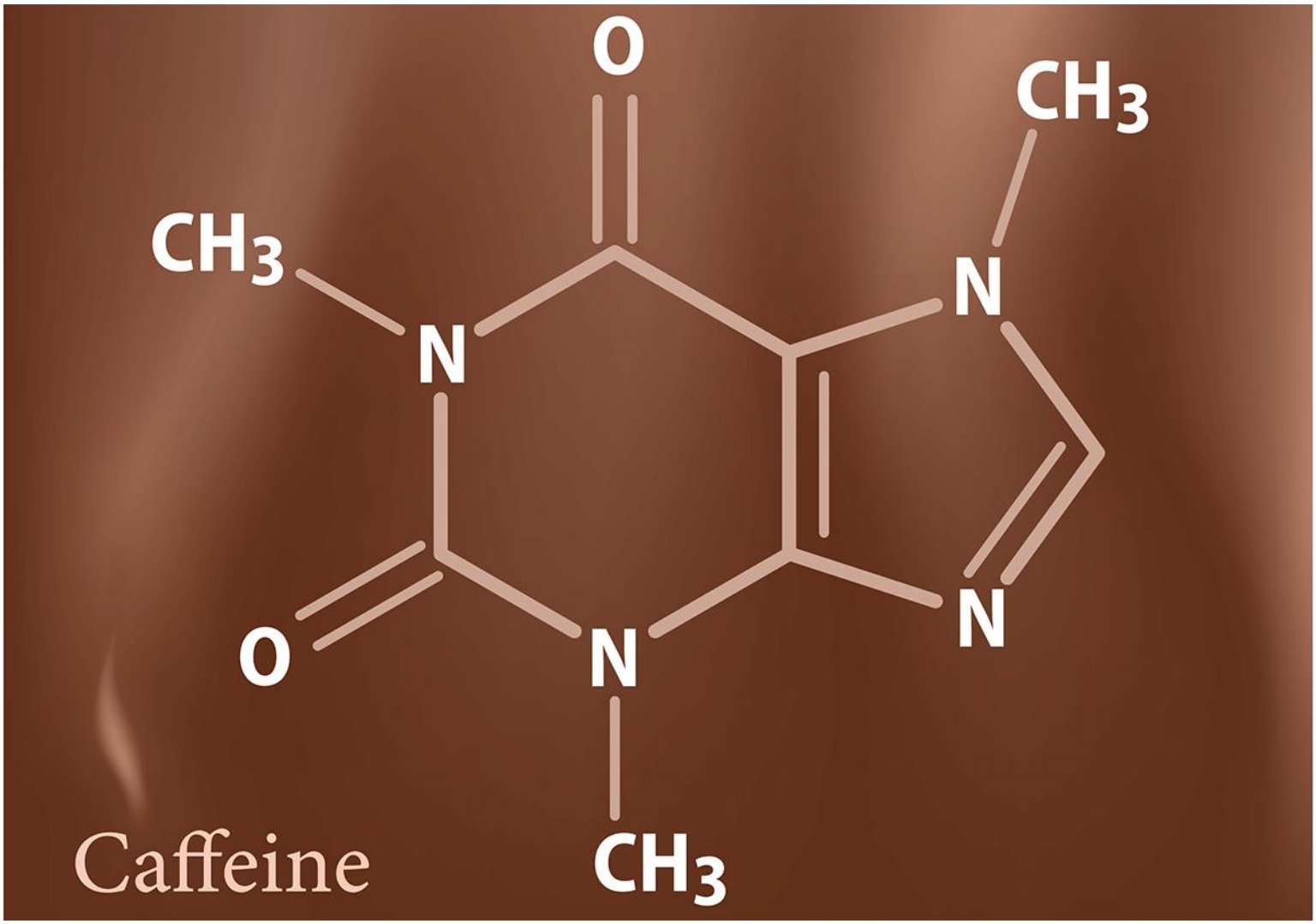
Vitenskapskomiteen for mat og miljø
Norwegian Scientific Committee for Food and Environment



VKM Report 2021: 05

Risk assessment of caffeine exposure from diet and personal care products

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

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Risk assessment of caffeine exposure from diet and personal care products

Preparation of the opinion

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to draft the opinion. Two referees commented on and reviewed the draft opinion. The Committee, by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics, assessed and approved the final opinion.

Authors of the opinion

The authors have contributed to the opinion in a way that fulfils the authorship principles of VKM. 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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Acknowledgement

VKM would like to thank Marita Heinz, Ragnhild Agathe Tornes and Anine Muggerud (Norwegian Institute of Public Health, the library) for valuable help in designing and performing the literature searches.

VKM would like to thank the referees Davide Arcella (The European Food Safety Authority) and Ulrike Bernauer (The German Federal Institute for Risk Assessment) for their valuable comments through critical review of the draft opinion. VKM emphasises that the referees are not responsible for the content of the final opinion. In accordance with VKM's routines for approval of a risk assessment, VKM received their comments before evaluation and approval, and before the opinion was finalised for publication.

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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Erratum

The following have been corrected:

- The text "In the Ungkost 3 study, exposure of caffeine from soda beverages could not be estimated. The web-based diary did not ask for specifications of whether the registered soda beverages were with or without caffeine" from the appendix (Section 10.4) is also included in Section 3.3.1.
- Table 6.2.3-1: "Energy drinks" is changed to "Soda and energy drinks"
- Table 10.5-4 has been included.

The corrections above do not change the discussion or conclusion of the risk assessment.

Summary

In our daily lives, we are exposed to caffeine from several sources. Caffeine is found in a range of food and beverages as well as in personal care products (PCPs), pharmaceuticals and caffeine supplements. The overall aim of the present risk assessment was to examine whether the total caffeine exposure from diet alone and diet in combination with PCPs constitutes a health risk to the Norwegian population.

Hazard
The doses established by the European Food Safety Authority (EFSA) "not to give rise to safety concerns for specific groups of the general population" were used as reference points for safe caffeine levels. These were by EFSA (2015) established for single caffeine exposures and habitual caffeine exposure. Adverse effects of single dose caffeine exposure on the central nervous system were assessed in children (including sleep, anxiety and behavioural changes) and adults (including sleep and anxiety). Adverse effects of habitual caffeine exposure were evaluated in children (behavioural changes), in pregnant women (adverse birth weight-related outcomes in the offspring), and adults (cardiovascular outcomes) (EFSA, 2015). EFSA (2015) stated that these doses do not apply to subgroups of the population selected on the basis of a disease condition. The same holds true for sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions which may require individual advice.

VKM denoted the adverse effects on sleep as "sleep disturbances", and the other adverse effects as "general adverse health effects". VKM interpreted single caffeine exposure as one intake, over a limited period during a day, e.g. one cup of coffee or tea, one meal with several caffeine sources or one portion of caffeine supplement. Habitual caffeine exposure was interpreted as the long-term regular exposure, expressed as the representative exposure throughout a day (daily exposure). VKM interpreted the doses "not to give rise to safety concerns for specific groups of the general population" established by EFSA (2015), for healthy groups of the general population as follows:

Children and adolescents

- Single caffeine exposure of about 1.4 mg/kg bw and 3 mg/kg bw, above which sleep disturbances and general adverse health effects, respectively, may occur.
- Habitual caffeine exposure of about 3.0 mg/kg bw per day, above which general adverse health effects may occur.

It should be noted that the reference points for children and adolescents were predominantly based on data from studies on adults.

Adults, not including pregnant and lactating women

- Single caffeine exposure of about 1.4 mg/kg bw and 3 mg/kg bw above which sleep disturbances and general adverse health effects, respectively, may occur.
- Habitual caffeine exposure of about 5.7 mg/kg bw per day above which general adverse health effects may occur.

Pregnant women

- Habitual caffeine exposure of about 3 mg/kg bw per day, above which there may be concern for the foetus.

No reference point was determined for single exposures for pregnant women due to lack of data, and data to characterise the risk of habitual caffeine consumption were scarce. Unborn children were considered by EFSA (2015) to be the most vulnerable group for adverse effects of caffeine among the general population.

Lactating women

- Single and habitual caffeine exposure of about 3 mg/kg bw per day, above which there may be concern for the breastfed infant.

Sleep disturbances, habitual (daily) exposure
EFSA has not established a dose "not to give rise to safety concerns for specific groups of the general population" for sleep disturbances related to habitual caffeine exposure. To enable risk characterisation for sleep disturbances for habitual caffeine exposure, VKM has used the dose established by EFSA for sleep disturbances from single caffeine exposures.

Exposure

Caffeine concentrations in foods were compiled through a literature search. All relevant food items were assigned a caffeine value. The concentration data and consumption data, see below, were further used in the dietary surveys' exposure estimations. Caffeine concentrations in PCPs were compiled through a literature search and a call for data from businesses and other interested public and private parties.

Caffeine exposure from diet was estimated using four dietary surveys (Ungkost 3, Norkost 3, EuroMix, and Tromsø 7), including children, adolescents, and adults. Caffeine exposure from both diet and PCPs in adults was estimated using EuroMix. Caffeine exposure showed skewed distribution in all surveys and age groups. Thus, in this risk assessment, median and the 95th percentile exposure values are used as the group representative and the high intake values, respectively.

The estimations showed that caffeine from PCPs made up a small part of the total exposure. The main habitual source of caffeine in adults was coffee. In children, the main habitual source of caffeine was cocoa flavored milk products, and in adolescents it was tea. In adults, exposure of caffeine varied throughout a day. The exposure of caffeine was higher around noon and lower towards the evening. Across the dietary surveys, the total caffeine exposure seemed to increase with age.

Risk characterisation

The estimated caffeine exposures used in the risk characterisation were the group median (representative exposure) and 95th percentile (high exposure), and these are compared to the reference points for adverse effects of caffeine.

The risk characterisation for estimated daily (habitual) caffeine exposure of healthy children, adolescents, and adults (not including pregnant and lactating women) is shown in Figure 1.

- Dietary caffeine exposure in children and adolescents; the representative exposure and the high exposure were both below the reference points for general adverse health effects and sleep disturbances. However, in eleven of the participants in Ungkost 3 (0.6%, all age groups), dietary caffeine exposure exceeded the reference points.
- Dietary caffeine exposure in adults; the representative exposure exceeded the reference point for sleep disturbances, but were below the reference point for general adverse health effects. The high exposure exceeded both reference points.
- PCP caffeine exposure in adults; the representative exposure and the high exposure were below both reference points.
- Total caffeine exposure from diet in combination with PCPs in adults; the representative exposure exceeded the reference point for sleep disturbances but was below the reference point for general adverse health effects. The high exposure exceeded both reference points.

The risk characterisation for estimated dietary caffeine exposure for given time periods during a day for healthy adults (not including pregnant and lactating women) is shown in Figure 2.

- The representative caffeine exposures for different time periods during a day were below reference points for both sleep disturbances and general adverse health effects.
- The high exposure exceeded both reference points for the two time periods from morning until 3 pm. The rest of the day, the high exposures exceeded the reference point for sleep disturbances but were below the reference point for general adverse health effects.

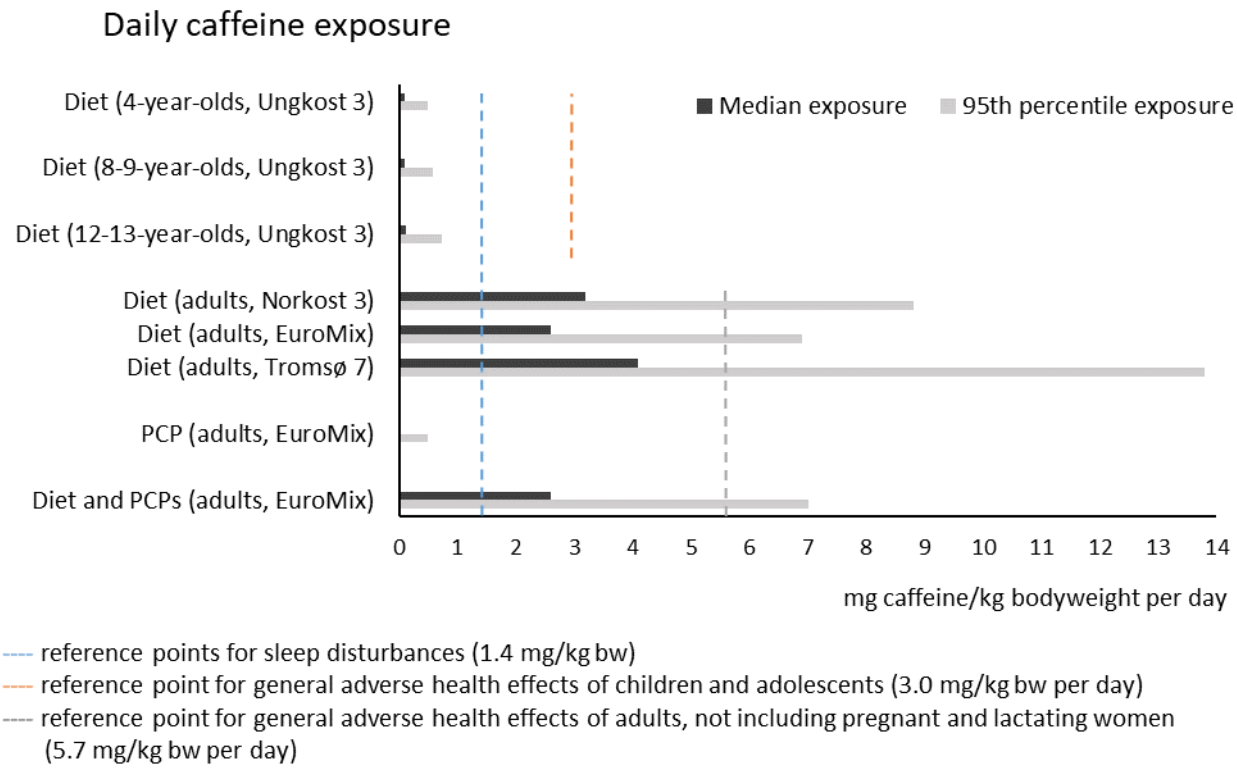


Figure 1. The risk characterisation for daily (habitual) caffeine exposure of healthy children, adolescents and adults, not including pregnant and lactating women.

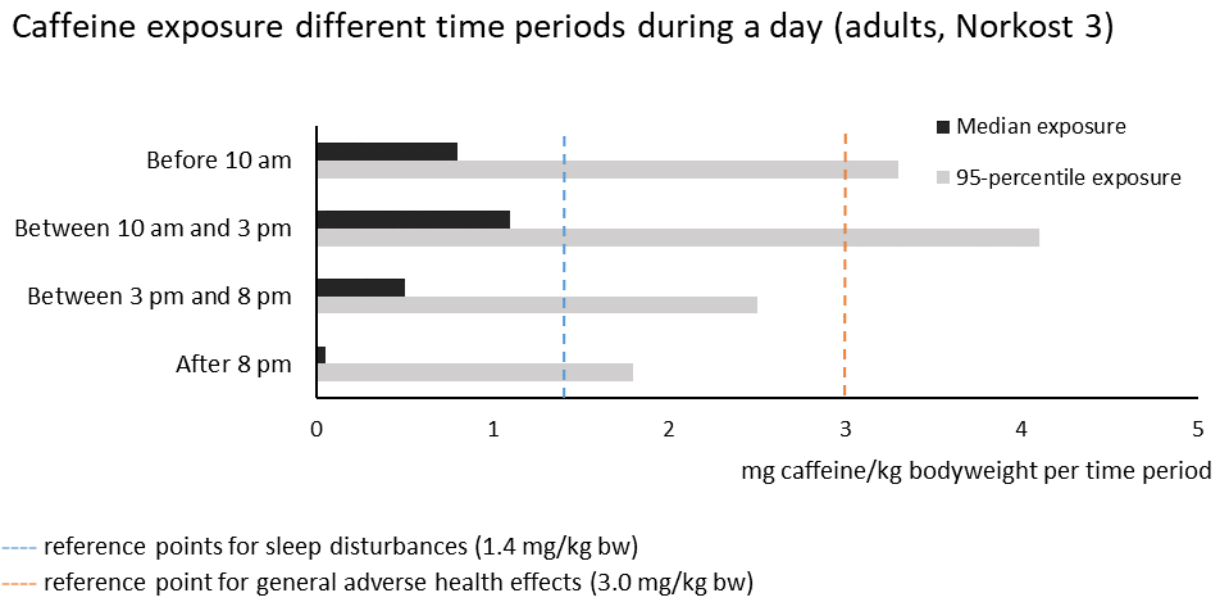


Figure 2. The risk characterisation for caffeine exposure of healthy adults (Norkost 3), not including pregnant and lactating women, for different periods during a day.

Conclusions

Conclusion are reached for healthy individuals, for the representative and the high exposure level. In addition, VKM comments on individuals with especially high exposure.

Daily dietary caffeine exposure in children and adolescents (4-year-olds, 8-9-year-olds and 12-13-year-olds)

- The exposure was below both reference points. VKM concludes that the estimated caffeine exposure is unlikely to cause risk for general adverse health effects and sleep disturbances.
- In a small number of participants, estimated dietary caffeine exposure exceeded both reference points. In children and adolescents with especially high intakes of caffeine containing products, exposures may induce sleep disturbances and general adverse health effects.

Daily caffeine exposure in adults (not including pregnant and lactating women)

- Caffeine exposure from PCP use was below both reference points. VKM concludes that the estimated caffeine exposure is unlikely to cause risk for general adverse health effects and sleep disturbances.
- The representative caffeine exposure from diet alone and diet in combination with PCPs exceeded the reference point for sleep disturbances. VKM concludes that the estimated caffeine exposure may represent a risk for sleep disturbances.
- The high caffeine exposure from diet alone and diet in combination with PCPs exceeded the reference points for sleep disturbances and general adverse health effects. VKM concludes that the estimated exposure may represent a risk for sleep disturbances and general adverse health effects.

Single dietary caffeine exposures in a given time period in adults

Caffeine exposures were divided into four time periods during a day: before 10 am, between 10 am and 3 pm, between 3 pm and 8 pm, and after 8 pm.

- The representative caffeine exposures were below both reference points. VKM concludes that the estimated caffeine exposure, within the time periods assessed, is unlikely to cause risk for sleep disturbances and general adverse health effects.
- In the time periods before 10 am and between 10 am and 3 pm, the high exposure exceeded the reference points for both sleep disturbances and general adverse health effects. VKM concludes that the estimated exposure may represent a risk for sleep disturbances and general adverse health effects.
- In the time periods between 3 pm and 8 pm and after 8 pm, the exposure exceeded the reference point for sleep disturbances but was below the reference point for general adverse health effects. VKM concludes that the estimated exposure may represent a risk for sleep disturbances.

Note that the risk of a sleep disturbance effect will be higher for caffeine intake close to bedtime and will vary between individuals, due to individual variability of the half-life of caffeine.

Pregnant and lactating women

Data on caffeine exposure in pregnant and lactating women were not available for this assessment. If VKM assumes that the exposure estimates for women from Norkost 3 may represent exposure in pregnant and lactating women, the exposure would exceed the reference points for adverse health effects in the foetus and infant. Due to lack of exposure data for pregnant and lactating women, VKM cannot conclude with regard to risk assessment of caffeine exposure in these groups.

Key words: Caffeine, cosmetics, food, multiple sources, Norwegian Scientific Committee for Food and Environment, personal care products, risk assessment, exposure, VKM.

Sammendrag på norsk

Vi eksponeres daglig for koffein fra ulike kilder. Det er koffein i en rekke mat- og drikkevarer, i kosmetikk og kroppspleieprodukter, og i tillegg finnes det koffein i noen legemidler og kosttilskudd. Målet med denne risikovurderingen er å undersøke om den samlede eksponering for koffein fra mat, drikke, kosmetikk og kroppspleieprodukter utgjør en risiko for negative helseeffekter for den norske befolkningen.

Fare

Den europeiske myndighet for næringsmiddeltrygghet (EFSA) har fastsatt doser for daglig koffeininntak og for enkeltinntak som ikke skal utgjøre en risiko for negative helseeffekter for ulike friske grupper av befolkningen (EFSA, 2015). I EFSA sin vurdering ble negative effekter på sentralnervesystemet fra enkeltinntak av koffein vurdert for barn (inkluderte effekter på søvn, angst og atferdsendringer) og voksne (inkluderte effekter på søvn og angst). Negative effekter av daglig koffeineksponering ble evaluert hos barn (atferdsendringer), hos gravide kvinner (effekter på fødselsvekt hos baby) og voksne (effekter på hjerte- og kar). EFSA (2015) påpekte at disse dosene kun gjelder for friske personer i de ulike gruppene, ikke personer med ulike sykdomstilstander. De gjelder heller ikke personer som er spesielt sårbare på grunn av for eksempel genetisk predisposisjon eller andre forhold som kan kreve individuell rådgivning.

VKM omtaler negative effekter på søvn som "søvnforstyrrelser", og de andre negative effektene som "generelle uønskede helseeffekter". VKM har tolket enkeltinntak som en (1) eksponering i en kortere periode i løpet av en dag, som for eksempel en kopp kaffe eller te, ett måltid som inkluderer flere koffein-kilder, eller en porsjon av et koffein-tilskudd. Daglig koffeininntak er tolket som langsiktig, vanlig representativ eksponering. VKM tolket EFSA sine doser for daglig koffeininntak og for enkeltinntak som ikke skal utgjøre en risiko for negative helseeffekter for ulike friske grupper av befolkningen slik:

Barn og ungdom

- Enkel eksponering på ca. 1,4 mg/kg kroppsvekt og 3 mg/kg kroppsvekt. Høyere eksponering kan gi henholdsvis søvnforstyrrelser og generelle negative helseeffekter.
- Daglig eksponering på ca. 3,0 mg/kg kroppsvekt. Høyere eksponering kan gi generelle negative helseeffekter.

Referansepunktene som ble satt for barn og ungdom er hovedsakelig basert på data fra studier på voksne.

Voksne, unntatt gravide og ammende kvinner

- Enkel eksponering på ca. 1,4 mg/kg kroppsvekt og 3 mg/kg kroppsvekt. Høyere eksponering kan gi henholdsvis søvnforstyrrelser og generelle negative helseeffekter.

- Daglig eksponering på ca. 5,7 mg/kg kroppsvekt. Høyere eksponering kan gi generelle negative helseeffekter.

Gravide

- Daglig eksponering på ca. 3 mg/kg kroppsvekt. Høyere eksponering kan påvirke fosteret.

På grunn av manglende data, ble det ikke bestemt noe referansepunkt for enkeltinntak for gravide.

Ammende

- Eksponering for enkeltdoser på 3 mg/kg kroppsvekt eller daglig eksponering for 3 mg/kg kroppsvekt. Høyere eksponering kan påvirke barnet som ammes.

Søvnforstyrrelser daglig eksponering

EFSA har ikke etablert en dose for daglig koffeininntak som ikke skal utgjøre en risiko for søvnforstyrrelser. VKM har brukt EFSA sin dose for enkeltinntak av koffein som ikke skal utgjøre en risiko for søvnforstyrrelser i karakteriseringen av risiko for søvnforstyrrelser ved daglig koffeineksponering.

Eksponering

Vi brukte kostholdsundersøkelsene Ungkost 3, Norkost 3, EuroMix, og Tromsø 7 for å beregne koffeineksponering fra kostholdet for barn, ungdom og voksne. EuroMix ble også brukt for å beregne koffeineksponering fra kosmetikk og kroppspleieprodukter, og for å beregne samlet eksponering fra begge disse kildene. I alle undersøkelsene, og for alle aldersgrupper, var koffeineksponeringen skjevfordelt, og derfor ble median og 95 persentil brukt for å vise gruppenes representative eksponering og høye eksponering.

Estimatene viste at koffein fra kroppspleieprodukter utgjorde en liten del av den totale koffeineksponeringen. Den viktigste kilden til koffein hos voksne var kaffe. Hos barn var den viktigste kilden til koffein melkeprodukter med kakao, og hos ungdommer var den te. Voksnes inntak av kaffe varierte gjennom dagen, og var høyest den første delen av dagen, og lavere på ettermiddagen og kvelden. På tvers av kostholdsundersøkelsene var det en trend at den totale koffeineksponeringen økte med alder.

Risikokarakterisering

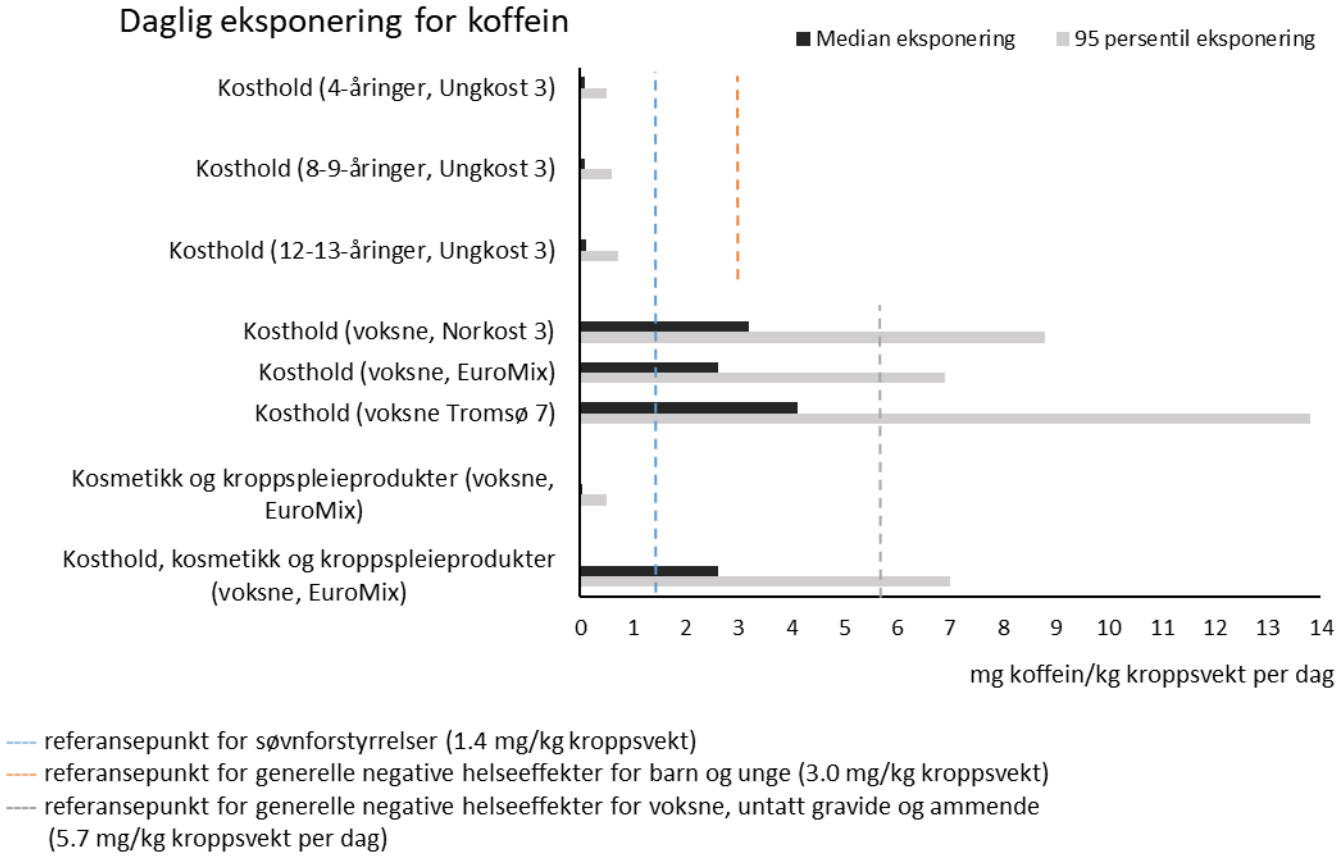
For å karakterisere risikoen ble beregnet eksponering for koffein, både median (representativ eksponering) og 95 persentil (høy eksponering), sammenlignet med referansepunktene for søvnforstyrrelser og generelle negative helseeffekter.

Karakteriseringen av risiko ved beregnet daglig koffeineksponeringen for friske barn, ungdommer og voksne, unntatt gravide og ammende, er vist i figur 1.

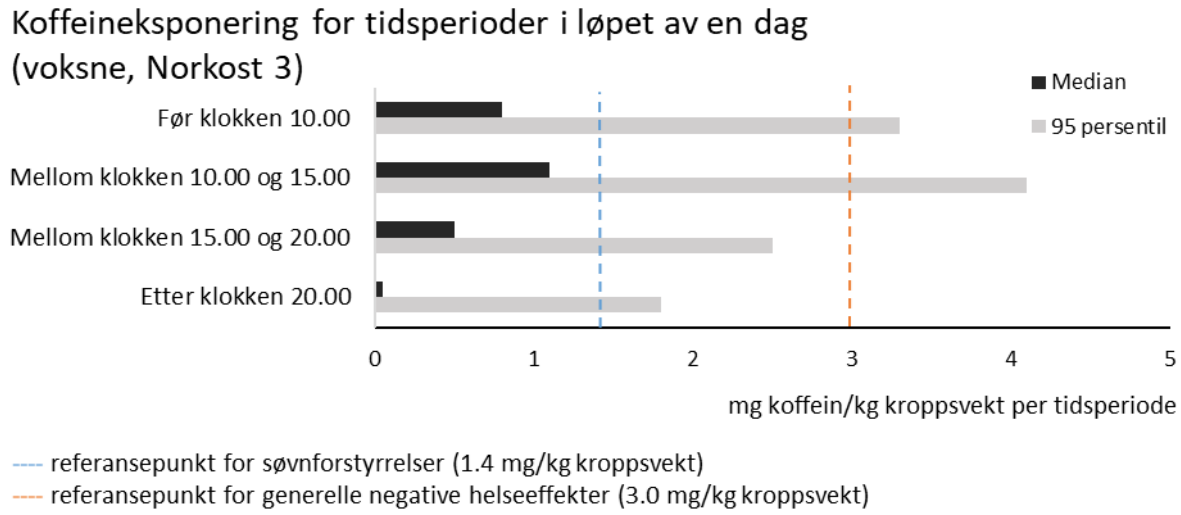
- Barn og ungdom fikk i seg mindre koffein fra kostholdet enn det som gir søvnforstyrrelser og generelle negative helseeffekter. Hos elleve av deltakerne i Ungkost 3 (0,6%, alle aldersgrupper) overskred beregnet eksponering fra kostholdet begge referansepunktene.
- Voksnes representative koffeineksponering fra kostholdet overskred referansepunktet for søvnforstyrrelser men var under referansepunktet for generelle negative helseeffekter. Høy koffeineksponeringen overskred begge referansepunktene.
- Voksne fikk i seg mindre koffein fra kosmetikk og kroppspleieprodukter enn det som gir søvnforstyrrelser og generelle negative helseeffekter.
- Voksnes samlede representative koffeineksponering fra kosmetikk, kroppspleieprodukter og kostholdet overskred referansepunktet for søvnforstyrrelser men var under referansepunktet for generelle negative helseeffekter. Høy koffeineksponeringen overskred begge referansepunktene.

Karakteriseringen av risiko ved beregnet koffeineksponering for tidsperioder i løpet av en dag for friske voksne, unntatt gravide og ammende, er vist i figur 2.

- Representativ koffeineksponering var under referansepunktene for søvnforstyrrelser og for generelle negative helseeffekter for alle de fire tidsperiodene i løpet av en dag.
- Fra morgen til klokken 15 overskred den høye koffeineksponeringen begge referansepunktene. Resten av dagen overskred den høye koffeineksponeringen referansepunktet for søvnforstyrrelser, men var under referansepunktet for generelle negative helseeffekter.



Figur 1. Karakterisering av risiko ved beregnet daglig koffeineksponering for friske barn, ungdommer og voksne, unntatt gravide og ammende kvinner.



Figur 2. Karakterisering av risiko ved beregnet koffeineksponering for tidsperioder i løpet av en dag for friske voksne (Norkost 3), unntatt gravide og ammende kvinner.

Konklusjoner

Konklusjonene gjelder for friske individer, for en representativ koffeineksponering (median) og for høy koffeineksponering (95 persentil). I tillegg kommenterer VKM på individer med spesielt høy eksponering.

Barn og ungdom (4-åringer, 8-9-åringer og 12-13-åringer), eksponering fra kosten

Barn og ungdom fikk i seg mindre koffein enn det som gir søvnforstyrrelser og generelle negative helseeffekter. VKM konkluderer med at det ikke er sannsynlig at den beregnede koffeineksponeringen vil medføre risiko for søvnforstyrrelser eller generelle negative helseeffekter.

Hos elleve av deltakerne i Ungkost 3 (0,6 %, alle aldersgrupper) overskred beregnet eksponering begge referansepunktene. VKM konkluderer med at koffeineksponering for barn og ungdom med spesielt høyt inntak av produkter med høye koffeinkonsentrasjoner kan føre til søvnforstyrrelser og generelle negative helseeffekter.

Voksne, unntatt gravide og ammende, daglig eksponering fra kosmetikk, kroppspleieprodukter og kosten

Voksne fikk i seg mindre koffein fra kosmetikk og kroppspleieprodukter enn det som gir søvnforstyrrelser og generelle negative helseeffekter. VKM konkluderer med at det ikke er sannsynlig at beregnet koffeineksponering vil medføre risiko for søvnforstyrrelser eller generelle negative helseeffekter.

Voksnes representative koffeineksponering fra kosten alene og fra kosmetikk, kroppspleieprodukter og kosten samlet, overskred referansepunktet for søvnforstyrrelser men var under referansepunktet for generelle negative helseeffekter. VKM konkluderer med at beregnet representativ koffeineksponering kan innebære en risiko for søvnforstyrrelser.

Voksnes høye koffeineksponering fra kosten alene og fra kosmetikk, kroppspleieprodukter og kosten samlet, overskred begge referansepunktene. VKM konkluderer med at beregnet høy koffeineksponering kan utgjøre en risiko for søvnforstyrrelser og generelle negative helseeffekter.

Voksne, unntatt gravide og ammende, eksponering for koffein fra kosten i ulike tidsperioder i løpet av en dag

Koffeineksponering fra kosten ble delt inn i fire tidsperioder i løpet av en dag.

Representativ koffeineksponering var under begge referansepunktene for alle tidsperiodene. VKM konkluderer med at det ikke er sannsynlig at beregnet koffeineksponeringen vil medføre risiko for søvnforstyrrelser eller generelle negative helseeffekter.

Fra morgen til klokken 15 overskred den høye koffeineksponeringen begge referansepunktene. Resten av dagen overskred den høye koffeineksponeringen referansepunktet for søvnforstyrrelser, men var under referansepunktet for generelle negative helseeffekter. VKM konkluderer med at beregnet koffeineksponering i tidsperiodene før kl. 10 og mellom kl. 10 og kl. 15 kan utgjøre en risiko for søvnforstyrrelser og generelle

negative helseeffekter, mens eksponeringen i tidsperiodene mellom kl. 15 og 20 og etter kl. 20 kan utgjøre en risiko for søvnforstyrrelser.

På grunn av individuell variasjon når det gjelder halveringstiden for koffein vil risikoen for søvnforstyrrelser være høyere for koffeininntak nær leggetid og den vil variere mellom individer.

Gravide og ammende kvinner

Siden VKM ikke har data på koffeininntak hos gravide og ammende, kan vi ikke konkludere om disse vil gruppene vil oppleve helseeffekter av koffeineksponering. Hvis VKM antar at gravide og ammende har samme eksponering som kvinner fra Norkost 3, vil eksponeringen overstige referansepunktene for skadelige helseeffekter hos fosteret og barnet som ammes.

Abbreviations and glossary

Abbreviations

bw	bodyweight
EFSA	European Food Safety Authority
FCD	food composition database
GI	gastrointestinal
IQR	interquartile range
LOD	limit of detection
LOQ	limit of quantification
MoS	margin of safety
NOAEL	no observed adverse effect level
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

Glossary

Adverse effect
An effect is considered "adverse" when leading to a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity to compensate for additional stress or an increase in susceptibility to other influences" (WHO, 1994).

Caffeine supplement
Caffeine-containing food supplements.

Cosmetic product
Any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours (Regulation (EC) No 1223/2009 of the European Parliament and of the Council, 2009).

Daily exposure
The long term, representative amount consumed, expressed as exposure throughout a day (habitual exposure).

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 caffeine supplements or pharmaceuticals.

Habitual exposure
The long term, representative amount consumed, expressed as exposure throughout a day (daily exposure).

Internal exposure
The total amount of caffeine absorbed from the gastrointestinal (GI) tract and the skin, which is systemically available**.**

I^2 statistic
Describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (Higgins and Green, 2011).

No observed adverse effect level (NOAEL)
The largest concentration or amount of a substance tested at which no detectable adverse effects occur in an exposed population.

Personal care products
Consumer products used for beautification (make up products) and in personal hygiene (shower gel, skin cream, shampoo, feminine hygiene products, diapers, toilet paper etc.) (SCCS (Scientific Committee on Consumer Safety), 2018).

Reference point (point of departure)
The point on a dose–response curve established from experimental data used to derive a safe level (EFSA Glossary). The POD may be derived from the no observed adverse effect level or the benchmark dose method. A POD is also known as a reference point.

Retention factor
The retention factor represents the fraction available for uptake (SCCS (Scientific Committee on Consumer Safety), 2018).

Single exposure
One intake, over a limited period during a day, e.g. one cup of coffee or tea, one meal with several caffeine sources or one portion of caffeine supplement.

Assessment

1 Introduction

Humans are exposed to caffeine from several sources in their daily lives. Potential caffeine sources are food, caffeine supplements and personal care products (PCPs). Estimations of the Norwegian population's total caffeine exposure, therefore, needs to include multiple sources.

Caffeine (1,3,7-trimethylxanthine) (Figure 1-1) is an alkaloid found in various plant constituents, such as coffee and cocoa beans, tea and yerba mate leaves, guarana berries and the kola nut (EFSA, 2015). Caffeine can also be produced by chemical synthesis. The molecular weight is 194.2 g/mol, and the CAS number is 58-08-2.

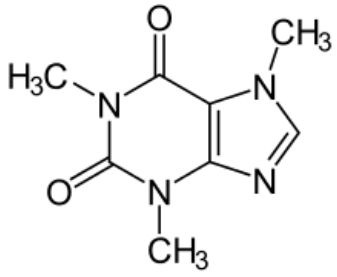


Figure 1-1. The chemical structure of caffeine.

Caffeine is found in a range of food and beverages, and is a natural ingredient in products such as coffee, tea and chocolate. Caffeine can also be added to beverages, such as so-called energy drinks. Caffeine may also be found in some PCPs, pharmaceutical and caffeine supplements marketed for sport performance or weight loss (EFSA, 2015). It is claimed that caffeine has various favourable effects on the skin (Herman and Herman, 2013).

