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Risk assessment of energy drinks and caffeine

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

Report from the Norwegian Scientific Committee for Food and Environment (VKM) 2019: 01
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Risk assessment of energy drinks and caffeine

Authors of the opinion

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to answer the request. The project group consisted of eight persons, including a project leader from the VKM secretariat. The VKM Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics (the Panel from now onward) evaluated and approved the final opinion:

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In addition to Ellen Bruzell, Monica Hauger Carlsen, Berit Granum, Trine Husøy, Josef Daniel Rasinger and Camilla Svendsen, these were (in alphabetical order):

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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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Short summary

The Royal Norwegian Ministry of Health and Care Services asked the Norwegian Food Safety Authority (NFSA) to investigate and recommend measures to protect children and adolescents from adverse health effects caused by high consumption of energy drinks. The NFSA requested the Norwegian Scientific Committee for Food and Environment (VKM) to assess potential adverse health effects of energy drinks and caffeine in children and adolescents.

The population groups included in the current assessment are children and adolescents aged 8 to (and including) 18 years. Possible effects of energy drinks and caffeine on pregnant and lactating women, foetuses, and children aged 0 to 7 years are not assessed.

Data from the following studies and surveys were used to estimate energy drink consumption for different drinking patterns: The Ungkost 3 study, the Norwegian Consumer Council study, the Norwegian Mother and Child Cohort Study follow-up study and the Ungdata survey. Median (the middle number) chronic (long-lasting) intake in consumers of energy drinks was estimated to be in the range of less than 1 to 81 ml per day, and high chronic intake (95-percentile) varied from 114 to 418 ml per day. The highest acute (24 hour short-term) intake ranged from 400 ml among children aged 8-9 in the Ungkost 3 study, to 10 litres consumed by one participant (16-18-year age group) in the Norwegian Consumer Council study.

Data from the Ungkost 3 study and the Norwegian Consumer Council study were also used to estimate caffeine exposure from other food and beverages with caffeine.

The hazard assessment was based on risk assessments, reports and randomised, controlled trials (RCTs) published in the period 2013 to 2018. Literature searches were performed by an expert librarian and the publication selection was based on predefined criteria. Risk of bias and the confidence in the evidence of the RCTs were evaluated.

The Panel could not establish a toxicological reference point for energy drinks due to lack of data. Since no additional adverse effects were observed and the effects were not expressed differently than those that could be attributed to the caffeine content of the energy drinks (up to the investigated dose of about 6 mg caffeine per kg bw per day), the Panel applied the two following toxicological reference points set by EFSA (2015) in the current assessment:

3 mg caffeine per kg body weight per day for general adverse health effects, such as effects on the cardiovascular and central nervous system.

1.4 mg caffeine per kg body weight per day for sleep disturbance.

VKM reached the following conclusions:

- The average caffeine intake of those who drink energy drinks tends to be higher than for similar groups who do not consume energy drinks.

- For energy drinks, given the following scenarios for caffeine concentrations: all energy drinks contain 15 mg caffeine per 100 ml; all energy drinks contain 32 mg caffeine per 100 ml; all energy drinks contain 40 mg caffeine per 100 ml; all energy drinks contain 55 mg per 100 ml:
  Risk for sleep disturbance
    - In the age group 8-12 years, high chronic intake of energy drinks may represent a risk for sleep disturbance for children if all consumed energy drinks contain either 40 or 55 mg caffeine/100 ml.
    - In the age group 13-15 years, high chronic intake of energy drinks may represent a risk for sleep disturbance for adolescents if all consumed energy drinks contain either 32, 40 or 55 mg caffeine/100 ml.
    - In the age group 16-18 years, high chronic intake of energy drinks may represent a risk for sleep disturbance for adolescents if all consumed energy drinks contain either 32, 40 or 55 mg caffeine/100 ml.

  Risk for general adverse health effects and sleep disturbance

  Note that all caffeine exposures that may represent a risk for general adverse health effects also may represent a risk for sleep disturbance.
    - In the age group 13-15 years, high chronic intake of energy drinks may represent a risk for general adverse health effects if all consumed energy drinks contain either 40 or 55 mg caffeine/100 ml.
    - The highest acute intake estimates of energy drinks, if all consumed energy drinks contain either 15, 32, 40 or 55 mg caffeine/100 ml and above, may all represent a risk for general adverse health effects in all age groups.

  For all other included scenarios of energy drink consumption, there was no or low risk. This was also the case for energy drink consumption combined with physical activity or alcohol consumption.

- For caffeine exposure from food and beverages (not including energy drinks):
  Risk for sleep disturbance
    - Among consumers and non-consumers of energy drinks aged 16 - 18 years, who had a high exposure of caffeine from other beverages than energy drinks, this exposure may represent a risk for sleep disturbances. In the age group 13 - 15 years of age, the same is true for consumers of energy drinks, but not for non-consumers.

  Risk for general adverse health effects and sleep disturbance

  Note that all caffeine exposures that may represent a risk for general adverse health effects also may represent a risk for sleep disturbance.
    - For consumers of energy-drinks aged 10 - 12 years who have a high intake of caffeine from other beverages than energy drinks, this exposure may in itself represent a risk for general adverse health effects.

  All other included exposure estimations from food and beverages represented no or low risk.

- Groups in the population that may be more susceptible to the adverse effects of energy drinks and caffeine include individuals with predispositions to certain heart conditions. The reference point of 3 mg per kg body weight per day, may not necessarily protect individuals in susceptible groups.

Key words: Adverse effect, caffeine, energy drink, Norwegian Scientific Committee for Food and Environment, risk assessment, VKM

Kort sammendrag

Helse- og omsorgsdepartementet har bedt Mattilsynet om å utrede tiltak for å beskytte barn og unge mot helseskader som følge av høyt inntak av energidrikker. Mattilsynet har på den bakgrunn bedt Vitenskapskomiteen for mat og miljø (VKM) å vurdere potensielle negative helseeffekter knyttet til barn og unges inntak av energidrikker og koffein.

I denne risikovurderingen er aldersgruppene 8 til og med 18 år inkludert. Mulige effekter av energidrikker hos gravide, ammende og barn under 8 år er ikke vurdert.

For å anslå ulike drikkemønstre av energidrikk, ble data fra følgende studier brukt: Ungkost 3, Forbrukerrådets studie («Energidrikk, barn og unge»), den norske mor og barn-undersøkelsen oppfølgingsstudien og Ungdata-undersøkelsen. Mediant (midterste verdi) kronisk (langvarig) inntak ble beregnet å være fra mindre enn 1 til 81 ml per dag, mens høyt kronisk inntak (95-persentilen) varierte fra 114 til 418 ml per dag. Det høyeste akutte inntaket (i en 24-timers periode) var fra 400 ml, blant barn i alderen 8-9 år i Ungkost 3, til 10 liter, som ble rapportert av én person i aldersgruppen 16-18 år i Forbrukerrådets studie.

VKM beregnet koffeineksponering fra andre mat- og drikkevarer enn energidrikker ved hjelp av data fra Ungkost 3 og Forbrukerrådets studie.

Farevurderingen er basert på tidligere risikovurderinger, rapporter og randomiserte, kontrollerte studier (RCT) publisert i perioden 2013 til 2018. En bibliotekar med søkeekspertise utførte litteratursøkene. Prosjektgruppen valgte ut vitenskapelige artikler ut i fra forhåndsdefinerte kriterier i henhold til protokollen for oppdraget (Protocol for the risk assessment of energy drinks and caffeine, VKM et al., 2018), og både risiko for systematiske feil og kvaliteten på evidensen i de inkluderte RCT ble vurdert.

På grunn av mangel på data ble det ikke fastsatt et referansepunkt for negative helseeffekter av energidrikker. Ingen ytterligere negative helseeffekter ble observert og effektene ble ikke uttrykt annerledes enn det som kunne tilskrives effektene av koffeininnholdet i energidrikkene (opp til undersøkte dose på 6 mg koffein per kg kroppsvekt per dag). Derfor valgte panelet følgende referansepunkter for negative helseeffekter som er fastsatt av EFSA (2015) i den nåværende vurderingen:

3 mg koffein per kg kroppsvekt per dag. Dette gjelder for generelle negative helseeffekter som affekterer hjerte- og karsystemet og sentralnervesystemet.

1,4 mg koffein per kg kroppsvekt per dag. Dette gjelder for søvnforstyrrelser.

VKM konkluderer:

- Det gjennomsnittlige koffeininntaket hos den gruppen som drikker energidrikk har en tendens til å være høyere enn hos den gruppen som ikke drikker energidrikk.
- For energidrikker vurderes risikoen slik i henhold til referansepunktene over gitte følgende scenarier for koffein: all energidrikker inneholder 15 mg koffein per 100 ml;

alle energidrikker inneholder 32 mg koffein per 100 ml; alle energidrikker inneholder 40 mg koffein per 100 ml; alle energidrikker inneholder 55 mg koffein per 100 ml:
Risiko for søvnproblemer

- Et høyt kronisk inntak av energidrikk kan gi risiko for søvnproblemer hos 8-12-åringer gitt at all konsumert energidrikk inneholder enten 40 eller 55 mg koffein/100 ml.
- Et høyt kronisk inntak av energidrikk kan gi risiko for søvnproblemer hos 13-15-åringer gitt at all konsumert energidrikk inneholder enten 32, 40 eller 55 mg koffein/100 ml.
- Et høyt kronisk inntak av energidrikk kan gi risiko for søvnproblemer hos 16-18-åringer gitt at all konsumert energidrikk inneholder enten 32, 40 eller 55 mg koffein/100 ml.

Risiko for generelle negative helseeffekter og søvnproblemer

Merk at all koffeineksponering som utgjør en risiko for generelle negative helseeffekter også vil utgjøre en risiko for søvnforstyrrelser.

- Et høyt kronisk inntak av energidrikk kan gi risiko for generelle negative helseeffekter hos 13-15-åringer gitt at all konsumert energidrikk inneholder enten 40 eller 55 mg koffein/100 ml.
- Det høyeste akutte inntaket kan gi risiko for generelle negative helseeffekter hos barn og ungdom i alle aldersgruppene gitt at all konsumert energidrikk inneholder enten 15, 32, 40 eller 55 mg koffein/100 ml.

Det er lav eller ingen risiko forbundet med de andre undersøkte drikkemønstrene og koffeinkonsentrasjoner av energidrikk. Dette gjelder også for risiko som skyldes kombinert inntak av energidrikk og alkohol og når energidrikk inntas i forbindelse med fysisk aktivitet.

- For koffeineksponering fra mat og drikke (som ikke er energidrikk) vurderes risikoen slik i henhold til referansepunktene over:

  Risiko for søvnproblemer

  - Høyt inntak av koffein fra andre drikkevarer enn energidrikker kan utgjøre en risiko for søvnforstyrrelser for 16-18-åringer, både hos de som drikker energidrikker og de som ikke drikker energidrikker. Det samme gjelder for 13-15-åringer, men da kun for den gruppen som drikker energidrikker.

  Risiko for generelle negative helseeffekter og søvnproblemer

  Merk at all koffeineksponering som utgjør en risiko for generelle negative helseeffekter også vil utgjøre en risiko for søvnforstyrrelser.

  - Høyt inntak av koffein fra andre drikkevarer enn energidrikk kan utgjøre en risiko for generelle negative helseeffekter for 10-12-åringer, men dette gjelder kun den gruppen som drikker energidrikker.

Det er lav eller ingen risiko forbundet med de andre undersøkte eksponeringene for koffein fra annen mat og drikke enn energidrikk.

- Noen grupper i befolkningen som er mer utsatt for negative helseeffekter fra energidrikk og koffein enn andre, er blant andre de som er predisponert for enkelte hjertesykdommer. Referansepunktet på 3 mg per kg kroppsvekt per dag som er satt for generelle negative helseeffekter vil ikke nødvendigvis beskytte disse utsatte gruppene.

Abbreviations and glossary

Abbreviations

ANSES	French Agency for Food, Environmental and Occupational Health & Safety
BL	Baseline
Bw	Body weight
COI	Conflict of interest
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
NOEL	No observed effect level
EFSA	European Food Safety Authority
KBS	Dietary calculation system (In Norwegian: KostBeregningsSystem)
IEHIAS	Integrated Environmental Health Impact Assessment
NCC	Norwegian Consumer Council
NFSA	Norwegian Food Safety Authority
NR	Not reported
NTP	National Toxicology Program
OHAT	Office of Health Assessment and Translation
RoB	Risk of bias
VKM	Norwegian Scientific Committee for Food and Environment
WoE	Weight of evidence
RCT	Randomized controlled trials

Glossary

Energy drink

The energy drink definition used in the present assessment is given by the Norwegian Food Safety Authority in the Terms of Reference.

Adverse effect

An effect is considered "adverse" when leading to "change in the morphology, physiology, growth, development, reproduction or lifespan 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, 2009).

Consumption

Consumption in this risk assessment refers to the intake of energy drinks, other beverages or food, often given in gram per day. The terms "consumption" and "intake" are used interchangeably throughout the document.

Susceptibility

Susceptibility refers to the degree to which individuals or groups may respond to a given exposure to a hazard. This can be subdivided into innate and acquired susceptibility. Innate susceptibility is to a large extent due to genetic predisposition or to incomplete development of normal (adult) physiological functions. For example, a young child may be susceptible to a given pollutant because detoxification processes are not yet fully developed. Such susceptibility is transient and disappears with age and growth. Acquired susceptibility may be due to disease, age or socioeconomic status (IEHIAS, 2019).

