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Risk assessment of "other substances" – Caffeine

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

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Competence of VKM experts

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

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Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet, NFSA), assessed the risk of "other substances" in food supplements and energy drinks sold in Norway. VKM has assessed the risk of doses given by NFSA. These risk assessments will provide NFSA with the scientific basis while regulating the addition of "other substances" to food supplements and other foods.

"Other substances" are described in the food supplement directive 2002/46/EC as *substances other than vitamins or minerals that have a nutritional or physiological effect*. It is added mainly to food supplements, but also to energy drinks and other foods. In this series of risk assessments of "other substances", VKM has not evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present risk assessment of caffeine is based on previous risk assessments and articles retrieved from a literature search.

According to information from NFSA, caffeine is an ingredient in food supplements and energy drinks sold in Norway. NFSA has requested a risk assessment of 100 and 300 mg/day of caffeine in food supplements, and of 32 mg/100 ml of caffeine in energy drinks. Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake were assessed.

The total exposure to caffeine from other sources than energy drinks, such as foods and cosmetic products, is not included in the risk assessment.

The main sources of caffeine in the diet include coffee, tea, caffeinated soft drinks (including energy drinks) and chocolate. The means and 95th percentiles of daily caffeine intake from all sources for adults (from 16 EU Member States) calculated by the European Food Safety Authority (EFSA) ranged from 37 to 319 mg and from 109 to 742 mg, respectively. The median daily caffeine intake from different sources among pregnant Norwegian women, self-reported at gestational weeks 17 and 30, was 126 mg/day pre-pregnancy, 44 mg/day at gestational week 17, and 62 mg/day at gestational week 30.

Caffeine is rapidly and completely absorbed after oral intake, and the peak plasma concentration can be reached within 30-120 minutes. Caffeine crosses the blood-brain barrier, the placental barrier and the blood-testicular barrier, and is excreted in breast milk.

Several studies and assessments addressing safety or risk of caffeine have been performed. With regard to caffeine intake and adverse birth weight-related outcomes, these outcomes were observed at all levels of caffeine intake, with no threshold below which this relationship was not observed (EFSA, 2015). In the risk characterization, VKM has applied the intake levels considered unlikely to cause adverse health effects in the new and comprehensive risk

assessment by EFSA (EFSA, 2015), also taking into account previous risk assessments and newer literature. The intake levels of caffeine for different population groups (children, adolescents, pregnant women and fetus, lactating women and the breastfed infant and adults) unlikely to cause adverse effects have been identified.

For the general adult population (not including pregnant women), these levels are

- Single intake of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) do not give rise to safety concerns.
- Intakes 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 adults in the general population, except for pregnant women (see below).
- Caffeine intake of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in adults.

For children and adolescents, these levels are:

- A daily intake of 3 mg/kg bw per day do not give rise to safety concerns.
- Caffeine doses of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents.

For pregnant women and the fetus, these levels are:

- 200 mg per day (about 3 mg/kg bw for a 70-kg adult) consumed throughout the day do not give rise to safety concerns.
- With regard to caffeine intake and adverse birth weight-related outcomes, it was concluded that these outcomes were observed at all levels of caffeine intake, with no threshold below which this relationship was not observed. It was considered that the risk becomes clinically relevant at total daily doses of about 200 mg of caffeine from all sources. Sengpiel et al. (2013) reported that caffeine intake from different sources was associated with lower birth weight, and that caffeine intake of 200 to 300 mg/day increased the odds for the baby being small for gestational age compared to 0 to 50 mg/day.

For lactating women and the breastfed infant, these levels are:

- Single doses of caffeine up to 200 mg (about 3 mg/kg bw) and habitual caffeine consumption at doses of 200 mg per day do not give rise to safety concerns.

Food supplements

From a daily dose of 100 mg caffeine, the calculated intake levels are 2.3, 1.6 and 1.4 mg/kg bw per day for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥ 18 years), respectively. From a daily dose of 300 mg caffeine, the calculated intake levels are 6.9, 4.9 and 4.3 mg/kg bw per day for the same age groups, respectively.

VKM concludes that it is unlikely that a dose of 100 mg of caffeine per day from food supplements causes adverse health effects in children (10 years and above), adolescents (14

to <18 years), pregnant women and the fetus, lactating women and the breastfed infant and adults (≥ 18 years). However, for children and adolescents, a dose of 100 mg per day is above the intake that may increase sleep latency and reduce sleep duration. For adults, a dose of 100 mg per day is equal to the intake that may increase sleep latency and reduce sleep duration.

VKM concludes that a dose of 300 mg of caffeine per day from food supplements may represent a risk of adverse health effects in children (10 years and above), adolescents (14 to <18 years), pregnant women and the fetus and lactating women and the breastfed infant. Consumed as a single dose, 300 mg of caffeine from food supplement may represent a risk of adverse health effects in adults (≥ 18 years). Consumed throughout the day, it is unlikely that a dose of 300 mg of caffeine per day from food supplements causes adverse health effects in adults. A dose of 300 mg per day is above the intake that may increase sleep latency and reduce sleep duration.

Energy drinks

The estimated exposure to caffeine from a drinking pattern reflecting a high acute intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) is 13.9 mg/kg bw per day for children (3 to <10 years), 11.1 mg/kg bw per day for children (10 to <14 years), 10.4 mg/kg bw per day for adolescents (14 to <18 years) and 9.1 mg/kg bw per day for adults (≥ 18 years).

VKM concludes that a drinking pattern reflecting a high acute intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) may represent a risk of adverse health effects in children (3 years and above), adolescents (14 to <18 years), pregnant women and the fetus, lactating women and the breastfed infant and adults (≥ 18 years). In addition, the intake is above the intake that may increase sleep latency and reduce sleep duration.

The estimated exposure to caffeine from a drinking pattern reflecting a mean chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) is 0.8 mg/kg bw per day for children (3 to <10 years), 0.5 mg/kg bw per day for children (10 to <14 years), 0.3 mg/kg bw per day for adolescents (14 to <18 years) and 0.3 mg/kg bw per day for adults (≥ 18 years).

VKM concludes that it is unlikely that a drinking pattern reflecting a mean chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) causes adverse health effects in children (3 years and above), adolescents (14 to <18 years), pregnant women and the fetus, lactating women and the breastfed infant and adults (≥ 18 years). In addition, the intake is below the intake that may increase sleep latency and reduce sleep duration.

The estimated exposure to caffeine from a drinking pattern reflecting a high chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) is 2.3 mg/kg bw per day for children (3 to <10 years), 1.3 mg/kg bw per day for children (10 to <14 years), 1.1 mg/kg

bw per day for adolescents (14 to <18 years) and 1.5 mg/kg bw per day for adults (≥ 18 years).

VKM concludes that it is unlikely that a drinking pattern reflecting a high chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) causes adverse health effects in children (3 years and above), adolescents (14 to <18 years), pregnant women and the fetus, lactating women and the breastfed infant and adults (≥ 18 years). For children (3 to <10 years) and adults (≥ 18 years), the intake is above the intake that may increase sleep latency and reduce sleep duration. For children (10 to <14 years) and adolescents (14 to <18 years), the intake is below the intake that may increase sleep latency and reduce sleep duration.

Short summary

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of 100 or 300 mg/day of caffeine in food supplements and in energy drinks containing 32 mg/100 ml. VKM concludes that:

- It is unlikely that a dose of 100 mg of caffeine per day from food supplements causes adverse health effects in children (10 years and above), adolescents (14 to <18 years), pregnant women and fetus, lactating women and the breastfed infant and adults (≥ 18 years).
- A dose of 300 mg of caffeine per day from food supplements may represent a risk of adverse health effects in children (10 years and above), adolescents (14 to <18 years), pregnant women and fetus and lactating women and the breastfed infant. Consumed as a single dose, 300 mg of caffeine from food supplement may represent a risk of adverse health effects in adults (≥ 18 years). Consumed throughout the day, it is unlikely that a dose of 300 mg of caffeine per day from food supplements causes adverse health effects in adults. The dose is above the intake that may increase sleep latency and reduce sleep duration.
- Drinking pattern reflecting a high acute intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) may represent a risk of adverse health effects in children (3 years and above), adolescents (14 to <18 years), pregnant women and fetus and lactating women and the breastfed infant and adults (≥ 18 years). In addition, the intake is above the intake that may increase sleep latency and reduce sleep duration.
- It is unlikely that a drinking pattern reflecting a mean chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) causes adverse health effects in children (3 years and above), adolescents (14 to <18 years), pregnant women and fetus, lactating women and the breastfed infant and adults (≥ 18 years). In addition, the intake is below the intake that may increase sleep latency and reduce sleep duration.
- It is unlikely that a drinking pattern reflecting a high chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) causes adverse health effects in

children (3 years and above), adolescents, pregnant women and fetus, lactating women and the breastfed infant and adults. The intake is above the intake that may increase sleep latency and reduce sleep duration for children (3 to <10 years) and adults, whereas it is below for children (10 to <14 years) and adolescents.

Key words: Adverse health effect, caffeine, energy drink, food supplement, negative health effect, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, VKM

Sammendrag på norsk

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved tilsetning av «andre stoffer» i kosttilskudd og energidrikk som selges i Norge. VKM har risikovurdert ulike bruksdoser oppgitt fra Mattilsynet. Disse risikovurderingene vil gi Mattilsynet vitenskapelige grunnlag for å regulere andre stoffer.

«Andre stoffer» er beskrevet i kosttilskuddsdirektivet 2002/46/EC som stoffer som har en ernæringsmessig eller fysiologisk effekt, og som ikke er vitaminer og mineraler. De tilsettes i hovedsak til kosttilskudd, men også til energidrikker og andre næringsmidler. I disse risikovurderingene har VKM ikke sett på påståtte gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

Denne risikovurderingen av koffein er basert på tidligere risikovurderinger og artikler hentet fra et litteratursøk.

Ifølge informasjon fra Mattilsynet er koffein en ingrediens i kosttilskudd og energidrikker som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere 100 og 300 mg/dag av koffein i kosttilskudd og 32 mg/100 ml av koffein i energidrikker. Drikkemønstre for energidrikker som reflekterer et høyt akutt inntak, et gjennomsnittlig kronisk inntak og et høyt kronisk inntak ble vurdert.

Andre kilder til koffein, som for eksempel mat og kosmetikk, er ikke inkludert i denne risikovurderingen.