1.1 Physiological effects of caffeine

The stimulating effects of caffeine are predominantly related to antagonistic activity at adenosine A1 and A2 receptors expressed in the central nervous system, in particular at the basal ganglia. The interaction with the adenosine A1 receptor in the kidney leads to inhibition of renal re-absorption of water and causes increased diuresis and natriuresis. In addition, caffeine facilitates dopamine D2 receptor transmission, and is known as a non-specific phosphodiesterase inhibitor. Polymorphisms in adenosine receptors have been described and for some effects of caffeine, the effect size might be related to the polymorphic state (EFSA, 2015).

Tolerance to some, but not to all, effects of caffeine is observed after repeated administration. Tolerance to e.g. the effects of caffeine on blood pressure and heart rate usually develops within a couple of days. The development of tolerance is highly variable among individuals in the population, and the mechanisms are not well understood (EFSA, 2015). Symptoms such as headache, fatigue, decreased energy and activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability and being not clear headed are observed 12–24 hours after abstinence and this clinical situation is called caffeine withdrawal syndrome (EFSA, 2015).

1.2 Absorption, distribution, metabolism and excretion (ADME)

With the exception of metabolism, caffeine absorption, distribution, excretion, clinical activity, and toxicity are similar in humans and most laboratory animals (Burdan, 2015). Caffeine is rapidly and completely absorbed from the gastrointestinal tract (GI tract) after oral intake in humans, and the peak plasma concentration is reached within 15 minutes to 2 hours after ingestion (EFSA, 2015). VKM, therefore, sets 100% as the oral absorption value for caffeine for the exposure assessment.

Human *in vivo* studies on dermal absorption of caffeine report values between 3.8% and 57.4% depending on factors such as dose applied, vehicle, site of application and exposure period (Table 1.2-1). When excluding two studies (Lotte et al., 1987; Lotte et al., 1993) due to very short exposure time (30 minutes), the mean absorption value is 36%. In Bronaugh and Franz (1986), exposure time was not reported. If also excluding this study, the mean absorption value is 40%.

Table 1.2-1 Summary of *in vivo* studies on dermal absorption of caffeine in humans.

Reference	N	Applied dose	Vehicle	Skin site/ characteristic	Exposure/ sampling	% absorbed (mean±SD/SE)
Feldmann and Maibach (1970)	17	4 µg/cm^2 (13 cm^2 area)	Acetone	Forearm No occlusion	Rinse-off after 24 hrs Urine sampling for 5 days	47.6±21.0
Franz (1978)	4	4 µg/cm^2	Aqueous ethanol/acetone	Abdomen	Rinse-off after 24 hrs Urine sampled until background levels were approached	22.1±15.8
Bronaugh and Franz (1986)		20–60 cm^2 area		Abdomen No occlusion	Urine sampled until background	
	5	60 µg caffeine/cm^2 (50 mg/cm^2)	Petrolatum			40.6±6.1

Reference	N	Applied dose	Vehicle	Skin site/ characteristic	Exposure/ sampling	% absorbed (mean±SD/SE)
	4	0.5 µg caffeine/cm^2 (25 mg/cm^2)	Ethylene glycol gel		levels were approached	32.2±7.3
	4	50 µg caffeine/cm^2 (400 mg/cm^2)	Water gel		(individual samples first 24 hrs, thereafter 8 hrs pools)	4.0±0.5
Lotte et al. (1987)	7	1000 nmol in 20 µl/cm^2	Aqueous ethyleneglycol/Triton X100	Arm	Rinse-off after 0.5 hr	6.0±0.9
	6			Abdomen		3.8±0.7
	7			Postauricular		5.9±0.5
	6			Forehead	Urine sampling for 24 hrs	11.2±1.2
Roskos et al. (1989)		4 µg/cm^2 (20 µl, 2.5 cm^2)	Acetone	Forearm Occlusion	Rinse-off after 24 hrs	
	5			22–40 years	Urine sampled for 7 ds	48.2±4.1
	7			>65 years		25.2±4.8
Lotte et al. (1993)	21	1 µm/cm^2 (20 µl/cm^2)l	Aqueous ethyleneglycol/Triton X100	Asian	Rinse-off after 0.5 hr	5.2±0.8
				Black		4.5±1.0
				Caucasian	Urine sampling for 24 hrs	5.9±0.6
Liu et al. (2011); Otberg et al. (2008)	6	10 µg caffeine/cm^2 (2 mg/cm^2 of 2.5% caffeine on 25 cm^{2}area)	Ethanol/propylene glycol	Chest No occlusion for 8 hrs	No rinse-off Blood samples after 5, 10, 20 and 30 min, 1, 2, 5, 8, 24 and 72 hrs	57.4±4.8

Table 1.2-2 shows dermal absorption values reported from guideline compliant *in vitro* studies using human or porcine skin. In *in vitro* dermal absorption tests, the amount of test item found in epidermis (without *stratum corneum*), dermis and the receptor fluid is considered as being dermally absorbed and thus, being systemically available. When estimating the total dermal absorption value to be used in risk assessments, the standard deviation (SD) is usually added to the mean value (SCCS, 2018). Based on *the in vitro* studies, the total dermal absorption values for caffeine are 36% and 44% for human and porcine skin, respectively. The dermal absorption value of 36% is comparable with the *in vivo* studies. Excluding the studies by Lotte et al. (1987; 1993) the mean+1SD is 40% and 50% when excluding Bronaugh and Franz (1986) (conversion of standard error into standard deviation: $SE * \sqrt{n}$). Since the *in vivo* studies varies greatly in the study designs, VKM used a dermal absorption value of 36% based on the *in vitro* studies using human skin for the exposure assessments.

Table 1.2-2 Summary of *in vitro* studies on dermal absorption of caffeine using human or porcine skin.

Source	Caffeine applied	No. skin samples	Receptor fluid	Exposure period (h)	Mass balance (%)	% dermally absorbed (Mean±SD)
Human skin						
Nielsen et al. (2007)	200 µg/cm^2	14	0.9% NaCl in water*	48	96	39 (28.6±10.1)
Trauer et al. (2009)	250 µg/cm^2	NR (4 donors)	PBS	24	89	37 (33.7±2.9)
van de Sandt et al. (2004) (Multi-centre study)	100 µg/cm^2	NR	0.9% NaCl in water	24	66-101	17 (13.1±3.7) 26 (21.1±5.3) 26 (22.6±3.7) 35 (25.7±9.5) 41 (33.5±7.6) 57 (44.5±12.4) Mean: 26.8
Gerstel et al. (2016)	40 µg/cm^2	6 (3 donors)	0.9% NaCl in water**	24	>96	33 (26.4±6.6)
Mean dermally absorbed						**36**
Porcine skin						
Gerstel et al. (2016) (ear)	1% (w/v)	6	0.9% NaCl in water**	24	>96	46 (34.1±11.8)
Gerstel et al. (2016) (back)	1% (w/v)	6	0.9% NaCl in water with**	24	88	52 (35.4±16.5)
Gerstel et al. (2016) (back)	1% (w/v)	6	0.9% NaCl in water with**	24	88	47 (27.1±20.3)
Muhammad et al. (2017)	40 µg/cm^2	>4	Krebs–Ringer bicarbonate buffer***	NR	NR	43 (32.4±10.7)
Muhammad et al. (2017)	40 µg/cm^2	NR	Krebs–Ringer bicarbonate buffer***	24	Samples with <50% discarded	32 (27.7±3.9)
Davies et al. (2017)	100 µg/cm^2	NR	NR	24	104	6 (5.0±0.6)
Mean dermally absorbed						**38**
Mean dermally absorbed (without Davies 2017)						**44**

NaCl: sodium chloride; NR: not reported; *with bovine serum albumin and hexamycin; ** with bovine serum albumin and gentamycin; ***spiked with dextrose and bovine serum albumin.

Caffeine is rapidly distributed throughout the body, including to the extravascular space. It freely crosses the blood-brain barrier, the testicular barriers, and the placenta and is excreted in breast milk (EFSA, 2015). Tissue distribution, including brain/plasma concentration ratios, were found to be dose dependent (Arnaud, 2011) and were reported to be close to one for rabbits and rats exposed to 4 mg/kg (intravenously) and 1 mg/kg (orally) caffeine, respectively (Beach et al., 1985; Latini et al., 1978).

Once caffeine is absorbed, there appears to be no hepatic first-pass metabolism (i.e., the liver does not appear to remove caffeine as it passes from the gut to the general circulation) (Arnaud, 1993). With no first-pass effect occurring in the liver, oral caffeine absorption is independent of age, sex, health status, and concomitant administration of alcohol, drugs and nicotine (Burdan, 2015). The main route of metabolism of caffeine is in the liver primarily by the cytochrome P450 enzyme system. The 1A2 isoenzyme of cytochrome P450, encoded by the *CYP1A2* gene, is directly involved in demethylation of caffeine to paraxanthine (1,7-dimethylxanthine, 84% of the parent compound), theobromine (3,7-dimethylxanthine, 12%) and theophylline (1,3-dimethylxanthine, 4%). The activity of CYP1A2 accounts for 95% of the caffeine clearance. Paraxanthine, theophylline and theobromine are further metabolised and then excreted in the urine. As the abundance of CYPs in the skin is very low (<300-fold lower than in the liver), there is minimal metabolism of caffeine in the skin (Luo and Lane, 2015; Oesch et al., 2018).

Caffeine has a plasma half-life of about 4 hours with a range of about 2-8 h. The kinetics of caffeine metabolism has been reported to be linear in doses up to 10 mg/kg bw, however, a later study reported non-linearity beginning at doses corresponding to about 7.1 mg/kg bw. Polymorphism in the *CYP1A2* gene is a likely reason for variations in the metabolism of caffeine among humans (EFSA, 2015). It is expected that due to minimal metabolism in the skin, systemically available caffeine after dermal penetration also undergoes metabolism in the liver.

CYP1A2 activity is reduced during pregnancy and, hence, the half-life of caffeine is increased. At the end of pregnancy, the half-life of caffeine is three to four times longer than in the non-pregnant state. Caffeine readily crosses the placenta. The metabolism of caffeine in neonates is reported to be much slower than in adults, with a caffeine half-life of 50-103 h. However, already in children 5 to 6 months of age the half-life of caffeine is reduced to 2-3 h, which remains stable during childhood and increases thereafter in adolescents and adults. Caffeine clearance from plasma has been estimated to be 5 to 20% faster in children than in adults (EFSA, 2015).

1.3 Aim and objectives

The overall aim was to examine whether the total caffeine exposure from diet alone and diet in combination with PCPs constitutes a health risk to the Norwegian population.

The objectives were to:

- Estimate caffeine exposure from multiple sources
    - Identify food and PCPs that contain caffeine, and compile caffeine concentrations.
    - Estimate the intake of caffeine-containing foods and use of caffeine-containing PCPs.
    - Estimate the total caffeine exposure from food and PCPs in different groups of the Norwegian population.
    - Identify the main caffeine sources that contribute to the estimated exposure.
    - 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 doses may be used as reference points for toxicity.
- Characterise risks associated with estimated caffeine exposure in different groups of the Norwegian population.
- Identify and describe main knowledge gaps that may have an impact on the conclusions.

In the current assessment, the Norwegian population includes children (from 4 years), adolescents, and adults (women and men).

The authors drafted a priori a protocol for this risk assessment. The protocol was reviewed and approved by the members 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 (VKM Panel). The final protocol was published March 9, 2020 (VKM et al., 2020).

1.4 Limitations to the risk assessment

- Children aged 0 to <4 years are not included.
- The literature search for the hazard assessment will be limited to randomised controlled trials (RCTs) as randomisation reduces bias and provides a rigorous tool to examine cause-effect relationships between an intervention and outcome (Hariton and Locascio, 2018).
- The exposure assessment is limited by the available data.
- Contribution of caffeine from pharmaceuticals and caffeine supplements are estimated using scenarios due to lack of person-specific exposure data.
- The risk assessment is limited to address possible adverse health effects of caffeine exposure from diet alone and diet in combination with PCPs in the general healthy population.
- The reference points for children and adolescents are based on studies on healthy adults, because there are insufficient number of studies for these groups.
- There are limited studies on pregnant and lactating women.

2 Hazard identification and characterisation

In an EFSA opinion on caffeine, possible adverse health effects of caffeine consumption from all dietary sources, in the general healthy population and in relevant subgroups of the general population including children, adolescents, adults, and pregnant and lactating women, were assessed (EFSA, 2015): "The effects of single and repeated doses of caffeine consumed within a day on the central nervous system were assessed in adults (sleep, anxiety, perceived exertion during exercise and subjective perception of alcohol intoxication) and children (sleep, anxiety and behavioural changes). Adverse effects of longer-term and habitual caffeine consumption were evaluated in children in relation to behavioural changes and in pregnant women in relation to adverse birth weight-related outcomes (e.g. fetal growth retardation, small for gestational age) in the offspring. In adults, the adverse effects of habitual caffeine consumption, either alone or in combination with other constituents of energy drinks and with p-synephrine, were evaluated in relation to cardiovascular outcomes".

The conclusions on caffeine intakes which do not give rise to safety concerns for specific groups of the general population (EFSA, 2015) were as follows:

- "Single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) from all sources do not give rise to safety concerns for the general healthy adult population".
- "Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg bw per day for a 70-kg adult) consumed throughout the day do not give rise to safety concerns for healthy adults in the general population, except pregnant women".
- "Caffeine intakes from all sources up to 200 mg per day consumed throughout the day by pregnant women in the general population do not give rise to safety concerns for the fetus".
- "Single doses of caffeine and habitual caffeine intakes up to 200 mg consumed by lactating women do not give rise to safety concerns for breastfed infants".
- "Single doses of 100 mg (about 1.4 mg/kg bw for a 70-kg adult) of caffeine may increase sleep latency and reduce sleep duration in some adult individuals, particularly when consumed close to bedtime".
- "Single doses of caffeine of no concern derived for adults (3 mg/kg bw per day) may also apply to children, considering that caffeine clearance in children and adolescents is at least that of adults, and that the limited studies available on the acute effects of caffeine on anxiety and behaviour in children and adolescents support this level of no concern".
- "A level of no safety concern of 3 mg/kg bw per day (i.e. the level of no concern derived for single doses of caffeine for adults) is proposed for habitual caffeine consumption by children and adolescents. This approach is rather conservative in relation to the effects of caffeine on the cardiovascular system, but the limited

studies available regarding the longer-term effects of caffeine on anxiety and behaviour in children and adolescents support the proposed caffeine intake level of no safety concern".
- "Like for adults, caffeine doses of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents, particularly when consumed close to bedtime".

EFSA stated that these doses do not apply to subgroups of the population selected on the basis of a disease condition. The same holds true for sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions which may require individual advice.

VKM denoted the adverse effects on sleep as "sleep disturbances", and the other adverse effects as "general adverse health effects".

In the included RCTs the outcomes addressed for general adverse health effects were blood pressure, heart rate, haematologic parameters (including white blood cell count, red blood cell count, haemoglobin, haematocrit, platelets, lymphocytes, monocytes, eosinophils, basophils), intraocular pressure, ocular perfusion pressure, and "other side effects" (including nervousness, muscular pain, headache, GI effects, muscle pain, irritability and diuresis). In addition, sleep disturbances were addressed.

In 2019, VKM published a risk assessment of energy drinks and caffeine. After examining RCTs on caffeine and adverse health effects published in 2015-2018, VKM concluded that there was no need for revision of "the doses which do not give rise to safety concerns" established by EFSA (VKM et al., 2019). In the present risk assessment, VKM re-evaluated whether new studies indicate a need for revision of these doses.

2.1 Identification and evaluation of RCTs on negative health effects related to caffeine published in the period 2013 - 2020

2.1.1 Literature search

Literature searches were performed to identify RCTs on caffeine and negative health effects. In the previous VKM assessment (VKM et al., 2019), we searched for RCTs published in the period 2013-2018. In the present risk assessment, we searched the electronic databases from MEDLINE (Ovid), Embase (Ovid), PsycINFO and Web of Science for RCTs published in the period 2019-2020 (see Appendix, Section 9.1 for search terms and search strategy).

A specialised research librarian was involved in the planning of the search and conducted the search. The identified records were imported into EndNote (Thomson Reuters, version X9), duplicates were removed, and the records were imported into the screening web-tool Rayyan (Ouzzani et al., 2016) for publication selection.

2.1.2 Publication selection

The publication selection was based on eligibility criteria predefined in the protocol (Table 2.1.2-1).

Table 2.1.2-1. Hazard: eligibility criteria.

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

Two independent reviewers performed the publication selection. Titles and abstracts of 588 records were screened prior to full-text assessment of 18 articles. Ten publications fulfilled the eligibility criteria. An overview of the publication selection is given in Figure 2.1.2-1.

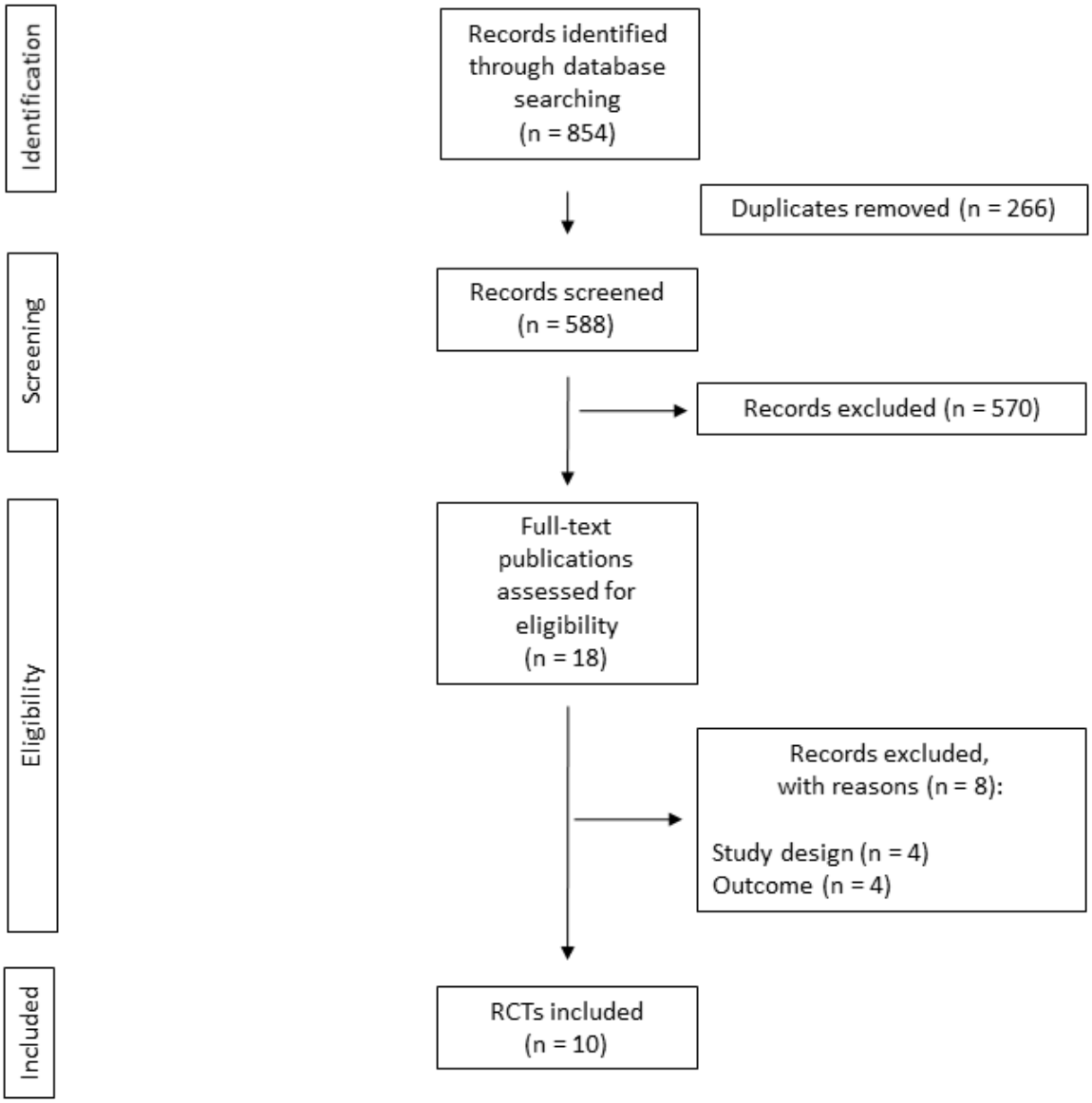


Figure 2.1.2-1. Flow diagram illustrating the process of selecting eligible RCTs.

2.1.3 Internal validity

Risk of bias (RoB) was evaluated using the OHAT (Office of Health Assessment and Translation) tool (OHAT, 2015; OHAT 2019). This tool includes eight questions considering aspects relevant for RoB evaluation of human controlled trials. The response options and symbols (in parentheses) used for the rating are i) definitely low risk of bias (++); ii) probably low risk of bias (+); iii) probably high risk of bias/not reported (NR) (-); and iv) definitely high risk of bias (- -) (Table 2.1.3-1). We defined questions 1 to 3 and 5 to 7 as key questions, whereas questions 4 and 8 were defined as non-key questions (Table 2.1.3-2). The key questions address the elements selection bias (randomisation and allocation to study groups), performance bias (identical experimental conditions across study groups and blinding of personnel and participants), detection bias (confidence in the exposure

characterisation and the outcome assessment), and selective reporting bias. The non-key questions address the elements attrition/exclusion bias and other sources of bias. The rating of key and non-key questions was integrated to classify the RCTs into tiers to characterise the overall RoB for each outcome/study (modified from EFSA et al. (2017)) as shown in Table 2.1.3-1. Tier 1 represents low RoB, tier 3 represents high RoB. Tier 2 studies did not meet the criteria for tier 1 or 3.

Table 2.1.3-1. Classification of studies into tiers according to overall RoB for each outcome/study.

Tier	**1**	**2**	**3**
Criteria for classification	All key questions are scored +/++ AND No more than one non-key question is scored – AND No non-key question is scored - -	All combinations not falling under tier 1 or 3	Any key or non-key question is scored - - OR More than one key question is scored -

Two reviewers independently assessed RoB for each outcome reported in the eligible RCTs on caffeine and negative health effects identified in the literature searches covering the periods 2015-2018 and 2019-2020.

The reviewers calibrated themselves once to ensure similar evaluation. For the outcomes blood pressure and heart rate, the RCTs were classified as follows: four tier 1, four tier 2, and five tier 3 (Table 2.1.3-2). The two eligible RCTs on the outcome haematologic parameters, were classified as tier 1 (Table 2.1.3-3). The only eligible study on intraocular pressure and ocular perfusion pressure, was classified as tier 2 (Table 2.1.3-4). The RCTs on "other side effects" and sleep disturbances were classified as two tier 1, one tier 2, and three tier 3 (Table 2.1.3-5). "Other side effects" includes nervousness, muscular pain, headache, GI effects, muscle pain, irritability and diuresis. The detailed evaluation for each RoB question for each outcome is included in the appendix (Section 9.3).

Table 2.1.3-2. An overview of the RoB rating and the classification into tiers for the outcomes blood pressure and heart rate for each study. *Key question.

	1. Was administered dose or exposure level adequately randomized?*	2. Was allocation to study groups adequately concealed?*	3. Were the research personnel and human subjects 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?	Tier
Bloomer et al. (2013)	+	+	++	++	++	++	++	+	1
Crooks et al. (2019)	+	+	-	+	-	++	++	+	3
Dodd et al. (2015)	++	++	++	+	-	+	++	+	2
Flueck et al. (2016)	++	++	++	++	-	++	++	++	2
Gonzaga et al. (2017)	++	+	-	++	-	++	++	+	3
Hansen et al. (2019)	+	+	-	+	-	++	++	+	3
Pajcin et al. (2019)	+	-	-	++	-	++	++	+	3
Puente et al. (2017)	+	+	++	-	++	+	++	+	1

	1. Was administered dose or exposure level adequately randomized?*	2. Was allocation to study groups adequately concealed?*	3. Were the research personnel and human subjects 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?	Tier
Ratamess et al. (2018)	+	+	++	-	+	++	++	+	1
Ruiz-Moreno et al. (2020)	+	+	++	-	++	++	++	+	1
Vera et al. (2019)	-	+	++	-	+	++	++	+	2
Yoshihara et al. (2019)	++	+	-	++	-	++	++	-	3
Zbinden-Foncea et al. (2018)	+	+	++	-	-	++	++	+	2

Table 2.1.3-3. An overview of the RoB rating and the classification into tiers for the outcome haematological parameters for each study. *Key question.

	1. Was administered dose or exposure level adequately randomized?*	2. Was allocation to study groups adequately concealed?*	3. Were the research personnel and human subjects 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?	Tier
Bloomer et al. (2013)	+	+	++	++	++	++	++	+	1
Bush et al. (2018)	+	+	++	++	+	++	++	++	1

Table 2.1.3-4. An overview of the RoB rating and the classification into a tier for the outcomes intraocular pressure and ocular perfusion pressure for this study. *Key question.

	1. Was administered dose or exposure level adequately randomized?*	2. Was allocation to study groups adequately concealed?*	3. Were the research personnel and human subjects 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?	Tier
Vera et al. (2019)	-	+	++	-	+	++	++	+	2

Table 2.1.3-5. An overview of the RoB rating and the classification into tiers for the outcome "other side effects" and sleep disturbance for each study. *Key question.

	1. Was administered dose or exposure level adequately randomized?*	2. Was allocation to study groups adequately concealed?*	3. Were the research personnel and human subjects 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?	Tier
Bloomer et al. (2013)	+	+	++	+	++	-	-	-	3
Puente et al. (2017)	+	+	++	-	++	+	++	+	1
Ratamess et al. (2018)	+	+	++	-	+	-	-	-	3
Ruiz-Moreno et al. (2020)	+	+	++	-	++	+	++	+	1
Salinero et al. (2017)	+	+	++	++	-	+	++	+	2
Zbinden-Foncea et al. (2018)	+	+	++	-	-	+	-	-	3

2.1.4 Evidence synthesis and rating of confidence in the body of evidence

RCTs classified as tier 1 or 2 were included in the rating of confidence in the body of evidence, whereas RCTs classified as tier 3 were excluded due to a high concern for bias on key element(s). Study characteristics from the RCTs published in the period 2019-2020 were extracted according to the protocol and are included in the Appendix (Section 9.4). Study characteristics of the RCTs published in the period 2015-2018 are available in VKM (2019).

Meta-analyses were performed for the outcomes heart rate and systolic and diastolic blood pressure. Confidence in the body of evidence were rated for the outcomes blood pressure (systolic and diastolic), heart rate, haematologic parameters, intraocular pressure and ocular perfusion pressure, "other side effects", and sleep disturbance.

2.1.4.1 Meta-analysis

A summary of main characteristics for each included study was compiled and reviewed by three reviewers to determine comparability between studies and to determine whether biological heterogeneity was a concern. The main characteristics evaluated across all eligible studies included study design, details on how participants were classified into exposure groups, details on source of exposure data, caffeine doses given, health outcomes reported, type of data, statistics presented in paper, and ability to access raw data. It was considered not appropriate to conduct a meta-analysis when data on exposure or outcome were too different to be combined or other circumstances indicated that averaging study results would not produce meaningful results. The outcomes heart rate and systolic and diastolic blood pressure were considered being eligible for meta-analyses.

Studies included in the meta-analyses were RCTs with cross-over design where the participants received one oral dose per period, outcomes reported before and within 180 minutes after administration of caffeine or placebo, and measurements reported as mean and standard deviation/error. Not included in the meta-analyses were studies administrating several oral doses of caffeine or placebo during the study period, where outcomes were not reported on day one or time between intake and measurements and outcome were not stated, or where results were shown in figures without stating the exact mean and standard deviation/error. Table 2.1.4.1-1 shows the studies included or excluded from the meta-analyses for the outcomes heart rate and blood pressure. Overview of the study parameters used in the meta-analysis is shown in Table 12.1-1 (see Appendix, section 12.1).

Table 2.1.4.1-1. An overview over studies included or excluded from the meta-analyses on the outcomes heart rate and blood pressure.

Heart rate		Systolic blood pressure		Diastolic blood pressure	
Included	**Excluded**	**Included**	**Excluded**	**Included**	**Excluded**
Dodd et al. 2015	Bloomer et al. 2013	Dodd et al. 2015	Bloomer et al. 2013	Dodd et al. 2015	Bloomer et al. 2013
Ratamess et al. 2018	Flueck et al. 2015	Ratamess et al. 2018	Flueck et al. 2015	Ratamess et al. 2018	Flueck et al. 2015

Heart rate		Systolic blood pressure		Diastolic blood pressure	
Ruiz-Moreno et al. 2020	Puente et al. 2017	Vera et al. 2019	Puente et al. 2017	Vera et al. 2019	Ruiz-Moreno et al. 2020
	Zbinden-Foncea et al. 2018		Zbinden-Foncea et al. 2018	Zbinden-Foncea et al. 2018	

A random effect model (Hartung-Knap; weighting by the inverse variance) estimating absolute mean difference using the raw effect size data were conducted (standard error values were transformed to standard deviations). Initial analyses were performed including all groups of habitual consumers (none-, low- and high-consumers), and studies not reporting on habitual caffeine consumption. Further *post-hoc* analysis for consumer groups was performed (high-consumers vs non-/low-consumers/not reported). Results from the *post-hoc* analyses are presented in the appendix (section 12.2). I^2 statistics was calculated to quantify the amount of variation across studies that is due to heterogeneity and provides a measure of the degree of inconsistency in the studies' results. The I^2 statistics was evaluated by considering the magnitude/direction of the effect and the extent of evidence of heterogeneity (similar point estimates with overlapping 95% CI; $I^2 \leq 50\%$, $P \geq 0.1$) based on criteria in OHAT (2019). The meta-analyses were performed in R version 4.0.2 using the package *meta*.

Heart rate

The point estimates for heart rate varied between -4.8 and 6.6 beats per minute (bpm), and there was an overlap between the 95% CI of point estimates (Figure 2.1.4.1-1). The I^2 was 0% (95% CI 0% to 43%) p=0.66, which can be considered as low degree of heterogeneity. The mean estimate was -0.9 bpm with a 95% CI -2.6 to 0.9, and a 95% prediction interval -5.7 to 4.0, indicating no effects of caffeine intake on heart rate. Due to the low mean estimate and the fact that both the 95% CI of the mean estimate and the 95% prediction interval include the value zero, VKM considers that the heart rate is not significantly affected up to 180 minutes after oral intake of caffeine.

Doses used in the different studies varied from 1.15 to 4.23 mg/kg bw per day, and the time point for outcome measurement ranged from 30 to 180 minutes after oral intake of caffeine. There were no apparent dose- or time point-related effects across studies.

Post-hoc analyses based on habitual caffeine consumption indicated that heart rate measured until 180 minutes after oral intake of caffeine was not affected in persons with low or no habitual caffeine consumption in that both the 95% CI of the mean estimate and 95% prediction interval include zero. In high habitual caffeine consumers, there was a tendency that caffeine intake may reduce heart rate (Table 2.1.4.1-2; Figure 12.2-1 (Appendix, Section 12.2)). However, since the mean values were within the normal physiological range for heart rate and the decrease of 3.1 bpm was small, the observed effect is likely of no biological relevance.

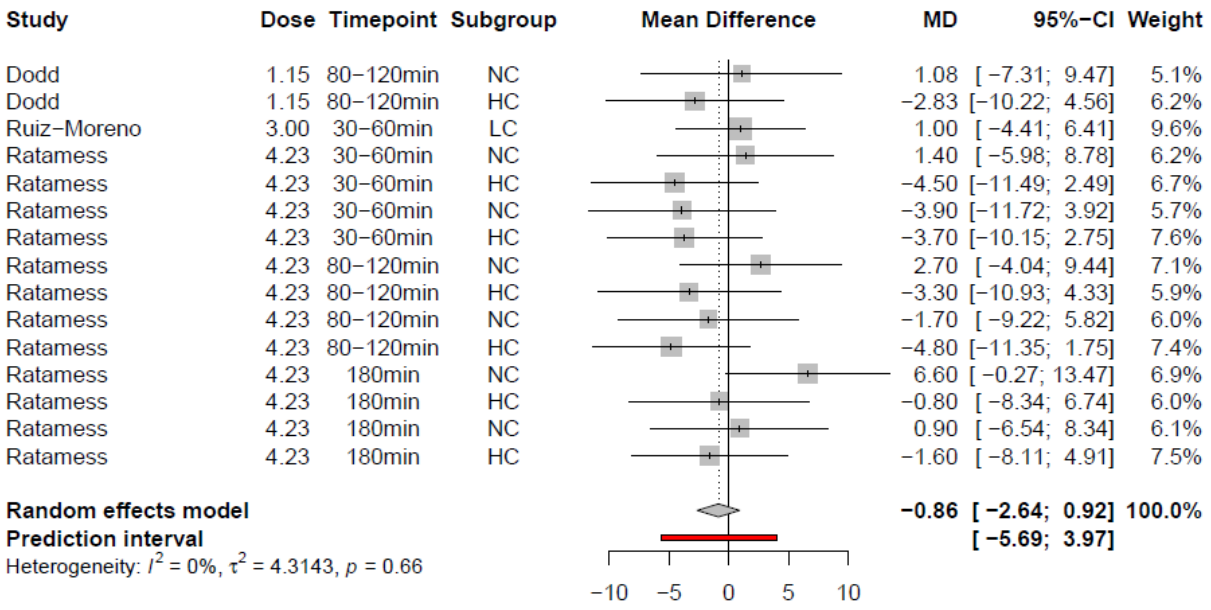


Figure 2.1.4.1-1. Meta-analysis on heart rate after oral administration of caffeine or placebo. CI: confidence interval; Dose: mg/kg bw per day; MD: mean difference; HC: high habitual caffeine consumption; LC: low habitual caffeine consumption; NC: no habitual caffeine consumption; Time point: time between exposure and measurement of outcome.

Table 2.1.4.1-2. Results from *post-hoc* meta-analysis based on habitual caffeine consumption for heart rate.

Habitual consumption	Point estimates (range)	Mean estimate	95% CI	95% prediction interval	I^2 (%)	95% CI	P
HC	-4.8; -0.8	-3.1	-4.5; -1.8	-5.1; -1.2	0	0; 0	0.99
NC/LC/NR	-3.9; 6.6	1.2	-1.3; 3.7	-4.1; 6.4	0	0; 53	0.69

HC: high habitual caffeine consumption; LC: low habitual caffeine consumption; NC: no habitual caffeine consumption; NR: not reported.

Blood pressure

The point estimates for systolic blood pressure varied between -4.6 and 9.8 mm Hg with overlapping 95% CI of the point estimates (Figure 2.1.4.1-2A). The mean estimate was 2.1 mm Hg with a 95% CI 0.4 to 3.8, and a 95% prediction interval -3.4 to 7.5, indicating that caffeine intake may increase the systolic blood pressure. The I^2 was 0% (95% CI 0% to 46%) p=0.47, which can be considered as a low degree of heterogeneity. With regard to diastolic blood pressure, the point estimates varied between -1.8 to 9.8 mm Hg with overlapping 95% CI (Figure 2.1.4.1-2B). The mean estimate was 2.4 mm Hg with a 95% CI 1.1 to 3.6, and a 95% prediction interval -2.1 to 6.8, indicating that caffeine intake may

increase the diastolic blood pressure. The I^2 was 0% (95% CI 0% to 44%) p=0.53, which can be considered as a low degree of heterogeneity.

Even though the 95% CI of the mean estimates of systolic and diastolic blood pressure indicate a statistically significant increase after oral intake of caffeine, the corresponding 95% prediction intervals indicate that values from similar studies may occur on both sides of the null. Further, the increase in systolic blood pressure of 2.1 mm Hg and in diastolic blood pressure or 2.4 mm Hg were small. Since the mean values were within the normal physiological range for systolic and diastolic blood pressure and the increases were small, the observed effect of caffeine on blood pressure is likely of no biological relevance.

Doses used in the different studies on blood pressure varied from 1.15 to 4.23 mg/kg bw per day for systolic blood pressure and 1.15 to 5.00 mg/kg bw per day for diastolic blood pressure, and the time point for outcome measurement ranged from 30 to 180 minutes after intake. There was no apparent dose- or time point-related effects on systolic blood pressure or diastolic blood pressure across studies.

Post-hoc analyses based on habitual caffeine consumption indicate that systolic blood pressure and diastolic blood pressure measured until 180 minutes after oral intake of caffeine were not affected in high consumers, thus both the 95% CI of the mean estimate and 95% prediction interval include zero (Table 2.1.4.1-3, Figure 12.2-2, Figure 12.2-3 (Appendix, Section 12.2)). With regard to the consumers with low or no habitual caffeine intakes, the 95% CI of the mean estimates of systolic and diastolic blood pressure indicate a statistically significant increase in blood pressure after oral intake of caffeine. However, the corresponding 95% prediction intervals indicate that values from similar studies are possible on either side of the null. Furthermore, the estimated increase in systolic and diastolic blood pressure was low (between 0.6 and 3.8 mmHg) for both consumer groups and thus, was not considered as biologically relevant. VKM considers that the increase in systolic blood pressure of 0.6 mm Hg and in diastolic blood pressure of 3.8 mm Hg were small and likely of no biological relevance.