QT interval

Q and T refer to waves in an electrocardiogram. The Q-wave is part of the QRS complex, which components are depolarisation waves, whereas the T-wave is a repolarisation wave. A contraction of the heart ventricle lasts for about the beginning of the Q-wave to the end of the T-wave, thereby the name QT interval. The interval lasts for about 0.35 s (Guyton and Hall, 2000).

Background as provided by the Norwegian Food Safety Authority

The Royal Norwegian Ministry of Health and Care Services has asked the Norwegian Food Safety Authority to investigate and recommend alternative measures to protect children and adolescents from adverse health effects caused by high consumption of energy drinks.

Support material for the study shall constitute amassed knowledge of the potential health risks and data pertaining to consumption among children and adolescents in Norway.

The Norwegian Food Safety Authority is required to present the findings of the investigation along with recommendations by 15 February 2019.

Terms of reference as provided by the Norwegian Food Safety Authority

VKM conducted a risk assessment of the ingredients of so-called energy drinks in 2009, as well as four separate assessments of caffeine, taurine, inositol, and glucuronolactone in 2015. The Norwegian Food Safety Authority (NFSA) seeks a new assessment of the potential adverse health effects of a) chronic mean consumption, b) chronic high consumption, and c) acute high consumption of energy drinks and caffeine among children and adolescents.

NFSA is predominantly interested in the age group between 9 and 18 years, but this will depend on the data available. A further breakdown of the material into different age ranges beyond this is likely also to be appropriate.

NFSA requests VKM to:

- Perform various scenario calculations pertaining to the caffeine content in energy drinks equivalent to 15, 32, 40 or 55 mg caffeine/100 ml
- Include other sources of caffeine (coffee drinks and tea drinks, chocolate milk, cocoa, etc.) in the exposure calculations, and perform a new literature search to ascertain any new knowledge of the health risks (post-2015) associated with the consumption of caffeine in addition to those indicated by the risk assessments conducted by VKM and EFSA
- Assess the potential health risks associated with the (simultaneous) consumption of energy drinks and alcohol
- Assess the potential health risks associated with the consumption of energy drinks in conjunction with physical activity and in relation to dehydration.

Definition (given by NFSA for the use in the present assessment)
The following definition of an energy drink applies to this request:
Energy drinks are non-alcoholic beverages that contain at least 150 mg of caffeine (from all sources) per litre, or at least 150 mg of caffeine (from all sources) per litre together with one or more additional substance or plant extract such as glucuronolactone, inositol, guarana alkaloids, ginseng, ginkgo extract, and taurine. They may also include added vitamins, minerals and/or amino acids.

The definition extends to energy drinks sweetened with sugar, or artificial sweetener, or both sugar and artificial sweetener.

Beverages based on coffee, tea, or coffee or tea extracts, where the name of the food includes the term "coffee" or "tea", are not covered by this definition of energy drinks. See Regulation on the Provision of Food Information to Consumers, Annex III.

Assessment

1 Introduction

The overall aim of the present risk assessment was to address and assess adverse health effects in children and adolescents (from 8-18 years) resulting from a) chronic mean consumption, b) chronic high consumption, and c) acute high consumption of energy drinks and caffeine.

VKM derived the following sub-objectives:

- Identify and characterise adverse health effects related to
    - intake of energy drinks as such
    - intake of caffeine as a single substance

  This separation will make it possible to evaluate whether energy drinks containing a given concentration of caffeine may result in other adverse effects than those resulting from similar concentration of caffeine from other sources
- Evaluate whether new studies imply revision of the caffeine doses that were established by the European Food Safety Authority (EFSA) «not to give rise to safety concern» (EFSA, 2015)
- Identify and assess adverse health effects related to combined intake of energy drinks and alcohol
- Identify and assess adverse health effects related to intake of energy drinks during physical activity, especially with respect to dehydration
- Estimate the total exposure to caffeine from food and beverages. This makes it possible to identify the main sources of caffeine for children and adolescents
- Estimate the consumption of energy drinks for three consumption patterns: high acute consumption, mean chronic and high chronic consumption
- Calculate the exposure to caffeine from the different consumption patterns if all consumed energy drinks contain 15, 32, 40 or 55 mg caffeine/100 ml
- Characterise the risk of energy drink consumption and caffeine exposure for the above-mentioned limitations
- Identify and describe factors contributing to uncertainty in the assessment

1.1 Limitations of the assignment

The included population groups are children and adolescents (from 8-18 years). Possible effects of energy drinks and caffeine on pregnant women, foetuses, lactating women and children aged 0 to-<8 years are not included.

The hazard assessment is based on risk assessments, reports and randomised controlled trials (RCTs) published in the period January 2013 to November 2018 (energy drinks) and

January 2013 to October 2018 (caffeine). The Panel chose to evaluate only the randomised controlled trials (RCT) identified from the literature search. A randomised controlled trial is "an experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body)" (Cochrane, 2019). As RCTs were the only type of articles included in the present risk assessment, endpoints, hypotheses and mechanisms of action described in human studies other than RCTs, in animal and *in vitro* studies were not included in this risk assessment.

With regard to the hazard assessment of energy drinks, the included literature was retrieved according to the energy drink definition given by NFSA.

2 General information

2.1 Regulation of energy drinks and caffeine

Energy drinks are regulated under the General Food Law, leaving the responsibility for their safety to the food business operator (article 17, Regulation (EC) No 178/2002 (Food law)(The European Parliament and The Council of the European Union, 2002)), implemented into Norwegian legislation through regulation "Forskrift 22 desember 2008 Nr. 1620 om generelle prinsipper og krav i næringsmiddelregelverket §1" (Lovdata, 2010a).

However, foods (energy drinks included) to which vitamins, minerals and certain other substances have been added, are regulated under Regulation (EC) No 1925/2006 on the addition of vitamins, minerals and certain other substances to foods(The European Parliament and the Council of the European Union, 2006), and implemented into Norwegian legislation through the regulation "Forskrift 26 februar 2010 Nr 247 om tilsetning av vitaminer, mineraler og visse andre stoffer til næringsmidler § 1" (Lovdata, 2010b). According to these national provisions in §§ 4 and 6, foods and drinks to which vitamins, minerals and/or amino acids have been added, cannot be placed on the Norwegian market without special permission from the Norwegian Food Safety Authority. This applies to energy drinks as well. The applications are handled on a case-by-case basis.

The addition of caffeine, and other «other substances» to energy drinks and other foods is also covered by the scope of the European Regulation (EC) No 1925/2006, but remains largely unregulated. Therefore, under the current national regulations, caffeine can be added to foods (including energy drinks) without prior permission as long as the food business operator can ensure their safety.

When added as a flavouring, caffeine is regulated under the Regulation (EC) No 1334/2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods (The European Parliament and Union, 2008), implemented into Norwegian legislation through the regulation "Forskrift 6 juni 2011 nr 669 om aroma og næringsmiddelingredienser med aromagivende egenskaper til anvendelse i og på næringsmidler § 1" (Lovdata, 2011).

When the caffeine content of beverages, energy drinks included, exceeds 150 mg caffeine/litre, the labelling of the product must state the following: "*High caffeine content. Not recommended for children or pregnant or breast-feeding women"* in the same field of vision as the name of the beverage, followed by a reference in brackets to the caffeine content expressed in mg per 100 ml. This is according to article 10 (1) and Appendix III in Regulation (EC) 1169/2011 on food information to consumers, implemented into Norwegian legislation through the regulation "Forskrift 28 november 2014 nr. 1497 om matinformasjon til forbrukerne" (Lovdata, 2014).

2.2 Caffeine

2.2.1 Chemistry

Caffeine (1,3,7-trimethylxanthine) (Fig. 2.2.1-1) is an alkaloid found in various plant constituents, such as coffee and cocoa beans, tea and yerba mate leaves, guarana berries and the kola nut (EFSA, 2015). Caffeine can also be produced by chemical synthesis. The molecular weight is 194.2 g/mol, and the CAS number is 58-08-2.

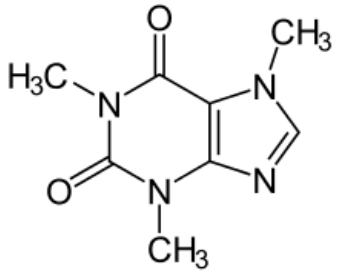

Figure 2.2.1-1. The chemical structure of caffeine.

2.2.2 Occurrence

In addition to caffeine in natural dietary sources, caffeine is an ingredient added to a variety of foods, e.g. baked goods, ice creams, soft candy, cola-type beverages and energy drinks. Some medicines and cosmetics also contain caffeine (EFSA, 2015).

2.2.3 Mode of action

Caffeine acts as an antagonist to adenosine A1 and A2A receptors that are expressed in the central nervous system, and binding of caffeine to these receptors is an important mechanism for its effects. 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 of water and causing increased 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, and for some effects of caffeine, the effect in a particular individual might be related to the polymorphism or induction status of his/her deactivation enzymes (EFSA, 2015).

2.2.4 Absorption, distribution, metabolism and excretion (ADME)

Caffeine is rapidly and completely absorbed in the gastro-intestinal tract after oral intake in humans, and the peak plasma concentration is reached within 15 minutes (min) to 2 hours

(h) after ingestion. Caffeine is rapidly distributed throughout the body, including to the extravascular space. It freely crosses the blood-brain barrier, the testicular barriers, and the placenta and is excreted in breast milk. In the brain, caffeine mainly acts as a competitive antagonist of adenosine A1 and A2A receptors (ANSES, 2013) (EFSA, 2015).

The main route of metabolism of caffeine is in the liver primarily by the cytochrome P450 enzyme system. The 1A2 isoenzyme of cytochrome P450, encoded by the CYP1A2 gene, is directly involved in demethylation of caffeine to paraxanthine (1,7-dimethylxanthine, 84% of the parent compound), theobromine (3,7-dimethylxanthine, 12%) and theophylline (1,3-dimethylxanthine, 4%). Activity of CYP1A2 accounts for 95% of caffeine clearance. Paraxanthine, theophylline and theobromine are further metabolised and then excreted in the urine. Caffeine has a plasma half-life of about 4 h with range of about 2-8 h. The kinetics of caffeine has been reported to be linear in doses up to 10 mg/kg bw, however, a later study reported non-linearity beginning at doses corresponding to about 7.1 mg/kg bw. Polymorphism in CYP1A2 is a likely reason for variations in the metabolism of caffeine among humans (EFSA, 2015).

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

2.2.5 Reference point for toxicity for children and adolescents

The Nordic Council of Ministers (NNT (Nordic Working Group on Food Toxicology and Risk Evaluation), 2008) identified NOEL (no observed effect level)- and LOEL (lowest observed effect level)-values of 0.3 and 1.0–1.3 mg/kg bw, respectively, for tolerance development. A LOAEL (lowest observed adverse effect level) for anxiety and jitteriness was identified at an intake of 2.5 mg/kg bw.

The Superior Health Council (Belgium) 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). The age of preadolescents was not defined.

EFSA (2015) concluded that single doses of caffeine and daily caffeine intakes of no concern for children and adolescents is 3 mg/kg bw per day. EFSA further noted that "like for adults, caffeine doses of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents, particularly when consumed close to bedtime".

3 Hazard identification and characterisation

This chapter includes the hazard identification and characterisation of energy drinks as a mixture and for caffeine as a single substance. Hazard identification and characterisation are based on previous reports and risk assessments, and articles retrieved from literature searches. Separate literature searches were performed for energy drinks and caffeine. A full systematic procedure was applied to identify articles reporting on adverse health effects in humans. Specific criteria for inclusion and exclusion of articles were used for the publication selection of articles on energy drinks and caffeine.

An overview of the sub-questions answered in the hazard identification and characterisation steps of energy drinks and caffeine is given in Tables 3-1 and 3-2, respectively.

Table 3-1. Energy drinks; sub-questions to be answered in the hazard identification and characterisation steps.

No.	Sub-questions
1	Is intake of energy drinks related to adverse health effects in humans? Identify adverse health effects and doses
2	Is combined intake of energy drinks and alcohol related to adverse health effects in humans? Identify adverse health effects and doses of energy drinks and alcohol
3	Is intake of energy drinks during physical activity, especially with respect to dehydration, related to adverse health effects in humans? Identify adverse effects, doses of energy drinks and levels of physical activity

Table 3-2. Caffeine; sub-questions to be answered in the hazard identification and characterisation steps.

No.	Sub-questions
1	Is intake of caffeine related to adverse health effects in humans? Identify adverse effects and doses
2	Evaluate whether studies published after 2013 imply revision of the caffeine doses that were established by EFSA «not to give rise to safety concern» (EFSA, 2015)

3.1 Literature energy drinks

3.1.1 Previous evaluations and assessments – energy drinks

3.1.1.1 Consumption and health risks of energy drinks by Dutch children and adolescents (Bemelmans et al., 2018)

Consumption of energy drinks by Dutch adolescents in relation to health complaints, e.g. heart palpitations and dizziness, resulting from excessive consumption of energy drinks, are included in this report. It was reported that a small number of Dutch adolescents (1-2%) regularly consumes at least three cans of energy drinks a day, amounting to a daily intake of at least 750 ml, and that this group may be at risk of developing health complaints. More than 60000 adolescents completed the questionnaires. The report is in Dutch with an English summary.

3.1.1.2 Energidrikke i Danmark. Undersøgelse af indtaget blandt 10-35-årige (Christensen LM et al., 2014) [In Danish]

The report from the Danish Technical University includes a survey of experienced adverse side effects related to consumption of energy drinks. The survey showed that 42% of the users of energy drinks have experienced adverse effects from the consumption. The adverse side effects were e.g. insomnia, increased heart rate and restlessness.