De viktigste kildene til koffein i kostholdet inkluderer kaffe, te, koffeinholdige brus (inkludert energidrikker) og sjokolade. Den europeiske myndighet for næringsmiddeltrygghet (European Food Safety Authority – EFSA) beregnet det daglige inntak av koffein for voksne fra 16 EU medlemsland. De fant at gjennomsnittet og 95-persentilen varierte fra henholdsvis 37 til 319 mg og fra 109 til 742 mg. Daglig inntak (det er medianen som er oppgitt) av koffein fra ulike kilder blant gravide norske kvinner ble selv-rapportert til å være henholdsvis 126 mg/dag før svangerskapet, 44 mg/dag i svangerskapsuke 17 og 62 mg/dag i svangerskapsuke 30.

Koffein tas raskt og fullstendig opp i kroppen etter oralt inntak, og maksimal plasmakonsentrasjon kan nås innen 30-120 minutter. Koffein krysser blod-hjerne-barrieren, placenta-barrieren og blod-testikkel-barrieren, og skilles ut i morsmelk.

Det er publisert mange humane studier av negative helseeffekter av koffein. Flere risikovurderingsorganer har vurdert sikkerhet/risiko ved inntak av koffein. I risikokarakteriseringen har VKM brukt inntaksnivåer som det er antatt er usannsynlig at vil forårsake negative helseeffekter fra en ny og omfattende risikovurderingen fra EFSA (EFSA, 2015), samtidig som andre tidligere risikovurderinger og nyere litteratur er tatt i betraktning. Det er identifisert hvor mye koffein ulike grupper i befolkningen (barn, ungdom, gravide kvinner (inkludert fosteret), ammende kvinner (inkludert barnet som ammes) og voksne) kan

innta uten at det er sannsynlig at det gir negative helseeffekter. Disse verdiene er gitt i listen nedenfor.

For den generelle voksne befolkningen (inkluderer ikke gravide kvinner):

- Enkelt doser opp til 200 mg anses som trygge.
- Inntil 400 mg som inntas i løpet av en dag (sedvanlig forbruk) anses som trygt.
- Inntak på 1.4 mg/kg kroppsvekt kan føre til økt innsovningstid og redusere søvnlengde.

For barn og ungdom:

- 3 mg/kg kroppsvekt per dag for enkelt doser eller som daglig inntak anses som trygt.
- Inntak på 1.4 mg/kg kroppsvekt kan føre til økt innsovningstid og redusere søvnlengde.

For gravide kvinner og fosteret:

- 200 mg per dag som inntas i løpet av dagen (sedvanlig forbruk) anses som trygt.

For ammende kvinner og barnet som ammes:

- Enkelt doser opp til 200 mg og sedvanlig inntak av 200 mg per dag anses som trygge.

Kosttilskudd

Ved inntak av en daglig dose på 100 mg koffein blir den estimerte eksponeringen henholdsvis 2,3 mg/kg kroppsvekt per dag for barn (10 til <14 år), 1,6 mg/kg kroppsvekt per dag for ungdom (14 til <18 år) og 1,4 mg/kg kroppsvekt per dag for voksne (≥ 18 år). Fra en daglig dose på 300 mg koffein blir den estimerte eksponeringen på henholdsvis 6,9, 4,9 og 4,3 mg/kg kroppsvekt per dag for de samme aldersgruppene.

VKM konkluderer med at det er usannsynlig at en dose på 100 mg koffein per dag fra kosttilskudd forårsaker negative helseeffekter hos barn (10 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret, ammende kvinner og barnet som ammes og voksne (≥ 18 år). For barn og ungdom er inntaket over det som vil kunne føre til økt innsovningstid og redusere søvnlengde. For voksne er inntaket likt med det som kan føre til økt innsovningstid og redusere søvnlengde.

VKM konkluderer med at en dose på 300 mg koffein per dag fra kosttilskudd vil kunne representere en risiko for negative helseeffekter hos barn (10 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret og ammende kvinner og barnet som ammes. Ved inntak som en enkelt dose vil 300 mg koffein fra kosttilskudd kunne utgjøre en risiko for negative helseeffekter hos voksne (≥ 18 år). Konsumert i løpet av dagen, er det usannsynlig at en dose på 300 mg koffein per dag fra kosttilskudd forårsaker negative helseeffekter hos voksne (≥ 18 år). For alle aldersgrupper er inntaket over det som vil kunne føre til økt innsovningstid og redusere søvnlengde.

Energidrikker

For det høye akutte drikkemønsteret var det estimerte inntaket av koffein fra energidrikker (som inneholder 32 mg koffein per 100 ml energidrikk) henholdsvis 13,9 mg/kg kroppsvekt per dag for barn (3 til <10 år), 11,1 mg/kg kroppsvekt per dag for barn (10 til <14 år), 10,4

mg/kg kroppsvekt per dag for ungdom (14 til <18 år) og 9,1 mg/kg kroppsvekt per dag for voksne (≥18 år).

VKM konkluderer med at et drikkemønster som gjenspeiler et høyt akutt inntak av koffein fra energidrikker (som inneholder 32 mg koffein/100 ml) vil kunne representere en risiko for negative helseeffekter for barn (3 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret, ammende kvinner og barnet som ammes og voksne (≥18 år). For alle aldersgrupper er inntaket over det som vil kunne føre til økt innsøvningstid og redusere søvnlengde.

For det gjennomsnittlige kroniske drikkemønsteret var det estimerte inntaket av koffein fra energidrikker (som inneholder 32 mg koffein per 100 ml energidrikk) henholdsvis 0,8 mg/kg kroppsvekt per dag for barn (3 til <10 år), 0,5 mg/kg kroppsvekt per dag for barn (10 til <14 år), 0,3 mg/kg kroppsvekt per dag for ungdom (14 til <18 år) og 0,3 mg/kg kroppsvekt per dag for voksne (≥18 år).

VKM konkluderer med at det er usannsynlig at et drikkemønster som gjenspeiler et gjennomsnittlig kronisk inntak av koffein fra energidrikker (som inneholder 32 mg koffein /100 ml) fører til negative helseeffekter hos barn (3 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret, ammende kvinner og barnet som ammes og voksne (≥18 år). For alle aldersgrupper er inntaket lavere enn det som vil kunne føre til økt innsøvningstid og redusere søvnlengde.

For det høye kroniske drikkemønsteret var det estimerte inntaket av koffein fra energidrikker (som inneholder 32 mg koffein per 100 ml energidrikk) henholdsvis 2,3 mg/kg kroppsvekt per dag for barn (3 til <10 år), 1,3 mg/kg kroppsvekt per dag for barn (10 til <14 år), 1,1 mg/kg kroppsvekt per dag for ungdom (14 til <18 år) og 1,5 mg/kg kroppsvekt per dag for voksne (≥18 år).

VKM konkluderer med at det er usannsynlig at et drikkemønster som gjenspeiler et høyt kronisk inntak av koffein fra energidrikker (som inneholder 32 mg koffein /100 ml) fører til negative helseeffekter hos barn (3 år og eldre), ungdom (14 til <18 år), og fosteret, ammende kvinner og barnet som ammes og voksne (≥18 år). For barn (3 til <10 år) og voksne (≥18 år) er inntaket over det som vil kunne føre til økt innsøvningstid og redusere søvnlengde. For barn (10 til <14 år) og ungdom (14 til <18 år) er inntaket under det som vil kunne føre til økt innsøvningstid og redusere søvnlengde.

Kort sammendrag

Vitenskapskomiteen for mattrygghet (VKM) har på oppdrag fra Mattilsynet vurdert risikoen ved 100 eller 300 mg/dag av koffein i kosttilskudd og energidrikker (som inneholder 32 mg/100 ml). VKM konkluderer med at:

- Det er usannsynlig at en dose på 100 mg koffein per dag fra kosttilskudd forårsaker negative helseeffekter hos barn (10 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret, ammende kvinner og barnet som ammes og voksne (≥18 år).

For barn og ungdom er inntaket over det som vil kunne føre til økt innsovningstid og redusere søvnlengde. For voksne er inntaket likt med det som kan føre til økt innsovningstid og redusere søvnlengde.

- En dose på 300 mg koffein per dag fra kosttilskudd vil kunne representere en risiko for negative helseeffekter hos barn (10 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret og ammende kvinner og barnet som ammes. Ved inntak som en enkelt dose vil 300 mg koffein fra kosttilskudd kunne utgjøre en risiko for negative helseeffekter hos voksne (≥ 18 år). Konsumert i løpet av dagen, er det usannsynlig at en dose på 300 mg koffein per dag fra kosttilskudd forårsaker negative helseeffekter hos voksne (≥ 18 år). For alle aldersgrupper er inntaket over det som vil kunne føre til økt innsovningstid og redusere søvnlengde.
- Et drikkemønster som gjenspeiler et høyt akutt inntak av koffein fra energidrikker (som inneholder 32 mg koffein/100 ml) vil kunne representere en risiko for negative helseeffekter for barn (3 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret, ammende kvinner og barnet som ammes og voksne (≥ 18 år). For alle aldersgrupper er inntaket over det som vil kunne føre til økt innsovningstid og redusere søvnlengde.
- Det er usannsynlig at et drikkemønster som gjenspeiler et gjennomsnittlig kronisk inntak koffein fra energidrikker (som inneholder 32 mg koffein /100 ml) fører til negative helseeffekter hos barn (3 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret, ammende kvinner og barnet som ammes og voksne (≥ 18 år). For alle aldersgrupper er inntaket lavere enn det som vil kunne føre til økt innsovningstid og redusere søvnlengde.
- Det er usannsynlig at et drikkemønster som gjenspeiler et høyt kronisk inntak av koffein fra energidrikker (som inneholder 32 mg koffein /100 ml) fører til negative helseeffekter hos barn (3 år og eldre), ungdom (14 til <18 år), gravide kvinner og fosteret, ammende kvinner og barnet som ammes og voksne (≥ 18 år). For barn (3 til <10 år) og voksne (≥ 18 år) er inntaket over det som vil kunne føre til økt innsovningstid og redusere søvnlengde. For barn (10 til <14 år) og ungdom (14 til <18 år) er inntaket under det som vil kunne føre til økt innsovningstid og redusere søvnlengde.

Abbreviations and glossary

Abbreviations

ADI	- acceptable daily intake
ADME	- absorption, distribution, metabolism, excretion
ANSES	- the French Agency for Food, Environmental and Occupational Health & Safety
COT	- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
EFSA	- European Food Safety Authority
LOAEL	- Lowest Observed Adverse Effect Level
LOEL	- Lowest Observed (Adverse) Effect Level
NFSA	- Norwegian Food Safety Authority [<i>Norw.</i> : Mattilsynet]
NOAEL	- no observed adverse effect level
NOEL	- no observed effect level
UL	- tolerable upper intake level
SCF	- Scientific Committee on Food
SHC	- Superior Health Council
VKM	- Norwegian Scientific Committee for Food Safety [<i>Norw.</i> : Vitenskapskomiteen for Mattrygghet]

Glossary

"Other substances": a substance other than a vitamin or mineral that has a nutritional or physiological effect (The European Parliament and the Council of the European Union, 2006).