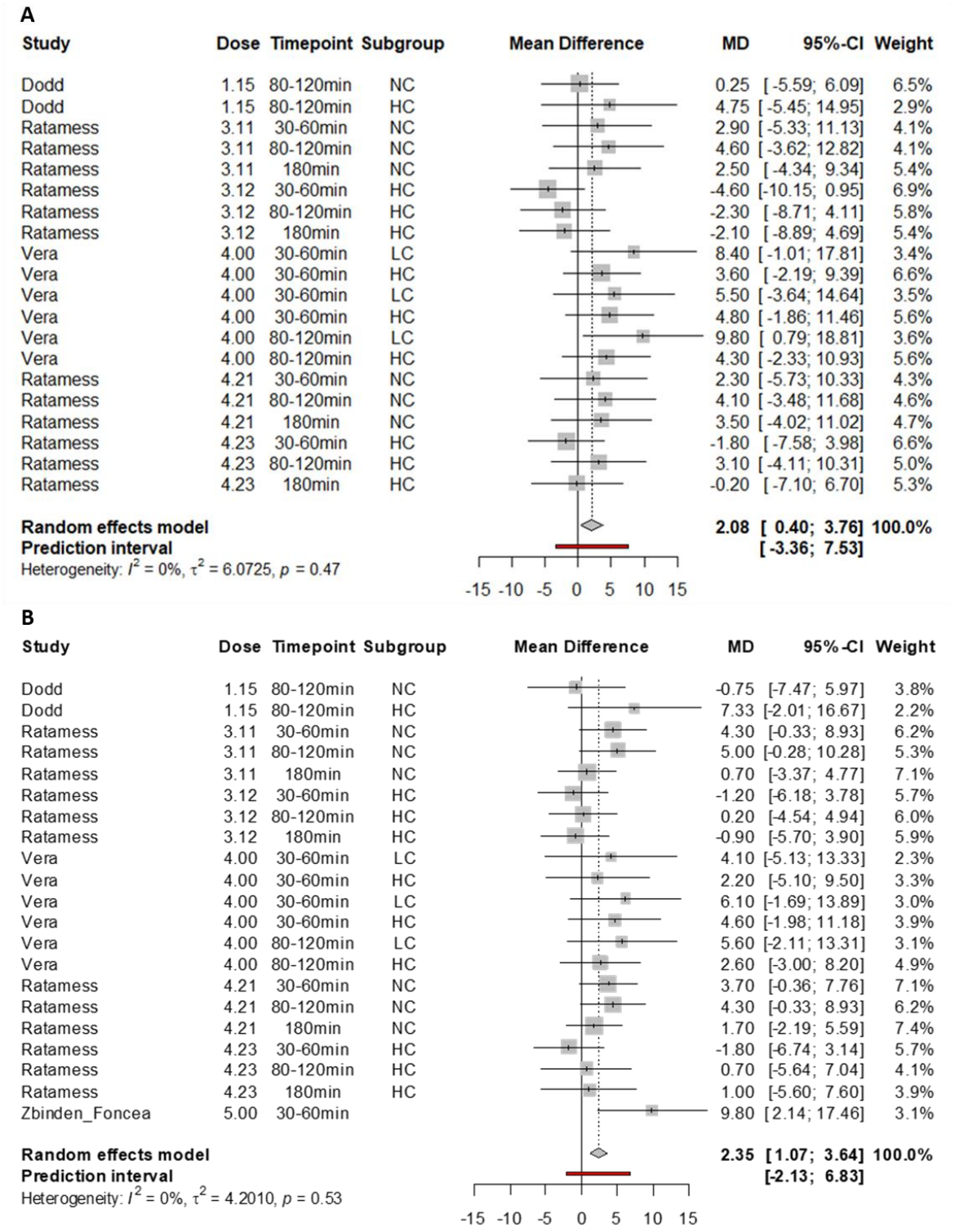


Figure 2.1.4.1-2. Meta-analysis on systolic (A) and diastolic (B) blood pressure after oral administration of caffeine or placebo. CI: confidence interval; Dose: mg/kg bw per day; MD: mean difference; HC: high habitual caffeine consumption; LC: low habitual caffeine consumption; NC: no

habitual caffeine consumption; blank: no habitual caffeine consumption reported; Time point: time between exposure and measurement of outcome.

Table 2.1.4.1-3. Results from *post-hoc* meta-analysis based on habitual caffeine consumption for systolic blood pressure and diastolic blood pressure.

Habitual consumption	Point estimates (range)	Mean estimate	95% CI[1]	95% prediction interval	I^2 (%)	95% CI[1]	P
Systolic blood pressure							
HC[2]	-4.6; 4.8	0.6	-1.9; 3.2	-5.7; 6.9	13	0; 54	0.33
NC[3]/LC[4]/NR[5]	0.25; 9.8	3.8	1.8; 5.6	-0.4; 8.1	0	0; 25	0.87
Diastolic blood pressure							
HC	-1.8; 7.3	0.8	-0.9; 2.6	-3.5; 5.1	0	0; 43	0.75
NC/LC/NR	-0.8; 9.8	3.6	1.9; 5.3	-0.9; 8.0	0	0; 51	0.63

[1]CI: confidence interval; [2]HC: high habitual caffeine consumption; [3]NC: no habitual caffeine consumption; [4]LC: low habitual caffeine consumption; [5]NR: not reported.

2.1.4.2 Confidence in the body of evidence

The confidence in the body of evidence was assessed for each outcome according to OHAT (2019) as shown in Table 2.1.4.2-1. Two or three reviewers independently evaluated the confidence in evidence for each outcome, and the reviewers calibrated themselves once to ensure similar evaluation. A more detailed evaluation of the confidence in evidence is given in Table 9.5-1 (Appendix, Section 9.5).

Table 2.1.4.2-1. The confidence in evidence profile for caffeine and the outcomes blood pressure (systolic and diastolic), heart rate, haematologic parameters, intraocular pressure and ocular perfusion pressure, "other side effects", and sleep disturbance.

RCTs (n) and initial rating	Elements triggering downgrading				Elements triggering upgrading			Overall rating
	Risk of bias	Unexplained inconsistency	Indirectness	Imprecision	Large effect	Dose–response relationship	Consistency	
Blood pressure, systolic								
7 RCTs Initial rating: ++++	Serious	Not serious	Not serious	Not serious	Not large	No	Yes	++++ High
Blood pressure, diastolic								
7 RCTs Initial rating: ++++	Serious	Not serious	Not serious	Not serious	Not large	No	Yes	++++ High
Heart rate								
6 RCTs Initial rating: ++++	Serious	Not serious	Not serious	Not serious	Not large	No	Yes	++++ High
Haematologic parameters								
2 RCTs Initial rating: ++++	Not serious	Not serious	Not serious	Serious	Not large	No	No	+++ Moderate
Intraocular pressure and ocular perfusion pressure								
1 RCT Initial rating: ++++	Serious	Not serious	Not serious	Serious	Not large	No	-	++ Low
"Other side effects"								
3 RCTs Initial rating: ++++	Not serious	Not serious	Not serious	Not serious	Not large	No	Yes	++++ High
Sleep disturbance								

3 RCTs Initial rating: ++++	Not serious	Not serious	Not serious	Not serious	Not large	No	No	++++ High

-: not possible to evaluate.

2.2 Summary: hazard identification and characterisation

Caffeine doses «not to give rise to safety concern» have been established by EFSA (2015). These were established for single caffeine exposures and habitual caffeine exposure. Adverse effects of single dose caffeine exposure on the central nervous system were assessed in children (including sleep, anxiety and behavioural changes) and adults (including sleep and anxiety). Adverse effects of habitual caffeine exposure were evaluated in children (behavioural changes), in pregnant women (adverse birth weight-related outcomes in the offspring), and adults (cardiovascular outcomes) (EFSA, 2015). EFSA stated that these doses do not apply to subgroups of the population selected on the basis of a disease condition. The same holds true for sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions which may require individual advice.

In a previous VKM risk assessment (VKM et al., 2019), it was concluded from the RCTs published in the period 2013-2018 that caffeine effects on blood pressure and heart rate were small and likely of no biological relevance, and that no effects of caffeine on psychobehavioural effects, such as insomnia, were observed in the included studies. Therefore, there were no reasons for changing the doses established by EFSA, and the caffeine doses «not to give rise to safety concern» were used as reference point for adverse effects of caffeine in the risk characterisation. In the present risk assessment, additional RCTs on negative effects related to caffeine published in the period 2019-2020 were identified. RCTs with high RoB (Tier 3) were excluded. Ten RCTs published in the period 2013-2020 were included in the evidence synthesis. The outcomes and the level of confidence in evidence are summarised below:

Cardiovascular effects

- Systolic and diastolic blood pressure changes were small and considered to have no physiological relevance. No statistically significant effects on heart rate; haematologic parameters (including white blood cell count, red blood cell count, haemoglobin, haematocrit, platelets, lymphocytes, monocytes, eosinophils, and basophils) were within the normal range.
- Confidence in evidence: *high (systolic blood pressure, diastolic blood pressure, heart rate)*
- Confidence in evidence: *moderate (haematologic parameters)*

Intraocular and ocular perfusion pressure

- Values were within the normal range.
- Confidence in evidence: *low*

"Other side effects" (including nervousness, muscular pain, headache, GI effects, muscle pain, irritability and diuresis)

- No significant effects (two studies; 3 mg caffeine/kg bw per day). Effects on the GI tract at two of the nine time points assessed in a period of 20 days (one study; 3 mg caffeine/kg bw per day).
- Confidence in evidence: *high*

Sleep disturbance

- Increase in self-reported insomnia (one study; 3 mg caffeine/kg bw per day administered in the evening). No effects (one study; 3 mg caffeine/kg bw per day administered in the morning). Effects reported at one of the nine time points assessed in a period of 20 days (1 study; 3 mg caffeine/kg bw per day administered in the morning)
- Confidence in evidence: *high*

In line with the above findings, VKM concludes that there is no need for revision of the doses «not to give rise to safety concern» for general adverse health effects established by EFSA (2015).

Sleep disturbance was reported in some of the RCTs. As the doses administered in the RCTs (3 mg/kg bw per day) were higher than the dose considered to increase sleep latency and reduce sleep duration in some individuals (1.4 mg/kg bw) (EFSA, 2015), VKM concludes that there is no need for revision of this dose.

Reference points for adverse effects of caffeine to be used in the risk characterisation

VKM interpreted single caffeine exposure as one intake, over a limited period during a day, e.g. one cup of coffee or tea, one meal with several caffeine sources or one portion of caffeine supplement. Habitual caffeine exposure was interpreted as the long-term regular exposure, expressed as the representative exposure throughout a day (daily exposure). VKM interpreted the doses "not to give rise to safety concerns for specific groups of the general population" established by EFSA (2015), for healthy groups of the general population as follows:

Children and adolescents

- Single caffeine exposure of about 1.4 mg/kg bw and 3 mg/kg bw, above which sleep disturbances and general adverse health effects, respectively, may occur.
- Habitual caffeine exposure of about 3.0 mg/kg bw per day, above which general adverse health effects may occur.

It should be noted that the reference points for children and adolescents were predominantly based on data from studies on adults.

Adults, not including pregnant and lactating women

- Single caffeine exposure of about 1.4 mg/kg bw and 3 mg/kg bw above which sleep disturbances and general adverse health effects, respectively, may occur.

- Habitual caffeine exposure of about 5.7 mg/kg bw per day above which general adverse health effects may occur.

Pregnant women

- Habitual caffeine exposure of about 3 mg/kg bw per day, above which there may be concern for the foetus.

No reference point was determined for single exposures for pregnant women due to lack of data, and data to characterise the risk of habitual caffeine consumption were scarce. Unborn children were considered by EFSA (2015) to be the most vulnerable group for adverse effects of caffeine among the general population.

Lactating women

- Single and habitual caffeine exposure of about 3 mg/kg bw per day, above which there may be concern for the breastfed infant.

Sleep disturbances, habitual (daily) exposure

EFSA has not established a dose "not to give rise to safety concerns for specific groups of the general population" for sleep disturbances related to habitual caffeine exposure. To enable risk characterisation for sleep disturbances for habitual caffeine exposure, VKM has used the dose established by EFSA for sleep disturbances from single caffeine exposures.

3 Exposure assessment

We estimated the caffeine exposure from diet and PCPs. This estimation included both the caffeine that reached the physical barriers of the body through the diet followed by absorption through the GI tract and through dermal application of PCPs followed by absorption through the skin.

To enable estimations of total caffeine exposure, data on occurrence of caffeine in food and PCPs and intakes of food and use of PCPs with caffeine had to be compiled. Caffeine concentrations in foods were compiled through a literature search, and all relevant food items assigned a caffeine value, which were used in the dietary exposure estimations. Caffeine concentrations in PCP were compiled through a literature search, and concomitantly a call for data from businesses and other interested public and private parties.

EuroMix which includes assessment of both diet and PCP was used to estimate the sum of exposure from both diet and PCPs (Husoy et al., 2019). Intake from national dietary surveys, including children, adolescents and adults were used to estimate dietary caffeine exposure (Hansen et al., 2016; Totland et al., 2012). In addition, reported intake of caffeine containing foods from The Tromsø Study: Tromsø 7, a large health cohort study with participants from 40 years and upward, was used to estimate dietary caffeine exposure (Lundblad et al. 2019).

Caffeine reaching the physical barriers of the body was defined as external exposure, whereas absorbed caffeine was defined as internal exposure. For adults both external caffeine exposure and combined internal caffeine exposure from food and in combination with PCPs were estimated. For children and adolescents only exposures from food were estimated.

In addition, we included scenarios for caffeine exposure from pharmaceuticals and caffeine supplements.

Table 3-1 shows the questions addressed in this section.

Table 3-1. Exposure assessment questions.

	No	Questions
Occurrence	1	Which foods and PCPs contain caffeine?
	2	What are the concentrations of caffeine in food?
	3	What are the concentrations of caffeine in PCPs?
Estimated intakes of food and use of PCPs	4	What are the estimated intakes of food containing caffeine?

	No	Questions
	5	What is the estimated use of caffeine-containing PCPs (amount used and frequency of use)?
Exposure	6	What is the external/internal exposure to caffeine from the diet?
	7	What is the dermal external exposure to caffeine from PCPs?
	8	What is the oral external exposure to caffeine from PCPs?
	9	What are the absorption factors for oral and dermal exposure of caffeine from PCPs, respectively?
	10	What is the total internal caffeine exposure from food and PCPs?
	11	What are the main dietary sources of caffeine exposure?
	12	What are the exposure scenarios including caffeine containing pharmaceuticals and caffeine supplements?

As there appears to be very low hepatic first-pass metabolism once caffeine is absorbed from the GI tract, i.e. the liver does not appear to remove caffeine as it passes from the gut to the general circulation (Arnaud, 1993), VKM considered that adjustment for differences in caffeine metabolism after oral and dermal exposures was not required. Therefore, the numerical amounts of caffeine absorbed from the GI tract and the skin were summed up to estimate the total internal caffeine exposure from diet in combination with PCPs.

3.1 Occurrence

We aimed to identify caffeine-containing food and PCPs as well as their caffeine concentrations to perform realistic exposure estimates.

3.1.1 Scientific literature

3.1.1.1 Literature search

To identify relevant data for answering questions 1 to 3 (Table 3-1), literature searches were performed in the electronic databases from Ovid MEDLINE(R), Embase, PsycINFO, Cochrane Database of Systematic Reviews, Web of Science and Epistemonikos. A specialised research librarian was involved in the planning of the search and conducted the search. Separate searches were performed for food and PCPs. For search terms and search strategy, see Appendix, Section 10.1 (food), and Appendix, Section 11.1 (PCPs). The literature search was not limited to publication year.

The identified records were imported into EndNote (Thomson Reuters, version X9), duplicates were removed, and the records were imported into the Rayyan screening program (Ouzzani et al., 2016) for the study selection.

3.1.1.2 Study selection

The study selection was based on the predefined eligibility criteria (Tables 3.1.1.2-1).

Table 3.1.1.2-1. Occurrence: eligibility criteria.

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

Two independent reviewers performed the publication selection. Titles and abstracts were screened prior to full-text assessment of articles. For publications on caffeine in food, 1838 records were screened followed by full-text assessment of 132 publications. The eligibility criteria were fulfilled in 71 publications. For publications on caffeine in PCPs, 207 records were screened followed by full-text assessment of three publications. One publication fulfilled the eligibility criteria (Figure 3.1.1.3-1).

3.1.1.3 Methodological quality

The quality of the method used in the analysis of the caffeine concentrations was evaluated for all eligible studies, based on expert assessment of technical and methodological details in combination with presentation of data and results, method feasibility and reproducibility. The evaluation was carried out by two experts and included scoring of the sample extraction method, the instrumental analysis, and the validation of the method and the data presentation on a scale from 1 to 5, where 1 is the lowest score and 5 is the highest (Table 3.1.1.3-1). To obtain the mean total score, the individual scores by both experts were weighted as follows: 1/5 from sample extraction, 1/5 from instrumental analysis, and 3/5 from validation and data presentation. Only studies with a total score of ≥ 3.5 were included for the exposure assessment.

Table 3.1.1.3-1. Quality evaluation of the method used for caffeine analyses.

Parameters evaluated	Score
Extraction method – appropriateness of sample preparation and processing steps, extraction solvent (polarity) and solvent system in relation to sample matrix.	1 - 5
Instrumental analysis – appropriateness and sensitivity of analytical instrument(s) used for quantitation (e.g. TLC, FIA, and spectrophotometry vs. liquid chromatography LC, gas chromatography GC, capillary electrophoresis CE, inductively-coupled plasma analysis ICP, etc.).	
Method validation and quality assurance – detail level of internal/external calibration, LOD/LOQ and recovery data, use of sample size, and statistical treatment of data.	
Total score	1/5 x sample extraction + 1/5 x instrumental analysis + 3/5 x validation and data presentation

A total of 53 studies on caffeine in food scored 3.5 or higher (Appendix, Section 10.3, Table 10.3-1), whereas 20 studies were excluded due to a total score below 3.5 (Appendix, Section 10.3, Table 10.3-2). One study on caffeine in PCPs scored 3.5 or higher (Appendix, Section 11.3, Table 11.3-1).

An overview of the study selection is given in Figure 3.1.1.3-1.

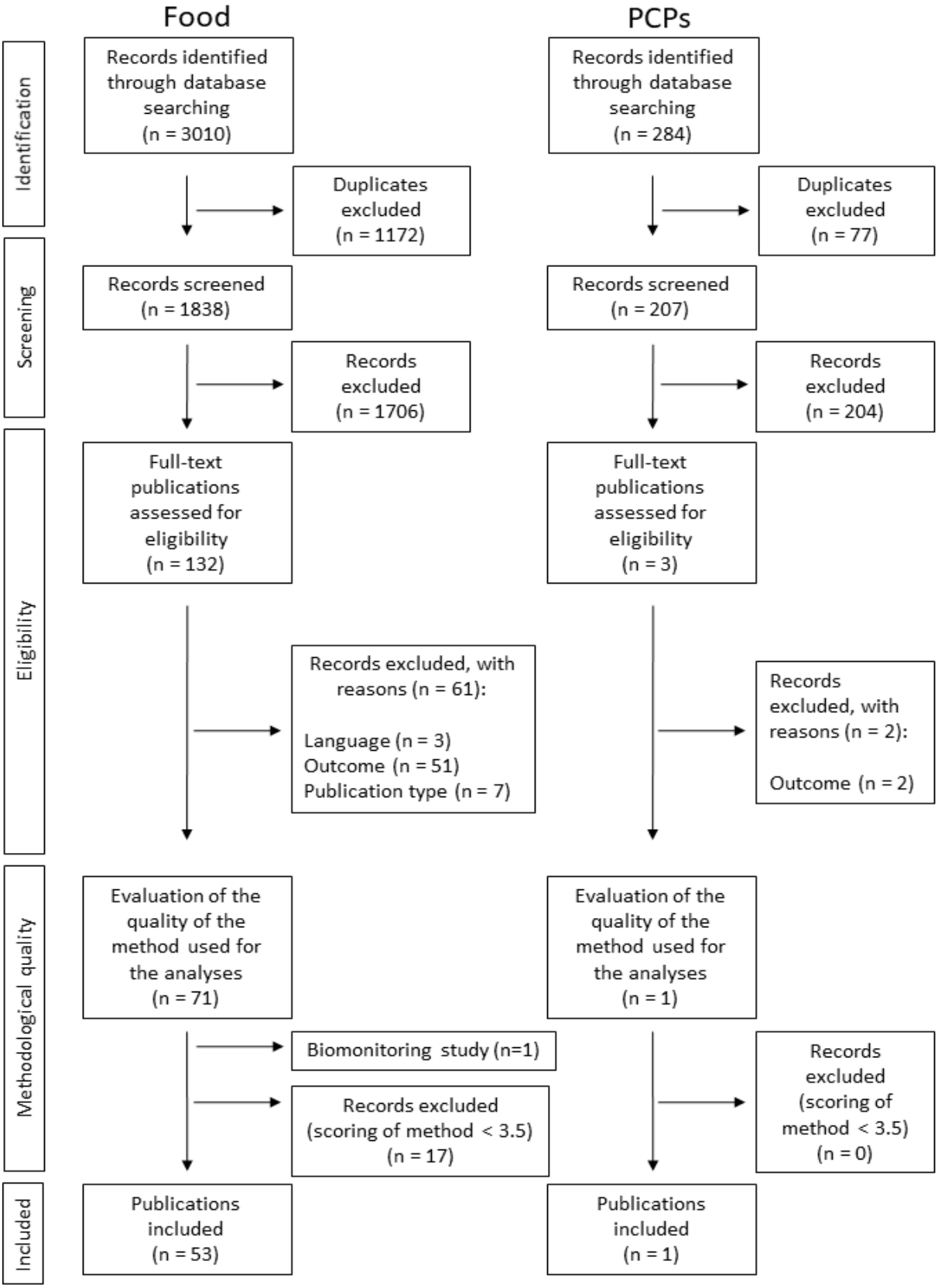


Figure 3.1.1.3-1. Flow diagram illustrating the process of selection of eligible publications of acceptable quality.

3.1.2 Food composition tables

A request for data on caffeine concentrations in foods in the EuroFIR database Food Explorer, was sent to EuroFIR autumn 2020. The EuroFIR AISBL, the European Food Information Resource (https://www.eurofir.org/), compiles and publishes national food composition tables from most of the European countries. In addition, the EuroFIR Food Explorer database includes food composition tables from Australia, New Zealand, Japan and USA. Upon request, we received data files with caffeine concentrations in all food entries, from all national food composition databases in the FoodExplorer that contain this information. The data files included food composition caffeine data from Australia, New Zealand and Japan. None of the European national food composition tables included caffeine information.

A request for data was also sent to the United States Department of Agriculture (USDA) for any caffeine concentrations available. We received caffeine concentrations for 949 food items. Mean values were estimated for corresponding food groups used in this assessment.

We used EuroFIR and USDA as reference to the caffeine concentrations from the literature search.

3.1.3 Call for data

As only one article from the literature search for concentration data on caffeine in PCPs was considered eligible and of sufficient quality, VKM launched a "Call for data on caffeine concentrations in cosmetics and personal care products" (shown in Section 11.4) to offer the opportunity to submit concentrations of caffeine in cosmetics and PCPs. The call was launched June 6, 2020, and the deadline for the submission of caffeine concentration data was August 31, 2020. The call was published on vkm.no. Information was sent to Cosmetics Europe, the Norwegian Cosmetics Association, the EU Scientific Committee on Consumer Safety, and the EFSA Focal Points. All these stakeholders were encouraged to pass on the information to relevant recipients.

VKM received two requests to submit data after the deadline. Since this would not interfere with the progress of the project, these were accepted. VKM received data from Amway Europe, Cosmetics Europe, Emil Kiessling GmbH, French EFSA Focal Point (ANSES), Herba Drug s.r.o., L'Oréal, and Splat Global LLC.

3.1.4 Occurrence databases

Two databases were created; one for the food concentration data and one for the PCP concentration data.

3.1.4.1 Compilation of caffeine in food

The caffeine concentration values from all eligible studies with a score of 3.5 or higher (in the evaluation of the methodological quality) (Section 3.1.1.3) were compiled and grouped according to relevant food items and food groups (i.e. coffee, tea, chocolate) in the food composition and calculation system KBS (University of Oslo). Caffeine concentrations not included in the compilation were values in studies with an analysis quality evaluation score lower than 3.5, or with missing description of type of coffee or tea, caffeine unit, and/or preparation methods. Also, studies that had analysed dried tea leaves, or dry coffee grounds, and not infusions, or where the aim was to analyse different roasting levels of coffee beans were also excluded. Analyses of espresso and coffee made from coffee capsules were included since capsules are used in Norway, both at home, at work and in restaurants.

A total of 417 data points were eligible across all foods containing caffeine. All values were recalculated into mg caffeine per 100 g edible portion of the food prior to import into KBS. Descriptive statistics were calculated for each food group, and results were compared to the values from the EuroFIR, the USDA food composition databases, and the caffeine values used in the EFSA 2015 report. All food items that contained caffeine were compiled a representative caffeine value, either by using the caffeine value directly (like for filter coffee) or calculating the value using recipes with a caffeine containing ingredient, e.g. like chocolate muffins which contain cocoa powder. All estimations of dietary caffeine intake were performed using the same database version, the same food categories and food items in all dietary surveys. Thus, all dietary intake of caffeine, from all dietary sources registered in the dietary surveys were covered and calculated.

The caffeine concentrations in mg per 100 g edible (prepared, ready to eat or drink) portion of food is presented in Table 3.1.4.1.-1. We have included commercially available coffees and teas, from coffee bars and restaurants as well as homemade coffee and tea beverages. Decaffeinated coffee are not taken into account. The caffeine concentration are low, around 2 mg/100g coffee, and decaffeinated coffee are not reported used by many in the included dietary studies (14 persons in Norkost 3 and 1 person in EuroMix, Tromsø 7 did not include questions on decaffeinated coffee). None of the included dietary studies did separate between caffeinated and decaffeinated tea and cola drinks. In this assessment intakes of tea and cola drinks are treated as caffeinated.

For many of the foods the concentration of caffeine compiled from the literature showed skewed distributions, thus the median values were used.

Table 3.1.4.1-1. Caffeine concentrations in main dietary sources, mg/100 g edible portion.

Food category	**Literature search results**						**EuroFIR[c]**	**EFSA**	**USDA**
	n	Mean	95% CI	Median	Min	Max			
Espresso coffee	89	294	261; 387	268	44	700	339	134	212
Coffee, filter brewed	17	40	36; 44	40	29	62	46	45	40

Food category	Literature search results						EuroFIR[c]	EFSA	USDA
	n	Mean	95% CI	Median	Min	Max			
Instant coffee[a]	11	45	36; 55	44	20	70	32	45	26
Black tea	65	25	22; 28	22	8	59	23	22	20
Green tea	42	22	18; 26	19	8	77	14	15	12
Energy drinks	68	28	26; 30	30[b]	0	53	30	32	30
Cola drinks	45	10	9; 11	10	6	16	11	10.8	10
Dark chocolate varieties	28	102	80; 124	90	48	240	71	52.5	83
Light chocolate varieties	9	17	10; 25	19	1.7	30	18	16.8	20
Cocoa powder[d]	13	208	133; 283	210	49	479	175	na[e]	na[e]

The median values are used in the present assessment.[a] Instant coffee made from powder; [b] 32 mg/100 g is used in the assessment, see also main text; [c] average values of the caffeine values from the food composition tables from Australia, New Zealand and Japan, compiled from the EuroFIR food composition table, [d]Cocoa powder is not edible as it is, but is used in recipes, [e]EFSA and USDA did not provide a value for cocoa powder.

For the final caffeine values compiled for the KBS and subsequent estimations of caffeine intake from diet, the following were used: the median values for espresso, filter-brewed coffee, instant coffee, black tea and green tea, as presented in Table 3.1.4.1-1. Furthermore, espresso-based coffee beverages with milk, such as for instance cappuccino and café au lait, was calculated using recipes in the KBS food composition database system. Based on recommended caffeine level in energy drinks from the Norwegian Food Safety Authority, caffeine values for energy drinks were set at 32 mg/100 g. Caffeine values for dark and light varieties of chocolate and cocoa powder were set as the median values presented in Table 3.1.4.1-1. Caffeine values for composite foods with either chocolate or cocoa powder or other caffeine containing ingredients were calculated using recipes in KBS. All composite food items with ingredients containing caffeine were recalculated with regard to caffeine content. All foods containing caffeine were thus identified, and all relevant food exposures included in the estimations.

As far as VKM has established there are no published values for analysed concentrations of caffeine in Norwegian made coffee blends. The concentrations data compiled through the literature search included caffeine values from coffees made from both *Coffea Arabica* and *Coffea Robusta*, of which the latter has a higher content of caffeine (Crozier et al., 2011). The majority of Norwegian coffee blends are however mainly made from coffee beans of *Coffea Arabica*, thus our caffeine concentration in coffee may overestimate caffeine concentrations in the most common Norwegian coffee blends.

For further details on the caffeine concentrations in food, please see Appendix 10.4.

3.1.4.2 Compilation of caffeine used as an ingredient in PCPs

The PCP product categories were adopted from SCCS Notes of Guidance (SCCS, 2018). An overview of the products types and categories included in the database is given in Table 3.1.4.2-1. Only concentration data for products sold in Europe were included (n=896). How representative the data on caffeine concentrations in PCP are for each product type and category is unknown to VKM, due to lack of data. So also, is the reasons for why the products contain caffeine; if caffeine is added intentionally for specific properties or is naturally present from ingredients.

Table 3.1.4.2-1. Caffeine concentration (%) in PCPs as obtained by literature search and call for data (see section 3.1.3).

Product category	Product type	n	Mean	Min	Max	Median	IQR[1]
Bathing, showering	Hand wash	10	0.52	0.01	1.88	0.06	0.01; 1.22
	Shower gel	18	0.04	<0.001	0.20	0.01	0.01; 0.05
	Body scrub	17	0.53	<0.001	2.25	0.10	0.001; 1.00
Fragrances	Eau de toilette/ Perfume	13	0.001	<0.001	0.001	0.001	0.001; 0.001
Hair care	Conditioner	17	0.25	<0.001	1.00	0.05	0.00001; 0.61
	Hair styling	9	0.14	0.09	0.35	0.10	0.09; 0.15
	Shampoo	31	0.15	<0.001	1.50	0.06	0.0004; 0.10
Make-up	Eye make-up products	47	0.01	0.01	0.10	0.01	0.01; 0.01
	Foundation	34	0.46	0.10	0.50	0.50	0.50; 0.50
	Make-up remover	11	0.21	<0.001	1.00	0.20	0.0001; 0.20
	Concealer	50	0.41	0.01	0.50	0.50	0.35; 0.50
Men's cosmetics	After-shave/ Beard cream	10	0.18	0.01	1.00	0.10	0.02; 0.15
	Shaving cream	7	0.08	<0.001	0.15	0.09	0.0001; 0.15
Skin care	Body lotion	191	0.97	<0.001	5.00	0.50	0.20; 1.50
	Body mask/oil (Leave-on)	7	0.57	<0.001	1.80	0.12	0.0001; 1.65
	Body mask (Rinse-off)	13	0.19	0.01	0.50	0.08	0.04; 0.48
	Facial moisturiser / Anti-wrinkle cream	212	0.33	<0.001	1.50	0.20	0.10; 0.50
	Face mask (Leave-on)	13	0.18	0.02	0.90	0.10	0.08; 0.20
	Face mask (Rinse-off)	6	0.84	0.001	2.00	0.52	0.02; 2.00
	Eye cream	128	0.51	0.002	5.00	0.45	0.20; 0.50
	Eye mask	9	0.16	0.01	0.30	0.15	0.02; 0.30
Sun care cosmetics	Tanning accelerator	43	0.15	0.01	0.23	0.22	0.04; 0.22

[1]IQR: Interquartile range.

3.2 Dietary intake and PCP use

3.2.1 Dietary surveys and studies included

The following dietary assessments and surveys were used for the exposure estimations:

- Ungkost 3 (Hansen et al., 2016); a nationwide dietary assessment survey 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-day validated web-based food diary. The study was conducted among 4-year-olds (n= 399), 8-9-year-olds (n=636) and 12-13-year-olds (n=687).
- Norkost 3 (Totland et al., 2012); a nationwide dietary assessment survey carried out in 2010/2011 among adults (n=1787), aged 18 - 70 years. Norkost 3 is based on two 24-hour recalls by telephone interviews, performed at least one month apart.
- EuroMix (Husoy et al., 2019); a biomonitoring study carried out between September 2016 and September 2017. The participants (n= 144), 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 PCP diary and a questionnaire with personal information. The participants were instructed to weigh and record all intakes of food for 24 hours.
- The seventh survey of the Tromsø Study (Tromsø 7) in 2015 - 2016 (Lundblad et al. 2019); a large health cohort study first initiated in 1974. A total of 11,425 participants aged 40-99 years were eligible for the present analyses. The food frequency questionnaire (FFQ) used in Tromsø 7 had 20 questions concerning caffeine-containing foods.

3.2.2 Data included to estimate PCP use

3.2.2.1 Frequency of use

Data on frequency of use (shown in Table 3.2.2.5-1) was obtained from the Norwegian biomonitoring study EuroMix (Husoy et al., 2019). 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.

3.2.2.2 Amount used per application

PCP amounts used per application were not recorded in EuroMix and had to be obtained from the literature. Only publications reporting amounts used per application were considered, and those with separate data for men and women were prioritised. If multiple data on amounts used per product were available, we assumed that Norwegian PCP use might be closest to other European countries, and the data were prioritised as follows: 1) France (Ficheux et al., 2016), 2) Switzerland (Garcia-Hidalgo et al., 2017) 3) USA (Loretz et al., 2006). The French data were prioritised over the Swiss data because the weight of PCP products before and after use was reported, which we considered to be a more precise method than the picture method used by Garcia-Hidalgo et al. (2017). The amount of PCP applied per use is shown in Table 3.2.2.5-1.

3.2.2.3 Retention factor

The fraction of PCPs available for uptake after application (retention factor; RF) was obtained from SCCS (Scientific Committee on Consumer Safety) (2018) (Table 3.2.2.5-1.)

3.2.2.4 Dermal absorption

Based on *in vitro* dermal absorption studies using human skin (Table 1.2-1), a dermal absorption value of 36% was used for the exposure calculations.

3.2.2.5 Summary of the parameters used to estimate caffeine exposure for PCPs

An overview of the parameters used to estimate caffeine exposure from PCPs is given in Table 3.2.2.5-1.

Table 3.2.2.5-1. Caffeine concentrations and parameters used to calculate caffeine exposure from PCPs. The last two columns show the fraction of individual-days with usage of the product as well as mean number of applications (derived from EuroMix; Husoy et al., 2019). M: male; F: female

Product category	Product	Amounts used per application (mg)	Caffeine concentrations (%)	Retention factor	Users (%)	Mean number of applications per day for users
Bathing, showering	Hand wash	1987.5 (F) 2900 (M)	0.52	0.01	95.1	9.1
	Shower gel	8000 (F) 8500 (M)	0.04	0.01	75.7	0.9
Fragrances	Perfume	222 (F) 225.5 (M)	0.001	1.0	34.0	0.7
Hair care	Conditioner	7500 (F) 5200 (M)	0.25	0.01	41.7	0.7
	Hair styling	2865.3 (F) 1929.5 (M)	0.14	0.1	18.8	1.0

Product category	Product	Amounts used per application (mg)	Caffeine concentrations (%)	Retention factor	Users (%)	Mean number of applications per day for users
	Shampoo	8100 (F) 8500 (M)	0.15	0.01	61.1	0.7
Make-up	Eye make-up products	6.8 (F)	0.01	1.0	38.2	1.2
	Foundation	91 (F) 600 (M)	0.46	1.0	27.8	0.8
	Make-up remover	2011.4 (F) 300 (M)	0.21	0.01	6.2	0.7
Men's cosmetics	Shaving products	7533.3 (F) 2820 (M)	0.18	0.01	7.6	0.7
Skin care	Body lotion	7550 (F) 5100 (M)	0.97	1.0	36.8	0.8
	Facial moisturiser	681 (F) 1237.5 (M)	0.33	1.0	63.9	1.4
	Anti-wrinkle cream	512 (F) 725 (M)	0.33	1.0	9.7	1.0

3.3 Exposure estimation

External caffeine exposure and internal caffeine exposure from food in combination with PCPs were estimated. The concentration data and consumption data considered to be the most realistic were used. Habitual (daily) dietary exposure, expressed in mg per day, was calculated from the dietary surveys based on average consumption over two days for Norkost 3, and EuroMix, and over 4 days for Ungkost 3. Single exposure estimations were based on estimated intakes of caffeine during four time periods during a day (periodical dietary data available from Norkost 3) and based on single dose scenarios of different products high in caffeine content. In Tromsø 7 habitual dietary exposure, expressed in mg per day, was calculated from a food frequency questionnaire.
The internal exposure of caffeine from PCP was estimated to identify the contribution of caffeine from PCP.
The exposure estimates were thus based on:

- Caffeine concentrations (Section 3.1)
- Consumption
    - Intake of food (Section 3.2.1)
    - Use of PCPs (Section 3.2.2)
- Body weight

- Individual body weights were used to calculate caffeine exposure per kg body weight per person. If individual body weights were not reported, mean body weights per gender and study were imputed.

- Absorption from the GI tract/skin
  - Absorption factors were derived from literature (Section 2.1). The absorption factors used for food and PCPs were 100% and 36%, respectively.

In addition, scenarios on intake of caffeine supplements and over-the-counter pharmaceuticals were performed. For caffeine supplements the regulatory maximum dose was used (Lovdata, 2020), and for pharmaceuticals one example of a caffeine-containing pain killer was included.

3.3.1 Estimated internal exposure of caffeine from diet

3.3.1.1 Adults

The estimated exposure to caffeine for adults (18-70 years) in Norkost 3 is shown in Table 3.3.1.1-1 and Table 3.3.1.1-2.

Table 3.3.1.1-1. Estimated exposure to caffeine in Norkost 3, mg/day.

Exposure Norkost 3 (18-70 years)	**Median**	**IQR**[1]	**P95**[2]	**Mean**	**95% CI**[3]
All, n=1787	242	235	677	283	272; 293
Women, n=925	227	210	599	262	250; 275
Men, n=862	257	265	741	304	289; 320

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

Figure 3.3.1.1-1 shows the skewed distribution of dietary caffeine exposure in the Norkost 3 population.

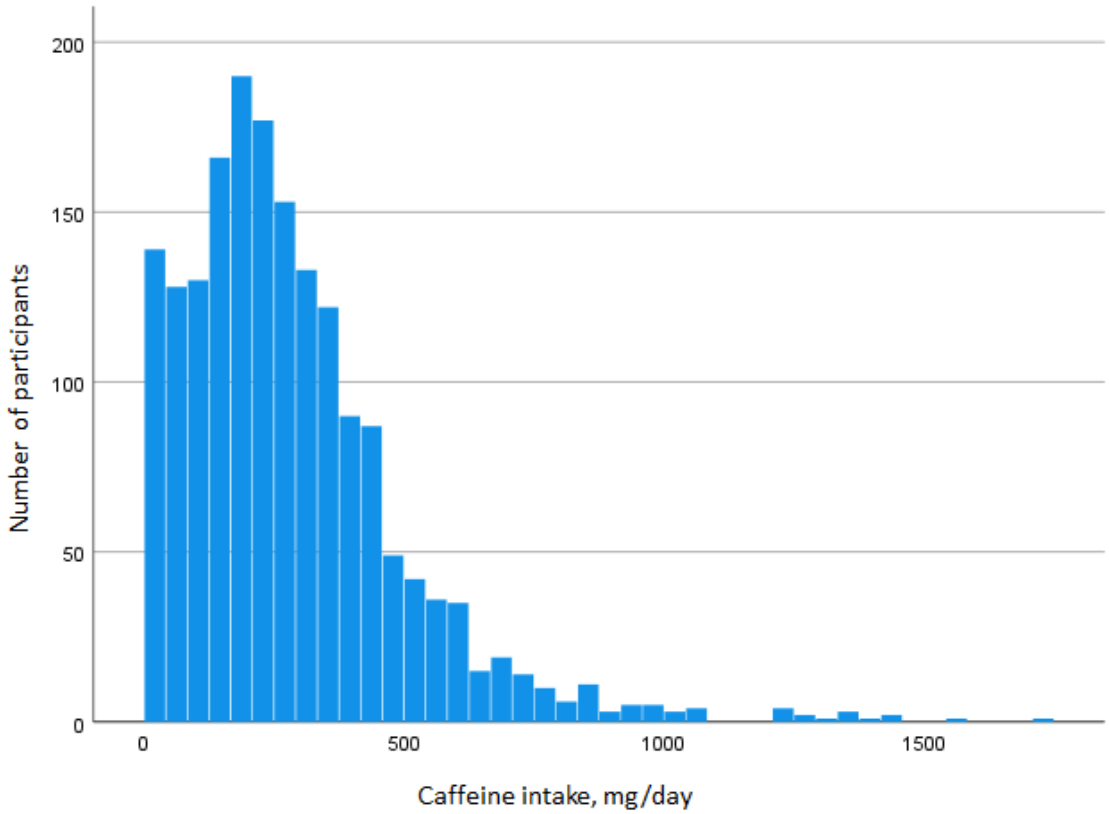


Figure 3.3.1.1-1. The distribution of dietary caffeine exposure in the Norkost 3 study population.

