Vegetables (1)
13-year-olds, Ungkost 3	Meat and meat products (37)	Meat and meat products (58)	Milk and dairy products (31)	Cheese (38)	Composite dishes and products (26)	Vegetables (2)
9-year-olds, Ungkost 3	Meat and meat products (41)	Meat and meat products (68)	Milk and dairy products (29)	Cheese (30)	Composite dishes and products (21)	Vegetables (1)
4-year-olds, Ungkost 3	Milk and dairy products (40)	Meat and meat products (66)	Meat and meat products (35)	Cheese (32)	Composite dishes and products (13)	Vegetables (1)

	Highest mean contribution to the total nitrite exposure (%)		Second highest mean contribution to the total nitrite exposure (%)		Third highest mean contribution to the total nitrite exposure (%)	
	OIM	Probabilistic	OIM	Probabilistic	OIM	Probabilistic
<b>2-year-olds, Småbarnskost 3</b>	Milk and dairy products (40)	NA	Meat and meat products (37)	NA	Vegetables (17)	NA
<b>1-year-olds, Spedkost 3</b>	Baby food (47)	NA	Meat and meat products (26)	NA	Milk and dairy products (15)	NA

**Table 3.8-5.** Food categories with the three highest contributions to the total external N-nitrosamine exposure (in %) depending on OIM or probabilistic estimations for two dietary guideline scenarios and all age groups. NA: Not included in the exposure estimations.

	Highest mean contribution to the total N-nitrosamine exposure (%)		Second highest mean contribution to the total N-nitrosamine exposure (%)		Third highest mean contribution to the total N-nitrosamine exposure (%)	
	OIM	Probabilistic	OIM	Probabilistic	OIM	Probabilistic
<b>Scenario 2, dietary guidelines</b>	Meat and meat products (98)	NA	Milk and dairy products (2)	NA	NA	NA
<b>Scenario 1, dietary guidelines</b>	Meat and meat products (95)	NA	Milk and dairy products (5)	NA	NA	NA
<b>18-80 years, Norkost 4</b>	Meat and meat products (85)	Meat and meat products (81)	Beer and spirits (7)	Alcoholic drinks, including beer (15)	Fish, shellfish and products (4)	Fish and fish products (4)
<b>13-year-olds, Ungkost 3</b>	Meat and meat products (58)	Meat and meat products (97)	Composite dishes and products (39)	Fish and fish products (3)	Milk and dairy products (3)	NA
<b>9-year-olds, Ungkost 3</b>	Meat and meat products (67)	Meat and meat products (96)	Composite dishes and products (28)	Fish and fish products (4)	Milk and dairy products (3)	NA
<b>4-year-olds, Ungkost 3</b>	Meat and meat products (75)	Meat and meat products (93)	Composite dishes and products (16)	Fish and fish products (7)	Fish and fish products (4)	NA
<b>2-year-olds, Småbarnskost 3</b>	Meat and meat products (83)	NA	Fish, shellfish and products (13)	NA	Milk and dairy products (4)	NA
<b>1-year-olds, Spedkost 3</b>	Meat and meat	NA	Fish, shellfish and products (14)	NA	Milk and dairy	NA

	Highest mean contribution to the total N-nitrosamine exposure (%)		Second highest mean contribution to the total N-nitrosamine exposure (%)		Third highest mean contribution to the total N-nitrosamine exposure (%)	
	OIM	Probabilistic	OIM	Probabilistic	OIM	Probabilistic
	products (83)				products (3)	

### 3.8.1 Main food sources nitrite exposure

As shown in Table 3.8-4, the main contributors to the mean external (dietary) nitrite exposure were “Meat and meat products” (all age groups included, 36-82%), “Milk and dairy products” (all age groups included except 1-year-olds, 15-43%), “Vegetables” (all age groups included, 1-26%), “Composite dishes and products” (4-, 9- and 13-year-olds, 10-22%), and “Baby food” (1-year-olds, 35%).

#### “Meat and meat products”

Seven food groups were included in the probabilistic exposure estimation of nitrite. An overview of the results from the probabilistic approach is provided in Table 3.8.1-1.

For adults, poultry was the primary contributor. This group includes all poultry, except for poultry contained within composite dishes. Concentration values for both “Poultry” and “Preserved poultry” (EFSA et al., 2017b) were used for the exposure assessment, and these values were found to be of a similar magnitude. Beef and pork were the second largest contributors. Beef included all meat from cattle except for salted and smoked meat, and pork included all pork except for salted and smoked meat and pork in composite dishes. Only concentration values for “Beef meat” (EFSA et al., 2017b) were utilised during the exposure assessment. Although the concentration in “Beef, dried” was of the same magnitude as “Beef meat”, all “Beef, dried” samples (n=20) were left-censored and were therefore excluded from the exposure assessment. Concentration values for both “Pork / piglet meat” and “Pork, dried” (EFSA et al., 2017b) were utilised during the exposure assessment, and these values were found to be of a similar magnitude. It should be noted that 88.3% of the “Pork, dried” samples (n=120) were left-censored. The daily consumption of poultry and beef was similar, whereas the daily consumption of pork was half their amount.

For 4-, 9- and 13-year-olds, sausage was the main contributor. This group included all sausages. The other main contributors were “Meat, other” which included all meat that is not pork, poultry, sausage or processed meat, and “Meat, processed” which included salted and smoked meat.

Nitrite is permitted to be added to “Preserved poultry”, “Beef, dried”, “Pork, dried”, “Sausage”, and to food items within the food groups “Meat, other” and “Meat, processed”. Nitrite is not permitted to be added to “Poultry», «Beef meat», or «Pork/piglet meat”.

**Table 3.8.1-1.** Percent contribution of “Meat and meat products” to the total external exposure based on the probabilistic approach (Section 3.5.2). The remaining nitrite exposure comes from other food groups.

Food group	% contribution (daily consumption in g/day)			
	Adults (18-80 years),	13-year-olds	9-year-olds	4-year-olds
Meat, other	7.9 (15)	13 (5)	14 (6)	20 (8)
Meat, processed	11 (9)	13 (2)	16 (3)	9.2 (1)
Beef	13 (42)	5.2 (3)	6.8 (5)	4.4 (3)
Pork	13 (19)	0.5 (<1)	0.7 (<1)	NA
Poultry	29 (38)	3.2 (1)	4.3 (2)	5.9 (1)
Sausage	7.3 (13)	23 (8)	26 (10)	27 (9)

### “Milk and dairy products”

The exposure assessment for this group mainly included cheese. The mean daily consumption was 44 g/day for adults and 20, 19, and 18 g/day for 13-, 9-, and 4-year-olds, respectively. Concentration values were taken from EFSA et al. (2017b), and 24% were left-censored.

### “Vegetables”

“Lettuce” was the only food group included for the probabilistic exposure estimation. This food group included all leafy vegetables (e.g. spinach, Romaine lettuce, lettuce), excluding rocket. The mean daily consumption was 17 g/day for adults and 6, 4, and 2 g/day for 13-, 9-, and 4-year-olds, respectively. The percent of left-censored samples ranged from 65 to 100. The nitrite content is naturally occurring.

### “Composite dishes”

This food group was included in the OIM approach to capture foods for which concentration data were available (EFSA et al., 2017b), but which were not covered by other predefined food groups (Table 3.5.1-1).

### “Baby food”

This food group was included applying the OIM approach for the dietary surveys Sped- and Småbarnskost 3 and was a main contributor to the total mean nitrite exposure for 1-year-olds. Concentration values were taken from EFSA et al. (2017b) and includes “Cereal-based food for infants and young children”, “Food for infants and small children”, and “Ready-to-eat meal for infants and young children”. The percent of left-censored samples ranged from 60 to 72. We have limited information on these food items such as ingredients in the dishes and cannot determine the nitrate source.

## 3.8.2 Main food sources N-NA exposure

As shown in Table 3.8-5, the main contributors to the mean external N-NA exposure were “Meat and meat products” (all age groups, 58-97%), “Composite dishes and products” (4-, 9-, and 13-year-olds, 28-39%), “Fish and fish products” (all age groups, 3-14%), “Beer and spirits” (adults, 8-15%), and “Milk and dairy products” (all age groups included adults, 2-4%).

### “Meat and meat products”

The probabilistic external N-NA exposure estimation included the food groups “Meat, other”, “Meat, processed”, “Bacon”, and “Sausage” (Table 3.8.2-1). The food group “Meat, other”

included all meat other than pork, poultry, sausage or processed meat. The food group “Meat, processed” included salted and smoked meat. The food group “Bacon”, which was only included in the probabilistic external exposure estimation for adults, included bacon only, whereas other salted and smoked meat are excluded. The food group “Sausage” included all sausages.

**Table 3.8.2-1.** Percent contribution to the total N-NA exposure to the mean “Meat and meat products” external exposure. Daily consumption from food groups (g/day) in parentheses. Values are estimated by the probabilistic approach (Section 3.5.2). The remaining N-NA exposure comes from other food groups. NA: Not included in the exposure estimation.

Food group	Adults (18-80 years)	13-year-olds	9-year-olds	4-year-olds
	% contribution (daily consumption in g/day)			
Meat, other	71 (124)	84 (32)	79 (31)	76 (22)
Meat, processed	6.6 (9)	6.3 (2)	9.0 (3)	6.1 (1)
Bacon	1.2 (3)	NA	NA	NA
Sausage	2.1 (13)	6.4 (8)	8.4 (11)	11 (11)

#### “Fish and fish products”

Concentration values were available for processed or preserved fish and smoked fish, and it should be noted that the percentage left-censored samples were above 95.

#### “Beer and spirits”

The number of samples analysed for spirits was 36, and none of these were left-censored. More than 2000 samples of beer were analysed and the percentage of left-censored samples ranged from 43 to 99.

#### “Composite dishes and products”

The food group “Composite dishes and products” in the database AE14 used for 4-, 9- and 13-year-olds contain more composite dishes as recipes than the database AE18 and N4. The composite dishes that contribute most to N-NA exposure are pizza, taco, and soups. The recipes will therefore reflect concentration values described in the other food groups relative to the amount of the given ingredient.

#### “Milk and dairy products”

Only cheese was included, and the concentration value used was identified from the literature search (Section 3.2.1, Mavelle et al., 1991).

## 4 Risk characterisation

In this risk characterisation, estimated dietary and gastrointestinal exposures to nitrite are compared with the established ADI for nitrite of 0.07 mg/kg bw per day, while estimated dietary and gastrointestinal exposures to N-NAs are compared to the BMDL<sub>10</sub> of 10 µg/kg bw per day. The risk characterisation was performed for the estimated median (P50), mean, and high consumer (P95) exposures.

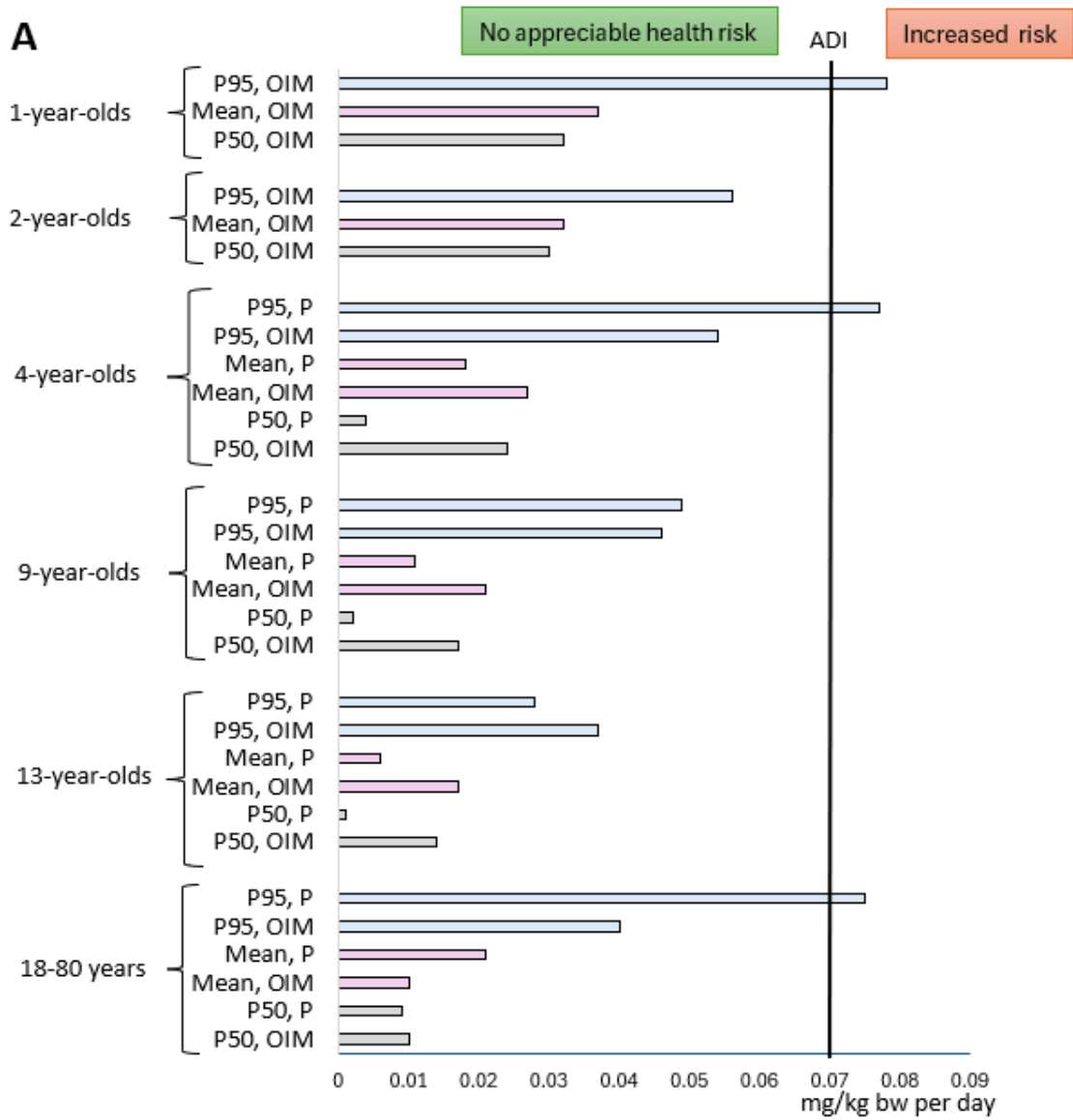
A separate risk characterisation for nitrate has not been performed. The critical health effect associated with nitrate exposure (methaemoglobin formation) is mediated via its conversion to nitrite, which is the toxicologically active compound driving the effect. The metabolic conversion of nitrate to nitrite is accounted for in the estimation of the total gastrointestinal nitrite exposure (Section 3.6). Consequently, VKM deemed a separate risk characterisation for nitrate to be unnecessary. The total gastrointestinal nitrite exposure was only estimated for adults, but we anticipate a conversion of nitrate to nitrite in the same range for all age groups.

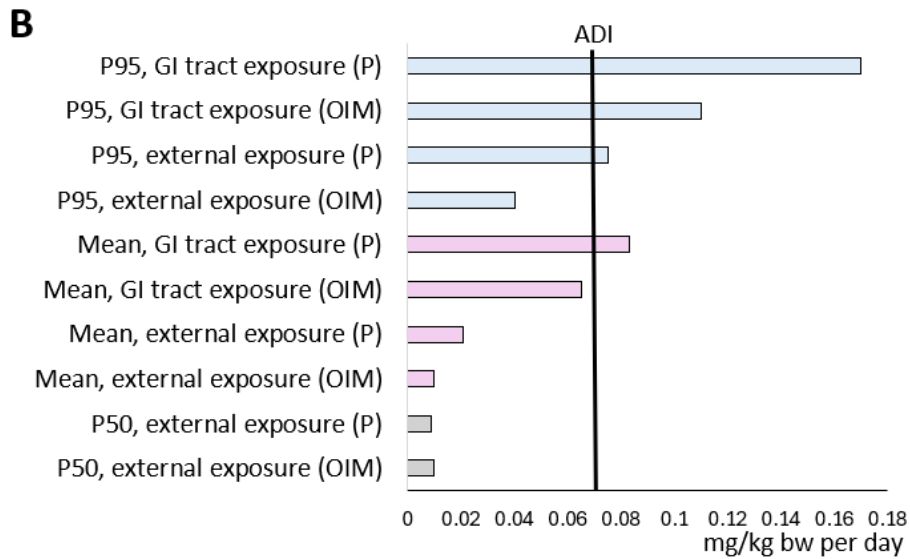
The endogenous formation of nitrite from dietary nitrate was modelled and included in the estimated gastrointestinal exposure to nitrite for adults. VKM considers that comparison of total gastrointestinal nitrite exposure (the estimated dietary nitrite exposure combined with the modelled endogenous nitrite formed from nitrate) with the ADI for nitrite is the most appropriate approach, as it reflects the total gastrointestinal exposure to the toxicologically relevant compound. For other age groups, endogenous formation of nitrite from dietary nitrate has not been modelled. Consequently, the exposure estimates for these groups reflect dietary intake of nitrite only and do not include the additional contribution from nitrate-derived endogenous nitrite. These exposure estimates therefore represent an underestimation of total internal nitrite exposure.

For the risk characterisation of nitrite, the ADI was used as the reference value. When the exposure is lower than the ADI, the risk for negative health effects is low. For all age groups, the estimated median (P50) and mean nitrite exposures were below the ADI, except for the gastrointestinal exposure estimate for adults (18-80 years) based on the external exposure estimate obtained probabilistically. For the high consumers (P95), one or more of the exposure estimates for 1- and 4-year-olds and adults were above the ADI, whereas the estimated exposures for the age groups 2-, 9- and 13-year-olds were below the ADI (Figure 4-1, Appendix 7 Table A7-1).

Having captured uncertainties arising from the different approaches applied for exposure estimation, and assuming that the true exposure lies within this range, VKM considers the risk for negative health effects related to P50 and mean nitrite exposure to be low for all age groups. This also applies to 9- and 13-year-old high consumers. For adult high consumers, three of the four approaches to estimate the exposure resulted in exposures exceeding the ADI, and it cannot be ruled out that such exposures may lead to negative health effects. For 1- and 4-year-olds, the estimated exposures (0.078 and 0.077 mg/kg bw per day, respectively) are also higher than the ADI of 0.07 mg/kg bw per day. Furthermore, the endogenous contribution to gastrointestinal exposure was not estimated for these age groups, and this would have been higher than the external exposure alone (Table 4-1). Therefore, it cannot be

ruled out that the exposure among 1-, and 4-year-old high consumers may result in negative health effects.



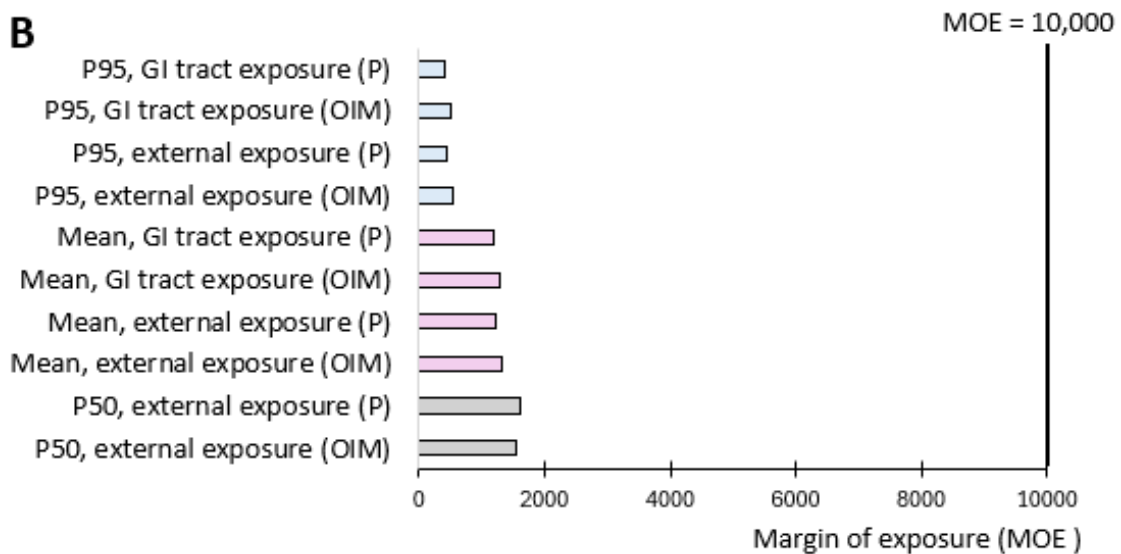
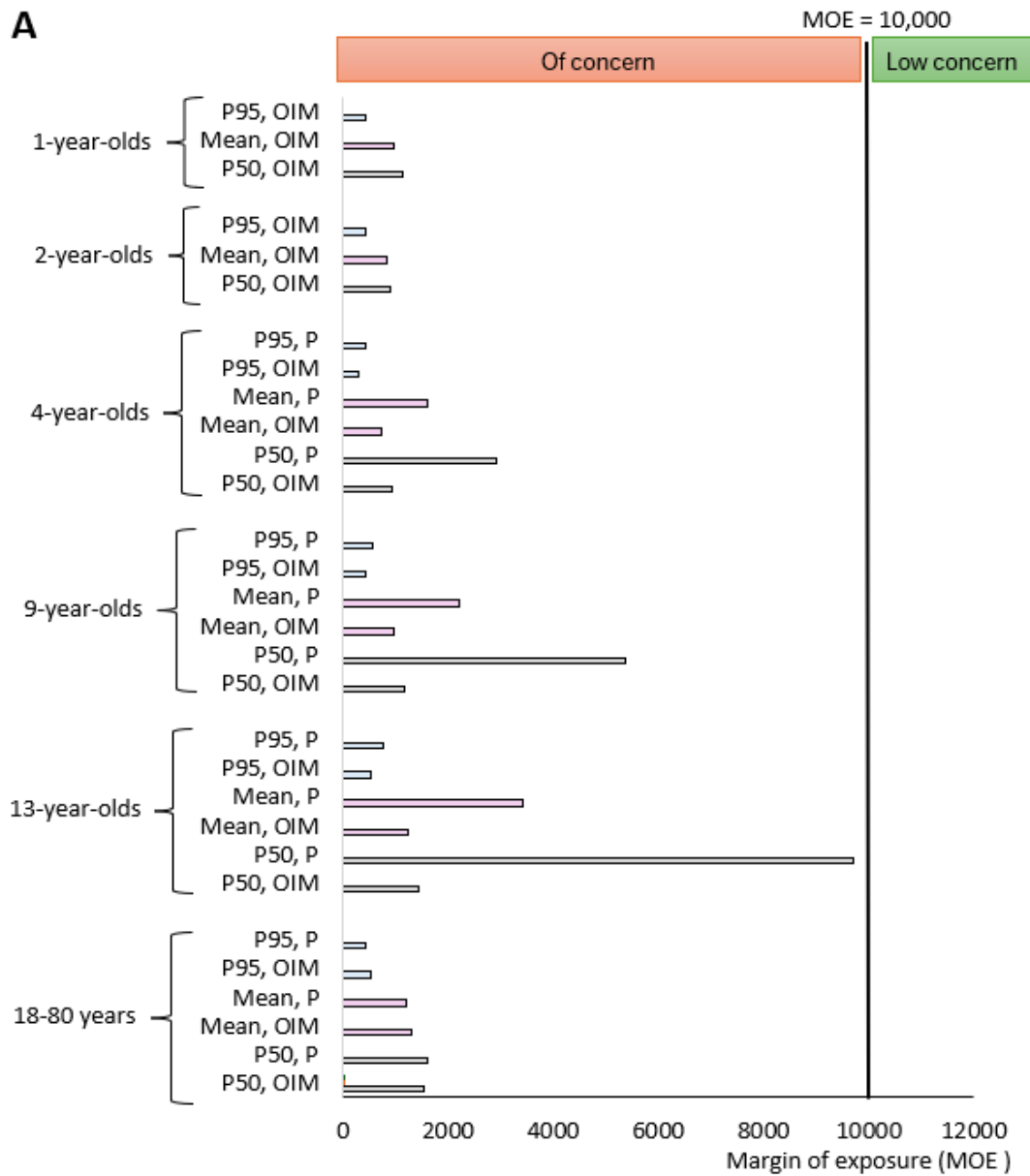


**Figure 4-1.** Estimated nitrite exposures (mg/kg bw per day) for different age groups, based on data from Tables 3.5.1-3, 3.5.2-3, and 3.8-2. The solid vertical line indicates the ADI of 0.07 mg/kg bw per day, above which exposure may result in negative health effects. A. Estimated external exposure. B. Adults only, estimated external exposure and modelled GI tract exposure. Abbreviations: OIM: Observed individual means; (OIM): OIM exposure estimates used as model input; GI: gastrointestinal exposure (external exposure combined with endogenous synthesis); P: probabilistic; (P): probabilistic exposure estimates used as model input. P50 (median): grey bars; Mean: pink bars; P95 (high consumers): blue bars.

**Table 4-1.** Comparison of dietary (external) exposure and combined dietary exposure with endogenous nitrite production (total exposure) expressed as below or above the ADI (0.07 mg/kg bw per day) for the age groups included in the risk characterisation. Combined exposure (to obtain “GI-tract exposure”) was estimated for adults only. For the other age groups and exposure levels (median, mean and P95), the fold-factors 3 and 5 obtained from the ratio of combined exposure to dietary exposure for adults, were used to predict the combined exposure termed “predicted combined”. Exposures are obtained either from observed individual mean (OIM) or probabilistic methods, and the highest exposure values are used in the assessment independent of method. N.A.: not applicable. The green- and red-shaded cells represent exposures below and above the ADI, respectively.

Age groups	Dietary exposure			Combined: Dietary + endogenous exposure			Predicted combined: Dietary + endogenous exposure. Factor 3			Predicted combined: Dietary + endogenous exposure. Factor 5			
	Median	Mean	P95	Median	Mean	P95	Median	Mean	P95	Median	Mean	P95	
1-year-olds	below	below	above	Not estimated			above	above	above	above	above	above	
2-year-olds	below	below	below				above	above	above	above	above	above	above
4-year-olds	below	below	above				above	above	above	above	above	above	above
9-year-olds	below	below	below				below	below	above	above	above	above	above
13-year-year olds	below	below	below				below	below	above	above	above	above	above
18-80-year-olds	below	below	above	Not estimated	above	above	below	Not estimated		below	N.A.		

For the risk characterisation of total *N*-NAs, the BMDL<sub>10</sub> was used as reference point, and the margin of exposure (MOE) was calculated (see glossary). The MOE is defined as the ratio between a toxicological reference point, such as the BMDL<sub>10</sub>, and the estimated human exposure to a particular substance. MOE is calculated by dividing the toxicological reference point with the estimated exposure. This ratio expresses the margin between the current level of exposure to the levels that are known to cause adverse effects. An MOE above 10,000 is typically considered to be of low public health concern for genotoxic and carcinogenic substances (EFSA, 2005; EFSA, 2012). The calculated MOEs are shown in Figure 4-2 and in Appendix 7 (Table A7-2). All MOEs were below 10,000. The true exposure lies within the range of exposure estimates below 10,000, which indicates a concern for negative health effects for all age groups for the median (P50), mean and P95 exposures.



**Figure 4-2.** Margin of exposure (MOE) between the estimated N-nitrosamines exposures and the BMDL<sub>10</sub> for N-nitrosamines. To be of low concern, the MOE for genotoxic and carcinogenic substances should be greater than 10,000. A. MOEs based on external exposure. B. Adults only, MOEs based on estimated external exposure and modelled GI tract exposure. The solid vertical line represents the MOE of 10,000. Abbreviations: OIM: Observed individual means; (OIM): OIM exposure estimates used as model input; GI: gastrointestinal exposure (external exposure combined with endogenous synthesis); P: probabilistic; (P): probabilistic exposure estimates used as model input. P50 (median): grey bars; Mean: pink bars; P95 (high consumers): blue bars.

## 5 Uncertainties

Included elements are limited to those identified by VKM as potentially introducing substantial uncertainty to the overall conclusions.

### Safety reference point

The safety reference point for *N*-NAs established by EFSA was used in this assessment (EFSA et al., 2023). We did not conduct literature searches for new primary studies to determine whether the BMDL<sub>10</sub> for *N*-NAs should be updated.

### Safety reference value

The safety reference value established by EFSA was used in this assessment (EFSA et al., 2017b). According to the protocol, VKM planned to assess whether the ADI of nitrite should be updated based on relevant SRs. No SRs fulfilling the eligibility criteria were identified; therefore, VKM could not perform this assessment. If new studies indicate that the reference values applied for nitrite and *N*-NAs are either insufficiently protective or overly conservative, this will introduce uncertainty into the risk characterisation.