"Negative health effect" and "adverse health effect" are broad terms. VKM uses the definition established by EFSA for "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (WHO, 1994).

Background as provided by the Norwegian Food Safety Authority

«Other substances» are substances other than vitamins and minerals, with a nutritional and/or physiological effect on the body. "Other substances" are mainly added to food supplements, but these may also be added to other foods and beverages, such as sports products and energy drinks. Ingestion of these substances in high amounts presents a potential risk for consumers.

In Norway, a former practice of classification of medicines had constituted an effective barrier against the sale of potentially harmful "other substances". Ever since this practice was changed in 2009, it has become challenging to regulate and supervise foods with added "other substances". Meanwhile, in the recent years, the Norwegian market has witnessed a marked growth in the sales of products containing "other substances". In 2011, food supplements containing "other substances" constituted more than 50% of the market share.

While within the European Economic Area, these substances fall under the scope of the European Regulation (EC) No. 1925/2006 on the addition of vitamins, minerals and certain other substances to foods and the European Regulation (EC) No 258/97 concerning novel foods and novel food ingredients, "other substances" remain largely unregulated. In order to ensure safe use of "other substances" many countries have regulated their use at a national level. For example, Denmark regulates these substances in a positive list i.e. a list of substances with maximal daily doses, permitted for use in food supplements and other foods (FVM, 2014).

The Norwegian Food Safety Authority (NFSA) is working on the establishment of a regulation on the addition of "other substances" to foods at a national level. The regulation will include a list of substances with permitted maximal doses, based on the substances and doses found in products on the Norwegian market. In preparation for a regulation, NFSA has therefore requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of "other substances" found on the Norwegian market. NFSA, in consultation with the industry, has compiled a list of "other substances" found in products marketed in Norway. Only substances with a purity of minimum 50% or concentrated 40 times or more have been included in the list. Substances regulated by other legislations like those for novel foods, food additives, flavourings, foods for special medical purposes, etc. have been excluded from the list.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of caffeine in food supplements at the following doses: 100 and 300 mg/day, and energy drinks at the following dose: 32 mg/100 ml.

NFSA requested VKM to assess the safety of "other substances" (in accordance to the guidance document developed in Phase 2) at the doses specified (Phase 3). Safety assessments of "other substances" present in food supplements shall be carried out for a general population, ages 10 years and above. Safety assessments of "other substances" present in energy drinks shall be carried out for a general population, ages 3 years and above. Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake should be assessed.

Assessment

1 Introduction

"Other substances" are described in the food supplement directive 2002/46/EC as *substances other than vitamins or minerals that have a nutritional and/or physiological effect*, and may be added to food supplements or e.g. energy drinks.

This risk assessment regards the substance caffeine per se, and no specific products.

VKM has in this series of risk assessments of "other substances" not evaluated documentation of any potential beneficial effects from these substances, but merely possible adverse effects at specified doses used in Norway. Thus, potential high intake consumer groups of the substance may not be identified and therefore not included in the assessment.

According to information from the Norwegian Food Safety Authority (NFSA), caffeine is an ingredient in food supplements and energy drinks purchased in Norway. NFSA has requested a risk assessment of the intake of 100 and 300 mg caffeine/day from food supplements, and a risk assessment of high acute, mean chronic and high chronic intake of energy drinks containing 32 mg caffeine/100 ml. The total exposure to caffeine from other sources than energy drinks, such as foods and cosmetic products, is not included in the risk assessment.

Caffeine is an alkaloid found in various plant constituents, such as coffee and cocoa beans, tea leaves, guarana berries and the kola nut. The median daily caffeine intake from different sources among pregnant Norwegian women, self-reported at gestational weeks 17 and 30, was 126 mg/day pre-pregnancy, 44 mg/day at gestational week 17, and 62 mg/day at gestational week 30. The daily intake of caffeine from all sources was calculated by EFSA using the EFSA Comprehensive European Food Consumption Database for adults from 16 EU Member States, where the means and 95th percentiles of daily caffeine intake ranged from 37 to 319 mg and from 109 to 742 mg, respectively (EFSA, 2015). According to EFSA, the main sources of caffeine in the diet include coffee, tea, caffeinated soft drinks (including energy drinks) and chocolate (EFSA, 2015). In this risk assessment, the concentrations of caffeine in food supplements are 100 and 300 mg/day and the concentration in energy drinks is 32 mg/100 ml.

Caffeine acts as an antagonist to adenosine A1 and A2A receptors that are expressed in the central nervous system, and this is an important mechanism for the effects of caffeine. In addition, caffeine facilitates dopamine D2 receptor transmission, and is known as a non-specific phosphodiesterase inhibitor. The interaction with the adenosine A1 receptor, leading to inhibition of renal re-absorption and causing diuresis and natriuresis, can explain the diuretic activity of caffeine (EFSA, 2015). The mechanisms for the tolerance to caffeine observed after repeated administration are not well understood.

2 Hazard identification and characterisation

2.1 Literature

The present risk assessment is based on previous risk assessments of caffeine and articles retrieved from a literature search.

2.1.1 Previous risk assessments

Opinion of the Scientific Committee on Food on Additional information on "energy" drinks. European Commission (SCF, 2003)

In 1999, the SCF adopted an opinion on so-called "energy drinks", which evaluated the safety of caffeine, taurine and D-glucurono- γ -lactone as constituents of "energy drinks" (SCF, 2003). In 2003, the Committee was asked to review additional information submitted on energy drinks and indicate if the conclusions in the 1999 needed to be modified. It was concluded that for caffeine, the 1999 opinion remained unchanged. The conclusions on caffeine in the 1999 opinion were "the contribution of "energy drinks" to overall caffeine intake was not a matter of concern for non-pregnant adults. For children who do not normally consume much tea or coffee, and who might substitute "energy drinks" for cola or other soft drinks, consumption of "energy drinks" might represent an increase in daily caffeine exposure compared with their previous intake. The Committee considered that this could result in transient behavioural changes, such as increased arousal, irritability, nervousness or anxiety. For pregnant adults, the Committee concluded that while intakes of caffeine up to 300 mg/day appeared to be safe, the question of possible effects on pregnancy and the offspring at regular intakes above 300 mg/day remained open. This suggested that moderation of caffeine intake, from whatever source, was advisable during pregnancy."

Risikovurdering av "energidrikker" med koffein, taurine, glukuronolakton, inositol og vitaminer. Norway (in Norwegian) (VKM, 2005)

New information on ingredients in so-called "energy drinks". Norway (VKM, 2009)

2005: VKM performed a risk assessment of the ingredients in the energy drink «Red Bull» (VKM, 2005). VKM was requested to base the risk assessment on SCF's opinion from 2003 and newer studies published since 2003. VKM endorsed the conclusions by the SCF. It was concluded that caffeine may induce adverse health effects to the population, and that children, adolescents, pregnant and lactating women are particularly vulnerable groups.

2009: VKM examined, on the basis of the EFSA 2009 opinion, whether the conclusion of the VKM opinion from 2005 needed to be revised (VKM, 2009). The estimated consumption of energy drinks and the increased intake of caffeine as described in the opinion were considered to be of concern for children. Potential adverse effects of "energy drink" consumption cannot be ruled out for adolescents with no or low tolerance for caffeine. The risk of adverse effects to caffeine from "energy drinks" is highest for adolescents aged 13-15 years old, when the consumption of coffee is low and the tolerance development to caffeine is expected to be lower than for adults. For adults, the caffeine intake from soft drinks, coffee, tea and chocolate is considerably lower than the LOAEL (Lowest Observed Adverse Effect Level) for anxiety and therefore of no safety concern for adults. Since the half-life of caffeine is doubled or tripled during pregnancy due to hormonal changes, the recommendations given in the VKM opinion from 2005 were maintained; that the intake of caffeine in pregnant women should not exceed 100-200 mg/day.

Intake of caffeine and other methylxanthines during pregnancy and risk for adverse effects in pregnant women and their fetuses. Nordic Council of Ministers (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2005)

The report summarises epidemiological information available on the relationship between intake of caffeine and other methylxanthines by mothers in childbearing age and adverse effects on pregnant women and their fetuses and young children. The adverse effects of methylxanthines studied are influence on fertility, spontaneous abortion, congenital malformation, pre-term delivery, foetal growth retardation, foetal behaviour, and effects on neonates, infants and older children." The following conclusions were reached:

- It could not be ruled out that an association existed between caffeine exposure and fertility (delayed conception), but the evidence for such an association was considered weak.
- It seemed probable that high intakes of caffeine may increase the risk of having a spontaneous abortion, although the results partly were contradictory.
- There was no correlation between high caffeine exposures and congenital malformations in humans.
- There was no relationship between maternal caffeine exposure and pre-term delivery.
- It was not possible to exclude a relationship between caffeine exposure and foetal growth retardation."

Overall, with regard to possible adverse effects related to caffeine, it was concluded that "caffeine, especially at high doses, could affect the pregnancy in a negative way (induce spontaneous abortion, and possibly result in foetal growth retardation). Hence, a reduction in (total) caffeine intake (from all sources) should be advised for women being pregnant or planning pregnancy and already having a high caffeine intake".

Risk assessment of caffeine among children and adolescents in the Nordic countries. Nordic Council of Ministers (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2008)

Several biological effects of low level caffeine exposure of children and adolescents were reported, such as tolerance development, withdrawal symptoms, anxiety and jitteriness, in this risk assessment (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2008). For tolerance development, No Observable Effect Level (NOEL) and Lowest Observed Effect Level (LOEL) values of 0.3 and 1.0–1.3 mg/kg bw per day, respectively, were identified, whereas a Lowest Observed Adverse Effect Level (LOAEL) value for anxiety and jitteriness was identified at an intake of 2.5 mg/kg bw per day. In non-habitual caffeine-consuming adults, sleep disturbance was induced at a very low intake (in the same range as that inducing tolerance development). For children, no studies in sleep disturbances were identified.

Statement On The Reproductive Effects Of Caffeine, Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. UK (COT, 2008)

The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that caffeine consumption during pregnancy was associated with an increased risk of fetal growth restriction, that it was not possible to identify a threshold level of caffeine intake below which there was no elevation of risk, and that it seemed likely that risk was increased in association with intakes in the order of 200 mg per day and perhaps even lower (COT, 2008). Based on an extensive review of the literature, a positive association of caffeine intake with miscarriage was suggested. Data on maternal caffeine consumption during pregnancy and associations with pre-term birth and congenital malformations were inconclusive.