In Norkost 3, 98.3% of the participants reported intake of caffeine containing foods.

Table 3.3.1.1-2. Estimated exposure to caffeine in Norkost 3, mg/kg bw per day.

Exposure Norkost 3 (18-70 years)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
All, n=1787	3.2	3.2	8.8	3.7	3.6; 3.8
Women, n=925	3.3	3.2	8.8	3.8	3.7; 4.0
Men, n=862	3.0	3.0	8.9	3.6	3.4; 3.8

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

Caffeine exposure in Norkost 3 varied through the day. Average exposure to dietary caffeine divided into four time periods during a day is presented for Norkost 3 in Table 3.3.1.1-3.

Table 3.3.1.1-3. Caffeine exposure from diet during the day in Norkost 3 (n=1787).

Exposure Norkost 3 (18-70 years)	Time periods			
	Before 10 am	10 am - 3 pm	3 pm - 8 pm	After 8 pm

Caffeine consumers, n	1307	1524	1292	1022
% consumers	73	85	72	57
Median caffeine, mg/time period	61	84	39	4
Median caffeine, mg/kg bw per time period	0.8	1.1	0.5	0.05
95-percentile caffeine, mg/kg bw per time period	3.3	4.1	2.5	1.8
% of total caffeine consumption	30	39	20	11

Caffeine exposure for different age groups participating in Norkost 3 is shown in Table 3.3.1.1-4 and 3.3.1.1-5.

Table 3.3.1.1-4. Estimated exposure to caffeine for different age groups in Norkost 3, mg/day.

Exposure Norkost 3 (age/years, number of participants)	**Median**	**IQR[1]**	**P95[2]**	**Mean**	**95% CI[3]**
18 to 29, n=299	130	183	550	172	151; 192
30 to 49, n=722	250	257	694	298	281; 315
50 to 70, n=766	273	209	698	311	297; 326

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

Table 3.3.1.1-5. Estimated exposure to caffeine for different age groups in Norkost 3, mg/kg bw per day.

Exposure Norkost 3 (age/years, number of participants)	**Median**	**IQR[1]**	**P95[2]**	**Mean**	**95% CI[3]**
18 to 29, n=299	1.8	2.6	6.8	2.4	2.1; 2.7
30 to 49, n=722	3.3	3.5	9.2	3.9	3.7; 4.2
50 to 70, n=766	3.6	2.6	8.9	4.0	3.8; 4.2

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

The percent contribution of caffeine from dietary sources in Norkost 3 is shown in Table 3.3.1.1-6.

Table 3.3.1.1-6. Dietary sources of caffeine in Norkost 3 (n=1787), shares of total exposure.

Dietary sources in Norkost 3	**Shares of total caffeine exposure (%)**
Cakes and cookies	0.2

Dietary sources in Norkost 3	Shares of total caffeine exposure (%)
Dairy products	0.4
Chocolate, dessert and sweets	0.5
Coffee	82.2
Tea	12.0
Other beverages	4.7

The estimated exposure to caffeine in the biomonitoring study EuroMix is shown in Table 3.3.1.1-7 and Table 3.3.1.1-8.

Table 3.3.1.1-7. Estimated exposure to caffeine from diet in EuroMix, mg/day.

Exposure EuroMix (24-72 years)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
All, n=144	179	177	462	199	172; 225
Women, n=100	169	177	493	197	167; 228
Men, n=44	189	180	411	201	146; 256[4]

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval; [4]95 percentile is reported, however, the value is not statistically robust due to a small number participants in this age group.

Table 3.3.1.1-8. Estimated exposure to caffeine from diet in EuroMix, mg/kg bw per day.

Exposure EuroMix (24-72 years)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
All, n=144	2.6	2.6	6.9	2.9	2.5; 3.3
Women, n=100	2.7	2.6	7.2	3.0	2.5; 3.5
Men, n=44	2.4	2.0	4.9	2.4	1.8; 3.1[4]

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval; [4]95 percentile is reported, however, the value is not statistically robust due to a small number participants in this age group.

The percent contribution from the dietary sources to the caffeine exposure in the biomonitoring study EuroMix is shown in Table 3.3.1.1-9.

Table 3.3.1.1-9. Dietary sources for caffeine in EuroMix.

Dietary sources in EuroMix	Shares of total caffeine exposure (%)
Cakes and cookies	0.1
Dairy products	0.3
Chocolate, dessert and sweets	1.0
Coffee	77.2

Dietary sources in EuroMix	Shares of total caffeine exposure (%)
Tea	15.9
Other beverages	5.5

The estimated exposure to caffeine in Tromsø 7 is shown in Table 3.3.1.1-10 and Table 3.3.1.1-11.

Table 3.3.1.1-10. Estimated exposure to caffeine in Tromsø 7, mg/day.

Exposure Tromsø 7 (40-99 years)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
All, n=11,425	323	269	1120	414	406; 421
Women, n=6,104	320	236	960	386	376; 396
Men, n=5,321	329	263	1201	445	433; 458

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

Table 3.3.1.1-11. Estimated exposure to caffeine in Tromsø 7, mg/kg bw per day.

Exposure Tromsø 7 (40-99 years)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
All, n=11,425	4.1	3.5	13.8	5.3	5.2; 5.4
Women, n=6,104	4.3	3.6	13.7	5.5	5.3; 5.6
Men, n=5,321	3.9	3.4	13.9	5.2	5.1; 5.3

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

Table 3.3.1.1-12. Estimated exposure to caffeine for different age groups in Tromsø 7, mg/day.

Exposure Tromsø 7 (age/years, number of participants)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
40 to 49, n=3266	302	235	889	360	347; 374
50 to 70, n=6648	329	256	1168	443	432; 453
Above 70, n=1491	321	283	939	400	381; 419

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

The percent contribution from the dietary sources to the caffeine exposure in Tromsø 7, is shown in Table 3.3.1.1-13.

Table 3.3.1.1-13. Dietary sources for caffeine in Tromsø 7.

Dietary sources in Tromsø 7	Shares of total caffeine exposure (%)
Cakes and cookies	0.1
Dairy products	0.2
Chocolate, dessert and sweets	0.5
Coffee	92.4
Tea	6.8

3.3.1.2. Children and adolescents

The estimated exposure to caffeine for 4 years old, 8-9 years old, and 12-13 years old children in Ungkost 3 is shown in Table 3.3.1.2-1 and Table 3.3.1.2-2. In Ungkost 3, 82%, 87% and 87% of the 4 years old, 8-9 years old and 12-13 years old children and adolescents, respectively, had intake of food and beverages containing caffeine. In the Ungkost 3 study, exposure of caffeine from soda beverages could not be estimated. The web-based diary did not ask for specifications of whether the registered soda beverages were with or without caffeine.

Table 3.3.1.2-1. Estimated exposure to caffeine in the Ungkost 3 study, mg/day.

Exposure Ungkost 3 (age/years, number of participants)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
4, n=399	1.5	3.4	8.7	2.6	2.3; 2.9
8-9, n=636	3.3	7.0	18.2	5.6	5.1; 6.2
12-13, n=687	5.0	9.9	37.2	9.8	8.5; 11.1
Consumers only					
4, n=328	2.2	3.4	10.1	3.2	2.8; 3.5
8-9, n= 552	4.3	6.9	19.4	6.5	5.9; 7.1
12-13, n=596	6.1	9.9	39.5	11.3	9.9; 12.8

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

Table 3.3.1.2-2. Estimated exposure to caffeine in the Ungkost 3 study, mg/kg bw per day.

Exposure Ungkost 3 (age/years, number of participants)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
4, n=399	0.09	0.2	0.50	0.16	0.13; 0.17
8-9, n=636	0.10	0.2	0.59	0.18	0.16; 0.20
12-13, n=687	0.11	0.2	0.73	0.20	0.17; 0.23
Consumers only					
4, n=328	0.13	0.2	0.54	0.18	0.16; 0.21

Exposure Ungkost 3 (age/years, number of participants)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
8-9, n= 552	0.13	0.2	0.61	0.21	0.19; 0.22
12-13, n=596	0.12	0.2	0.82	0.23	0.20; 0.26

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

In Ungkost 3 age group 12-13 years, 2 participants had an exposure above 3.0 mg/kg bw per day (3.1 and 3.8 respectively) and 10 participants had exposure between 1.4 and 3.0 mg/kg bw per day. In age group 8-9 years, 2 participants had exposure above 1.4 mg/kg bw (1.7 and 1.9 respectively).

The percent contribution from the dietary sources to the total caffeine exposure for the children and adolescents in the Ungkost 3 study, is shown in Table 3.3.1.2-3.

Table 3.3.1.2-3. Dietary sources for caffeine in the Ungkost 3 study.

Shares of total caffeine exposure (%) Dietary source	Age groups		
	4 years	8-9 years	12-13 years
Cakes and cookies	24	24	11
Dairy products	40	33	20
Chocolate, dessert, sweets	24	20	21
Coffee	0	0	9
Tea	12	20	23
Energy drinks	0	3	16

3.3.2 Estimated internal exposure to caffeine from PCPs

Caffeine exposure from PCPs were estimated using the EuroMix study (Tables 3.3.2-1 and 3.3.2-2). Four participants in EuroMix had only one day registration of PCP use and their exposures are thus based on one registration.

For estimations of caffeine from PCP VKM applied a conservative approach, assuming that all PCPs reported contained caffeine and applied the mean concentrations for each PCP group.

Table 3.3.2-1. Estimated internal caffeine exposure from PCPs in EuroMix, mg/day.

Exposure EuroMix (24-72 years)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
All, n=144	1.9	14.5	29.4	9.2	7.3; 11.1
Women, n=100	3.3	26.1	29.9	11.8	9.3;14.2
Men, n=44	0.6	1.2	19.1	3.3	1.3; 5.3[4]

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval; [4]95 percentile is reported, however, the value is not statistically robust due to a small number participants in this age group.

Table 3.3.2-2. Estimated internal caffeine exposure from PCPs in EuroMix, mg/kg bw per day.

Exposure EuroMix (24-72 years)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
All, n=144	0.03	0.23	0.49	0.14	0.11; 0.17
Women, n=100	0.05	0.35	0.56	0.18	0.14; 0.22
Men, n=44	0.01	0.02	0.24	0.04	0.02; 0.06[4]

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval; [4]95 percentile is reported, however, the value is not statistically robust due to a small number participants in this age group.

The percent contribution of caffeine from PCP products in EuroMix is shown in Table 3.3.2-3.

Table 3.3.2-3. PCP sources for caffeine EuroMix.

Product	Shares of total caffeine exposure (%)
Hand wash	3.0
Shower gel	0.07
Perfume	0.002
Conditioner	0.2
Hair styling	0.2
Shampoo	0.18
Eye make-up products	-
Foundation	0.4
Make-up remover	0.8
Shaving products	0.01
Body lotion	84.0
Facial moisturiser	8.3
Anti-wrinkle cream	0.76

3.3.3 Total estimated internal exposure from diet in combination with PCPs

The total caffeine exposure from diet and PCPs were estimated using the EuroMix study (Tables 3.3.3-1 and 3.3.3-2). Four participants in EuroMix had only one day registration of PCP use and their exposures are thus based on one registration.

Table 3.3.3-1. Estimated total internal exposure to caffeine from diet in combination with PCPs, in EuroMix, mg/day.

Exposure EuroMix (24-72 years, n=144)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
Diet and PCPs	182	168	492	208	181; 234
Diet	179	177	462	199	172; 225
PCP	1.9	14.5	29.4	9.2	7.3; 11.1

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

On average, in EuroMix, the PCPs contributed 4.4% of the total internal caffeine exposure.

Table 3.3.3-2. Estimated total internal exposure of caffeine from diet in combination with PCPs, in EuroMix, mg/kg bw per day.

Exposure EuroMix (24-72 years, n=144)	Median	IQR[1]	P95[2]	Mean	95% CI[3]
Diet in combination with PCPs	2.6	2.7	7.0	3.0	2.6; 3.4
Diet	2.6	2.6	6.9	2.9	2.5; 3.3
PCP	0.03	0.22	0.48	0.14	0.11; 0.17

[1]IQR: interquartile range; [2]P95: 95th percentile; [3]CI: confidence interval.

3.3.4 Scenario estimations including relevant sources of caffeine

In addition to the estimated exposures above, there are also other sources of caffeine in our everyday lives. Pharmaceuticals such as pain killers may contain caffeine, and caffeine-containing supplements are also available. An overview of the exposure from single units of some selected caffeine sources is given in Table 3.3.4-1.

Table 3.3.4-1. Exposure from single units of selected caffeine sources, in mg/kg bw.

Caffeine source	Caffeine, mg/unit	Children/adolescents 12-13 years; bw = 50.3 kg*	Women 18-70 years; bw = 69.2 kg**	Men 18-70 years; bw = 86.2 kg**
Coffee, one cup (2 dl)	80	1.6	1.2	0.9
Espresso, one cup (0.4 dl)	107	2.1	1.5	1.2
Tea, one cup (2 dl)	44	0.9	0.6	0.5
Cola drinks (0.5 l)	50	1.0	0.7	0.6
Dark chocolate varieties (50 g)	45	0.9	0.7	0.5
Light chocolate varieties (50 g)	9.5	0.2	0.1	0.1
Energy drink, one can (250 ml, 32 mg caffeine/100 ml)	80	1.6	1.2	0.9
Energy drink, one can (500 ml, 32 mg caffeine/100 ml)	160	3.2	2.3	1.9
Painkiller, one pill	65	1.3	0.9	0.8
Caffeine supplement, maximum daily dose 300 mg divided in three doses per day	300	6.0	4.3	3.5

*bw from Ungkost 3; ** bw from Norkost 3.

We have estimated scenarios based on the representative exposures derived from the Norkost 3 and the relative contribution of caffeine from PCPs, derived from EuroMix. Thus, the median habitual caffeine exposure used in the scenarios are calculated as the median values from Norkost 3 added 4% contribution from PCP. Caffeine exposure from other relevant sources are added. The scenarios are described below.

First scenario: Adult female, average weight 69.2 kg with a median daily caffeine exposure from diet (227 mg/day) and PCP (4%), of 3.4 mg/kg bw per day. If she uses one dose of pain killer with 65 mg caffeine, this will equal an additional exposure of 0.9 mg/kg bw per day, which totals 4.3 mg/kg bw per day.

Second scenario: Adult male, average weight 86.2 kg, with a median daily caffeine exposure from diet (257 mg/day) and PCP (4%), of 3.1 mg/kg bw per day. If he uses two doses pain killer with 65 mg caffeine per dose, this will give an additional 1.5 mg/kg bw per day, and a total exposure of 4.6 mg/kg bw per day.

In caffeine supplements, the concentrations of caffeine are regulated to maximum 300 mg caffeine per day, divided into three doses per day (Lovdata, 2020).

Scenario three: Adult female, average weight 69.2 kg with a median daily caffeine exposure from diet in combination with PCP of 3.4 mg/kg bw per day. With an additional exposure

from supplements of 300 mg caffeine per day, the total exposure will be 7.7 mg/kg bw per day.

Scenario four: Adult male, average weight 86.2 kg, with a median daily caffeine exposure from diet and PCP of 3.1 mg/kg bw per day. With an additional exposure from supplements of 300 mg caffeine per day, the total exposure will be 6.6 mg/kg bw per day.

Scenario five: Adolescent 13 years, average weight 50.3 kg, with a median exposure of caffeine from diet of 0.12 mg/kg bw per day. An addition of one can (500 ml) of energy drink to this, adds 160 mg of caffeine, which totals 3.3 mg/kg bw per day.

Scenario six: pregnant woman, average weight 69.2 kg. If VKM imputes the exposure estimates for women from Norkost 3 to represent exposure in pregnant women, of 3.4 mg/kg bw per day, the exposure would exceed the reference points for adverse health effects in the foetus. Note that the dietary data from Norkost 3 and the data on PCP use from EuroMix do not discriminate between pregnant women and other women. Therefore, this scenario for pregnant women is based on the estimated exposure for all women.

4 Risk characterisation

VKM evaluated whether new studies indicated a need for revision of the doses «not to give rise to safety concern» for sleep disturbances and for general adverse health effects, established by EFSA (2015). VKM concluded that there was no need for revision of these doses, and these doses were therefore used as reference points for adverse effects of caffeine in the risk characterisation. As caffeine is rapidly and completely absorbed from the GI tract after oral intake in humans, the reference points were used for risk characterisation of internal caffeine exposure.

The doses from EFSA (2015) were interpreted as follows:

Children and adolescents

- Single caffeine exposure of about 1.4 mg/kg bw and 3 mg/kg bw, above which sleep disturbances and general adverse health effects, respectively, may occur.
- Habitual caffeine exposure of about 3.0 mg/kg bw per day, above which general adverse health effects may occur.

Adults, not including pregnant and lactating women

- Single caffeine exposure of about 1.4 mg/kg bw and 3 mg/kg bw above which sleep disturbances and general adverse health effects, respectively, may occur.
- Habitual caffeine exposure of about 5.7 mg/kg bw per day above which general adverse health effects may occur.

Pregnant women

- Habitual caffeine exposure of about 3 mg/kg bw per day, above which there may be concern for the foetus.

Lactating women

- Single and habitual caffeine exposure of about 3 mg/kg bw per day, above which there may be concern for the breastfed infant.

EFSA stated that these doses do not apply to subgroups of the population selected on the basis of a disease condition. The same holds true for sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions which may require individual advice. It should be noted that the reference points for children and adolescents were predominantly based on data from studies on adults. No reference point was determined for single exposure for pregnant women due to lack of data.

EFSA has not established a dose "not to give rise to safety concerns for specific groups of the general population" for sleep disturbances related to habitual caffeine exposure. To

enable risk characterisation for sleep disturbances for habitual caffeine exposure, VKM used the dose established by EFSA for sleep disturbances from single caffeine exposures.

Caffeine exposure from the diet was estimated for the age groups 4 years, 8-9 years and 12-13 years, using the dietary survey Ungkost 3 (Section 3.3.1.2). Both Norkost 3, Tromsø 7 and the biomonitoring study EuroMix were used to estimate the caffeine exposure from the diet for adults (18-70 years) (Section 3.3.1.1).

Caffeine exposure from PCPs was estimated for adults (18-70 years) using the data from the biomonitoring study EuroMix (Section 3.3.2).

The total caffeine exposure from diet in combination with PCPs was estimated using data from the biomonitoring study EuroMix (Section 3.3.3).

For the age groups 4 years, 8-9 years, and 12-13 years, the estimated daily dietary exposures (median and 95th percentile) were below 1.4 mg/kg bw; that is, it was below all reference points for adverse effects of caffeine. Of note, 0.6% of the participants in the Ungkost 3 survey had caffeine exposure above the reference points. The VKM report investigating caffeine exposure from energy drinks (VKM et al., 2019), which included data from other dietary surveys focusing mainly on energy drink consumption (Bakken, 2018; Forbrukerrådet, 2019), also identified a share of children and adolescents with caffeine exposures above the 3.0 mg/kg bw reference point.

For healthy adults, not including pregnant and lactating women, a comparison of the estimated daily caffeine exposures to the reference points for adverse effects of caffeine, is shown in Table 4-1.

Table 4-1. Estimated daily caffeine exposure and reference points for sleep disturbances (1.4 mg/kg bw) and general adverse health effects (5.7 mg/kg bw per day) for adults, not including pregnant and lactating women.

Exposure source	Exposure below 1.4 mg/kg bw	Exposure in the range: 1.4 - <5.7 mg/kg bw per day	Exposure equal to or above 5.7 mg/kg bw per day
Diet, median		EuroMix, all participants, women and men Norkost 3, all participants, women and men Tromsø 7, all participants, women and men	
Diet, 95th percentile		EuroMix, men	Norkost 3, all participants, women and men EuroMix, all participants, and women Tromsø 7, all participants, women and men

Exposure source	Exposure below 1.4 mg/kg bw	Exposure in the range: 1.4 - <5.7 mg/kg bw per day	Exposure equal to or above 5.7 mg/kg bw per day
PCPs, median	EuroMix, all participants, women and men		
PCPs, 95th percentile	EuroMix, all participants, women and men		
Diet in combination with PCPs, median		EuroMix, all participants	
Diet in combination with PCPs, 95th percentile			EuroMix, all participants

For healthy adults, not including pregnant and lactating women, a comparison of the estimated caffeine exposure for different time periods during a day to the reference points for adverse effects of caffeine, is shown in Table 4-2.

Table 4-2. Estimated caffeine exposure for given time periods during a day and reference points for sleep disturbances (1.4 mg/kg bw) and general adverse health effects (3.0 mg/kg bw) for adults (Norkost 3, all participants).

Time period	Below 1.4 mg/kg bw	In the range 1.4 - <3.0 mg/kg bw	Above 3.0 mg/kg bw
Before 10 am	Median exposure		95th percentile exposure
Between 10 am and 3 pm	Median exposure		95th percentile exposure
Between 3 pm and 8 pm	Median exposure	95th percentile exposure	
After 8 pm	Median exposure	95th percentile exposure	

The risk characterisation for the scenarios described in Section 3.3.4 is shown in Figure 4-1, 4-2 and 4-3.

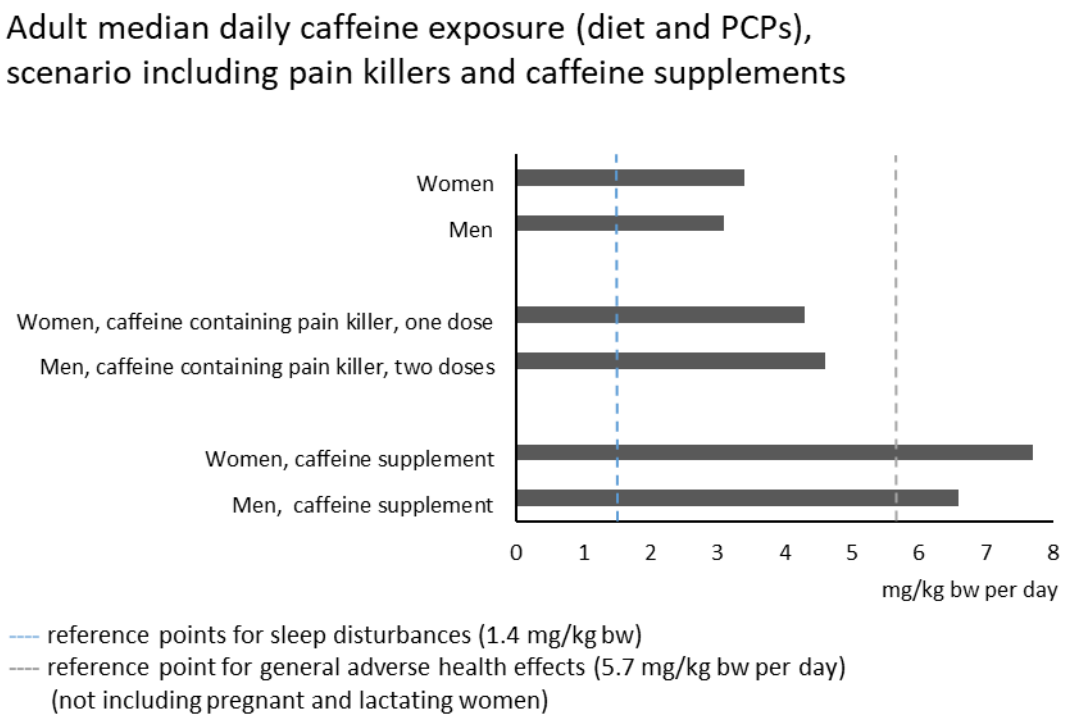


Figure 4-1. Scenario estimations for adults including caffeine containing painkillers and caffeine supplements. The exposure from painkillers and caffeine supplements is added to the median dietary exposure (Norkost 3) and mean PCP exposure (EuroMix) (shown in the top for women and men, respectively).

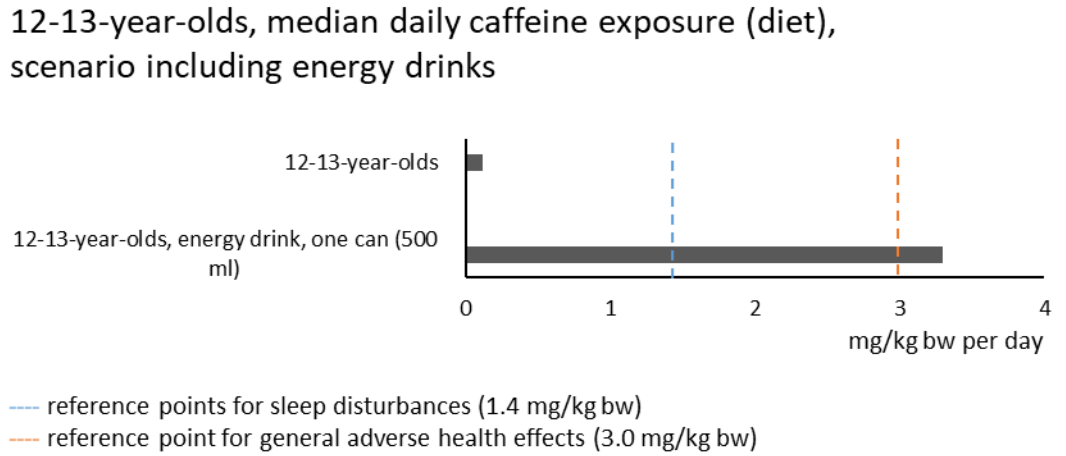


Figure 4-2. Scenario estimation including caffeine from energy drinks. The exposure from energy drink is added to the median dietary exposure (Ungkost 3) for 12-13-year-olds (shown in the top).

In the scenario for pregnant women, due to missing data on the caffeine exposure in pregnant women specifically, VKM assumes that pregnant women have the same median

(representative) habitual (daily) exposure of caffeine from diet and PCPs as other adult women (Figure 4-3).

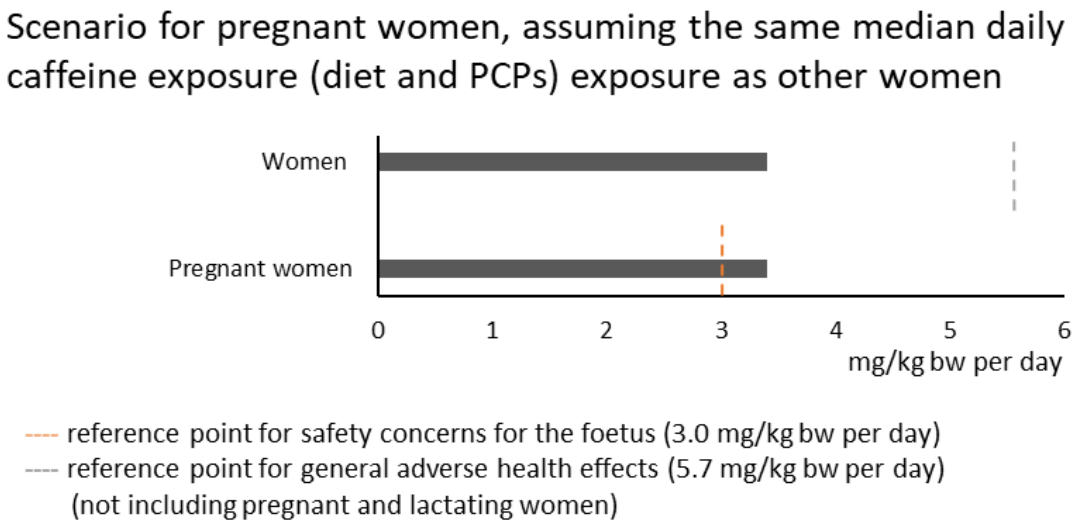


Figure 4-3. Scenario estimation including caffeine from energy drinks for pregnant women. The exposure from energy drink is added to the median dietary exposure (Norkost 3) and mean exposure from PCPs (EuroMix) for women (shown in the top).

5 Uncertainties

5.1 Uncertainty in the hazard identification and characterisation

Due to the choice of limiting the literature to RCTs, endpoints, hypotheses and mechanisms of action described in other human studies than RCTs, animal and *in vitro* studies were not included in this risk assessment. Although several major endpoints have been assessed, there is a possibility that endpoints having a plausible biological effect might have been left out of the risk assessment.

For children and adolescents, the hazard identification and characterisation are predominantly based on data from studies on adults. Also, there is scarcity of studies and data on pregnant and lactating women. This introduces uncertainty in the hazard identification and characterisation in these sub-populations.

Due to lack of studies investigating effects of chronic exposure, high caffeine doses, or dose-responses, conclusions related to chronic oral intake must be interpreted with caution.

The lack of effect of caffeine on insomnia in the included studies may be explained by the intervention time point; test substance was usually given in the morning or afternoon, not close to bedtime.

A dose "not to give rise to safety concerns for specific groups of the general population" for sleep disturbances related to habitual (daily) caffeine exposure was not established by EFSA (2015). VKM assumed that the dose established by EFSA for sleep disturbances from single caffeine exposures would be relevant to use to characterise the risk for sleep disturbances from habitual caffeine consumption. As the actual dose may be higher or lower, this introduces uncertainty in the risk characterisation for sleep disturbances from habitual caffeine exposure.

5.2 Uncertainty in the exposure assessment

All dietary assessment studies and lifestyle surveys using self-reported data are prone to measurement errors, including reporting errors. Evaluations of uncertainties in the estimates to exposure of caffeine from diet and PCPs are presented in Table 5.2-1, highlighting the main sources of uncertainty and indicating, if possible, whether the respective source of uncertainty might have led to an over- or underestimation of exposure and, consequently, the resulting risk characterisation (EFSA 2018).

Although VKM undertook a comprehensive literature search and method quality assessment for caffeine concentrations in food, there is still uncertainty with regard to how representative the occurrence data compiled in this risk assessment is for food in the

Norwegian diet. Analysed values for caffeine content in coffee blends sold in Norway would have enhanced the quality of the occurrence data and the exposure assessments.

Due to lack of information about the number of caffeine-containing products in each PCP category that are available on the Norwegian market, VKM assumed that all caffeine-containing products are available in Norway. Further, when caffeine concentration data were available for one or more products within a category, e.g. body lotion, VKM assumed that all body lotions contained caffeine. This may give an overestimation of the caffeine exposure from PCPs. Although data on caffeine concentrations in PCPs were obtained in the present evaluation, there may be PCPs that do contain caffeine that we did not include in our estimations due to missing information. This may give an underestimation of the caffeine exposure from PCPs.

The EuroMix participants did not record the amounts of PCPs applied and amounts from literature was thus used instead. Several factors influence the degree of dermal absorption of caffeine from the use of PCPs (*e.g.* thickness and composition of the stratum corneum (which depends on the body site), skin integrity, duration of exposure, amount applied, concentration of caffeine, occlusion of the skin, formula of the PCP). Since the product types used in the exposure estimations differs with respect to several of these factors, using 36% dermal absorption for all product types may cause uncertainty in the estimations.

When estimating caffeine exposure from PCPs in adults, mean concentration values for groups of PCPs were used. Consumers using products with higher caffeine concentrations than the mean concentration, will have higher caffeine exposure from PCPs. However, VKM applied a conservative approach in the exposure estimation, assuming that all PCPs in a category where caffeine concentrations were available actually contained caffeine, and applying the mean concentrations for each PCP group. Due to lack of data on PCP use in children and adolescents, with regards to product types, frequency, and amount used, no exposure estimates for PCPs were included for these age groups. Thus, this may give an underestimation of the total caffeine exposure in children and adolescents.

The Ungkost 3 survey 8-9 years and 12-13 years was conducted as a national, school based, online dietary diary. Although the survey was designed to be nationally representative the study population had fewer boys than girls included and more children with parents with higher education than in the general population. Thus, the results may be biased towards a slightly healthier diet than what we may assume is true in this population. How this may affect the caffeine exposure is difficult to say.

Norkost 3 was conducted in 2011. Now, ten years later, the patterns of intake of dietary caffeine sources in the adult population may have changed. The next national dietary survey Norkost 4, planned to be conducted in 2022, will shed new light on intake of caffeine and its dietary sources.

The dietary data from Norkost 3 and the data on PCP use from EuroMix do not discriminate between pregnant/lactating women and other women. If there are differences in the caffeine

exposure between pregnant/lactating women and other women the datasets included do not provide this information. Therefore, all estimations and scenarios for pregnant/lactating women are based on estimates for all women.

Uncertainties affecting the estimation of exposure to caffeine were evaluated using a tabular format similar to suggestions of EFSA et al. (2018). The impact of each uncertainty was expressed using symbols defined on a quantitative scale. A plus symbol means that the true caffeine exposure value could be higher than the estimate (between 20% and 100% higher), minus symbols mean that the true value could be lower (between 20% and 100% lower), and a dot (•) means that the impact of the uncertainty of the caffeine exposure value is estimated to be less than +/– 20%. Two plusses mean that the caffeine exposure value could be more than 100% above the estimated value. Each symbol represents a range of possible values. Pairs of symbols are used where the uncertainty spans a larger range: for example, "–/+" would mean that the true caffeine exposure value is judged to be between 100% lower and 100% higher than the estimate.

It is emphasised that all the evaluations are approximate expert judgements and should not be interpreted as precise estimates.

Table 5.2-1. Qualitative evaluation of impacts of uncertainties on the estimation of caffeine exposure

Source	Description	Impact of the uncertainty
Dietary surveys/studies	Self–reported data rely on the participant's memory, the ability to remember what you ate and/or drank during a certain time period and correctly translate this into frequencies and amounts. This may introduce uncertainties in the data when it comes to caffeine containing food. This study design also relies on the participants' ability to understand the questions as intended by those who design the assessment/survey. However, intake of coffee is often regular and do not vary much between most days, and could therefore be reported more accurately than other food items containing caffeine.	•
	Social desirability may influence the participants to underestimate the intakes of foods and beverages perceived as "undesirable/unhealthy" and overestimate the intake of healthy foods and beverages. In the studies upon which this risk assessment is based, the effect of the social desirability may be both negative and positive, depending on the perspective of each individual participant. For coffee the main contributor to caffeine exposure in adults there are no clear undesirable/unhealthy stigma. For adolescent's caffeine containing drinks like coffee drinks and energy drinks can have a more daring aspect, which can influence the reporting both ways.	• -/+

Source	Description	Impact of the uncertainty
	In EuroMix and Norkost 3, a higher share of female participants and participants with higher education than in the general population, may have resulted in a lower intake of food and beverages perceived as unhealthy, than in the general population.	•
	Tromsø 7 consist of older participants than the general population. The coffee intake are higher in the older age groups.	•
	Direct comparisons between results from different dietary methods have to be done with caution. Tromsø 7 have used FFQ, while the other studies have used 2-4 days of recall/record.	-/+
PCP concentration data	PCP concentrations were obtained through a call for data. VKM does not know how well the caffeine concentration data represents the PCP products on the Norwegian market.	•
PCP use	PCP exposure was measured in one biomonitoring study in Norway, EuroMix. VKM does not know how well the data on PCP use represents the PCP use in the general population. However, the PCP do not represent a major contribution to the combined exposure from diet and PCP.	•
Dietary intake/exposure	Food exposure – episodic consumption. Foods seldom eaten are underreported in the dietary surveys, covering 2-4 days, included in this risk assessment. Foods seldom consumed are best assessed using long term dietary tools such as frequency questionnaires. However, coffee is by far the main source to caffeine exposure among adults, and drinking patterns are often more regular than other food intakes. Therefore, VKM considers errors introduced from missing seldom consumed food items to be minor for habitual exposure to caffeine from coffee at the representative level. The use of few record/recall days for the estimation of habitual exposure is an overestimation for the high level (P95 exposure).	• +
	Since the caffeine exposure in adolescents is lower than in adults, episodic consumption of high caffeine containing foods will give higher variation in the exposure. Four days registrations might not cover the episodic consumption of for instance coffee drinks, and energy drinks, which can be consumed in large amounts during one time period.	•/++

6 Summary, discussion and conclusion

In our daily lives, we are exposed to caffeine from several sources. Caffeine is found in a range of food and beverages as well as in PCPs, pharmaceuticals and caffeine supplements (EFSA, 2015). The overall aim of the present risk assessment was to examine whether the total caffeine exposure from diet in combination with PCPs constitutes a health risk to the Norwegian population.

6.1 Hazard identification and characterisation

Caffeine intakes «not to give rise to safety concern» have been established by EFSA (2015). These were established for single caffeine exposures and habitual caffeine exposure. Adverse effects of single dose caffeine exposure on the central nervous system were assessed in children (including sleep, anxiety and behavioural changes) and adults (including sleep and anxiety). Adverse effects of habitual caffeine exposure were evaluated in children (behavioural changes), in pregnant women (adverse birth weight-related outcomes in the offspring), and adults (cardiovascular outcomes) (EFSA, 2015). EFSA stated that these doses do not apply to subgroups of the population selected on the basis of a disease condition. The same holds true for sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions which may require individual advice.

