



## Protocol for a risk assessment of caffeine exposure from multiple sources

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

The Norwegian Scientific Committee for Food and Environment (VKM)  
Protocol for a risk assessment of caffeine exposure from multiple sources

The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food,  
and Cosmetics of the Norwegian Scientific Committee for Food and Environment  
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# **Protocol for a risk assessment of caffeine exposure from multiple sources**

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## **Competence of VKM experts**

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

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# Abbreviations and glossary

|      |   |
|------|---|
| bw   | bodyweight  |
| EFSA | European Food Safety Authority                          |
| GI   | gastrointestinal  |
| LOD  | limit of detection                                      |
| LOQ  | limit of quantification                                 |
| OHAT | The Office of Health Assessment and Translation         |
| PCPs | personal care products                                  |
| RCT  | randomised controlled trial                             |
| RF   | retention factor  |
| RoB  | risk of bias  |
| VKM  | Norwegian Scientific Committee for Food and Environment |

## **External exposure**

Caffeine reaching the physical barriers of the body, either through diet or oral and dermal application of PCPs.

## **Food**

The term food includes food items and beverages; it does not include dietary supplements or medicines.

## **Total internal exposure**

The total amount of absorbed caffeine, that is, from the GI-tract and the skin.

# 1 Introduction

## 1.1 Background

In our daily lives, we are exposed to caffeine from several sources. Food, dietary supplements and personal care products (PCPs) are examples of potential caffeine sources. Estimations of the Norwegian population's total caffeine exposure, therefore, needs to include multiple sources. To our knowledge, risk assessments including exposure estimates for caffeine from multiple sources have not been performed previously.

With this background, the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics of the Norwegian Scientific Committee for Food and Environment (VKM) has self-initiated a risk assessment of caffeine including caffeine exposure estimates from multiple sources.

## 1.2 Terms of reference

The overall aim is to examine whether the total caffeine exposure from multiple sources constitutes a health risk to the Norwegian population.

The objectives:

- Estimate caffeine exposure from multiple sources
  - Identify food and PCPs that contain caffeine and compile, evaluate and decide the caffeine concentrations.
  - Estimate the intake of caffeine containing foods and use of caffeine containing PCPs.
  - Estimate the total caffeine exposure from multiple sources including food and PCPs, for different groups in the Norwegian population.
  - Identify the caffeine sources that contribute to the estimated exposure due to high consumption and/or high concentration.
  - Identify and describe uncertainties related to the outcome of the exposure estimation.
- Evaluate whether new studies indicate a need for revision of the caffeine doses reported «not to give rise to safety concern» (EFSA, 2015) or if these may be used as reference points for toxicity.
- Characterise risks related to estimated caffeine exposure for different groups in the Norwegian population.
- Identify and describe main knowledge gaps that may have an impact on the conclusions.

### **1.3 Target population**

The Norwegian population, including children (from 4 years), adolescents, women and men.

### **1.4 Limitations to risk assessment**

Children aged 0 to <4 years will not be included.

The literature search for the hazard assessment will be limited to randomised controlled trials (RCTs) as this study design may provide data on causal relationship and, therefore, may be used to identify and characterise effects.

## 2 Hazard identification and characterisation

Caffeine doses «not to give rise to safety concern» have been reported by EFSA (2015). After examining RCTs published in the period January 2015 to November 2018, VKM concluded that there was no need for revision of these doses (VKM et al., 2019). A literature search, covering the period from November 2018 until the search date, will be performed to evaluate whether new studies indicate a need for revision of the caffeine doses «not to give rise to safety concern».

### 2.1 Literature search

A literature search will be performed to identify RCTs on adverse effects related to caffeine exposure published in the period November 2018 until the search date. An experienced research librarian will perform the literature searches. The search result will be screened based on predefined inclusion criteria (Table 2.1-1).

**Table 2.1-1.** Hazard: inclusion criteria.

|                                       |  |
|---------------------------------------|--|
| Study design                          | Randomised controlled trials                   |
| Population                            | Humans, all age groups, males and females      |
| Exposure route                        | Oral and dermal                                |
| Intervention                          | Caffeine                                       |
| Outcome                               | Any adverse health effect related to caffeine  |
| Language of the full text publication | English, Norwegian, Swedish, Danish and German |

#### Screening of titles and abstracts

To ensure reviewer calibration, all reviewers will screen a sample of the retrieved titles and abstracts. Then the reviewers will meet to ensure a consistent application of the inclusion criteria. Following calibration, pairs of reviewers will screen titles and abstracts independently. A publication should be included, when there is doubt about whether the publication meets the eligibility criteria.