“The use of caffeine in foodstuffs”, Advisory Report of the Superior Health Council no. 8689. Belgium (The Superior Health Council, 2012)

The Superior Health Council concluded that for healthy adults, most studies indicate that a moderate exposure to caffeine of 5.7 mg/kg bw per day (400 mg/day for a 70 kg adult) is not linked to any adverse effects such as general toxicity, cardiovascular effects, altered behaviour, increased incidence of cancer and effects on male fertility (The Superior Health Council, 2012). However, in some publications this value is set at 3 mg/kg bw per day (210 mg/day for 70 kg males), which is the limit above which increased anxiety can be observed. For children, including preadolescents, the upper intake level is 2.5 mg/kg bw per day (the limit above which altered behaviour is liable to appear, including anxiety as well as a potentially altered development of the nervous system). For women of childbearing age, the maximum daily intake should not exceed 300 mg/day, or even 200 mg/day.

Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the assessment of risks concerning the consumption of so-called “energy drinks”. France (ANSES, 2013)

Cases of suspected adverse effects related to consumption of energy drinks were collected as part of the nutriviigilance scheme, and the implication of the consumption of energy drinks in the onset of adverse effects was judged to be very likely or likely for 25 of 212 cases

(ANSES, 2013). The principal symptoms observed in these cases were cardiovascular, psycho-behavioural or neurological. ANSES stated that a risk situation may result from the multiplication of sources of caffeine combined with current consumption patterns of these drinks. ANSES recommended that consumers refrain from consuming energy drinks in association with alcohol and during physical exercise; that pregnant women and nursing mothers, children and adolescents, and individuals sensitive to the effects of caffeine or presenting certain pathologies (especially certain cardiovascular or psychiatric and neurological disorders, kidney failure or serious liver diseases), are particularly vigilant concerning their caffeine intake, and that all consumers in general moderate their consumption of caffeinated beverages.

Scientific Opinion on the safety of caffeine. The European Food Safety Authority (EFSA, 2015)

The opinion addressed possible adverse health effects of caffeine consumption from all dietary sources, including food supplements, in the general healthy population and in relevant specific subgroups of the general population (e.g. children, adolescents, adults, the elderly, pregnant and lactating women, subjects performing physical exercise) (EFSA, 2015). Both acute and chronic exposures were addressed; adverse effects of a single caffeine dose, of repeated doses of caffeine consumed within a day, and of longer-term (>7 days) and habitual caffeine consumption were included. Caffeine consumption acutely increases blood pressure in the adult, and the effect was observed at single doses of caffeine ranging from 80-300 mg, the most tested doses were in the range of 200-300 mg. Repeated doses of caffeine (250 mg) taken four hours apart also induced an increase in blood pressure (of about 3-4 mm Hg). High doses of caffeine (4-6 mg/kg bw per day, corresponding to about 280-420 mg for a 70-kg adult) ingested 45-60 minutes prior to exercise could add to the blood pressure-raising effect of resistance training and attenuate the decrease in blood pressure observed after resistance training. High doses (≥ 400 –500 mg) consumed either on a single occasion or within short periods of time have been reported to increase anxiety upon oral consumption, mostly in patients with psychiatric anxiety disorders, but also in healthy adults, particularly if they are non-habitual caffeine consumers. In some individuals, a dose of 100 mg of caffeine (about 1.5 mg/kg bw) may increase sleep latency and reduce sleep duration, particularly when consumed close to bedtime. Caffeine intake of 10 mg/kg bw per day may increase anxiety and adversely affect behaviour and sleep in habitual low caffeine consumers.

The main conclusions on caffeine intakes which do not raise safety concerns for the general healthy adult population were that 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, however, that single doses as low as 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, and that caffeine intake 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.

For children and adolescents, the information available was insufficient to derive a safe caffeine intake. Since the rate at which children and adolescents process caffeine is at least similar to that of adults, caffeine intakes of no concern derived for acute caffeine consumption by adults (3 mg/kg bw per day) were used to derive single doses of caffeine and daily caffeine intakes of no concern for children and adolescents. However, as in adults, caffeine doses of about 1.5 mg/kg bw per day may increase sleep latency and reduce sleep duration, particularly in some children and adolescents. The studies available on the acute effects of caffeine on anxiety and behaviour in children and adolescents support this level. A safety level of 3 mg/kg bw per day was also proposed for habitual caffeine consumption by children and adolescents. Caffeine doses of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents, as in adults.

With regard to caffeine intake and adverse birth weight-related outcomes, it was concluded that these outcomes are observed at all levels of caffeine intake, with no threshold below which the relationship is not observed. It was considered that the risk becomes clinically relevant at total daily doses of about 200 mg of caffeine from all sources, and that decreasing caffeine intake from about 300 mg per day to about 100 mg per day in the third trimester of pregnancy did not decrease the risk, as observed in one human intervention study (Bech et al., 2007). Regarding safety of the fetus, the main conclusion was that 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. For the breastfed infant, the main conclusion was that single doses of caffeine up to 200 mg or habitual caffeine consumption at doses of 200 mg per day consumed by lactating women in the general population do not give rise to safety concerns for the breastfed infant.

2.1.2 Summary of previous risk assessments

Risk/safety assessments of caffeine have been performed by several authoritative bodies.

The Superior Health Council reported that for adults, the limit above which increased anxiety can be observed is 3 mg/kg bw per day, and that most studies indicate that a moderate exposure to caffeine of 5.7 mg/kg/day (400 mg/day for a 70 kg adult) is not linked to any adverse effects (The Superior Health Council, 2012). EFSA (2015) reported that caffeine doses of about 1.4 mg/kg bw per day may increase sleep latency and reduce sleep duration in adults. EFSA concluded that single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) and intakes 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 (EFSA, 2015).

For children and adolescents, a LOAL of 2.5 mg/kg bw per day for anxiety and jitteriness, and NOEL and LOEL values of 0.3 and 1.0–1.3 mg/kg bw per day for tolerance development, respectively, were identified by the Nordic Council of Ministers (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2008). The Superior Health Council concluded that for children, including preadolescents, the upper intake level of caffeine is 2.5 mg/kg bw per

day (The Superior Health Council, 2012). EFSA (2015) concluded that caffeine doses of about 1.4 mg/kg bw per day may increase sleep latency and reduce sleep duration in some children and adolescents. EFSA (2015) proposed a safety level of 3 mg/kg bw per day for single doses of caffeine and daily caffeine intake for children and adolescents.

For pregnant women (adults), SCF concluded that intakes of caffeine up to 300 mg/day appeared to be safe (SCF, 2003). VKM concluded that the intake of caffeine in pregnant women should not exceed 100-200 mg/day (VKM, 2005; VKM, 2009). NNT (Nordic Working Group on Food Toxicology and Risk Evaluation) (2005) concluded that "caffeine, especially at high doses, could affect the pregnancy in a negative way (induce spontaneous abortion, and possibly result in foetal growth retardation). Hence, a reduction in (total) caffeine intake (from all sources) should be advised for women being pregnant or planning pregnancy and already having a high caffeine intake". COT concluded that caffeine consumption during pregnancy was associated with an increased risk of fetal growth restriction, and that it seemed likely that risk was increased in association with intakes in the order of 200 mg per day and perhaps even lower (COT, 2008). The Superior Health Council concluded that the maximum daily intake should not exceed 300 mg/day, or even 200 mg/day (The Superior Health Council, 2012). EFSA concluded that caffeine intakes up to 200 mg per day consumed throughout the day by pregnant women do not give rise to safety concerns for the fetus (EFSA, 2015).

For lactating women, EFSA concluded that single doses of caffeine up to 200 mg or habitual caffeine consumption at doses of 200 mg per day consumed by lactating women in the general population do not give rise to safety concerns for the breastfed infant (EFSA, 2015).

2.1.3 Literature search

2.1.3.1 Search strategy

Literature searches were performed in MEDLINE and EMBASE for the period 2013-2015. The search strategy is included in Appendix 1.

2.1.3.2 Publication selection

The literature search identified 256 articles. In the primary screening, titles and abstracts of all publications retrieved were independently screened against the inclusion criteria checklist. Owing to the abundance of available scientific literature from human studies, animal studies were excluded.

Inclusion criteria checklist:

- Adverse effects in humans in relation to the substance alone are addressed
- Route of exposure for humans is oral
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal absorption and metabolism of the assessed substance.

The inclusion criteria checklist was developed by members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the Panel on Nutrition, Dietetic Products, Novel Food and Allergy. Articles that did not appear to meet the inclusion criteria were excluded from further analysis. In situations where it was unclear whether the publication was of relevance to the study, it was retained for further screening. The primary screening was performed by one person.

The full text of articles that passed the primary screening (22) was retrieved for secondary screening. In this screening, the full text articles were reviewed and compared against the inclusion criteria checklist. The secondary screening was performed by one person.

The secondary screening resulted in 10 full text articles included in the results in this report (see Figure 2.1.3.2-1).

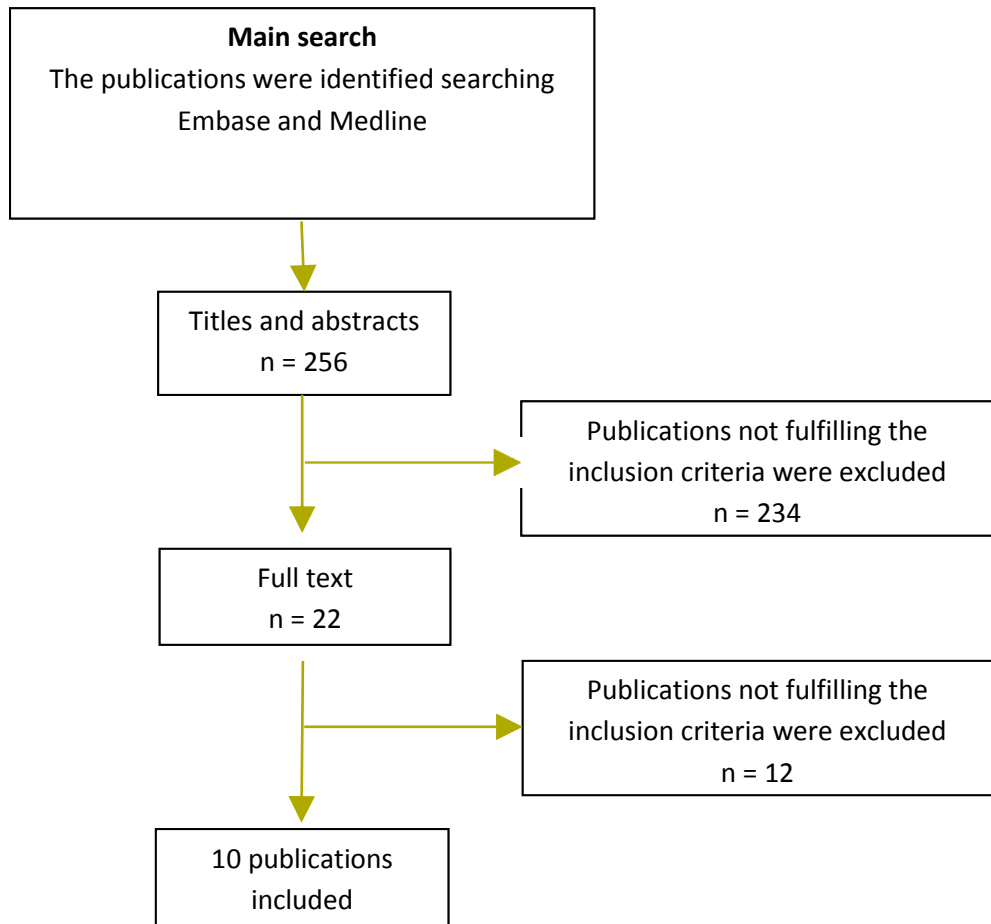


Figure 2.1.3.2-1 Flowchart for the literature search for caffeine and the subsequent publication selection.