VKM performed literature searches for the period 2013-2020 to identify RCTs on negative effects related to caffeine; a literature search covering the period 2013-2018 was performed in a previous risk assessment of energy drinks and caffeine (VKM et al., 2019), and a literature search covering the period 2019-2020 was performed for the present risk assessment. In the included RCTs the outcomes addressed for general adverse health effects were blood pressure, heart rate, haematologic parameters (including white blood cell count, red blood cell count, haemoglobin, haematocrit, platelets, lymphocytes, monocytes, eosinophils, basophils), intraocular pressure, ocular perfusion pressure, and "other side effects" (including nervousness, muscular pain, headache, GI effects, muscle pain, irritability and diuresis). In addition, sleep disturbances were addressed. The blood pressure effects reported were considered not to be of physiological relevance. No changes in heart rate were reported. Effects on haematologic parameters, intraocular pressure and ocular perfusion pressure were within the normal range, and few "other side effects" were reported. Therefore, VKM concludes that there is no need for revision of the doses «not to give rise to safety concern» for general adverse health effects established by EFSA (2015). Sleep disturbances were reported in some of the RCTs. As the doses administered in these RCTs (3 mg/kg bw per day) were higher than the dose considered to increase sleep latency and reduce sleep duration in some individuals (1.4 mg/kg bw) (EFSA, 2015), VKM concluded that there is no need for revision of this reference point.

VKM decided to use the doses established by EFSA (2015) "not to give rise to safety concerns for specific groups of the general population" for the risk characterisation. VKM

denoted the adverse effects on sleep as "sleep disturbances", and the other adverse effects as "general adverse health effects". VKM interpreted single caffeine exposure as one intake, over a limited period during a day, e.g. one cup of coffee or tea, one meal with several caffeine sources or one portion of caffeine supplement. Habitual caffeine exposure was interpreted as the long-term regular exposure, expressed as the representative exposure throughout a day (daily exposure). VKM interpreted the doses "not to give rise to safety concerns for specific groups of the general population" established by EFSA (2015), for healthy groups of the general population as follows:

Children and adolescents

- Single caffeine exposure of about 1.4 mg/kg bw and 3 mg/kg bw, above which sleep disturbances and general adverse health effects, respectively, may occur.
- Habitual caffeine exposure of about 3.0 mg/kg bw per day, above which general adverse health effects may occur.

It should be noted that the reference points for children and adolescents were predominantly based on data from studies on adults.

Adults, not including pregnant and lactating women

- Single caffeine exposure of about 1.4 mg/kg bw and 3 mg/kg bw above which sleep disturbances and general adverse health effects, respectively, may occur.
- Habitual caffeine exposure of about 5.7 mg/kg bw per day above which general adverse health effects may occur.

Pregnant women

- Habitual caffeine exposure of about 3 mg/kg bw per day, above which there may be concern for the foetus.

No reference point was determined for single exposures for pregnant women due to lack of data, and data to characterise the risk of habitual caffeine consumption were scarce. Unborn children were considered by EFSA (2015) to be the most vulnerable group for adverse effects of caffeine among the general population.

Lactating women

- Single and habitual caffeine exposure of about 3 mg/kg bw per day, above which there may be concern for the breastfed infant.

<u>Sleep disturbances, habitual (daily) exposure</u>
EFSA has not established a dose "not to give rise to safety concerns for specific groups of the general population" for sleep disturbances related to habitual caffeine exposure. To enable risk characterisation for sleep disturbances for habitual caffeine exposure, VKM has used the dose established by EFSA for sleep disturbances from single caffeine exposures.

6.2 Exposure assessment

6.2.1 Concentration data

The median caffeine concentrations were used, because the distributions of concentration data for many of the food categories were skewed to the right. For PCP, the mean concentration values were used for the exposure estimation.

The concentration data for caffeine in food were obtained through a literature search. In addition, we obtained information about caffeine values in food from FCDs, through EuroFIR and USDA. These latter datasets were used for comparison of the results from the literature search.

The PCP concentration data used were for products on the European market. VKM did not limit this to products on the Norwegian market as we lack this information for several of the products and since not all PCPs used by Norwegian consumers are bought from Norwegian stores. VKM assumed that all products of a certain type contained caffeine if we had concentration data for any such products. This is most likely a source of overestimation.

6.2.2 Consumption/use

Ungkost 3 and Norkost 3 are national dietary surveys designed to estimate habitual intake in a representative sample of the Norwegian population. Tromsø 7 (Lundblad et al., 2019) was also used to gain dietary data on habitual consumption of caffeine-containing food. The three surveys used different dietary assessment methods which may introduce variance in the intake estimates between the surveys. However, all dietary caffeine exposures were calculated using the same food composition database version in KBS.

The EuroMix biomonitoring study was used to estimate contribution of caffeine from PCPs and food in combination with PCPs, using its detailed information on both diet and PCPs used during two days of the participants' life. As seen from the results, the median caffeine exposure from diet was smaller in EuroMix as compared to Norkost 3 and Tromsø 7. This may result partly from the dietary assessment method (weighed food records versus 2 x 24 hour recalls versus FFQ) and partly from the variations in demographics of the study populations. See also discussion on study designs below.

The dataset of EuroMix (Husoy et al., 2019) with data from a cosmetic diary contained information on frequency of use. The amount applied per application was obtained from the literature. VKM does not know how well the frequency data for PCP use from EuroMix represents PCP use in the general population. It is however the best estimate available.

6.2.3 Exposure estimation

The concentrations of caffeine in food and PCPs were combined with the data on consumption (food) and use (PCPs), respectively, to estimate caffeine exposures.

To estimate total internal caffeine exposure, the absorption value used for uptake from the GI-tract was 100% and the dermal absorption value used was 36%.

The total caffeine exposure seemed to increase with age. This is seen in both Norkost 3 and Ungkost 3 (Table 6.2.3-1). The sources of caffeine also seem to change through life, and main sources of caffeine exposure from different dietary sources also changed with age (Figure 6.2.3-1).

Table 6.2.3-1. Mean dietary caffeine exposure and dietary sources in age groups in Ungkost 3 and Norkost 3.

Shares of total caffeine exposure (%) **Age (years)**	**Cakes**	**Dairy products**	**Chocolate, desserts and sweets**	**Tea**	**Soda and energy drinks**	**Coffee**	**Intake (mg/day)**
Ungkost 3							
4, n=399	24	40	24	12	-	-	3
8-9, n=636	24	33	20	20	3	-	6
12-13, n=687	11	20	21	23	16	9	10
Norkost 3							
18-29, n=299	<1	1	1	11	11*	75	130
30-49, n=722	<1	<1	1	12	6*	81	250
50-70, n=766	<1	<1	<1	12	3*	84	273

*including energy drinks and other soft drinks with caffeine.

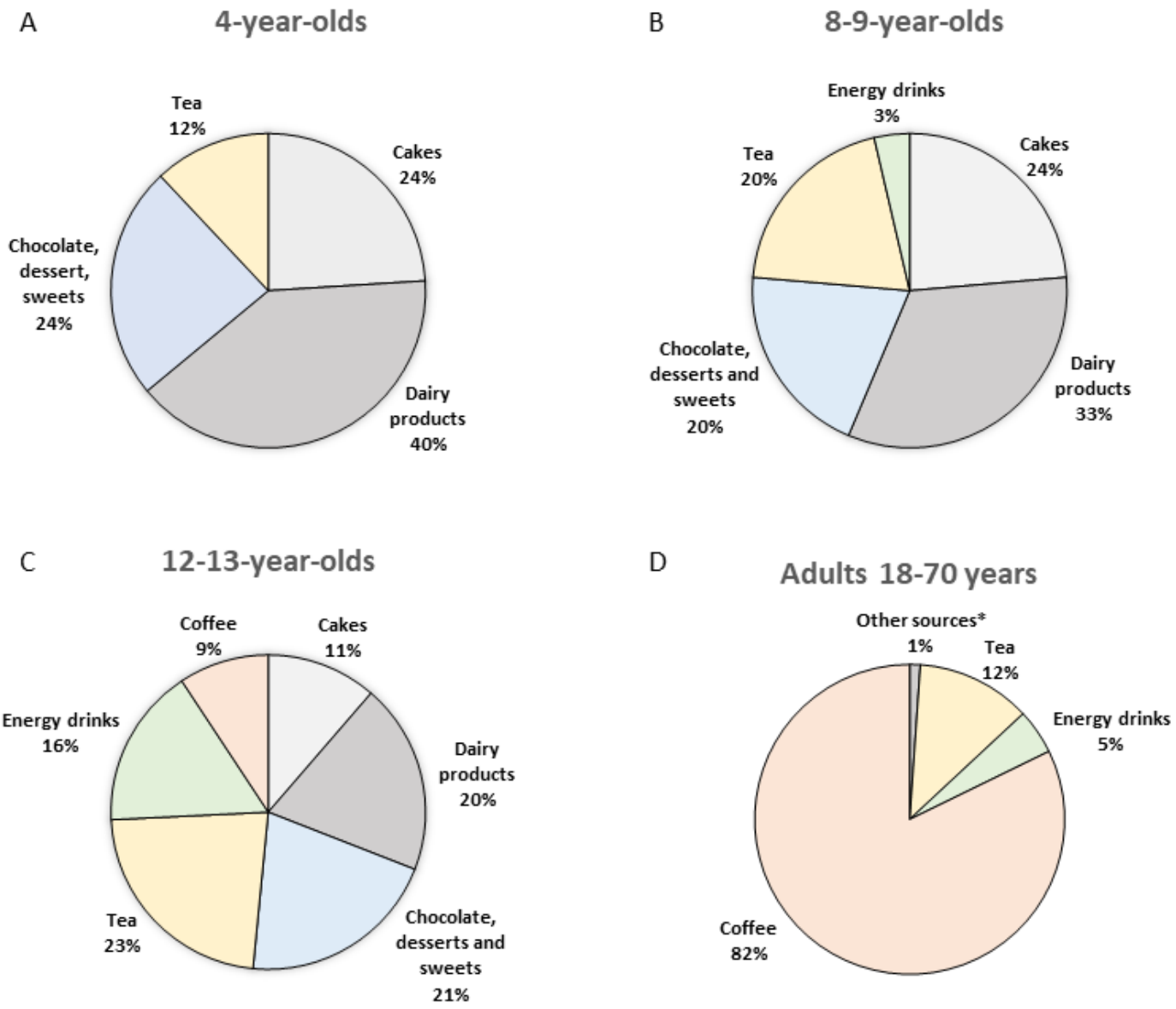


Figure 6.2.3-1. Dietary sources in A) Ungkost 3, 4-year-old children. Mean caffeine exposure was 2.6 mg/day. B) Ungkost 3, 8-9-year-old children. Mean caffeine exposure was 5.6 mg/day. C) Ungkost 3, 12-13-year-old children. Mean caffeine exposure was 9.8 mg/day. D) Norkost 3, 18-70 years. Mean caffeine exposure was 283 mg/day. *Cakes (0.2%), dairy products (0.4%), chocolate, dessert and sweets (0.5%).

The PCP exposure was not estimated for children as data on use were missing. The mean caffeine exposure from PCPs was low (mean=9.2 mg/day) compared to food (mean=199 mg/day) for the EuroMix participants. The main PCP source was body lotion (84%), followed by facial moisturiser (8%) and hand wash (3%). The total median and 95th percentile caffeine exposure from food and PCPs was 182 and 492 mg/day for the EuroMix participants, respectively.

High intake consumers

In a previous risk assessment of intake of energy drinks and caffeine (VKM 2019), VKM focused on high consumers of energy drinks. In the present risk evaluation, all sources of caffeine have been evaluated and median (due to skewed distribution of exposures) total exposure has been the focus. However, high consumers of any dietary sources with high concentrations of caffeine may reach exposures of caffeine, both from single sources, such as coffee or energy drinks, and from combined exposure from several sources, both acute and throughout a day, that exceeds the reference points for adverse effects of caffeine. Young high consumers of energy drinks, identified in the previous risk evaluation of energy drinks in 2019 (VKM2019), may be at higher risk of exceeding the references points of caffeine exposure when combining energy drink consumption with other sources of caffeine, such as coffee, tea and chocolate.

Another potential high exposure group is those who use caffeine supplements in connection with physical training. Caffeine supplements are readily available as e.g. pills, "shots" and in powders that are dissolved in water before intake. Consumers of these products may be at higher risk of exceeding the reference points of caffeine exposure if these products are used in excess, or are combined with other sources of caffeine. Due to lack of consumption data VKM does not know the magnitude of these exposures.

Study design implications

In the present risk assessent we used Norkost 3, Tromsø 7 and the biomonitoring study EuroMix to estimate caffeine exposure in adults. There are differences in the study designs between these studies that may explain the discrepancies in the data. Firstly, Norkost 3 was a national survey designed to include a representative study population with regard to age, gender, socio-economic factors and geography. The total study population was 1787 persons, 52% female, and a slightly higher share of persons with higher education than in the society as a whole (Totland et al., 2012). EuroMix recruited study participants among governmental institutes and authorities and universities in Oslo and former Akershus counties. The majority of the study population was thus highly educated and 71% were female (Husøy et al 2019). Tromsø 7, recruited and included participants 40 years old and above, in the municipality of Tromsø.

In the present risk evaluation, Norkost 3 was used as the survey with the most representative dietary data. Tromsø 7 was included to have more recent dietary intake data. EuroMix was exploited for its combined dataset of both dietary intake and PCP use, thus estimating the contribution of caffeine from PCPs relative to that from diet.

Variations in exposure during a day

From the Norkost 3 VKM estimated dietary caffeine exposure during four time periods of a day (Figure 6.2.3-2). These data show that the majority of caffeine exposure is in the

morning and in the middle of the day and then decreasing in the afternoon and evening. However, the data showed large individual variations, see Figure 6.2.3.-2.

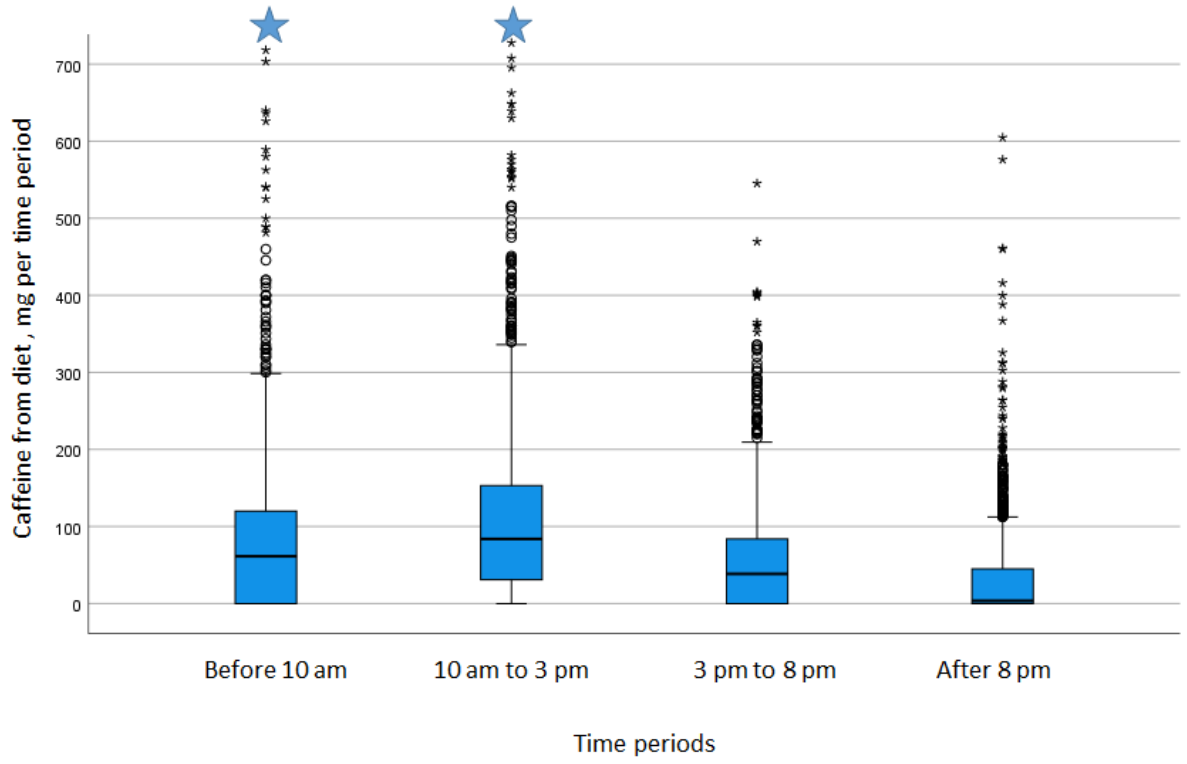


Figure 6.2.3-2. Dietary caffeine exposure during the day in Norkost 3, n=1787. The blue box lowest line is the 25th percentile, the middle line is the median, and the upper line of the box is the 75th percentile. Blue stars denote extreme values above max value for y-axis, 955 mg per time period and 1235 mg per time period, for "before 10 am" and "10 am to 3 pm", respectively.

6.3 Risk characterisation

The estimated caffeine exposures used in the risk characterisation were the group median (representative exposure) and 95th percentile (high exposure), and these are compared to the reference points for adverse effects of caffeine.

The estimated daily dietary caffeine exposures were below the reference points for general adverse health effects and sleep disturbances for 4-year-olds, 8-9-year-olds, and 12-13-year-olds (Figure 6.3-1).

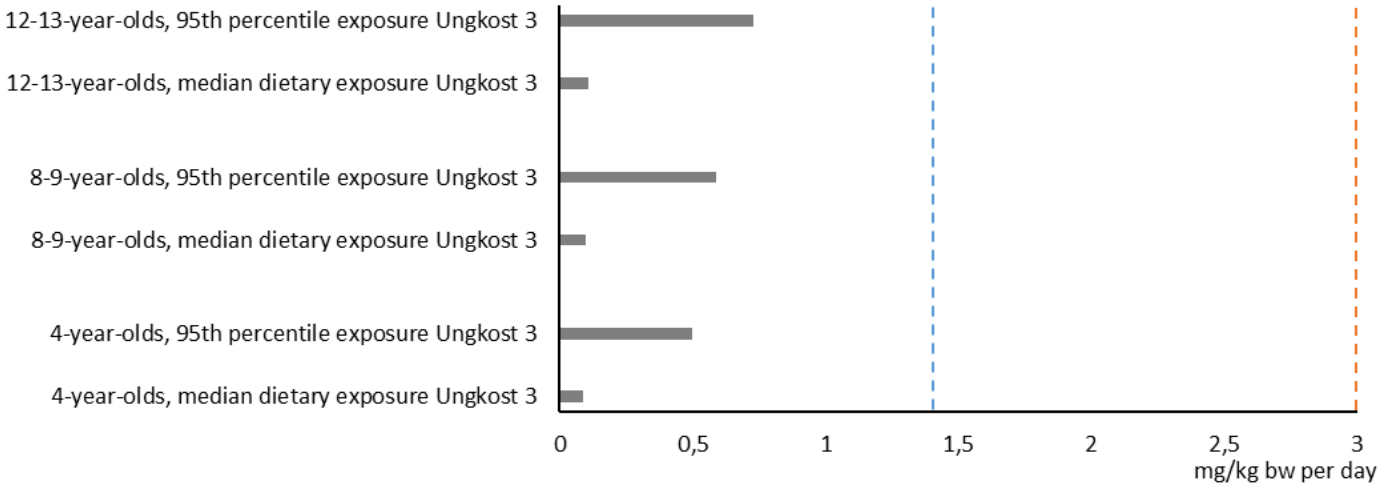


Figure 6.3-1. Median (representative) and 95th percentile (high) daily exposure of caffeine for 4-years-olds, 8-9-year-olds and 12-13-year-olds (Ungkost 3). Reference point for sleep disturbances (1.4 mg/kg bw; ----). Reference point for general adverse health effects (----).

The Ungkost 3 survey was designed to assess the habitual diet and the dietary method may therefore have underestimated periodically and seldom eaten foods. This may have led to underestimation of acute high exposures and is why VKM included exposure scenarios, please see section 3.3.4.

All estimated median daily dietary caffeine exposure in adults, not including pregnant and lactating women, were above the reference point for sleep disturbances and below the reference point for general adverse health effects for habitual intake. With the exception of the men in EuroMix, all 95th percentile estimated daily dietary caffeine exposure were above both reference points. All estimated daily PCP caffeine exposure, median and 95th percentile, were below both reference points. The median estimated daily total caffeine exposure from diet in combination with PCPs was above the reference point for sleep disturbances and below the reference point for general adverse health effects for habitual exposure, whereas the 95th percentile estimated daily exposure was above both reference points (Figure 6.3-2).

In Norkost 3 the caffeine exposure increased with age, from 1.8 mg/kg bw among participants 18 to 29 years, to 3.3 mg/kg bw in participants 30 to 49 years to 3.6 mg/kg bw in participants 50 to 70 years ($p<0.001$).

The dietary caffeine exposures in adults showed different median intakes across the dietary surveys, with lowest exposure in EuroMIX, followed by Norkost 3 and Tromsø 7 with the highest caffeine exposures. This may be due to demographic differences, such as age, gender, education level and/or food culture. It may also be due to the variability in dietary assessment methods used in each study: 2 days weighed food diary in EuroMix, 2 x 24 hour recalls in Norkost 3 and the use of a paper based FFQ in Tromsø 7. However, having dietary data from several different dietary surveys, conducted in different time periods from 2011 until 2017, in one national sample and two different sub-populations is viewed as an advantage in the risk assessment as it shows the diversity and range of exposures.

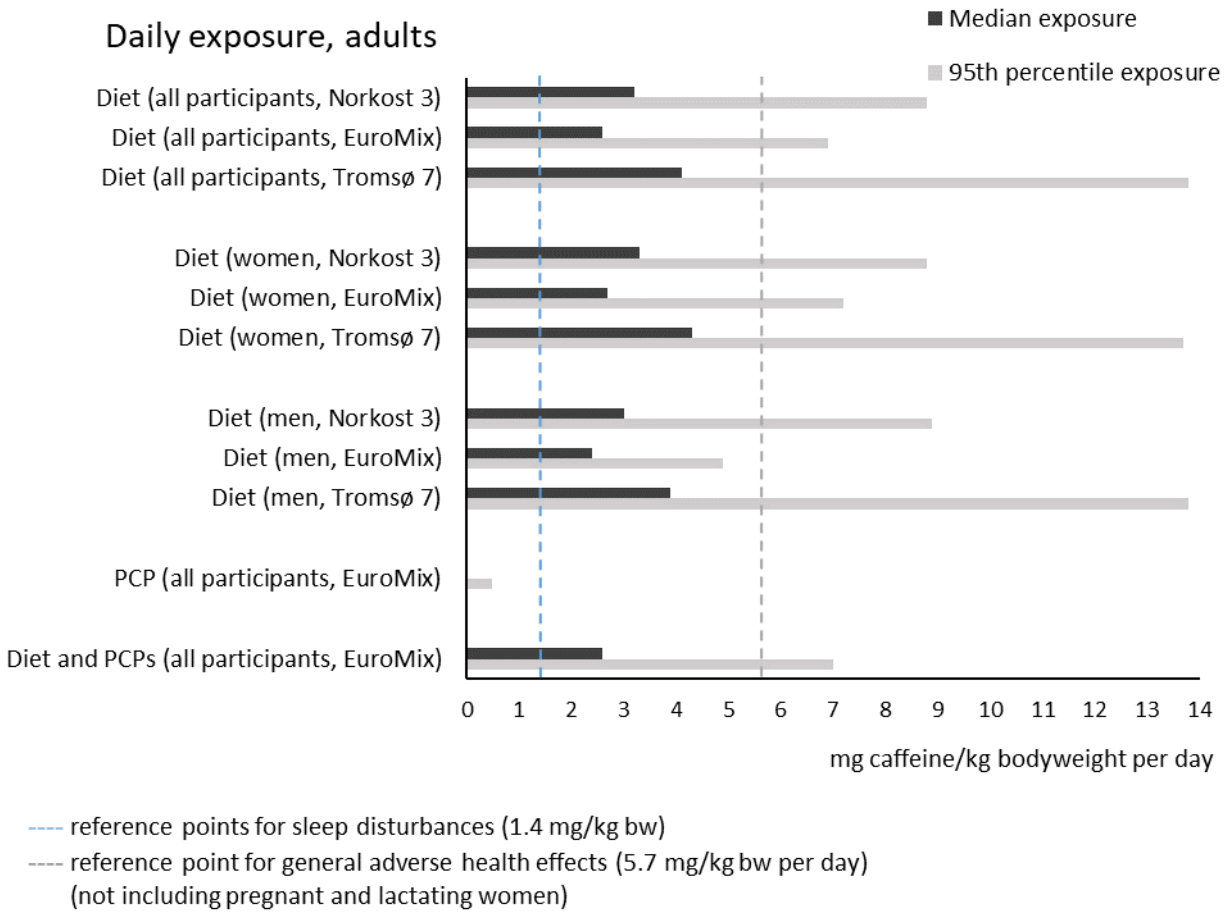


Figure 6.3-2. Median (representative) and 95th percentile (high) daily exposure of caffeine for adults in the Norkost 3, EuroMix, and Tromsø 7, from diet alone, and diet in combination with PCPs. For PCPs alone the median exposure is not presented because it accounted for a very small proportion of the total exposure.

All estimated median dietary caffeine exposures of adults for different time periods during a day were below both reference points for single exposures. From the morning until 3 pm, the estimated 95th percentile exposures were above the reference point for general adverse health effects for single exposure. The rest of the day, the estimated 95th percentile exposures were above the reference point for sleep disturbances but below the reference point for general adverse health effects for single exposures (Figure 6.3-3).

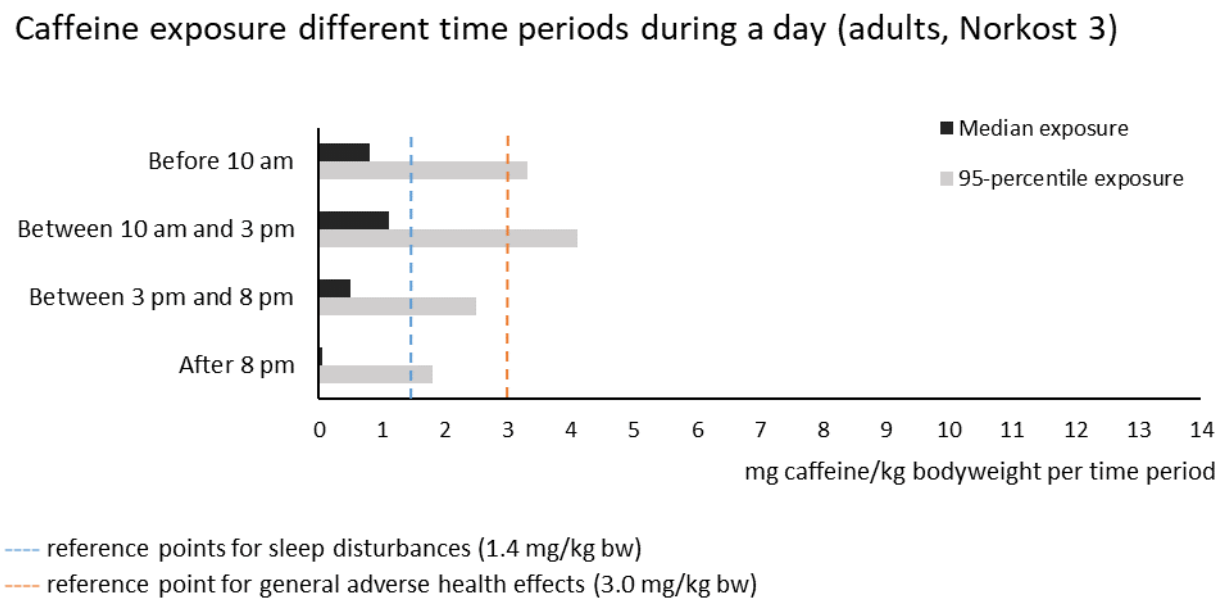


Figure 6.3-3. Median (representative) and 95th percentile (high) dietary caffeine exposure for adults in Norkost 3 for different time periods in the day.

6.4 Conclusions

Conclusion are reached for healthy individuals, for the representative and the high exposure level. In addition, VKM comments on individuals with especially high exposure.

<u>Daily dietary caffeine exposure in children and adolescents (4-year-olds, 8-9-year-olds and 12-13-year-olds)</u>

- The exposure was below both reference points. VKM concludes that the estimated caffeine exposure is unlikely to cause risk for general adverse health effects and sleep disturbances.
- In a small number of participants, estimated dietary caffeine exposure exceeded both reference points. In children and adolescents with especially high intakes of caffeine containing products, exposures may induce sleep disturbances and general adverse health effects.

<u>Daily caffeine exposure in adults (not including pregnant and lactating women)</u>

- Caffeine exposure from PCP use was below both reference points. VKM concludes that the estimated caffeine exposure is unlikely to cause risk for general adverse health effects and sleep disturbances.
- The representative caffeine exposure from diet alone and diet in combination with PCPs exceeded the reference point for sleep disturbances. VKM concludes that the estimated caffeine exposure may represent a risk for sleep disturbances.

- The high caffeine exposure from diet alone and diet in combination with PCPs exceeded the reference points for sleep disturbances and general adverse health effects. VKM concludes that the estimated exposure may represent a risk for sleep disturbances and general adverse health effects.

Single dietary caffeine exposures in a given time period in adults

Caffeine exposures were divided into four time periods during a day: before 10 am, between 10 am and 3 pm, between 3 pm and 8 pm, and after 8 pm.

- The representative caffeine exposures were below both reference points. VKM concludes that the estimated caffeine exposure, within the time periods assessed, is unlikely to cause risk for sleep disturbances and general adverse health effects.
- In the time periods before 10 am and between 10 am and 3 pm, the high exposure exceeded the reference points for both sleep disturbances and general adverse health effects. VKM concludes that the estimated exposure may represent a risk for sleep disturbances and general adverse health effects.
- In the time periods between 3 pm and 8 pm and after 8 pm, the high exposure exceeded the reference point for sleep disturbances but was below the reference point for general adverse health effects. VKM concludes that the estimated exposure may represent a risk for sleep disturbances.

Note that the risk of a sleep disturbances will be higher for caffeine intake close to bedtime and will vary between individuals, due to individual variability of the half-life of caffeine.

Pregnant and lactating women

Data on caffeine exposure in pregnant and lactating women were not available for this assessment. If VKM assumes that the exposure estimates for women from Norkost 3 may represent exposure in pregnant and lactating women, the exposure would exceed the reference points for adverse health effects in the foetus and infant. Due to lack of exposure data for pregnant and lactating women, VKM cannot conclude with regard to risk assessment of caffeine exposure in these groups.

7 Data gaps

The lack of toxicity data for high acute intakes and data for children and adolescents introduces uncertainties and limit the risk assessment and the conclusions that can be drawn.

No reference point for single exposures for pregnant women is established due to lack of data.

More occurrence data on PCPs and coffee varieties and blends on the Norwegian market would have strengthened the results.

Consumption data on the use of caffeine supplements would have strengthened the risk assessment.

Data on PCP use for children and adolescents are needed to estimate the exposure from this source for these groups.

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9 Appendix: Literature addressing adverse health effects related to caffeine

9.1 Literature search

Population	Intervention	Comparison	Outcome
Humans, all age groups, males and females	Caffeine	-	Any adverse health effect related to caffeine

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 06, 2020>
Date: 09.03.2020
Result: 218

#	Searches	Results
1	Caffeine/	23108
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffeine* or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw,kf.	28770
3	1 or 2	33835
4	"Drug-related side effects and adverse reactions"/ or Risk/ or exp Risk assessment/ or Risk factors/	1129602
5	(risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or association? or associate? or relationship or connection? or pertaining or induction?).tw,kf.	8325612
6	4 or 5	8581427
7	3 and 6	11523
8	limit 7 to "therapy (maximizes specificity)"	626
9	("randomized controlled trial" or "controlled clinical trial").pt. or (randomized or randomised or randomly or rct or placebo or trial or groups).tw,kf,bt.	3017457
10	7 and 9	2217
11	8 or 10	2217
12	Animal/ not (animal/ and human/)	4642531

13	11 not 12	1892
14	(2019* or 2020*).ed,ep,yr,dp,dt.	2360724
15	(201811* or 201812*).ep,ed,dt.	387076
16	14 or 15	2561069
17	13 and 16	218

Database: Embase <1974 to 2020 March 05>
Date: 09.03.2020
Result: 193

#	Searches	Results
1	Caffeine/	45423
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffeine* or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw,kw.	34757
3	1 or 2	51541
4	exp Adverse Drug Reaction/ or Adverse event/ or exp Side effect/ or exp Health hazard/ or Risk/ or Risk assessment/ or Risk factor/ or Toxicity/ or Acute toxicity/ or Hazard assessment/	2978404
5	(risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or association? or associate? or relationship or connection? or pertaining or induction?).tw,kw.	11169906
6	4 or 5	11810010
7	3 and 6	21270
8	limit 7 to "therapy (maximizes specificity)"	1465
9	limit 8 to (randomized controlled trial or controlled clinical trial)	610
10	(randomized or randomised or randomly or rct or placebo or trial or groups).tw,kw.	4018123
11	7 and 10	3674
12	8 or 9 or 11	3827
13	(animal/ or exp nonhuman/ or Animal experiment/) not ((animal/ or exp nonhuman/ or Animal experiment/) and exp human/)	5954296
14	12 not 13	3321
15	limit 14 to (conference abstracts or embase)	2972
16	(2019* or 2020*).yr,dd,dp,dc.	2539690
17	(201811* or 201812*).dd,dc.	240351

18	16 or 17	2746359
19	15 and 18	193

Database: PsycINFO <1806 to March Week 1 2020>
Date: 09.03.2020
Result: 23

#	Searches	Results
1	Caffeine/	2805
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffeine* or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw.	4652
3	1 or 2	4746
4	"Side effect (Drug)"/ or Risk assessment/ or Risk factors/ or Toxicity/	93015
5	(risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or association? or associate? or relationship or connection? or pertaining or induction?).tw.	1705158
6	4 or 5	1706644
7	3 and 6	2052
8	limit 7 to "therapy (maximizes specificity)"	137
9	randomized controlled trials/ or randomized clinical trials/ or (randomized or randomised or randomly or rct or placebo or trial or groups).tw.	667442
10	7 and 9	497
11	8 or 10	503
12	(animal not (animal and human)).po.	357878
13	11 not 12	463
14	(2019* or 2020*).yr,dp,up.	201007
15	(201811* or 201812*).up.	23762
16	14 or 15	217606
17	13 and 16	23

Database: Web of Science
Date: 09.03.2020
Result: 420

Set	Results	Save History / Create AlertOpen Saved History
# 6	420	#4 AND #3 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2018-2020*
# 5	2,746	#4 AND #3 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 4	3,703,633	TOPIC: (("randomized" or "randomised" or "randomly" or "rct" or "placebo" or "trial" or "groups")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 3	12,641	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 2	11,050,057	TOPIC: (("risk*" OR "safety" OR "adverse" OR "side effect$" OR "sideeffect$" OR "hazard*" OR "harm*" OR "negative" OR "toxicity" OR "toxic" OR "association$" OR "associate$" OR "relationship" OR "connection$" OR "pertaining" OR "induction$")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 1	33,605	TOPIC: (("1,3,7 trimethylxanthine" OR "1,3,7 trimethyl xanthine" OR "caffeine*" OR "coffein*" OR "methyltheobromine" OR "theine" OR "3g6a5w338e" OR "58-08-2" OR "C8H10N4O2")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

9.2 Assessment of full text RCTs - excluded publications

An overview of the publications considered not to fulfil the eligibility criteria is given in Table 9.2-1.

Table 9.2-1. Publications considered not eligible.