#### Screening of full texts

A sample of the full text publications that have passed the initial screening (title and abstract), will be screened by all reviewers to ensure calibration of reviewers. Following calibration, pairs of reviewers will screen the full text publications independently. In case of disagreement, the two reviewers will discuss the paper to reach consensus. If the disagreement persists, the Panel will reach a final decision.

An overview of the results of the study selection will be presented in a flowchart.

## 2.2 Data extraction

The data extraction will be performed by one reviewer and checked for quality/consistency by a different reviewer. Data will be extracted using Table 2.2-1.

**Table 2.2-1.** Data extraction form for the RCTs.

|   |
|---|
| <b>Study characteristics</b> <ul style="list-style-type: none"><li>• Title</li><li>• Author(s)</li><li>• Year</li><li>• Country</li><li>• Funding</li><li>• Reported conflict of interest</li></ul>   |
| <b>Methods/intervention</b> <ul style="list-style-type: none"><li>• Type of blinding</li><li>• Method for randomisation</li><li>• Intervention</li><li>• Intervention design (amount applied, frequency of application)</li><li>• Number of exposed/non-exposed</li></ul>   |
| <b>Participants</b> <ul style="list-style-type: none"><li>• Number of participants (invited, accepted, drop-out, included in follow-up if applicable)</li><li>• Inclusion/exclusion criteria for participants</li><li>• Completion rate</li><li>• Gender</li><li>• Age</li><li>• Confounders and other variables as reported</li><li>• Health status and socioeconomic status of participants</li><li>• Other</li></ul> |
| <b>Results</b> <ul style="list-style-type: none"><li>• Reported outcome</li><li>• Parameters measured and methods used</li><li>• Measurement time points</li></ul>  |
| <b>Statistical analysis</b> <ul style="list-style-type: none"><li>• Power analysis</li><li>• Statistical test</li></ul>   |

## 2.3 Evaluation of internal validity

The included RCTs will be divided between pairs of reviewers for evaluation of internal validity/risk of bias (RoB) as described in "Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration" (OHAT, 2019). The questions to be addressed are:

1. Was administered dose or exposure level adequately randomised?
2. Were subjects blinded to the study group during the study?
3. Were research personnel blinded to the study group during the study?
4. Were outcome data complete without attrition or exclusion from analysis?
5. Can we be confident in the exposure characterisation?
6. Can we be confident in the outcome assessment?
7. Were all measured outcomes reported?
8. Were there no other potential threats to internal validity?

The criteria for the response options, specified in the handbook, will be used. When information is inadequate or not available, the response will be "Not reported" (NR). Response options and symbols (in parentheses) are:

- Definitely low risk of bias (++)
- Probably low risk of bias (+)
- Probably high risk of bias/not reported (NR) (-)
- Definitely high risk of bias (--)

Questions 1-3 and 5-7 will be rated as key questions whereas questions number 4 and 8 are non-key questions. The rating of key and non-key questions will be integrated to classify the studies in tiers 1 to 3 corresponding to decreasing levels of internal validity.

Tier 1:

- All the key questions are scored + /++  
AND
- No more than one non-key question is scored –  
AND
- No non-key question is scored --

Tier 2:

- All the other combinations not falling under tier 1 or 3

Tier 3:

- Any key or any non-key question is scored --  
OR

- More than one key question is scored –

## **2.4 Evidence synthesis and rating the confidence in evidence**

### **2.4.1 Evidence synthesis**

The main results on adverse health outcomes will be presented in summary of findings tables.

### **2.4.2 Rating of confidence in evidence**

#### ***2.4.2.1 Initial level of confidence in evidence***

For each study, an initial confidence rating will be determined by the ability of the study design to ensure that exposure preceded and was associated with the outcome. The following four study design features will be evaluated to determine the initial level of confidence for each study (OHAT, 2019):

“

- the exposure to the substance is experimentally controlled
- the exposure assessment demonstrates that exposures occurred prior to the development of the outcome (or concurrent with aggravation/amplification of an existing condition)
- the outcome is assessed on the individual level (i.e., not through population aggregate data)
- an appropriate comparison group is included in the study”

Fulfilment of all features will receive an initial rating of high confidence (++++). Lower ratings, i.e. moderate (+++), low (++) or very low (+), correspond to the number of features fulfilled. Studies rated high or moderate will be included for further analysis. Studies rated low or very low will be excluded.