2.2 General information

2.2.1 Chemistry

Caffeine (cas no. 58-08-2; EINECS no. 200-362-1) is a stable, unionised alkaloid (EFSA, 2015). The molecular formula is $C_8H_{10}N_4O_2$, the molecular weight is 194.19 g/mol, and the chemical name is 1,3,7-trimethylxanthine. The structural formula of caffeine is shown in Figure 2.2.1-1.

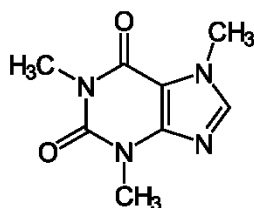


Figure 2.2.1-1 The structural formula of caffeine.

2.2.2 Occurrence

Caffeine is found in various plant constituents, such as coffee and cocoa beans, tea leaves, guarana berries and the kola nut. The median daily caffeine intake from different sources among pregnant Norwegian women, self-reported at gestational weeks 17 and 30, was 126 mg/day pre-pregnancy, 44 mg/day at gestational week 17, and 62 mg/day at gestational week 30. The daily intake of caffeine from all sources was calculated by EFSA using the EFSA Comprehensive European Food Consumption Database, and for adults from 16 EU Member States, where the means and 95th percentiles ranged from 37 to 319 mg and from 109 to 742 mg, respectively (EFSA, 2015).

2.3 Absorption, distribution, metabolism and excretion (ADME)

2.3.1 In humans

Caffeine is rapidly and completely absorbed after oral intake, and the peak plasma concentration can be reached within 30-120 minutes. Caffeine crosses the blood–brain barrier, the placental barrier and the blood–testicular barrier, and is excreted in breast milk (ANSES, 2013; EFSA, 2015)

The main route of metabolism in humans, catalysed by cytochrome P4501A2 (CYP1A2) in the liver is via demethylation to paraxanthine. Other primary metabolites are theophylline and theobromine, and these metabolites are further metabolised and then excreted in the urine (ANSES, 2013; EFSA, 2015). In adults, nearly 98% of an oral dose is found metabolised in the urine, 1-3% in the faeces (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2005). The half-life of caffeine varies widely, depending on

factors such as e.g. age, body weight, pregnancy, medication intake and liver health. In healthy adults, the average half-life is approximately four hours; with a range of two to eight hours. The rate at which children and adolescents metabolise caffeine is similar or higher than that of adults (EFSA, 2015). In several studies, a prolonged half-life of caffeine for pregnant women is reported, which can be explained by the interaction of caffeine with oestrogens and gestagens that has been shown to inhibit the activity of CYP1A2 (EFSA, 2015). The half-life of caffeine is about 10 hours in pregnant women (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2005). In the fetus and the newborn child, the half-life of caffeine is prolonged (4 days) (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2005). Thus, fetuses of caffeine-consuming women are exposed to caffeine and its metabolites for a significantly longer time compared to non-pregnant women.

2.4 Toxicological data/Adverse effects

In the safety assessment of caffeine by EFSA, it was concluded that unborn children are the most vulnerable group for adverse effects of caffeine among the general population (EFSA, 2015). It was stated that short-term adverse effects of caffeine on adults and children can include issues related to the central nervous system such as interrupted sleep, anxiety and behavioural changes. In the longer term, excessive caffeine consumption has been linked to cardiovascular problems and, in pregnant women, it can affect the fetus development. Tolerance to caffeine is observed after repeated administration.

2.4.1 Human studies

An overview of the included studies investigating caffeine and adverse health effects in humans is given in Table 2.4.1-1.

Table 2.4.1-1 An overview of human studies on caffeine and adverse health effects.

Reference	Study design/ participant characteristics	Country	Participants/number in treatment group		Dose	Main endpoint	Length of follow-up	Adverse effect
			Caffeine	Control/ placebo				
Li et al. (2015)	Prospective study	USA	Caffeine intake <150 mg/day, n = 373. Caffeine intake ≥150 mg/day, n = 118	No caffeine, n = 124	The maternal caffeine intake was grouped into two categories, the high-dose and the low- dose group. For the high-dose group, the maternal caffeine intake was ≥150 mg per day during pregnancy, and for the low-dose group, maternal caffeine intake <150 mg per day	Childhood obesity	15 years follow-up of the offspring	Increased risk of childhood obesity was associated with <i>in utero</i> exposure to caffeine. A dose-response relationship for maternal daily caffeine intake was demonstrated.
Okubo et al. (2015)	Prospective birth cohort (the Osaka Maternal and Child Health Study)	Japan	858		Median maternal caffeine intake during pregnancy was 258 mg/day	Low birth weight (LBW; <2500 g), preterm birth (PTB; <37 weeks of gestation) and small for gestational age (SGA; <10 th percentile)		Maternal total caffeine intake during pregnancy was associated with increased risk of preterm birth.

Reference	Study design/ participant characteristics	Country	Participants/number in treatment group		Dose	Main endpoint	Length of follow-up	Adverse effect
			Caffeine	Control/ placebo				
Greenwood et al. (2014)	Meta-analysis (included 60 unique publications)		Data for the association between caffeine and miscarriage (26 studies), caffeine and stillbirth (5 studies), caffeine and preterm delivery (15 studies), caffeine and low birth weight (11 studies), caffeine and small for gestational age (15 studies)		Different levels of intake, including non- consumers and over 1000 mg/day. Pooled estimates of relative risk from linear dose- response meta-analysis per 100 mg/day	Spontaneous abortion, stillbirth, preterm delivery, low birth weight and small for gestational age infants		An increment of 100 mg in caffeine intake was associated with an increase in spontaneous abortion, stillbirth, low birth weight, and small for gestational age. RR from linear dose-response meta-analysis was 1.14 (95 % confidence interval: 1.10 - 1.19).

A meta-analysis (including 60 publications) of the association of caffeine and spontaneous abortion, stillbirth, preterm delivery, low birth weight and small for gestational age infants was performed by Greenwood et al. (2014). The meta-analysis included nearly 15 000 cases of miscarriage from 180 000 women, 700 still births from 120 000 women, 8000 preterm deliveries from nearly 110 000 women, 5000 low birth weight infants from nearly 78 000 women, and nearly 12 000 small for gestational age infants from 160 000 women. Different levels of intake were included; from non-consumers to intake of over 1000 mg/day. An association was observed between caffeine intake during pregnancy and incidence of miscarriage, stillbirth, low birth weight and small for gestational age (pooled estimates of relative risk from linear dose-response meta-analysis per 100 mg/day; RR was 1.14 (95 % confidence interval: 1.10-1.19) per 100 mg/day of caffeine). There was no evidence of an association between caffeine intake and preterm delivery. The following conclusions were stated by the authors: "In summary, combining results from a large number of studies has allowed associations between caffeine intake and adverse pregnancy outcomes to be quantified with precision and discern a modest but significant association with caffeine intake that could only be adequately quantified by pooling results. A number of questions still remain to be answered. These include confirming causality, such as identifying whether caffeine is the causal agent, one of its metabolites, or whether the associations are completely explained by publication bias or caffeine being a marker of healthy pregnancy. Whilst these issues are unresolved, our results confirm the precautionary guidance adopted by countries recommending limiting caffeine consumption during pregnancy". "Given the observational nature of the studies, the heterogeneity and small-study effects, it is not possible to conclude that these associations are causal. The modest sizes of the associations are such that it is possible that they could be explained by any or all of these potential biases. However, the plausible biological mechanisms, the evidence from animal studies, the mounting evidence from different observational human studies and the dose-response slopes, provide some evidence to support the current recommendations limiting caffeine intake during pregnancy, such as restricting to less than 200 mg/day, as a precaution in case the associations really are causal. Whilst the associations are modest in size, they are potentially important at a public health level, and for infants already at elevated risk of adverse outcomes."

In a prospective study of pregnant women with 15 years follow-up of their offspring by Li et al. (2015), the impact of *in utero* exposure to caffeine on the risk of childhood obesity was examined. Maternal caffeine consumption during pregnancy was ascertained during an in-person interview conducted during the first or early second trimesters. Women were asked to report their intake of beverages since their last menstrual period, including caffeine-containing beverages. They were asked about the types of drinks, timing of initial drink, the frequency and amount of intake. Caffeine from all sources was totaled to calculate the amount of daily caffeine intake, and the maternal caffeine intake was grouped into two categories, the high-dose group and the low-dose group. For the high-dose group, the maternal caffeine intake was ≥ 150 mg per day during pregnancy, and for the low-dose group, maternal caffeine intake was < 150 mg per day. Through medical charts and electronic medical records, information on weight and height was ascertained longitudinally,

and body mass index was calculated if both weight and height were measured on the same day. The average number of measurements for BMI was 17 per child. The caffeine intake overall was associated with 87% increased risk of obesity in the offspring, and there was a dose–response relationship for the observed association. A dose-response relationship for maternal daily caffeine intake was demonstrated; for intake during pregnancy of <150 mg per day, OR = 1.77 (95% confidence interval: 1.05-3.00) and for caffeine intake during pregnancy of \geq 150 mg per day, OR = 2.37 (95% confidence interval: 1.24-4.52). A linear relationship was observed: every one unit increase (log₁₀ scale) in the amount of maternal caffeine intake was associated with 23% increased risk of obesity in offspring. The dose-response relationship appeared stronger for persistent obesity than for transitory obesity (occasional high BMI), and for girls than for boys.