*3.1.1.3 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"** (ANSES, 2013)*

ANSES assessed risks related to consumption of energy drinks (ANSES, 2013). ANSES concluded that consumption of energy drinks should be avoided by children and adolescents, in pregnant and breast-feeding women, individuals who are sensitive to the effects of caffeine, and in patients with specific disease states such as certain cardiovascular disorders, psychiatric and neurological disorders, kidney failure, and severe liver conditions. ANSES concluded that consumption of energy drinks in risk situations such as co-consumption with alcohol and physical exercise (especially in hot conditions) exposes the subject to a well-documented risk of serious, mainly cardiovascular, effects, especially in subjects with a predisposition. ANSES noted that some forms of predisposition of genetic origin cannot be known in advance.

3.1.1.4 Energy Drinks: An Assessment of the Potential Health Risks in the Canadian Context (Rotstein et al., 2013)

Rotstein et al. (2013) assessed the potential health risk related to the consumption of energy drinks in Canada. The authors concluded that the available published information about

energy drinks was insufficient to characterise the potential hazards of these drinks. Therefore, a review of each of the major ingredients was conducted. Two servings of a typical energy drink per day was not expected to pose a health risk for the general adult population, despite the uncertainties about possible interactions between some of the ingredients. This conclusion was based on the safety of the non-caffeine ingredients in two servings, and the fact that the caffeine content in these two servings together with caffeine from other dietary sources would not exceed Health Canada's recommended maximum daily intake of caffeine for the general adult population. For other sub-groups, Rothstein et al (2013) concluded that the consumption of energy drinks must be limited based on the respective recommended maximum daily intake of caffeine. A typical energy drink was reported to contain (in mg per 250 ml serving) 80 mg of caffeine, 1000 mg of taurine, 600 mg of glucuronolactone, 18 mg niacin, 2 mg vitamin B6, 0.001 mg vitamin B12, 6 mg pantothenic acid, 2 mg thiamine, 1.65 mg riboflavin and 50 mg inositol.

For caffeine, Health Canada established a recommended maximum daily intake value for children at 2.5 mg/kg bw per day. Due to insufficient data, a separate recommended daily intake for adolescents was not determined. As a precautionary approach, adolescents were considered to be as sensitive as children to caffeine, and Health Canada suggested that daily caffeine intake for this age group be no more than 2.5 mg/kg bw. A daily dose of 2.5 mg/kg bw would not cause adverse health effects in the majority of adolescent caffeine consumers.

3.1.2 Literature search and publication selection – energy drinks

3.1.2.1 Literature search energy drinks

Literature searches were performed in Medline, Embase and ISI Web of Science in order to retrieve publications on adverse effects caused by the consumption of energy drinks (according to the definition of energy drinks given by the NFSA). These databases were chosen to ensure a comprehensive study retrieval. The search strategy is included in Chapter 12.1 (Appendix Literature search energy drinks). The literature searches were performed by a librarian and were limited to the period January 2013 - November 31, 2018.

The literature search identified 1719 articles after removal of duplicates.

3.1.2.2 Publication selection and data extraction energy drinks

The publication selection was based on the inclusion/exclusion criteria checklist (Table 3.1.2.2-1).

Table 3.1.2.2-1. Inclusion/exclusion criteria checklist for studies on energy drinks. "In": literature will be included; "Out": literature will be excluded.

Literature screening for data related to the following sub-questions: 1: Is intake of energy drinks related to adverse health effects in humans? Identify adverse effects and doses 2: Is combined intake of energy drinks and alcohol related to adverse health effects in humans? Identify adverse effects and doses 3: Is intake of energy drinks during physical activity, especially with respect to dehydration, related to adverse health effects in humans? Identify adverse effects and doses		
Study design	In	Human studies
	Out	Animal studies and *in vitro/in silico* studies
Population	In	All age groups
Exposure	In	Oral
	Out	All other exposure routes
Outcome of interest	In	Adverse health effects related to oral intake of energy drinks
	Out	Studies not addressing adverse effects of energy drinks at all Studies reporting solely on specific energy drink components in isolation, but not on the fully formulated product
Publication type	In	Scientific articles, systematic reviews, reports
	Out	Editorials Letters to the editor Commentaries Book chapters Meeting abstracts and posters

A large number of articles were retrieved from the literature search. The Panel chose to evaluate only randomised controlled trials (RCT). A randomised controlled trial is "an experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body)" (Cochrane, 2019).

The total number of RCTs retrieved from the literature searches was 74. Two persons independently compared the 74 RCTs with the inclusion/exclusion criteria checklist (Table 3.1.2.2-1).The first screening, based on analysis of title/abstracts, resulted in 47 articles. The full text of articles that passed the primary screening was retrieved for the secondary screening, with application of the very same inclusion/exclusion criteria. The secondary screening resulted in 15 articles included in the hazard identification and characterisation section of energy drinks. An overview of the publication selection is given in Figure 3.1.2.2-1.

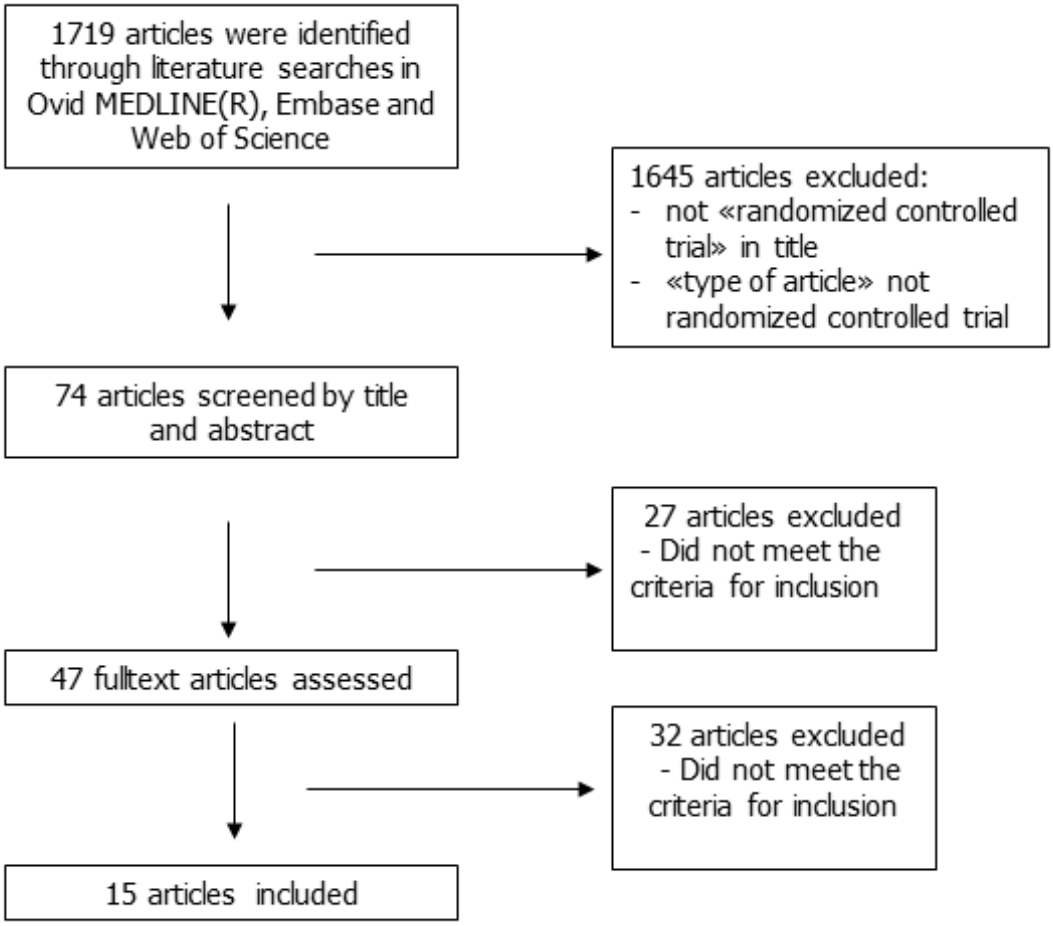

Figure 3.1.2.2-1. An overview of the publication selection of studies on energy drinks.

Articles that did not meet the inclusion criteria were excluded. When it was unclear whether the publication was of relevance to the assessment, the publication was retained for further screening.

Data extraction from the included articles are included in Chapter 13-1 (Appendix: Data extraction energy drinks). An overview of the included RCTs is shown in Table 3.1.2.2.-2.

Table 3.1.2.2-2. An overview of the included randomised controlled trials (RCTs) on energy drinks based on data extraction tables in Chapter 13.1. *A body weight of 70 kg was used. BL=Baseline.

Ref.	Study design	Participants (number)	Treatment	Caffeine mg/kg bw/day	Consumption duration	End point investigated	Measurement time points
Brothers et al. (2017)	RCT, crossover with four arms	15	Protocol 1: Energy drink Vs Coffee and water Protocol 2: Energy drink (~473 ml and ~946 ml) vs Coffee and water	Protocol 1: 2 and 3 Protocol 2: no information	20 min	Cardiovascular, hemodynamic	BL Post intervention: after 30 min and every 60 min until 6.5 h
Fletcher et al. (2017)	RCT, crossover, two arms	18	Energy drink (946 ml) Vs Caffeinated drink	3.6-5.2 (mean: 4.3)	45 min	Cardiovascular	BL Post intervention: 1, 2, 4, 6, and 24 h
Garcia et al. (2017)	RCT parallell design with four groups	80	Energy drink (460 ml) Vs Carbonated water	2.1-2.2*	5 min	Cardiovascular, psychobehavioural	BL Post intervention: blood pressure: 30 min All tests: 1 h

Ref.	Study design	Participants (number)	Treatment	Caffeine mg/kg bw/day	Consumption duration	End point investigated	Measurement time points
Gray et al. (2017)	RCT, crossover, two arms	24	Energy drink (500 ml) Vs Control drink	2.3*	–	Cardiovascular	Post intervention: for 90 min
Shah et al. (2016a)	RCT crossover design with two arms	26	5-Hour ENERGY Lemon Lime flavour (59 ml) Vs Placebo	Unknown	–	Cardiovascular	BL Post intervention: 1, 3 and 5 h on days 1, 7 (in the morning)
Shah et al. (2016b)	RCT, crossover, three arms	27	Energy drink (~473 ml in each) Vs Ginseng drink Vs Placebo drink	320 mg: 3.7-5.8 (mean: 4.5) Caffeine amount is not explicitly stated (whether the amount is in 473 or 946 ml). Assume 473 ml	–	Cardiovascular	BL Post intervention: 1, 2, 3.5, and 5.5 h
Grasser et al. (2015)	RCT with a crossover design with two arms. No	20	Red Bull (355 ml) Vs Tap water	1.7-1.8 (mean: 1.7)	4 min	Cardiovascular, hemodynamic, cerebrovascular	BL Post intervention: 80 min

Ref.	Study design	Participants (number)	Treatment	Caffeine mg/kg bw/day	Consumption duration	End point investigated	Measurement time points
	participant blinding of test substance						
Lara et al. (2015)	RCT crossover design with two arms	14	Energy drink + exercise Energy drink (250 ml) Vs Placebo drink	3	–	Psychobehavioural, muscular, cardiovascular	Post intervention: 1 –24 h
Svatikova et al. (2015)	RCT crossover design with two arms	25	Energy drink +/– physical stress Energy drink (480 ml) Vs Placebo beverage	3.4*	5 min	Cardiovascular, metabolic	BL Post intervention: 30 min At regular intervals: blood pressure and heart rate measurement
Grasser et al. (2014)	RCT, crossover, two arms	25	Red Bull (355 ml) Vs Tap water	1.6-1.7 (mean: 1.6)	4 min	Cardiovascular, cerebrovascular effects and microvascular endothelial function	BL Post intervention: 2 h
Lara et al. (2014)	RCT crossover	18	Energy drink + exercise	3	–	Cardiovascular, psychobehavioural	BL: Urine samples. Post intervention: Urine

Ref.	Study design	Participants (number)	Treatment	Caffeine mg/kg bw/day	Consumption duration	End point investigated	Measurement time points
	design with two arms		Energy drink (250 ml) Vs Control drink				samples 30–60 min after the exercise. Bodyweight before and after each trial. Questionnaire just after the game. Survey the following morning
Peacock et al. (2014)	RCT, crossover, 4 arms	28	Energy drink + alcohol Energy drink (3.57 ml/kg bw) Vs alcohol vs energy drink + alcohol vs placebo	Unknown	5 min	Cardiovascular, psychological, muscle	BL Post intervention: 30 and 125 min
Phan and Shah (2014)	RCT crossover design with two arms	10	Energy shot (Beverage liquid amount was not reported) Vs Non-caffeinated energy shot	Energy shot: 3.1-4.4 (mean: 3.6) Non-caffeinated energy shot: 0.08-0.12 (mean: 0.10)	–	Cardiovascular, psychobehavioural	BL Post intervention: 1 and 3 h

Ref.	Study design	Participants (number)	Treatment	Caffeine mg/kg bw/day	Consumption duration	End point investigated	Measurement time points
Salinero et al. (2014)	RCT, crossover with two arms	90	Energy drink + exercise Energy drink (250 ml) Vs Non-caffeinated energy drink	3	–	Psychobehavioural, muscular, gastrointestinal	Before going to sleep on the day of testing and in the morning next day
Kurtz et al. (2013)	RCT, crossover with two arms	20	5-hour energy shot (~57 ml) Vs Non-caffeinated 5-hour energy shot	Energy shot (138 mg): 1.7-2.6 (mean: 2.0) Energy shot (215 mg): 2.7-4.0 (mean: 3.2) Non-caffeinated energy shot: 0.07-0.11 (mean: 0.09)	–	Cardiovascular, psychobehavioural	BL Post intervention: 1, 3, and 5 h

3.1.3 Evaluation of risk of bias for the RCTs on energy drink

The procedure for the evaluation of risk of bias (RoB) described below was used for the included RCT articles both on energy drink consumption (Table 3.1.2.2-2) and on caffeine exposure (Table 3.2.2.2-2). The RoB of caffeine can be found in Chapter 3.2.3.