### Exposure estimates

Most available concentration data refer to raw materials rather than ready-to-eat foods. Concentration values measured in raw materials may not accurately reflect the concentrations in consumed foods, as processing steps such as storage, heating, and handling can either increase or decrease levels of nitrate, nitrite, and *N*-NAs. These limitations contribute to uncertainty in the estimated exposures and, consequently, in the risk characterisation. A general determination of direction of the uncertainty (over- or underestimation of the total exposure) cannot be made because it will depend on several factors such as the substance in question and different types of processing.

### Concentration values

Insufficient concentration data reduce the representativeness of the input values and may also lead to incomplete coverage of relevant food groups. Some foods in addition to food supplements containing either nitrate, nitrite, or *N*-NAs, separately or combined, were not included in the external exposure estimates due to missing concentration values. This may have led to an underestimation of the total exposure.

### External exposure estimation, probabilistic approach

The probabilistic external exposure estimation is based on well-known principles of using distributions rather than single point estimates in the calculation. However, this is a new and explorative method in the use of the national dietary surveys, since these databases are not constructed for probabilistic approaches. The method depends on correctly extracting food items based on the description connected to the NFC code in the databases. Automatically extracting food items based on the description of the food item code in R using a text string can lead to inclusion of food items not belonging to a particular food group and/or not detecting food items that should have been included. This has been controlled to the best of our ability by checking the food codes included in the food groups.

The codes for the food items across the dietary surveys (e.g. Norkost4 and Ungkost3) are not identical, and the same code in the two surveys can have deviating descriptions. Also, the Norkost 4 survey has more detailed descriptions of the diet, and thereby more food codes for some food groups. This might lead to variations in the food items included in the calculations for the different age group from the surveys and adds to the uncertainty in correctly extracting the food items to the major food groups. However, we have carefully checked that no major food items are missing or misplaced.

For the probabilistic approach, food items within each food group were initially organised using the EFSA FoodEX2 grouping as a starting point. Subsequently, items were combined to create groups with concentration values of similar magnitude. As a result, some groups became quite broad, while others were very specific. This strategy was implemented to prevent a single food item with exceptionally high concentrations from skewing the calculations for other, similar products with lower levels. By doing so, we aimed to achieve a more representative exposure assessment for each food group. There were no strict criteria for this grouping (see Section 3.4) which was performed by expert judgement, and this could lead to some uncertainties in the exposure assessment.

For the N-NAs we only had mean values (LB, MB and UB) for the concentration data, and we made summary data from the mean (MB) of the included food items. Therefore, the distributions used for the probabilistic exposure estimate will have a truncated tail and underestimate the true high exposure.

#### **Gastrointestinal exposure estimation**

The uncertainty in the modelling of endogenous formation of nitrite from nitrate is primarily related to the parameter coefficients, as the model was calibrated using concentration measurements from the central compartment (i.e. blood) rather than from the gastrointestinal (GI) compartment. Although both nitrate and nitrite concentrations are well fitted to external validation data, we cannot exclude the possibility that the predicted GI concentrations do not fully reflect the true *in vivo* values. This limitation should be considered when interpreting the modelling results. Furthermore, the modelling was performed assuming a single time-point consumption scenario. This simplification may influence the predicted kinetics and should therefore be taken into account when evaluating the results.

Endogenous formation of carcinogenic N-NAs was estimated using a simplified chemical-kinetics model. While formation is theoretically possible, there is no quantitative *in vivo* evidence at typical dietary exposures. This means that both over- and underestimation are possible. Major uncertainties include the size of the nitrosatable amine pool (DMA, endogenous DMA, and other secondary amines), nitrosation kinetics (K<sub>am</sub>, pH, and dietary inhibitors, Figure A6-6; Figure A6-7), gastric nitrite concentration, and gastric residence time. Also, the model assumes homogeneous mixing and constant concentrations, ignoring depletion of reactants and local variations in the stomach. To account for physiological variability, plausible ranges were applied for key parameters, but the resulting estimates should still be interpreted as approximate indicators rather than precise predictions. The model assumes homogeneous mixing within the gastric compartment, constant concentrations during the reaction period, and no depletion of reactants. It therefore provides

a theoretical upper-bound estimate of potential formation rather than a prediction of *actual in vivo* concentrations. Results should be interpreted accordingly as screening-level estimates suitable for comparative risk assessment.

## 6 Discussion and conclusions

### 6.1 Hazard identification and characterisation

Given the extensive body of research published over many years in this field, VKM considered it both appropriate and efficient to base its assessment on whether the acceptable daily intake (ADI) for nitrite should be updated based on existing systematic reviews (SRs) rather than performing a systematic review of primary studies. However, the lack of numerical exposure data in the identified SRs through the literature search precluded a summary of ranges expressed as nitrite per kg body weight per day associated with adverse health outcomes. Consequently, the request from the NFSA to evaluate the necessity for an ADI update could not be completed within the timeframe.

Requests for missing numerical data were sent to authors of SRs. The authors who responded (Appendix 2, Table A2-3) reported data already available in papers or supplementary material. A limitation was that several exposure estimates were reported in categorical formats (e.g. quartiles or tertiles) without providing the corresponding numerical ranges. As a result, the magnitude of exposure within each category could not be determined. Examination of the primary studies included in the SRs confirmed that the data were originally reported in the same categorical format, rather than as continuous numerical values. Thus, data reporting can preclude efficient use of previous research results. Broader evidence shows that sharing of underlying data and analytical materials occurs in only about seven percent of SRs, based on an analysis of 300 SRs included in an overview of patterns of reporting and sharing of review data in systematic reviews (Nguyen 2022). The reuse of data in SRs and overviews of SRs can be enhanced by using data repositories, as suggested by (Wilkinson et al., 2016).

Several SRs reported estimates of association based on pooled data from cohort studies and case-control studies, introducing a high risk of bias in the methods used to synthesise the data. Methodological concerns regarding the comprehensiveness, rigour, transparency, and objectivity of systematic reviews, such as insufficient reporting of study characteristics and errors in effect estimate calculations or data synthesis, have been documented by Uttley et al. (2023).

While overviews of SRs may be a reasonable, time- and cost-effective way of addressing and making use of a broader scope of the literature than in individual systematic reviews, the utility of overviews is contingent on the type and amount of outcome data presented (Cochrane handbook, Chapter V). The two main ways of analysing and presenting outcome data from systematic reviews suggested in the Cochrane Handbook (Higgins et al., 2024) are by summarising pooled effect estimates or by re-analysis of relevant data. Re-analysis of data from cohort and case-control studies separately could have been feasible in our overview of SRs but was not possible due to insufficient reporting of data.

## 6.2 Food concentration values for nitrate, nitrite, and N-NAs

### 6.2.1 Sources for food concentration values

A pragmatic approach was adopted in this assessment: EFSA reports and Norwegian data sources (see Section 3.2) formed the basis for identification of concentration values for the exposure assessment. A fully systematic literature search was conducted only for N-nitrosamines (N-NAs) concentration values for food categories for which EFSA reported lack of data (EFSA et al., 2023). This implies that relevant data may have been missed; however, given the time-consuming nature of the task, VKM considered this prioritisation appropriate.

### 6.2.2 Literature search for N-NA food concentration values

The search was conducted without time restrictions. However, analytical methods have evolved considerably over time, and applying a date limit might have been beneficial to avoid assessing studies using outdated or less suitable analytical methods. We also recognised that it might have been more appropriate to search for all food categories rather than limiting the search to those missing in EFSA's dataset, to capture more recent analyses. Such additional analyses could have been useful e.g. for examining temporal trends in concentrations potentially linked to changes in food additive use or food processing practices.

### 6.2.3 Raw materials vs ready-to-eat foods

Many of the available food concentration values were retrieved from analyses on raw ingredients rather than ready-to-eat foods or in foods intended for further heating. To better understand how concentrations might change during e.g. storage, food preparation and processing, a model predicting net change in concentration for different food items and processing conditions was developed. The model estimated potential changes in levels of nitrate, nitrite, and N-NAs across different food types under various conditions, providing a basis for approximating levels in consumed foods.

Using the model (Section 3.2.2), the net changes in nitrate and nitrite concentrations for sausage (pan-fried and air-fried) and cured meat (refrigerated) were minimal, expressed as absolute differences ( $\Delta$ ), defined as the difference between post-processing and initial concentrations (Table 6.2.3-1). Small decreases in nitrate were accompanied by corresponding increases in nitrite ( $\Delta \approx +0.05$  to  $+0.19$  mg/kg), consistent with low conversion efficiencies (PNC). In contrast, the conversion of nitrite to N-NAs resulted in measurable increases in N-NA concentrations ( $\Delta \approx +0.0007$  to  $+0.013$  mg/kg), despite similarly low PNC values (Table 6.2.3-2). These increases occurred without appreciable changes in nitrite concentrations, reflecting the substantially higher initial levels of nitrite relative to N-NAs. This pattern is consistent with precursor-driven formation and is coherently represented in the model structure, where conversion is proportional to the available precursor. Consequently, conversion of a small fraction of a relatively large nitrite pool can result in detectable increases in compounds present at low baseline concentrations. The magnitude of the predicted N-NA increases is

within the range of reported occurrence data for comparable products, supporting the role of nitrite as a precursor for N-NA formation.

For vegetables, nitrate-to-nitrite conversion varied markedly with storage conditions (Table 6.2.3-3). In rocket stored at ambient temperature, a substantial decrease in nitrate corresponded to a large increase in nitrite ( $\Delta \approx +1532$  mg/kg), consistent with a relatively high PNC. In celery, ambient storage resulted in smaller but variable changes ( $\Delta$  nitrate  $\approx -18$  mg/kg;  $\Delta$  nitrite  $\approx +18$  mg/kg), whereas frozen storage led to negligible changes ( $\Delta \approx \pm 0.6$  mg/kg) and very low PNC.

In general, cooking resulted in larger concentration changes than storage in meat products, while in vegetables, ambient storage led to greater conversion than refrigerated or frozen conditions. This is consistent with the estimated PNC values and precursor concentrations, is captured by the model and is highlighting variability in concentration changes under processing conditions.

**Table 6.2.3-1.** Predicted changes in nitrate and nitrite concentrations in meat following storage (refrigeration) and cooking ( $\Delta$ , mg/kg).

Food / Process	Initial concentration (mg/kg)		Change from initial concentration ( $\Delta$ , mg/kg, 95% CI)	
	Nitrate	Nitrite	$\Delta$ Nitrate	$\Delta$ Nitrite
Sausage/Pan fry	60.60	9.79	-0.19 (-0.65 to -0.06)	+0.19 (0.06 to 0.65)
Sausage/Air fry	60.60	9.79	-0.06 (-0.07 to -0.05)	+0.06 (0.05 to 0.07)
Cured meat/Stored	54.50	0.55	-0.05 (-0.08 to -0.03)	+0.05 (0.03 to 0.08)

**Table 6.2.3-2.** Predicted changes in nitrite and N-nitrosamine concentrations in meat following storage (refrigeration) and cooking ( $\Delta$ , mg/kg).

Food / Process	Initial concentration (mg/kg)		Change from initial concentration ( $\Delta$ , mg/kg, 95% CI)	
	Nitrite	N-NAs	$\Delta$ Nitrite	$\Delta$ N-NAs
Sausage/Air fry	9.79	0.0034	$\sim 0$ (negligible)	+0.0130 (0.0096 to 0.0234)
Cured meat/Stir-fry	0.55	0.0411	$\sim 0$ (negligible)	+0.00072 (0.00049 to 0.00434)
Bacon/Stored	9.30	0.0006	$\sim 0$ (negligible)	+0.0116 (0.0068 to 0.0126)

**Table 6.2.3-3.** Predicted changes in nitrate and nitrite concentrations in vegetables following storage (ambient, refrigeration, frozen) ( $\Delta$ , mg/kg).

Food / Process	Initial concentration (mg/kg)		Change from initial concentration ( $\Delta$ , mg/kg, 95% CI)	
	Nitrate	Nitrite	$\Delta$ Nitrate	$\Delta$ Nitrite
Rocket/Ambient	3816	0.06	-1531.81 (-2379.45 to -3.85)	+1531.81 (3.85 to 2379.45)
Celery/Ambient	579	0.06	-18.14 (-156.75 to -0.57)	+18.14 (0.57 to 156.75)
Celery/Frozen	619	0.06	-0.62 (-0.92 to -0.61)	+0.62 (0.61 to 0.92)

### 6.3 Estimation of dietary (external) exposure

The OIM approach is considered an appropriate method because it averages exposure over repeated observation days at the individual level, which is assumed to be the case for chronic exposure. The exposure of each substance is calculated for each person as following: for each food item, a central estimate of the concentration (e.g. a mean or median) is multiplied with the corresponding mean consumed amount per registration day. In the applied probabilistic approach, all available concentration values were included and used to describe the full distribution of concentrations of a food item or category rather than selecting a single point value (such as a mean or median). In each simulation, concentration values were drawn from the underlying distribution (log-normal), sampling the concentration around the central estimates more often than from the tail of the distribution. Depending on the allocation of the food concentration data to food items or categories, the two methods should give mean and medians in the same range. This was the case for all three substances, with less than two-fold difference between the methods. The estimated high exposure (P95) for the two methods will potentially show larger differences since the probabilistic method use all concentrations including potential outliers. This is shown with up to a 4-fold difference between the P95 for all age groups in Ungkost3.

The OIM approach applied in this risk assessment uses a detailed method for assigning concentration data to individual food items by selecting one or a few representative central estimate concentration values. In contrast, the probabilistic approach groups concentration data into broader food categories (Section 3.4). Both approaches depend on the quality and availability of input data and require expert judgement, particularly when grouping foods or applying concentration values from similar items in the absence of direct measurements (EPA, 2023).

A comparison of the estimated daily exposures obtained from the two approaches (Table 6.3-1) shows that for all substances the exposure estimates were within the same magnitude despite the methodological differences. For example, the OIM approach may be more restrictive when imputing concentration values for “similar” food items, compared with the broader food groupings used in the probabilistic approach. Another factor is that the OIM method gave priority to Norwegian concentration data, whereas the probabilistic approach relied on EFSA data. Given that Norwegian data typically included 10–100 analyses of a food item, while EFSA’s datasets ranged from 100 to several thousand, including Norwegian data in the probabilistic analysis would not substantially affect the distribution.

Overall, VKM consider the OIM and the probabilistic approaches to be relevant and complementary for chronic exposure assessment. Together, they provide a broad perspective on external exposure, which strengthens the assessment by defining a plausible range within which the true exposures are likely to occur.

**Table 6.3-1.** The relative magnitude of the mean probabilistic daily exposure estimates compared with the mean OIM daily exposure estimates (mg/day for nitrate and nitrite, ng/day for N-nitrosamines) (see Section 3.5). D: OIM; P: probabilistic.

Age group, name of survey	Nitrate		Nitrite		N-nitrosamines	
	D	P	D	P	D	P
18- to 80-year-olds, Norkost 4	1	1.9	1	1.6	1	1.1
13-year-olds, Ungkost 3	1	0.2	1	0.4	1	0.5
9-year-olds, Ungkost 3	1	1.9	1	0.8	1	0.4
4-year-olds, Ungkost 3	1	2.0	1	0.8	1	0.5

The endogen production of nitrite from nitrate was not estimated for the children and adolescents due to limited resources in rebuilding the model to different age groups. Therefore, the total nitrite exposure in the GI tract is not available for these age groups. Knowing that the endogen production of nitrite contributes equally or more than the external exposure for adults, the exposure estimates for children and adolescents are clearly underestimated.

## 6.4 Modelling of gastrointestinal exposure

The comparison between external and gastrointestinal nitrite exposure estimates for adults (18–80 years) reveals that endogenous synthesis plays a substantial role, meaning that gastrointestinal exposure may be considerably higher than that predicted from external sources alone. This contrasts with exposure to N-NAs, for which endogenous formation contributes proportionally less, and external sources remain the more dominant driver of total gastrointestinal exposure. This also contradicts studies reporting that endogenous formation of N-NAs may be equal to or greater than exogenous exposure (Eisenbrand et al., 2024; Tricker, 1997). The reasons for this apparent contradiction are not known, but it could reflect limitations of the static model (Section 3.6.2).

The choice of parameter values influences the exposure estimates for endogenous nitrite formation from nitrate generated by the dynamic model (Section 3.6.1). These parameters were previously curated from the literature and calibrated against measured concentrations of nitrate and nitrite in blood. As such, they provided a sound starting point for our estimations with a well calibrated model for central compartment and saliva.

The gastrointestinal (GI) tract was of relevance to our research question since it is the primary site for endogenous N-NA formation. However, the model was not specifically calibrated using

stomach content data, and therefore a certain degree of uncertainty is expected when modelling the GI compartment and the part that is relevant for nitrosation (i.e. stomach).

A strength of the used dynamic model lies in its ability to explicitly describe the fluxes of nitrate and nitrite between compartments, as well as the *in vivo* conversion of nitrate to nitrite, which is the nitrosating agent. The modelling results indicate that both nitrate and nitrite are rapidly absorbed from the GI tract and distributed to the central compartment.

No dynamic models for endogenous formation of *N*-NAs were available. There is therefore a need to develop such models to better understand their toxicokinetic. In the absence of a dynamic framework, we applied a static model for endogenous *N*-NA formation based on a model from Health Canada (2013).

Due to the lack of substance specific models, NDMA was used as a surrogate to estimate endogenous *N*-NA formation. The choice of using NDMA as a surrogate to represent the potential formation of all carcinogenic *N*-NAs was a pragmatic approach to estimate total endogenous *N*-NA formation without modelling each compound individually. To address variability, we conducted a sensitivity analysis (Appendix 6), in which the nitrosation rate constant, substrate concentration (DMA), and residence time were varied. This analysis revealed that, under stochastic conditions, in addition to nitrite concentration, the substrate concentration and residence time are the rate-limiting factors governing nitrosamine formation rather than the nitrosation rate constant.

While other secondary amines can also form nitrosamines, applying NDMA in combination with ranges for amine concentration, nitrosation rate constant, and gastric residence time captured the potential variability and magnitude of *N*-NA formation.

## 6.5 Exposure scenarios based on the Norwegian dietary guidelines

To allow for comparison of the exposure estimates of nitrate, nitrite, and nitrosamines from the dietary surveys with those from the dietary guideline scenarios, exposure estimates were adjusted for energy intake. Comparing the estimated exposure in mg/day from the two scenarios with the mean exposure estimated from Norkost 4 (adults 18–80 years), nitrate exposure was higher in both scenarios, nitrite was slightly lower in scenario 1 and higher in scenario 2, and *N*-NA exposure were lower in both scenarios. For the same comparison adjusted for energy (kJ), nitrate and nitrite exposures were higher in both scenarios, whereas exposure to *N*-NAs was lower in the Scenario 1 and about similar in the Scenario 2 (see Table 3.7-2). The higher nitrate exposure estimated from the scenarios were primarily driven by the higher recommended intake of vegetables compared to the intake in Norkost 4, whereas the nitrite exposure in the scenarios primarily was driven by meat and meat products (white meat only in scenario 1). For the exposure estimates based on the dietary surveys, the primary contributor to nitrate exposure was vegetables in all age groups except 1-year-olds, and the primary contributor to nitrite exposure was meat for most age groups. Vegetables contribute more to both scenarios because the meat intake is lower compared to the mean intake reported in the dietary surveys. Meat was the dominant contributor to *N*-NAs in both scenarios as well as in most age groups estimated from the dietary surveys.

Fish products and foods such as composite dishes, sauces, spices, snacks, and meal replacers were included in the exposure estimates based on the dietary surveys, but not in the scenarios. This is because concentration values were only available for processed fish, and processed fish, composite dishes, sauces, spices, snacks, and meal replacers were not included in the dietary guideline. Due to insufficient concentration data for nitrate, nitrite and N-NAs for food groups important to the exposure scenarios, it was not possible to evaluate whether the higher nitrite exposure based on the dietary guideline scenarios compared to that from the Norkost 4 dietary survey would pose a health risk to the Norwegian population.

## 6.6 Risk characterisation

Across all age groups, at high level exposure to N-NAs (P95) the MOEs ranged from 281 to 775, and at the mean and median (P50) exposures, MOE ranged from 730 to 9709 (Figure 4-2A and Table A7-2).

The results of the risk characterisation in the current risk assessment are in accordance with EFSA (2023). EFSA concluded that MOEs for the high exposure to N-NAs was highly likely to be less than 10,000 in all age groups, which raises a health concern. EFSA's estimated MOEs for maximum (across surveys) mean exposure ranged from 644 to 8608 and the MOEs for the maximum high (P95) exposure ranged from 215 to 3546. These values are of the same magnitude as the MOEs estimated in this risk assessment, demonstrating that the Norwegian population are exposed at the same level as people in other European countries. EFSA concluded that the MOE for N-NAs at the P95 exposure is highly likely (98–100% certain) to be less than 10,000 for all age groups, which raises a health concern. EFSA also quantified the endogenous formation of N-NAs from the theoretical amount of NDMA upon digestion of nitrite at the level of the ADI (0.07 mg/kg bw per day). Applying several conservative assumptions, the EFSA Panel estimated that the margin of exposure (MOE) would be much greater than 10,000 and that the exposure would therefore be of low concern (EFSA, 2005; EFSA Scientific Committee, 2012a). This is also in accordance with our endogenous modelling on N-NAs, for which we found that the contribution of endogenous production of N-NAs was approximately 80-fold lower than the external exposure. It should be noted that the endogenous modelling of N-NAs is highly uncertain.

In the current assessment, the mean external nitrite exposure was below ADI of 0.07 mg/kg bw per day (EFSA et al., (2017b) for all age groups. However, for adults, ADI was exceeded (0.083 mg/kg bw per day) when the mean estimation included the endogenous production of nitrite from nitrate, i.e. the modelled GI tract exposure, and the estimation was probabilistic (Fig. 4-1 B). For high consumers (P95) in the age groups 1- and 4-year-olds and adults, external exposure estimates exceeded ADI (ranging from 0.075 to 0.078 mg/kg bw per day). The GI tract exposure was also above ADI (0.11 to 0.17 mg/kg bw per day) for adult high consumers (P95). The endogenous production of nitrite from nitrate that was modelled only for adults was estimated to be 3- to 5-fold higher than the mean external exposure. Therefore, it is likely that we underestimate the nitrite exposure in all other age groups than adults. Assuming a 5-fold contribution also for children and adolescents, the total GI tract exposure would have exceeded the ADI for 1-, 2-, 4-, 9- and 13-year-olds, as shown in Table 4-1.

In the risk assessment of nitrite by EFSA (2017), the mean exposure of nitrite from all sources was estimated to be in the range of 0.03 to 0.15 mg/kg bw per day, while the high exposure ranged from 0.05 to 0.2 mg/kg bw per day. This is in the same range as estimated in the current risk assessment taking endogenous production of nitrite into account.

## 6.7 Sources for nitrite and N-NA exposures

### 6.7.1 Endogenous production of nitrite and N-NA

The estimated external exposure to N-NAs was the dominating source of the total exposure compared to the modelled endogenous synthesis (Table 6.7.1-1), which was associated with major uncertainties (see Section 5 Uncertainties). This is opposite to Eisenbrand et al. (2024) who reported that the endogenous production of e.g. NDMA is higher than the dietary exposure. The information on the major food sources that contributed to the dietary exposure is discussed in Section 6.7.2.

**Table 6.7.1-1.** Comparison of the mean external N-NA exposure estimates and the mean modelled N-NA endogenous synthesis. OIM: Observed individual means; P: probabilistic.

Exposure type	Mean (ng/kg bw per day)	The relative magnitude of the endogenous synthesis compared with the estimated external exposure
External exposure, OIM	7.68	1
Endogenous synthesis (OIM external exposure used as input)	0.04	0.005
External exposure, P	8.26	1
Endogenous synthesis (probabilistic external exposure used as input)	0.06	0.007

The modelled endogenous synthesis of nitrite from nitrate was 3- to 5-fold higher than the estimated external exposure (Table 6.7.1-2). This is in accordance with van den Brand et al. (2020), who reported that endogenous formation of nitrite from nitrate represents an important contributor to total nitrite exposure. An overview of the major food sources that contributed to nitrate and nitrite dietary exposure is discussed in Section 6.7.2.

**Table 6.7.1-2.** Comparison of the mean external nitrite exposure estimates and the mean modelled nitrite endogenous synthesis. OIM: Observed individual means; P: probabilistic.

Exposure type	Mean (mg/kg bw per day)	The relative magnitude of the endogenous synthesis compared with the estimated external exposure
External exposure, OIM	0.01	1
Endogenous synthesis (OIM external exposure used as input)	0.05	5
External exposure, P	0.02	1
Endogenous synthesis (probabilistic external exposure used as input)	0.06	3

### 6.7.2 Main food sources

#### **Nitrate**

Nitrate is naturally occurring in plant-based foods. Nitrate exposure is largely driven by plant-based foods, with vegetables representing the dominant source across all age groups with the exception of 1-year-olds. The endogenous synthesis of nitrite from nitrate was up to five-fold higher than the estimated nitrite exposure from food (external exposure).

#### **Nitrite**

Nitrite exposure has significant contributions from both animal products and plant-based foods. Meat and meat products represent a major contributor in all age groups, although patterns differ by age. In adults, the main contributors include poultry, beef, and pork, while in children, sausages and other processed meat products dominate. Nitrite is permitted as an additive in several processed meat products. The available concentration values for beef, pork and poultry permitted added and not permitted added nitrite were similar, thus nitrite concentrations are of a similar magnitude in meat categories where nitrite addition is permitted and where it is not permitted. According to EFSA, both the transfer of nitrate and nitrite from feed to food products of animal origin and the nitrate- and nitrite-mediated formation of *N*-NAs and their transfer into these products are likely to be negligible according to the conclusion by EFSA based on a limited data set (EFSA et al., 2020). Thus, VKM cannot identify the source(s) for nitrite in beef, pork and poultry, for which added nitrite is not permitted.

Other important contributors to nitrite exposure include milk and dairy products (mainly cheese) and vegetables, particularly leafy vegetables. Whereas nitrite is naturally occurring in vegetables, it is uncertain whether the nitrite source for cheese is added nitrite, natural occurrence, or both, due to lack of information. Similarly, due to limited information, VKM cannot identify the source(s) of nitrite ion composite dishes and baby food.

#### ***N*-NAs**

*N*-NA exposure is mainly driven by meat sources (all age groups, 58-97%), and the main contributing meat source was the category “meat, other” which includes all meat other than pork, poultry, sausage or processed (salted and smoked) meat. This indicates that *N*-NA occurrence is widespread across meat types. It is likely that the *N*-NA is formed from nitrite, but VKM cannot identify the source(s) of nitrite, whether it was added or naturally occurring.

A major limitation of the present assessment is the lack of concentration values for several food groups identified as important contributors to nitrite exposure, particularly vegetables. This has limited the ability to assess whether, and to what extent, these food groups contribute to dietary exposure to *N*-NAs. Supplementary Materials 1 include some concentration values for grilled vegetables, demonstrating that *N*-NA can also form in such products. However, due to the limited availability and representativeness of these data, vegetables were not included in the *N*-NA exposure assessment.

## 6.8 Conclusions

The conclusions are based on the available data on concentrations of nitrate, nitrite and *N*-nitrosamines (*N*-NAs) in a wide range of food groups including drinking water (Section 3.2) as well as consumption data from Norwegian national dietary surveys for different age groups (Section 3.3). VKM has estimated the dietary exposure to nitrite and nitrosamines (“external exposure”) and the exposure in the gastrointestinal tract, “GI exposure”, i.e. the total exposure consisting of dietary exposure and endogenous synthesis. To characterise the risk related to the nitrite exposure, the estimated exposures were compared with the ADI. To characterise the level of concern related to *N*-NA exposure, the MOEs were calculated using the BMDL<sub>10</sub>. The critical health effects for which the ADI for nitrite and the BMDL<sub>10</sub> for *N*-NA exposure are derived are methaemoglobinaemia and cancer, respectively. Methaemoglobinaemia is an adverse but relatively rare and potentially reversible condition which can occur after acute exposure leading to reduced transport of oxygen in the blood. Since the ADI for nitrite includes a safety margin of 100, this effect is unlikely to occur after a small exceedance of ADI. DNA-interactive substances such as *N*-NAs have no safe levels and can induce chronic DNA damage which can accumulate with time and may lead to cancer. An MOE greater than 10,000 is considered to be of low concern for human health due to exposure to genotoxic and carcinogenic chemicals (EFSA, 2005; EFSA, 2012).

For nitrite, VKM concludes on the risk:

- High (P95) dietary nitrite exposure in age groups 1- and 4-year-olds as well as adults was above ADI. This exposure level may pose a health risk (methaemoglobinaemia) for individuals in these age groups.
- Median and mean dietary nitrite exposure was below the ADI for all age groups assessed, and the high (P95) exposure was below ADI for 2-, 9- and 13-year-olds. Thus, the risk for negative health effects (methaemoglobinaemia) is low for the stated age groups at these exposure levels.
- Both mean and high (P95) GI tract exposure exceeded ADI for adults. The added endogenous nitrite to the dietary exposure contributed up to 5-fold to the GI tract exposure in adults. GI tract exposure was not estimated for other age groups. Predicting a similar contribution of endogenous nitrite for age groups below 18 years as adults, VKM cannot exclude that the mean, median, and high GI tract exposure for all age groups can exceed the ADI. These exposure levels may therefore pose a health risk (methaemoglobinaemia) for all age groups included.
- Nitrite estimations by EFSA (2017b) and VKM were in the same range taking endogenous production of nitrite in the current assessment into account.