Reference	Reason for exclusion
Anderson et al. (2018)	Outcome
Beaullieu et al. (2019)	Study design
Fair et al. (2019)	Study design
Gray et al. (2019)	Study design
Redondo et al. (2020)	Outcome
Russell et al. (2020)	Outcome
Stone et al. (2019)	Study design
Williamson et al. (2018)	Outcome

9.3 Internal validity

The eight questions considering aspects relevant for RoB evaluation of human controlled trials in the OHAT tool (OHAT, 2015; OHAT, 2019) were used to evaluate RoB in the eligible RCTs. The RoB evaluation for each study is shown in the tables below. The response options and symbols used for the rating:

- Definitely low risk of bias ++
- Probably low risk of bias +
- Probably high risk of bias -
- Definitely high risk of bias - -

9.3.1 Outcome: blood pressure and heart rate

Bloomer et al. (2013); tier 1

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Subjects were randomly assigned to one of four conditions. The method for randomisation was not described.	+
	2	Was allocation to study groups adequately concealed?	Allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The authors state that the study was double-blinded. The study sponsor retained the blinding code until study completion.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	Outcome data were complete.	++
Detection bias	5	Can we be confident in the exposure characterisation?	A dietary supplement contract manufacturer produced caffeine and placebo supplements under standard good manufacturing practices. Quality assurance procedures confirmed the purity and potency of each condition	++
	6	Can we be confident in the outcome assessment?	Well established methods were used.	++
Selective reporting bias	7	Were all measured outcomes reported?	All measured outcomes were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study procedures were approved by the University Institutional Review Board for Human Subjects Research. Power analysis was not performed. Statistical methods used are adequate.	+

Crooks et al. (2019); tier 3

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	The participants received 0 mg (placebo), 200 mg, or 300 mg of caffeine in a randomized, counter-balanced order. The method for randomization was not reported.	+
	2	Was allocation to study groups adequately concealed?	The allocation to the study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The authors state that caffeine or placebo was administered double-blind. The method was not reported.	-
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	12 participants completed the study.	+
Detection bias	5	Can we be confident in the exposure characterisation?	The authors did not report sufficiently.	-
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	+ +
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods were reported.	+ +
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study was reviewed and approved by the Institutional Review Board of Washington State University, and conformed with the Code of Ethics of the World Medical Association (Declaration of Helsinki). No information regarding power analysis. Statistical methods used are adequate.	+

Dodd et al (2015); tier 2

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	The order in which participants received each treatment was determined by Latin square and random allocation to treatment order for each group (habitual consumers and non-habitual consumers).	++
	2	Was allocation to study groups adequately concealed?	Allocation to study groups was adequately concealed.	++
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	Each treatment was administered in the form of two capsules in order to mask any taste differences and to ensure that participants remained blind to the treatment they had received. The capsules were prepared and coded by an independent third party who had no further involvement with the study.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	+
Detection bias	5	Can we be confident in the exposure characterisation?	No information on the purity of caffeine. The authors state that pharmaceutical grade caffeine powder was used.	-
	6	Can we be confident in the outcome assessment?	Blood pressure and heart rate readings were taken from the left arm.	+
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study was approved by Northumbria University's School of Psychology and Sport Sciences' ethics committee. Statistical methods used are adequate. Power analysis was not performed.	+

Flueck et al. (2016); tier 2

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Randomization was applied using the data management which randomized trials automatically. Randomization of treatment sequence with a fixed block size of 5 and stratified by group was applied.	++
	2	Was allocation to study groups adequately concealed?	Allocation to study groups was adequately concealed.	++
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	Placebo and caffeine capsules were not distinguishable from each other due to equal color, size and taste. The number of capsules was kept identical in the placebo trial. Neither the head of study, nor participants and staff knew the assignment of interventions during the study phase. The blinding process was done by the Clinical Trial Unit in their centre where the key for trial assignment was stored.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	In total 39 healthy non-smoking men were recruited to participate in the study whereas 7 must have been excluded due to not fulfilling inclusion criteria or due to participation declination. Data was analysed finally from 28 healthy, non-smoking men (12 able-bodied, 9 paraplegic and 7 tetraplegic participants) at the end of the study. Data from 4 participants were excluded for analysis due to incomplete HRV measurements (technical problems).	++
Detection bias	5	Can we be confident in the exposure characterisation?	No information on the purity of caffeine.	-
	6	Can we be confident in the outcome assessment?	The outcomes were assessed using well established methods.	++
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes were reported.	++

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	Trial Registration ClinicalTrials.gov NCT02083328. Statistical methods used are adequate. A two-sided power analysis was performed	++

Gonzaga et al. (2017); tier 3

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	The order of placebo and caffeine was established through a randomization process using a coin.	++
	2	Was allocation to study groups adequately concealed?	Allocation was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The volunteers were blinded as caffeine and placebo capsules were identical. The researcher was not blinded at any time in the study.	-
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The loss of participants was adequately addressed.	++
Detection bias	5	Can we be confident in the exposure characterisation?	The authors did not report sufficiently.	-
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	++

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods have been reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study's procedures were all approved by the Research Ethics Committee of the Faculty of Philosophy and Sciences at the Paulista State University, Marilia – São Paulo, SP, Brazil (fle no. CEP-2200/11) and conformed with resolution 466/12 of the National Health Council of 12/12/2012. The present study's crossover clinical trial is registered in the Clinical Trials network by the identification code NCT02917889. Power analysis was performed. Statistical methods used are adequate.	+

Hansen et al. (2019); tier 3

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	The authors state that subjects received the caffeine doses in different order. The method for randomization was not described.	+
	2	Was allocation to study groups adequately concealed?	The allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The authors state that the study was double-blinded. The method was not described.	-

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	There was one missing rating for one subject. The authors state that the analyses were robust to this missing data point.	+
Detection bias	5	Can we be confident in the exposure characterisation?	The authors did not report sufficiently.	-
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	+ +
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods were reported.	+ +
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	A study protocol was not available. The study was approved by the Institutional Review Board (IRB) of Washington State University. Power analysis was performed. Statistical methods used are adequate.	+

Pajcin et al. (2019); tier 3

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Participants was randomly assigned to caffeine or placebo. The method for randomisation was not described.	+
	2	Was allocation to study groups adequately concealed?	Insufficient information was provided about allocation to study groups	-

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The authors state that the study was double-blinded. The caffeine–containing gum and placebo gum were similar in taste and appearance, indicating that the participants were blinded. The authors did not report on blinding of research personnel.	-
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors report that data for caffeine and placebo were collected from all 23 participants.	++
Detection bias	5	Can we be confident in the exposure characterisation?	The authors did not report sufficiently.	-
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	+ +
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods have been reported.	+ +
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	This study was approved by the University of South Australia Human Research Ethics Committee and carried out in accordance with the Australian Code for the Responsible Conduct of Research and the National Statement on Ethical Conduct in Human Research established by the National Health and Medical Research Council of Australia and Universities. No information regarding power calculations. Statistical methods used are adequate.	+

Puente el at. (2017); tier 1

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Caffeine or placebo were ingested in a randomised order. The method for randomisation was not reported.	+
	2	Was allocation to study groups adequately concealed?	Allocation was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The caffeine and placebo containing capsules were identical. The capsules were prepared by an investigator who did not take part in the experimental trials, who assigned an alphanumeric code to each trial to blind participants and researchers to the substance ingested by each team. This code was unveiled after the analysis of the variables.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	99% purity, BulkPowders, Colchester, UK.	++
	6	Can we be confident in the outcome assessment?	Well established methods were used.	+
Selective reporting bias	7	Were all measured outcomes reported?	All measured outcomes were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The investigation was approved by the University Ethics Committee. No information regarding power calculations. Statistical methods used are adequate.	+

Ratamess et al. (2018); tier 1

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Subjects were given the supplements in random sequence each time they arrived at the laboratory. The method for randomisation was not described.	+
	2	Was allocation to study groups adequately concealed?	Allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The capsules were packaged in identical plastic containers marked with letters only to adhere to the double-blinded study design.	+ +
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	The authors state that the purity and amount of p-synephrine and caffeine in each supplement was verified by an independent laboratory. However, the results of the analysis were not described	+
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	++
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study was approved by The College of New Jersey's Institutional Review Board. No information regarding power calculations. Statistical methods used are adequate.	+

Ruiz Moreno et al. (2020); tier 1

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Caffeine or placebo were ingested in a randomised order. The method for randomisation was not reported.	+
	2	Was allocation to study groups adequately concealed?	The allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The caffeine–containing gum and placebo gum were similar in taste and appearance, indicating that the participants were blinded. In all trials, the same experimenter, blinded to the treatments under investigation, placed the cuff around the participant's arm and the same internal bladder was used for all measurements.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	The authors state that the purity of caffeine was 100%.	++
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	++
Selective reporting bias	7	Were all measured outcomes reported?	All measured outcomes outlined in the methods were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study was approved by the Research Ethics Committee of the Camilo José Cela University, in accordance with the latest version of the Declaration of Helsinki. Power analysis was performed. Statistical methods used are adequate.	+

Vera et al. (2019); tier 2

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	No information on randomisation was given by the authors.	-
	2	Was allocation to study groups adequately concealed?	The allocation to the study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	Each treatment dose was administered in an identical color, size, and shape capsule. The capsules were prepared and coded by a third person.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	A pharmacist laboratory prepared the caffeine-containing capsules (caffeine anhydrous) and placebo capsules (corn starch); the contents of which were certified safe for human consumption.	+
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	++
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The experimental protocol followed the guidelines of the Declaration of Helsinki, and it was approved by the University of Granada Institutional Review Board (IRB approval, 438/CEIH/2017). No information regarding power analysis. Statistical methods used are adequate.	+

Yoshihara et al. (2019); tier 3

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	The participants were randomly allocated to the caffeine and decaffeinated groups using computer-generated randomised numbers.	++
	2	Was allocation to study groups adequately concealed?	The allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	All participants were given the same decaffeinated coffee. For the caffeine-group, caffeine was added. The similar appearance indicate that the participants were blinded. The authors did not report on blinding of research personnel.	-
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	Loss of subjects was adequately addressed, and reasons were documented.	++
Detection bias	5	Can we be confident in the exposure characterisation?	The authors did not report sufficiently.	-
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	++
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	Ethical approval for this trial was provided by the Kyushu University Hospital Clinical Research Ethics Board, Fukuoka, Japan (Approval number: 24092), and the Kyushu University Institutional Review Board for Human Genome/Gene Research (Approval number: 724-00) and registered in the UMIN Clinical Trial Registration (Registration number: UMIN000010360). The trial was conducted in compliance with the Declaration of Helsinki, Ethical Guidelines for Clinical Research, Japan, and Ethical Guidelines for Human Genome/Gene Analysis Research, Japan. No information regarding power analysis. No adjustment for confounders.	-

Zbinden-Foncea et al. (2018); tier 2

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	The participants were randomly allocated to ingest either placebo or caffeine. The method for randomisation was not reported.	+
	2	Was allocation to study groups adequately concealed?	The allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The caffeine and placebo gum capsules were identical, indicating that the participants were blinded. The caffeine- and placebo-capsule assignment was performed by an independent person to double-blind the participants and researchers.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	The authors did not report sufficiently.	-
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-described methods.	++
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate, and researchers adhered to the study protocol)?	Ethical approval was obtained from the scientific ethics committee of the Finis Terrae University in accordance with the latest version of the Declaration of Helsinki. No information regarding power analysis. Statistical methods used are adequate.	+

9.3.2 Outcome: haematologic parameters

Bloomer et al. (2013); tier 1

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Subjects were randomly assigned to one of four conditions. The method for randomisation was not described.	+
	2	Was allocation to study groups adequately concealed?	Allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The authors state that the study was double-blinded. The study sponsor retained the blinding code until study completion.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	Outcome data were complete.	++
Detection bias	5	Can we be confident in the exposure characterisation?	A dietary supplement contract manufacturer produced caffeine and placebo supplements under standard good manufacturing practices. Quality assurance procedures confirmed the purity and potency of each condition	++
	6	Can we be confident in the outcome assessment?	Well established methods were used.	++
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes were reported	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study procedures were approved by the University Institutional Review Board for Human Subjects Research. Power analysis was not performed. Statistical methods used are adequate.	+

Bush et al. (2018); tier 1

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	The participants were given the doses in a randomized double-blind manner, the sequence of supplement consumption was randomized among the six different supplement doses to negate an order effect of supplementation. The method for randomization was not reported.	+
	2	Was allocation to study groups adequately concealed?	Allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The research personnel and subjects were adequately blinded to study group as capsules were packaged in identical plastic containers marked with letters only to adhere to the double-blinded study design.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	Loss of subjects was adequately addressed, and reasons were documented.	++
Detection bias	5	Can we be confident in the exposure characterisation?	The authors state that the purity and amount of p-synephrine and caffeine in each supplement were verified by an independent laboratory. The results were not reported.	+
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	++
Selective reporting bias	7	Were all measured outcomes reported?	All outcomes outlined in the methods have been reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study was approved by The College of New Jersey's Institutional Review Board. Power analysis was performed. Statistical methods used are adequate.	++

9.3.3 Outcome: intraocular pressure and ocular perfusion pressure

Vera et al. (2019); tier 2

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	No information on randomisation was given by the authors.	-
	2	Was allocation to study groups adequately concealed?	The allocation to the study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	Each treatment dose was administered in an identical color, size, and shape capsule. The capsules were prepared and coded by a third person.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	A pharmacist laboratory prepared the caffeine-containing capsules (caffeine anhydrous) and placebo capsules (corn starch); the contents of which were certified safe for human consumption.	+
	6	Can we be confident in the outcome assessment?	The outcome was assessed using well-established methods.	++
Selective reporting bias	7	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The experimental protocol followed the guidelines of the Declaration of Helsinki, and it was approved by the University of Granada Institutional Review Board (IRB approval, 438/CEIH/2017). No information regarding power analysis. Statistical methods used are adequate.	+

9.3.4 Outcome: "other side effects" and sleep disturbance

Bloomer et al. (2013); tier 3

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Subjects were randomly assigned to one of four conditions. The method for randomisation was not described.	+
	2	Was allocation to study groups adequately concealed?	Allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The authors state that the study was double-blinded. The study sponsor retained the blinding code until study completion.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The outcome data were complete.	+
Detection bias	5	Can we be confident in the exposure characterisation?	All conditions were produced under standard good manufacturing practices by a dietary supplement contract manufacturer. Quality assurance procedures confirmed the purity and potency of each condition	++
	6	Can we be confident in the outcome assessment?	NR	-
Selective reporting bias	7	Were all measured outcomes reported?	NR	-
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	NR	-

Puente et al. (2017); tier 1

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Caffeine or placebo were ingested in a randomised order. The method for randomisation was not reported.	+
	2	Was allocation to study groups adequately concealed?	Allocation was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The caffeine and placebo containing capsules were identical. The capsules were prepared by an investigator who did not take part in the experimental trials, who assigned an alphanumeric code to each trial to blind participants and researchers to the substance ingested by each team. This code was unveiled after the analysis of the variables.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	99% purity, BulkPowders, Colchester, UK.	++
	6	Can we be confident in the outcome assessment?	The survey was not validated.	+
Selective reporting bias	7	Were all measured outcomes reported?	All measured outcomes were reported	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The investigation was approved by the University Ethics Committee. No information regarding power calculations. Statistical methods used are adequate.	+

Ratamess et al. (2018); tier 3

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Subjects were given the supplements in random sequence each time they arrived at the laboratory. The method for randomisation was not described.	+
	2	Was allocation to study groups adequately concealed?	Allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The capsules were packaged in identical plastic containers marked with letters only to adhere to the double-blinded study design.	+ +
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	The authors state that the purity and amount of p-synephrine and caffeine in each supplement was verified by an independent laboratory. However, the results of the analysis were not described	+
	6	Can we be confident in the outcome assessment?	No description on how the side effects were reported. Side effects for all participants were recorded.	-
Selective reporting bias	7	Were all measured outcomes reported?	Not reported.	-
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	Cannot be evaluated as data were not shown.	-

Ruiz Moreno et al. (2020); tier 1

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Caffeine or placebo were ingested in a randomised order. The method for randomisation was not reported.	+
	2	Was allocation to study groups adequately concealed?	The allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The caffeine–containing gum and placebo gum were similar in taste and appearance, indicating that the participants were blinded. In all trials, the same experimenter, blinded to the treatments under investigation, placed the cuff around the participant's arm and the same internal bladder was used for all measurements.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors do not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	The authors state that the purity of caffeine was 100% purity.	++
	6	Can we be confident in the outcome assessment?	The outcome was assessed using a previously used online survey.	+
Selective reporting bias	7	Were all measured outcomes reported?	All of the study's measured outcomes outlined in the methods were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study was approved by the Research Ethics Committee of the Camilo José Cela University, in accordance with the latest version of the Declaration of Helsinki. A protocol was not available. Power analysis was performed. Statistical methods used are adequate.	+

Salinero et al. (2017); tier 2

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias	1	Was administered dose or exposure level adequately randomized?	Caffeine or placebo were ingested in a randomised order. The method for randomisation was not reported.	+
	2	Was allocation to study groups adequately concealed?	The allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The caffeine–containing capsules and placebo capsules were identical. An alphanumeric code was assigned to each trial to blind participants and investigators to the substance tested in each session. This code was unveiled after the analysis of the variables.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	Outcome data for all participants were reported.	++
Detection bias	5	Can we be confident in the exposure characterisation?	The authors did not report sufficiently.	-
	6	Can we be confident in the outcome assessment?	This questionnaire was previously used, but no information on validation was given.	+
Selective reporting bias	7	Were all measured outcomes reported?	Data for all outcomes in the questionnaire were reported.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The study was approved by the Camilo Jose Cela University Research Ethics Committee. Statistical methods used are adequate.	+

Zbinden-Foncea et al. (2018); tier 3

Type of bias	No	Question	Risk of bias evaluation	Risk of bias rating
Selection bias (	1	Was administered dose or exposure level adequately randomized?	The participants were randomly allocated to ingest either placebo or caffeine. The method for randomisation was not reported.	+
	2	Was allocation to study groups adequately concealed?	The allocation to study groups was adequately concealed.	+
Performance bias	3	Were the research personnel and human subjects blinded to the study group during the study?	The caffeine and placebo gum capsules were identical, indicating that the participants were blinded. The caffeine- and placebo-capsule assignment was performed by an independent person to double-blind the participants and researchers.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The authors did not report on the number included in the different analyses.	-
Detection bias	5	Can we be confident in the exposure characterisation?	The authors did not report sufficiently as the data were not shown.	-
	6	Can we be confident in the outcome assessment?	Twenty-four hours after the second and the third trials, the participants were contacted to answer an adapted version of a previously used questionnaire that assessed possible caffeine-related side effects.	+
Selective reporting bias	7	Were all measured outcomes reported?	NR	-
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	Cannot be evaluated as data were not shown.	-

9.4 Data extraction

Study characteristics for the eligible studies identified in the literature search covering the period 2019-2020 was extracted, and are shown in the tables below.

Study characteristics	
Title	Acute hematological and mood perception effects of bitter orange extract (p-synephrine) consumed alone and in combination with caffeine: A placebo-controlled, double-blind study
Author(s)	Jill A. Bush, Nicholas A. Ratamess, Sidney J. Stohs, Nicole L. Ellis, Ira T. Vought, Elizabeth A. O'Grady, Jeremy D. Kuper, Jie Kang, Avery D. Faigenbaum
Year	2018
Country	USA
Funding	The work was supported by Novel Ingredients LLC, East Hanover, NJ (Grant N1765).
Reported conflict of interest	One author (S. J. S.) has served as a consultant for Novel Ingredients, a company that markets bitter orange (*C. aurantium*) extracts. No other conflicts of interest were reported.
Objective	Examine acute hematological and mood perception responses to supplementation with p-synephrine alone and in combination with caffeine during quiet sitting.
Study type	Crossover
Method for randomisation	Not reported
Type of blinding	Double-blind
Participants	
Recruitment	Participants were recruited via posted flyers and word-of-mouth recruitment from the college campus.
Number of participants (invited, accepted, drop-out, included in follow-up if applicable)	16 participants, no drop-outs

Study characteristics	
Inclusion/exclusion criteria for participants	• Body mass index: 30 kg/m^2 or less • Bodyweight: 75.0 to 79.5 kg • Non-smoking regular caffeine consumers (more than 300 mg or three cups per day; CAF; N = 8) or non-caffeine consumers (<10 mg per day; NON; N = 8). • Free of chronic disease
Gender	Men (n=13), women (n=3)
Age	19-25 years
Confounders and other variables as reported	
Health status and socioeconomic status of participants	The participants were healthy and physically active university students.
Other	Participants in the NON group reported no regular consumption of coffee, soda, tea, energy drinks, or chocolate.
Intervention	
Intervention (dose, preparation, purity)	• P-synephrine (103 mg) (S) • Caffeine (233 mg) + p-synephrine (104 mg) (LC+S) • Caffeine (LC; 240 mg) • Caffeine (337 mg) + p-synephrine (46 mg) (HC+S) • Caffeine (HC; 325 mg) • Placebo (PL; maltodextrin)

Study characteristics	
Intervention design	• Participants arrived at the laboratory at a standard time of day (either 6:00 a.m. or 9:30 a.m.) after a 10-h overnight fast. In addition, participants in the CAF group refrained from caffeine consumption for 24 hours prior to each session. • The supplements were in capsule form. The purity and amount of p-synephrine and caffeine in each supplement were verified by an independent laboratory (Intertek, Champaign, IL). Each capsule was identical in appearance. • Participants consumed two capsules with water following preassessments, and subsequently each participant sat quietly for 3 hours. The official protocol time began upon swallowing of both capsules. • Capsules were packaged in identical plastic containers marked with letters only to adhere to the double-blinded study design. • Six interventions in total, given in a randomised order, with a 7-day washout period was in between each supplement protocol.
Results	
Parameters measured and methods used	• Upon arrival, each participant was weighed on a standard physician scale and subsequently sat quietly for 15 minutes prior to collection of a preblood sample (T1) via venepuncture with a 21-gauge sterile needle (Becton Dickinson, Hunt Valley, MD) was taken. • Participants completed two separate questionnaires regarding mood (the POMS survey; Profile of Mood State Questionnaire) and attitude state (VAS; the Visual Analog Scale). • Venous blood samples were collected to determine immune, lipid, and chemistry panels. Biochemical analyses included 48 analytes consisting of a complete blood count with differential/platelets, comprehensive metabolic panel, lipid panel, and iron.
Measurement time points	• Mood state questionnaires (POMS survey) were collected every 30 minutes and was completed at seven time points: upon arrival (T1) at the lab and every 30 minutes for the 3-hour period (T2-T7). • VAS was completed at seven time points: upon arrival (T1) at the lab and every 30 minutes for the 3-hour period (T2-T7). • Venous blood samples were collected at baseline (pre intervention; T0) and 3 hours (post intervention; T2-T7).

Reported outcome	Hematology measures: • Significant time effects were observed for red blood cells (RBCs) where elevations were seen during the LC and HC trials (3 hour study) in the NON group. For both groups the pre caffeine RBC (×10E6/µl) was 4.8±0.3 and the post caffeine RBC was 5.0±0.3. • Significant time and group effects were observed in neutrophils where elevations were shown from pre to post in both groups during the LC trial and only in the NON group during the HC trial. For the NON group the pre caffeine neutrophils (×10E3/µl) for LC was 3.2±1.2 and the post caffeine neutrophils was 3.7±1.3; the pre caffeine neutrophils for HC was 2.5±0.5 and the post caffeine neutrophils was 3.5±1.1. For the CAF group the pre caffeine neutrophils (×10E3/µl) for LC was 2.7±1.1 and the post caffeine neutrophils was 2.9±1.5 • Significant time effects were observed in eosinophils where reductions were observed during the HC trial. For the NON group the pre caffeine eosinophils (×10E3/µl) for HC was 0.2±0.1 and the post caffeine eosinophils was 0.1±0.1. For the CAF group the pre caffeine eosinophils (×10E3/µl) for HC was 0.2±0.2 and the post caffeine eosinophils was 0.1±0.2. Metabolic blood measures: • For total protein, significant pre-to-post elevations were observed for NON and CAF groups during the LC and HC trials compared with PL. For the NON group the pre caffeine total protein (g/dl) for LC was 6.8±0.4 and the post caffeine total protein was 7.1±0.4; the pre caffeine total protein for HC was 6.9±0.5 and the post caffeine total protein was 7.1±0.4. For the CAF group the pre caffeine total protein for LC was 6.9±0.3 and the post caffeine total protein was 7.0±0.3; the pre caffeine total protein for HC was 6.8±0.5 and the post caffeine total protein was 7.0±0.4. • For bilirubin, a significant time effect was observed where pre-to-post elevations were shown in NON and CAF groups during the LC and HC trials. For the NON group the pre caffeine bilirubin (g/dl) for LC was 0.54±0.2 and the post caffeine bilirubin was 0.58±0.2; the pre caffeine bilirubin for HC was 0.51±0.3 and the post caffeine bilirubin was 0.63±0.3 For the CAF group the pre caffeine bilirubin for LC was 0.44±0.2 and the post caffeine bilirubin was 0.57±0.2; the pre caffeine bilirubin for HC was 0.59±0.3 and the post caffeine bilirubin was 0.69±0.3. • For high-density lipoproteins (HDLs), significant time and supplement effects were observed where pre-to-post elevations were seen in NON and CAF groups during the HC trial. For the NON group the pre caffeine HDLs (mg/dl) for HC was 54.2±11.5 and the post caffeine HDLs was 59.1±11.2. For the CAF group the pre caffeine HDLs for HC was 59.8±13.2 and the post caffeine HDLs was 61.1±13.6.

	Visual Analog Scale: • For alarm to drowsy, significant supplement effects were observed. No changes were observed during the PL condition. However, all other supplement trials produced greater feelings of alarm. For the NON group the pre caffeine alarm (mm) to drowsy (mm) for LC was 55.6±11.2 and the post caffeine alarm/drowsy was 47.9±5.3; the pre caffeine alarm/drowsy for HC was 51.1±15.4 and the post caffeine alarm/drowsy was 39.9±17.0. For the CAF group the pre caffeine alarm/drowsy for LC was 68.8±27.9 and the post caffeine alarm/drowsy was 40.9±17.0; the pre caffeine alarm/drowsy for HC was 52.6±26.5 and the post caffeine alarm/drowsy was 39.2±13.1. • For the HC trial significant feelings of greater strength were observed. For the NON group the pre caffeine strong to feeble (mm) for HC was 49.1±14.8 and the post caffeine strong/feeble was 37.9±16.7; for the CAF group the pre caffeine strong/feeble for HC was 37.5±19.1 and the post caffeine strong/feeble was 37.4±15.0. • Mean values reflecting feelings of energy were greater during the LC and HC trials compared with PL. For the NON group the pre caffeine lethargic to energetic (mm) for LC was 52.0±8.9 and the post caffeine lethargic/energetic was 58.6±6.3; the pre caffeine lethargic/energetic for HC was 55.8±17.1 and the post caffeine lethargic/energetic was 65.9±16.6. For the CAF group the pre caffeine lethargic/energetic for HC was 44.0±23.6 and the post caffeine alarm/drowsy was 56.0±17.1 • For tense to relaxed, mean values were significantly lower during the LC and HC trials (in the NON group) compared with PL. The pre caffeine tense/relaxed (mm) for LC was 61.3±8.6 and the post caffeine tense/relaxed was 60.9±9.0; the pre caffeine tense/relaxed for HC was 54.1±17.1 and the post caffeine tense/relaxed was 57.9±17.8. • For attentive to dreamy, mean protocol values were significantly lower during all trials with caffeine compared with PL. For the NON group the pre caffeine attentive to dreamy (mm) for LC was 49.0±9.2 and the post caffeine attentive/dreamy was 46.7±7.2; the pre caffeine attentive/dreamy for HC was 47.1±19.8 and the post caffeine attentive/dreamy was 38.6±16.9. For the CAF group the pre caffeine attentive/dreamy for LC was 42.4±17.7 and the post caffeine attentive/dreamy was 41.3±14.1; the pre caffeine attentive/dreamy for HC was 37.8±26.9 and the post caffeine attentive/dreamy was 34.6±20.5. • For incompetent to proficient, significant increases over time were seen during the LC and HC trials. Participants felt significantly more proficient during the LC and HC trials compared with PL in the CAF group. The pre caffeine incompetent to proficient (mm) for LC was 66.3±10.7 and the post caffeine

Study characteristics	
	incompetent/proficient was 68.0±9.8; the pre caffeine incompetent/proficient for HC was 64.5±22.6 and the post caffeine incompetent/proficient was 73.0±13.2. • For withdrawn to gregarious, significant effects were observed where participants in the NON and CAF groups self-reported greater feelings of interest during the HC trial compared with PL. For the NON group the pre caffeine withdrawn to gregarious (mm) for HC was 53.4±11.1 and the post caffeine attentive/dreamy was 58.8±10.4. For the CAF group the pre caffeine withdrawn/gregarious for HC was 56.4±19.6 and the post caffeine withdrawn/gregarious was 62.0±10.4. • Participants in the NON group reported greater feelings of being gregarious during the HC condition compared with PL whereas participants in the CAF group reported greater feelings of being gregarious during all trials containing caffeine compared with PL. For the NON group the pre caffeine attentive to dreamy (mm) for LC was 49.0±9.2 and the post caffeine attentive/dreamy was 46.7±7.2; the pre caffeine attentive/dreamy for HC was 47.1±19.8 and the post caffeine attentive/dreamy was 38.6±16.9. For the CAF group the pre caffeine attentive/dreamy for LC was 42.4±17.7 and the post caffeine attentive/dreamy was 41.3±14.1; the pre caffeine attentive/dreamy for HC was 37.8±26.9 and the post caffeine attentive/dreamy was 34.6±20.5.
Statistical analysis	
Power analysis	A power analysis at 80% with the significance level set at 0.05 indicated a target sample size of 12.
Statistical test	• Descriptive statistics (means ±SD) were calculated for all dependent variables. • A two-way (treatment × time Point) analysis of variance with repeated measures was used to analyse all within-participant data. Subsequent Tukey's post hoc tests were utilised to determine differences when significant main effects were obtained. • For variables collected at T2–T7, an aggregate mean across the six outcomes was used in statistical analysis to compare against T1 within the NON and CAF groups and between the supplement conditions. Partial eta-square(η2) effect sizes were determined for treatment effects. • For all statistical tests, a probability level of p≤.05 denoted statistical significance.
Comments • Two participants in the non-caffeine user group reported feeling "extra alert" and "jittery" after consuming the high dose of caffeine (325 mg). • This study was part of a larger study where acute cardiovascular responses to the supplements were investigated (Ratamess et al., 2017).	

Study characteristics	
Title	Acute cardiovascular effects of bitter orange extract (p-synephrine) consumed alone and in combination with caffeine in human subjects: A placebo-controlled, double-blind study
Author(s)	Nicholas A. Ratamess, Jill A. Bush, Sidney J. Stohs, Nicole L. Ellis, Ira T. Vought, Elizabeth A. O'Grady, Jeremy D. Kuper, Saif B. Hasan, Jie Kang, Avery D. Faigenbaum
Year	2018
Country	USA
Funding	Novel Ingredients LLC, East Hanover, NJ (grant N1765), supported this work.
Reported confilct of interest	One author (S. J. S.) has served as a consultant for Novel Ingredients, a company that markets bitter orange (*Citrus aurantium*) extracts.
Objective	Examine cardiovascular responses to supplementation with p-synephrine alone and in combination with caffeine during quiet sitting.
Study type	Crossover
Method for randomisation	Not reported
Type of blinding	• Double-blind • Each capsule was identical in appearance and packaged in identical plastic containers marked with letters only to adhere to the double-blinded study design.
Participants	
Recruitment	Not reported
Number of participants (invited, accepted, drop-out, included in follow-up if applicable)	16
Inclusion/exclusion criteria for participants	• Body mass index of 30 kg/m^2 or less • Body weight approximately 75.0 to 79.5 kg
Gender	Men (13), women (3)
Age	19-25 years
Confounders and other variables reported	Participants were non-smoking regular caffeine consumers (more than 300 mg or 3 cups per day; CAF) or non-caffeine consumers (<10 mg per day; NON) free of chronic disease. Participants in the NON group reported no regular consumption of coffee, soda, tea, energy drinks, or chocolate.

Study characteristics	
Health status and socioeconomic status of participants	The participants were healthy and physically active.
Other	All participants were required to refrain from consuming any caffeinated beverage for 24hours prior to the study visits and were carefully instructed to maintain their normal dietary intake throughout the experimental period (via 3-day diet records) and to replicate a similar diet the day prior to each visit. Participants subsequently signed documents stating they complied with these procedures. No differences were observed between groups with the exception of caffeine intake.
Intervention	
Intervention (dose, preparation, purity)	Six interventions in total, given in a randomised order: • 103 mg of p-synephrine (S) • 233 mg of caffeine + 104 mg of p-synephrine (LC+S) • 240 mg of caffeine (LC) • 337 mg of caffeine + 46 mg of p-synephrine (HC+S) • 325 mg of caffeine (HC) • Placebo (PL; maltodextrin)
Intervention design (amount applied, frequency of application)	• The purity and amount of caffeine was verified by an independent laboratory (Intertek, Champaign, IL). • Participants, in a fasted state, reported to the laboratory on seven occasions at a standard time of day, with the last six separated by 1 week. A 7-day washout period was used in between each supplement protocol. • After assessments of pre-protocol heart rate (HR) and blood pressure (BP) measures, each participant consumed two capsules with water. The supplements were given in random sequence. The official protocol time began upon swallowing of both capsules. • The participants sat quietly for 3 hours, and HR and BP were measured throughout the period.
Results	
Parameters measured and methods used	• HR data were collected via Polar heart rate monitors and via electrocardiograph (ECG). • ECG measures were obtained using a single-channel (Lead II) ECG system (BIOPAC MP-150, BIOPAC Systems, Inc., Goleta, CA). • An automated blood pressure (BP) cuff (Omron 10 Series Model BP785N, Omron Healthcare, Kyoto, Japan) was used to record BP. The cuff also measured HR.
Measurement time points	• HR data collected via Polar heart rate monitors was recorded every 5 minutes. HR data collected via ECG was recorded continuously throughout the 3 hour period. • BP was recorded every 15 minutes.

Study characteristics	
Reported outcome	• Minimal side effects were observed during the study. During the HC trial, one participant from the NON group reported a racing HR, feeling irritable, and perspired. These side effects dissipated within 30 minutes.
Statistical analysis	
Power analysis	Not reported
Statistical tests	• Descriptive statistics (means ±SD) were calculated for all dependent variables. • A two-way (treatment × time point) analysis of variance with repeated measures was used to analyse all within-participant data. • Tukey's post hoc tests were utilised to determine differences when significant main effects were obtained. • Partial eta-square (η2) effect sizes were determined for treatment effects. • For all statistical tests, a probability level ofp≤.05 denoted statistical significance.
Comments	

Study characteristics	
Title	Time course of tolerance to adverse effects associated with the ingestion of a moderate dose of caffeine
Author(s)	Carlos Ruiz Moreno, Beatriz Lara, Juan José Salinero, Diego Brito de Souza, José M. Ordovás, Juan Del Coso
Year	2020
Country	Spain
Funding	The authors report that the investigation did not receive any funding.
Reported conflict of interest	All authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.
Objective	To identify and describe the time course of tolerance to the most common caffeine-induced side effects.
Study type	Crossover
Method for randomisation	Not reported
Type of blinding	Double-blind • The capsules were identical, filled with either caffeine or placebo. • Experimenter was blinded to the treatments under the investigations

Study characteristics	
Participants	
Recruitment	Participants were recruited through advertisements placed on the university campus.
Number of participants (invited, accepted, drop-out, included in follow-up if applicable)	11 participants
Inclusion/exclusion criteria for participants	• Low caffeine consumers (less than 100 mg/day of caffeine) • Non-smokers • Not taking medication or dietary supplements for the duration of the study
Gender	Men (n=8), women (n=3)
Age	32.3±4.9 years
Confounders and other variables as reported	
Health status and socioeconomic status of participants	The participants were healthy, active individuals.
Other	
Intervention	
Intervention (dose, preparation, purity)	Caffeine: 3mg/kg bw per day, 100% purity, Bulk Powders, United Kingdom Placebo: cellulose; 100% purity, Guinama, Spain
Intervention design	• A double-blind placebo-controlled crossover trial. • Participants refrained from all sources of dietary caffeine the month before the onset of the experiments, and for the duration of the experiments. Compliance was verified with dietary recalls. Participants resumed their daily routines that comprised office work or university tasks while keeping a regular and stable diet and fluid regime. Participants were also encouraged to maintain a stable schedule for each daily activity, especially regarding waking up, eating and resting schedules. • In a randomised order, participants ingested 3 mg/kg caffeine per day or placebo for 20 days.
Results	

Study characteristics	
Parameters measured and methods used	• Participants arrived at the laboratory (09.00 am) in a fasted state (at least 8 hours after their last meal). Following ingestion, participants rested supine for 60 minutes. Resting heart rate (HR; H10, Polar, Finland), and systolic and diastolic blood pressure BP; (M7 Comfort, Omron, Japan; by triplicate) were measured during the last 5 minutes of the resting period. • On the day after each trial visit, participants completed an online survey to rate their feelings of nervousness, vigour, and irritability, and to rate the magnitude of symptoms, if any, of headache, gastrointestinal distress and muscle pain and the magnitude of other side effects such as insomnia and diuresis. • In all trials, the same experimenter, blinded to the treatments under investigation, placed the cuff around the participant's arm. The same internal bladder, inserted within the cuff, was used for all measurements.
Measurement time points	Resting HR and blood pressure were measured 2 days before the onset of each protocol of ingestion and three times per week during each 20-day phase during the last 5 minutes of the resting period.
Reported outcome	• The data are presented as mean± standard deviation. • In the pairwise comparison with the placebo, the ingestion of caffeine increased systolic (+7.8±10.1%) and diastolic blood pressure (+6.4±12.9%) for the first 8 days of ingestion, but then this effect became attenuated for both outcomes (on day 20, −1.1±4.3% and +0.9±9.6%, respectively). • The ingestion of caffeine did not affect HR at any time point. • Caffeine increased the feelings of nervousness and vigour and the rating of gastrointestinal complaints, insomnia and diuresis at several time points in the treatment and they did not disappear after 20 days of ingestion.
Statistical analysis	
Power analysis	The sample size calculation, performed to have a statistical power of at least 80%, indicated that at least two participants were needed to obtain a caffeine-induced effect on systolic blood pressure after 1 day of caffeine ingestion (expected difference = 11.7 mmHg), while at least 11 participants were needed to detect an effect of caffeine on this variable after 3 days of consecutive ingestion (expected difference = 4.0 mmHg)

Study characteristics	
Statistical test	• Data were blindly introduced into the statistical package SPSS v 20.0 and subsequently analysed. Data on systolic blood pressure, diastolic blood pressure and resting heart rate were analysed with two-way (treatment × day) analysis of variance (ANOVA). When the ANOVA showed a significant effect on the treatment, differences in all pairwise caffeine–placebo comparisons were assessed using the Tukey post hoc test. Differences in the self-rated variables were analysed using the Wilcoxon signed-rank test. The criterion for statistical significance in all these tests was set at $P<0.05$. • The effect size was calculated in all pairwise comparisons, and the effect size statistic ± 95% confidence interval was used on log-transformed data. • A qualitative descriptor was included to represent the likelihood of caffeine–placebo difference in each variable and for each day of the experimental trial.
Comments	

Study characteristics	
Title	Effects of caffeine on intraocular pressure are subject to tolerance: a comparative study between low and high caffeine consumers
Author(s)	Jesús Vera, Beatriz Redondo, Rubén Molina, Javier Bermúdez, Raimundo Jiménez
Year	2019
Country	Spain
Funding	No information
Reported conflict of interest	The authors declare that they have no conflicts of interest
Objective	To compare the short-term effects of caffeine intake on intraocular pressure and ocular perfusion pressure between low- (≤ one cup of coffee per day) and high (≥ two cups of coffee per day)-caffeine consumers.
Study type	Crossover
Method for randomisation	Not reported
Type of blinding	Double-blind • Each treatment dose (placebo vs. caffeine) was administered in an identical color, size, and shape capsule. • The capsules were prepared and coded by a third person.

Study characteristics	
Participants	
Recruitment	University students were recruited
Number of participants (invited, accepted, drop-out, included in follow-up if applicable)	40
Inclusion/exclusion criteria for participants	Criteria for the participants: • free of any systemic or ocular disease • not taking any medication • not presenting allergy to xanthines • have a intraocular pressure (IOP) ≤21 mmHg (considered as the upper limit for normal intraocular pressure) • have a blood pulse difference lower than 60 mmHg at baseline conditions (considered an indicator of possible cardiovascular disorders) • smokers were excluded (as smoking causes an acute rise in blood pressure)
Gender	• Low-caffeine (LC) consumers: 8 males/13 females • High caffeine (HC) consumers: 7 males/12 females
Age	• LC consumers: 22.3 ± 4.7 years • HC consumers: 21.9 ± 2.8 years
Confounders and other variables as reported	
Health status and socioeconomic status of participants	The participants were healthy individuals
Other	All participants were asked to refrain for alcohol and caffeine-based drinks before attending to the laboratory in both experimental conditions, and to sleep at least 7 hours the night prior to testing. All participants were university students.
Intervention	

Study characteristics	
Intervention (dose, preparation, purity)	• Caffeine (4 mg/kg) or placebo (corn starch) administered with a cup of water (100 ml). • A pharmacist laboratory (Acofarma distribución S.A., Madrid, Spain) prepared the caffeine-containing capsules (caffeine anhydrous) and placebo capsules. The contents were certified safe for human consumption.
Intervention design (amount applied, frequency of application)	• Placebo-controlled, double-blind, balanced crossover design. • Participants consuming one or less cup of coffee (or other caffeinated drink) per day were defined as low caffeine consumers (n=21), those consuming two or more cups (or other caffeinated drink) per day were defined as high caffeine consumers (n= 19). • The within-participants factors were the caffeine consumption (placebo and caffeine) and point of measure (baseline, 30, 60, and 90 minutes), whereas the between-participants factor was the habitual caffeine intake (low consumers and high consumers). • Two experimental sessions (on two different days), and both sessions were scheduled at the same time of day (± 1 h). Both sessions were identical, with the exception of caffeine/placebo.
Results	
Parameters measured and methods used	The dependent variables were intraocular pressure (IOP), ocular perfusion pressure (OPP), blood pressure (BP). • A rebound tonometer (Icare Tonometer, TiolatOy, INC., Helsinki, Finland), which was clinically validated and showed a good level of agreement with the Goldmann tonometer was used to assess IOP. Both eyes were measured in randomized order. • BP was evaluated by an RX3 wrist digital automatic blood pressure monitor (Omron, Hoofddorp, The Netherlands), which was clinically validated according to manufacturer's specifications. • OPP was indirectly calculated from the IOP and BP values. The perceived level of activation and the participant's subjective level of alertness/sleepiness at the beginning of each experimental session was also recorded. • The participants filled in the questionnaire Stanford Sleepiness Scale at the beginning of both experimental sessions. This survey evaluates individuals' self-reported activation. • The participant completed a visual analog scale in order to evaluate the subjective level of activation before the commencement of the experimental session, and 30, 60, and 90 minutes after capsule ingestion.