All the included articles were divided between two pairs of reviewers who evaluated the risk of bias independently according to eight questions (Tables 3.1.3-1 and 3.2.3-1) specifically made for the purpose of rating human controlled studies (NTP, 2015b) . The response options and symbols (in parenthesis) associated with each question were:

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

The criteria for the response options above were outlined in the Protocol for this risk assessment (VKM et al., 2018) and in amendments to the Protocol (Appendix 16) and were further specified according to OHAT Risk of Bias rating Tool for Human and Animal Studies, NTP (2015b). In addition, specific descriptions and criteria were made by the project group to answer question 5: "Can we be confident in the exposure characterisation"? (Chapter 14 Appendix: Risk of bias). When information was inadequate or not available in the article under evaluation, the rating "Not reported" (NR) was used. Following evaluation, each of the eight questions was rated as key (numbers 1-3, 5-7) or non-key (numbers 4 and 8) questions. The responses to non-key questions were expected to have less influence on the evidence of effects than did key questions. The rating of key and non-key questions was integrated to classify the studies in tiers 1 to 3 corresponding to decreasing levels of internal validity, modified from EFSA et al. (2017a). The tiers were defined in a manner that ensured a sufficient distinction between the levels of internal validity (see Chapter 17 Appendix: Deviations from the protocol). The four reviewers calibrated themselves on two occasions to ensure similar evaluation.

Tier 1:

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

Tier 2:

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

Tier 3:

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

- More than one key question is scored –

Four articles investigating effects of energy drinks were rated tier 1, five were rated tier 2 and six were rated tier 3. The evaluation of risk of bias of each article is included in Chapter 14.1 (Appendix: Risk of bias). An overview of the outcome of the RoB evaluation of RCTs on energy drink consumption is shown in Table 3.1.3-1.

Bias related to funding/conflict of interest is not included in the risk of bias evaluation, but rather included in the weight of evidence evaluation. In the weight of evidence evaluation form (Table 3.1.4-1 in Chapter 3.1.4), the tier level was designated a concern level according to (EFSA et al., 2017a) as follows: Tier 3: very serious concern; tier 2: serious concern; tier 1: not serious concern (see Chapter 8: Methodological considerations).

Table 3.1.3-1. Risk of Bias (RoB) evaluation for studies on energy drinks.*: non-key questions (numbers 4 and 8).

RoB question Reference	1. Was administered dose or exposure level adequately randomized?	2. Were subjects blinded to the study group during the study?	3. Were research personnel blinded to the study group during the study?	4.* Were outcome data complete without attrition or exclusion from analysis?	5. Can we be confident in the exposure characterization?	6. Can we be confident in the outcome assessment?	7. Were all measured outcomes reported?	8.* Were there no other potential threats to internal validity?	Tier
Brothers et al. (2017)	+	–	– (NR)	–	+	– –	– –	+	3
Fletcher et al. (2017)	++	+	+	++	+	–	++	+	2
Garcia et al. (2017)	+	–	–	– (NR)	+	–	++	–	3
Gray et al. (2017)	+	++	++	++	–	++	++	+	2
Shah et al. (2016a)	+	++	++	– (NR)	+	+	++	–	2
Shah et al. (2016b)	++	++	++	++	–	++	++	+	2
Grasser et al. (2015)	+	– –	– –	– (NR)	+	–	++	–	3
Lara et al. (2015)	+	++	+	++	++	+	++	–	1

Svatikova et al. (2015)	++	++	++	++	+	++	++	++	1
Grasser et al. (2014)	++	– –	– (NR)	– (NR)	+	–	++	–	3
Lara et al. (2014)	+	++	++	++	+	+	++	+	1
Peacock et al. (2014)	+	++	+	++	–	+	+	–	2
Phan and Shah (2014)	+	++	– (NR)	++	– –	– (NR)	++	–	3
Salinero et al. (2014)	++	++	++	++	+	+	++	+	1
Kurtz et al. (2013)	++	++	+	++	– –	–	++	–	3

3.1.4 Weighting the body of evidence of energy drink consumption RCTs

The procedure for the evaluation of weight of evidence (WoE) described below was identical for the included RCTs on energy drinks (Table 3.1.2.2-2) and caffeine (Table 3.2.2.2-2).

Endpoints identified in the included RCT articles were evaluated through the WoE method described in the Protocol (VKM et al., 2018) and in amendments to the Protocol, Chapter 17 (Appendix: Deviations from the protocol) using a modified version from EFSA et al. (2017a) and OHAT (NTP, 2015a). The following text is modified from EFSA et al. (2017a):

To potentially establish an association between the intake of energy drinks and/or exposure to caffeine and a subsequent effect, an initial confidence rating of the human RCT studies was performed. The following four descriptors were used to determine this initial level of confidence:

- Controlled exposure conditions
- Exposure preceding the effect onset
- Outcome being assessed at individual level (i.e., not through population aggregate data)
- Presence of an appropriate comparison group

Fulfilment of all features received an initial rating of high confidence (++++). Lower ratings, i.e. moderate (+++), low (++) or very low (+), corresponded to the number of features fulfilled. Considerations on whether the exposure proceeded the outcome was done at internal validity level (RoB, see 3.1.3), which fulfilled this aspect. For the included RCT studies, the Panel considered that fulfilment of all features would receive an initial rating of high confidence (++++).

The studies grouped for a given outcome/endpoint were further evaluated for elements that would downgrade or upgrade confidence in the evidence. In brief, the following elements were considered for downgrading the initial ratings of the confidence in the body of evidence:

- Internal validity (Risk of bias-evaluation)
- Bias related to funding/conflict of interest
- Unexplained inconsistency
- Imprecision

Elements considered for upgrading the confidence in the body of evidence were:

- Dose-response
- Consistency across study design type/dissimilar populations
- Residual confounding (if a study reports an effect or association despite the presence of residual confounding, confidence in the association is increased)
- Large magnitude of effect (e.g. incidence, degrees of severity)

After downgrading and upgrading the evidence, the overall confidence in the evidence was determined. The terms used to describe the overall confidence in the evidence were defined as follows (NTP, 2015a):

- High confidence (++++) in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected in the apparent relationship.
- Moderate confidence (+++) in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.
- Low confidence (++) in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship.
- Very low confidence (+) in the association between exposure to the substance and the outcome. The true effect is highly likely to be different from the apparent relationship (further termed "inadequate" in OHAT Handbook (NTP, 2015a)).

Table 3.1.4-1 was used for downgrading and upgrading of the evidence.

The OHAT interpretation of the risk of bias downgrading criteria in Table 3.1.4-1 are described in Chapter 8: Methodological considerations. When the overall confidence in the evidence was high (++++) for an endpoint where the effect was absent, the absence of an effect was considered "highly likely". Furthermore, if the evidence was scored less than ++++, the level of evidence of a health effect was considered inadequate ("There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s)). See also Chapter 8: Methodological considerations.

Table 3.1.4-1. Weight of Evidence (WoE) profile form for downgrading and upgrading the evidence for a given endpoint across studies.

Endpoint (describe)									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual studies
Reference Initial rating	Risk of bias (tiers 1-3)	Funding/COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose-response relationship	Residual confounding	Consistency	
Study number 1	3: Very serious concern 2: Serious concern 1: No serious concern	Very serious concern, serious concern, no serious concern	Very serious concern, serious concern, no serious concern	Very serious concern, serious concern, no serious concern	Large or not large	Yes or no	Yes or no	Yes or no	
Study number 2 (Repeat procedure for relevant studies)									
All studies (Initial rating **≥+++)**	Describe trend Describe key questions Describe issues	Describe issues	Describe results in terms of consistency Explain apparent inconsistency (if it can be explained)	Discuss ability to distinguish treatment from control Describe confidence intervals (if relevant)	Describe magnitude of response	Outline evidence for or against dose-response	Presence of effect or association despite the presence of residual confounding increases confidence in the association	Describe model or population consistency	Final rating: +/++/+++/++++ For health effect: Very likely/likely/as likely as not/unlikely/very unlikely For no effect:

Endpoint (describe)									
									If ++++: Very likely If <++++: Inadequate level of evidence

COI: Conflict of interest

The overall confidence in the evidence for each endpoint/group of endpoints was transformed to likelihood as shown in Table 3.1.4-2.

Table 3.1.4-2. Set of terms used to transform the final rating of confidence in the evidence per endpoint of all relevant randomised controlled trials to overall likelihood.

	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks/exposure to caffeine and the adverse effect under consideration
Health effect present	++++	Very likely
	From ++++ to +++	Likely
	From +++ to ++	As likely as not
	From ++ to +	Unlikely
	+	Very unlikely/inadequate evidence of health effect
Health effect not present	++++	Evidence of no health effect
	From +++ to +	Inadequate evidence of health effect

It must be emphasised that the likelihood assessed by the WoE approach addresses only the likelihood of an association between the effect under consideration and the exposure to energy drinks or caffeine applied. It does not address the likelihood or frequency of the effect actually occurring in humans, which depends on additional factors including the dose-response relationship of the effect (considered in hazard characterisation) and the levels of human exposure (considered in exposure assessment).

Only the endpoint effects that received a score of *"likely/very likely"* were considered for risk characterisation assessment.

Outcomes from intake of energy drinks and exposure to caffeine were grouped separately, and they were further grouped according to intake/exposure conditions: The identified endpoints were merged to fit into the outcome groups: cardiovascular, psychobehavioural and metabolic effects. The Panel notes that the biological/medical classification (e.g. hormonal or metabolic) and grouping (e.g. cardiovascular and respiratory) of some of the endpoints may seem arbitrary and that other classifications and combinations of endpoints could be chosen. However, the Panel considers that the confidence in the association between an outcome and the substance in question would remain the same regardless of grouping of the endpoints. One WoE form (Table 3.1.4-1) was used for each combination of intake/exposure conditions (i.e. energy drink or caffeine alone or in combination with another exposure) and endpoint as follows (Table 3.1.4-3).

Table 3.1.4-3. The combination of endpoints and intake/exposure condition subject to weight of evidence (WoE) evaluation

Intervention	Endpoints described
Energy drink only	Cardiovascular, metabolic, and psychobehavioural effects
Energy drink and physical exercise	Cardiovascular and psychobehavioural effects
Energy drink and alcohol	Cardiovascular and psychobehavioural effects
Caffeine alone	Cardio-, cerebrovascular and cardiorespiratory effects; psychobehavioural effects; oxidative stress, haematological and metabolic effects
Caffeine and physical exercise	Cardiovascular effects; metabolic effects; psychobehavioural, insomnia, gastrointestinal and muscular effects

The resulting confidence rating/WoE forms are presented in Chapter 15 (Appendix: Weight of evidence).

3.2 Literature caffeine

3.2.1 Previous evaluations and assessments caffeine

3.2.1.1 EFSA Scientific Opinion on Flavouring Group Evaluation 49, Revision 1 (FGE.49Rev1): Xanthine alkaloids from the priority list (EFSA et al., 2017b)

EFSA assessed the safety of the flavouring substance caffeine [FL-no: 16.016]. The assessment was based on the safety thresholds established in the assessment of caffeine (EFSA, 2015).

3.2.1.2 Scientific Opinion on the safety of caffeine (EFSA, 2015)

In the opinion on the safety of caffeine, EFSA 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, elderly, pregnant women, lactating women, subjects performing physical exercise). Whether alcohol or substances present in energy drinks may modify the possible adverse health effects of caffeine and/or the doses at which such adverse effects may occur was also addressed.

EFSA provided advice on total caffeine intakes that do not give rise to concerns about adverse health effects for the general healthy population and subgroups thereof. EFSA concluded (for adults, adolescents and children):

- Adults (70 kg), not including pregnant or breastfeeding women
    - Single doses of caffeine up to 200 mg (about 3 mg/kg bw) do not give rise to safety concerns, and the same amount does not give rise to safety concerns when consumed < 2 h prior to intense physical exercise under normal environmental conditions
    - Single doses of 100 mg (about 1.4 mg/kg bw for a 70-kg adult) of caffeine may increase sleep latency and reduce sleep duration in some adult individuals, particularly when consumed close to bedtime
    - Habitual caffeine consumption up to 400 mg per day (about 5.7 mg/kg) does not give rise to safety concerns
- Children and adolescents; the information available was insufficient to derive a safe caffeine intake. EFSA considered that caffeine intakes of no concern derived for acute caffeine consumption by adults (3 mg/kg bw per day) may serve as a basis to derive single doses of caffeine and daily caffeine intakes of no concern
    - Single doses and daily intake of caffeine up to 200 mg (about 3 mg/kg bw) do not give rise to safety concerns

- Doses of about 1.4 mg/kg bw per day may increase sleep latency and reduce sleep duration in some children and adolescents, particularly when consumed close to bedtime

*3.2.1.3 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"** (ANSES, 2013)*

ANSES states that in the general population there is a wide variability of sensitivity to the effects of caffeine due to e.g. different genetic profiles (50% of the population are considered to be made up of "poor metabolisers", more sensitive to caffeine), physiological factors (age, pregnancy, etc.), caffeine consumption patterns, state of health or co-exposures such as with tobacco, alcohol and various medicines. According to ANSES, this variability makes it complicated to assess the dose of caffeine associated with the adverse effects. Adverse effects related to caffeine are e.g. anxiety, tachycardia, sleep disorders and migraines.