For *N*-NAs, VKM concludes on the risk:

- The MOE values for the median, mean, and high dietary *N*-NA exposures were below 10,000 for the age groups included in the assessment. This indicates a concern for negative health effects (cancer) in individuals in these age groups.
- The MOE values for the GI tract exposure of *N*-NA in adults were in the same range as those for dietary exposure, indicating that the endogenous production of *N*-NAs was

negligible. The MOE values estimated by EFSA and VKM are of the same magnitude, demonstrating that the Norwegian population are exposed at the same level as people in other European countries.

The endogenous synthesis of nitrite from nitrate was up to five-fold higher than the estimated nitrite exposure from food (external exposure). Vegetables were the main contributing food group to mean nitrate exposure for all age groups except 1-year-olds, for which baby food contributed the most. For nitrite, meat and meat products were the main contributors for all age groups except 4-year-olds, for which milk and dairy products were the main contributors. Meat and meat products were also the main contributors to the mean total N-NA exposure for all age groups included.

Generally, both the OIM and probabilistic approaches resulted in dietary exposure estimates of the same order of magnitude. The endogenous production of nitrite was 3-5 times higher than exposure estimated from external sources alone. This contrasts with N-NAs exposure, for which endogenous formation contributes less to the total, and external sources remain the more dominant driver of total gastrointestinal exposure. It should be noted that concentration values of nitrate, nitrite, and N-NAs were not identified for all relevant food groups, including food supplements (see Section 7 Data gaps).

Both scenarios from the dietary guideline recommendations (Norwegian Directorate of Health, 2024) would have led to higher exposure to nitrate and nitrite than the mean exposure estimated from the dietary survey Norkost 4 (adults 18–80 years), adjusted for energy intake. In contrast, exposure to N-NAs would have been lower in scenario 1 (the lowest guidance amounts) and similar in scenario 2 (the highest guidance amounts) compared to Norkost 4. The concentration data were scarce for nitrate, nitrite and N-NAs in food groups of importance to the exposure scenarios. This shortcoming precluded evaluation of whether the potentially higher nitrite exposure estimated in the dietary intake scenarios may pose a health risk to the Norwegian population when following the national dietary recommendations.

The request from the NFSA to assess whether the ADI for nitrite should be updated could not be addressed as planned. The assessment was intended to be based on evidence from systematic reviews; however, none of the available reviews fulfilled the predefined inclusion criteria. This was due to methodological shortcomings, including insufficient reporting of exposure estimates associated with observed adverse health outcomes in the Norwegian dietary context.

## 7 Data gaps

### Systematic reviews on hazard nitrite

Full reporting of exact numerical values for nitrite intake were lacking in the systematic reviews identified by the literature search, preventing assessment of whether the ADI for nitrite should be updated. Pooling of data from case-control studies and cohort studies in several of the meta analyses introduced a high risk of bias in the data synthesis methods.

### **Nitrate**

Concentration values for nitrate were mainly available for vegetables, but some data were available also for other food groups. The main food groups with limited data were dairy products (except cheese), fish, meat, egg, bread and cereals, and sugar and sweets.

### **Nitrite**

Concentration values for nitrite were mainly available for meat and processed meat, and data were limited for all other food groups including fish, vegetables, bread and cereals, beverages, and dairy products.

### **N-NAs**

Concentration values for N-NAs were mainly available for meat and processed meat and fish. There was little or no data on all other food groups, such as (unprocessed) fish, vegetables, dairy products, fruit and berries, bread and cereals and beverages.

### **Concentration values for ready-to-eat foods**

Because concentration values measured in raw materials may not accurately represent the concentrations in foods as consumed, concentration data for ready-to-eat foods are needed to perform realistic exposure assessments.

## Appendix 1. Model for prediction of nitrate, nitrite, and N-nitrosamines in ready-to-eat foods

A linear mixed-effects (LME) modelling framework was applied to paired before–after concentration measurements of nitrate ( $\text{NO}_3^-$ ), nitrite ( $\text{NO}_2^-$ ) and N-nitrosamines (N-NAs) in ready-to-eat food products subjected to storage and heat-treatment conditions. Predicted net change (PNC) fractions were estimated for the  $\text{NO}_3^- \rightarrow \text{NO}_2^-$  and  $\text{NO}_2^- \rightarrow \text{NAs}$  chemical changes using processing-related fixed effects including process type, temperature and processing time and random effects accounting for variability between food products. The PNC fractions quantify the relative concentration changes due to processing with respect to the initial precursor concentrations and therefore infer, directly from paired experimental data, how processing may update measured concentrations within foods. Bootstrap-derived confidence intervals (CIs) were subsequently estimated for the PNC fractions and used to evaluate updated processed concentrations and their potential impact on more realistic exposure-assessments of  $\text{NO}_3^-$ ,  $\text{NO}_2^-$  and N-NAs containing inside food products.

### Data and purpose of statistical analysis

Paired before–after concentration measurements of  $\text{NO}_3^-$ ,  $\text{NO}_2^-$  and N-NAs in vegetables, fish and meat products subjected to storage and heat-treatment conditions were used from the published literature in Chih et al. (2025) and Clayton-Cuch et al. (2025). An example is given here how data were organised from Chih et al. (2025), while the data from Clayton-Cuch et al. (2025) were organised similarly. They reported median concentrations and corresponding ranges of  $\text{NO}_3^-$  (mg/kg wet weight),  $\text{NO}_2^-$  (mg/kg wet weight), and total N-NAs ( $\mu\text{g}/\text{kg}$  wet weight) across 135 food samples. They report food types of (e.g. ham, bacon, sausage, cured meat, poultry, dried or salted fish), processing status (non-cooked versus cooked), specific cooking method, and storage duration of 0, 3, and 7 days at 4 °C. There is also information on precise cooking protocols (pan-frying, roasting, air-frying, stir-frying, reheating), target temperatures (e.g. 180, 200, and 220 °C) and cooking times (2, 5, and 25 min), post-cooking storage and reheating cycles, and analytical handling procedures. Further, data were organised in a paired structure, where the initial (“before processing”) and processed (“after processing”) concentrations for the same food item and processing condition were linked within each observation. The units of the quantities in the data were standardised, before used as input for statistical modelling. The final curated dataset consists of 34 rows, each representing a unique combination of food product, processing type, storage duration, and cooking condition.

This paired structuring of the data enabled the estimation of processing-induced concentration changes within foods while accounting for differences in initial precursor concentrations across food products and processing conditions. The objective of the statistical analysis is to quantify processing-induced concentration changes in  $\text{NO}_3^-$ ,  $\text{NO}_2^-$  and N-NAs and evaluate how this concentration updates may influence exposure assessment. The first seven lines of this dataset are shown in Table A1-1.

**Table A1-1.** The first seven lines of the curated dataset used in the statistical modelling.

pair_id	product_id_before	product_id_after	ProcessType	NO3_before	NO3_after	NO2_before	NO2_after	NAs_before	NAs_after	Time_h	Temp_C
Bacon_Stored_0_to_3	Bacon_Stored	Bacon_Stored	Storage	50.1	83.2	9.3	5.83	0.000552	0.00136	72	4
Bacon_Stored_0_to_7	Bacon_Stored	Bacon_Stored	Storage	50.1	86.9	9.3	5.97	0.000552	0.00136	168	4
Ham_0_cook	Ham_Stored	Ham_Pan-fry	Cooking	59.9	59	2.35	2.99	0.000977	0.00138	0.0195	200
Ham_3_cook	Ham_Stored	Ham_Pan-fry	Cooking	51.3	60.5	5.12	6.19	0.000612	0.0016	0.0195	200
Ham_7_cook	Ham_Stored	Ham_Pan-fry	Cooking	48.5	68.4	5.66	6.25	0.00118	0.00132	0.0195	200
Sausage_0_cook	Sausage_Stored	Sausage_Roast	Cooking	60.6	52.4	9.79	9.7	0.00341	0.00256	0.416667	180
Sausage_3_cook	Sausage_Stored	Sausage_Roast	Cooking	67.7	61.8	3.98	3.48	0.00302	0.00156	0.416667	180

The PNC fractions estimated using the LME modelling framework and the organised dataset can be used to modify the concentration values measured in ready-to-eat food items to make the exposure assessments more realistic by predicting the concentration values in consumed foods after storage and heat treatment.

### **Linear Mixed Effects (LME) Model: Nitrate → Predicted Net Change Fractions**

Predicted net change concentration fractions were estimated using linear mixed-effects (LME) models applied to paired before–after concentration measurements. The modelling framework was implemented for both the apparent NO<sub>3</sub>→NO<sub>2</sub>– and NO<sub>2</sub>→N-NAs pathways. In both cases, the fractions quantified the relative increase in product concentration after processing with respect to the corresponding precursor concentration available prior to, and during, processing.

The PNC fractions were modelled using the following equation:

$$\text{logit}(\text{PNC}_{ij}) = \beta_0 + \beta_1(\text{ProcessType}) + \beta_2(\log\text{Time}) + \beta_3(\text{ProcessType} \times \log\text{Time}) + \beta_4(\text{Temperature}) + b_i + \epsilon_{ij} \text{ (Eq.1)}$$

where  $\beta$  terms represent fixed effects associated with processing conditions, processing duration and temperature,  $b_i$  represents the random intercept for food product  $i$ , and  $\epsilon_{ij}$  represents residual variability. Logit transformation was applied to stabilise the bounded proxy fractions between 0 and 1.

Bootstrap resampling ( $B = 500$  iterations) was subsequently applied to estimate uncertainty distributions and derive 95% confidence intervals (CIs) for the average food- and process-specific PNC fractions. At each bootstrap iteration, paired observations were resampled with replacement, the LME model was refitted and updated average PNC estimates were recalculated. The resulting bootstrap distributions were used to derive empirical 2.5th and 97.5th percentile confidence intervals for the estimated PNC fractions.

#### *Conversion Fraction Definition*

The apparent nitrate-to-nitrite predicted net change (PNC) fraction was defined as:

$$\text{PNC}_{\text{NO}_3 \rightarrow \text{NO}_2} = \max(0, \text{NO}_2_{\text{after}} - \text{NO}_2_{\text{before}}) / \text{NO}_3_{\text{before}} \text{ (Eq. 2)}$$

where the increase in nitrite concentration after processing was expressed relative to the initial nitrate concentration available prior to processing.

Similarly, the nitrite-to- N-NAs fraction was defined as:

$$\text{PNC}_{\text{NO}_2 \rightarrow \text{NAs}} = \max(0, \text{NAs}_{\text{after}} - \text{NAs}_{\text{before}}) / (\text{NO}_2_{\text{before}} + \max(0, \text{NO}_2_{\text{after}} - \text{NO}_2_{\text{before}})) \text{ (Eq. 3)}$$

where the denominator represented the available nitrite precursor pool before and during processing.

The use of  $\max(0, \dots)$  constrained the proxy fractions to positive concentration increases associated with apparent processing-induced formation.

Updated processed concentrations were subsequently estimated as:

Nitrite processed  $\approx$  initial nitrate  $\times$  PNC + initial nitrite (Eq. 4)

Nitrate processed  $\approx$  initial nitrate  $\times$  (1 – PNC) (Eq. 5)

NAs processed  $\approx$  initial nitrite  $\times$  PNC + initial NAs (Eq. 6)

The estimated PNC fractions therefore quantified relative processing-induced concentration updates inferred directly from paired experimental observations.

### *Diagnostics of the LME model*

The LME model converged successfully and showed stable estimation of both fixed and random effects. Residual variability (SD = 0.92) remained within the same order of magnitude as the between-product random-effect variability (SD = 1.11), indicating that the model captured a meaningful proportion of the product-specific concentration variability. Standardised residuals were centred around zero without evidence of substantial instability, supporting overall model fit for the relatively limited paired dataset used in the analysis. Validation was performed by comparing experimentally measured after-processing concentrations with the model-predicted processed concentrations and their corresponding bootstrap-derived confidence intervals. To account for expected analytical uncertainty and inherent processing variability, limited validation tolerances were applied without modifying the fitted models or estimated PNC fractions. Tolerances of  $\pm 5\%$  of the initial precursor concentration were applied for refrigerated and frozen conditions, and  $\pm 10\%$  for ambient storage or thermal processing conditions, reflecting the higher variability associated with these processing scenarios. These tolerance ranges are small and are considered justified within the context of food chemical measurements and enable a more realistic validation of the predicted concentration ranges against the experimentally observed after-processing measurements.

### *Conversion fractions output*

The estimated PNC fractions are aggregated across paired observations to derive average food- and process-specific estimates representing the overall processing effect for a given food product and processing condition. Although the estimated PNC fractions are generally small, when applied to foods containing elevated precursor concentrations may result in significant increases in predicted processed nitrite and nitrosamine concentrations and corresponding dietary exposure estimates. The highest predicted concentration and exposure increases were associated with thermal processing conditions, whereas storage and refrigeration conditions generally resulted in smaller, though still measurable increases. Few examples of the estimated PNC values for both pathways per food product and processing condition shown in Table A1-2.

**Table A1-2.** Average conversion fractions by food item and processing type.

product_id_before	product_id_after	PNC	Pathway	2.5% CI	97.5% CI
Bacon_Stored	Bacon_Pan-fry	0.002450165	NO3_to_NO2	0.000805095	0.010124
Bacon_Stored	Bacon_Stored	0.001505253	NO3_to_NO2	0.000660694	0.003295
Dried salted fish_Stored	Dried salted fish_Roast	0.001039132	NO3_to_NO2	0.000927751	0.001223
Dried salted fish_Stored	Dried salted fish_Stored	0.00113498	NO3_to_NO2	0.000903601	0.001497
Ham_Stored	Ham_Pan-fry	0.021921516	NO3_to_NO2	0.007644645	0.048083
Ham_Stored	Ham_Stored	0.01347361	NO3_to_NO2	0.006407764	0.042932
Sausage_Stored	Sausage_Air-fry	0.000986926	NO3_to_NO2	0.000795531	0.001151
Sausage_Stored	Sausage_Pan-fry	0.003064886	NO3_to_NO2	0.001041644	0.010718
Sausage_Stored	Sausage_Roast	0.001063339	NO3_to_NO2	0.000876387	0.001358
Sausage_Stored	Sausage_Stored	0.002209412	NO3_to_NO2	0.000991541	0.004752
Bacon_Stored	Bacon_Pan-fry	0.001233032	NO2_to_NA	0.000929254	0.001611
Bacon_Stored	Bacon_Stored	0.001246254	NO2_to_NA	0.000729476	0.001359
Ham_Stored	Ham_Pan-fry	0.001232711	NO2_to_NA	0.000939845	0.001633
Sausage_Stored	Sausage_Air-fry	0.001326341	NO2_to_NA	0.000977593	0.002395
Sausage_Stored	Sausage_Pan-fry	0.001240028	NO2_to_NA	0.000910119	0.001492
Sausage_Stored	Sausage_Roast	0.001309316	NO2_to_NA	0.000789639	0.001777
Sausage_Stored	Sausage_Stored	0.001245599	NO2_to_NA	0.000720958	0.001479

## Appendix 2. Literature search: Hazard assessment of nitrite

### Search terms and search strategy

A research librarian performed literature searches in the electronic databases Ovid MEDLINE(R), Embase, CAB Abstracts, Cochrane Database of Systematic Reviews, Web of Science Core Collection, Scopus, and Epistemonikos. An overview of the search and the search result is given below.

#### Negative health effects caused by nitrites

<b>Search:</b>	Ragnhild Agathe Tornes
<b>Peer review:</b>	Nataliya Byelyey
<b>Duplicate control in EndNote:</b>	Before duplicate control: 1190 After duplicate control: 561

**Database:** Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to May 07, 2025>

**Date:** 08 May 2025

**Number of hits:** 200

1	Nitrites/	21334
2	(nitrite? or sodiumnitrite? or "nitrous acid salt?" or "E 249" or "E 250" or "7758-09-0" or "7632-00-0").tw,kf.	42446
3	1 or 2	48446
4	limit 3 to "reviews (maximizes specificity)"	146
5	Meta-Analysis/ or Network Meta-Analysis/ or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw,kf,bt.	630759
6	4 or (3 and 5)	200

**Database:** Embase <1974 to 2025 May 07> via Ovid

**Date:** 08 May 2025

**Number of hits:** 107

1	nitrite/	38477
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2	(nitrite? or sodiumnitrite? or "nitrous acid salt?" or "E 249" or "E 250" or "7758-09-0" or "7632-00-0").tw,kf.	48830
3	1 or 2	57630
4	limit 3 to "reviews (maximizes specificity)"	211
5	exp Meta-Analysis/ or "systematic review"/ or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw,kf,bt.	892559
6	4 or (3 and 5)	354
7	limit 6 to "remove medline records"	107

**Database:** CAB Abstracts <1973 to 2025 Week 19> via Ovid

**Date:** 08 May 2025

**Number of hits:**327

1	Nitrite/ or exp nitrites/	24530
2	(nitrite? or sodiumnitrite? or "nitrous acid salt?" or "E 249" or "E 250" or "7758-09-0" or "7632-00-0").tw.	38531
3	1 or 2	38531
4	limit 3 to "systematic review"	320
5	(meta-analysis or systematic reviews).sh. or ((systematic* adj2 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) adj2 search*)) or "integrative review*" or (evidence adj2 review*)).tw.	141042
6	4 or (3 and 5)	327

**Database:** Cochrane Database of Systematic Reviews

Issue 5 of 12, May 2025

**Date:** 08 May 2025

**Number of hits:** 2 (systematic reviews)

1	[mh ^Nitrites]	483
#2	(nitrite? or sodiumnitrite? or ("nitrous acid" NEXT salt?) or "E 249" or "E 250" or "7758-09-0" or "7632-00-0"):ti,ab	1720
#3	#1 or #2	1801

#4	#3 in Cochrane Reviews	2
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**Database:**Web of Science Core Collection: Science Citation Index Expanded (SCI-EXPANDED) --1987-present, Social Sciences Citation Index (SSCI) --1987-present, Arts & Humanities Citation Index (A&HCI) --1987-present, Emerging Sources Citation Index (ESCI) --2015-present

**Date:**08 May 2025

**Number of hits:**256

3	#1 AND #2	Exact search	256
2	TS=(("systematic*" NEAR/1 "review*" or ("review" and (("structured" or "database*" or "systematic*") NEAR/1 "search*")) or "integrative review*" or ("evidence" NEAR/1 "review*")) OR TI=("metaanal*" or "meta anal*") OR AB=("metaanal*" or "meta anal*")	Exact search	730,623
1	TS=(nitrite\$ or sodiumnitrite\$ or "nitrous acid salt\$" or "E 249" or "E 250" or "7758-09-0" or "7632-00-0")	Exact search	70,252

**Database:**Scopus

**Date:** 08 May 2025

**Number of hits:** 132

1	TITLE-ABS(nitrite or nitrites or sodiumnitrite or sodiumnitrites or "nitrous acid salt" or "nitrous acid salts" or "E 249" or "E 250" or "7758-09-0" or "7632-00-0") OR AUTHKEY(nitrite or nitrites or sodiumnitrite or sodiumnitrites or "nitrous acid salt" or "nitrous acid salts" or "E 249" or "E 250" or "7758-09-0" or "7632-00-0")	2335
2	TITLE-ABS((systematic* W/1 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) W/1 search*)) or "integrative review*" or (evidence W/1 review*)) OR AUTHKEY((systematic* W/1 review*) or metaanal* or "meta anal*" or (review and ((structured or database* or systematic*) W/1 search*)) or "integrative review*" or (evidence W/1 review*))	793504
3	1 and 2	132

**Database:** Epistemonikos

**Date:** 08 May 2025

**Number of hits:** 166

(title:((nitrite OR nitrites OR sodiumnitrite OR sodiumnitrites OR "nitrous acid salt" OR "nitrous acid salts" OR "E 249" OR "E 250" OR "7758-09-0" OR "7632-00-0")) OR abstract:((nitrite OR nitrites OR sodiumnitrite OR sodiumnitrites OR "nitrous acid salt" OR "nitrous acid salts" OR "E 249" OR "E 250" OR "7758-09-0" OR "7632-00-0"))))

Publication type: Systematic Review

## Study selection and deviations from the protocol

The study selection was based on the predefined eligibility criteria (Table A2-1), as reported in the protocol (VKM et al., 2025), as well as specifications of eligibility criteria after the protocol was published (Table A2-2). We aimed at collecting reported estimates of associations with and estimates of effects (causal impact) of nitrite intake and negative health outcomes of that intake from systematic reviews (SRs). This required extraction of reported numerical values of nitrite exposure in all studies included in the meta-analyses in the SRs. However, exact numerical data on the intake of nitrite was not consistently reported in the main text or in supplementary files of the systematic reviews included for full text assessment. Neither did the eligibility criteria (VKM et al., 2025) specify the need for exact numerical intakes. Thus, it was pertinent to specify the eligibility criteria concerning exposure and outcome.

**Table A2-1.** Prespecified eligibility criteria for studies on negative health outcomes of nitrite.

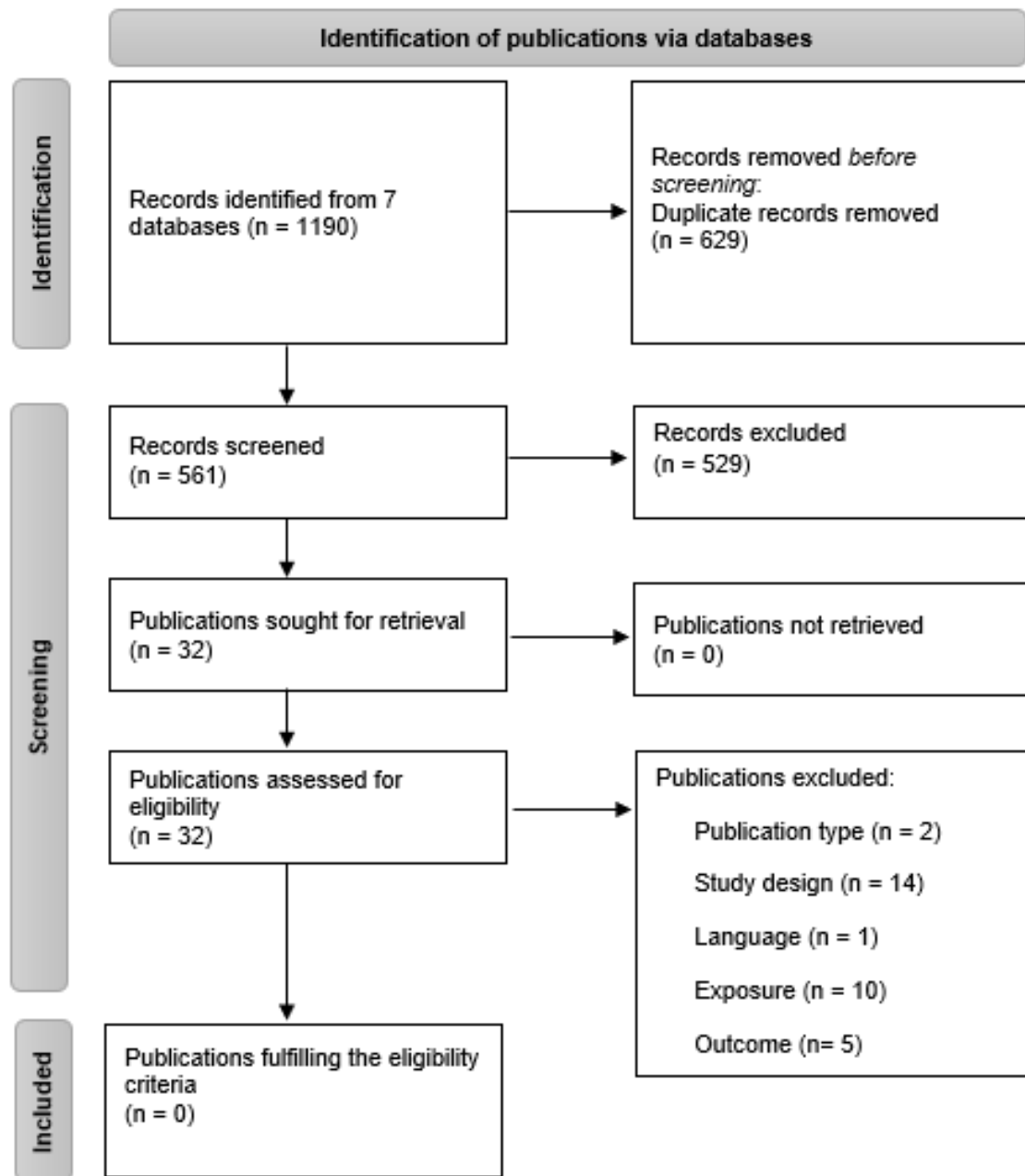
Population	Humans of all age groups, males, and females Non-human mammals
Exposure	Oral exposure to nitrite in foods
Comparison	No intake Placebo Dose comparison
Outcomes	Any negative health effect, including, but not restricted to: <u>Humans</u> <ul style="list-style-type: none"> <li>•Carcinogenicity</li> <li>•Genotoxicity</li> <li>•Cardiovascular effects</li> <li>•Endocrine effects</li> <li>•Haematotoxicity</li> <li>•Immunotoxicity</li> <li>•Reproductive and developmental effects</li> </ul> <u>Animals</u> <ul style="list-style-type: none"> <li>•Body weight changes</li> <li>•Carcinogenicity (non-genotoxic/genotoxic)</li> <li>•Cardiovascular effects</li> <li>•Clinical signs of toxicity</li> <li>•Endocrine toxicity</li> <li>•Food and drink consumption</li> <li>•Haematotoxicity</li> <li>•Immunotoxicity</li> </ul>

	<ul style="list-style-type: none"> <li>•Neurotoxicity</li> <li>•Organ weight changes and histopathological changes</li> <li>•Reproductive and developmental toxicity</li> </ul>
Study design	<p>Systematic reviews*</p> <p>* A publication qualifies as a systematic review if 1) it describes a specific research question and the specific criteria used for selecting studies, 2) the authors have performed a systematic literature search, and 3) it includes a quality assessment of the selected studies (Cochrane Glossary, 2020). We will exclude systematic reviews that do not contain one or more of the specified study designs</p>
Publication year	No restriction
Country	No restriction
Language	Danish, English, German, Norwegian, Polish, and Swedish

**Table A2-2.** Specifications of the eligibility criteria shown in Table A2-1.

Exposure	Numerical values for oral exposure to nitrite in food must be reported (in the main body of the article or in supplementary material) and described in units of e.g. mg/day or units that can be estimated to mg/kg body weight per day using default factors, such as mg nitrite/kcal.
Outcomes	<p>For each reported outcome, the estimate of association or effect (e.g. relative risk, odds ratio, mean difference) resulting from a meta-analysis must be based on reported numerical values in all studies included in any meta-analysis, as further specified in the eligibility criteria on exposure (see above).</p> <p>We will not include negative side-effects such as upset stomach, nausea and similar effects that are e.g. transient and not relevant for setting a reference point.</p>

The identified records were imported into EndNote (Thomson Reuters, version X9), duplicates were removed, and the records were imported into Rayyan (Ouzzani et al., 2016) for screening of title and abstracts and full text. Screening of records was performed independently by four reviewers. To ensure between-reviewer calibration, all reviewers screened 50 of the retrieved titles and abstracts, and conflicts were discussed and clarified in a calibration meeting. In total, 32 publications were included for full text assessment. The full texts were evaluated independently by pairs of reviewers. The study selection is presented in Figure A2-1. No SRs fulfilled the eligibility criteria.



**Figure A2-1.** PRISMA flowchart for the selection of systematic reviews for nitrite hazard assessment (modified from Moher et al. (2009)).

### *Studies assessed in full text*

Several publications lacked numerical data. Requests for additional data were sent to the corresponding authors of seven SRs, resulting in one response. In several SRs, results from both cohort studies and case-control studies were synthesised to obtain a pooled estimate of association or effect. Subgroup or sensitivity analyses were lacking in all but one review. None of the 32 publications that were assessed in full text were judged to fulfill the eligibility criteria. The reasons for exclusion are listed in Table A2-3.