Study characteristics	
Measurement time points	BP and IOP were measure while the participants were seated with neutral neck position. At this moment, the corresponding capsule (placebo or caffeine) along with a cup of water (100 ml) was administered. Then, the level of activation, OPP, IOP and BP were assessed at the minutes 30, 60, and 90 after capsule ingestion.
Reported outcome	• Caffeine (4 mg/kg) induced an acute IOP rise, and low-caffeine consumers exhibited a more accentuated IOP increment compared to high-caffeine consumers. The greatest IOP change induced by caffeine intake was measured after 90 minutes from capsule ingestion. • Low- and high-caffeine consumers reported higher activation (similar subjective perceptions) after caffeine consumption. • OPP did not vary after caffeine consumption.
Statistical analysis	
Power analysis	Not reported.
Statistical test	• The normal distribution of the data was confirmed using the Shapiro-Wilk test. • The homogeneity of variances was confirmed using the Levene's test. • For all the dependent variables (IOP, OPP, SBP, DBP, and subjective level of activation), a mixed ANOVA with caffeine consumption and point of measure as the within-participants factors, and the habitual caffeine intake as the between-participants factor, was carried out. • The magnitude of the differences was reported by the partial eta squared and Cohen's effect size for *F*s and *t* tests, respectively. • Statistical significance was set at an alpha level of 0.05. • Post hoc tests were corrected with Holm-Bonferroni procedure. • Statistical analyses were performed using the JASP statistics package (version 0.8.1.0).
Comments	

Study characteristics	
Title	Effects of Caffeine on Countermovement-Jump Performance Variables in Elite Male Volleyball Players

Study characteristics	
Author(s)	Hermann Zbinden-Foncea, Isabel Rada, Jesus Gomez, Marco Kokaly, Trent Stellingwerff, Louise Deldicque, and Luis Peñailillo
Year	2018
Country	Chile (*corresponding author)
Funding	The project was funded by the Chilean National Science and Technology Fund No 11150576.
Reported conflict of interest	Not reported
Objective	To examine the effects of a moderate dose of caffeine in elite male volleyball players on countermovement-jump (CMJ) performance, as well as temporal concentric- and eccentric-phase effects.
Study type	Crossover
Method for randomisation	Not reported
Type of blinding	The caffeine- and placebo-capsules were identical, and the assignment was performed by an independent person to double-blind the participants and researchers.
Participants	
Recruitment	Participants were recruited from the Chilean national volleyball team.
Number of participants (invited, accepted, drop-out, included in follow-up if applicable)	10
Inclusion/exclusion criteria for participants	Elite volleyball players of the Chilean national team
Gender	Male
Age	18.8 ± 2.0 years
Confounders and other variables as reported	
Health status and socioeconomic status of participants	Participants trained for approximately 2 hours/day, 4 or 5 days/week during the previous year.
Other	Participants' caffeine consumption was 61.60 ± 54.32 mg/day.
Intervention	

Study characteristics	
Intervention (dose, preparation, purity)	Capsules with either 5 mg/kg of anhydrous caffeine or placebo (dextrose) was ingested with 200 ml of water.
Intervention design (amount applied, frequency of application)	Two experimental days separated by one week. Participants arrived at the laboratory at 7:00 AM after an 8-hour fast to minimise all nutritional and diurnal effects. The capsules (caffeine or placebo) + 200 ml water were ingested 60 minutes before the countermovement-jump (CMJ) trials. The treatments were crossed over on the second experimental day.
Results	
Parameters measured and methods used	• After 5 minutes in resting supine position, heart rate (HR) (Polar®S625X, Polar Electro Oy, Kempele, Finland) and blood pressure (BP) were measured by a digital sphygmomanometer (HEM431CINT, Omron Healthcare Inc, USA). • Three CMJ trials were performed with 1 minute rest between trials. The trials were sampled at 1000 Hz using the Tesys 1000 Globus Ergo System and software (Globus System, Codogne Italy), consisting of 2 force plates (Globus Twin Plates, Codogne Italy) and a linear position transducer (LPT; Real Power Pro 1, Codogne Italy). The system was calibrated to convert the voltage of the force plate into vertical ground-reaction force and LPT into movement displacement. The LPT was positioned between the two force plates attached to a belt placed on the participant's waist, and participants were instructed to put their hands on this belt. Before each CMJ trial, LPT was zeroed to the height of the participant, and the participants were instructed to jump as high as possible while the data were recorded until the jump completion. The average of the 3 jumps and the jump with greatest height were used for analysis. The maximal values achieved during the eccentric phase and concentric phase were assessed for each jump. Variables obtained were peak force during the eccentric phase, peak power (PP), peak force during the concentric phase, peak velocity (PV), and peak dis-placement (PD). In addition, the rates of force development during the eccentric and concentric phases were evaluated, the rate of power development was measured from the start of the concentric phase until the PP was achieved during this phase, and the duration of several phases of the jump were determined. • The participants filled out a questionnaire that assessed possible caffeine-related side effects.
Measurement time points	• Heart rate and blood pressure were measured at baseline and 60 minutes post-ingestion. • Three CMJ trials were performed 60 minutes post-ingestion. • A questionnaire on possible side effects were filled out 24 hours post-trial.

Study characteristics	
Reported outcome	• Caffeine increased diastolic blood pressure (BP) by 13.0% ± 8.9% (71.4 ± 5.0 before vs 81.2 ± 11.3 mm Hg after). • No side effects such as insomnia, nervousness, anxiety, gastrointestinal discomforts, headache, irritability, or tachycardia derived from caffeine intake were reported in the questionnaire (data not shown).
Statistical analysis	
Power analysis	Not reported
Statistical test	• Data were blindly introduced and analysed in GraphPad Prism version 6.00 for Windows (GraphPad Software, San Diego, CA, USA). To confirm the normal distribution of the CMJ data and calculate the coefficient of variation for each variable, a Shapiro-Wilk test was performed. • The CMJ variable differences between the placebo and caffeine trials were analysed using paired-sample *t* test. • To analyse the treatment effect (caffeine or placebo) and the interactions with cardiovascular parameters (HR and BP, two-way repeated-measures ANOVA was used followed by a Bonferroni post hoc test when appropriate. • To detect differences in caffeine side effects, the McNemar nonparametric test for paired nominal data was used. • Values are presented as mean ± SD, and the significance level was set at P<.05.
Comments	

9.5 Confidence in the level of evidence

The reasons for the upgrading/downgrading of the confidence in the body of evidence is shown in Table 9.5-1.

Table 9.5-1. Detailed evaluation of the confidence in evidence.

	Elements triggering downgrading				Elements triggering upgrading			Overall rating
RCTs (n) and initial rating	**Risk of bias**	**Unexplained inconsistency**	**Indirectness**	**Imprecision**	**Large effect**	**Dose–response relationship**	**Consistency**	
Blood pressure, systolic								
Ruiz-Moreno et al. (2020), Vera et al. (2019), Ratamess et al. (2018), Zbinden-Foncea et al. (2018), Flueck et al. (2016), Dodd et al. (2015), Bloomer et al. (2013) Initial rating: ++++	Three RCTs tier 1, four RCTs tier 2 Serious	Point estimates similar, confidence intervals overlap, and I^2<50% Not serious	The population was relevant, and the endpoint measured of direct relevance for the health outcome Not serious	The ratio from the upper to the lower 95% CI for the meta-estimate was <10 Not serious	No effect or low effects considered not to be physiologically relevant Not large	Doses in mg/kg bw/day: 3.0, 4.0, 5.0, 5.8-6.2. Doses in mg/day: 75, 250, 500 No dose-response	No effect or low increase Yes	++++ High
Blood pressure, diastolic								
Ruiz-Moreno et al. (2020), Vera et al. (2019), Ratamess et	Three RCTs tier 1, four	Point estimates similar, confidence	The population was relevant, and the endpoint measured of direct relevance	The ratio from the upper to the lower 95% CI for the	No effect or low effects considered not to be	Doses in mg/kg bw/day: 3.0,	No effect or low increase Yes	++++ High

al. (2018), Zbinden-Foncea et al. (2018), Flueck et al. (2016), Dodd et al. (2015), Bloomer et al. (2013) Initial rating: ++++	RCTs tier 2 Serious	intervals overlap, and I^2<50% Not serious	for the health outcome Not serious	meta-estimate was <10 Not serious	physiologically relevant Not large	4.0, 5.0, 5.8-6.2. Doses in mg/day: 75, 250, 500 No dose-response		
Heart rate								
Ruiz-Moreno et al. (2020), Ratamess et al. (2018), Zbinden-Foncea et al. (2018), Puente et al. (2017), Flueck et al. (2016), Dodd et al. (2015) Initial rating: ++++	Three RCTs tier 1, three RCTs tier 2 Serious	Point estimates similar, confidence intervals overlap, and I^2<50% Not serious	The population was relevant, and the endpoint measured of direct relevance for the health outcome Not serious	The ratio from the upper to the lower 95% CI for the meta-estimate was <10 Not serious	No effects reported Not large	Doses in mg/kg bw/day: 3.0, 4.0, 5.0, 5.8-6.2. No dose-response	No effects reported Yes	++++ High
Haematologic parameters								
Bush et al. (2018) Bloomer et al.	Both RCTs tier 1	All parameters measured were	The population was relevant, and the endpoint measured of	All parameters measured were within the normal range.	All parameters measured were	All parameters measured were within	No	+++ Moderate

(2013) Initial rating: ++++	Not serious	within the normal range Not serious	direct relevance for the health outcome Not serious	Only two studies, Serious	within the normal range Not large	the normal range No		
Intraocular pressure and ocular perfusion pressure								
Vera et al. (2019) Initial rating: ++++	One RCT, tier 2 Serious	Cannot be evaluated as only one RCT addressing this outcome is included	The population was relevant, and the endpoint measured of direct relevance for the health outcome Not serious	All parameters measured were within the normal range. Only one study. Serious	All parameters measured were within the normal range Not large	Only one dose tested No	Cannot be evaluated as only one RCT addressing this outcome is included	++ Low
"Other side effects"								
Ruiz-Moreno et al. (2020), Puente et al. (2017), Salinero et al. (2017) Initial rating: ++++	Two RCTs tier 1, one RCT tier 2 Not serious	Not serious	The population was relevant, and the endpoint measured of direct relevance for the health outcome Not serious	The results was similar Not serious	Several possible side effects addressed by self-reporting using questionnaires, few effects reported Not large	Few effects reported No	No effect or low increase Yes	++++ High
Sleep disturbance								
Ruiz-Moreno et al. (2020), Puente et al. (2017),	Two RCTs tier 1, one	Differences could be explained from the time point of exposure Not serious	The population was relevant, and the endpoint measured of direct relevance	Self-reported data Not serious	Increase in self-reported insomnia for caffeine exposure in the evening in one RCT,	No	Time point for caffeine administration in the day varied	++++ High

Salinero et al. (2017) Initial rating: ++++	RCT tier 2 Not serious		for the health outcome Not serious		very few reported effects from caffeine administration in the morning (in two RCTs) Not large		No	

10 Appendix: Concentrations of caffeine in food

10.1 Literature search

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 03, 2020>
Date: 04.03.2020
Result: 768

1	Caffeine/	23096
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw,kf.	28718
3	1 or 2	33761
4	exp Food/ or exp Candy/ or Chocolate/ or Coffee/ or exp Tea/	1275251
5	(Food? or diet* or meal? or sustenance? or snack? or grocer* or Mint? or "Breath freshener?" or Gum or Chocolate? or Cocoa or Cacao or Confection? or Sweets or candy or candies or cake? or cookie? or oreo or Cereal? or Granola or "Instant oatmeal" or (Protein adj1 (bar? or powder? or shake? or concentrate? or whey)) or icecream or "ice cream" or yogurt? or pudding? or Beverage? or coffee or coffea or tea? or ((caffeinated or energy or fitness or sport? or cola or flavoured) adj (drink? or beverage? or milk or dairy or dairies)) or kombucha or matcha or guarana).tw,kf.	1181875
6	4 or 5	2139139
7	Food analysis/	20297
8	(Food adj2 (composition? or analysis)).tw,kf.	5248
9	7 or 8	24076
10	(("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2) adj2 (Concentration? or occurrence or content?)).tw,kf.	1601
11	3 and 9	114
12	6 and 10	673
13	11 or 12	768

Database: Embase 1974 to 2020 March 03
Date: 04.03.20
Result: 1007

1	Caffeine/	45388
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw,kw.	34790
3	1 or 2	51516
4	exp Food/ or Sugar confectionary/ or Breakfast cereal/ or Coffee/ or Tea/ or Herbal tea/ or Kombucha/ or Mate tea/ or Medicinal tea/	988922
5	(Food? or diet* or meal? or sustenance? or snack? or grocer* or Mint? or "Breath freshener?" or Gum or Chocolate? or Cocoa or Cacao or Confection? or Sweets or candy or candies or cake? or cookie? or oreo or Cereal? or Granola or "Instant oatmeal" or (Protein adj1 (bar? or powder? or shake? or concentrate? or whey)) or icecream or "ice cream" or yogurt? or pudding? or Beverage? or coffee or coffea or tea? or ((caffeinated or energy or fitness or sport? or cola or flavoured) adj (drink? or beverage? or milk or dairy or dairies)) or kombucha or matcha or guarana).tw,kw.	1507939
6	4 or 5	2115450
7	(Food adj2 (composition? or analysis)).tw,kw.	7302
8	Food composition/ or Food analysis/	44188
9	7 or 8	47823
10	(("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2) adj2 (Concentration? or occurrence or content?)).tw,kw.	1956
11	3 and 9	427
12	6 and 10	884
13	11 or 12	1251
14	limit 13 to (conference abstracts or embase)	1007

Database: Cochrane Central Register of Controlled Trials. Issue 3 of 12, March 2020
Date: 04.03.20
Result: 123 trials

#1	[mh ^"Caffeine"]	2050
#2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2)ti,ab	86
#3	#1 or #2	2127
#4	[mh "Food"]	32989
#5	[mh "Candy"]	773
#6	[mh ^"Chocolate"]	49
#7	[mh ^"Coffee"]	371
#8	[mh "Tea"]	469
#9	(Food? or diet* or meal? or sustenance? or snack? or grocer* or Mint? or "Breath freshener?" or Gum or Chocolate? or Cocoa or Cacao or Confection? or Sweets or candy or candies or cake? or cookie? or oreo or Cereal? or Granola or "Instant oatmeal" or (Protein NEAR/1 (bar? or powder? or shake? or concentrate? or whey)) or icecream or "ice cream" or yogurt? or pudding? or Beverage? or coffee or coffea or tea? or ((caffeinated or energy or fitness or sport? or cola or flavoured) NEXT (drink? or beverage? or milk or dairy or dairies)) or kombucha or matcha or guarana):ti,ab	126345
#10	#4 or #5 or #6 or #7 or #8 or #9	140631
#11	[mh ^"Food analysis"]	168
#12	(Food NEAR/2 (composition? or analysis)):ti,ab	280
#13	#11 or #12	448
#14	(("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2) NEAR/2 (Concentration? or occurrence or content?)):ti,ab	207
#15	#3 and #13	0
#16	#10 and #14	123
#17	#15 or #16	123

Database: Web of Science
Date: 04.03.20
Result: 1036

# 7	1,036	#6 OR #5 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 6	977	#4 AND #2 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 5	73	#3 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

# 4	1,728	TOPIC: ((("1,3,7 trimethylxanthine" OR "1,3,7 trimethyl xanthine" OR "caffein$" OR "coffein*" OR "methyltheobromine" OR "theine" OR "3g6a5w338e" OR "58-08-2" OR "C8H10N4O2") NEAR/1 ("Concentration$" OR "occurrence" OR "content$"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 3	11,288	TOPIC: (("Food" NEAR/1 ("composition$" OR "analysis"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 2	1,726,756	TOPIC: (("Food$" OR "diet*" OR "meal$" OR "sustenance$" OR "snack$" OR "grocer*" OR "Mint$" OR "Breath freshener$" OR "Gum" OR "Chocolate$" OR "Cocoa" OR "Cacao" OR "Confection$" OR "Sweets" OR "candy" OR "candies" OR "cake$" OR "cookie$" OR "oreo" OR "Cereal$" OR "Granola" OR "Instant oatmeal" OR ("Protein" NEAR/0 ("bar$" OR "powder$" OR "shake$" OR "concentrate$" OR "whey")) OR "icecream" OR "ice cream" OR "yogurt$" OR "pudding$" OR "Beverage$" OR "coffee" OR "coffea" OR "tea$" OR (("caffeinated" OR "energy" OR "fitness" OR "sport$" OR "cola" OR "flavoured") NEAR/0 ("drink$" OR "beverage$" OR "milk" OR "dairy" OR "dairies")) OR "kombucha" OR "matcha" OR "guarana")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 1	33,598	TOPIC: (("1,3,7 trimethylxanthine" OR "1,3,7 trimethyl xanthine" OR "caffein$" OR "coffein*" OR "methyltheobromine" OR "theine" OR "3g6a5w338e" OR "58-08-2" OR "C8H10N4O2")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

Database: PsycINFO <1806 to February Week 4 2020>

Date: 04.03.20

Result: 76

1	caffeine/	2805
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw.	4695
3	1 or 2	4790
4	exp Food/ or "Beverages (Nonalcoholic)"/	15836
5	(Food? or diet* or meal? or sustenance? or snack? or grocer* or Mint? or "Breath freshener?" or Gum or Chocolate? or Cocoa or Cacao or Confection? or Sweets or candy or candies or cake? or cookie? or oreo or Cereal? or Granola or "Instant oatmeal" or (Protein adj1 (bar? or powder? or shake? or concentrate? or whey)) or icecream or "ice cream" or yogurt? or pudding? or Beverage? or coffee or coffea or tea? or ((caffeinated or energy or fitness or sport? or cola or flavoured) adj (drink? or beverage? or milk or dairy or dairies)) or kombucha or matcha or guarana).tw.	185262

6	4 or 5	185974
7	(Food adj2 (composition? or analysis)).tw.	397
8	(("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2) adj2 (Concentration? or occurrence or content?)).tw.	125
9	3 and 7	0
10	6 and 8	76
11	9 or 10	76

Database: Epistemonikos

Date: 03.03.2020

Result: 11

(title:(coffeine OR caffeine) OR abstract:(coffeine OR caffeine)) AND (title:("Food analysis" OR "Food composition" OR "Food compositions") OR abstract:("Food analysis" OR "Food composition" OR "Food compositions")) OR (title:(Food* OR drink* OR beverage* OR snack*) OR abstract:(Food* OR drink* OR beverage* OR snack*)) AND (title:("caffeine concentration" OR "caffeine concentrations" OR "coffeine concentration" OR "coffeine concentrations" OR "caffeine content" OR "caffeine contents") OR abstract:("caffeine concentration" OR "caffeine concentrations" OR "coffeine concentration" OR "coffeine concentrations" OR "caffeine content" OR "caffeine contents"))

10.2 Assessment of full-text articles – excluded publications

An overview of the publications considered not to fulfil the eligibility criteria is given in Table 10.2-1.

Table 10.2-1. Publications considered not eligible.

Reference	Reason for exclusion
Ahuja et al. (2006)	Outcome
Andersen et al. (2019)	Outcome
Arai et al. (2015)	Outcome
Assemat et al. (2005)	Outcome
Attipoe et al. (2016a)	Outcome
Attipoe et al. (2014)	Publication type
Babova et al. (2016)	Outcome
Balyaya and Clifford (1995)	Outcome
Bartella et al. (2019)	Outcome
Bempong et al. (1993)	Outcome
Bicho et al. (2011a)	Outcome

Reference	Reason for exclusion
Bicho et al. (2011b)	Outcome
Caporaso et al. (2018)	Outcome
Casal et al. (2000)	Outcome
Ciftaslan and Inanc (2017)	Outcome
Clifford and Ramirezmartinez (1991)	Outcome
Cruz et al. (2012)	Outcome
da Silva et al. (2018)	Outcome
Danhelova et al. (2012)	Outcome
del Campo et al. (2010)	Outcome
Dias and Benassi (2015)	Outcome
Do et al. (2019)	Outcome
Goldberger et al. (2003)	Publication type
Goodacre and Gilbert (1999)	Outcome
Goto and Yoshida (1999)	Outcome
Gotti et al. (2004)	Outcome
Gramza-Michalowska (2013)	Outcome
Hakim et al. (2000)	Outcome
Hanci et al. (2013)	Language
Hecimovic et al. (2011)	Outcome
Injac et al. (2008)	Outcome
Karadeniz and Koca (2009)	Outcome
Khanum et al. (2015)	Outcome
Khokhar and Magnusdottir (2002)	Outcome
Komes et al. (2009)	Outcome
Ky et al. (2001)	Outcome
Lisko et al. (2017)	Outcome
Litt and Nagy (1974)	Outcome
Luca et al. (2016)	Outcome
Madison et al. (1976)	Outcome
Maier and Weidner (2000)	Outcome
Malafarina and Cabrerizo (2015)	Publication type
McCusker et al. (2003)	Outcome
Menden (1976)	Publication type
Monte and Ashoor (1985)	Outcome
Nekouei et al. (2014)	Publication type
Newton (1979)	Outcome
Obanda et al. (1997)	Outcome
Passos et al. (2017)	Outcome
Plonka (2012)	Outcome
Poroch-Seritan et al. (2018)	Outcome
Regan and Shakalisava (2005)	Outcome
Santos and Rangel (2012)	Outcome
Schakel et al. (2003)	Outcome
Segneanu et al. (2012)	Outcome
Self and Cossey (2016)	Publication type
Severini et al. (2016)	Outcome
Trandafir et al. (2013)	Outcome
Weidner and Istvan (1985)	Publication type
Yeh and Kuo (1998)	Language
Zukiewicz-Sobczak et al. (2018)	Language

10.3 Methodological quality

An overview of the included articles, all with a total score of 3.5 or higher, is given in Table 10.3-1. An overview of articles excluded due to a total score less than 3.5 is shown in Table 10.3-2.

Table 10.3-1. An overview of the scoring of the caffeine analyses in the included articles.

Reference	How appropriate was the solvent used for the extraction method?	Which instrumental analysis was used?	Which validation method was used, and how were the data presented?	Total score
Ali et al. (2017)	3.5	4.0	3.5	3.6
Angelino et al. (2018)	4.25	4.75	4.25	4.35
Arce et al. (1998)	4.25	4.0	4.0	4.05
Armenta et al. (2005)	3.75	3.25	3.75	3.65
Ayala et al. (2009)	3.5	4.0	3.75	3.75
Bell et al. (1996)	4.25	3.25	3.5	3.6
Berger and Berger (2013)	4.0	3.5	3.5	3.6
Boros et al. (2016)	4.25	3.5	3.5	3.65
Candeias et al. (2009)	4.0	3.5	4.5	4.2
Caudle et al. (2001)	4.0	3.5	3.9	3.84
Chin et al. (2008)	4.0	3.5	4.0	3.9
Chou and Bell (2007)	4	3,5	3,25	3.5
Czernicka et al. (2017)	4.0	3.5	4.0	3.9
Elik et al. (2019)	3.5	4.0	5.0	4.5
Gennaro and Abrigo (1992)	4.25	4.0	3.25	3.6
Gilbert et al. (1976)	4.75	4.5	3.0	3.65
Grand and Bell (1997)	4.25	3.75	3.5	3.7
Groisser (1978)	3,75	3	3,5	3.5
Hawthorne et al. (1992)	3.75	4.5	4.5	4.35
Jeszka-Skowron et al. (2018)	4.75	4.75	4.5	4.6
Jimidar et al. (1993)	4.25	4.0	4.0	4.05

Reference	How appropriate was the solvent used for the extraction method?	Which instrumental analysis was used?	Which validation method was used, and how were the data presented?	Total score
Khasanov et al. (2005)	4.0	3.75	3.75	3.8
Lage-Yusty et al. (2019)	3.5	3.75	4.5	4.15
Lino and Pena (2010)	3.75	3.5	4.0	3.85
Liotta et al. (2012)	3.75	3.75	4.5	4.2
Llorent-Martinez et al. (2005)	3.75	3.75	4.0	3.9
Lucena et al. (2005)	3.75	3.75	4.0	3.9
Ludwig et al. (2014)	3.75	4.0	4.0	3.95
Lugasi et al. (2015)	4.25	3.75	4.0	4.0
Manchon et al. (2013)	4.25	3.75	4.0	4.0
McCusker et al. (2006b)	3.5	4.5	4.5	4.3
Muller et al. (2014)	4.0	4.75	4.75	4.6
Musilova and Kubickova (2018)	4.25	4.0	3.5	3.75
Oellig et al. (2018)	4.25	3.65	3.65	3.77
Paradkar and Irudayaraj (2002)	4.25	4	3.25	3.6
Ranic et al. (2015)	4.0	3.5	3.5	3.6
Redivo et al. (2018)	4.25	3.5	3.75	3.8
Reto et al. (2007)	4.25	4.0	4.5	4.35
Rostagno et al. (2011)	4.0	4.0	4.5	4.3
Rudolph et al. (2012)	4.0	4.0	4.25	4.15
Rybak et al. (2015)	3.5	4.75	3.75	3.9
Sanchez (2017)	4.25	4.0	3.25	3.6
Shannon et al. (2018)	4.25	3.75	3.5	3.7
Sik (2012)	4.0	3.75	4.25	4.1
Srdjenovic et al. (2008)	4.0	3.75	4.25	4.1
Todorovic et al. (2015)	4.0	3.75	3.5	3.65
Torres et al. (2014)	3.75	3.75	3.75	3.75
Turak et al. (2017)	4.0	3.75	4.25	4.1

Reference	How appropriate was the solvent used for the extraction method?	Which instrumental analysis was used?	Which validation method was used, and how were the data presented?	Total score
Tzanavaras and Themelis (2007)	4.0	3.75	4.0	3.95
Vasilescu et al. (2015)	4.0	3.75	3.75	3.8
Vochyanova et al. (2014)	4.0	3.75	3.75	3.8
Waizenegger et al. (2011)	3.5	3.75	3.5	3.55
Weiss and Anderton (2003)	4.0	3.75	3.5	3.65

Table 10.3-2. An overview of the scoring in articles excluded due to a total score less than 3.5.

Reference	How appropriate was the solvent used for the extraction method?	Which instrumental analysis was used?	Which validation method was used, and how were the data presented?	Total score
Alanon et al. (2016)	4	3.5	2.25	2.9
Albanese et al. (2009)	3.75	3	3	3.2
Alpdogan et al. (2002)	4	3.25	2.75	3.1
Attipoe et al. (2016b)	2.25	2.75	2.75	2.7
Bunker and McWilliams (1979)	2.0	2.0	2.0	2
Caporaso et al. (2014)	3.5	3.5	2.5	2.9
Caprioli et al. (2015)	Not possible to score methods			
Demir et al. (2016)	3.0	3.0	1.0	1.8
Derossi et al. (2018)	4	3.5	2.5	3
Fujioka and Shibamoto (2008)	Not possible to score methods			
Horzic et al. (2009)	3.75	4	2.5	3.1
Ivanisova et al. (2019)	3.25	4	1.25	2.2
James (1989)	Not possible to score methods			
Kazimierczak et al. (2015)	4.25	4	1.75	2.7
Komes et al. (2010)	3.75	3.75	1.5	2.4
McCusker et al. (2006a)	3	3.5	3	3.1

Reference	How appropriate was the solvent used for the extraction method?	Which instrumental analysis was used?	Which validation method was used, and how were the data presented?	Total score
Smith et al. (2016)	4	3	3	3.2

10.4. Caffeine concentrations in food, details

Espresso coffee

A total of 89 analysis samples of espressos were available in five papers retrieved from the literature search. Angelino et al. (2018) provided 57 analyses of espressos from espresso capsules. Ludwig et al. (2014) provided 26 analyses of espressos bought in Italy, Scotland, and Spain. Rudolph et al. (2012) provided four analyses from capsules, and McCusker et al. (2006b) and Candeias et al. (2009) each provided one sample.

In this opinion the caffeine value of 268 mg/100 g is used for espresso. This is the median caffeine value for all espressos from the literature search included in the database. This value was used for espresso, and for all espresso used in espresso-based coffee drinks, such as cappuccino and caffè latte.

The publication by Angelino et al., (2018) which provided as many as 57 analyses of espresso coffee may have influenced the median value of espresso.

Filter brewed coffee

A total of 17 analysis samples of filter brewed coffee were available in three papers retrieved from the literature search. Bell et al. (1996) provided 12 analyses of filter brewed coffee. Rudolph et al. (2012) provided 4 analyses, and Gilbert et al. (1976) provided 1 sample of filter brewed coffee.

In this opinion the caffeine value of 40 mg/100 g is used for filter brewed coffee. This is the median caffeine value for all filter brewed coffees from the literature search included in the database.

Instant coffee

A total of 11 samples of instant coffee was available from the literature search. The data were from three different papers. Ludwig et al. (2014) provided nine analyses of instant coffee. Rudolph et al. (2012) provided two analyses, and Gilbert et al. (1976) provided one sample of instant coffee.

In this opinion the caffeine value of 44 mg/100 g is used for instant coffee. This is the median caffeine value for all instant coffees from the literature search included in the database.

Black tea

A total of 65 samples of black tea was available from the literature search. The data were compiled from eight different papers. Groisser et al. (1978) provided 31 analyses of black tea. Boros et al. (2016) provided 12 analyses of black tea, Chin et al. (2008) provided 11 analyses, Czernicka et al. (2017) provided six samples, Rudolph et al. (2012) provided two samples, and Rostagno et al. (2011), Srdjenovic et al. (2008), Musilova and Kubickova (2018) each provided one sample of black tea.

In this opinion the value of 22 mg/100g is used for black tea. This is the median caffeine value for all black tea samples from the literature search included in the database.

Green tea

A total of 42 samples of green tea was available from the literature search. The data were compiled from eight different papers. Groisser et al. (1978) provided 31 analyses of green tea. Boros et al. (2016) provided 12 analyses of green tea, Chin et al. (2008) provided 11 analyses, Czernicka et al. (2017) provided six samples, Rudolph et al. (2012) provided two samples, and Rostagno et al. (2011), Srdjenovic et al. (2008), Musilova and Kubickova (2018) each provided one sample of green tea.

In this opinion the value of 19 mg/100 g is used for green tea. This is the median caffeine value for all green tea samples from the literature search included in the database.

Energy drinks

The caffeine concentration in energy drinks was set to 32 mg/100 g based on the available energy drinks on the Norwegian market at present. The same level was used in the risk evaluation of intake of energy drinks conducted by VKM in 2019 after a recommendation from the Norwegian Food Safety Authority. The concentration is comparable to the median caffeine value from the literature search of 30 mg/100 g (Table 3.1.4.1-1).

Cola drinks with caffeine

VKM decided to use an average of the most popular cola drinks in Norway. An average caffeine value of 10 mg/100 g was chosen. This is comparable to the median caffeine value from the literature search of 10 mg/100 g.

In the Ungkost 3 study, exposure of caffeine from soda beverages could not be estimated. The web-based diary did not ask for specifications of whether the registered soda beverages were with or without caffeine.

Dark chocolate varieties

A total of 18 samples of dark chocolate was available from the literature search. The data were compiled from two different papers. Todorovic et al. (2015) provided 7 analyses, and Langer et al. (2011) provided 11 analyses of dark chocolate.

In this opinion, the caffeine value of 90 mg/100 g is used for dark chocolate. This is the median caffeine value for all dark chocolate samples from the literature search included in the database.

Light chocolate varieties

A total of nine samples of light chocolate was available from the literature search. The data were compiled from four different papers. Sredjenovi et al. (2008) and Rudolph et al. (2012) provided one analyse each, Langer et al. (2011) provided 2 analyses, and Todorovic et al. (2015) provided five analyses of light chocolate.

In this opinion the caffeine value of 19 mg/100g is used for light chocolate. This is the median caffeine value for all light chocolate samples from the literature search included in the database.

Cocoa powder

A total of 13 samples of cocoa powder was available from the literature search. The data were compiled from four different papers. Sredjenovi et al. (2008) provided one analyse, Todorovic et al. (2015) and Russo et al. (2018) provided two analyses each, and Zoumas et al. (1980) provided eight analyses of cocoa powder.

In this opinion the caffeine value of 210 mg/100g is used for cocoa powder. This is the median caffeine value for all cocoa powder samples from the literature search included in the database. The cocoa powder caffeine value was used in recipes in which cocoa powder was an ingredient, e.g. cakes and hot cocoa.

10.5 Intake of caffeine containing food

Norkost 3

Table 10.5-1 presents the mean intake of foods containing caffeine, on group level, in gram per person per day (habitual intake), in Norkost 3. Foods are grouped according to food categories in the Norwegian food composition table. Food items belonging to the food categories presented but not containing caffeine are not included in the estimations. Coffee is the food item with caffeine, with the highest intake in gram per person per day, in the diet of participants of Norkost 3. Of the 530 gram per person per day of total coffee intake, 410 gram where filter coffee.

Table 10.5-1. Mean and 95-percentile (P95) intake of caffeine containing foods from Norkost 3, divided in food groups (n=1787).

Food group	Mean intake, g/day	P95, g/day
Coffee	517	1437
Filtered coffee	505	1400
Instant coffee	47	300

Food group	Mean intake, g/day	P95, g/day
Espresso	12	74
Tea	166	766
Black tea	126	617
Green tea	40	286
Cola drinks	128	718
Energy drinks	2	na
Cocoa drinks (hot and cold)	16	146
Chocolate, all types, light, dark and bars	9	43
Bakery (cakes, biscuits etc.)	4	30

Table 10.5-2 presents the mean intake of foods containing caffeine, on group level, in gram per person per day (habitual intake), in Ungkost 3, 12-13 years old adolescents. Foods are grouped according to food categories in the Norwegian food composition table. Food items belonging to the food categories presented but not containing caffeine are not included in the estimations.

Table 10.5-2. Mean and 95-percentile (P95) intake of caffeine containing foods from Ungkost 3, 13-year-olds, divided in food groups (n=687).

Food group	Mean intake, g/day	P95, g/day
Coffee	1	na
Instant coffee	1	na
Espresso	>1	na
Tea	23	150
Black tea	20	125
Green tea	2	na
Energy drinks	5	na
Cocoa drinks (hot and cold)	44	200
Chocolate, all types, light, dark and bars	9	38
Bakery (cakes, biscuits etc.)	11	68

Table 10.5-3. Mean and 95-percentile (P95) intake of caffeine containing foods from Ungkost 3, 9-year-olds, divided in food groups (n=636).

Food group	Mean intake, g/day	P95, g/day
Tea	23	150
Black tea	20	125
Green tea	2	na
Cocoa drinks (hot and cold)	44	200
Chocolate, all types, light, dark and bars	9	38
Bakery (cakes, biscuits etc.)	6	40

Table 10.5-4. Mean and 95-percentile (P95) intake of caffeine containing foods from Ungkost 3, 4-year-olds, divided in food groups (n=399).

Food group	Mean intake, g/day	P95, g/day
Cocoa drinks	19	100
Bakery	5	31
Chocolate	3	13
Icecream	3	20
Tea	2	<1
Spread	1	10

Table 10.5-5. Mean and 95-percentile (P95) intake of caffeine containing foods from Tromsø 7, divided in food groups (n=11.425).

Food group	Mean intake, g/day	P95, g/day
Coffee	927	2800

Food group	Mean intake, g/day	P95, g/day
Filter and boiled coffee	808	2300
Instant coffee	110	600
Espresso	9	60
Tea	136	614
Black tea (hot and ice tea)	96	400
Green tea	40	200
Cocoa drinks (hot and cold)	10	42
Bakery (cakes and biscuits)	4	16
Chocolate	9	30
Spread	<1	2

Table 10.5-6. Mean, median and 95-percentile (P95) intake of caffeine containing foods from EuroMix, divided in food groups (n=144).

Food group	Mean intake, g/day	P95, g/day
Coffee	304	798
Filter and boiled coffee	265	697
Instant coffee	24	181
Espresso	15	118
Tea	151	682
Black tea (hot and ice tea)	119	538
Green tea	32	218
Cocoa drinks (hot and cold)	9	na[1]
Cola drinks	91	495
Energy drinks	5	na[1]
Bakery (cakes and biscuits)	3	34
Chocolate	8	38

Food group	Mean intake, g/day	P95, g/day
Spread	<1	na[1]

[1]na: not applicable, less than 5% of the participants have reported this drink.