3.2.2 Publication selection and data extraction - caffeine

3.2.2.1 Literature search caffeine

Literature searches were performed in Medline, Embase and ISI Web of Science in order to retrieve publications on adverse effects caused by caffeine. These databases were chosen to ensure a comprehensive study retrieval. The search strategy is included in Chapter 12.2 (Appendix: Literature search caffeine). The literature searches were performed by a librarian and cover the period January 2013 to October 31, 2018.

The literature search identified 7301 articles after duplicates were removed.

3.2.2.2 Publication selection and data extraction caffeine

The publication selection was based on the inclusion/exclusion criteria checklist (Table 3.2.2.2-1).

Table 3.2.2.2-1. Inclusion/exclusion criteria checklist for studies on energy drinks. "In": literature will be included; "Out": literature will be excluded.

Literature screening for data related to the following sub-questions 1. Is intake of caffeine related to adverse health effects in humans? Identify adverse effects and doses 2. Evaluate the need for revision of safe doses as established by EFSA 2015		
Study design	In	Human studies
	Out	Animal studies and *in vitro/in silico* studies
Population	In	All age groups

Exposure	In	Oral
	Out	All other exposure pathways
Outcome of interest	In	Adverse effects related to oral intake of caffeine
	Out	Studies not reporting on adverse effects of caffeine
Publication type	In	Scientific articles, systematic reviews, reports
	Out	Editorials Letters to the editor Commentaries Book chapters Meeting abstracts and posters

A large number of articles were retrieved from the literature search. As for energy drinks, the Panel decided to include only RCTs in the present risk assessment (Chapter 3.1.2.2).

The total number of RCTs retrieved from the literature searches was 331. Two persons independently compared the 331 RCTs with the inclusion/exclusion criteria checklist (Table 3.2.2.2-1). The first screening, based on analysis of title/abstracts, resulted in 25 articles. The full text of articles that passed the primary screening was retrieved for the secondary screening, with application of the very same inclusion/exclusion criteria. The secondary screening resulted in 12 articles included in the hazard identification and characterization section of caffeine. An overview the publication selection is given in Figure 3.2.2.2-1.

Some studies investigated effects of exposure to mixtures of caffeine and other substances frequently added to energy drinks. However, only exposure to caffeine and not any other energy drink ingredient, were reported and further processed in this opinion.

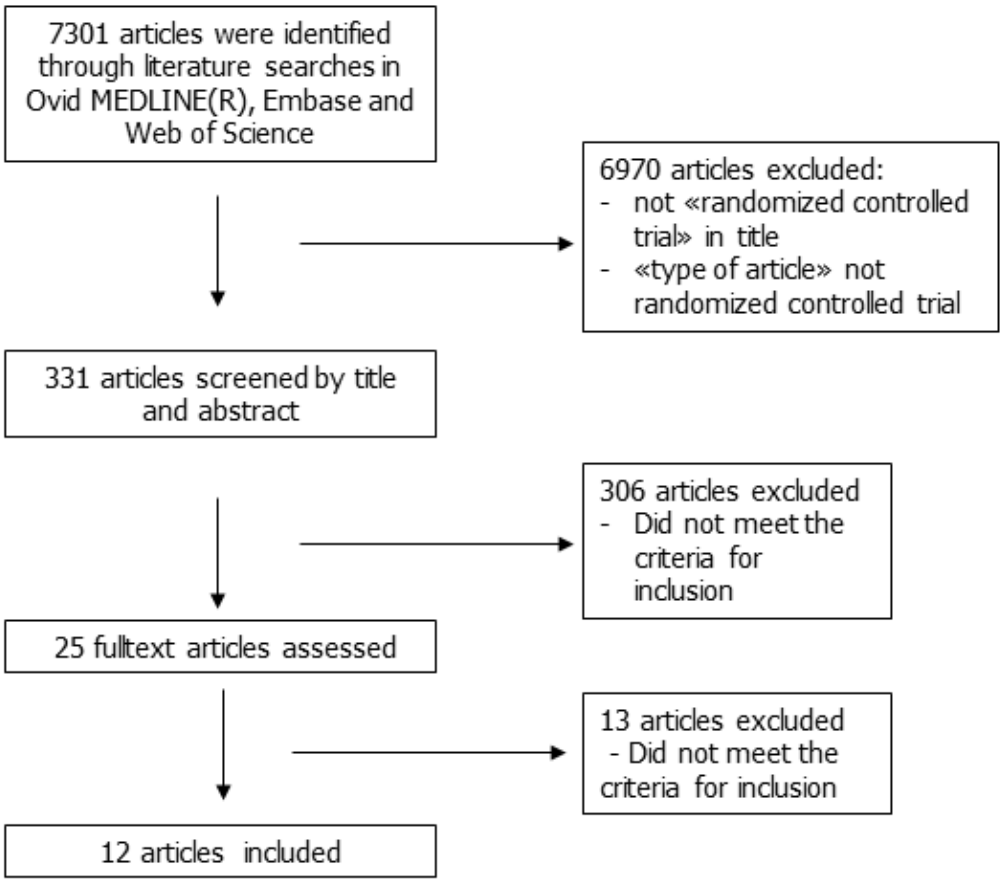

Figure 3.2.2.2-1. An overview of the publication selection of studies on caffeine.

Data extraction from the included articles are included in Chapter 13-2 (Appendix: Data extraction caffeine). An overview of the included RCTs is shown in Table 3.2.2.2.-2. The caffeine doses used ranged from 1 to 6.2 mg/kg bw per day. Three studies did not report the body weight of the participants. For these studies, all investigated in adults, a default body weight of 70 kg for adults was used to calculate the dose in mg/kg bw/day.

Table 3.2.2.2-2. An overview of the included randomised controlled trials (RCTs) on caffeine based on data extraction Tables in Chapter 13.2. *A body weight of 70 kg was used. BL=Baseline.

Ref.	Study design	Participants (number)	Treatment	Caffeine dose (mg/kg bw per day)	End point investigated	Measurement time-points
Puente et al. (2017)	RCT crossover design with two arms	20	Caffeine Vs placebo (cellulose)	3	Cardiovascular and psychobehavioural	Post intervention (60 min): Heart rate pre-and during match Later (the same day): Questionnaire on psychobehavioural effects
Salinero et al. (2017)	RCT crossover design with two arms	21	Caffeine Vs placebo (cellulose)	3	Ergogenic effects	Post intervention: Visual attention test at 60 min, then Wingate test, then perceptual evaluation. Next morning: Questionnaire on side effects
Flueck et al. (2016)	RCT, crossover, 2 arms	28	Caffeine Vs placebo	5.8-6.2	Cardiovascular	Before and after ingestion: heart rate variability
Bloomer et al. (2015)	RCT with four parallel groups	51	caffeine Vs Placebo (cellulose)	1-3 d: 1.2-1.8 Up to 8 weeks: (max) 3.7-5.4	Cardiovascular, respiratory effects, metabolic effects, haematology	Before intervention. Post intervention: 4 and 8 weeks
Bunsawat et al. (2015)	RCT crossover study with two arms	18	Caffeine Vs Placebo	5.7*	Cardiovascular	BL Post intervention: 5, 15, and 30 min post-exercise

Ref.	Study design	Participants (number)	Treatment	Caffeine dose (mg/kg bw per day)	End point investigated	Measurement time-points
Dodd et al. (2015)	RCT crossover design with four arms	24	Caffeine vs Placebo	1.1*	Cardiovascular and psychobehavioural	Upon arrival and following 80 min post intervention: blood pressure and heart rate From 20 min prior to treatment, baseline, and until 80 min post intervention: brain blood flow changes
Lemery et al. (2015)	RCT with two parallel groups	80	Caffeine Vs Placebo	5	Cardiovascular	BL: blood pressure, heart rate, and intracardiac measurements Post intervention: Parameters were measured after ingestion
Wu (2015)	RCT, crossover with four arms	12	Caffeine (3 doses) vs Placebo	2, 4, 6	Metabolic effects	BL, prior to exercise, and 0, 15 and 30 min after exercise Post-exercise; 100, 115 and 130 min post intervention
Souza et al. (2014)	RCT, crossover with two arms	15	Placebo + physical activity Vs Caffeine + physical activity	4	Cardiovascular	45 minutes (pre-exercise) and fifteen minutes (post-exercise)
Temple et al. (2014)	RCT crossover design with three arms (two age groups)	101	Caffeine Vs Placebo	1 and 2	Cardiovascular and psychobehavioural	BL and every 10 min for 1 h; heart rate and blood pressure at 20-30 min after arrival; BL a and 60 min post intervention; psychobehavioural parameters

Ref.	Study design	Participants (number)	Treatment	Caffeine dose (mg/kg bw per day)	End point investigated	Measurement time-points
Bloomer et al. (2013)	RCT, parallel design with four groups	50	Caffeine Vs Placebo	1st week: 2.8-3.3 2-11 wk: 5.6-6.7	Cardiovascular effects, haematology, metabolic effects	BL Post intervention: Week 6 and 12
Rogers et al. (2013)	RCT, parallel design, medium-high and non-low caffeine consumers	369	Caffeine or Placebo	3.6*	Psychobehavioural effects	BL Post intervention: 45 min, and starting at 60 and 135 min after the second dose

3.2.3 Evaluation of risk of bias for the RCTs on caffeine

The procedure for the evaluation of risk of bias of the included RCTs is described in Chapter 3.1.3.

One article investigating effects of caffeine was rated tier 1, four were rated tier 2 and seven were rated tier 3. The evaluation of risk of bias of each article is included in Chapter 14.2 (Appendix: Risk of bias of caffeine articles). An overview of the outcome of the RoB evaluation is shown in Table 3.2.3-1.

Table 3.2.3–1. Risk of bias evaluation for studies on caffeine. *: Non–key questions (numbers 4 and 8)

RoB question Reference	1. Was administered dose or exposure level adequately randomized?	2. Were subjects blinded to the study group during the study?	3. Were research personnel blinded to the study group during the study?	4.* Were outcome data complete without attrition or exclusion from analysis?	5. Can we be confident in the exposure characterization?	6. Can we be confident in the outcome assessment?	7. Were all measured outcomes reported?	8.* Were there no other potential threats to internal validity?	Tier
Puente et al. (2017)	–	++	++	++	++	+	++	+	2
Salinero et al. (2017)	++	++	++	– (NR)	– (NR)	++	++	–	2
Flueck et al. (2016)	++	++	++	++	+	++	++	++	1
Bloomer et al. (2015)	+	+	– (NR)	–	– –	++	++	–	3
Bunsawat et al. (2015)	+	+	– (NR)	– (NR)	– (NR)	– (NR)	++	+	3
Dodd et al. (2015)	++	++	++	+	–	+	++	–	2
Lemery et al. (2015)	++	– (NR)	– (NR)	+	–	– (NR)	++	+	3
Wu (2015)	+	– (NR)	– (NR)	– (NR)	– –	+	++	–	3
Souza et al. (2014)	+	– (NR)	– (NR)	++	–	– –	++	+	3
Temple et al. (2014)	++	+	+	++	– –	+	++	–	3

RoB question Reference	1. Was administered dose or exposure level adequately randomized?	2. Were subjects blinded to the study group during the study?	3. Were research personnel blinded to the study group during the study?	4.* Were outcome data complete without attrition or exclusion from analysis?	5. Can we be confident in the exposure characterization?	6. Can we be confident in the outcome assessment?	7. Were all measured outcomes reported?	8.* Were there no other potential threats to internal validity?	Tier
Bloomer et al. (2013)	+	++	++	–	+	+	++	–	2
Rogers et al. (2013)	+	++	++	– (NR)	– (NR)	–	++	–	3

NR = Not reported

3.2.4 Weighting the body of evidence of caffeine exposure RCTs

The procedure for the evaluation of WoE is described in Chapter 3.1.4. The completed confidence rating forms for each endpoint are presented in Chapter 15 (Appendix: Weight of evidence).

3.3 Outcome of weight of evidence evaluation per endpoint and intervention for the included RCTs

In the following chapters, the outcome of the overall WoE for each endpoint or group of related endpoints is presented, both for energy drink consumption and caffeine exposure described in the included RCTs. The outcome is further divided into interventions, e.g. cardiovascular endpoints due to energy drinks alone and cardiovascular effects due to energy drink intake in combination with physical activity (Tables 3.5.2 -3.7.6).

3.4 Hazard characterisation of energy drinks and caffeine based on relevant literature

This hazard characterisation was based on previous risk assessments by EFSA (2015), ANSES (2013) and on the included RCTs retrieved from the literature searches. The endpoints identified in the RCTs that received a likelihood of evidence score of "likely/very likely" for the presence of an adverse health effect (see Table 3.1.4-2) or "very likely" for the lack of such effects were included in the hazard characterisation conclusions and were further considered in the risk characterisation assessment.

In the following chapters on outcome, the Panel has summarised the reported effects of energy drink consumption and caffeine exposure according to intervention and (group of) endpoint(s) in the included RCTs. Conclusions follow each intervention and/or intervention combination for each major group of endpoints, such as e.g. cardiovascular effects. In the conclusions, case reports have not been emphasised as, although they represent valuable information, they are not associated with the same high, scientific quality level as RCTs. Therefore, they will not serve as basis for the determination of toxicological reference points.

Energy drinks contain caffeine, according to the definition given in the terms of reference by NFSA. The remaining ingredients were not specifically defined. The ingredients in the energy drinks in the included RCTs were not well described in all studies. Therefore, in the outcome assessment below, when a particular endpoint of energy drinks was not described in EFSA (2015) or ANSES (2013), the caffeine dose in the energy drink was used to evaluate any effects.