**Table A2-3.** List over excluded publications in the full text screening with reasons for exclusions. SR: systematic review

Reference	Exclude, with reason	Request for missing information sent to corresponding author (X)
Adilah et al. (2024)	Exposure (salted food)	
Avila-Nava et al. (2025)	Exposure (dietary components)	
Bahadoran et al. (2016)	Study design (not SR)	
Bahadoran et al. (2015)	Study design (not SR)	
Bryan and Ivy (2015)	Study design (not SR)	
Chan et al. (2013)	Study design (not SR)	
Clifford et al. (2019)	Exposure (numerical values for nitrite intake were not reported)	X, reply not received
Cook et al. (2020)	Publication type (conference abstract)	
Crowe et al. (2019)	Study design (not SR)	
de Andrade Junior et al. (2021)	Study design (not SR)	
Eichholzer and Gutzwiller (1998)	Study design (not SR)	
Feskens et al. (2013)	Study design (not SR)	
García Díaz et al. (1987)	Language	
Ghasemi et al. (2024)	Exposure (numerical values for nitrite intake were not reported)	X, reply not received
Hosseini et al. (2021)	Outcome (combined case control and cohort studies, combined diagnoses, and combined nitrate and nitrite in meta-analyses. Two studies included in meta-analysis did not report numerical values for nitrite intake)	X, data received
Jackson et al. (2018)	Outcome (one of the included studies reported numerical nitrite values. The publication is a review of beneficial effects of nitrites of which one reports mild adverse events not appropriate for setting an ADI)	
Jakszyn and Gonzalez (2006b)	Study design (not SR)	
Karimi and Samadi (2018)	Study design (exposure only, drinking water)	
McNulty et al. (2022)	Study design (not SR)	

Reference	Exclude, with reason	Request for missing information sent to corresponding author (X)
Nguyen et al. (2024)	Exposure (numerical values for nitrite intake were not reported)	X, reply not received
Nguyen et al. (2023)	Publication type (conference abstract)	
Norouzzadeh et al. (2025)	Exposure (nitrite exposure not included)	
Padovano et al. (2022)	Study design (not SR)	
Picetti et al. (2022)	Exposure (numerical values for nitrite intake were not reported)	
Said Abasse et al. (2022)	Outcome (Estimates of association consisted of case-control, cohort and randomised controlled studies. One of the studies included in the association estimates combined nitrate and nitrite intake, and some studies did not report numerical intake values. Heterogeneity was reported for nitrate and nitrite data combined and not for each endpoint).	
Seyyedsalehi et al. (2023)	Outcome (Estimates of association consisted of case-control and cohort studies. For some of the reported nitrite values, it was unclear which were used in the meta-analysis. Some of the primary studies did not provide numerical nitrite intake values).	
Song et al. (2015)	Outcome (Tertiles rather than numerical intake values were reported in one of the studies included in the association estimate of cohort studies. Three of the studies included in the meta-analysis of case-control studies did not report numerical intake values for nitrite).	
Wang et al. (2016)	Study design (not SR)	
Xie et al. (2016)	Study design (not SR)	
Yu et al. (2020)	Exposure (numerical values for nitrite intake were not reported)	X, reply not received
(Zhang et al., 2019)	Exposure (numerical values for nitrite intake were not reported)	X, reply not received
(Zhang et al., 2022)	Exposure (numerical values for nitrite intake were not reported)	X, reply not received

## Data extraction and further data management

According to the protocol (VKM et al., 2025), data listed in Table A2-4 were to be extracted from the SRs and their primary studies and risk of bias in the SRs, using the ROBIS tool (University of Bristol, 2025), was to be assessed. Numerical nitrite intake values from the

individual studies, had they been reported in the meta-analysis of the SR, would have been recalculated into ranges of mg/kg body weight per day of nitrite. We would have presented the data in tables and figures along with the reported estimates of association or effect to allow comparison with the current ADI.

**Table A2-4.** Overview of information to be extracted from the systematic reviews and the primary studies included in each systematic review.

<b>Information to be extracted from the systematic review</b>
Authors
Title
Journal
Year of publication
Funding
Reported conflict of interest
Main objective(s), including PECO(s) (Population, Exposure, Comparison, Outcome)
Number of primary studies included and their study designs
Publication years (range) of the included primary studies
List of the main outcomes/endpoints considered
The risk of bias tool used
Method of synthesis (meta-analysis, narrative)
Measures of association/effect (e.g. relative risk, odds ratio, mean difference)
Estimates of association/effect with 95% confidence intervals (95% CI)
<b>Information to be extracted from the primary studies included in each systematic review</b>
The country where the study was conducted
The year the study was conducted
Population, including number of participants or animals
Exposure, including administration of the substance (in food or tested separately), dose, duration of exposure, and follow-up time
Comparison, including placebo, no treatment, dose comparison
Outcomes measured
Reported estimates of association/effect

## Appendix 3. Literature search: N-nitrosamine levels in selected foods

### Search terms and search strategy

A research librarian performed literature searches in the electronic databases Ovid MEDLINE(R), Embase, CAB Abstracts, Web of Science Core Collection, and Scopus. An overview of the search and the search result given below.

#### N-NITROSAMINES IN FOOD

<b>Search:</b>	Ragnhild Agathe Ternes
<b>Peer review:</b>	Astrid Nøstberg
<b>Duplicate control in EndNote:</b>	Before duplicate control: 3431 After duplicate control: 1470

**Database:** Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 18, 2025>

**Date:** 19.06.25

**Number of hits:** 852

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 18, 2025>

1	Dimethyl N-nitrosamine/ or Diethyl N-nitrosamine/ or N-Nitrosopyrrolidine/	6627
2	(dimethylnitrosamin* or dimethylnitrosoamin* or nitrosodimethylamin* or ((dimethyl or "di n butyl" or diethyl or "di n propyl") adj2 (nitrosamin* or nitrosoamin*)) or "di n butylnitrosamin*" or "n nitrosodi n butylamin*" or nitrosodibutylamin* or diethylnitrosamin* or diethylnitrosoamin* or diethylnitrosamid* or nitrosodiethylamin* or "nitroso diethylamin*" or diethylnitrosoamin* or nitrosodipropylamin* or "di n propylnitrosamin*" or "n nitroso di n propylamin*" or "n nitrosodi n propylamin*" or nitrosomethylethylamin* or methylethylnitrosamin* or "n nitroso n methylethylamin*" or "n nitrosoethylmethylamin*" or (n adj (nitrosodiisobutylamin* or "nitroso n methylanilin*" or nitrososarcosin* or nitrosomorpholin* or nitrosopiperidin*)) or nitrosomethylanilin* or methylnitrosoanilin* or methylphenylnitrosamin* or phenylmethylnitrosamin* or "4 nitroso morpholin*" or nitrosopyrrolidin*).tw,kf.	9920

3	(62-75-9 or 55-18-5 or 621-64-7 or 10595-95-6 or 924-16-3 or 997-95-5 or 614-00-6 or 13256-22-9 or 59-89-2 or 100-75-4 or 930-55-2).tw,kf.	30
4	1 or 2 or 3	11175
5	Fruit/ or Vegetables/ or "Fruit and Vegetable Juices"/ or Edible Grain/ or Nuts/ or Seeds/ or Milk/ or exp Cultured Milk Products/ or Kefir/ or Koumiss/ or Whey/ or Drinking Water/ or exp Mineral Waters/	248339
6	(fruit? or fructus or "averrhoa carambola" or avocado* or banana* or berry or berries or blackcurrant? or redcurrant? or currant? or blackberr* or blueberr* or breadfruit? or caraway or citrus or calamondin? or citrange? or citron? or clementine? or grapefruit? or lemon? or lime? or mandarin? or orange? or pummelo? or satsuma? or tangelo? or tangerine? or colocynth? or cranberr* or date or dates or feijoa? or fig or figs or gooseberr* or grape? or guava? or huckleberr* or kiwi* or (actinidia adj (arguta or chinesis or deliciosa)) or lingonberr* or loquat? or lychee? or "maclura pomifera" or mango? or "momordica charantia" or mulberr* or muskmelon? or cantaloupe or cucumis or melon? or olive? or papaya? or persimmon? or diospyros or pineapple? or ananas or apple? or pear? or quince? or malus or pomegranate? or raspberr* or sapodilla? or drupe or apricot? or cherry or cherries or prunus or nectarine? or peach* or plum? or damson or strawberr* or tomato* or watermelon?).tw,kf.	797177
7	(vegetable? or alfalfa? or artichoke? or asparagus or aubergine? or "barrel medic" or "Basella alba" or bean or beans or beet or beets or (beta adj (altissima or vulgaris)) or "bok choy" or broccoli or "Brussels sprout?" or cabbage or "Canavalia ensiformis" or Capsicum or cardoon or carob or carrot? or cassava or cauliflower? or celeriac? or celery or Chenopodium or chickpea? or chicory or chive or ((colic or rheumatism) adj root?) or cocoyam? or collard or cornsalad or courgette or cowpea? or cress or cucumber? or Cucurbita* or Cyclopia or dasheen or "Daucus carota" or Dioscorea or (edible adj (mushroom? or seaweed or "sea weed")) or endive or fennel or gardencress or garlic or girasole or "Glebionis coronaria" or guar or "Helianthus tuberosus" or horseradish or "Ipomoea aquatica" or kale or kimchi or kohlrabi or komatsuna or "Lablab purpureus" or "Lactuca sativa" or leek or legume or legumes or lentil? or Lepidium or lettuce or lupin or lupine or lupinus or "Macrotyloma uniflorum" or "Oenanthe javanica" or okra? or onion? or "Oxalis tuberosa" or "Pachyrhizus erosus" or paprika or parsley or parsnip? or pea or peas or peanut? or pepper? or (Phaseolus adj (coccineus or unguiculatus or vulgaris)) or pigeonpea or potato* or "Psophocarpus tetragonolobus" or pumpkin or radish* or rapeseed? or rhubarb or rutabaga or ((salad or leguminous) adj crop?) or sauerkraut or shallot? or soybean? or spinach or squash or sweetcorn or "Swiss chard" or Tamus or taro or topinambour or turnip? or vetch or "Vicia faba" or "vigna unguiculata" or watercress or yam or yams or zucchini? or "sugar plant?" or sugarbeet?).tw,kf.	392029

8	((edible or food or refined or unrefined or polished or processed or whole or pseudo) adj grain?) or wholegrain? or cereal? or barley or "Hordeum vulgare" or bread or "bakery product?" or "Coix lac?ryma" or adlay or "Job* tear?" or millet? or "Eleusine coracana" or "Setaria italica" or ragi or maize or "Zea mays" or corn or malt or oat? or "Avena sativa" or "Cenchrus americanus" or (Pennisetum adj (glaucum or typhoides or typhoideum or americanum)) or "Setaria glauca" or rice or "Oryza sativa" or rye or sorghum or durra or wheat or "graminis leaf" or Triticum or emmer or spelt or triticale or (Triticum adj (dicoccum or turgidum or aestivum or vulgare or "x Secale" or durum or monococcum)) or Triticosecale or Zizania or wildrice or (grain adj2 (flour or legum* or oil?)) or oatmeal or semolina or ((oil or cotton or lin or rape or safflower or sesame or sunflower) adj seed?) or oilseed? or cottonseed? or linseed? or rapeseed? or safflowerseed? or sesameseed? or sunflowerseed? or pseudograin? or pseudocereal? or buckwheat or quinoa or chia or "Salvia hispanica" or nixtamal).tw,kf.	330049
9	(milk or milkshake? or butter or buttermilk or ghee or cheese? or ((dairy or sourmilk) adj product?) or whey or ((ice or sour* or cultured or fermented or dairy) adj cream) or "sour dairy" or yoghurt or yogurt or yoghurt or zabadi or kefir or koumiss).tw,kf.	194028
10	((drinking or potable or bottled or mineral or soda or seltzer or sparkling or carbonated) adj water) or "club soda?").tw,kf.	70377
11	or/5-10	1644724
12	(analys* or analyz* or ((level? or amount) adj3 (nitros* or NOC)) or ((NDMA or NDEA or NDPA or NMEA or NDBA or NDiBA or NMA or NSAR or NMOR or NPIP or NPYR) adj2 (content? or increas* or decreas*)) or concentration? or estimat* or exposure? or occurrence? or ("total diet" or analytical) adj stud*).tw,kf.	11900096
13	4 and 11 and 12	852

Database:Embase <1974 to 2025 June 18> via Ovid

Date: 19.06.25

Number of hits: 846

1	dimethyl N-nitrosamine/ or dibutyl N-nitrosamine/ or diethyl N-nitrosamine/ or dipropyl N-nitrosamine/ or ethylmethyl N-nitrosamine/ or n methyl n nitrosoaniline/ or nitrosomorpholine/ or 1 nitrosopiperidine/ or n nitrosopyrrolidine/	12279
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2	(dimethylnitrosamin* or dimethylnitrosoamin* or nitrosodimethylamin* or ((dimethyl or "di n butyl" or diethyl or "di n propyl") adj2 (nitrosamin* or nitrosoamin*)) or "di n butylnitrosamin*" or "n nitrosodi n butylamin*" or nitrosodibutylamin* or diethylnitrosamin* or diethylnitrosoamin* or diethylnitrosamid* or nitrosodiethylamin* or "nitroso diethylamin*" or diethylnitrosoamin* or nitrosodipropylamin* or "di n propylnitrosamin*" or "n nitroso di n propylamin*" or "n nitrosodi n propylamin*" or nitrosomethylethylamin* or methylethylnitrosamin* or "n nitroso n methylethylamin*" or "n nitrosoethylmethylamin*" or (n adj (nitrosodiisobutylamin* or "nitroso n methylanilin*" or nitrososarcosin* or nitrosomorpholin* or nitrosopiperidin*)) or nitrosomethylanilin* or methylnitrosoanilin* or methylphenylnitrosamin* or phenylmethylnitrosamin* or "4 nitroso morpholin*" or nitrosopyrrolidin*).tw,kf.	11416
3	(62-75-9 or 55-18-5 or 621-64-7 or 10595-95-6 or 924-16-3 or 997-95-5 or 614-00-6 or 13256-22-9 or 59-89-2 or 100-75-4 or 930-55-2).tw,kf.	33
4	1 or 2 or 3	14511
5	exp fruit/ or exp vegetable/ or exp "fruit and vegetable juice"/ or exp food grain/ or exp milk/ or drinking water/	716822
6	(fruit? or fructus or "averrhoa carambola" or avocado* or banana* or berry or berries or blackcurrant? or redcurrant? or currant? or blackberr* or blueberr* or breadfruit? or caraway or citrus or calamondin? or citrange? or citron? or clementine? or grapefruit? or lemon? or lime? or mandarin? or orange? or pummelo? or satsuma? or tangelo? or tangerine? or colocynth? or cranberr* or date or dates or feijoa? or fig or figs or gooseberr* or grape? or guava? or huckleberr* or kiwi* or (actinidia adj (arguta or chinesis or deliciosa)) or lingonberr* or loquat? or lychee? or "maclura pomifera" or mango? or "momordica charantia" or mulberr* or muskmelon? or cantaloupe or cucumis or melon? or olive? or papaya? or persimmon? or diospyros or pineapple? or ananas or apple? or pear? or quince? or malus or pomegranate? or raspberr* or sapodilla? or drupe or apricot? or cherry or cherries or prunus or nectarine? or peach* or plum? or damson or strawberr* or tomato* or watermelon?).tw,kf.	1167407
7	(vegetable? or alfalfa? or artichoke? or asparagus or aubergine? or "barrel medic" or "Basella alba" or bean or beans or beet or beets or (beta adj (altissima or vulgaris)) or "bok choy" or broccoli or "Brussels sprout?" or cabbage or "Canavalia ensiformis" or Capsicum or cardoon or carob or carrot? or cassava or cauliflower? or celeriac? or celery or Chenopodium or chickpea? or chicory or chive or ((colic or rheumatism) adj root?) or cocoyam? or collard or cornsalad or courgette or cowpea? or cress or cucumber? or Cucurbita* or Cyclopia or dasheen or "Daucus carota" or Dioscorea or (edible adj (mushroom? or seaweed or "sea weed")) or endive or fennel or gardencreas or garlic or girasole or "Glebionis coronaria" or	414390

	guar or "Helianthus tuberosus" or horseradish or "Ipomoea aquatica" or kale or kimchi or kohlrabi or komatsuna or "Lactuca purpureus" or "Lactuca sativa" or leek or legume or legumes or lentil? or Lepidium or lettuce or lupin or lupine or lupinus or "Macrotyloma uniflorum" or "Oenanthe javanica" or okra? or onion? or "Oxalis tuberosa" or "Pachyrhizus erosus" or paprika or parsley or parsnip? or pea or peas or peanut? or pepper? or (Phaseolus adj (coccineus or unguiculatus or vulgaris)) or pigeonpea or potato* or "Psophocarpus tetragonolobus" or pumpkin or radish* or rapeseed? or rhubarb or rutabaga or ((salad or leguminous) adj crop?) or sauerkraut or shallot? or soybean? or spinach or squash or sweetcorn or "Swiss chard" or Tamus or taro or topinambour or turnip? or vetch or "Vicia faba" or "vigna unguiculata" or watercress or yam or yams or zucchini? or "sugar plant?" or sugarbeet?).tw,kf.	
8	(((edible or food or refined or unrefined or polished or processed or whole or pseudo) adj grain?) or wholegrain? or cereal? or barley or "Hordeum vulgare" or bread or "bakery product?" or "Coix lac?ryma" or adlay or "Job* tear?" or millet? or "Eleusine coracana" or "Setaria italica" or ragi or maize or "Zea mays" or corn or malt or oat? or "Avena sativa" or "Cenchrus americanus" or (Pennisetum adj (glaucum or typhoides or typhoideum or americanum)) or "Setaria glauca" or rice or "Oryza sativa" or rye or sorghum or durra or wheat or "graminis leaf" or Triticum or emmer or spelt or triticale or (Triticum adj (dicoccum or turgidum or aestivum or vulgare or "x Secale" or durum or monococcum)) or Triticosecale or Zizania or wildrice or (grain adj2 (flour or legum* or oil?)) or oatmeal or semolina or ((oil or cotton or lin or rape or safflower or sesame or sunflower) adj seed?) or oilseed? or cottonseed? or linseed? or rapeseed? or safflowerseed? or sesameseed? or sunflowerseed? or pseudograin? or pseudocereal? or buckwheat or quinoa or chia or "Salvia hispanica" or nixtamal).tw,kf.	336520
9	(milk or milkshake? or butter or buttermilk or ghee or cheese? or ((dairy or sourmilk) adj product?) or whey or ((ice or sour* or cultured or fermented or dairy) adj cream) or "sour dairy" or yoghurt or yogurt or yoghurt or zabadi or kefir or koumiss).tw,kf.	221363
10	(((drinking or potable or bottled or mineral or soda or seltzer or sparkling or carbonated) adj water) or "club soda?").tw,kf.	89935
11	or/5-10	2107900
12	(analys* or analyz* or ((level? or amount) adj3 (nitros* or NOC)) or ((NDMA or NDEA or NDPA or NMEA or NDBA or NDiBA or NMA or NSAR or NMOR or NPIP or NPYR) adj2 (content? or increas* or decreas*)) or concentration? or estimat* or exposure? or occurrence? or ("total diet" or analytical) adj stud*).tw,kf.	15493177
13	4 and 11 and 12	1075
14	limit 13 to embase	846

Database: CAB Abstracts <1973 to 2025 Week 24>

Date: 19.06.25

Number of hits: 636

1	N-nitrosodimethylamine/ or nitrosopyrrolidine/	423
2	(dimethylnitrosamin* or dimethylnitrosoamin* or nitrosodimethylamin* or ((dimethyl or "di n butyl" or diethyl or "di n propyl") adj2 (nitrosamin* or nitrosoamin*)) or "di n butylnitrosamin*" or "n nitrosodi n butylamin*" or nitrosodibutylamin* or diethylnitrosamin* or diethylnitrosoamin* or diethylnitrosamid* or nitrosodiethylamin* or "nitroso diethylamin*" or diethylnitrosoamin* or nitrosodipropylamin* or "di n propylnitrosamin*" or "n nitroso di n propylamin*" or "n nitrosodi n propylamin*" or nitrosomethylethylamin* or methylethylnitrosamin* or "n nitroso n methylethylamin*" or "n nitrosoethylmethylamin*" or (n adj (nitrosodiisobutylamin* or "nitroso n methylanilin*" or nitrososarcosin* or nitrosomorpholin* or nitrosopiperidin*)) or nitrosomethylanilin* or methylnitrosoanilin* or methylphenylnitrosamin* or phenylmethylnitrosamin* or "4 nitroso morpholin*" or nitrosopyrrolidin*).tw.	2977
3	(62-75-9 or 55-18-5 or 621-64-7 or 10595-95-6 or 924-16-3 or 997-95-5 or 614-00-6 or 13256-22-9 or 59-89-2 or 100-75-4 or 930-55-2).tw.	2
4	1 or 2 or 3	2978
5	exp fruit/ or exp fruit products/ or fruits/ or exp vegetables/ or vegetable products/ or exp food grains/ or exp nuts/ or nut products/ or exp oilseeds/ or exp milk/ or exp milks/ or exp root crops/ or exp starch crops/ or exp drinking water/ or mineral waters/	1711786
6	(fruit? or fructus or "averrhoa carambola" or avocado* or banana* or berry or berries or blackcurrant? or redcurrant? or currant? or blackberr* or blueberr* or breadfruit? or caraway or citrus or calamondin? or citrange? or citron? or clementine? or grapefruit? or lemon? or lime? or mandarin? or orange? or pummelo? or satsuma? or tangelo? or tangerine? or colocynth? or cranberr* or date or dates or feijoa? or fig or figs or gooseberr* or grape? or guava? or huckleberr* or kiwi* or (actinidia adj (arguta or chinesis or deliciosa)) or lingonberr* or loquat? or lychee? or "maclura pomifera" or mango? or "momordica charantia" or mulberr* or muskmelon? or cantaloupe or cucumis or melon? or olive? or papaya? or persimmon? or diospyros or pineapple? or ananas or apple? or pear? or quince? or malus or pomegranate? or raspberr* or sapodilla? or drupe or	1631573

	apricot? or cherry or cherries or prunus or nectarine? or peach* or plum? or damson or strawberr* or tomato* or watermelon?).tw.	
7	(vegetable? or alfalfa? or artichoke? or asparagus or aubergine? or "barrel medic" or "Basella alba" or bean or beans or beet or beets or (beta adj (altissima or vulgaris)) or "bok choy" or broccoli or "Brussels sprout?" or cabbage or "Canavalia ensiformis" or Capsicum or cardoon or carob or carrot? or cassava or cauliflower? or celeriac? or celery or Chenopodium or chickpea? or chicory or chive or ((colic or rheumatism) adj root?) or cocoyam? or collard or cornsalad or courgette or cowpea? or cress or cucumber? or Cucurbita* or Cyclopia or dasheen or "Daucus carota" or Dioscorea or (edible adj (mushroom? or seaweed or "sea weed")) or endive or fennel or gardencress or garlic or girasole or "Glebionis coronaria" or guar or "Helianthus tuberosus" or horseradish or "Ipomoea aquatica" or kale or kimchi or kohlrabi or komatsuna or "Lablab purpureus" or "Lactuca sativa" or leek or legume or legumes or lentil? or Lepidium or lettuce or lupin or lupine or lupinus or "Macrotyloma uniflorum" or "Oenanthe javanica" or okra? or onion? or "Oxalis tuberosa" or "Pachyrhizus erosus" or paprika or parsley or parsnip? or pea or peas or peanut? or pepper? or (Phaseolus adj (coccineus or unguiculatus or vulgaris)) or pigeonpea or potato* or "Psophocarpus tetragonolobus" or pumpkin or radish* or rapeseed? or rhubarb or rutabaga or ((salad or leguminous) adj crop?) or sauerkraut or shallot? or soybean? or spinach or squash or sweetcorn or "Swiss chard" or Tamus or taro or topinambour or turnip? or vetch or "Vicia faba" or "vigna unguiculata" or watercress or yam or yams or zucchini? or "sugar plant?" or sugarbeet?).tw.	1624454
8	((edible or food or refined or unrefined or polished or processed or whole or pseudo) adj grain?) or wholegrain? or cereal? or barley or "Hordeum vulgare" or bread or "bakery product?" or "Coix lac?ryma" or adlay or "Job* tear?" or millet? or "Eleusine coracana" or "Setaria italica" or ragi or maize or "Zea mays" or corn or malt or oat? or "Avena sativa" or "Cenchrus americanus" or (Pennisetum adj (glaucum or typhoides or typhoideum or americanum)) or "Setaria glauca" or rice or "Oryza sativa" or rye or sorghum or durra or wheat or "graminis leaf" or Triticum or emmer or spelt or triticale or (Triticum adj (dicoccum or turgidum or aestivum or vulgare or "x Secale" or durum or monococcum)) or Triticosecale or Zizania or wildrice or (grain adj2 (flour or legum* or oil?)) or oatmeal or semolina or ((oil or cotton or lin or rape or safflower or sesame or sunflower) adj seed?) or oilseed? or cottonseed? or linseed? or rapeseed? or safflowerseed? or sesameseed? or sunflowerseed? or pseudograin? or pseudocereal? or buckwheat or quinoa or chia or "Salvia hispanica" or nixtamal).tw.	1604751
9	(milk or milkshake? or butter or buttermilk or ghee or cheese? or ((dairy or sourmilk) adj product?) or whey or ((ice or sour* or cultured or fermented or dairy) adj cream) or "sour dairy" or yoghurt or yogurt or yoghurt or zabadi or kefir or koumiss).tw.	590713

10	((drinking or potable or bottled or mineral or soda or seltzer or sparkling or carbonated) adj water) or "club soda?").tw.	93096
11	or/5-10	4497152
12	(analys* or analyz* or ((level? or amount) adj3 (nitros* or NOC)) or ((NDMA or NDEA or NDPA or NMEA or NDBA or NDiBA or NMA or NSAR or NMOR or NPIP or NPYR) adj2 (content? or increas* or decreas*)) or concentration? or estimat* or exposure? or occurrence? or ("total diet" or analytical) adj stud*).tw.	6355259
13	4 and 11 and 12	636

**Database:Web of Science Core Collection**

Science Citation Index Expanded (SCI-EXPANDED) --1987-present, Social Sciences Citation Index (SSCI) --1987-present, Arts & Humanities Citation Index (A&HCI) --1987-present, Emerging Sources Citation Index (ESCI) --2015-present

**Date:** 19.06.25

**Number of hits:** 1333

11	#3 AND #9 AND #10	Exact search	1,333
10	TS=(analys* or analyz* or ((level\$ or amount) NEAR/2 (nitros* or NOC)) or ((NDMA or NDEA or NDPA or NMEA or NDBA or NDiBA or NMA or NSAR or NMOR or NPIP or NPYR) NEAR/1 (content\$ or increas* or decreas*)) or concentration\$ or estimat* or exposure\$ or occurrence\$ or ("total diet" or analytical) NEAR/0 stud*))	Exact search	23,451,175
9	#4 OR #5 OR #6 OR #7 OR #8	Exact search	3,458,580
8	TS=(((drinking or potable or bottled or mineral or soda or seltzer or sparkling or carbonated) NEAR/0 water) or "club soda\$")	Exact search	137,043
7	TS=(milk or milkshake\$ or butter or buttermilk or ghee or cheese\$ or ((dairy or sourmilk) NEAR/0 product\$) or whey or ((ice or sour* or cultured or fermented or dairy) NEAR/0 cream) or "sour dairy" or yoghurt or yogurt or yoghurt or zabadi or kefir or koumiss)	Exact search	329,807
6	TS=(((edible or food or refined or unrefined or polished or processed or whole or pseudo) NEAR/0 grain\$) or wholegrain\$ or cereal\$ or barley or "Hordeum vulgare" or bread or "bakery product\$" or "Coix lac\$ryma" or adlay or "Job* tear\$" or	Exact search	895,671