Possible associations of maternal consumption of total caffeine (including culture-specific major sources of caffeine) with birth outcomes among Japanese pregnant women were studied by Okubo et al. (2015). The study subjects (858 Japanese women) were participants in the Osaka Maternal and Child Health Study. The median maternal caffeine intake during pregnancy was 258 mg/day. Birth outcomes considered were low birth weight (<2500 g), preterm birth (<37 weeks of gestation) and small for gestational age (<10th percentile). The main caffeine sources were Japanese and Chinese tea (73.5%), coffee (14.3%), black tea (6.6%), and soft drinks (3.5%). The maternal total caffeine intake during pregnancy was significantly associated with an increased risk of preterm birth; odds ratio per 100 mg/day caffeine increase was 1.28 (95% confidence interval: 1.03-1.58).

2.4.1.1 Interactions

EFSA (2015) concluded that other common constituents of energy drinks at concentrations commonly present in such beverages (typically about 400 mg/100 ml and 240 mg/100 ml of taurine and D-glucurono- γ -lactone, respectively) would not affect the safety of single doses of caffeine up to 200 mg. Alcohol consumption at doses up to about 0.65 g/kg bw, leading to a blood alcohol concentration of about 0.08 %, would not affect the safety of single doses of caffeine up to 200 mg. EFSA also assessed whether p-synephrine, a substance present in combination with caffeine in a number of food supplements, modifies the acute cardiovascular effects of single doses of caffeine. They concluded that this has not been adequately investigated in humans and no conclusions could therefore be drawn.

2.4.1.2 Allergic sensitisation (including adjuvant effects)

There was no information concerning allergic sensitisation or allergy adjuvant effects in the literature reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

2.4.2 Mode of action for adverse effects

Caffeine acts as an antagonist to adenosine A1 and A2A receptors that are expressed in the central nervous system, and this is an important mechanism for the effects of caffeine. In addition, caffeine facilitates dopamine D2 receptor transmission, and is known as a non-specific phosphodiesterase inhibitor. The interaction with the adenosine A1 receptor, leading to inhibition of renal re-absorption and causing diuresis and natriuresis, can explain the diuretic activity of caffeine (EFSA, 2015). The mechanisms for the tolerance to caffeine observed after repeated administration is not well understood. The different sensitivity to levels to caffeine may be explained by polymorphisms in adenosine receptors (ANSES, 2013; EFSA, 2015). However, genetic polymorphisms for genes involved in caffeine metabolism have been shown to explain only a small proportion of the inter-individual variability in caffeine intake during and after pregnancy, and there is no evidence that such polymorphisms influence the risk of adverse birth weight-related outcomes significantly, although prospective studies investigating this topic are lacking (EFSA, 2015).

2.4.3 Vulnerable groups

For children and adolescents, a LOAL of 2.5 mg/kg bw per day for anxiety and jitteriness, and NOEL- and LOEL-values of 0.3 and 1.0–1.3 mg/kg bw per day for tolerance development, respectively, were identified by the Nordic Council of Ministers (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2008). The Superior Health Council concluded that for children, including preadolescents, the upper intake level of caffeine is 2.5 mg/kg bw per day (The Superior Health Council, 2012). EFSA proposed a safety level of 3 mg/kg bw per day for single doses of caffeine and habitual caffeine consumption (EFSA, 2015).

For pregnant women (adults), SCF concluded that intakes of caffeine up to 300 mg/day appeared to be safe. VKM concluded that the intake of caffeine in pregnant women should not exceed 100-200 mg/day (VKM, 2005; VKM, 2009). NNT 2005 concluded that "caffeine, especially at high doses, could affect the pregnancy in a negative way (induce spontaneous abortion, and possibly result in foetal growth retardation). Hence, a reduction in (total) caffeine intake (from all sources) should be advised for women being pregnant or planning pregnancy and already having a high caffeine intake". COT (2008) concluded that caffeine consumption during pregnancy was associated with an increased risk of fetal growth restriction, and that it seemed likely that risk was increased in association with intakes in the order of 200 mg per day and perhaps even lower. The Superior Health Council (2012) concluded that the maximum daily intake should not exceed 300 mg/day, or even 200 mg/day. EFSA (2015) specified that two prospective cohort studies showed a dose-dependent positive association between caffeine intake during pregnancy from all dietary sources and the risk of adverse birth weight-related outcomes. EFSA (2015) also specified that the relationship between caffeine intakes and adverse birth weight-related outcomes was observed at all levels of intake, with no threshold below which the relationship is not observed. EFSA (2015) concluded that caffeine intake up to 200 mg per day consumed

throughout the day by pregnant women do not give rise to safety concerns (effects of clinical relevance) for the fetus.

A study by Sengpiel et al. (2013) was included in the safety assessment by EFSA (2015). Since this is based on a Norwegian cohort (the Norwegian Mother and Child Cohort Study) including a large number of participants, it is also included in the present risk assessment. The association between maternal caffeine intake from different sources and gestational length, particularly the risk for spontaneous preterm delivery birth weight and the baby being small for gestational age, was investigated. A total of 59123 participants were included, and caffeine intake from different sources was self-reported at gestational weeks 17, 22 and 30. Median caffeine intake pre-pregnancy was 126 mg/day, at gestational week 17 it was 44 mg/day, and at gestational week 30 it was 62 mg/day. Caffeine was not associated with spontaneous preterm delivery risk. Caffeine intake from different sources was associated with lower birth weight, and caffeine intake of 200 to 300 mg/day significantly increased the odds for the baby being small for gestational age compared to 0 to 50 mg/day.

For lactating women, EFSA (2015) concluded that single doses of caffeine up to 200 mg per day do not give rise to safety concerns for the breastfed infant.

2.5 Summary of hazard identification and characterisation

Several studies and assessments addressing safety or risk of caffeine have been performed. An overview of the conclusions in the included literature is given in Tables 2.5-1 (general population), 2.5-2 (children and adolescents), 2.5-3 (pregnant women) and 2.5-4 (lactating women). Some of the previous reports included in the present risk assessment (ANSES, 2013; NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2008; SCF, 1999; SCF, 2003; The Superior Health Council, 2012) were also included in the safety assessment of caffeine prepared by EFSA (2015). An overview of the caffeine intake unlikely to cause adverse health effects that is used for the risk characterisation in the present risk assessment (chapter 4) is given in Table 2.5-5.

Table 2.5-1 An overview of conclusions in the included literature with regard to the general adult population.

Safety/risk assessment	General adult population
EFSA (2015)	<p>Single intake of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) do not give rise to safety concerns.</p> <p>Intakes 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 adults in the general population, except for pregnant women.</p> <p>Caffeine intake of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in adults.</p>

Safety/risk assessment	General adult population
The Superior Health Council (2012)	<p>The limit above which increased anxiety can be observed is 3 mg/kg bw per day.</p> <p>Most studies indicate that exposure to 5.7 mg/kg/day (400 mg/day for a 70 kg adult) of caffeine is not linked to any adverse effects.</p>

Table 2.5-2 An overview of conclusions in the included literature with regard to children and adolescents.

Safety/risk assessment	Children and adolescents
EFSA (2015)	<p>3 mg/kg bw per day for a daily intake do not give rise to safety concerns.</p> <p>Caffeine doses of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents.</p>
The Superior Health Council (2012)	The safe upper intake level of caffeine is 2.5 mg/kg/day.
NNT (Nordic Working Group on Food Toxicology and Risk Evaluation) (2008)	<p>A LOAL of 2.5 mg/kg bw per day for anxiety and jitteriness was identified.</p> <p>NOEL and LOEL values of 0.3 and 1.0–1.3 mg/kg bw per day for tolerance development were identified.</p>

Table 2.5-3 An overview of conclusions in the included literature with regard to pregnant women and fetus.

Safety/risk assessments and articles	Pregnant women and the fetus
EFSA (2015)	Caffeine intake up to 200 mg per day consumed throughout the day by pregnant women does not give rise to safety concerns for the fetus.
Li et al. (2015)	<p>Prospective cohort study.</p> <p><i>In utero</i> exposure to caffeine overall was associated with 87% increased risk of childhood obesity. A dose-response relationship for maternal daily caffeine intake was demonstrated; for intake <150 mg per day during pregnancy, OR = 1.77 (95% confidence interval: 1.05-3.00) and for caffeine intake ≥150 mg per day during pregnancy, OR = 2.37 (95% confidence interval: 1.24-4.52).</p>
Okubo et al. (2015)	<p>Prospective birth cohort (the Osaka Maternal and Child Health Study).</p> <p>The maternal total caffeine intake during pregnancy was associated with an increased risk of preterm birth; odds ratio per 100 mg/day caffeine increase was 1.28 (95% confidence interval: 1.03-1.58).</p>

Safety/risk assessments and articles	Pregnant women and the fetus
Greenwood et al. (2014)	Meta-analysis. An association between caffeine intake (pooled estimates of relative risk from linear dose-response meta-analysis per 100 mg/day) and incidence of miscarriage, stillbirth, low birth weight and small for gestational age was observed.
Sengpiel et al. (2013)	Norwegian cohort (the Norwegian Mother and Child Cohort Study). Caffeine intake from different sources was associated with lower birth weight, and caffeine intake of 200 to 300 mg/day significantly increased the odds for the baby being small for gestational age compared to 0 to 50 mg/day.
The Superior Health Council (2012)	The maximum daily intake should not exceed 300 mg/day, or even 200 mg/day.
COT (2008)	Caffeine consumption during pregnancy is associated with an increased risk of fetal growth restriction, and it seems likely that risk is increased in association with intakes in the order of 200 mg per day and perhaps even lower.
VKM (2005) VKM (2009)	Intake of caffeine in pregnant women should not exceed 100-200 mg/day.
NNT (Nordic Working Group on Food Toxicology and Risk Evaluation) (2005)	Caffeine, especially at high doses, could affect the pregnancy in a negative way (induce spontaneous abortion, and possibly result in foetal growth retardation). Hence, a reduction in (total) caffeine intake (from all sources) should be advised for women being pregnant or planning pregnancy and already having a high caffeine intake.
SCF (2003)	An intake of caffeine up to 300 mg/day appears to be safe.

Table 2.5-4 An overview of conclusions in the included literature with regard to lactating women and the breastfed infant.

Safety/risk assessment	Lactating women and the breastfed infant
EFSA (2015)	Single doses of caffeine up to 200 mg and habitual caffeine consumption at doses of 200 mg per day do not give rise to safety concerns for the breastfed infant.

Table 2.5-5 An overview of the caffeine intake unlikely to cause adverse health effects used in the risk characterization.