EFSA (2015) concludes that common constituents of energy drinks at concentrations commonly present in such beverages (typically about 300-320 mg/l caffeine; 4000 mg/l taurine; 2400 mg/l D-glucorono-γ-lactone) would not affect the safety of single doses of

caffeine up to 200 mg (3 mg/kg bw per day in a 70 kg adult, which may also apply to children and adolescents).

Note that the energy drink consumption studies are categorised based on the intervention control (see e.g. Table 3.4.2). When the doses of caffeine in the included RCTs were not given per bodyweight, the Panel calculated a dose based on a 70 kg adult.

3.5 Outcome of cardiovascular effects

The cardiovascular system is a target organ for acute effects of caffeine, and effects above a certain level are therefore expected (EFSA, 2015). The Panel chose to divide intake /caffeine doses in energy drinks into single and repeated doses and habitual doses in the same manner as presented in EFSA (2015).

An overview of the studies evaluated for cardiovascular effects is given in Table 3.5-1.

Table 3.5-1. Number of studies of cardiovascular and related effects of energy drink consumption and caffeine exposure and corresponding tables of evidence evaluation.

Endpoints (effects)	Intervention	No. of studies	Table presenting the overall evaluation of the evidence evaluation
Cardiovascular and various physiological effects	Energy drinks	12	Table 3.5-2
Cardiovascular	Energy drinks and physical activity	3	Table 3.5-3
Cardio-, cerebrovascular and cardiorespiratory	Caffeine	6	Table 3.5-4
Cardiovascular	Caffeine and physical activity	3	Table 3.5-5

Table 3.5-2. Likelihood evaluation of cardiovascular and other physiological effects of energy drink consumption reported in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Energy drink (ml)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Energy drink	Water	Garcia (2017) Grasser (2015) Grasser (2014) Brothers (2017)	1.6-3	355-946	Blood pressure	Increase	From + to +/++	Unlikely
Energy drink	Sugar/juice/de-caffeinated control drink	Gray (2017) Kurtz (2013) Phan (2014) Shah (2016a) Shah (2016b) Svatikova (2015)	1.7-5.8	56-500			From + to ++++	Likely
Energy drink	Caffeine drink	Fletcher (2017) Brothers (2017)	2–5.2	473-946			From + to ++	As likely as not/unlikely
Energy drink	Water	Brothers (2017)	2-3	473-946			+	Inadequate
Energy drink	Sugar/juice/de-caffeinated control drink	Grey (2017) Phan (2014) Shah (2016a) Shah (2016b)	2.3-5.8	59-500	Heart arrhythmia Heart rate	No effect No effect/ small increase (water control)	From + to ++	Inadequate
Energy drink	Caffeine drink	Fletcher (2017) Brothers (2017)	3.6-5.2	473-946			From + to ++	Inadequate
Energy drink	Water	Grasser (2015) Grasser (2014)	1.6-1.8	355			+/++	Unlikely

Energy drink	Sugar/juice/de-caffeinated control drink	Shah (2016a) Shah (2016b) Lara (2014) Lara (2015) Svatikova (2015)	2-5.8	59-480	Heart rate Heart palpitations	No effect/ small increase (water control) No effect	From +/++ to ++++	Inadequate
Energy drink	Caffeine drink	Fletcher (2017) Brothers (2017)	3.6-5.2	473-946			From + to ++	Inadequate
Energy drink (RedBull)	Red Bull placebo	Peacock (2014)	NR	NR			++/+++	Inadequate
Energy drink (RedBull)	Red Bull placebo	Peacock (2014)	NR	NR	Other physiological effects	No effect	++/+++	Inadequate

Table 3.5-3. Likelihood evaluation of cardiovascular effects of energy drink consumption combined with physical activity reported in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Energy drink (ml)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Energy drink	Sugar/juice/de-caffeinated control drink	Lara (2015)	3	250	Heart palpitations	No effect	+++	Inadequate evidence
Energy drink	Sugar/juice/de-caffeinated control drink	Svatikova (2015)	3.4	480	Blood pressure	No effect	++++	Very likely no health effect

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Energy drink (ml)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Energy drink	Sugar/juice/de-caffeinated control drink	Lara (2014) Lara (2015) Svatikova (2015)	3-3.4	250-480	Heart rate	No effect	From +++ to ++++	Very likely no health effect

Table 3.5-4. Likelihood evaluation of cardio-, cerebrovascular and cardiorespiratory effects of caffeine exposure in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Bloomer (2013) Bloomer (2015) Dodd (2015) Flueck (2016) Lemery (2015) Temple (2014)	1-6.7	Blood pressure	Increase (except Bloomer 2013, 2015)	From+ to ++++	Likely
Caffeine	Placebo	Dodd (2015) Flueck (2016) Lemery (2015) Temple (2014)	1-6.2	Heart rate	No effect/small decrease	From ++/+++ to++++	Inadequate
Caffeine	Placebo	Bloomer (2013) Bloomer (2015)	1.2-6.7	Respiratory rate	No effect	From+ to ++	Inadequate
Caffeine	Placebo	Dodd (2005)	1.1	Cerebrovascular (blood oxygenation)	Small, within normal physiological variations	+++	Inadequate
Caffeine	Placebo	Flueck (2016)	5.8-6.2	Tidal volume	Small, within normal physiological variations	++++	Very likely no health effect

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Lemery (2015)	5	Inducibility/cycle length of tachycardia	No effect	++/+++	Inadequate

Table 3.5-5. Likelihood evaluation of cardiovascular effects of caffeine exposure and physical activity in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Pre-/post-exercise	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Souza (2014)	4	Pre-exercise	Blood pressure	Small increase	++	Unlikely
Caffeine	Placebo	Puente (2017) Souza (2014)	3-4		Heart rate	No effect	From++ to +++	Inadequate
Caffeine	Placebo	Souza (2014) Bunsawat (2015)	4-5.7	Post-exercise	Blood pressure	Small increase	From+ to ++	Unlikely
Caffeine	Placebo	Souza (2014) Bunsawat (2015)	4-5.7		Heart rate	No effect	From+ to ++	Inadequate

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Pre-/post-exercise	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Bunsawat (2015)	5.7		Arrhythmia	Small increase	+	Inadequate

3.5.1 Cardiovascular effects of energy drinks alone

The included RCTs referred to in this chapter are summarised per endpoint in Table 3.5-2 and referred to in Table 1, Chapter 15, Appendix: Weight of evidence.

3.5.1.1 Blood pressure

Single dose and repeated doses within a day

All energy drink interventions in the RCTs were given as single doses, with one exception (Shah et al., 2016a), in which the caffeine concentration was unknown. The only study with a sufficiently high score of likelihood of evidence for a health effect (Svatikova et al. 2015), demonstrated that a caffeine dose of 3.4 mg/kg bw (based on a default weight of 70 kg), induced a mean increase in resting systolic and diastolic blood pressures of 6.6 and 4.2 mm Hg, respectively (Table 3.5.-2). This observation is in line with previous reviews and assessments. Note that all the included RCTs that investigated the effect of energy drink consumption on blood pressure found an increase; however, most had shortcomings that made conclusions unreliable.

Svatikova et al. (2015) also investigated the effect of energy drinks on noradrenaline levels and found an increase of 73.6%. The increase was accompanied by an increase in blood pressure, as expected.

Among other cardiovascular effects, caffeine increases blood pressure. This fact is expressed as follows by EFSA (2015): "Caffeine consumption acutely increases blood pressure in virtually all adult populations subgroups tested, regardless of baseline blood pressure, regular caffeine consumption/ time of withdrawal, age, sex and hormonal status". The EFSA assessment included test doses of about 200-300 mg (2.9-4.3 mg/kg bw for a 70 kg adult), (range: 80-300 mg). The resulting increases in blood pressures observed were 3-8 mm Hg and 4-6 mm Hg for systolic and diastolic blood pressure, respectively. Nurminen et al. (1999)(a review in EFSA (2015)) found that a single dose of caffeine (200-250 mg) increased systolic and diastolic blood pressures by 3-14 mm Hg and 4-13 mm Hg, respectively. Repeated doses of 250 mg caffeine taken 4 h apart induced a blood pressure increase of 3-4 mm Hg that lasted up to 9-12 h.

Regarding energy drinks, EFSA (2015) concludes that common constituents of energy drinks at concentrations commonly present in such bevarages (typically about 300-320 mg/l caffeine; 4000 mg/l taurine; 2400 mg/l D-glucorono-γ-lactone) would not affect the safety of single doses of caffeine up to 200 mg (3 mg/kg bw per day in a 70 kg adult, which may also apply to children and adolescents). "Up to these levels of intake, other common constituents of "energy drinks" are not expected to adversely interact with caffeine on its effects on the cardiovascular system, on the central nervous system or hydration status".

Habitual consumption

No RCTs of energy drinks included in this risk assessment investigated consumption for more than 7 days. The one study that investigated consumption of 59 ml energy drink twice daily for 7 days did not report the caffeine concentration (Shah et al., 2016a).

EFSA (2015) states that doses ≤ 400 mg caffeine per day (5.7 mg caffeine/kg bw for a 70 kg adult) do not raise fasting blood pressure significantly after habituation to caffeine takes place. Furthermore, EFSA considered that (although not formally tested) "changes in blood pressure induced by repeated intakes of caffeine at doses and time intervals which would not exceed the maximum plasma concentrations achieved with a single dose of 200 mg caffeine (about 3 mg/kg bw for 70 kg person) would be of low clinical relevance for healthy individuals in the general population under normal environmental conditions" (EFSA, 2015). Prospective cohort studies evaluated by EFSA (2015) "on the relationship between habitual caffeine intake and long-term changes in blood pressure and on the risk of incident hypertension are conflicting and difficult to interpret".

As caffeine is a competitive antagonist of adenosine receptors, exposure leads to the release of adrenaline (epinephrine) and noradrenaline (norepinephrine). During caffeine tolerance development, "the effects of caffeine on blood pressure and heart rate usually develops within a couple of days and it is accompanied by lower release of adrenaline, noradrenaline and renin than in the non-tolerant state" (EFSA, 2015).

3.5.1.2 Heart rate, arrhythmia and palpitations

Single dose and repeated doses within a day

The outcome of the evaluation of the included RCTs on energy drink consumption could not convincingly demonstrate that changes in heart rate were induced by caffeine concentrations of 1.6 – 5.8 mg/kg bw (70 kg adult) in energy drinks. On the contrary, Shah et al., (2016a, b) and Svatikova et al. (2015) indicated that no increase in heart rate occurred. These RCTs had the highest level of confidence in the evidence for this effect. The RCTs investigating arrhythmias had limitations that rendered them unqualified for further assessment. Svatikova et al. (2015) did not investigate electrophysiological parameters/arrhythmia.

One of the main cardiovascular symptoms identified by ANSES (2013) after intake of energy drinks was tachycardia. This finding was obtained after analysing 212 cases of adverse effects reported through the French Nutritional Vigilance Scheme. In EFSA's (2015) reference to the ANSES report, it was highlighted that additional risks could arise from the different pattern of consumption of energy drinks compared with other dietary sources of caffeine, such as very high acute intakes. An epidemiological study did not support that caffeine consumption could induce supra-ventricular tachycardia (Frost and Vestgaard, 2005 in ANSES, 2013). Case studies have concluded on the contrary (Di Rocco et al., 2011; Berger and Alford, 2009 in ANSES, 2013). EFSA reported on a repeated dose study using two 250 mg doses of caffeine 4 h apart that increased heart rate with 2 beats per min.

Due to the observed effects of energy drinks on arrhythmia (ANSES, 2013), ANSES reports that some authors have suggested that "energy drinks may reproduce the effects of stress tests or adrenaline provocation tests used to screen for long QT syndromes or other genetic disorders of cardiac rhythm" (Dufendach et al., 2012; Gray et al., 2012; Rutledge et al., 2012 (all in ANSES, 2013)).

3.5.1.3 Conclusion on cardiovascular effects of energy drinks alone

Consuming a single dose of 480 ml energy drink with a caffeine dose of 3.4 mg/kg bw (Svatikova et al., 2015) led to an increase in blood pressure similarly to effects observed previously (EFSA, 2015) for equal caffeine concentrations. The Panel did not identify any RCTs on habitual consumption exceeding 7 days. EFSA (2015) noted that there are conflicting reports on the association between habitual coffee intake and long-term changes in blood pressure. No increase in heart rate occurred following energy drink consumption (Shah et al., 2016a, b; Svatikova et al., 2015). The Panel cannot conclude with respect to the relationship between arrhythmias and consumption of energy drinks.

3.5.2 Cardiovascular effects of energy drinks in combination with exercise

The included RCTs referred to in this chapter are summarised per endpoint in Table 3.5-3 and referred to in Table 4, Chapter 15, Appendix: Weight of evidence.

None of the included RCTs addressed dehydration related to physical activity. EFSA (2015) notes that caffeine doses of 3 mg/kg bw ingested about one hour prior to endurance exercise induced only a modest increase in body temperature compared with placebo. Doses up to 6 mg/kg bw, equivalent to the intervention doses in the included RCTs, ingested one hour before and during prolonged endurance exercise in a hot environment did not affect body temperature or hydration status (EFSA, 2015).

3.5.2.1 Blood pressure

Single dose and repeated doses within a day

One included RCT (Svatikova et al., 2015) investigated the effect on blood pressure after intake of 480 ml energy drink (3.4 mg caffeine/kg bw) followed by a physical stress test. The energy drinks were ingested about 30 min prior to the stress test that lasted for 2 min. No effects on blood pressure were observed in this study.

EFSA (2015) evaluated three RCTs for the association between caffeine ingestion and resistance exercise. Despite small study sizes and difficulties in comparing the RCTs, it was stated that the outcome "suggest an additive effect of caffeine and resistance training on blood pressure during exercise, and that caffeine could attenuate the decrease in blood pressure observed after resistance training". The studies used caffeine doses of 4-6 mg/kg bw ingested 45-60 min pre-exercise.