	<p>millet\$ or "Eleusine coracana" or "Setaria italica" or ragi or maize or "Zea mays" or corn or malt or oat\$ or "Avena sativa" or "Cenchrus americanus" or (Pennisetum NEAR/0 (glaucum or typhoides or typhoideum or americanum)) or "Setaria glauca" or rice or "Oryza sativa" or rye or sorghum or durra or wheat or "graminis leaf" or Triticum or emmer or spelt or triticale or (Triticum NEAR/0 (dicoccum or turgidum or aestivum or vulgare or "x Secale" or durum or monococcum)) or Triticosecale or Zizania or wildrice or (grain NEAR/1 (flour or legum* or oil\$)) or oatmeal or semolina or ((oil or cotton or lin or rape or safflower or sesame or sunflower) NEAR/0 seed\$) or oilseed\$ or cottonseed\$ or linseed\$ or rapeseed\$ or safflowerseed\$ or sesameseed\$ or sunflowerseed\$ or pseudograin\$ or pseudocereal\$ or buckwheat or quinoa or chia or "Salvia hispanica" or nixtamal)</p>		
5	<p>TS=(vegetable\$ or alfalfa\$ or artichoke\$ or asparagus or aubergine\$ or "barrel medic" or "Basella alba" or bean or beans or beet or beets or (beta NEAR/0 (altissima or vulgaris)) or "bok choy" or broccoli or "Brussels sprout\$" or cabbage or "Canavalia ensiformis" or Capsicum or cardoon or carob or carrot\$ or cassava or cauliflower\$ or celeriac\$ or celery or Chenopodium or chickpea\$ or chicory or chive or ((colic or rheumatism) NEAR/0 root\$) or cocoyam\$ or collard or cornsalad or courgette or cowpea\$ or cress or cucumber\$ or Cucurbita* or Cyclopia or dasheen or "Daucus carota" or Dioscorea or (edible NEAR/0 (mushroom\$ or seaweed or "sea weed")) or endive or fennel or garden cress or garlic or girasole or "Glebionis coronaria" or guar or "Helianthus tuberosus" or horseradish or "Ipomoea aquatica" or kale or kimchi or kohlrabi or komatsuna or "Lactuca purpureus" or "Lactuca sativa" or leek or legume or legumes or lentil\$ or Lepidium or lettuce or lupin or lupine or lupinus or "Macrotyloma uniflorum" or "Oenanthe javanica" or okra\$ or onion\$ or "Oxalis tuberosa" or "Pachyrhizus erosus" or paprika or parsley or parsnip\$ or pea or peas or peanut\$ or pepper\$ or (Phaseolus NEAR/0 (coccineus or unguiculatus or vulgaris)) or pigeonpea or potato* or "Psophocarpus tetragonolobus" or pumpkin or radish* or rapeseed\$ or rhubarb or rutabaga or ((salad or leguminous) NEAR/0 crop\$) or sauerkraut or shallot\$ or soybean\$ or spinach or squash or sweetcorn or "Swiss chard" or Tamus or taro or topinambour or turnip\$ or vetch or "Vicia faba" or "vigna unguiculata" or watercress or yam or yams or zucchini\$ or "sugar plant\$" or sugarbeet\$)</p>	Exact search	910,260
4	<p>TS=(fruit\$ or fructus or "averrhoa carambola" or avocado* or banana* or berry or berries or blackcurrant\$ or redcurrant\$ or</p>	Exact search	1,696,916

	currant\$ or blackberr* or blueberr* or breadfruit\$ or caraway or citrus or calamondin\$ or citrange\$ or citron\$ or clementine\$ or grapefruit\$ or lemon\$ or lime\$ or mandarin\$ or orange\$ or pummelo\$ or satsuma\$ or tangelo\$ or tangerine\$ or colocynth\$ or cranberr* or date or dates or feijoa\$ or fig or figs or gooseberr* or grape\$ or guava\$ or huckleberr* or kiwi* or (actinidia NEAR/0 (arguta or chinesis or deliciosa)) or lingonberr* or loquat\$ or lychee\$ or "maclura pomifera" or mango\$ or "momordica charantia" or mulberr* or muskmelon\$ or cantaloupe or cucumis or melon\$ or olive\$ or papaya\$ or persimmon\$ or diospyros or pineapple\$ or ananas or apple\$ or pear\$ or quince\$ or malus or pomegranate\$ or raspberr* or sapodilla\$ or drupe or apricot\$ or cherry or cherries or prunus or nectarine\$ or peach* or plum\$ or damson or strawberr* or tomato* or watermelon\$)		
3	#1 OR #2	Exact search	9,335
2	TS=("62-75-9" or "55-18-5" or "621-64-7" or "10595-95-6" or "924-16-3" or "997-95-5" or "614-00-6" or "13256-22-9" or "59-89-2" or "100-75-4" or "930-55-2")	Exact search	31
1	TS=(dimethylnitrosamin* or dimethylnitrosoamin* or nitrosodimethylamin* or ((dimethyl or "di n butyl" or diethyl or "di n propyl") NEAR/1 (nitrosamin* or nitrosoamin*)) or "di n butylnitrosamin*" or "n nitrosodi n butylamin*" or nitrosodibutylamin* or diethylnitrosamin* or diethylnitrosoamin* or diethylnitrosamid* or nitrosodiethylamin* or "nitroso diethylamin*" or diethylnitrosoamin* or nitrosodipropylamin* or "di n propylnitrosamin*" or "n nitroso di n propylamin*" or "n nitrosodi n propylamin*" or nitrosomethylethylamin* or methylethylnitrosamin* or "n nitroso n methylethylamin*" or "n nitrosoethylmethylamin*" or (n NEAR/0 (nitrosodiisobutylamin* or "nitroso n methylanilin*" or nitrososarcosin* or nitrosomorpholin* or nitrosopiperidin*)) or nitrosomethylanilin* or methylnitrosoanilin* or methylphenylnitrosamin* or phenylmethylnitrosamin* or "4 nitroso morpholin*" or nitrosopyrrolidin*)	Exact search	9,308

**Database:**Scopus

**Date:** 19.06.25

**Number of hits:** 1097

1	<p>TITLE-ABS(dimethylnitrosamin* or dimethylnitrosoamin* or nitrosodimethylamin* or ((dimethyl or "di n butyl" or diethyl or "di n propyl") W/1 (nitrosamin* or nitrosoamin*)) or "di n butylnitrosamin*" or "n nitrosodi n butylamin*" or nitrosodibutylamin* or diethylnitrosamin* or diethylnitrosoamin* or diethylnitrosamid* or nitrosodiethylamin* or "nitroso diethylamin*" or diethylnitrosoamin* or nitrosodipropylamin* or "di n propylnitrosamin*" or "n nitroso di n propylamin*" or "n nitrosodi n propylamin*" or nitrosomethylethylamin* or methylethylnitrosamin* or "n nitroso n methylethylamin*" or "n nitrosoethylmethylamin*" or (n PRE/O (nitrosodiisobutylamin* or "nitroso n methylanilin*" or nitrososarcosin* or nitrosomorpholin* or nitrosopiperidin*)) or nitrosomethylanilin* or methylnitrosoanilin* or methylphenylnitrosamin* or phenylmethylnitrosamin* or "4 nitroso morpholin*" or nitrosopyrrolidin*) OR AUTHKEY(dimethylnitrosamin* or dimethylnitrosoamin* or nitrosodimethylamin* or ((dimethyl or "di n butyl" or diethyl or "di n propyl") W/1 (nitrosamin* or nitrosoamin*)) or "di n butylnitrosamin*" or "n nitrosodi n butylamin*" or nitrosodibutylamin* or diethylnitrosamin* or diethylnitrosoamin* or diethylnitrosamid* or nitrosodiethylamin* or "nitroso diethylamin*" or diethylnitrosoamin* or nitrosodipropylamin* or "di n propylnitrosamin*" or "n nitroso di n propylamin*" or "n nitrosodi n propylamin*" or nitrosomethylethylamin* or methylethylnitrosamin* or "n nitroso n methylethylamin*" or "n nitrosoethylmethylamin*" or (n PRE/O (nitrosodiisobutylamin* or "nitroso n methylanilin*" or nitrososarcosin* or nitrosomorpholin* or nitrosopiperidin*)) or nitrosomethylanilin* or methylnitrosoanilin* or methylphenylnitrosamin* or phenylmethylnitrosamin* or "4 nitroso morpholin*" or nitrosopyrrolidin*)</p>	12,469
2	<p>TITLE-ABS("62-75-9" or "55-18-5" or "621-64-7" or "10595-95-6" or "924-16-3" or "997-95-5" or "614-00-6" or "13256-22-9" or "59-89-2" or "100-75-4" or "930-55-2") OR AUTHKEY("62-75-9" or "55-18-5" or "621-64-7" or "10595-95-6" or "924-16-3" or "997-95-5" or "614-00-6" or "13256-22-9" or "59-89-2" or "100-75-4" or "930-55-2")</p>	59
3	1 or 2	12,498
4	<p>TITLE-ABS(fruit* or fructus or "averrhoa carambola" or avocado* or banana* or berry or berries or blackcurrant* or redcurrant* or currant* or blackberr* or blueberr* or breadfruit* or caraway or citrus or calamondin* or citrange* or citron* or clementine* or grapefruit* or lemon* or lime* or mandarin* or orange* or pummelo* or satsuma* or tangelo* or tangerine* or colocynth* or cranberr* or date or dates or feijoa* or fig or figs or gooseberr* or grape* or guava* or huckleberr* or kiwi* or (actinidia PRE/O (arguta or chinesis or deliciosa)) or lingonberr* or loquat* or lychee* or "maclura pomifera" or mango* or</p>	2,622,204

	<p>"momordica charantia" or mulberr* or muskmelon* or cantaloupe or cucumis or melon* or olive* or papaya* or persimmon* or diospyros or pineapple* or ananas or apple* or pear* or quince* or malus or pomegranate* or raspberr* or sapodilla* or drupe or apricot* or cherry or cherries or prunus or nectarine* or peach* or plum* or damson or strawberr* or tomato* or watermelon*) OR AUTHKEY(fruit* or fructus or "averrhoa carambola" or avocado* or banana* or berry or berries or blackcurrant* or redcurrant* or currant* or blackberr* or blueberr* or breadfruit* or caraway or citrus or calamondin* or citrange* or citron* or clementine* or grapefruit* or lemon* or lime* or mandarin* or orange* or pummelo* or satsuma* or tangelo* or tangerine* or colocynth* or cranberr* or date or dates or feijoa* or fig or figs or gooseberr* or grape* or guava* or huckleberr* or kiwi* or (actinidia PRE/O (arguta or chinesis or deliciosa)) or lingonberr* or loquat* or lychee* or "maclura pomifera" or mango* or "momordica charantia" or mulberr* or muskmelon* or cantaloupe or cucumis or melon* or olive* or papaya* or persimmon* or diospyros or pineapple* or ananas or apple* or pear* or quince* or malus or pomegranate* or raspberr* or sapodilla* or drupe or apricot* or cherry or cherries or prunus or nectarine* or peach* or plum* or damson or strawberr* or tomato* or watermelon*)</p>	
5	<p>TITLE-ABS(vegetable* or alfalfa* or artichoke* or asparagus or aubergine* or "barrel medic" or "Basella alba" or bean or beans or beet or beets or (beta PRE/O (altissima or vulgaris)) or "bok choy" or broccoli or "Brussels sprout*" or cabbage or "Canavalia ensiformis" or Capsicum or cardoon or carob or carrot* or cassava or cauliflower* or celeriac* or celery or Chenopodium or chickpea* or chicory or chive or ((colic or rheumatism) PRE/O root*) or cocoyam* or collard or cornsalad or courgette or cowpea* or cress or cucumber* or Cucurbita* or Cyclopia or dasheen or "Daucus carota" or Dioscorea or (edible PRE/O (mushroom* or seaweed or "sea weed")) or endive or fennel or gardencress or garlic or girasole or "Glebionis coronaria" or guar or "Helianthus tuberosus" or horseradish or "Ipomoea aquatica" or kale or kimchi or kohlrabi or komatsuna or "Lablab purpureus" or "Lactuca sativa" or leek or legume or legumes or lentil* or Lepidium or lettuce or lupin or lupine or lupinus or "Macrotyloma uniflorum" or "Oenanthe javanica" or okra* or onion* or "Oxalis tuberosa" or "Pachyrhizus erosus" or paprika or parsley or parsnip* or pea or peas or peanut* or pepper* or (Phaseolus PRE/O (coccineus or unguiculatus or vulgaris)) or pigeonpea or potato* or "Psophocarpus tetragonolobus" or pumpkin or radish* or rapeseed* or rhubarb or rutabaga or ((salad or leguminous) PRE/O crop*) or sauerkraut or shallot* or soybean* or spinach or squash or "Swiss chard" or Tamus or taro or topinambour or turnip* or vetch or "Vicia faba" or "vigna unguiculata" or watercress or yam or yams or zucchini* or "sugar plant*" or sugarbeet*) OR</p>	1,045,286

	<p>AUTHKEY(vegetable* or alfalfa* or artichoke* or asparagus or aubergine* or "barrel medic" or "Basella alba" or bean or beans or beet or beets or (beta PRE/O (altissima or vulgaris)) or "bok choy" or broccoli or "Brussels sprout*" or cabbage or "Canavalia ensiformis" or Capsicum or cardoon or carob or carrot* or cassava or cauliflower* or celeriac* or celery or Chenopodium or chickpea* or chicory or chive or ((colic or rheumatism) PRE/O root*) or cocoyam* or collard or cornsalad or courgette or cowpea* or cress or cucumber* or Cucurbita* or Cyclopia or dasheen or "Daucus carota" or Dioscorea or (edible PRE/O (mushroom* or seaweed or "sea weed")) or endive or fennel or gardencress or garlic or girasole or "Glebionis coronaria" or guar or "Helianthus tuberosus" or horseradish or "Ipomoea aquatica" or kale or kimchi or kohlrabi or komatsuna or "Lalab purpureus" or "Lactuca sativa" or leek or legume or legumes or lentil* or Lepidium or lettuce or lupin or lupine or lupinus or "Macrotyloma uniflorum" or "Oenanthe javanica" or okra* or onion* or "Oxalis tuberosa" or "Pachyrhizus erosus" or paprika or parsley or parsnip* or pea or peas or peanut* or pepper* or (Phaseolus PRE/O (coccineus or unguiculatus or vulgaris)) or pigeonpea or potato* or "Psophocarpus tetragonolobus" or pumpkin or radish* or rapeseed* or rhubarb or rutabaga or ((salad or leguminous) PRE/O crop*) or sauerkraut or shallot* or soybean* or spinach or squash or sweetcorn or "Swiss chard" or Tamus or taro or topinambour or turnip* or vetch or "Vicia faba" or "vigna unguiculata" or watercress or yam or yams or zucchini* or "sugar plant*" or sugarbeet*)</p>	
6	<p>TITLE-ABS (((edible or food or refined or unrefined or polished or processed or whole or pseudo) PRE/O grain*) or wholegrain* or cereal* or barley or "Hordeum vulgare" or bread or "bakery product*" or "Coix lacryma" or "Coix lachryma" or adlay or "Job* tear*" or millet* or "Eleusine coracana" or "Setaria italica" or ragi or maize or "Zea mays" or corn or malt or oat* or "Avena sativa" or "Cenchrus americanus" or (Pennisetum PRE/O (glaucum or typhoides or typhoideum or americanum)) or "Setaria glauca" or rice or "Oryza sativa" or rye or sorghum or durra or wheat or "graminis leaf" or Triticum or emmer or spelt or triticale or (Triticum PRE/O (dicoccum or turgidum or aestivum or vulgare or "x Secale" or durum or monococcum)) or Triticosecale or Zizania or wildrice or (grain W/1 (flour or legum* or oil*)) or oatmeal or semolina or ((oil or cotton or lin or rape or safflower or sesame or sunflower) PRE/O seed*) or oilseed* or cottonseed* or linseed* or rapeseed* or safflowerseed* or sesameseed* or sunflowerseed* or pseudograin* or pseudocereal* or buckwheat or quinoa or chia or "Salvia hispanica" or nixtamal) OR AUTHKEY (((edible or food or refined or unrefined or polished or processed or whole or pseudo) PRE/O grain*) or wholegrain* or cereal* or barley or "Hordeum vulgare" or bread or "bakery product*" or "Coix lacryma" or "Coix lachryma" or</p>	985,496

	adlay or "Job* tear*" or millet* or "Eleusine coracana" or "Setaria italica" or ragi or maize or "Zea mays" or corn or malt or oat* or "Avena sativa" or "Cenchrus americanus" or (Pennisetum PRE/O (glaucum or typhoides or typhoideum or americanum)) or "Setaria glauca" or rice or "Oryza sativa" or rye or sorghum or durra or wheat or "graminis leaf" or Triticum or emmer or spelt or triticale or (Triticum PRE/O (dicoccum or turgidum or aestivum or vulgare or "x Secale" or durum or monococcum)) or Triticosecale or Zizania or wildrice or (grain W/1 (flour or legum* or oil*)) or oatmeal or semolina or ((oil or cotton or lin or rape or safflower or sesame or sunflower) PRE/O seed*) or oilseed* or cottonseed* or linseed* or rapeseed* or safflowerseed* or sesameseed* or sunflowerseed* or pseudograin* or pseudocereal* or buckwheat or quinoa or chia or "Salvia hispanica" or nixtamal)	
7	TITLE-ABS (milk or milkshake* or butter or buttermilk or ghee or cheese* or ((dairy or sourmilk) PRE/O product*) or whey or ((ice or sour* or cultured or fermented or dairy) PRE/O cream) or "sour dairy" or yoghurt or yogurt or yoghurt or zabadi or kefir or koumiss) OR AUTHKEY (milk or milkshake* or butter or buttermilk or ghee or cheese* or ((dairy or sourmilk) PRE/O product*) or whey or ((ice or sour* or cultured or fermented or dairy) PRE/O cream) or "sour dairy" or yoghurt or yogurt or yoghurt or zabadi or kefir or koumiss)	372,726
8	TITLE-ABS (((drinking or potable or bottled or mineral or soda or seltzer or sparkling or carbonated) PRE/O water) or "club soda*") OR AUTHKEY (((drinking or potable or bottled or mineral or soda or seltzer or sparkling or carbonated) PRE/O water) or "club soda*")	165,179
9	4 or 5 or 6 or 7 or 8	4,665,812
10	TITLE-ABS(analys* or analyz* or ((level or levels or amount) W/2 (nitros* or NOC)) or ((NDMA or NDEA or NDPA or NMEA or NDBA or NDIBA or NMA or NSAR or NMOR or NPIP or NPYR) W/1 (content* or increas* or decreas*)) or concentration or concentrations or estimat* or exposure* or occurrence* or ("total diet" or analytical) PRE/O stud*) OR AUTHKEY(analys* or analyz* or ((level or levels or amount) W/2 (nitros* or NOC)) or ((NDMA or NDEA or NDPA or NMEA or NDBA or NDIBA or NMA or NSAR or NMOR or NPIP or NPYR) W/1 (content* or increas* or decreas*)) or concentration or concentrations or estimat* or exposure* or occurrence* or ("total diet" or analytical) PRE/O stud*)	31,524,665
11	3 and 9 and 10	1,097

### Studies assessed in full text with reason for exclusion

An overview of the studies assessed for eligibility is presented in Table A3-1.

Table A3-1. Studies assessed for eligibility.

Reference	Include	Exclude	Reason for exclusion
(Aidjanov and Sharmanov, 1982)		X	Country
(Amron and Konsue, 2018)		X	Outcome
(Asami et al., 2009)		X	Country
(Bara et al., 2011)		X	Outcome
(Cao et al., 2018)		X	Outcome
(Castegnaro, 1991)		X	Outcome
(Cornee et al., 1992)		X	Outcome
(Dean-Raymond and Alexander, 1976)		X	Outcome
(Dich et al., 1996)		X	Outcome
(Dressel, 1976)	X		
(Eisenbrand et al., 1978)		X	Outcome
(El-Shamy and Farag, 2022)		X	Outcome
(Fazio and Havery, 1982)		X	Outcome
(Gavinelli et al., 1988)	X		
(Gough et al., 1978)		X	Outcome
(Groenen et al., 1987)		X	Outcome
(Groenen et al., 1980)		X	Outcome
(Hedler and Marquardt, 1968)		X	Outcome
(Hedler et al., 1979)		X	Outcome
(Heisler et al., 1974)		X	Outcome
(Heyns and Roeper, 1974)		X	Outcome
(IARC)		X	Outcome
(Jakszyn et al., 2006)		X	Outcome
(Jakszyn and Gonzalez, 2006a)		X	Outcome
(János, 2010)		X	Language
(Jansen and Elgersma, 1984)		X	Outcome
(Jansen and Elgersma, 1985)		V	Outcome
(Karlowski and Bojewski, 1982)		X	Outcome
(Karlowski and Bojewski, 1983)			Not retrieved
(Karlowski and Bojewski, 1986)			Not retrieved
(Keybets et al., 1970)		X	Outcome
(Kimoto et al., 1984)		X	Outcome
(Kocak et al., 2012)	X		
(Kohler, 1982)		X	Outcome
(Lakritz et al., 1982)		X	Country
(Lakritz and Pensabene)		X	Outcome
(Lakritz and Pensabene, 1984)		X	Outcome
(Lee and Huang, 2019)		X	Country
(Li et al., 2019)		X	Country
(Libbey et al.)		X	Country
(Lijinsky, 1999)		X	Study design
(Mavelle et al., 1991)	X		
(McIntyre and Scanlan, 1993)		X	Country
(McWeeny, 1983)		X	Study design
(Miller et al., 1984)		X	Outcome

Reference	Include	Exclude	Reason for exclusion
(Ministry of Agriculture, 1987)		X	Outcome
(Mizuishi et al., 1987)		X	Country
(Moehler et al., 1974)		X	Country
(Osterdahl, 1988a)		X	Outcome
(Osterdahl, 1988b)	X		
(Osterdahl, 1990)		X	Outcome
(Poirier et al., 1987a)		X	Outcome
(Poirier et al., 1987b)		X	Outcome
(Preussmann et al., 1982)			Not retrieved
(Riedmann, 1974)		X	Study design
(Scanlan, 1983)		X	Study design
(Scanlan, 1995)		X	Study design
(Sen et al., 1984)		X	Outcome
(Sen et al., 1980)		X	Country
(Sen et al., 1982)		X	Country
(Seo JungEun et al., 2016)		X	Country
(Seyyedsalehi et al., 2023)		X	Study design
(Smiechowska et al., 1994)	X		
(Spiegelhalder et al., 1980a)		X	Outcome
(Spiegelhalder et al., 1980b)		X	Outcome
(Stephany et al., 1978)	X		
(Tauts and Loigom, 1978)		X	Not retrieved
(Terplan et al., 1980)	X		
(Terplan et al., 1978)	X		
(Uibu et al., 1996)		X	Outcome
(UK, 1974)		X	Not retrieved
(van Maanen et al., 1998)		X	Study design
(Walters et al., 1978)		X	Study design
(Walters et al., 1974)		X	Outcome
(Webb and Gough, 1980)		X	Study design

## Appendix 4 Food groups included for the OIM dietary exposure estimation

### Compilation of nitrate concentrations

#### *Dairy*

In the dairy food group, we found four entries from EFSA et al. (2017a) and one from EFSA (2008). They were quite similar when comparing fluid milk with fermented and concentrated products. The dairy values for nitrate were thus based on the EFSA et al. (2017a) values.

#### *Eggs*

No concentration values for nitrate were available for eggs, and eggs were therefore not included in the dietary exposure estimation. This may contribute to underestimation of the intake estimations of nitrate from food. How much this will influence the total intake estimations is unclear.

#### *Fish and fish products*

The available concentration values on nitrate in fish were only 4 data entries in EFSA et al. (2017a). Weighted average of three of these entries were used for fish and fish products, except for pickled herring and sprat, and farmed salmon, which were given other concentrations based on data entries specific for this type of fish products. Nitrate concentrations for salmon were compiled from data retrieved from the NFSA (unpublished data). Shellfish were given the same concentration as fish and fish products.

#### *Fruit and berries*

Nitrate values for fruit were only available on aggregated level (Fruit and fruit products, Fruit juices, Mixed Fruit juice) from the EFSA et al. (2017a) report, EUROFIR had two entries for nitrate in apples from Slovenia. Therefore, the nitrate concentrations for fruit were based on the one value for fruit on an aggregated level. Concentration values on nitrate levels in berries were missing. Here we chose to assign the nitrate in berries based on the fruit value. Fruit juices were given the weighted average of the two entries for fruit juices. Vine leaves were assigned a specific nitrate value based on the specific concentration from the EFSA et al. (2017a) report. Dried fruits were assigned to the fruit value multiplied with 1,5 to adjust for water evaporation.

#### *Grains*

There were no concentration values on nitrate levels in grains. All intakes of grains, grain products and other cereal products will therefore have missing values. How much this will influence the total intake estimations is unclear.

## *Meat*

### **Turkey, chicken, duck**

Only one entry of nitrate concentration was found in the source material EFSA et al., (2017a). This value was for “Ham turkey”, and thus this concentration was assigned to all white meat, including turkey, chicken and duck, and products thereof.

### **Beef, mutton, pork, game, and products thereof**

Beef and products thereof were assigned the value for “Beef meat” from the EFSA et al. (2017a) report. Meat balls were assigned the same value, and sausages were assigned a weighted average based on all the entries for beef sausages in EFSA et al. (2017a). There were no concentration values for liver.

Four entries for nitrate were found for pork and pork products. Pork and pork products were assigned the weighted average of these, excluding the value for dried pork meat which was used for only that specific food group.

One entry of nitrate in mutton and lamb was available in EFSA et al. (2017a). This value was thus assigned to all mutton and lamb intakes and products.

The EFSA et al. (2017a) report included one entry for nitrate in game meat, thus all game meat in the project were assigned this value.

## *Vegetables*

Both EFSA et al. (2017a) and EFSA (2008) included concentration values on nitrate in potatoes. A weighted average of all relevant entries from both reports were used for potatoes and potato products. Nitrate levels for carrots, cauliflower, cabbage, onion, and tomato were based on analytical data from NFSA (NFSA, 2024; NFSA, 2025).

## *Food for infants*

There were three food categories for infants in EFSA et al. (2017a). In our assessment, we used two of these categories: “Food for infants and small children” (FoodEx2 level 2), which includes 524 entries, and “Follow-on formulae, liquid” (FoodEx2 level 2), represented by 14 samples, of which 11 were left-censored.

A key source of uncertainty is that the “Food for infants and small children” category does not distinguish between product types, making it unclear which specific foods the entries represent (e.g. porridge or vegetable casserole).

For the follow-on formulae, all products in the Spedkost 3 questionnaire were reported as liquid formulas, consistent with the EFSA category used.

### Drinking water (tap water)

Concentration values for nitrate were extracted from the Norwegian Waterworks Registry (VREG, 2024). For each waterworks, the reported concentration was linked to the number of inhabitants supplied. Weighted population distributions were then calculated to estimate cumulative population counts and corresponding concentration percentiles (5<sup>th</sup>, 10<sup>th</sup>, 25<sup>th</sup>, median (50<sup>th</sup>), 75<sup>th</sup>, 90<sup>th</sup>, and 95<sup>th</sup>). This population-weighted approach ensures that waterworks supplying larger populations contribute proportionally to the overall distribution.

Data on nitrate concentrations in Norwegian drinking water were obtained from the Norwegian Waterworks Registry (VREG), representing values reported in 2024. The dataset includes information on water quality from registered waterworks and the number of inhabitants supplied. Weighted concentration values were calculated to reflect the distribution of exposure across the population, providing a national overview of nitrate levels in drinking water. The weighted distribution of nitrate concentrations in Norwegian drinking water was calculated from data reported by 943 waterworks to VREG in 2024 (Table A4-1). The data covers 64% of the Norwegian population. Median nitrate concentration (50th percentile) was 0.132 mg/L, with most of the population receiving water well below the Norwegian guideline value of 50 mg/L. Only a small proportion of the population at the higher percentiles experienced elevated concentrations, and the maximum recorded concentration was 36 mg/L, remaining below the guideline value. Overall, these data indicate that nitrate levels in Norwegian drinking water are generally low and well within recommended limits.

**Table A4-1.** Weighted distribution of nitrate concentration in Norwegian drinking water

Summary measure	Cumulative population (n)	Weighted nitrate concentration (mg/L)
Minimum	–	0.000
5th percentile	176,906	0.031
10th percentile	353,812	0.050
25th percentile	884,529	0.080
Median	1,769,058	0.133
75th percentile	2,653,586	0.290
90th percentile	3,184,304	0.516
95th percentile	3,361,209	0.760
Maximum	–	36.000
Mean	–	0.319
SD	–	0.867

### Compilation of nitrite concentrations

The availability of concentration data for nitrite was limited to the following food groups: vegetables, red and white meat, milk and dairy products, infant food, and composite dishes. For other food groups, the number of analyses was either fewer than three or available only at FoodEx2 level 1, as described in Section 3.4.1. Consequently, nitrite concentrations were not assigned to these groups.

### *Vegetables*

Norwegian concentration values were used for the following vegetables: cauliflower, carrot, cabbage, onion, tomato, celeriac, rutabaga, cucumber, red cabbage, celery, leek, iceberg lettuce, and spinach. These vegetables are widely consumed in Norway and account for the majority of vegetable intake. Four analyses were available for each vegetable, except for cauliflower, for which eight analyses were conducted. All samples, except one sample of rutabaga, were below the limit of quantification (LOQ); therefore, half the LOQ ( $\frac{1}{2}$  LOQ) was applied as the concentration value. For other vegetables, values from EFSA et al. (2017a) were used.

### *Red meat and meat products*

Fifteen food categories from EFSA et al. (2017a) were used to match occurrence data to Norwegian foods. A wide variety of sausages and types of ham were included, and these appeared to have similar nitrite levels. However, it is not known to what extent nitrite had been added to the samples presented in EFSA et al. (2017a), nor is it known whether the foods reported as consumed contained added nitrite.

### *White meat and meat products*

Values were derived from EFSA et al. (2017a). For poultry, two food categories were used. However, it is not known to what extent nitrite had been added to the samples presented in EFSA et al. (2017a), nor is it known whether the foods reported as consumed contained added nitrite.

### *Milk and dairy products*

Values were derived from EFSA et al. (2017a). There were two food groups with liquid milk, and *cheese*, and all milk and cheese were given these median values.