11 Appendix: Data on concentrations of caffeine in PCPs

11.1 Literature search

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 03, 2020>
Date: 04.03.2020
Result: 56

1	Caffeine/	23103
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw,kf.	28747
3	1 or 2	33791
4	exp Cosmetics/ or Skin care/ or Soap/	53979
5	(cosmetic? or ((care or beauty or face or body) adj (product? or care)) or sunscreen* or "sun screen*" or ((skin or "skin care" or body or dermal) adj (cream? or lotion? or oil? or moisturi?er? or salve? or butter or toner or exfoliator? or cleanser? or mask? or peeling? or scrub?)) or "setting spray" or lipstick? or "lip stick?" or lipgloss or "lip gloss*" or lipbalm or "lip balm?" or mascara? or eyeliner? or "eye shadow?" or eyeshadow or "eyebrow pencil?" or blush* or rouge? or facepowder? or "face powder?" or foundation* or perfume? or concealer? or deodourant? or deodorant? or antipersipirant? or "anti persipirant?" or (hair adj (care or preparation? or spray? or bleech* or dye? or rinse?)) or shampoo? or conditioner? or serum? or ((lip or skin or face) adj primer?) or "mouth wash*" or percutafeine or (shower adj (gel? or soap? or milk?)) or "body wash*" or toiletry or toiletries).tw,kf.	1166465
6	4 or 5	1207640
7	(Concentration? or occurrence or content? or composition? or analysis).tw,kf.	6382284
8	3 and 6 and 7	932
9	exp Europe/	1394232

10	(Europe or european or Abkhazia* or Abkhaz or Albania or Albanian? or Andorra or Andorran? or Armenia or Armenian? or Austria* or Azerbaijan* or Balkan or Basque? or Belarus or Belarusian? or Belgium or Bosnia or Herzegovina or Bosnian? or Bulgaria* or Catalan? or Croatia or Croatian? or "Czech Republic" or Czech? or Danish or Denmark or Dutch or Estonia or Estonian? or "Faroe Islands" or Faroes* or Finland or Finnish or France or French or Georgia or Georgian? or German? or Germany or Greece or Greek? or Greenland or Guernsey or Hebrides or Hungarian? or Hungary or Iceland or Icelandic? or Ireland or Irish or "Isle of Man" or Italian? or Italy or "Jan Mayen" or Jersey or Kazakh* or Kosovo or Kosovar? or Kosovan? or Latvia or Latvian? or Liechtenstein or Lithuania or Lithuanian? or Luxembourg* or Macedonia* or Malta or Maltes* or Mingrelian? or Moldova or Moldovian? or Monaco or Monegasque? or Monacan? or Montenegrin? or Montenegro or Netherland* or Norway or Norwegian? or Poland or Polish or Portugal or Portuguese or Romania or Romanian? or Russia or Russian? or "San Marino" or Sammarinese or Scots or Scottish or Serbia or Serbian? or Sicily or Sicilian? or Slovak* or Slovakia or Sloven* or Slovenia or "South Ossetia" or "South* Caucasus" or Spain or Spanish or Svalbard or Sweden or Swedish or Switzerland or Transcaucasia or Turkey or Turkish or Ukraine or Ukrainian? or "United Kingdom" or Britain or British or England or "Vatican City" or Wales or Welsh or aaland or aalandi* or Scandinavia*).tw,kf.	1327113
11	9 or 10	2095893
12	8 and 11	56

Database: Embase 1974 to 2020 March 03
Date: 04.03.2020
Result: 84

1	Caffeine/	45388
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw,kw.	34790
3	1 or 2	51516
4	exp Cosmetic/ or Sunscreen/ or Skin care/ or Soap/ or Lotion/	131590
5	(cosmetic? or ((care or beauty or face or body) adj (product? or care)) or sunscreen* or "sun screen*" or ((skin or "skin care" or body or dermal) adj (cream? or lotion? or oil? or moisturi?er? or salve? or butter or toner or	1557435

	exfoliator? or cleanser? or mask? or peeling? or scrub?)) or "setting spray" or lipstick? or "lip stick?" or lipgloss or "lip gloss*" or lipbalm or "lip balm?" or mascara? or eyeliner? or "eye shadow?" or eyeshadow or "eyebrow pencil?" or blush* or rouge? or facepowder? or "face powder?" or foundation* or perfume? or concealer? or deodourant? or deodorant? or antipersipirant? or "anti persipirant?" or (hair adj (care or preparation? or spray? or bleech* or dye? or rinse?)) or shampoo? or conditioner? or serum? or ((lip or skin or face) adj primer?) or "mouth wash*" or percutafeine or (shower adj (gel? or soap? or milk?)) or "body wash*" or toiletry or toiletries).tw,kw.	
6	4 or 5	1653378
7	(Concentration? or occurrence or content? or composition? or analysis).tw,kw.	8167580
8	3 and 6 and 7	1556
9	exp Europe/	1537132
10	(Europe or european or Abkhazia* or Abkhaz or Albania or Albanian? or Andorra or Andorran? or Armenia or Armenian? or Austria* or Azerbaijan* or Balkan or Basque? or Belarus or Belarusian? or Belgium or Bosnia or Herzegovina or Bosnian? or Bulgaria* or Catalan? or Croatia or Croatian? or "Czech Republic" or Czech? or Danish or Denmark or Dutch or Estonia or Estonian? or "Faroe Islands" or Faroes* or Finland or Finnish or France or French or Georgia or Georgian? or German? or Germany or Greece or Greek? or Greenland or Guernsey or Hebrides or Hungarian? or Hungary or Iceland or Icelandic? or Ireland or Irish or "Isle of Man" or Italian? or Italy or "Jan Mayen" or Jersey or Kazakh* or Kosovo or Kosovar? or Kosovan? or Latvia or Latvian? or Liechtenstein or Lithuania or Lithuanian? or Luxembourg* or Macedonia* or Malta or Maltes* or Mingrelian? or Moldova or Moldovian? or Monaco or Monegasque? or Monacan? or Montenegrin? or Montenegro or Netherland* or Norway or Norwegian? or Poland or Polish or Portugal or Portuguese or Romania or Romanian? or Russia or Russian? or "San Marino" or Sammarinese or Scots or Scottish or Serbia or Serbian? or Sicily or Sicilian? or Slovak* or Slovakia or Sloven* or Slovenia or "South Ossetia" or "South* Caucasus" or Spain or Spanish or Svalbard or Sweden or Swedish or Switzerland or Transcaucasia or Turkey or Turkish or Ukraine or Ukrainian? or "United Kingdom" or Britain or British or England or "Vatican City" or Wales or Welsh or aaland or aalandi* or Scandinavia*).tw,kw.	2205103
11	9 or 10	2878003
12	8 and 11	93
13	Limit 12 to (conference abstracts or embase)	84

Database: PsycINFO <1806 to February Week 4 2020>
Date: 04.03.2020
Result: 1

1	Caffeine/	2805
2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2).tw.	4695
3	1 or 2	4790
4	(cosmetic? or ((care or beauty or face or body) adj (product? or care)) or sunscreen* or "sun screen*" or ((skin or "skin care" or body or dermal) adj (cream? or lotion? or oil? or moisturi?er? or salve? or butter or toner or exfoliator? or cleanser? or mask? or peeling? or scrub?)) or "setting spray" or lipstick? or "lip stick?" or lipgloss or "lip gloss*" or lipbalm or "lip balm?" or mascara? or eyeliner? or "eye shadow?" or eyeshadow or "eyebrow pencil?" or blush* or rouge? or facepowder? or "face powder?" or foundation* or perfume? or concealer? or deodourant? or deodorant? or antipersipirant? or "anti persipirant?" or (hair adj (care or preparation? or spray? or bleech* or dye? or rinse?)) or shampoo? or conditioner? or serum? or ((lip or skin or face) adj primer?) or "mouth wash*" or percutafeine or (shower adj (gel? or soap? or milk?)) or "body wash*" or toiletry or toiletries).tw.	90294
5	(Concentration? or occurrence or content? or composition? or analysis).tw.	958970
6	3 and 4 and 5	30
7	(Europe or european or Abkhazia* or Abkhaz or Albania or Albanian? or Andorra or Andorran? or Armenia or Armenian? or Austria* or Azerbaijan* or Balkan or Basque? or Belarus or Belarusian? or Belgium or Bosnia or Herzegovina or Bosnian? or Bulgaria* or Catalan? or Croatia or Croatian? or "Czech Republic" or Czech? or Danish or Denmark or Dutch or Estonia or Estonian? or "Faroe Islands" or Faroes* or Finland or Finnish or France or French or Georgia or Georgian? or German? or Germany or Greece or Greek? or Greenland or Guernsey or Hebrides or Hungarian? or Hungary or Iceland or Icelandic? or Ireland or Irish or "Isle of Man" or Italian? or Italy or "Jan mayen" or Jersey or Kazakh* or Kosovo or Kosovar? or Kosovan? or Latvia or Latvian? or Liechtenstein or Lithuania or Lithuanian? or Luxembourg* or Macedonia* or Malta or Maltes* or Mingrelian? or Moldova or Moldovian? or Monaco or Monegasque? or Monacan? or Montenegrin? or Montenegro or Netherland* or Norway or Norwegian? or Poland or Polish or	430161

	Portugal or Portuguese or Romania or Romanian? or Russia or Russian? or "San Marino" or Sammarinese or Scots or Scottish or Serbia or Serbian? or Sicily or Sicilian? or Slovak* or Slovakia or Sloven* or Slovenia or "South Ossetia" or "South* Caucasus" or Spain or Spanish or Svalbard or Sweden or Swedish or Switzerland or Transcaucasia or Turkey or Turkish or Ukraine or Ukrainian? or "United Kingdom" or Britain or British or England or "Vatican City" or Wales or Welsh or aaland or aalandi* or Scandinavia*).tw.	
8	6 and 7	1

Database: Cochrane Database of Systematic Reviews. Issue 3 of 12, March2020. Cochrane Central Register of Controlled Trials. Issue 3 of 12, March 2020
Date: 04.03.20
Result: 5 (4 trials, 1 systematic review)

#1	[mh ^"Caffeine"]	2050
#2	("1,3,7 trimethylxanthine" or "1,3,7 trimethyl xanthine" or caffein? or coffein* or methyltheobromine or theine or 3g6a5w338e or "58-08-2" or C8H10N4O2)ti,ab	86
#3	#1 or #2	2127
#4	[mh "Cosmetics"]	3146
#5	[mh ^"Skin care"]	330
#6	[mh ^"Soap"]	217
#7	(cosmetic? or ((care or beauty or face or body) NEXT (product? or care)) or sunscreen* or "sun screen*" or ((skin or "skin care" or body or dermal) NEXT (cream? or lotion? or oil? or moisturi?er? or salve? or butter or toner or exfoliator? or cleanser? or mask? or peeling? or scrub?)) or "setting spray" or lipstick? or "lip stick?" or lipgloss or "lip gloss*" or lipbalm or "lip balm?" or mascara? or eyeliner? or "eye shadow?" or eyeshadow or "eyebrow pencil?" or blush* or rouge? or facepowder? Or "face powder?" or foundation* or perfume? or concealer? or deodourant? or deodorant? or antipersipirant? or "anti persipirant?" or (hair NEXT (care or preparation? or spray? or bleech* or dye? or rinse?)) or shampoo? or conditioner? or serum? Or ((lip or skin or face) NEXT primer?) or "mouth wash*" or percutafeine or (shower NEXT (gel? or soap? or milk?)) or "body wash*" or toiletry or toiletries):ti,ab	107449
#8	#4 or #5 or #6 or #7	110475
#9	(Concentration? or occurrence or content? or composition? or analysis):ti,ab	436889
#10	[mh "Europe"]	27634

#11	(Europe or european or Abkhazia* or Abkhaz or Albania or Albanian? or Andorra or Andorran? or Armenia or Armenian? or Austria* or Azerbaijan* or Balkan or Basque? or Belarus or Belarusian? or Belgium or Bosnia or Herzegovina or Bosnian? or Bulgaria* or Catalan? or Croatia or Croatian? or "Czech Republic" or Czech? or Danish or Denmark or Dutch or Estonia or Estonian? or "Faroe Islands" or Faroes* or Finland or Finnish or France or French or Georgia or Georgian? or German? or Germany or Greece or Greek? or Greenland or Guernsey or Hebrides or Hungarian? or Hungary or Iceland or Icelandic? or Ireland or Irish or "Isle of Man" or Italian? or Italy or "Jan Mayen" or Jersey or Kazakh* or Kosovo or Kosovar? or Kosovan? or Latvia or Latvian? or Liechtenstein or Lithuania or Lithuanian? or Luxembourg* or Macedonia* or Malta or Maltes* or Mingrelian? or Moldova or Moldovian? or Monaco or Monegasque? or Monacan? or Montenegrin? or Montenegro or Netherland* or Norway or Norwegian? or Poland or Polish or Portugal or Portuguese or Romania or Romanian? or Russia or Russian? or "San Marino" or Sammarinese or Scots or Scottish or Serbia or Serbian? or Sicily or Sicilian? or Slovak* or Slovakia or Sloven* or Slovenia or "South Ossetia" or "South* Caucasus" or Spain or Spanish or Svalbard or Sweden or Swedish or Switzerland or Transcaucasia or Turkey or Turkish or Ukraine or Ukrainian? or "United Kingdom" or Britain or British or England or "Vatican City" or Wales or Welsh or aaland or aalandi* or Scandinavia*):ti,ab	110954
#12	#10 or #11	125861
#13	#3 and #8 and #9 and #12	5

Database: Web of Science
Date: 04.03.2020
Result: 138

# 5	138	#4 AND #3 AND #2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 4	3,549,514	TOPIC: (("Europe" OR "european" OR "Abkhazia*" OR "Abkhaz" OR "Albania" OR "Albanian$" OR "Andorra" OR "Andorran$" OR "Armenia" OR "Armenian$" OR "Austria*" OR "Azerbaijan*" OR "Balkan" OR "Basque$" OR "Belarus" OR "Belarusian$" OR "Belgium" OR "Bosnia" OR "Herzegovina" OR "Bosnian$" OR "Bulgaria*" OR "Catalan$" OR "Croatia" OR "Croatian$" OR "Czech Republic" OR "Czech$" OR "Danish" OR "Denmark" OR "Dutch" OR "Estonia" OR "Estonian$" OR "Faroe Islands" OR "Faroes*" OR "Finland" OR "Finnish" OR "France" OR "French" OR "Georgia" OR "Georgian$" OR "German$" OR "Germany" OR "Greece" OR "Greek$" OR "Greenland" OR "Guernsey" OR "Hebrides" OR "Hungarian$" OR "Hungary" OR "Iceland" OR "Icelandic$" OR "Ireland" OR "Irish" OR "Isle of Man" OR "Italian$" OR "Italy" OR "Jan mayen" OR "Jersey" OR "Kazakh*" OR "Kosovo" OR "Kosovar$" OR "Kosovan$" OR "Latvia" OR "Latvian$" OR "Liechtenstein" OR "Lithuania" OR "Lithuanian$" OR "Luxembourg*" OR "Macedonia*" OR "Malta" OR "Maltes*" OR "Mingrelian$" OR "Moldova" OR "Moldovian$" OR "Monaco" OR "Monegasque$" OR

		"Monacan$" OR "Montenegrin$" OR "Montenegro" OR "Netherland*" OR "Norway" OR "Norwegian$" OR "Poland" OR "Polish" OR "Portugal" OR "Portuguese" OR "Romania" OR "Romanian$" OR "Russia" OR "Russian$" OR "San Marino" OR "Sammarinese" OR "Scots" OR "Scottish" OR "Serbia" OR "Serbian$" OR "Sicily" OR "Sicilian$" OR "Slovak*" OR "Slovakia" OR "Sloven*" OR "Slovenia" OR "South Ossetia" OR "South* Caucasus" OR "Spain" OR "Spanish" OR "Svalbard" OR "Sweden" OR "Swedish" OR "Switzerland" OR "Transcaucasia" OR "Turkey" OR "Turkish" OR "Ukraine" OR "Ukrainian$" OR "United Kingdom" OR "Britain" OR "British" OR "England" OR "Vatican City" OR "Wales" OR "Welsh" OR "aaland" OR "aalandi*" OR "Scandinavia*")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 3	10,993,367	TOPIC: (("Concentration$" OR "occurrence" OR "content$" OR "composition$" OR "analysis")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 2	1,206,785	TOPIC: (("cosmetic$" OR (("care" OR "beauty" OR "face" OR "body") NEAR/0 ("product$" OR "care")) OR "sunscreen*" OR "sun screen*" OR (("skin" OR "skin care" OR "body" OR "dermal") NEAR/0 ("cream$" OR "lotion$" OR "oil$" OR "moisturi$er" or "moisturi$ers" OR "salve$" OR "butter" OR "toner" OR "exfoliator$" OR "cleanser$" OR "mask$" OR "peeling$" OR "scrub$")) OR "setting spray" OR "lipstick$" OR "lip stick$" OR "lipgloss" OR "lip gloss*" OR "lipbalm" OR "lip balm$" OR "mascara$" OR "eyeliner$" OR "eye shadow$" OR "eyeshadow" OR "eyebrow pencil$" OR "blush*" OR "rouge$" OR "facepowder$" OR "face powder$" OR "foundation*" OR "perfume$" OR "concealer$" OR "deodourant$" OR "deodorant$" OR "antipersipirant$" OR "anti persipirant$" OR ("hair" NEAR/0 ("care" OR "preparation$" OR "spray$" OR "bleech*" OR "dye$" OR "rinse$")) OR "shampoo$" OR "conditioner$" OR "serum$" OR (("lip" OR "skin" OR "face") NEAR/0 "primer$") OR "mouth wash*" OR "percutafeine" OR ("shower" NEAR/0 ("gel$" OR "soap$" OR "milk$")) OR "body wash" OR "toiletry" OR "toiletries")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 1	33,569	TOPIC: (("1,3,7 trimethylxanthine" OR "1,3,7 trimethyl xanthine" OR "caffein$" OR "coffein*" OR "methyltheobromine" OR "theine" OR "3g6a5w338e" OR "58-08-2" OR "C8H10N4O2")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

11.2 Assessment of full-text articles – excluded publications

An overview of the publications considered not to fulfil the eligibility criteria is given in Table 11.2-1.

Table 11.2-1. Publications considered not eligible.

Reference	Reason for exclusion
Sainio et al. (2000)	Outcome
Wojciechowska et al. (2014)	Outcome

11.3 Methodological quality

One article was included, and an overview of the scoring is given in Table 11.3-1. An overview of articles excluded due to a total score less than 3.5 is shown in Table 10.3-2.

Table 11.3-1. The scoring of the included article.

Reference	How appropriate was the solvent used for the extraction method?	Which instrumental analysis was used?	Which validation method was used, and how were the data presented?	Total score
Marchei et al. (2013)	4.0	4.5	4.5	4.4

11.4 Call for data on caffeine concentrations in PCPs

The call was as follows:

"Background

We are exposed to caffeine from various sources; food, caffeine supplements, cosmetics and personal care products. Therefore, estimates of the Norwegian population's total caffeine exposure should include multiple sources of caffeine.

For this reason, the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food, and Cosmetics at the Norwegian Scientific Committee for Food and Environment (VKM) has initiated a risk assessment of caffeine, which will include exposure estimates from multiple sources. Data on caffeine concentrations in cosmetics and personal care products are required to make estimates about exposure.

The protocol for this risk assessment is available here.

Overall objective

The purpose of this call for data is to offer the opportunity to submit documented information (published or unpublished) about concentrations of caffeine found in cosmetics and personal care products.

Requested information

VKM invites businesses and other interested public and private parties (including authorities, organisations, universities, research and other institutions, and companies) to submit information about concentrations of caffeine found in cosmetics and personal care products, including shampoo, hand soap, shower gels, moisturizing creams and lotions. In the risk assessment of caffeine from multiple sources, this information will be used for estimating caffeine exposure.

In addition to extensive information about the product being analysed, details should be included about the methods of analysis used. These details should include the methods used for validation of data, the limit of detection (LOD) and limit of quantification (LOQ).

Submission of data

The deadline for the submission of data for caffeine concentrations found in cosmetics and personal care products is 31 August 2020.

The information requested above should be submitted to VKM in electronic form, with an electronic cover letter containing contact details (name of contact person, name of company/organisation, e-mail address and telephone number) of the person responsible for the submission of data. All submissions will be treated confidentially."

12 Appendix: Meta-analysis

12.1 Database

Table 12.1-1. Overview of the cross-over design studies used in the meta-analysis of heart rate showing mean beats per minute, standard deviation (SD) and the number of participants for each treatment, and habitual caffeine consumption, time point for heart rate measurement after administration of test item (minutes) and caffeine dose administered (mg/kg bw per day).

Author	Year	Placebo			Caffeine			Subgroup	Time point	Dose
		Mean	SD	N	Mean	SD	N			
Dodd	2015	62.2	8.1	12	63.3	12.4	12	NC	80	1
Dodd	2015	62.1	9.2	12	59.3	9.3	12	HC	80	1
Ratamess	2018	65.8	10.4	16	68.5	9.0	16	NC	120	4
Ratamess	2018	66.0	12.1	16	62.7	9.8	16	HC	120	4
Ratamess	2018	65.8	10.4	16	64.1	11.3	16	NC	120	4
Ratamess	2018	66.0	12.1	16	61.2	5.7	16	HC	120	4
Ratamess	2018	65.9	9.3	16	72.5	10.5	16	NC	180	4
Ratamess	2018	65.5	11.7	16	64.7	10.0	16	HC	180	4
Ratamess	2018	65.9	9.3	16	66.8	12.0	16	NC	180	4
Ratamess	2018	65.5	11.7	16	63.9	6.3	16	HC	180	4
Ratamess	2018	67.3	10.3	16	68.7	11.0	16	NC	60	4
Ratamess	2018	65.7	12.0	16	61.2	7.7	16	HC	60	4
Ratamess	2018	67.3	10.3	16	63.4	12.2	16	NC	60	4
Ratamess	2018	65.7	12.0	16	62.0	5.4	16	HC	60	4
Ruiz-Moreno	2019	52.0	8.0	19	53.0	9.0	19	LC	60	3

HC: high-consumer; LC: low-consumer; NC: none-consumer; blank: no habitual caffeine consumption reported

Table 12.1-2. Overview of the cross-over design studies used in the meta-analysis of blood pressure showing mean (mmHg), standard deviation (SE) and the number of participants for each treatment, and habitual caffeine consumption, time point for heart rate measurement after administration of test item (minutes) and caffeine dose administered (mg/kg bw per day).

Author	Year	Placebo			Caffeine			Sub-group	Time-point	Dose
		Mean	SD	N	Mean	SD	N			
Systolic blood pressure										
Dodd et al. (2015)	2015	114.5	5.8	12	114.8	8.6	12	NC	80	1
Dodd et al. (2015)	2015	114.9	12.0	12	119.7	13.4	12	HC	80	1

Author	Year	Placebo			Caffeine			Sub-group	Time-point	Dose
		Mean	SD	N	Mean	SD	N			
Ratamess et al. (2018)	2018	113.8	13.0	16	118.4	10.6	16	NC	120	3
Ratamess et al. (2018)	2018	113.6	9.3	16	111.3	9.2	16	HC	120	3
Ratamess et al. (2018)	2018	113.8	13.0	16	117.9	8.4	16	NC	120	4
Ratamess et al. (2018)	2018	113.6	9.3	16	116.7	11.4	16	HC	120	4
Ratamess et al. (2018)	2018	115.4	11.9	16	117.9	7.3	16	NC	180	3
Ratamess et al. (2018)	2018	116.6	9.8	16	114.5	9.8	16	HC	180	3
Ratamess et al. (2018)	2018	115.4	11.9	16	118.9	9.7	16	NC	180	4
Ratamess et al. (2018)	2018	116.6	9.8	16	116.4	10.1	16	HC	180	4
Ratamess et al. (2018)	2018	113.4	13.2	16	116.3	10.4	16	NC	60	3
Ratamess et al. (2018)	2018	114.4	7.0	16	109.8	8.9	16	HC	60	3
Ratamess et al. (2018)	2018	113.4	13.2	16	115.7	9.7	16	NC	60	4
Ratamess et al. (2018)	2018	114.4	7.0	16	112.6	9.5	16	HC	60	4
Vera et al. (2019)	2019	116.7	14.6	21	125.1	16.45	21	LC	30	4
Vera et al. (2019)	2019	111.8	10.0	19	115.4	8.11	19	HC	30	4
Vera et al. (2019)	2019	116.6	17.1	21	122.1	12.8	21	LC	60	4
Vera et al. (2019)	2019	112.6	6.3	19	117.4	13.4	19	HC	60	4
Vera et al. (2019)	2019	115.9	14.7	21	125.7	15.1	21	LC	90	4
Vera et al. (2019)	2019	113.4	9.7	19	117.7	11.1	19	HC	90	4

Author	Year	Placebo			Caffeine			Sub-group	Time-point	Dose
		Mean	SD	N	Mean	SD	N			
Diastolic blood pressure										
Dodd et al. (2015)	2015	75.8	7.9	12	75.0	8.9	12	NC	80	1
Dodd et al. (2015)	2015	75.8	13.7	12	83.1	9.2	12	HC	80	1
Ratamess et al. (2018)	2018	68.9	8.2	16	73.9	7.0	16	NC	120	3
Ratamess et al. (2018)	2018	68	6.1	16	68.2	7.5	16	HC	120	3
Ratamess et al. (2018)	2018	68.9	8.2	16	73.2	4.7	16	NC	120	4
Ratamess et al. (2018)	2018	68	6.1	16	68.7	11.4	16	HC	120	4
Ratamess et al. (2018)	2018	70.8	5.3	16	71.5	6.4	16	NC	180	3
Ratamess et al. (2018)	2018	68.7	6.3	16	67.8	7.5	16	HC	180	3
Ratamess et al. (2018)	2018	70.8	5.3	16	72.5	5.9	16	NC	180	4
Ratamess et al. (2018)	2018	68.7	6.3	16	69.7	11.9	16	HC	180	4
Ratamess et al. (2018)	2018	70.5	5.6	16	74.8	7.6	16	NC	60	3
Ratamess et al. (2018)	2018	68.5	4.9	16	67.3	8.9	16	HC	60	3
Ratamess et al. (2018)	2018	70.5	5.6	16	74.2	6.1	16	NC	60	4
Ratamess et al. (2018)	2018	68.5	4.9	16	66.7	8.8	16	HC	60	4
Vera et al. (2019)	2019	77.7	13.7	21	81.8	16.66	21	LC	30	4
Vera et al. (2019)	2019	75.2	10.6	19	77.4	12.29	19	HC	30	4
Vera et al. (2019)	2019	74.6	13.7	21	80.7	12.0	21	LC	60	4

Author	Year	Placebo			Caffeine			Sub-group	Time-point	Dose
		Mean	SD	N	Mean	SD	N			
Vera et al. (2019)	2019	74.1	8.1	19	78.7	12.2	19	HC	60	4
Vera et al. (2019)	2019	75.7	11.6	21	81.3	13.8	21	LC	90	4
Vera et al. (2019)	2019	74.6	8.7	19	77.2	8.9	19	HC	90	4
Zbinden-Foncea et al. (2018)	2018	71.4	5.0	10	81.2	11.3	10		60	5

HC: high-consumer; LC: low-consumer; NC: none-consumer; blank: no habitual caffeine consumption reported

12.2 Post-hoc meta-analysis

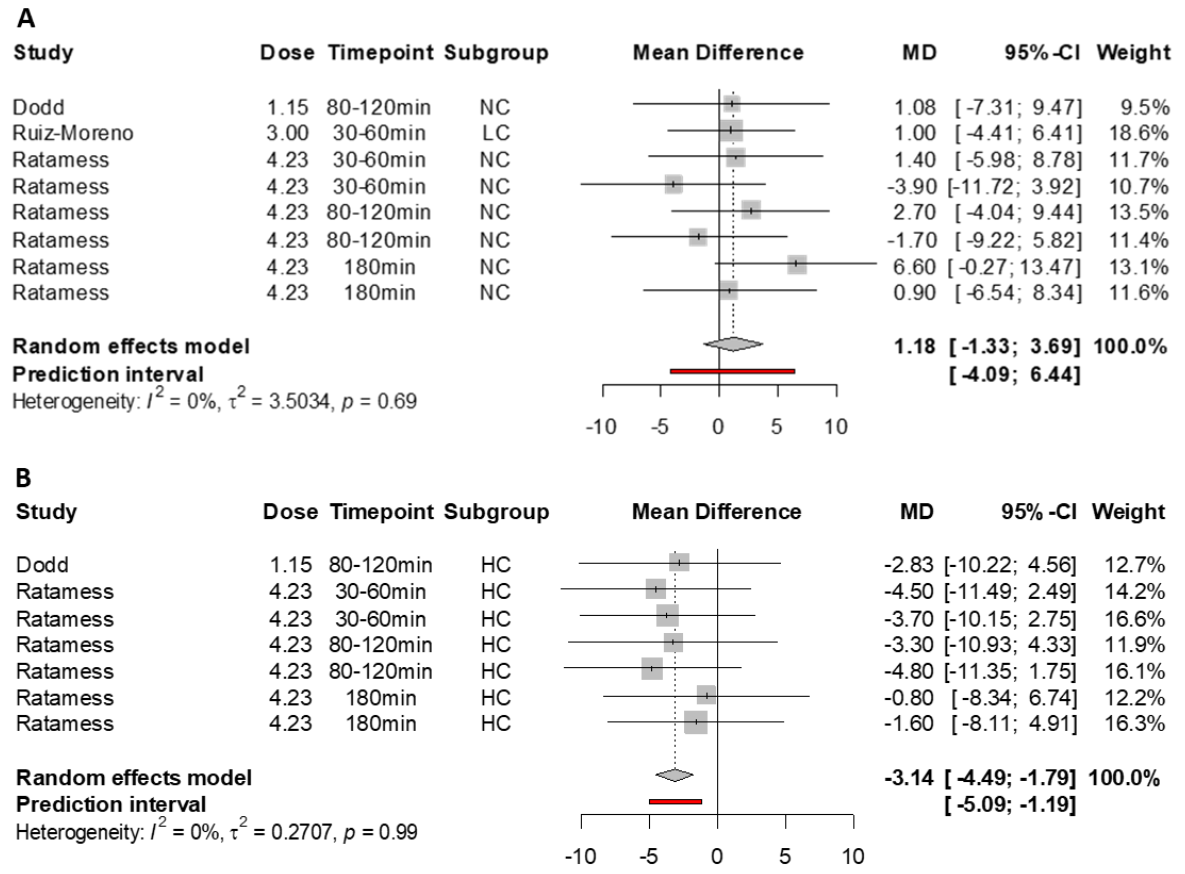

Figure 12.2-1. Meta-analysis heart rate after oral administration of caffeine or placebo habitual no/low consumers (A) and high consumers (B) of caffeine. CI: confidence interval; Dose: mg/kg bw per day; MD: mean difference; Subgroup: HC high habitual caffeine consumption, LC low habitual

caffeine consumption, NC no habitual caffeine consumption, blank: not reported; Time point: time between exposure and measurement of outcome.

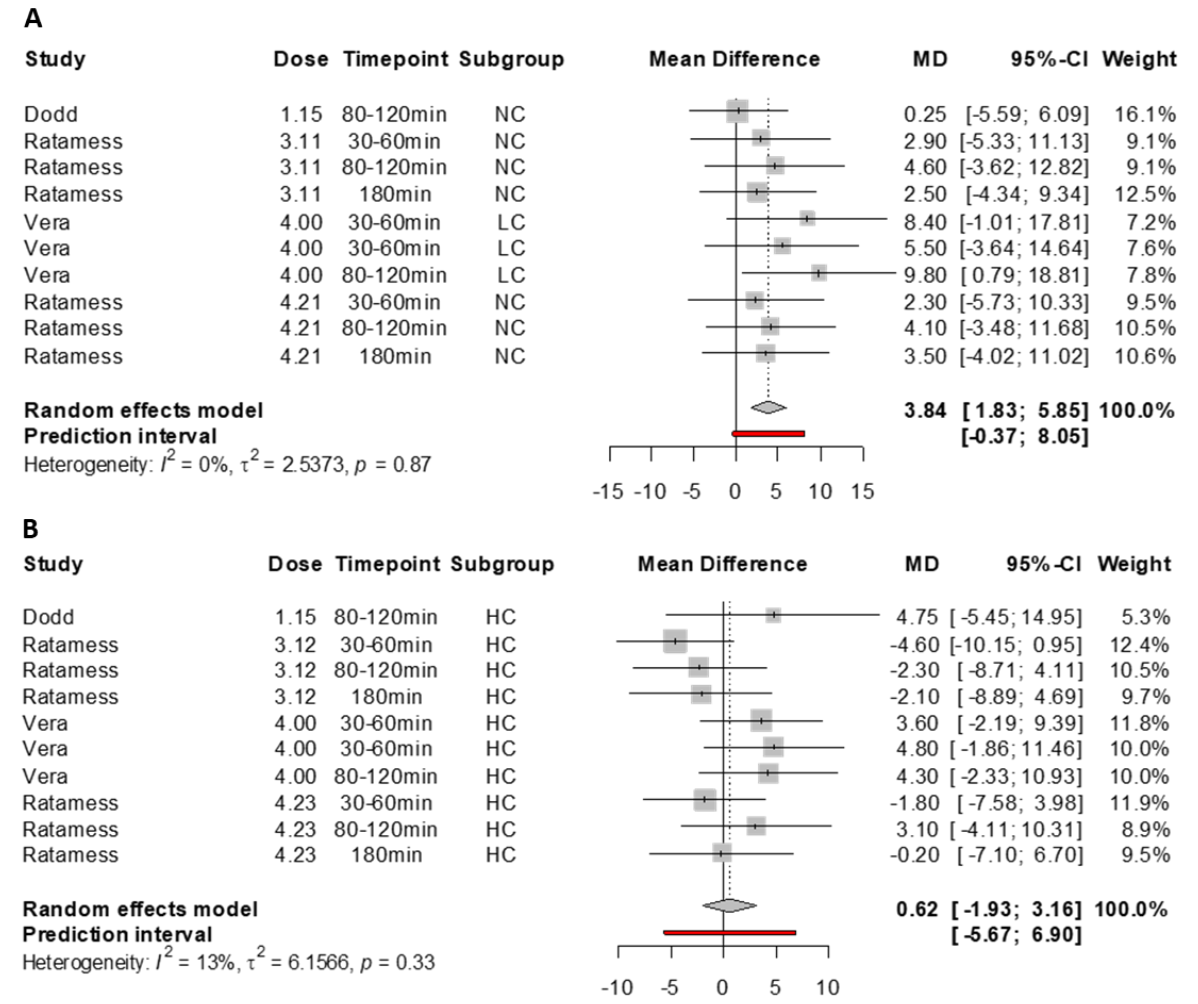

Figure 12.2-2. Meta-analysis on systolic blood pressure after oral administration of caffeine or placebo in habitual no/low consumers (A) and high consumers (B) of caffeine. CI: confidence interval; Dose: mg/kg bw per day; MD: mean difference; Subgroup: HC high habitual caffeine consumption, LC low habitual caffeine consumption, NC no habitual caffeine consumption, blank: not reported; Time point: time between exposure and measurement of outcome.

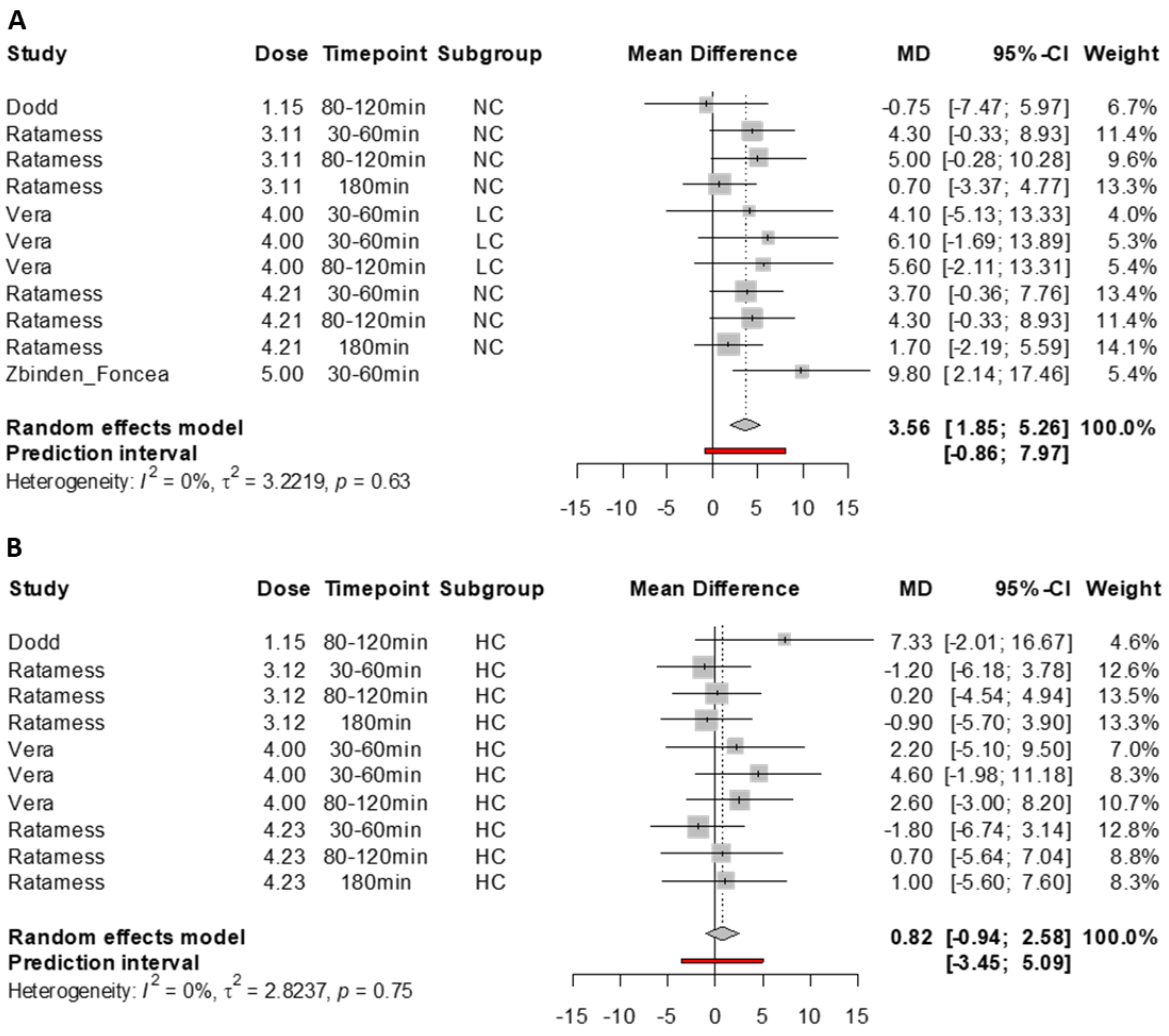

Figure 12.2-3. Meta-analysis on diastolic blood pressure after oral administration of caffeine or placebo in habitual no/low consumers (A) and high consumers (B) of caffeine. CI: confidence interval; Dose: mg/kg bw per day; MD: mean difference; Subgroup: HC high habitual caffeine consumption, LC low habitual caffeine consumption, NC no habitual caffeine consumption, blank: not reported; Time point: time between exposure and measurement of outcome.

13 Appendix: Deviations from the protocol

As only one article from the literature search for concentration data on caffeine in PCPs was considered eligible and of sufficient quality, VKM launched a "Call for data on caffeine concentrations in cosmetics and personal care products" (shown in Section 11.4) to offer the opportunity to submit concentrations of caffeine in cosmetics and PCPs.

In the search for occurrence data for caffeine in food the protocol planed a ranking of concentration data based upon country of origin. The literature search results were however not ranked in this way. All data on concentrations of caffeine in food was included if the data was evaluated with a high enough score in the quality assessment of analytical methods. Thus food composition data from other geographical regions than those presented in the protocol were included in this risk assessment.