#### ***2.4.2.2 Overall confidence in evidence***

Factors that may downgrade or upgrade the initial level of confidence in evidence will be evaluated for each study. Factors that may downgrade the initial level of confidence are:

- Internal validity/risk of bias
- Bias related to funding/conflict of interest
- Unexplained inconsistency
- Imprecision

Factors that may upgrade the initial level of confidence are:

- Large magnitude of effect (e.g., incidence, degrees of severity)

- The presence of a dose-response relationship
- Residual confounding (if a study reports an effect or association despite the presence of residual confounding, confidence in the association is increased)
- Consistency across study design type/dissimilar populations for the relevant studies combined

Following downgrading and upgrading, for each study the confidence in the evidence for a given effect will be determined using the following terms (OHAT, 2019):

“

- High confidence (++++) in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected in the apparent relationship.
- Moderate confidence (++++) in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.
- Low confidence (++) in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship.
- Very low confidence (+) in the association between exposure to the substance and the outcome. The true effect is highly likely to be different from the apparent relationship.”

Next, all studies addressing a given outcome will be grouped, and the overall level of confidence in evidence across all studies will be determined using the same rating terms as for single studies.

## 2.5 Level of evidence for health effect

The confidence ratings (3.4.2.2) will be translated into level of evidence for health effect according to OHAT (2019). Five descriptors are used to categorise the level of evidence: “high,” “moderate,” “low,” “evidence of no health effect,” and “inadequate evidence”. The definition of the descriptors, as given by OHAT (2019), is as follows:

“

- High Level of Evidence. There is high confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- Moderate Level of Evidence. There is moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- Low Level of Evidence. There is low confidence in the body of evidence for an association between exposure to the substance and the health outcome(s), or no data are available.
- Evidence of No Health Effect. There is high confidence in the body of evidence that exposure to the substance is not associated with the health outcome(s).
- Inadequate Evidence. There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s)”.

## **2.6 Uncertainty in the hazard identification and characterisation**

Factors that may cause under- or overestimation of the reference points for adverse health effects will be identified and described qualitatively.

# 3 Exposure assessment

Caffeine exposure, from diet as well as from oral and dermal application of PCPs, will be included in the exposure estimates. Caffeine reaching the physical barriers of the body, either through diet or oral and dermal application of PCPs, is defined as **external exposure**. The total amount of absorbed caffeine, that is, from the GI-tract and the skin, is defined as total **internal exposure**. External and total internal caffeine exposure will be estimated. In addition, scenarios for caffeine exposure from drugs and dietary supplements will be included.

## 3.1 Research questions

An overview of the research questions is given in Table 3.1-1.

**Table 3.1-1.** Exposure assessment: research questions.

|  | <b>Research questions</b>  |
|--|--|
| <b>Occurrence</b>                                | Which foods and PCPs contain caffeine?   |
|  | What are the concentrations of caffeine in food?   |
|  | What are the concentrations of caffeine in PCPs?   |
| <b>Estimated intakes of food and use of PCPs</b> | What are the estimated intakes of caffeine-containing food?                                  |
|  | What is the estimated use of caffeine-containing PCPs (amount used and frequency of use)?    |
| <b>Exposure</b>                                  | What is the external exposure to caffeine from the diet?                                     |
|  | What is the dermal external exposure to caffeine from PCPs?                                  |
|  | What is the oral external exposure to caffeine from PCPs?                                    |
|  | What are the oral and dermal absorption factors for caffeine?                                |
|  | What is the total internal caffeine exposure from food and PCPs?                             |
|  | What are the exposure scenarios including caffeine containing dietary supplements and drugs? |

## 3.2 Occurrence

We aim to identify caffeine containing food and PCPs, and the caffeine concentrations, through searches. For food, data from food composition tables and scientific publications will be included. For PCPs, European data from scientific publications will be included.