### *Infant food*

Infant food values were applied to children aged 1 and 2 years. All values were obtained from EFSA et al. (2017a). In total, eight different food categories were included within this group, encompassing foods containing cereals, meat, fish, and vegetables. Foods not specifically intended for infants were assigned values from the corresponding general food groups.

### *Composite dishes*

This category includes ready-made foods such as pizza, tacos, and soups. The occurrence values for these foods are therefore derived as composites, based on the contributions of ingredients from the relevant underlying food groups.

### *Drinking water (tap water)*

Concentration values for nitrite were extracted from the Norwegian Waterworks Registry (VREG, 2024). For each waterworks, the reported concentration was linked to the number of inhabitants supplied. Weighted population distributions were then calculated to estimate

cumulative population counts and corresponding concentration percentiles (5<sup>th</sup>, 10<sup>th</sup>, 25<sup>th</sup>, median (50<sup>th</sup>), 75<sup>th</sup>, 90<sup>th</sup>, and 95<sup>th</sup>). This population-weighted approach ensures that waterworks supplying larger populations contribute proportionally to the overall distribution.

Data on nitrite concentrations in Norwegian drinking water were obtained from the Norwegian Waterworks Registry (VREG), representing values reported in 2024. The dataset includes information on water quality from registered waterworks and the number of inhabitants supplied. Weighted concentration values were calculated to reflect the distribution of exposure across the population, providing a national overview of nitrite levels in drinking water.

The weighted distribution of nitrite concentrations in Norwegian drinking water was calculated from data reported by 958 waterworks to VREG in 2024 (Table A4-2). The data covers 55% of the Norwegian population. Median nitrite concentration (50th percentile) was very low (0.002 mg/L), with the majority of the population receiving water well below the Norwegian guideline value of 0.5 mg/L. Only a small proportion of the population at the higher percentiles (90th–95th) experienced slightly higher concentrations, and the maximum recorded concentration exceeded the guideline at 1.01 mg/L. Overall, these data indicate that nitrite levels in Norwegian drinking water are generally low, with few waterworks supplying water above recommended limits.

**Table A4-2.** Weighted distribution of nitrite concentration in Norwegian drinking water.

Summary measure	Cumulative population (n)	Weighted nitrite concentration (mg/L)
Minimum	–	0.000
5th percentile	153,094	0.001
10th percentile	306,189	0.001
25th percentile	765,472	0.002
50th percentile (median)	1,530,944	0.002
75th percentile	2,296,415	0.010
90th percentile	2,755,698	0.020
95th percentile	2,908,793	0.033
Maximum	–	1.010
Mean	–	0.0122
SD	–	0.0356

## Compilation of N-nitrosamine concentrations

The availability of concentration values for N-NAs was limited to a relatively small number of food groups. Most concentration values were available for meat products, with more limited data for fish. Additional values were available for selected food groups, including cheese, cocoa, and alcoholic beverages.

### *Meat and meat products*

For meat products, EFSA FoodEx2 classification codes were applied where possible. White meat was represented using EFSA level 3 categories “Birds meat” and “Poultry fresh meat (muscle meat)”. Pork and lamb were represented by “Pig fresh meat” and “Lamb fresh meat”, respectively. For beef, where specific values were not available, broader level 2 and 3 categories (“Processed whole meat products” and “Mammals meat”) were used. Norwegian concentration data were applied for several processed meat products, including sausages (excluding those based on white meat), meat spreads and pâtés (excluding white meat), cured meats (excluding white meat), bacon, and canned meat products. No values were assigned to processed products based on white meat (e.g. sausages, pâtés, and cured products).

### *Infant food*

No concentration values were available for foods intended for infants. Consequently, infant foods were assigned values based on corresponding ingredients, primarily meat-containing components in recipes from the Norwegian Food Composition Table (NFC), where considered relevant.

### *Fish and fish products*

For fish and seafood, some concentration values were available from EFSA, although not for all N-NAs included in the current assessment. VKM applied FoodEx2 level 4 categories where possible. “Smoked fish” was used for all smoked fish products, “canned/jarred fish” for products such as mackerel in tomato, tuna, and brisling in oil, and “marinated/pickled fish” for products such as pickled herring. “Processed or preserved seafood” was applied to shellfish such as shrimp and mussels in brine or canned form. The category “processed or preserved fish (including processed offal)” was applied to products such as lutefisk, dried fish, gravad salmon, caviar, and cod liver and roe pâté. This category was not applied to composite products such as fish cakes, where fish typically constitutes only around 50% of the product. For certain composite food categories, such as “pickled herring in sauce”, this approach may lead to overestimation, as these products contain multiple ingredients. However, given the limited coverage of fish categories with assigned nitrosamine values, this approach was considered appropriate.

### *Beverages*

In addition to meat and fish, concentration values were applied for beer (represented using EFSA level 3 “Beer” for all alcoholic beer types), unsweetened spirits, and cocoa.

### *Literature search results*

The literature search (see Section 3.2.1) identified only a limited number of additional data points, summarised below:

- **Kocak (2012)** analysed tomatoes, aubergines, and peppers grilled over coal, with three samples included for each food item. These data were not used in the OIM exposure assessment because the preparation method (grilling over coal) is uncommon and may

influence the measured concentrations in ways that are difficult to interpret. In addition, the small number of samples underlying each composite value limits the reliability of the dataset.

- **Mavelle (1991)** reported concentrations in cheese, frozen vegetables, and cocoa products such as milk and milk-free chocolate. The dietary surveys did not report consumption for most foods included in this study. For those foods that were consumed according to the surveys, the N-NA concentrations were generally based on only a single sample and were therefore not considered suitable for use in the OIM exposure assessment. Cheese was an exception, with 21 samples analysed for NDEA and a reported mean concentration of 0.00044 mg/kg. Five of these samples were below the detection limit, and no information was provided on how non-detects were treated in calculating the mean. We decided to use the mean value of 0.00044 mg/kg for the cheese category in the OIM exposure assessment, as this corresponds to the relevant FoodEx2 level.
- **Gavinelli (1988)** analysed milk and powdered milk formula for infants. Nine samples were included, and none were above the detection limit of 0.00005 mg/kg. Because the dataset is old and formulation changes in powdered milk are likely, these values were not included in the OIM exposure assessment.

## Appendix 5. Methods for summarising occurrence data and estimating dietary exposure for nitrate, nitrite and nitrosamines

The first draft was written by Claude (Anthropic AI), and controlled and redrafted by Trine Husøy.

### Overview

This document describes the methods used to process and summarise occurrence data for nitrate, nitrite, and nitrosamines, and to estimate dietary exposure in the Norwegian adult population using consumption data from the Norkost 4 dietary survey. The workflow covers four main areas: (1) processing EFSA occurrence data for nitrate and nitrite in food using ROS-based imputation of non-detects and calculate new summary data per included food groups, (2) calculation of population-weighted summary statistics for nitrate and nitrite in Norwegian drinking water, (3) extraction of occurrence summaries across multiple nitrosamines in food, and (4) probabilistic dietary exposure assessment for nitrate, nitrite, and nitrosamines using Monte Carlo simulation applied to Norkost 4 consumption data. The methods are shown for Norkost4, but was also performed for children age 4-, 9- and 13- years old according to the same approach.

The methods, R-scripts and data files are available at [https://github.com/TrineHusoy/Nitrate\\_Nitrite.git](https://github.com/TrineHusoy/Nitrate_Nitrite.git)

### Nitrate and nitrite in Food (EFSA data)

#### *Occurrence data sources*

Three data files were used, nitrate from EFSA 2008 and EFSA 2017, and nitrite from EFSA 2017.

#### *Consumption data sources*

The consumption data is confidential due to individual information on all participants. According to GDPR these cannot be shared. We therefore created fictive data for testing of the code.

#### *Data cleaning and column standardisation*

Each EFSA 2017 file contains occurrence statistics reported as lower bound (LB), middle bound (MB) and upper bound (UB) scenarios for left-censored (non-detected) samples. Relevant columns are selected and renamed to a consistent short-name scheme:

Column	Description
<b>N</b>	Total number of samples

Column	Description
<b><i>N_censor</i></b>	Number of left-censored (non-detected) samples
<b><i>Mean_LB</i></b>	Mean concentration, lower bound (non-detects = 0)
<b><i>Mean_MB</i></b>	Mean concentration, middle bound (non-detects = LOD/2)
<b><i>Mean_UB</i></b>	Mean concentration, upper bound (non-detects = LOD)
<b><i>P50_LB/MB/UB</i></b>	Median for each bound scenario
<b><i>P95_LB/MB/UB</i></b>	95th percentile for each bound scenario
<b><i>Min/Max_LOD</i></b>	Detection limit range
<b><i>Min/Max_LOQ</i></b>	Quantification limit range

NFC food category codes are joined from to form a ***Samlet\_Database.csv*** via a ***left\_join()*** on the ***Foodex*** category name from Norkost4 (2 days) and Ungkost3 (4 days). These NFC codes are used to filter each food group in the subsequent steps.

For nitrate 2008, the does not contain information on non-detects, and concentrations are used directly.

### *Estimating lognormal distribution parameters from summary statistics*

The EFSA occurrence data are reported as summary statistics (mean, median, P95) for each food item, not as individual measurements. To generate a pseudo-individual dataset suitable for further analysis, the underlying lognormal distribution must first be reconstructed for each food item. This is done separately for the LB, MB and UB scenarios, since these data already includes imputations of non-detects

#### **Mathematical background**

A lognormal distribution is fully described by two parameters: the location parameter  $\mu$  (mean of the log-transformed values) and the shape parameter  $\sigma$  (standard deviation of the log-transformed values). For a lognormal random variable  $X$  with parameters  $\mu$  and  $\sigma$ , the arithmetic mean and a given quantile  $z_\alpha$  at probability  $\alpha$  satisfy:

$$\text{Mean} = e^{\mu + \sigma^2/2}$$

$$z_\alpha = e^{\mu + \sigma \cdot \Phi^{-1}(\alpha)}$$

where  $\Phi^{-1}(\alpha)$  is the standard normal quantile at probability  $\alpha$ . Taking the ratio of the log-quantile to the log-mean gives:

$$\log(z_\alpha) - \log(\text{Mean}) = \sigma \cdot \Phi^{-1}(\alpha) - \sigma^2/2$$

Rearranging yields a quadratic equation in  $\sigma$ :

$$\sigma^2 - 2\Phi^{-1}(\alpha) \cdot \sigma + 2(\log(\text{Mean}) - \log(z_\alpha)) = 0$$

which is solved using the quadratic formula. The positive root is retained as the valid  $\sigma$ , and  $\mu$  is then back-calculated as:

$$\mu = \log(\text{Mean}) - \sigma^2/2$$

#### Implementation — `mu_sigma()`

The function `mu_sigma()` applies this calculation for all three censoring scenarios (LB, MB, UB) and for both the P95 and P50 quantiles, using six helper functions (`f_lb_95`, `f_lb_50`, `f_mb_95`, `f_mb_50`, `f_ub_95`, `f_ub_50`). Each helper works row-by-row on the occurrence data frame and returns  $\mu$  and  $\sigma$  for that scenario and quantile combination.

P95 is used as the primary basis for parameter estimation, as it provides better leverage for characterising the upper tail of the distribution. Where the P95-based solution yields **NA** or infinite values (e.g. when the P95 is zero or equal to the mean), the function automatically falls back to the P50-based estimate:

```
mu_sigma_vals <- mu_sigma(group_data)
# Returns columns: mu_lb, sigma_lb, mu_mb, sigma_mb, mu_ub, sigma_ub
```

For the EFSA 2008 data, where only a single set of summary statistics is available (no LB/MB/UB breakdown), the equivalent functions `mu_sigma_2008()`, `f_95()` and `f_50()` are used in the same way.

#### Generating pseudo-individual concentration data from LB, MB and UB scenarios

Once  $\mu$  and  $\sigma$  have been estimated for each food item and scenario, pseudo-individual concentration values are drawn by random sampling from the fitted lognormal distributions. The function `f_conc_ind()` does this separately for the LB, MB and UB scenarios, generating one random draw per non-censored observation (`N_not_censor = N - N_censor`) for each food item:

```
f_conc_ind <- function(y) {
  set.seed(123)
  for (i in 1:nrow(y)) {
    lb_list[[i]] <- rlnorm(n = y$N_not_censor[i], meanlog = y$mu_lb[i], sdlog = y$sigma_lb[i])
    mb_list[[i]] <- rlnorm(n = y$N_not_censor[i], meanlog = y$mu_mb[i], sdlog = y$sigma_mb[i])
    ub_list[[i]] <- rlnorm(n = y$N_not_censor[i], meanlog = y$mu_ub[i], sdlog = y$sigma_ub[i])
  }
  # ...
}
```

Censored observations (non-detects) are added back as zeros for all three scenarios. The output is a long-format data frame with columns `value`, `scenario` (LB, MB or UB), and

**foodgroup**. At this stage, the zeros serve as placeholder values for the non-detects — these will subsequently be replaced by ROS-imputed values.

This approach means that for each food item, the uncertainty associated with how non-detects are handled is carried forward explicitly as three parallel datasets, rather than collapsed to a single point estimate. The complete pipeline — food group filtering, quality control, parameter estimation, and individual data generation — is wrapped in **process\_all\_food\_groups()**. Each food subgroup is defined by a list entry with a **name** and **keywords** for pattern matching on the **Foodex** column (case-insensitive regex). The last group uses **keywords = NULL** to capture all remaining rows:

```
food_groups <- list(
  list(name = "rucola",          keywords = c("(?)Rucola")),
  list(name = "lettuce",        keywords = c("(?)lettuce", "(?)Spinach")),
  list(name = "other_vegetables", keywords = NULL)
)

individual_per_vegetablegroup <- process_all_food_groups(nitrate_2017_vegetable, food_g
roups)
combined_vegetable_ind        <- individual_per_vegetablegroup$combined_group_ind
```

Before parameter estimation, food items with fewer than 3 non-censored observations are excluded ( **$N_{not\_censor} < 3$** ), as too few detections make lognormal parameter estimation unreliable. Food items yielding infinite parameter values (e.g. due to zero variance) are also removed.

The output **combined\_group\_ind** is a long-format data frame with columns **value**, **scenario**, and **foodgroup**, ready for ROS imputation.

For the 2008 data, **process\_all\_food\_groups\_2008()** and **f\_conc\_ind\_2008()** are used instead. These work identically but without the LB/MB/UB distinction, since the 2008 dataset does not report separate censoring scenarios.

### *Imputation of non-detects by the ROS method*

#### **Background**

The pseudo-individual datasets from **f\_conc\_ind()** contain zeros as placeholders for all left-censored (non-detected) observations. These zeros are replaced with statistically plausible values using the **Regression on Order Statistics (ROS)** method, implemented via **cenros()** from the **NADA** package (Lee, 2020).

ROS is a well-established approach for handling left-censored environmental and food occurrence data. The method proceeds as follows:

1. The detected (non-censored) observations are ranked and plotted on a normal probability scale (using their log-transformed values).

2. A regression line is fitted through the detected values on this probability plot.
3. The fitted regression line is used to predict values for the censored observations based on their expected positions in the distribution — i.e. the positions they would occupy if the full distribution were observed.

This preserves the shape of the distribution and avoids the bias introduced by simpler substitution methods (such as replacing non-detects with 0, LOD, or LOD/2), particularly when the censoring fraction is high.

#### Implementation — `ros_impute()`

```
ros_impute <- function(data) {
  results <- lapply(unique(data$foodgroup), function(fg) {
    df_fg <- data %>% filter(foodgroup == fg)
    values <- df_fg$value
    censored <- ifelse(values == 0, TRUE, FALSE) # zeros = non-detects

    if (sum(!censored) < 3) return(NULL) # skip if too few detections

    ros_result <- cenros(values, censored)
    df_fg$imputed <- ros_result$modeled
    return(df_fg)
  })
  list(imputed_data = bind_rows(results), skipped_groups = skipped)
}
```

The function loops over each food group, identifies zeros as censored values, and applies `cenros()`. Food groups with fewer than 3 detected values are skipped and reported in `$skipped_groups`. The output column `imputed` contains the final concentration values — observed values are unchanged, while censored values are replaced by ROS-modelled estimates.

The ROS imputation is applied separately within each LB, MB and UB scenario, meaning the three parallel datasets are maintained through to the final summary step. Because the non-detects represent genuine analytical zeros under the LB scenario but half-LOD values under MB, the imputed values will differ between scenarios even for the same food group, correctly reflecting the underlying uncertainty.

```
combined_vegetable_ind[is.na(combined_vegetable_ind)] <- 0
imputed_vegetables <- ros_impute(combined_vegetable_ind)
nitrate_2017_imputed_vegetables <- imputed_vegetables$imputed_data
```

#### *Food categories included*

The following food categories are processed for nitrate (EFSA 2017 and 2008 combined) and nitrite (EFSA 2017 only). Categories excluded due to insufficient positive detections or no data are noted.

**Nitrate — food categories included:**

Category	Subgroups	Notes
Vegetables	rucola, peas, bean/legume, kale/root, lettuce/spinach, other_vegetables	Rare vegetables (cardoons, purslane etc.) excluded
Meat	meat (single group)	
Beverages	alcoholic, beverage	Drinking water extracted separately; tea excluded
Fruit	fruit (single group)	
Dairy	cheese	Infant formula excluded
Fish	fish (single group)	
Grain	pasta, grain	
Infant food	infant (single group)	
Butter/oil	—	Excluded (only one analysis)
Compound dish	—	Excluded (mainly sauerkraut after vegetable subsets removed)
Various	—	Excluded (insufficient metadata)

**Nitrite — food categories included:**

Category	Subgroups	Notes
Meat	poultry, sausage, pastrami pork, pork/bacon, corned beef, beef, other_meat	Offal excluded (unrepresentative high values)
Vegetables	lettuce/rucola/spinach	
Dairy	cheese	
Compound dish	composite	
Infant food	cereal, ready-to-eat	Two subcategories removed before processing
Beverages	—	Excluded (too few positive analyses)
Fruit	—	Excluded (too few positive analyses; unrealistic imputed values)
Fish	—	Excluded (ROS calculation failed due to no positive values)
Grain	—	Excluded (only one positive analysis)

*Combining food groups and computing summary statistics*

After imputation, all food group datasets are bound together into a single data frame. The **imputed** column is renamed to **value** and the dataset is passed to **Sum\_1()**:

```
# Nitrate
```

```
Nitrate_2017_imputed <- bind_rows(
  nitrate_2017_imputed_vegetables, nitrate_2017_imputed_meat,
  nitrate_2017_imputed_beverage,   nitrate_2017_imputed_dairy,
  nitrate_2017_imputed_fish,       nitrate_2017_imputed_fruit,
```

```
nitrate_2017_imputed_grain
)
Nitrate_2017 <- Nitrate_2017_imputed %>% select(foodgroup, imputed) %>%
  rename(value = imputed)

Nitrate_2017_sum <- Sum_1(Nitrate_2017)
```

For nitrate, the EFSA 2017 and 2008 datasets are also combined before final summarisation, to maximise the number of observations across food groups:

```
Nitrate_individual <- bind_rows(Nitrate_2017, Nitrate_2008)
Nitrate_sum <- Sum_1(Nitrate_individual)
```

**Sum\_1(x)** groups the data by **foodgroup** and computes N, mean, sd, min, P05, P50, P95 and max for the **value** column. Because the input contains one row per pseudo-individual observation (expanded from summary statistics via **process\_all\_food\_groups()**), N reflects the total number of simulated individuals across all food items in that group.

Results are saved to Excel:

```
write_xlsx(Nitrate_sum, path = file.path(newday, "Nitrate_sum.xlsx"))
write_xlsx(Nitrite_sum, path = file.path(newday, "Nitrite_sum.xlsx"))
```

### Exploratory visualisation

Density plots of the imputed values are produced for each food category using **ggplot2** with **facet\_wrap(~ foodgroup)**, allowing visual inspection of the concentration distributions before and after combining datasets. Plots are saved as JPEG files to the date-stamped results folder.

## Nitrate and Nitrite in Drinking Water

### Data import and cleaning

The raw data file (**Nitritt\_nitrat\_2022\_2023\_VANN\_rapportert\_2022.csv**) is read using **read.csv2()** with Latin-1 encoding. Before any analysis, all character columns are converted to UTF-8 using the utility function **f\_df\_convert\_utf8()**:

```
analyses_water_raw <- f_df_convert_utf8(analyses_water_raw)
```

#### **f\_df\_convert\_utf8(df\_data)**

Converts all character columns in a data frame from Windows-1252 encoding to UTF-8, silently dropping any characters that cannot be converted. This is necessary when data originates from Norwegian Windows-based systems where special characters (e.g. æ, ø, å) may be stored in legacy encodings.

The data are then split by analyte type:

```
nitrate_water <- analyses_water_raw %>% filter(analysetype == "Nitrat")
nitrite_water <- analyses_water_raw %>% filter(analysetype == "Nitritt")
```

Relevant columns are selected: county number (*fylkenr*), monitoring region (*mtregion*), municipality name (*kommavn*), number of connected persons (*ant\_tilknyttet*), number of analyses (*ant\_analyser*), and the min, max, mean and median concentration values.

### Weighted summary statistics

Because each data row represents a water supply serving a different number of connected persons, simple (unweighted) statistics would give equal weight to a small and a large supply. Instead, the number of connected persons (*ant\_tilknyttet*) is used as a frequency weight throughout. Two helper functions are defined inline in the occurrence script for this purpose.

*wtd\_quantile(x, w, probs)*

```
wtd_quantile <- function(x, w, probs = c(0.5)) {
  Hmisc::wtd.quantile(x, weights = w, probs = probs, na.rm = TRUE)
}
```

Calculates weighted quantiles using *Hmisc::wtd.quantile()*. The input *x* is the concentration vector (median values per water supply), *w* is the vector of weights (number of connected persons), and *probs* specifies which quantiles to return. For nitrate, the 5th, 50th and 95th percentiles are computed:

```
nitrate_quantiles <- wtd_quantile(
  x = nitrate_water$verdi_median,
  w = nitrate_water$ant_tilknyttet,
  probs = c(0.05, 0.5, 0.95)
)
```

*wtd\_mean\_sd(x, w, sd\_type)*

```
wtd_mean_sd <- function(x, w, sd_type = c("unbiased", "population"), na.rm = TRUE) {
  sd_type <- match.arg(sd_type)
  mu <- stats::weighted.mean(x, w)
  W <- sum(w)
  ssd <- sum(w * (x - mu)^2)
  var_w <- if (sd_type == "population") {
    ssd / W
  } else {
    (W / (W - 1)) * (ssd / W)
  }
  c(mean_w = mu, sd_w = sqrt(var_w))
}
```

Calculates the weighted mean and weighted standard deviation. Two variance estimators are available: *"population"* divides by the total weight sum *W*, while *"unbiased"* applies the

Bessel-like correction  $W / (W - 1)$ . For nitrate, the population estimator is used with mean concentration (*verdi\_gjsn*) as the input:

```
nitrate_mean_sd <- wtd_mean_sd(
  x      = nitrate_water$verdi_gjsn,
  w      = nitrate_water$ant_tilknyttet,
  sd_type = "population"
)
```

### Assembling the summary table

The mean, standard deviation, and percentiles are combined into a single wide-format summary table and labelled with *foodgroup = "drinking\_water"*:

```
nitrate_sum <- bind_rows(nitrate_mean_sd, nitrate_quantiles) %>%
  pivot_wider(names_from = Unit, values_from = value)

nitrate_sum$foodgroup <- "drinking_water"
```

The resulting table contains one row with the columns *foodgroup, mean, sd, P5, P50, and P95*, representing the population-weighted concentration distribution for nitrate in drinking water. The final table is saved to Excel.

## Nitrosamines in Food

### Data import and cleaning

The raw data file (*Nitrosamines\_EFSA\_2023.csv*) originates from the EFSA occurrence database and is read with *read.csv2()* using Latin-1 encoding. The file contains metadata rows and non-standard column names, which require manual cleaning:

```
# Select relevant columns
nitrosamines <- nitrosamines_2023_raw %>%
  dplyr::select(c("X.1", "X.2", "X.3", "X.4", "X.5",
                 "X.6", "X.7", "X.8", "X.9", "Selected.concentration",
                 "X.20", "X.21", "X.22", "X.23", "X.24"))

# Promote first row to column names and remove it
colnames(nitrosamines) <- as.character(unlist(nitrosamines[1, ]))
nitrosamines <- nitrosamines[-1, ]

# Assign clean names
colnames(nitrosamines) <- c(
  "substance", "foodex_1", "foodex_2", "foodex_3", "foodex_4",
  "foodex_5", "foodex_6", "foodex_7", "foodex_level",
  "n", "% l_censor", "mean_lb", "mean_mb", "mean_ub"
```

```
)
nitrosamines <- nitrosamines[, -15] # remove unnamed trailing column
```

Numeric columns use a comma as the decimal separator (Norwegian locale), which is replaced with a period before coercion to **numeric**:

```
col_num <- c("n", "% l_censor", "mean_lb", "mean_mb", "mean_ub")
nitrosamines[col_num] <- sapply(nitrosamines[col_num], function(col) {
  as.numeric(gsub(",", ".", col))
})
```

The key concentration columns are:

Column	Description
<b>mean_lb</b>	Mean concentration assuming non-detects = 0 (lower bound)
<b>mean_mb</b>	Mean concentration assuming non-detects = LOD/2 (middle bound)
<b>mean_ub</b>	Mean concentration assuming non-detects = LOD (upper bound)
<b>n</b>	Number of analytical measurements for that food/substance combination

### *Extracting summaries for a single nitrosamine*

The function `extract_nitrosamine_summary()` (from **Utility\_functions\_nitrosamines\_220426.R**) processes the full occurrence dataset and returns descriptive statistics for a single nitrosamine across the predefined food categories.

```
ndma_summary <- extract_nitrosamine_summary(nitrosamines, substance_name = "NDM
A")
```

```
extract_nitrosamine_summary(nitrosamines, substance_name, mean_col, n_col,
sum_fun, drop_level1_pattern)
```

The function proceeds in the following steps:

#### **Step 1 — Filter by substance and FoodEx level.**

Rows are filtered to the specified substance, and rows classified at FoodEx level 1 (i.e. broad food categories with no analytical detail) are removed using a pattern match on the **foodex\_level** column.

#### **Step 2 — Build weighted value blocks per food category.**

For each of the predefined food categories (listed below), the matching rows are extracted and a “block” of values is created by the internal helper `make_block()`. This function replicates each mean concentration value a number of times equal to the number of analyses **n** for that food item. This produces a vector where each observation is effectively weighted by how many measurements it is based on — a frequency-weighted representation of the occurrence data.

meat	Mammals and birds meat	(foodex_2)
bacon	Bacon	(foodex_5)
meat processed	Processed whole meat products	(foodex_2)
sausages	Sausages	(foodex_2)
fish_processed	Fish and seafood processed	(foodex_2)
beer	Beer and beer-like beverage	(foodex_2)
alcohol	Unsweetened spirits and liqueurs	(foodex_2)

Each category is extracted and removed from the working dataset sequentially, so that bacon (identified at the more specific foodex\_5 level) is correctly separated from the broader meat group.

### Step 3 — Compute summary statistics.

All value blocks are bound together and passed to the summary function `Sum_1()` (see Section 3.4), which calculates N, mean, sd, min, P05, P50, P95 and max grouped by food category.

### Step 4 — Finalise output.

Food groups are ordered according to the fixed sequence above, and the nitrosamine name is appended as a column.

The `mean_col` argument controls which concentration bound is used. The default is `"mean_lb"` (lower bound), but `"mean_mb"` or `"mean_ub"` can be specified to obtain middle- or upper-bound summaries.

## Extracting summaries for all nitrosamines

The wrapper function `extract_all_nitrosamines_summary()` calls `extract_nitrosamine_summary()` for each substance in a list and combines the results into a single data frame:

```
all_nitrosamine_summaries <- extract_all_nitrosamines_summary(
  nitrosamines,
  substances = c("NDMA", "NDPA", "NDEA", "NPYR", "NPIP", "NMA", "NDBA",
                 "NMOR", "NMEA", "NSAR", "NTCA", "NMTCA", "NPRO"),
  mean_col   = "mean_lb"
)
```

### `extract_all_nitrosamines_summary(nitrosamines, substances, mean_col, n_col, sum_fun, drop_level1_pattern)`

Iterates over the `substances` vector using `lapply()`, passing all arguments through to `extract_nitrosamine_summary()`. Empty results (substances with no matching data) are silently dropped before binding with `dplyr::bind_rows()`. The output is a long-format table with one row per food group per nitrosamine.

The combined table can be filtered to inspect individual food categories across all nitrosamines:

```
sum_sausages <- all_nitrosamine_summaries %>% filter(foodgroup == "sausages")
sum_bacon <- all_nitrosamine_summaries %>% filter(foodgroup == "bacon")
```

Results are saved to Excel:

```
write_xlsx(all_nitrosamine_summaries_LB,
           path = file.path(newday, "all_nitrosamine_summaries_LB.xlsx"))
```

### Summary statistic functions

Two summary functions are defined in the utility files.