EFSA (2015) considers single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70 kg adult) from all sources not to give rise to safety concerns when consumed less than two hours prior to intense physical exercise under normal environmental conditions. These doses may also apply to children.

3.5.2.2 Heart rate and palpitations

Single dose and repeated doses within a day

In the included RCTs, energy drink volumes of 250-480 ml which gave final caffeine doses of 3.0-3.4 mg/kg bw were combined with physical activity (Lara et al., 2014, 2015) or a physical stress test (Svatikova et al., 2015), in normotensive young adults. These RCTs failed to demonstrate any effects of the combination of energy drinks and physical activity/physical stress test on heart rate (all three RCTs) or heart palpitations (Lara et al., 2015). The overall quality of the studies was sufficient to conclude that energy drinks in combination with physical activity did not affect heart rate; however, the evidence was insufficient to determine that heart palpitations was not an effect of the intervention. The volumes of energy drinks described in these studies were smaller than many of those described as "acute high consumption" in Table 4.2.1 of the chapter on exposure. However, the Panel cannot conclude about higher caffeine doses in larger volumes of energy drinks.

The ANSES' (2013) description of cases of the French Nutritional Vigilance Scheme included one case of a 16-year-old male who suffered cardiac arrest followed by recovery after energy drink consumption (2-6 cans/day, specific volume unknown) in combination with sports. ANSES rated the causality between exposure and effect as "possible".

3.5.2.3 Conclusion on cardiovascular effects of energy drinks in combination with physical activity

Consumption of 480 ml energy drink, containing caffeine equivalent to 3.4 mg caffeine/kg bw for a 70 kg adult, in combination with a physical stress test, did not alter blood pressure (Svatikova et al., 2015). Although the study is of high quality, the Panel does not consider this short test to represent "physical activity" or "exercise". Thus, the Panel cannot conclude on the relationship of blood pressure and energy drink consumption in combination with physical activity.

Energy drink intakes of 250-480 ml (caffeine doses of 3.0-3.4 mg/kg bw for a 70 kg adult) combined with physical activity (Lara et al., 2014, 2015) or a stress test (Svatikova et al., 2015) were investigated with respect to effects on heart rate and heart palpitations (Lara et al., 2015). Evidence was insufficient to conclude on the effect of heart palpitations. Heart rate was not affected by the energy drink intake in combination with physical activity (Lara et al., 2014, 2015; Svatikova et al., 2015). None of the included RCTs addressed dehydration related to physical activity.

3.5.3 Cardio-, cerebrovascular and cardiorespiratory effects of caffeine alone

The included RCTs referred to in this Chapter are summarised per endpoint in Table 3.5-4 and referred to in Table 7, Chapter 15, Appendix: Weight of evidence.

3.5.3.1 Blood pressure

Single dose and repeated doses within a day

Four of the included RCT studies on effects of caffeine on cardiovascular system outcomes, described endpoints with respect to single doses. The doses used were in the range 1- 6.2 mg/kg bw. Blood pressure increases were in the ranges 0.5-19 mm Hg and 1- 27 mm Hg for systolic and diastolic blood pressures, respectively. Note that tetraplegic subjects in the study by Flueck et al. (2016) experienced the highest increases in blood pressure (19 and 27 mm Hg for systolic and diastolic pressures, respectively). This group cannot be considered representative for the general population as tetraplegic individuals show an inability to activate the sympathetic nervous system to various degrees (Flueck et al., 2016). The ranges of blood pressure increases reported in the included RCTs were wider than those described by EFSA (2015) above; however, the caffeine dose range was wider as well. Note that the included studies that investigated the effect of a single dose of caffeine on blood pressure found an increase. Boys (8-17 years) demonstrated a greater caffeine response than girls of the same age (Temple et al., 2014).

Flueck et al. (2016) also investigated the effect of caffeine on adrenaline (epinephrine) concentrations. A three-fold increase in epinephrine level was observed after exposure to 5.8-6.2 mg/kg bw caffeine. The increase was accompanied by the increase in blood pressure described above. The effect was seen in able-bodied and paraplegic study subjects; however, the effects seen in paraplegics may not be representative of that of the general population although in these individuals, sympathetic nerve activity is almost fully conserved (See "Susceptible groups").

According to EFSA (2015), test doses of about 200-300 mg (2.9-4.3 mg/kg bw for a 70 kg adult; range: 80-300 mg) can induce blood pressure increases of 3-8 mm Hg and 4-6 mm Hg for systolic and diastolic blood pressure, respectively. The same single dose level has been reported in a review (Nurminen et al., 1999; in EFSA (2015)) to give increases in systolic and diastolic blood pressures by 3-14 mm Hg and 4-13 mm Hg, respectively. Repeated doses of 250 mg caffeine taken 4 h apart have been shown to induce blood pressure increases of 3-4 mm Hg that lasted up to 9-12 h.

Habitual consumption

In two RCTs the intervention lasted for up to 12 weeks (Bloomer et al., 2013 and 2015). Uncertain caffeine doses of up to 250 mg/day for 12 weeks and 125-375 mg/day for 8 weeks

did not raise systolic or diastolic blood pressure in the study participants. The studies were of insufficient quality for risk characterisation.

EFSA (2015) states that doses ≤ 400 mg per day (5.7 mg/kg bw for a 70 kg adult) do not raise fasting blood pressure significantly after caffeine habituation takes place. EFSA considers that (although not formally tested) "changes in blood pressure induced by repeated intakes of caffeine at doses and time intervals which would not exceed the maximum plasma concentrations achieved with a single dose of 200 mg caffeine [about 3 mg/kg bw for 70 kg person] would be of low clinical relevance for healthy individuals in the general population under normal environmental conditions" (EFSA, 2015). Prospective cohort studies evaluated by EFSA (2015) "on the relationship between habitual caffeine intake and long-term changes in blood pressure and on the risk of incident hypertension are conflicting and difficult to interpret".

3.5.3.2 Heart rate

Single dose and repeated doses within a day

Altoghether, six included RCTs on caffeine could not convincingly demonstrate that changes in heart rate were induced by caffeine doses from 1 mg/kg bw (Temple et al., 2014) to 6.2 mg/kg bw (Flueck et al., 2016). However, a small, significant reduction in heart rate (3-8 beats/min) was observed in the children and adolescents (8-17 years) studied in Temple et al. (2014). The caffeine doses were 1 and 2 mg/kg bw (with no dose-response relationship).

One included RCT (Lemery et al., 2015) investigated the effects of inducibility and cycle length of tachycardia after caffeine exposure in patients with supraventricular tachycardia (see Susceptible groups, Chapter 3.8.2.4). No effects were found. However, this study did not demonstrate a sufficient level of evidence.

Habitual consumption

The two included RCTs that investigated caffeine exposure for up to 12 weeks could not demonstrate any effect of caffeine on changes in heart rate (Bloomer et al., 2013 and 2015). The studies were of insufficient quality for risk characterisation.

3.5.3.3 Respiratory and cerebrovascular effects

The included RCTs could not demonstrate any effect on respiratory rate after exposure to not verifiable doses of caffeine between 1.2-6.7 mg/kg bw per day given for up to 12 weeks (Bloomer et al., 2013 and 2015). The studies were of insufficient quality for risk characterisation.

The tidal volume investigated after 5.8-6.2 mg/kg bw caffeine ingestion in able-bodied in the study by Flueck et al. (2016) increased significantly; however this increase may reflect a

normal variation, and was below e.g. an increase of up to 25% that can be observed as normal physiological changes during night time.

Ingestion of a caffeine dose of 1.1 mg/kg bw induced a small effect on cerebral blood oxygenation within the normal physiological range (Dodd et al., 2015). The evidence for effect was insufficient.

3.5.3.4 Conclusions on cardio-, cerebrovascular and cardiorespiratory effects of caffeine alone

Caffeine intakes in single doses from 1 mg/kg to 6.2 mg/kg bw induced blood pressure increases of 0.5-9 mm Hg and 1-9 mm Hg for systolic and diastolic blood pressures, respectively, for the healthy, general population (including children and adolescents 8-17 years). Based on the included RCTs, the Panel cannot draw any conclusions about blood pressure effects of habitual caffeine exposure; however, EFSA (2015) considers that "changes in blood pressure induced by repeated intakes of caffeine at doses and time intervals which would not exceed the maximum plasma concentrations achieved with a single dose of 200 mg caffeine (about 3 mg/kg bw for 70 kg person) would be of low clinical relevance for healthy individuals in the general population under normal environmental conditions".

A single dose of caffeine in the range from 1 to 6.2 mg/kg bw, did not influence heart rate in adults, whereas a single dose of 1-2 mg caffeine/kg bw induced a small, but significant reduction in heart rate in children and adolescents (Temple et al., 2014). Since the reduction was small and seen after a single dose, the Panel has no concerns about this specific result. The Panel cannot conclude on the association between caffeine exposure and heart rate.

The Panel cannot conclude on heart rate effects resulting from habitual exposure (up to 12 weeks) or electrophysiological effects of single doses due to inadequate evidence. There is not sufficient information available to conclude about effects on tidal volume or cerebrovascular effects.

3.5.4 Cardiovascular effects of caffeine in combination with physical activity

The included RCTs referred to in this chapter are summarised in Table 3.5-5 and referred to in Table 10, Chapter 15, Appendix: Weight of evidence.

None of the included RCTs addressed dehydration related to physical activity. EFSA (2015) notes that caffeine doses of 3 mg/kg bw ingested about one hour prior to endurance exercise induced only a modest increase in body temperature compared with placebo. Doses up to 6 mg/kg bw, equivalent to the intervention doses in the included RCTs, ingested one hour before and during prolonged endurance exercise in a hot environment did not affect body temperature or hydration status (EFSA, 2015).

3.5.4.1 Blood pressure, heart rate and arrhythmia

Single dose

Two included RCTs in this risk assessment demonstrated a small increase in blood pressure after combined intervention of caffeine (4-5.7 mg/kg bw) and physical activity (Souza et al., 2014; Bunsawat et al., 2015). The intervention had no effect on the heart rate measured post-exercise. A third study (Puente et al., 2017) observed no effect on mean or peak heart rate during exercise after caffeine exposure of 3 mg/kg bw. A caffeine dose of 5.7 mg/kg bw induced a small increase in arrhythmia (Bunsawat et al., 2015). However, these studies were non-informative. Note that the EFSA (2015) statement on the combination of caffeine and resistance exercise quoted below was based on Souza et al. (2014) and two other studies. The post-exercise differences in blood pressures (statistically significant) between caffeine and placebo were not observed continuously during the 9 h measurement period, rather they were observed at about 3 h and at 0.5, 5-6.5 h for systolic and diastolic blood pressures, respectively.

EFSA (2015) evaluated three RCTs for the association between caffeine ingestion and resistance exercise. Despite small study sizes and difficulties in comparing the RCTs, it was stated that the outcome "suggest an additive effect of caffeine and resistance training on blood pressure during exercise, and that caffeine could attenuate the decrease in blood pressure observed after resistance training". The studies used caffeine doses of 4-6 mg/kg bw ingested 45-60 min pre-exercise.

3.5.4.2 Conclusions on cardiovascular effects of caffeine in combination with physical activity

The overall evidence in the included RCTs was insufficient to conclude on an association between caffeine exposure combined with physical activity and the endpoints blood pressure, heart rate and arrhythmia. EFSA (2015) refers to studies suggesting that an additive effect of caffeine and resistance training on blood pressure during physical activity occurred, and that caffeine could attenuate the decrease in blood pressure observed after resistance training. These studies used caffeine doses of 4-6 mg/kg bw ingested 45-60 min pre-exercise. The Panel does not find the effect on blood pressure post-exercise (Souza et al., 2014; Bunsawat et al., 2015) convincing. None of the included RCTs addressed dehydration related to physical activity.

3.6 Outcome of metabolic effects

An overview of the included RCTs subject to evaluation of metabolic effects is given in Table 3.6-1.

Table 3.6-1. Number of studies on metabolic effects of energy drink consumption and caffeine exposure and corresponding tables of evidence evaluation.

Endpoint	Intervention	Number of studies	Table presenting the overall evaluation of the evidence
Metabolic effects	Energy drinks	1	Table 3.6-2
Oxidative stress, and haematological and metabolic effects	Caffeine	3	Table 3.6-3
Metabolic effects	Caffeine and physical activity	1	Table 3.6-4

Table 3.6-3. Likelihood evaluation of oxidative stress, and haematological and metabolic effects of caffeine in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Bloomer (2015) Bloomer (2013)	1.2-6.7	Haematology	No effect	From + to ++/+++	Inadequate
Caffeine	Placebo	Bloomer (2015) Bloomer (2013)	1.2-6.7	Metabolic effects	No effects	From + to ++/+++	Inadequate
Caffeine	Placebo	Bloomer (2013)	2.8 – 6.7	Advanced oxidation protein product	Low increase	++/+++	Unlikely

Table 3.6-4. Likelihood evaluation of metabolic effects of caffeine and physical activity in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Wu (2015)	2, 4, 6	Metabolic	Small changes	++	Unlikely

3.6.1 Metabolic, oxidative stress and haematological effects of caffeine alone

The included RCT referred to in this chapter are summarised per endpoint in Table 3.6-3 and referred to in Table 8, Chapter 15, Appendix: Weight of evidence.

Please see Chapter 3.6.1.1 for general information on metabolic effects of caffeine.