The compiling of food caffeine data will be done according to the guidelines from Greenfield and Southgate 2003 (Greenfield and Southgate, 2003). Thus, searches will be done in Nordic, other European and the USDA food composition tables, in that order. Food composition data from recent analytical projects will be evaluated as more reliable than older values.

### 3.2.1 Literature search, publication selection and data extraction

Literature searches will be performed to identify publications reporting caffeine concentrations in food and PCPs. An experienced research librarian will perform the literature searches.

#### 3.2.1.1 Publication selection

The retrieved literature will be screened based on the criteria presented in Table 3.2.1.1-1.

**Table 3.2.1.1-1.** Exposure: inclusion criteria.

| <b>Literature screening for data on caffeine concentrations in food and PCPs</b> |   |
|--|---|
| <b>Outcome of interest</b>   | Concentration data on caffeine in food and PCPs.<br>Biomonitoring studies related to caffeine exposure. |
| <b>Language of the full text</b>   | English, German, Norwegian, Swedish and Danish  |
| <b>Publication type</b>  | Scientific articles, reports, risk assessments and posters  |

#### Screening of titles and abstracts

To ensure reviewer calibration, all reviewers will screen a sample of the retrieved titles and abstracts. Then the reviewers will meet to ensure a consistent application of the eligibility criteria. Following calibration, pairs of reviewers will screen titles and abstracts independently. A publication should be included, when there is doubt about whether the publication meets the eligibility criteria.

#### Screening of full texts

A sample of the full text publications that have passed the initial screening (title and abstract), will be screened by all reviewers to ensure calibration of reviewers. Following calibration, pairs of reviewers will screen the full text publications independently. In case of disagreement, the two reviewers will discuss the paper to reach consensus. If the

disagreement persists, the Panel will reach a final decision. An overview of the results of the study selection will be presented in a flowchart.

### Evaluation of data quality

For all included studies, the data quality will be evaluated. An overview of the questions addressed in the evaluation of data quality is given in Table 3.2.1.1-2. The method includes scoring of the sample extraction, the instrumental analysis, the validation of the method and the data presentation. The score will be deduced according to a scale of scores from 1 (lowest quality) to 5 (highest quality). To obtain the total score, the individual scores are weighted: 1/5 from sample extraction, 1/5 from instrumental analysis, and 3/5 from validation and data presentation. Only articles with a total score of  $\geq 3.5$  will be included and used for the exposure assessment. The evaluation of data quality will be performed by one reviewer and checked by a different reviewer.

**Table 3.2.1.1-2.** Evaluation of data quality.

| No. | Question  | Rating (1-5) |
|-----|---|--------------|
| 1   | How appropriate was the solvent used for the extraction method?   |              |
| 2   | How appropriate was the instrumental analysis that was used?  |              |
| 3   | Which validation method was used, and how was the data presented (LOD*/LOQ**, internal/external calibration, number of samples, statistical methods)? |              |
|     | <b>Total score</b> (1/5 x sample extraction+1/5 x instrumental analysis+3/5 x validation and data presentation)                                       |              |

\*Limit of detection

\*\*Limit of quantification

### **3.2.1.2 Data extraction**

The data extraction will be performed by one reviewer and checked for quality/consistency by a different reviewer. Data will be extracted using Table 3.2.1.2-1.

**Table 3.2.1.2-1.** Data extraction form.

| <b>Study characteristics</b>   |
|--|
| <ul style="list-style-type: none"> <li>• Title</li> <li>• Author(s)</li> <li>• Year of publication</li> <li>• Country</li> <li>• Funding</li> <li>• Reported conflict of interest</li> </ul> |

|   |
|---|
| <p><b>Methods for analysis</b></p> <ul style="list-style-type: none"> <li>• Sample extraction</li> <li>• Calibration</li> <li>• Limit of detection/limit of quantification</li> <li>• Recovery data</li> <li>• Instrument/detector</li> </ul> |
| <p><b>Results</b></p> <ul style="list-style-type: none"> <li>• Number of samples and reported concentrations</li> </ul>   |
| <p><b>Comments</b></p>  |

### 3.3 Consumption

#### 3.3.1 Food

This opinion will use national dietary data to the greatest extent possible as basis for the food intake estimations. The following dietary assessments and surveys will be included.