**Sum(x)** — used for ungrouped data. Calculates N, mean, sd, min, P05, P50, P95 and max across all rows of a data frame containing a **value** column.

**Sum\_1(x)** — used inside **extract\_nitrosamine\_summary()**. Identical to **Sum()** but groups by **foodgroup** before summarising, producing one summary row per food category:

```
Sum_1 <- function(x) {
  x %>%
  group_by(foodgroup) %>%
  summarise(
    N = n(),
    mean = mean(value, na.rm = TRUE),
    sd = sd(value, na.rm = TRUE),
    min = min(value, na.rm = TRUE),
    P05 = quantile(value, 0.05, na.rm = TRUE),
    P50 = quantile(value, 0.50, na.rm = TRUE),
    P95 = quantile(value, 0.95, na.rm = TRUE),
    max = max(value, na.rm = TRUE)
  )
}
```

Because the input to **Sum\_1()** consists of replicated mean values (one replicate per analysis), N in the output reflects the total number of analytical measurements for that food group and substance, not the number of food items.

These summary concentration files for nitrate, nitrite and nitrosamines are used in the exposure assessments for all age groups.

### Dietary Exposure Assessment (Norkost 4)

The detailed description of the exposure assessment is found for adults (Norkost 4) in the GitHub repository ([https://github.com/TrineHusoy/Nitrate\\_Nitrite.git](https://github.com/TrineHusoy/Nitrate_Nitrite.git)), including R codes and fictive data. The detailed R codes for the other age groups are not presented but the exposure assessment is done in the same way as for adults.

## Software and packages

Key packages used:

- **R version 4.5.2 (2025-10-31 ucrt)**
- **tidyverse** — data manipulation and reshaping (**dplyr**, **tidyr**, **stringr**)
- **NADA** — ROS imputation of left-censored values (**cenros()**) {Lee, 2020 #125}
- **Hmisc** — weighted quantile calculation (**wtd.quantile**)
- **writexl / openxlsx** — Excel export
- **rlang** — tidy evaluation in utility functions (**.data**, **sym**, **!!**)
- **ggplot2**, **ggridges**, **viridis** — exploratory visualisation
- **reshape2** — reshaping 3D arrays to long format (**melt()**)
- **janitor** — promoting header rows (**row\_to\_names()**)
- **fitdistrplus** — distribution fitting diagnostics

## Appendix 6. Gastrointestinal exposure assessment

### Dynamic model

VKM adheres to the FAIR principles, and the full model code and documentation are publicly available in the [GitHub repository](#).

#### *Description of model parameters*

Gastrointestinal exposure to nitrate and nitrite was estimated using a previously developed model (Lin et al., 2020a; Zeilmaker et al., 2010) that integrates dietary nitrate and nitrite intakes with additional endogenous nitrite production from the enterosalivary circulation and conversion from nitrate by oral bacteria. The gastrointestinal nitrite burden is derived from kinetic descriptions of active nitrate secretion from plasma into saliva and its subsequent reduction by oral bacteria.

The parameters are categorized below by their physiological and chemical functions, and an overview of the parameters are summarised in Table A6-1. The equations describe necessary physiological parameters, nitrate, nitrite and methaemoglobin dynamic in human body.

**Physiological parameters** define the anatomical volumes and flow rates characteristic of the adult human population used in the simulation. These are:

- Body Weight (BW)
- Blood Volume ( $V_{\text{blood}}$ )
- Salivary Flow Rate (B): The rate of saliva production, which drives the transport of secreted nitrate into the digestive tract, is modelled as a log-normal distribution with a mean of approximately  $0.069 \text{ L h}^{-1}$  (range  $0.042\text{--}0.120 \text{ L} \cdot \text{h}^{-1}$ ). This value corresponds to the mean salivary flow during waking hours established in earlier kinetic studies together with known range of variation around the mean.
- Saliva Compartment Volume ( $V_{\text{sal}}$ ): The volume of saliva present in the mouth is fixed at  $0.001 \text{ L}$  consistent with assumptions in the Zeilmaker et al. (1996) calibration.
- Stomach Volume ( $V_{\text{s}}$ ): The volume of the gastric region relevant for nitrosation reactions is fixed at  $0.5 \text{ L}$ . This value is derived from the Guidelines for Canadian Drinking Water Quality, which estimates the volume of the esophageal/cardia region where maximal luminal nitrosation occurs.

**Nitrate kinetics:** Nitrate kinetics are governed by absorption, distribution, renal/metabolic elimination, and active secretion into saliva:

- Absorption ( $k_{\text{abs,Na}}$ ): The first-order rate constant for nitrate absorption from the gastrointestinal tract is set at  $5 \text{ h}^{-1}$ , with a bioavailability fraction ( $f_{\text{a}}$ ) of 1 (100% of nitrate is absorbed). This aligns with experimental data showing peak absorption 30–60 min post-ingestion.

- Volume of Distribution ( $V_d, Na$ ): Modelled as a uniform distribution ranging from 0.29 to  $0.33 \text{ L} \cdot \text{kg}^{-1}$  (fraction of body weight).
- Systemic Elimination ( $k_{el}, Na$ ): The rate constant for total nitrate elimination (renal excretion added to metabolic conversion) is modelled as a log-normal distribution centred around  $0.14 \text{ h}^{-1}$  (range 0.12–0.16).
- Secretion to Saliva ( $k_{sec}$ ): The active transport of nitrate from blood into the salivary compartment is described by a log-normal distribution with a mean of  $0.077 \text{ h}^{-1}$  (range 0.02–0.2  $\text{h}^{-1}$ ) This value is based on the Kortboyer study calibration, which noted a relatively fast secretion rate compared to other studies.
- Salivary Conversion ( $k_{conv}$ ): The bacterial reduction of nitrate to nitrite in the oral cavity is modelled as a log-normal distribution around  $10.68 \text{ h}^{-1}$ .
- Endogenous Synthesis ( $k_{end}, Na$ ): A zero-order rate constant representing the body's endogenous production of nitrate is set at  $0.109 \text{ mmol/h}$  (approx.  $162 \text{ mg day}^{-1}$ ).

#### Nitrite kinetics:

- Absorption ( $k_{abs}, Ni$ ): The absorption rate for nitrite is set identical to nitrate at  $5 \text{ h}^{-1}$ .
- Volume of Distribution ( $V_d, Ni$ ): Modelled as a normal distribution with a mean of  $0.65 \text{ L} \cdot \text{kg}^{-1}$ .
- Gastric Decay ( $k_{dec}$ ): The rate constant for the chemical decomposition of nitrite in the acidic stomach environment (pH 1.5) is set at  $0.67 \text{ h}^{-1}$ .

The following parameters model the oxidation of haemoglobin (Hb) by nitrite and the enzymatic reduction of methaemoglobin (MetHb):

- Nitrite-haemoglobin reaction ( $k_3$ ): The rate constant for the oxidation of haemoglobin by nitrite is  $4.23 \text{ mM}^{-1} \text{ h}^{-1}$ .
- Methaemoglobin Reductase ( $V_{max}, K_m$ ): The enzymatic repair of MetHb is described by Michaelis-Menten kinetics with a maximal velocity ( $V_{max}$ ) of  $1 \text{ mM} \cdot \text{h}^{-1}$  and a Michaelis constant ( $K_m$ ) of  $0.124 \text{ mM}$ . The total concentration (CHb) of haemoglobin in the blood is set at  $8 \text{ mM}$ .

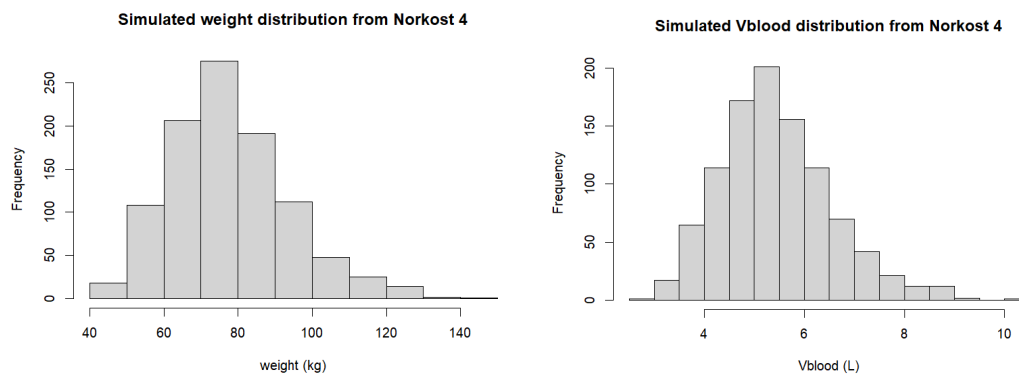
Endogenous nitrate synthesis rates, renal clearance, and salivary secretion kinetics were primarily parameterised using data from (Wagner et al., 2015). Parameters describing salivary nitrate reduction and gastrointestinal absorption following vegetable consumption were evaluated and refined using data from (Kortboyer et al., 1995; Kortboyer, 1997; Shapiro et al., 1991; Spiegelhalder et al., 1976).

**Table A6-1.** Overview of the parameters in the dynamic model for estimating endogenous nitrite formation and methaemoglobin generation (Lin et al., 2020a; Zeilmaker et al., 2010).

Category	Parameter	Symbol	Value / Distribution	Units	Description / Source
Physiological	Body Weight	BW	Adult human (model-specific)	kg	Characteristic adult body weight used in simulation
	Blood Volume	Vblood	Model-specific	L	Total blood volume
	Salivary Flow Rate	B	Log-normal, mean 0.069 (range 0.042–0.120)	L h <sup>-1</sup>	Saliva production during waking hours; based on kinetic studies
	Saliva Compartment Volume	Vsal	Fixed at 0.001	L	Volume of saliva in oral cavity; from Zeilmaker et al. (1996)
	Stomach Volume	Vs	Fixed at 0.5	L	Gastric/esophageal region relevant for nitrosation (Canadian DWQ guidelines)
Nitrate kinetics	Absorption Rate	kabs,Na	5	h <sup>-1</sup>	First-order GI absorption; peak at 30–60 min post-ingestion
	Bioavailability	fa	1.0	–	Assumes 100% absorption
	Volume of Distribution	Vd,Na	Uniform 0.29–0.33	L kg <sup>-1</sup>	Fraction of body weight
	Systemic Elimination	kel,Na	Log-normal, mean 0.14 (range 0.12–0.16)	h <sup>-1</sup>	Renal excretion + metabolic conversion
	Secretion to Saliva	ksec	Log-normal, mean 0.077 (range 0.02–0.2)	h <sup>-1</sup>	Active transport from blood to saliva; Kortboyer calibration
	Salivary Conversion	kconv	Log-normal, mean 10.68	h <sup>-1</sup>	Bacterial reduction of nitrate to nitrite in oral cavity
	Endogenous Synthesis	kend,Na	0.109	mmol/h <sup>-1</sup>	Zero-order endogenous nitrate

Category	Parameter	Symbol	Value / Distribution	Units	Description / Source
					production (~162 mg/day)
Nitrite kinetics	Absorption Rate	kabs,Ni	5	h <sup>-1</sup>	Identical to nitrate absorption
	Volume of Distribution	Vd,Ni	Normal, mean 0.65	L kg <sup>-1</sup>	Distribution in body water
	Gastric Decay	kdec	0.67	h <sup>-1</sup>	Chemical decomposition at gastric pH 1.5
Hb / MetHb kinetics:	Hb Oxidation by Nitrite	k3	4.23	mM <sup>-1</sup> ·h <sup>-1</sup>	Characteristic adult body weight used in simulation
	MetHb Reductase Capacity	Vmax	1.0	mM h <sup>-1</sup>	Total blood volume
	MetHb Reductase Affinity	Km	0.124	mM	Saliva production during waking hours; based on kinetic studies
	Haemoglobin Concentration	CHb	8	mM	Volume of saliva in oral cavity; from Zeilmaker et al. (1996)

For dynamic modeling, we did not use individual body weight data from Norkost 4 but rather calculated distribution of the weights (Figure A6-1). The body weight distribution was first derived from the individual data Norkost 4 from Trusted Research Environment (TSD) that summarized data were delivered to modeling group. Volumes of blood were scaled proportionally to account for body weight differences. Parameter sampling was subsequently performed based on these distributions.

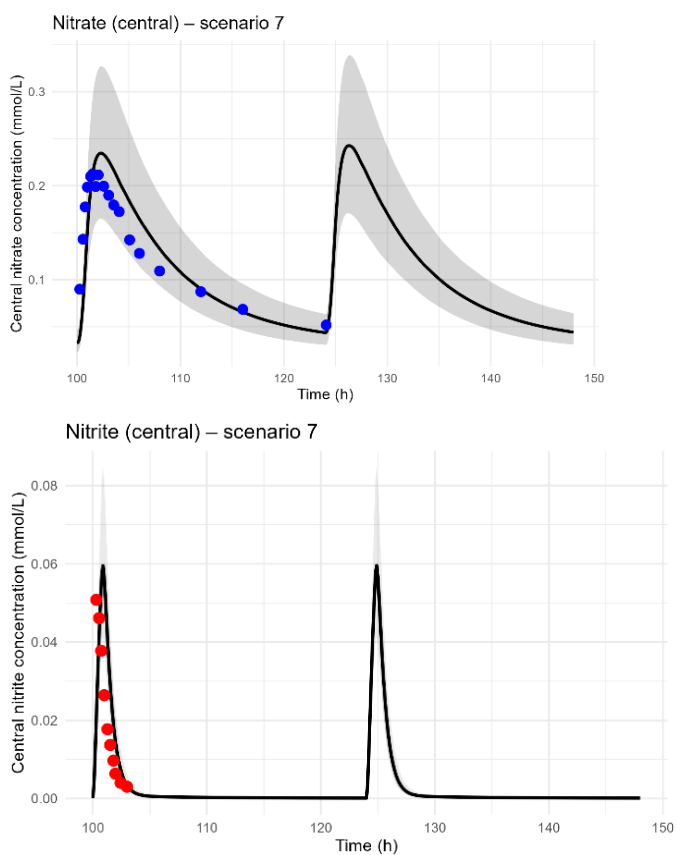


**Figure A6-1.** Simulated body weights (left) and blood volumes (right) for 1000 virtual individuals, based on body weight distribution values derived from Norkost 4.

### Validation of the model.

Prior to application of the dynamic model describing the systemic kinetics of nitrate and nitrite in humans, model validation was performed using published experimental data (Kortboyer et al., 1997).

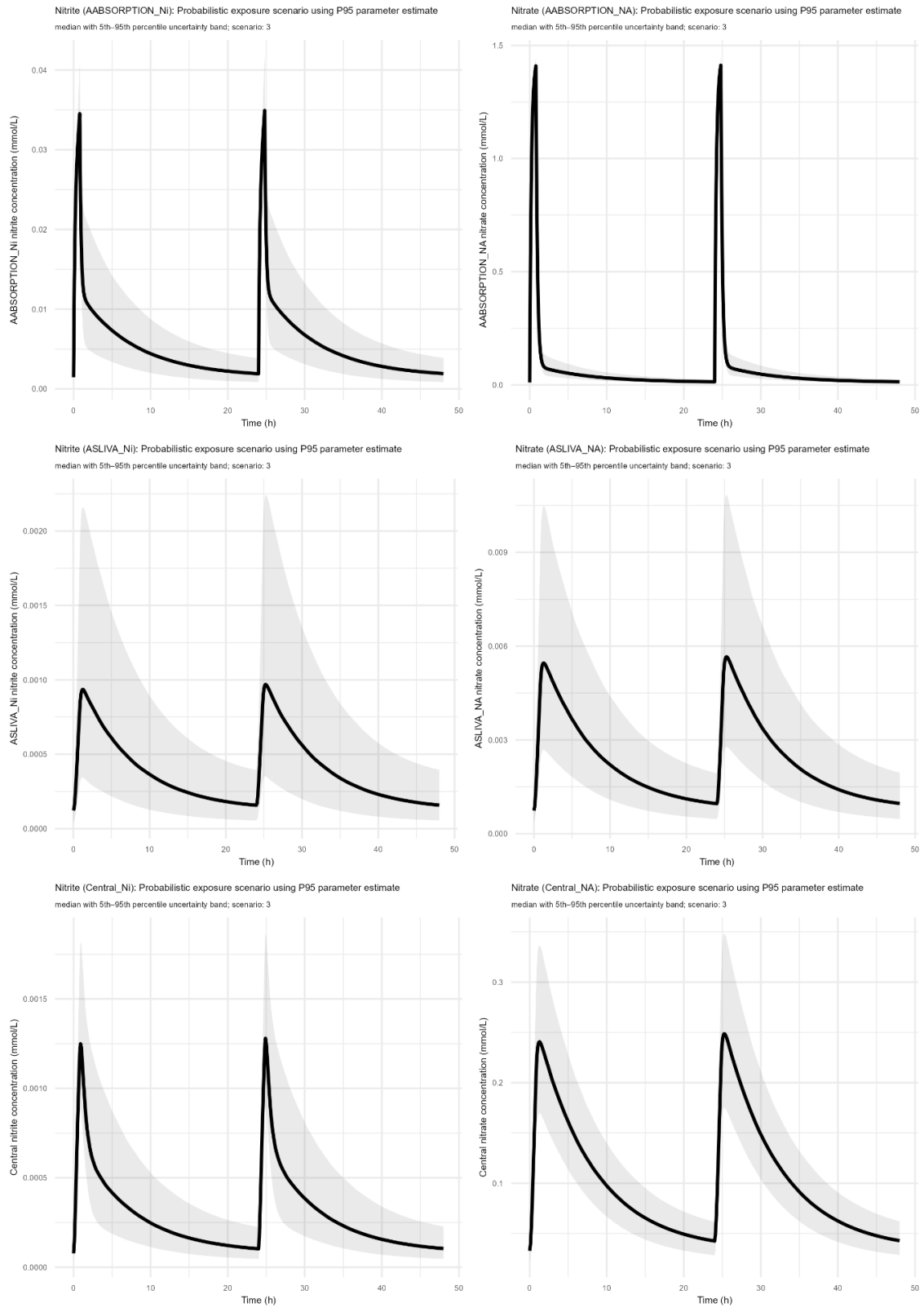
Simulated concentrations of nitrate and nitrite in the central compartment were compared with corresponding measured values reported in the literature. The model predictions were in good agreement with observed data (Figure A6-2), supporting the validity of the model structure and parameterization for subsequent analyses. This model adequately described the observed data for nitrate and nitrite, providing confidence in its use for external exposure inputs derived from exposure assessments in this report. This model was not calibrated on GI compartment or stomach as such data were not available.



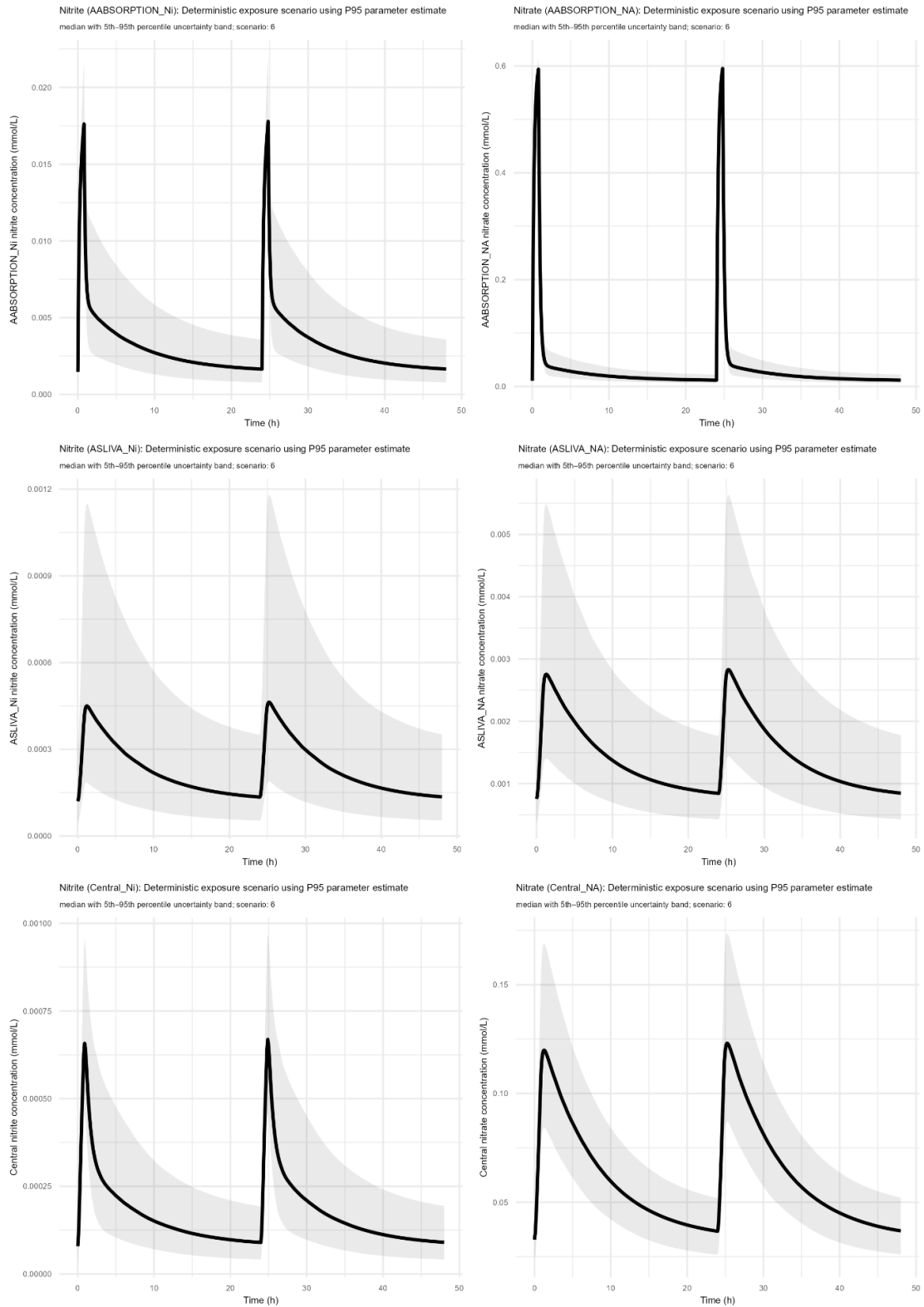
**Figure A6-2.** Simulated nitrate and nitrite concentration–time profiles following administration of 4.84 mg kg<sup>-1</sup> nitrate using the dynamic model. Points indicate observed concentrations measured in the central compartment (blood). Validation data were obtained from Kortboyer et al. (1997).

To run the dynamic model, estimated dietary exposures to nitrate under different intake scenarios (mean, median, and 95th percentile) were used as inputs. These exposure estimates were provided as CSV files. The simulations were conducted using both OIM exposure values and probabilistic exposure distributions to characterise variability and high-end exposure conditions derived from the external exposure assessment.

The model was simulated over a 48-hour period, with doses administered as single doses at time points 0 and 24 hours. Integration of nitrate and nitrite in the gastrointestinal compartment was performed over a 24-hour period. In addition, time-dependent concentrations were simulated in saliva, in the central compartment, and in the absorption compartment containing the stomach, which represents the organ of primary interest for subsequent modelling. The P95 scenarios are presented in Figures A6-3 and A6-4 for probabilistic and OIM scenarios respectively. Detailed instructions for running the model are available in the GitHub repository [documentation](#).



**Figure A6-3.** Simulated nitrate and nitrite concentration–time profiles following P95 exposure (probabilistic external exposure scenario) using the dynamic model. Solid lines represent mean values, and the grey shaded area indicates the confidence interval based on the modelling.



**Figure A6-4.** Simulated nitrate and nitrite concentration–time profiles following P95 exposure (OIM external exposure scenario) using the dynamic model. Solid lines represent mean values, and the grey shaded area indicates the confidence interval based on the modelling.

## Static model

### Description of model and model parameters

Endogenous formation of N-NAs in the gastrointestinal tract was estimated using a static chemical reaction model (Health Canada, 2013; EFSA, 2023). The model describes nitrosamine formation as a second-order chemical reaction between nitrite-derived nitrosating species and secondary amines in the acidic gastric compartment.

**Table A6-2.** Parameters used for the static model.

Parameter	Symbol	Value / Assumption	Units	Description / Source
Gastric nitrite concentration	$[\text{NO}_2^-]$	Output from model A (e.g. $6.53 \times 10^{-4}$ )	$\text{mol} \cdot \text{L}^{-1}$	Sum of nitrite concentration in the stomach originating from nitrate to nitrite conversion, integrated over 24h in model A (dynamic model) and the calculated external exposure to nitrite
Precursor amine intake (DMA)	Diam	$1.91 \times 10^{-4}$	$\text{mmol} \cdot \text{day}^{-1}$	Daily dietary intake of dimethylamine; Health Canada (2013)
Nitrosation rate constant	Kam	0.0017	$(\text{mol/L})^{-2} \cdot \text{s}^{-1}$	Rate constant describing nitrosation potential of DMA
Reaction time	t	7200	s	Estimated time during which amine and nitrite concentrations are constant in the oesophageal/cardia region
Molecular weight of NDMA	MWnitros	$74 \times 10^3$	$\text{mg} \cdot \text{mol}^{-1}$	Molecular weight used for mass conversion
Body weight	bw	Drawn from body weight distribution from Norkost 4	kg	Average adult body weight used in VKM modelling
Volume of stomach	Vst	Cantered at 0.5	L	Average adult volume of stomach relevant for nitrosamination
Daily NDMA formation dose	DDnitros	Calculated	$\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$	Endogenous NDMA formation from gastric nitrosation
Gastric residence time	t	Tested between 0.5–2	h	Time of food present in GI

Mathematical formulation:

The daily dose of NDMA formed endogenously ( $DD_{\text{nitros}}$ , ng/kg bw/day) was calculated as:

$$DD_{\text{nitros}} = ([\text{NO}_2^-]^2 \times DI_{\text{amine}} \times K_{\text{am}} \times t \times \text{MW}) / \text{BW}$$

where  $[\text{NO}_2^-]$  is gastric nitrite concentration (mol/L)/Vst (L) sum up with the calculated nitrite external exposure (mol),  $DI_{\text{amine}}$  is the daily intake of dimethylamine (mol · /day day<sup>-1</sup>),  $K_{\text{am}}$  is the nitrosation rate constant ((mol/L)<sup>-2</sup>·s<sup>-1</sup>),  $t$  is gastric residence time (s), MW is the molecular weight of NDMA (mg/mol), and BW is body weight (kg).

Health Canada and EFSA applied fixed values for the model parameters. Daily dimethylamine intake was assumed to be  $1.91 \times 10^{-4}$  mol · day<sup>-1</sup> based on dietary exposure estimates. Body weight was fixed at 70 kg, and the molecular weight of NDMA was set to 74,08 mg · mol<sup>-1</sup>. For reaction kinetics, a nitrosation rate constant of 0.002 mol<sup>-2</sup>·s<sup>-1</sup> and a gastric residence time of 3,600 seconds (1 hour) were applied. A constant gastric nitrite concentration of  $2.1 \times 10^{-4}$  mol · L<sup>-1</sup> (~ 210 µM) was used. Together, these inputs were treated OIM ally to provide a conservative upper-bound estimate of endogenous NDMA formation.

In the present assessment, the same mathematical structure was used. However, certain inputs were adapted to better reflect physiological variability. These adaptations and reasonings are provided below.

**Gastric nitrite concentration [ $\text{NO}_2^-$ ]:** Gastric nitrite concentration was derived from the dynamic nitrate–nitrite conversion model.

**DMA daily intake ( $DI_{\text{amine}}$ ):** A sensitivity analysis was also applied to see if a higher DMA pool would have a large impact on the estimated amount of NDMA formed.

**Body weight (BW):** Centered around 78 kg and sampled for 1000 virtual persons.

**NDMA molecular weight (MW):** Not changed

Nitrosation rate constant ( $K_{\text{am}}$ ): 0.0005–0.0017 mol<sup>-2</sup>·s<sup>-1</sup>. This range reflects variability in the intrinsic nitrosability of dimethylamine (DMA) under acidic conditions. Experimental studies show that the rate constant is highest near pH 3–4, relevant for gastric conditions, with a value of  $1.7 \times 10^{-3}$  mol<sup>-2</sup>·s<sup>-1</sup> under optimal conditions (Mirvish, 1975). Lower values, approximately an order of magnitude smaller, can occur under stronger acidity or in the presence of inhibitors such as ascorbate and polyphenols. The upper bound corresponds to optimal conditions, while the lower bound accounts for interindividual differences in gastric chemistry, including pH variation and antioxidant effects.

Gastric residence time ( $t$ ): 1,800–7,200 s (0.5–2 h). The 2 h was chosen as a default. We have also performed sensitivity analysis of 24 h residence time.