Population group	Caffeine intake unlikely to cause adverse health effects
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Population group	Caffeine intake unlikely to cause adverse health effects
General population (not including pregnant women)	<p>Single intake of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) do not give rise to safety concerns.</p> <p>Intakes 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 adults in the general population, except for pregnant women.</p> <p>Caffeine intake of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in adults.</p>
Children and adolescents	<p>3 mg/kg bw per day for a daily intake do not give rise to safety concerns.</p> <p>Caffeine doses of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents.</p>
Pregnant women and fetus	<p>200 mg per day (about 3 mg/kg bw for a 70-kg adult) consumed throughout the day do not give rise to safety concerns.</p> <p>With regard to caffeine intake and adverse birth weight-related outcomes, it was concluded that these outcomes were observed at all levels of caffeine intake, with no threshold below which the relationship was not observed. It was considered that the risk becomes clinically relevant at total daily doses of about 200 mg of caffeine from all sources. Sengpiel et al. (2013) reported that caffeine intake from different sources was associated with lower birth weight, and caffeine intake of 200 to 300 mg/day significantly increased the odds for the baby being small for gestational age compared to 0 to 50 mg/day. Therefore, the safety of doses of 50 to 200 mg/kg bw caffeine per day is still uncertain for pregnant women and fetus.</p>
Lactating women and the breastfed infant	<p>Single doses of caffeine up to 200 mg (about 3 mg/kg bw) and habitual caffeine consumption at doses of 200 mg per day do not give rise to safety concerns.</p>

The values used for comparison with the estimated exposure in the risk characterization are the intake levels considered unlikely to cause adverse health effects in the new and comprehensive risk assessment by EFSA (2015), see Table 2.5-5. With regard to the value used for pregnant women and fetus, the results from the study by Sengpiel et al. (2013) are also used in the risk characterisation.

3 Exposure / Intake

Exposure to caffeine was estimated from the intake of food supplements and energy drinks. For food supplements, the intake of caffeine was estimated for the age groups 10 to <14 years, 14 to <18 years and adults (≥ 18 years), whereas for energy drinks the age group 3 to <10 years was included in addition to the above-mentioned groups.

3.1 Food supplements

NFSA requested VKM to perform a risk assessment of 100 and 300 mg/day of caffeine in food supplement for children above 10 years, adolescents and adults. The default body weights (bw) for age groups determined by EFSA were used (EFSA, 2012): 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and adults; 70.0 kg. From a daily dose of 100 mg caffeine, the calculated intake levels are 2.3, 1.6 and 1.4 mg/kg bw per day for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥ 18 years), respectively. From a daily dose of 300 mg caffeine, the calculated intake levels are 6.9, 4.9 and 4.3 mg/kg bw per day for the same age groups, respectively (Table 3.1-1).

Table 3.1-1 Estimated exposure of caffeine from food supplements.

Intake (mg/kg bw per day)	Daily doses (mg)	
	100	300
Children (10 to <14 years)	2.3	6.9
Adolescents (14 to <18 years)	1.6	4.9
Adults (≥ 18 years)	1.4	4.3

3.2 Energy drinks

NFSA requested VKM to perform a risk assessment of 32 mg/100 ml of caffeine for the age groups children (3 to <10 and 10 to <14 years), adolescents (14 to <18 years) and adults (≥ 18 years). The default body weights (bw) for these groups determined by EFSA were used: 3 to <10 years; 23.1 kg, 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and adults; 70.0 kg (EFSA, 2012).

The consumption of energy drinks has been estimated for three drinking patterns: high acute consumption, mean chronic and high chronic consumption. In Table 3.2-1, the estimated intake of energy drinks for the various age groups in the three intake scenarios is shown.

High acute consumption

For children (3 to <10 and 10 to <14 years), the high acute consumption was based on a small Norwegian food consumption survey (Johansen and Andersen, 2013) and an actual

case of high acute intake of energy drinks reported in the media (Storvik, 2014). Based on expert judgment, the values used are about 0.5 l higher than the maximum reported intake of soft drinks and "saft" in this survey ("saft" is a concentrate that shall be mixed with water before drinking).

For adolescents (14 to <18 years) and adults (≥ 18 years), the high acute consumption was based on the food consumption survey Norkost 3 (Totland et al., 2012). The 97.5 percentile for total intake of soft drinks and "saft" in this survey (18-70 years) was 1.5 l and the maximum reported intake of soft drinks and "saft" in Norkost 3 was about 2 l. Based on expert judgement, the value used is the maximum reported intake of soft drinks and "saft".

Mean chronic and high chronic consumption

The daily mean and high chronic intakes were based on a report from the Technical University of Denmark (DTU) (Christensen LM et al., 2014) for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥ 18 years). Children aged 3 to <10 years were not included in the report from DTU (Christensen LM et al., 2014). To estimate mean chronic and high chronic intake for this age group, the ratio for the intake of energy drinks per day and kg bw were calculated for the age group 10 to <14 years using the intake reported by DTU and the default bw set by EFSA (EFSA, 2012). Based on the default values for intake of drinks per day and bw, this ratio was used to estimate the intake for the age group 3 to <10 years.

Table 3.2-1 The estimated intake of energy drinks (ml/day) for the various age groups in the three intake scenarios.

Age groups	Consumption (ml/day)		
	High acute	Mean chronic	High chronic
Children (3 to <10 years)	1000	58	163
Children (10 to <14 years)	1500	65	180
Adolescents (14 to <18 years)	2000	64	211
Adults (≥ 18 years)	2000	71	320

Estimated exposures

The estimated exposure to caffeine from energy drinks (containing 32 mg caffeine per 100 ml) for the various age groups in the three scenarios is presented in Table 3.2-2.

For 3 to <10 year old children, the intake level of caffeine has been estimated to be 13.9 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels were 0.8 and 2.3 mg/kg bw per day, respectively.

For 10 to <14 year old children, the intake level of caffeine has been estimated to be 11.1 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels were 0.5 and 1.3 mg/kg bw per day, respectively.

For 14 to <18 year old adolescents, the intake level of caffeine has been estimated to 10.4 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels were 0.3 and 1.1 mg/kg bw per day, respectively.

For adults (≥ 18 years), the intake level of caffeine has been estimated to be 9.1 mg/kg bw per day for high acute consumption of energy drinks. For mean and high chronic consumption of energy drinks, the intake levels were 0.3 and 1.5 mg/kg bw per day, respectively.

Table 3.2-2 Estimated exposure to caffeine from energy drinks for the various age groups in the three scenarios.

Age groups	Intake scenarios	Estimated exposure (mg/kg bw per day)
		32 mg/100 ml
Children (3 to <10 years)	High acute	13.9
	Mean chronic	0.8
	High chronic	2.3
Children (10 to <14 years)	High acute	11.1
	Mean chronic	0.5
	High chronic	1.3
Adolescents (14 to <18 years)	High acute	10.4
	Mean chronic	0.3
	High chronic	1.1
Adults (≥ 18 years)	High acute	9.1
	Mean chronic	0.3
	High chronic	1.5

3.3 Other sources

The main sources of caffeine in the diet include coffee, tea, caffeinated soft drinks (including energy drinks) and chocolate (EFSA, 2015). The daily intake of caffeine from all sources was calculated by EFSA using the EFSA Comprehensive European Food Consumption Database and for adults from 16 EU Member States, where the means and 95th percentiles ranged from 37 to 319 mg and from 109 to 742 mg, respectively (EFSA, 2015).

In the EU, caffeine can be used in cosmetic products (European Commission Health and Consumers, 2015).

3.4 Summary of exposure / intake

NFSA requested VKM to perform a risk assessment of caffeine in food supplements (100 and 300 mg per day) and energy drinks (32 mg caffeine/100 ml). For food supplements, this was performed for the general population, ages 10 years and above. For energy drinks, this was

performed for the general population, ages 3 years and above, and for drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake.

For food supplements, the intake of caffeine from the doses of 100 and 300 mg/day was 2.3 and 6.9 mg/kg bw per day for children, 1.6 and 4.9 mg/kg bw per day for adolescents, and 1.4 and 4.3 mg/kg bw per day for adults, respectively.

For energy drinks, the highest intake of caffeine was found for the age group 3 to <10 year old children with high acute, mean chronic and high chronic exposure of 13.9, 0.8 and 2.3 mg/kg bw per day, respectively. For the other age groups, the exposure to caffeine ranged from 9.1 to 11.1 mg/kg bw per day for high acute exposure, from 0.3 to 0.5 mg/kg bw per day for mean chronic exposure and from 1.1 to 1.5 mg/kg bw per day for high chronic exposure.

4 Risk characterisation

The risk characterisation in the present risk assessment is based on the caffeine doses assumed to be unlikely to cause adverse health effects in different population groups presented in Table 4-1.

Table 4-1 The values for comparison used in the risk characterization.

Population group	Caffeine intake unlikely to cause adverse health effects
General population (not including pregnant women)	<p>Single intake of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) do not give rise to safety concerns.</p> <p>Intakes 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 adults in the general population, except for pregnant women.</p> <p>Caffeine intake of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in adults.</p>
Children and adolescents	<p>3 mg/kg bw per day for a daily intake.</p> <p>Caffeine doses of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents.</p>
Pregnant women and fetus	<p>200 mg per day (about 3 mg/kg bw for a 70-kg adult) consumed throughout the day.</p> <p>With regard to caffeine intake and adverse birth weight-related outcomes, it was concluded that these outcomes are observed at all levels of caffeine intake, with no threshold below which the relationship is not observed. It was considered that the risk becomes clinically relevant at total daily doses of about 200 mg of caffeine from all sources. Sengpiel et al. (2013) reported that caffeine intake from different sources was associated with lower birth weight, and that caffeine intake of 200 to 300 mg/day significantly increased the odds for the baby being small for gestational age compared to 0 to 50 mg/day.</p> <p>Therefore, the safety of doses of 50 to 200 mg/kg bw caffeine per day is still uncertain for pregnant women and fetus.</p>
Lactating women and the breastfed infant	<p>Single doses of caffeine up to 200 mg (about 3 mg/kg bw) and habitual caffeine consumption at doses of 200 mg per day.</p>

4.1 Food supplements

NFSA requested VKM to perform a risk assessment of 100 and 300 mg/day of caffeine in food supplement for the general population, ages 10 years and above.

For the dose of **100 mg/day**, the intakes were 2.3, 1.6 and 1.4 mg/kg bw per day for children, adolescents and adults, respectively (Table 3.1-1).

For children (10 to <14 years), this value is below the intake reported not to induce adverse effects. However, the intake is also above the intake that may increase sleep latency and reduce sleep duration.

For adolescents (14 to <18 years), this value is below the intake reported not to induce adverse effects. However, the intake is also above the intake that may increase sleep latency and reduce sleep duration.

For adults (≥ 18 years), this value is below the intake reported not to induce adverse effects. However, the intake is equal to the intake that may increase sleep latency and reduce sleep duration. For pregnant women and fetus and lactating women and the breastfed infant, this is below the intake reported not to induce adverse effects.

For the dose of **300 mg/day**, the intakes were 6.9, 4.9 and 4.3 mg/kg bw per day for children, adolescents and adults, respectively (Table 3.1-1).