The Ungkost 3 study (Hansen et al., 2016; Hansen et al., 2015); a nationwide dietary assessment study carried out in 2015 and 2016 by the University of Oslo, the Norwegian Food Safety Authority, the Norwegian Directorate of Health and the Norwegian Institute of Public Health. The dietary assessment tool was a 4-days validated web-based food diary and the study was conducted among 4-year-olds, 8-9-year-olds and 12-13-year-olds.

The Norkost 3 survey (Totland et al., 2012); a nationwide dietary assessment study carried out in 2010/2011 among adults, aged 18 to 70 years. Norkost 3 is based on two 24-hour recalls by telephone surveys, performed at least one month apart.

The EuroMix study (Husoy et al., 2019); a biomonitoring study carried out between September 2016 and September 2017. The participants, aged 24 to 72 years, were recruited among employees from governmental institutes and authorities, and universities in the counties Oslo and (former) Akershus in Norway. The recording and sampling period consisted of two times 24 hours, with 2-3 weeks between the sampling periods. During the two sampling periods, the participants were asked to fill in a weighed food-diary, a cosmetic diary and a questionnaire with personal information. The participants were instructed to weigh and record all intakes of food for 24 hours.

In addition, the project will apply for dietary data from the Norwegian Consumer Council survey 2019 (Forbrukerrådet, 2019), the PreventADALL study (Oslo University Hospital) (Saunders et al., 2019) and the Tromsø Study (Tromsø 7 2015-16) (Lundblad et al., 2019).

- The Norwegian Consumer Council study (Forbrukerrådet, 2019); an online data collection among children and adolescents in May and June 2019 performed via Norstat (www.norstat.no). Members of the Norstat Respondent Panel were invited and received the survey. Children and adolescents 10 to 14 years of age were contacted through their parents. Participants 15 to 18 years of age received invitation to participate in the survey directly (Forbrukerrådet, 2019).
- The PreventADALL Study; an ongoing mother and child cohort study at the Oslo University Hospital investigating the development of atopic dermatitis and allergy in children. The study has assessed the habitual diet in the pregnant mothers.
- The Tromsø Study; a large health cohort study first initiated in 1974. In 2015-2016 the 7<sup>th</sup> Tromsø study assessment was done, including assessment of habitual diet in a large population.

For scenarios of dietary supplements, doses recommended by manufacturers will be used. For over-the-counter drugs, recommended doses will be used.

### **3.3.2 Personal care products**

#### ***3.3.2.1 Frequency of use***

Data on frequency of use will be obtained from the Norwegian biomonitoring study EuroMix (Husoy et al., 2019) and from literature. In EuroMix, the frequency of use was recorded in a diary that allowed for detailed description of time of application and brand names of the PCPs used. The participants did not record the amount of PCPs applied, only the frequency.

#### ***3.3.2.2 Amount used***

The amount of PCP applied per use will be obtained from surveys and literature, and studies reporting on PCP use with separate data for men and women will be prioritised.

#### ***3.3.2.3 Retention factor***

The fraction of PCPs available for uptake after application (retention factor; RF) will be obtained from SCCS (Scientific Committee on Consumer Safety) (2018).

## **3.4 Exposure estimation**

The estimates will be based on:

- Caffeine concentrations (section 3.2)
  - Values below limit of detection (LOD) will be evaluated
  - The prioritisation of concentration data will be as follows: Norwegian>other Nordic> other European>USA.

- Consumption (intake of food and use of PCPs, section 3.3)
- Body weight
  - Individual body weights will be used to calculate caffeine exposure per kg body weight per person. If individual body weights are not reported, mean body weights will be used
- Absorption from the GI tract/skin
  - Absorption factors will be derived from literature

The caffeine exposure will be estimated for habitual and acute intakes of food and median or high use of PCPs. In addition, scenarios including additional exposures from dietary supplements and/or drugs will be performed. We aim to use concentration data and consumption data considered to be the most realistic for the target populations. External and total internal caffeine exposure from multiple sources will be estimated.

#### **3.4.1 Uncertainty in the exposure estimation**

Factors that may cause under-estimation or over-estimation of the exposure will be identified and described qualitatively.

## 4 Risk characterisation

The risk characterisation will be based on the estimated caffeine exposures (section 3) and caffeine doses not to give rise to safety concern (section 2).

## 5 References

- EFSA (2015) Scientific Opinion on the safety of caffeine. EFSA Journal 13:4102. DOI: 10.2903/j.efsa.2015.4102.
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