This range captures physiological variability in gastric emptying. Liquids empty rapidly from the stomach, typically within 0.5–2 h, as shown in scintigraphic studies (Maurer, 2015; Parkman et al., 2025). Solids undergo an initial lag (trituration) phase followed by exponential emptying, with half-emptying times ( $T_{1/2}$ ) of 50–109 min and most solids cleared within 3–4 h (Drew et al., 2025; Abell et al., 2008). For modelling endogenous NDMA formation, the 2 h upper limit

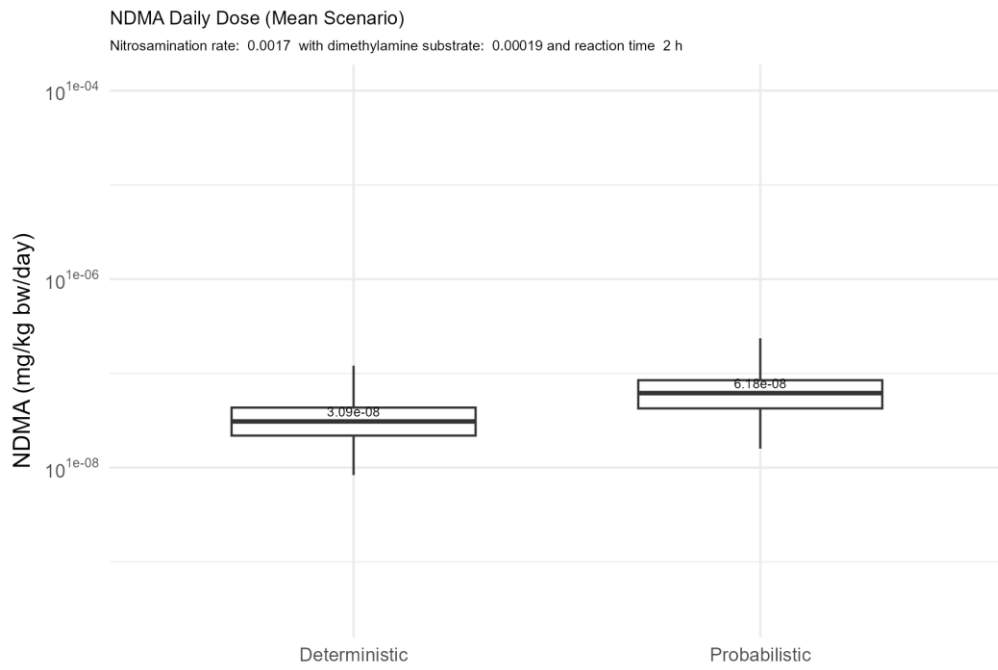
reflects the period during which sufficient nitrite and DMA are likely present for nitrosation; beyond this point, substrate depletion becomes significant, and EFSA's model which assumes constant nitrite and DMA would overestimate NDMA formation. Variability in NDMA formation beyond this period is captured separately by the range of the nitrosation rate constant. Using the single 0.5–2 h range therefore provides a conservative yet physiologically realistic basis for estimating NDMA formation in humans.

The modelling part is available in [GitHub](#):

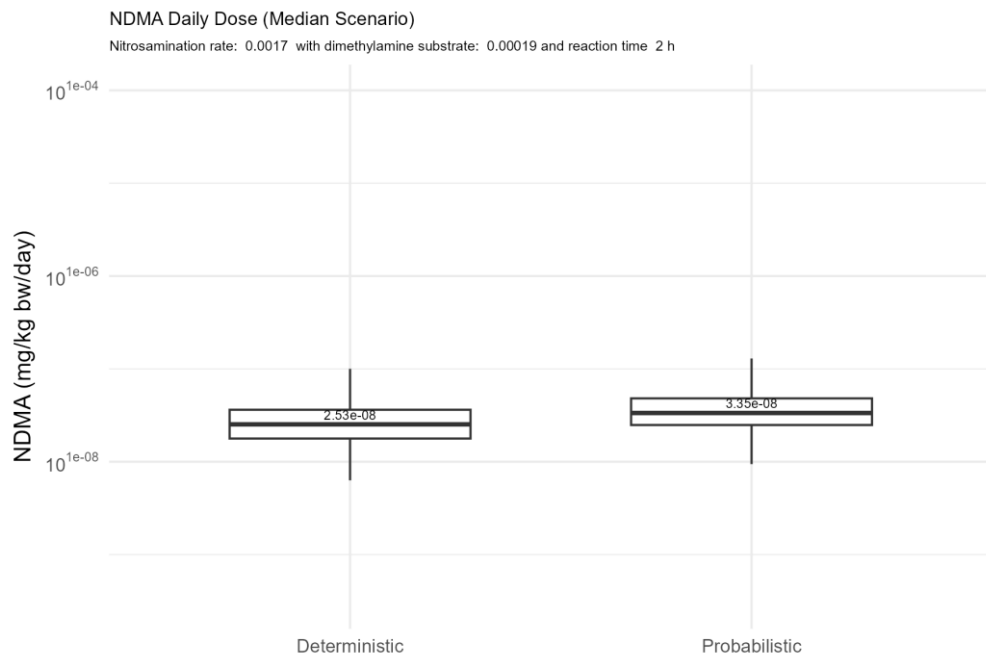
[https://github.com/TrineHusoy/Nitrate\\_Nitrite/blob/main/Code/NiNa\\_kinetic\\_model\\_MoE-18012026.Rmd](https://github.com/TrineHusoy/Nitrate_Nitrite/blob/main/Code/NiNa_kinetic_model_MoE-18012026.Rmd)

NDMA formation was modelled assuming a 2-hour gastric residence time, a nitrosation rate constant of  $0.0017 \text{ mol}^{-2}\cdot\text{s}^{-1}$ , and a dimethylamine substrate level of  $0.0019 \text{ mol}\cdot\text{day}^{-1}$ . This parameter combination represents the central or most likely scenario. In addition, alternative combinations of residence time, nitrosation rate constant, and substrate concentration were systematically evaluated within the predefined parameter space to characterize model sensitivity and upper-bound conditions. Endogenous production shown in Figure A6-5.

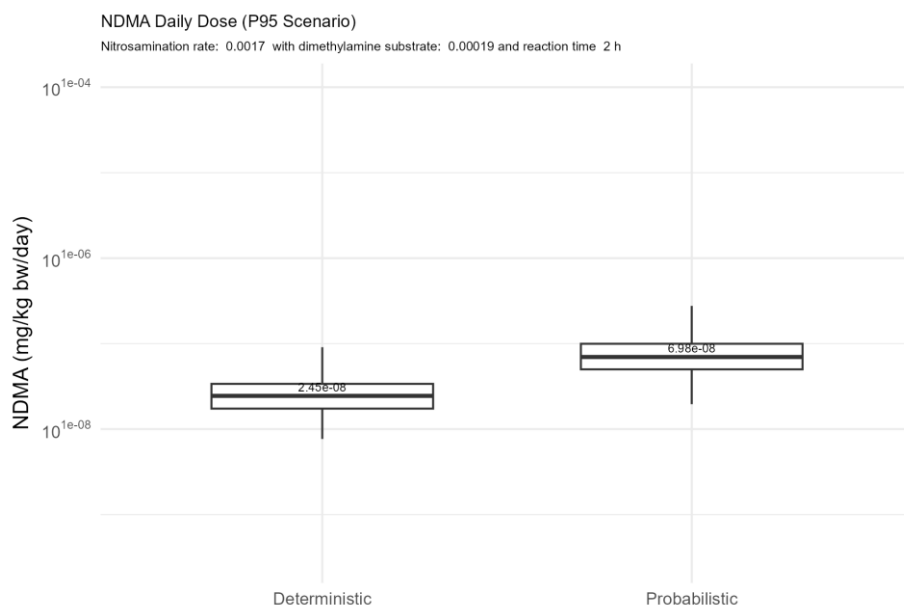
A



B



C



**Figure A6-5.** Endogenous formation of NDMA from the static model using gastrointestinal nitrite exposure estimates mean (A), median (B), and P95 (C).

### Sensitivity Analysis of NDMA Formation

A structured sensitivity analysis was conducted to evaluate the influence of key determinants governing nitrosation chemistry and subsequent NDMA formation within the modelled system. NDMA generation was examined as a function of three primary parameters: (i) the nitrosation rate constant ( $\text{mol}^{-2}\cdot\text{s}^{-1}$ ), (ii) dimethylamine (DMA) intake ( $\text{mol}\cdot\text{day}^{-1}$ ), and (iii) residence time (hours). The nitrate amount was given from our modelling thus was set constant for given scenario.

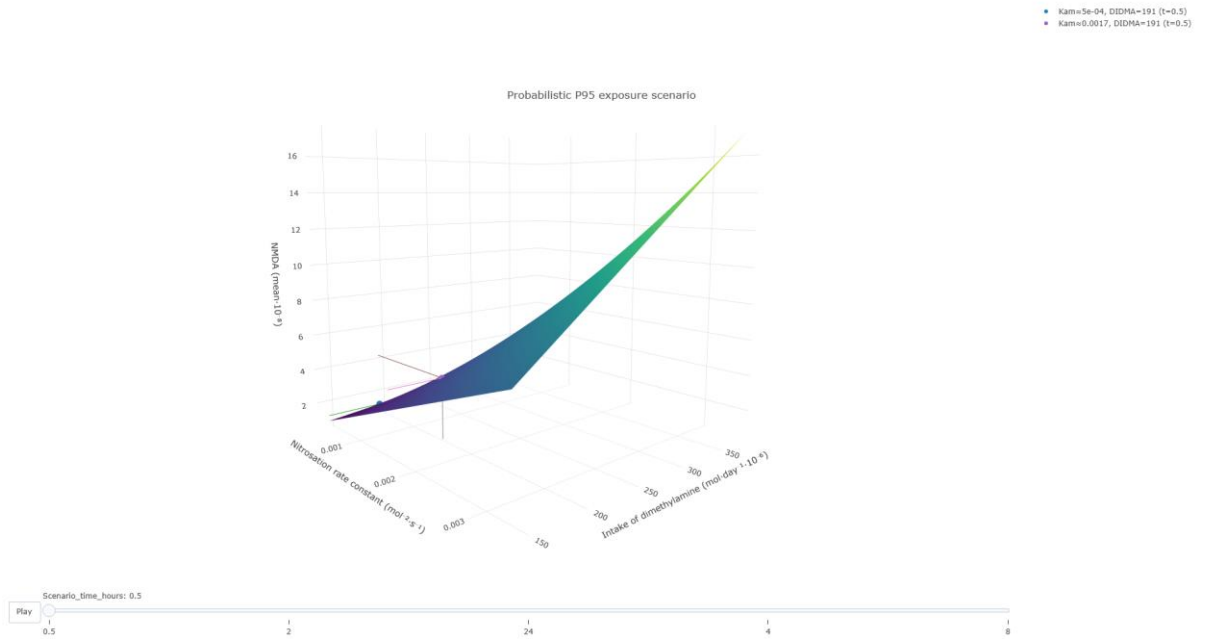
#### Parameter Space Definition

Discrete parameter values were selected to reflect plausible exposure conditions calculated by VKM. The nitrosation rate constant was evaluated at 0.00050, 0.00170, 0.00200, 0.00255, and 0.00340  $\text{mol}^{-2}\cdot\text{s}^{-1}$ . The range 0.0005–0.0017  $\text{mol}^{-2}\cdot\text{s}^{-1}$  corresponds to the most likely interval as suggested by our expertise in VKM, while 0.002  $\text{mol}^{-2}\cdot\text{s}^{-1}$  represents the OIM value applied by EFSA. Higher values were included to explore upper-bound sensitivity. DMA intake levels were set at 0.000191, 0.00023875, 0.00028650, and 0.000382  $\text{mol}\cdot\text{day}^{-1}$ , with 0.000191  $\text{mol}\cdot\text{day}^{-1}$  considered the most likely exposure scenario. Higher values were included to explore upper-bound sensitivity. Residence times of 0.5, 2, and 24 hours were evaluated to represent short, intermediate, and prolonged contact durations, respectively. The interval between 0.5 and 2 hours was considered the most plausible under typical physiological conditions. Higher values were included to explore upper-bound sensitivity. All parameter combinations were evaluated in a full factorial design, resulting in  $5 \times 4 \times 3 = 60$  distinct scenario combinations.

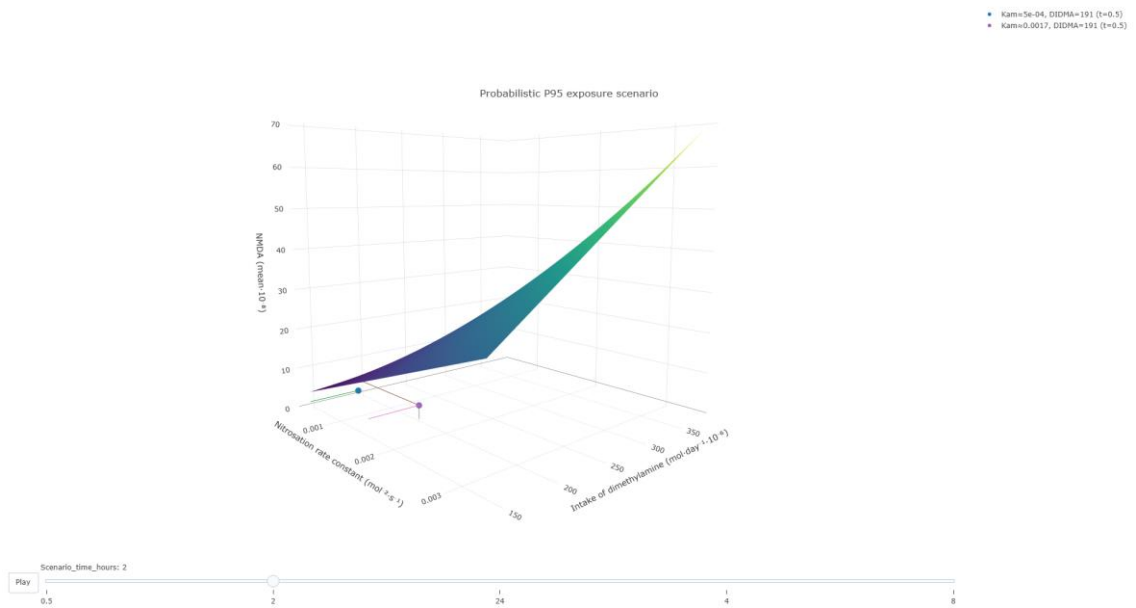
#### Simulation Framework and Output Metrics

For each scenario, the model was executed using the previously described parameterization and simulation framework. Probabilistic simulations (n = 1000 iterations per scenario) were performed to propagate parameter variability and uncertainty. Summary statistics of predicted NDMA formation were extracted, including mean, median, minimum, maximum, and 95th percentile (P95). Sensitivity was assessed by examining variation in central tendency (mean) and across the multidimensional parameter space for both OIM and probabilistic exposure P95 scenarios to characterize potential high-end exposure conditions. Three-dimensional response surfaces were constructed to visualize the joint influence of the nitrosation rate constant and DMA intake at each residence time. The visualization of the output from the sensitivity analysis is presented in [GitHub](#) and Zenodo (10.5281/zenodo.20495212).

A.

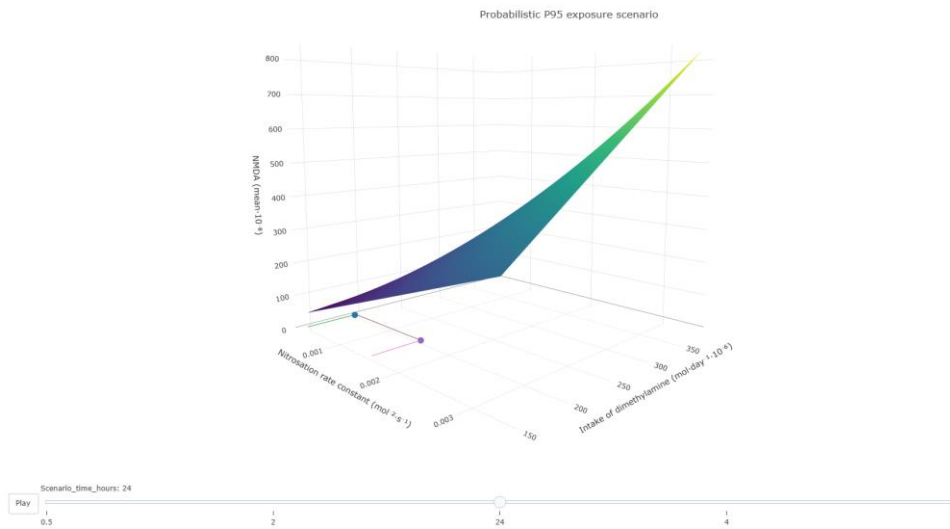


B.



C.

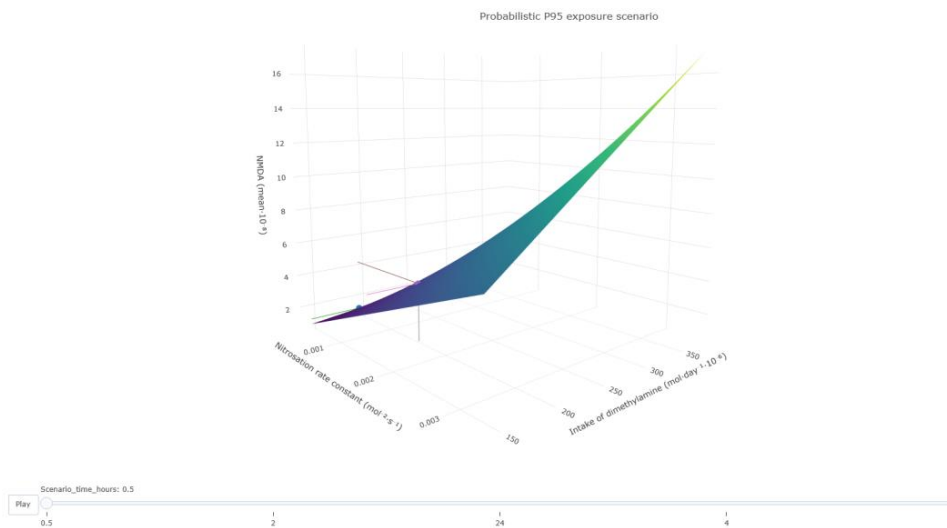
• Kam=5e-04, DIDMA=191 (t=0.5)  
 • Kam=0.0017, DIDMA=191 (t=0.5)



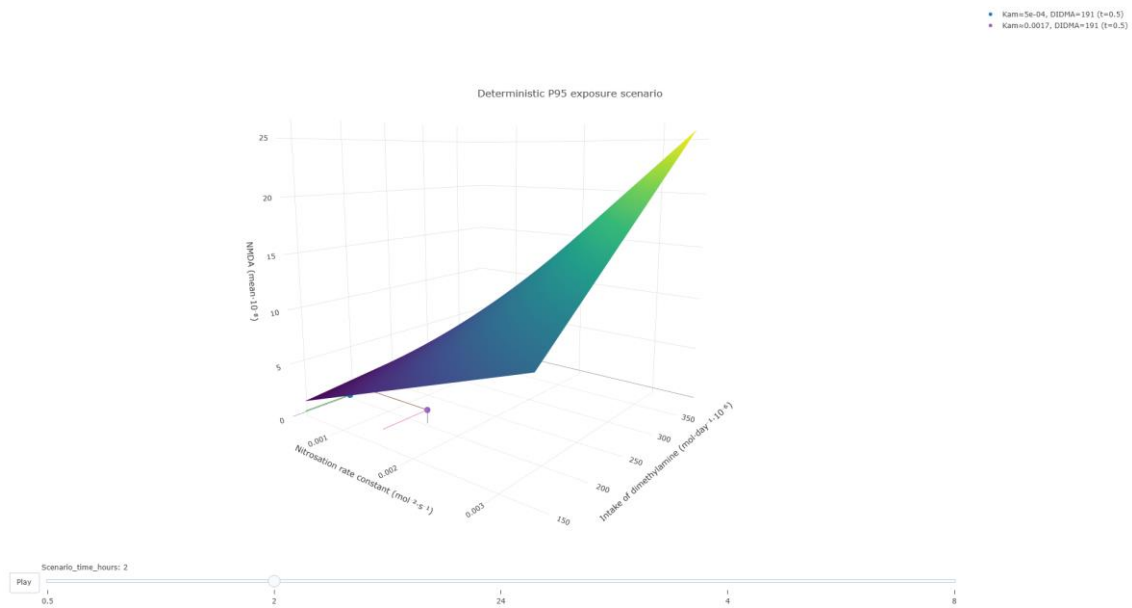
**Figure A6-6.** Probabilistic estimates of mean NDMA formation across scenario combinations. Three-dimensional response surfaces illustrate the influence of the nitrosation rate constant ( $\text{mol}^{-2}\cdot\text{s}^{-1}$ ), dimethylamine (DMA) intake ( $\text{mol}\cdot\text{day}^{-1}$ ), and residence time (hours A=0.5h, B=2h, C=24h) on the predicted mean NDMA concentration. For each parameter combination, 1,000 Monte Carlo simulations were performed, and the mean of the probabilistic distribution was calculated. Separate surfaces represent different residence times (0.5, 2, and 24 hours). Values are shown after scaling for visualization purposes as indicated on the axes.

A

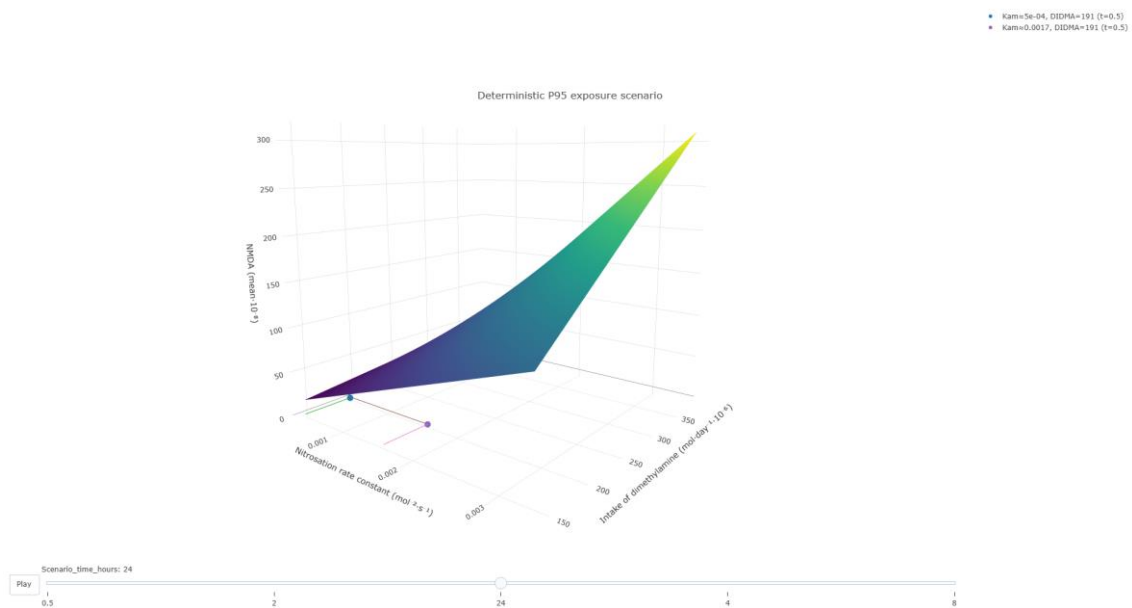
• Kam=5e-04, DIDMA=191 (t=0.5)  
 • Kam=0.0017, DIDMA=191 (t=0.5)



B



C



**Figure A6-7.** OIM estimates of mean NDMA formation across scenario combinations. Three-dimensional response surfaces illustrate the influence of the nitrosation rate constant ( $\text{mol}^{-2} \cdot \text{s}^{-1}$ ), dimethylamine (DMA) intake ( $\text{mol} \cdot \text{day}^{-1}$ ), and residence time (hours) on the predicted mean NDMA concentration. For each parameter combination, 1,000 Monte Carlo simulations were performed, and the mean of the probabilistic distribution was calculated. Separate surfaces represent different residence times (0.5, 2, and 24 hours). Values are shown after scaling for visualization purposes as indicated on the axes.

## Appendix 7. Risk characterisation

**Table A7-1.** The estimated exposures for nitrite (mg/kg bw per day) for different age groups (numbers from Tables 3.5.1-3, 3.5.2-3, and 3.8-2). Exposure above the ADI of 0.07 mg/kg bw per day is indicated as yellow-shaded cells. D: OIM; (D): OIM exposure estimates as input to the model; E: External exposure; I: Gastrointestinal exposure (external exposure combined with endogenous synthesis); M: Modelled; P: Probabilistic; (P): Probabilistic exposure estimates as input to the model; NA: Not included in the exposure assessment. Blue-shaded cells: Exposure was not estimated applying this approach.

Age group, survey	Nitrite, P50 exposure		Nitrite, mean exposure				Nitrite, P95 exposure			
	E, D	E, P	E, D	E, P	GI, M (D)	GI, M (P)	E, D	E, P	GI, M (D)	GI, M (P)
18-80 years, Norkost 4	0.01	0.009	0.010	0.021	0.065	0.083	0.040	0.075	0.11	0.17
13-year-olds, Ungkost 3	0.014	0.001	0.017	0.006	NA	NA	0.037	0.028	NA	NA
9-year-olds, Ungkost 3	0.017	0.002	0.021	0.011	NA	NA	0.046	0.049	NA	NA
4-year-olds, Ungkost 3	0.024	0.004	0.027	0.018	NA	NA	0.054	0.077	NA	NA
2-year-olds, Småbarnskost 3	0.03	NA	0.032	NA	NA	NA	0.056	NA	NA	NA
1-year-olds, Spedkost 3	0.032	NA	0.037	NA	NA	NA	0.078	NA	NA	NA

**Table A7-2.** The margin of exposure between the estimated exposures and the BMDL<sub>10</sub> for N-nitrosamines. OIM: Observed individual means; (OIM): OIM exposure estimates as input to the model; E: External exposure; I: Gastrointestinal exposure; M: Modelled; P: Probabilistic; (P): Probabilistic exposure estimates as input to the model; NA: Not included in the exposure assessment. Yellow-shaded cell: MOE is below 10,000 (more intense colour for MOE-values below 1000). Blue-shaded cells: Exposure could not be estimated applying this approach.

Age group, dietary survey	N-nitrosamines, BMDL <sub>10</sub> / P50 exposures		N-nitrosamines, BMDL <sub>10</sub> / mean exposures				N-nitrosamines, BMDL <sub>10</sub> / P95 exposures			
	E, D	E, P	E, D	E, P	GI, M (OIM)	GI, M (P)	E, D	E, P	GI, M (IOM)	GI, M (P)
18-80 years, Norkost 4	1553	1597	1302	1211	1284	1190	532	426	520	417
13-year-olds, Ungkost 3	1435	9709	1250	3413	NA	NA	538	775	NA	NA

Age group, dietary survey	N-nitrosamines, BMDL <sub>10</sub> / P50 exposures		N-nitrosamines, BMDL <sub>10</sub> / mean exposures				N-nitrosamines, BMDL <sub>10</sub> / P95 exposures			
	E, D	E, P	E, D	E, P	GI, M (OIM)	GI, M (P)	E, D	E, P	GI, M (IOM)	GI, M (P)
9-year-olds, Ungkost 3	1167	5376	962	2222	NA	NA	415	559	NA	NA
4-year-olds, Ungkost 3	935	2933	730	1603	NA	NA	281	420	NA	NA
2-year-olds, Småbarnskost 3	909	NA	820	NA	NA	NA	415	NA	NA	NA
1-year-olds, Spedkost 3	1124	NA	962	NA	NA	NA	424	NA	NA	NA

## Appendix 8. Deviations from protocol

### Hazard identification and characterisation of nitrite

- The study selection was based on the predefined eligibility criteria (Table A1.2-1), as reported in the protocol (VKM et al., 2025), as well as specifications of eligibility criteria after the protocol was published (Table A1.2-2). We aimed at collecting reported estimates of associations with and estimates of effects (causal impact) of nitrite intake and negative health outcomes of that intake from systematic reviews (SRs). This required extraction of reported numerical values of nitrite exposure in all studies included in the meta-analyses in the SRs. However, exact numerical data on the intake of nitrite was not consistently reported in the main text or in supplementary files of the systematic reviews included for full text assessment. Neither did the eligibility criteria (VKM et al., 2025) specify the need for exact numerical intakes. Thus, it was pertinent to specify the eligibility criteria concerning exposure and outcome.
- One item that was originally planned for extraction from the systematic reviews, as specified in the protocol (VKM et al., 2025), has been removed from Table A1.3-1 ('List of key findings related to the systematic review questions')."

### Exposure assessment

Only the OIM approach, not the probabilistic, was applied to the dietary guideline scenarios.

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