For children (10 to <14 years), this value is above the intake reported not to induce adverse effects. The intake is also above the intake that may increase sleep latency and reduce sleep duration.

For adolescents (14 to <18 years), this value is above the intake reported not to induce adverse effects. The intake is also above the intake that may increase sleep latency and reduce sleep duration.

For adults (≥ 18 years), the intake is above the single dose assumed to be safe and the intake that may increase sleep latency and reduce sleep duration. Further, the intake is below the total daily intake assumed to be safe. For pregnant women and fetus and lactating women and the breastfed infant, this intake is above the intake reported not to induce adverse effects. The intake is also above the intake that may increase sleep latency and reduce sleep duration.

4.2 Energy drinks

NFSA requested VKM to perform a risk assessment of 32 mg caffeine/100 ml energy drink for the general population, ages 3 years and above, and for drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake.

High acute drinking pattern

The estimated exposures to caffeine from a drinking pattern reflecting a high acute intake of caffeine from energy drinks were 13.9, 11.1, 10.4 and 9.1 mg/kg bw per day for children (3

to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥ 18 years), respectively (Table 3.2-2).

For children (3 to <10 years), the exposure is above the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

For children (10 to <14 years), the exposure is above the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

For adolescents (14 to <18 years), the exposure is above the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

For adults (≥ 18 years), including pregnant women and fetus and lactating women and the breastfed infant, the exposure is above the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

Mean chronic drinking pattern

The estimated exposures to caffeine from a drinking pattern reflecting a mean chronic intake of caffeine from energy drinks were 0.8, 0.5, 0.3 and 0.3 mg/kg bw per day for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥ 18 years), respectively (Table 3.2-2).

For children (3 to <10 years), the exposure is below the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

For children (10 to <14 years), the exposure is below the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

For adolescents (14 to <18 years), the exposure is below the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

For adults (≥ 18 years), including pregnant women and fetus and lactating women and the breastfed infant, the exposure is below the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

High chronic drinking pattern

The estimated exposures to caffeine from a drinking pattern reflecting a high chronic intake of caffeine from energy drinks were 2.3, 1.3, 1.1 and 1.5 mg/kg bw per day for children (3 to <10 years), children (10 to <14 years), adolescents (14 to <18 years) and adults (≥ 18 years), respectively (Table 3.2-2).

For children (3 to <10 years), the exposure is below the intake reported not to induce adverse effects. However, it is above the intake that may increase sleep latency and reduce sleep duration.

For children (10 to <14 years), the exposure is below the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

For adolescents (14 to <18 years), the exposure is below the intake reported not to induce adverse effects and the intake that may increase sleep latency and reduce sleep duration.

For adults (≥ 18 years), including pregnant women and fetus and lactating women and the breastfed infant, the exposure is below the intake reported not to induce adverse effects. However, it is above the intake that may increase sleep latency and reduce sleep duration.

5 Uncertainties

5.1 Hazard identification and characterisation

Caffeine intakes of no concern derived for acute caffeine consumption by adults were used to derive intakes of no concern for children and adolescents, both single doses and daily intake.

There is uncertainty regarding the effects on the fetus from doses of caffeine in pregnant women between 50 and 200 mg/kg bw per day.

5.2 Exposure

With use of the default (mean) body weight of an age (population) group, the variance in all individuals in the group will not be covered.

Drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake are included in the present risk assessment. The intakes of energy drinks for the various age groups for the three drinking patterns are estimates based on previous dietary surveys and expert judgement.

6 Conclusions with answers to the terms of reference

The Norwegian Food Safety Authority (NFSA) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of caffeine in food supplements at the following doses: 100 and 300 mg/day, and energy drinks at the following dose: 32 mg/100 ml.

Many human studies of adverse effects of caffeine have been published, including e.g. adverse birth weight-related outcomes, increased sleep latency and reduced sleep duration. Risk/safety assessments of caffeine have been performed by several authoritative bodies, and intake levels of caffeine for different population groups (children, adolescents, pregnant women and the fetus, lactating women and the breastfed infant and adults) that do not induce adverse effects have been reported.

The present risk assessment includes 100 and 300 mg/day of caffeine in food supplements for the general population, ages 10 years and above, and 32 mg caffeine/100 ml energy drink for the general population, ages 3 years and above for drinking patterns reflecting a high acute intake, a mean chronic intake and a high chronic intake. Also the vulnerable groups pregnant women and the fetus and lactating women and the breastfed infant, were considered in this risk assessment.

VKM concludes that it is unlikely that a dose of 100 mg of caffeine per day from food supplements causes adverse health effects in children (10 years and above), adolescents (14 to <18 years), pregnant women and the fetus, lactating women and the breastfed infant and adults (≥ 18 years). However, for children and adolescents, a dose of 100 mg per day is above the intake that may increase sleep latency and reduce sleep duration. For adults, a dose of 100 mg per day is equal to the intake that may increase sleep latency and reduce sleep duration.

VKM concludes that a dose of 300 mg of caffeine per day from food supplements may represent a risk of adverse health effects in children (10 years and above), adolescents (14 to <18 years), pregnant women and the fetus and lactating women and the breastfed infant. Consumed as a single dose, 300 mg of caffeine from food supplement may represent a risk of adverse health effects in adults (≥ 18 years). Consumed throughout the day, it is unlikely that a dose of 300 mg of caffeine per day from food supplements causes adverse health effects in adults. A dose of 300 mg per day is above the intake that may increase sleep latency and reduce sleep duration.

An overview of the conclusions on caffeine in food supplements is given in Table 6-1. Estimated exposures unlikely to cause adverse health effects (below the value for comparison) is shown in green, whereas estimated exposures that may represent a risk of

adverse health effects or may increase sleep latency and reduce sleep duration (above the respective values for comparison) is shown in red.

Table 6-1. An overview of the conclusions on caffeine in food supplements. Green: estimated exposure unlikely to cause adverse health effects. Red: estimated exposure that may represent a risk of adverse health effects or may increase sleep latency and reduce sleep duration.

Caffeine				
Food supplement	100 mg/day	100 mg/day	300 mg/day	300 mg/day
Age groups	May represent a risk of adverse health effects	May increase sleep latency and reduce sleep duration	May represent a risk of adverse health effects	May increase sleep latency and reduce sleep duration
Children (10 to <14 years)				
Adolescents (14 to <18 years)				
Adults (≥18 years), not including pregnant or lactating women			Consumed as a single dose	
			Consumed throughout the day	
Pregnant women and the fetus				
Lactating women and the breastfed infant				

The estimated exposure to caffeine from a drinking pattern reflecting a high acute intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) is 13.9 mg/kg bw per day for children (3 to <10 years), 11.1 mg/kg bw per day for children (10 to <14 years), 10.4 mg/kg bw per day for adolescents (14 to <18 years) and 9.1 mg/kg bw per day for adults (≥18 years).

VKM concludes that a drinking pattern reflecting a high acute intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) may represent a risk of adverse health effects in children (3 years and above), adolescents (14 to <18 years), pregnant women and the fetus, lactating women and the breastfed infant and adults (≥18 years). In addition, the intake is above the intake that may increase sleep latency and reduce sleep duration.

The estimated exposure to caffeine from a drinking pattern reflecting a mean chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) is 0.8 mg/kg bw per day for children (3 to <10 years), 0.5 mg/kg bw per day for children (10 to <14 years), 0.3

mg/kg bw per day for adolescents (14 to <18 years) and 0.3 mg/kg bw per day for adults (≥18 years).

VKM concludes that it is unlikely that a drinking pattern reflecting a mean chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) causes adverse health effects in children (3 years and above), adolescents (14 to <18 years), pregnant women and the fetus, lactating women and the breastfed infant and adults (≥18 years). In addition, the intake is below the intake that may increase sleep latency and reduce sleep duration.

The estimated exposure to caffeine from a drinking pattern reflecting a high chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) is 2.3 mg/kg bw per day for children (3 to <10 years), 1.3 mg/kg bw per day for children (10 to <14 years), 1.1 mg/kg bw per day for adolescents (14 to <18 years) and 1.5 mg/kg bw per day for adults (≥18 years).

VKM concludes that it is unlikely that a drinking pattern reflecting a high chronic intake of caffeine from energy drinks (containing 32 mg caffeine/100 ml) causes adverse health effects in children (3 years and above), adolescents (14 to <18 years), pregnant women and the fetus, lactating women and the breastfed infant and adults (≥18 years). For children (3 to <10 years) and adults (≥18 years), the intake is above the intake that may increase sleep latency and reduce sleep duration. For children (10 to <14 years) and adolescents (14 to <18 years), the intake is below the intake that may increase sleep latency and reduce sleep duration.

An overview of the conclusions on caffeine in food supplements is given in Table 6-2. Estimated exposures unlikely to cause adverse health effects (below the value for comparison) is shown in green, whereas estimated exposures that may represent a risk of adverse health effects or may increase sleep latency and reduce sleep duration (above the respective values for comparison) is shown in red.

Table 6-2. An overview of the conclusions on caffeine in energy drinks. Green: estimated exposure unlikely to cause adverse health effects. Red: estimated exposure that may represent a risk of adverse health effects or may increase sleep latency and reduce sleep duration.

Caffeine						
Energy drink 32 mg/ 100 ml	High acute drinking pattern		Mean chronic drinking pattern		High chronic drinking pattern	
	May represent a risk of adverse health effects	May increase sleep latency and reduce sleep duration	May represent a risk of adverse health effects	May increase sleep latency and reduce sleep duration	May represent a risk of adverse health effects	May increase sleep latency and reduce sleep duration
Age groups						
Children (3 to <10 years)	Red	Red	Green	Green	Green	Red
Children (10 to <14 years)	Red	Red	Green	Green	Green	Green
Adolescents (14 to <18 years)	Red	Red	Green	Green	Green	Green
Adults (≥18 years), not including pregnant or lactating women	Red	Red	Green	Green	Green	Red
Pregnant women and the fetus	Red	Red	Green	Green	Green	Red
Lactating women and the breastfed infant	Red	Red	Green	Green	Green	Red

7 Data gaps

There is lack of data to derive single doses of caffeine and daily caffeine intakes of no concern from studies performed specifically on children and adolescents.

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9 Appendix

Search Strategy

Database: Ovid MEDLINE(R) <1946 to June Week 2 2015>, Embase <1974 to 2015 June 18>

1. caffeine*.ti. (20310)
2. (risk* or safety or adverse or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or toxicity or toxic).tw. (8800681)
3. 1 and 2 (4475)
4. (conference abstract* or letter* or editorial*).pt. (4470284)
5. 3 not 4 (4151)
6. limit 5 to (danish or english or norwegian or swedish) (3953)
7. limit 6 to yr="2013 -Current" (427)
8. remove duplicates from 7 (256)