3.6.1.1 Potassium

A battery of blood sample tests were performed in the 8-12 week studies by Bloomer et al. (2013, 2015). Variable and unverifiable doses were given in the range of 1.2-6.7 mg/kg bw per day. Only the 2013-study demonstrated a small, but within normal range, increase in potassium level. These studies were considered to be non-informative by the Panel. Nevertheless, the finding was supported by the following reference on caffeine effects on sodium and potassium excretion and presence in serum: "Doses of caffeine up to 6 mg/kg bw per day consumed for four days by habitual caffeine consumers (one week run-in with doses of 3 mg/kg bw per day) did not lead to significant changes in [...] 24-hr Na+ and K+ excretion, [...] serum Na+ and K+, [...] compared with placebo (Armstrong et al., 2005 in EFSA (2015))".

3.6.1.2 Oxidative stress

Among five markers for oxidative stress measured in the above-mentioned study by Bloomer et al. (2013), a significantly higher level of "advanced oxidation protein products" after ingestion of caffeine than placebo was observed. Caffeine was given at a dose of 2.8-3.3 mg/kg bw for 1 week followed by 5.6-6.7 mg/kg bw for the next ten weeks. The Panel considered the study to be non-informative.

3.6.1.3 Haematological effects

No effects of caffeine were found in the 15 parameters of blood count data presented in the studies by Bloomer et al. (2013 and 2015). The Panel considered the studies to be non-informative.

3.6.1.4 Conclusion on metabolic and oxidative stress effects of caffeine alone

A single dose of caffeine of 5.8-6.2 mg/kg bw increased epinephrine levels three-fold (Flueck et al., 2016).

The included RCTs provide insufficient evidence to conclude on the effects of caffeine on potassium levels, oxidative stress or haematological parameters.

3.6.2 Metabolic effects of caffeine in combination with physical activity

The included RCT referred to in this chapter is the one presented in Table 3.6-4 and referred to in Table 11, Chapter 15, Appendix: Weight of evidence.

3.6.2.1 Glucose, insulin and cortisol levels

Wu (2015) investigated the level of the glucose, insulin and cortisol in response to caffeine doses of 2, 4 and 6 mg/kg bw at time points 0, 15 and 30 min after resistance exercise. The authors observed a small increase in cortisol and glucose levels and a small decrease in insulin levels without an apparent dose-response relationship. The magnitude of response was within normal, physiological variations. However, due to the limitations of this single study, the Panel considers the study to be non-informative.

The effect of caffeine exposure on glucose and hormones such as insulin and cortisol is not mentioned by EFSA (2015) and only as caffeine alone (not combined with physical activity) in relation to carbohydrates (insulin) in energy drinks by ANSES (2013). Nevertheless, changes in blood glucose and insulin levels are to be expected after consumption of sugar-containing energy drinks. Whether caffeine would modify these responses can only be observed in a glucose tolerance test with or without simultaneous exposure to caffeine. Such a procedure was not included in the study by Wu (2015) described above.

3.6.2.2 Conclusion on metabolic effects of caffeine in combination with physical activity

The Panel cannot conclude on glucose, insulin or cortisol levels after combined exposure to caffeine and physical activity as only one study with insufficient evidence was included (Wu, 2015) and the topic was not addressed by EFSA (2015). The Panel did not identify any studies that address metabolic effects after energy drink consumption in combination with physical activity.

3.7 Outcome psychobehavioural effects

An overview of the studies used to evaluate psychobehavioural and related effects is given in Table 3.7-1.

Table 3.7-1. Number of studies on psychobehavioural effects of energy drink consumption and caffeine exposure and corresponding tables of evidence evaluation.

Endpoint	Intervention	Number of studies	Table presenting the overall evaluation of the evidence
Psychobehavioural effects	Energy drinks	3	Table 3.7-2
Psychobehavioural effects	Energy drinks combined with exercise	3	Table 3.7-3
Psychobehavioural effects	Energy drinks combined with alcohol	1	Table 3.7-4
Psychobehavioural effects	Caffeine	2	Table 3.7-5
Psychobehavioural, insomnia, gastrointestinal and muscular effects	Caffeine combined with physical activity	2	Table 3.7-6

Table 3.7-2. Likelihood evaluation of psychobehavioural effects of energy drinks in the included RCTs.

Intervention	Control	No of studies	Caffeine (mg/kg bw/day)	Energy drink (ml)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Energy drink	Placebo	1	NR	NR	Psychological	No effect	++/+++	Inadequate (no effect)
Energy drink	Placebo	2	1.7-4.4	57/NR	Psychobehavioural	No effect	+	Inadequate (no effect)

Table 3.7-3. Likelihood evaluation of psychobehavioural effects of energy drinks combined with physical activity in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Energy drink (ml)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Energy drink	Placebo	Salinero (2014) Lara (2014) Lara (2015)	3	250	Headache, anxiety, irritability, gut discomfort	No effect	++++	Very likely no health effect
Energy drink	Placebo	Lara (2014) Lara (2015) Salinero (2014)	3	250	Insomnia	Moderate effect/no effect	From +++ to ++++	Very likely no health effect

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Energy drink (ml)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Energy drink	Placebo	Salinero (2014)	3	250	Nervousness	Small effect	++++	Very likely no health effect

Table 3.7-4. Likelihood evaluation of psychobehavioural effects of energy drinks combined with alcohol in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Energy drink	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Energy drink	Placebo	Peacock (2014)	NR	3.57 ml/kg bw	Muscular tension	Small effect	++	Unlikely
Energy drink	Placebo	Peacock (2014)	NR	3.57 ml/kg bw	Other psychological outcomes	No effects	++	Inadequate

Table 3.7-5. Likelihood evaluation of psychobehavioural effects of caffeine in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Rogers (2013)	3.6	Sleepiness	Small reduction in test score	++	Unlikely

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Rogers (2013)	3.6	Anxiety/jitteriness	Small or no increase	++	Unlikely/inadequate
Caffeine	Placebo	Dodd (2015)	1.1	Mood	No effect	+++/++	Inadequate

Table 3.7-6. Likelihood evaluation of psychobehavioural, insomnia, gastrointestinal and muscular effects of caffeine and physical activity reported in the included RCTs.

Intervention	Control	Ref.	Caffeine (mg/kg bw/day)	Effect	Effect direction	Overall confidence of evidence rating range	Likelihood of an association between intake of energy drinks and the adverse effect under consideration
Caffeine	Placebo	Puente (2017) Salinero (2017)	3	Insomnia/sleep quality	Small effect/no effect	From +++ to ++++	As likely as not
Caffeine	Placebo	Salinero (2017)	3	Muscular effects	No effect	+++	Inadequate
Caffeine	Placebo	Salinero (2017)	3	Gastrointestinal effects	No effect	+++	Inadequate
Caffeine	Placebo	Salinero (2017)	3	Psychobehavioral effects	No effect	+++	Inadequate

3.7.1 Psychobehavioural effects of energy drinks

The included RCTs referred to in this Chapter are summarised per endpoint in Table 3.7-2 and referred to in Table 3, Chapter 15, Appendix: Weight of evidence.

Possible mechanisms of energy drinks on the central nervous system are presented in ANSES, 2013. The effects of caffeine on the central nervous system are well described (see e.g. EFSA, 2015). Rogers et al. (2010; in EFSA, 2015) stated that intake may lead to anxiety, sleep disturbances and behavioral changes. Furthermore, "tolerance to the anxiogenic effect to caffeine develops with frequent consumption, even in genetically susceptible individuals".

Single dose

Three included RCT studies (Kurtz et al., 2013; Phan & Shah, 2014; Peacock et al 2014) reported psychological and psychobehavioural effects of energy drinks. The caffeine doses in the beverages were 3.1-4.4 mg/kg bw, and two caffeine concentrations were unknown. Kurtz et al. (2013) anticipated that the caffeine amount was between 138 and 215 mg, resulting in a dose range of 1.7 – 4.0 mg/kg bw. None of the studies could demonstrate any psychobehavioural effect, and they were considered non-informative.

The following toxicological reference point on caffeine was given by EFSA (2015) based on Landholt et al., 1995: Single doses of caffeine of about "100 mg (1.4 mg/kg bw for a 70 kg adult) may increase sleep latency and reduce sleep duration in some individuals, particularly when consumed close to bedtime". Doses of < 100 mg did not have the same effect (Dorfman and Jarvik, 1970 in EFSA, 2015).

EFSA (2015) did not find that three single doses of caffeine (2.5-10 mg/kg bw) showed an effect on most self-reported measures of anxiety in children. EFSA noted the following limitations: few studies were available, study sizes were small, the testing tools used to assess anxiety and behavioural changes, varied. Thus, EFSA concluded that the studies could not be used to derive single doses of caffeine of no concern for children or adolescents. Inter-individual variability in relation to habitual caffeine intakes has not been studied.

EFSA (2015) concludes that common constituents of energy drinks at concentrations commonly present in such beverages (typically about 300-320 mg/l caffeine; 4000 mg/l taurine; 2400 mg/l D-glucorono-γ-lactone) would not affect the safety of single doses of caffeine up to 200 mg (3 mg/kg bw per day in a 70 kg adult, which may also apply to children and adolescents). "Up to these levels of intake, other common constituents of "energy drinks" are not expected to adversely interact with caffeine on its effects on the cardiovascular system, on the central nervous system or hydration status".

Regarding energy drink consumption, ANSES (2013) reported two cases from the French Nutritional Vigilance Scheme, both occurred after consumption of energy drinks without any concomitant intake. In one instance, a four-year-old boy showed agitation and excitement after consuming four cans of energy drink (causality termed "very likely" by ANSES). In

another instance, a female 21-year-old suffered panic attacks, headache and palpitations following consumption of one can of energy drink (causality termed "likely" by ANSES). The exact volume and caffeine content leading to the observed effects was uncertain.

Long-term habitual caffeine consumption

None of the included RCTs evaluated the psychobehavioural effects for more than 7 days.

EFSA (2015) notes that "regular consumption of caffeine up to about 3 mg/kg bw per day does not appear to induce behavioural changes in children and adolescents, whereas higher intakes (10 mg/kg bw per day) may increase anxiety and adversely affect behaviour and sleep in habitual low caffeine consumers. Children appear to develop tolerance to the central effects of caffeine at high habitual intakes (> 300 mg per day) and show withdrawal symptoms". EFSA also notes that "the studies available at doses of ≤ 3 mg/kg bw have small sample sizes and are heterogeneous in design, and that doses between 3 and 10 mg/kg bw per day have not been investigated".

3.7.1.1 Conclusion on psychobehavioural effects of energy drinks

The Panel did not identify any psychobehavioural effects of energy drinks in the single dose RCTs included. No habitual consumption studies were included.

According to EFSA (2015), single doses of caffeine of about 100 mg (1.4 mg/kg bw) consumed by adults, adolescents and children increased sleep latency and reduced sleep duration when intake was close to bedtime. In children, 3 mg/kg bw was considered by EFSA (2015) not to induce anxiety or behavioural changes. Furthermore, for habitual consumption, EFSA (2015) notes that "regular consumption of caffeine up to about 3 mg/kg bw per day does not appear to induce behavioural changes in children and adolescents, whereas higher intakes (10 mg/kg bw per day) may increase anxiety and adversely affect behaviour and sleep in habitual low caffeine consumers. Children appear to develop tolerance to the central effects of caffeine at high habitual intakes (> 300 mg per day) and show withdrawal symptoms".

3.7.2 Psychobehavioural effects of energy drinks combined with physical activity

The included RCTs referred to in this chapter are summarised per endpoint in Table 3.7-3 and referred to in Table 5, Chapter 15, Appendix: Weight of evidence.

No specific information on the psychobehavioural effects of energy drink combined with physical activity was described in EFSA (2015) or ANSES (2013) risk assessments. Please refer to the text under "Energy drinks: psychobehavioural effects" (Chapter 3.6.1).

Single dose

Three included RCTs assessed psychobehavioural effects of energy drinks combined with physical activity. The energy drinks were given in single volumes of 250 ml which provided caffeine dose levels of 3 mg/kg bw (Lara et al., 2014; Lara et al., 2015; Salinero et al., 2014). Insomnia was demonstrated in a few individuals in Lara et al. (2014), but not in the studies by Lara et al. (2015) or Salinero et al. (2014). However, the result of insomnia could not be evaluated for statistical significance in the study by Lara et al. (2014). Salinero et al. (2014) failed to demonstrate an effect of energy drink on headache, fatigue, irritability, nervousness and gut discomfort effects. The quality of the three studies was overall high, leading to a high confidence in the lack of effect.

3.7.2.1 Conclusion on psychobehavioural effects of energy drinks combined with physical activity

Intake of energy drinks in combination with physical activity did not induce insomnia or other psychoehavioural effects when the single caffeine doses were 3 mg/kg bw.

3.7.3 Psychobehavioural effects of energy drinks in combination with alcohol

The included RCT referred to in this chapter is summarised per endpoint in Table 3.7-4 and referred to in Table 6, Chapter 15, Appendix: Weight of evidence.

Please see "Energy drinks and psychobehavioural effects" (Chapter 3.7.1) for general information on psychobehavioural effects of caffeine.

The one included study (Peacock et al., 2014) investigated a battery of self-reported psychological effects (as well as physiological) after intake of Red Bull energy drink combined with 0.50 g/kg Smirnoff Red Label vodka. The caffeine concentration was unknown. No psychological effects were observed. This study was considered non-informative. None of the included RCTs in the present risk assessment investigated the effect of energy drinks on subjective perception of alcohol intoxication.

One of the main focuses of the combined intake of energy drinks and alcohol is related to the effect on the self-perceived perception of alcohol intoxication. Some authors have suggested that, through a "masking" phenomenon, energy drinks containing caffeine may lead to increased risk-taking behaviour. EFSA (2015) considers that caffeine consumed at doses up to 3 mg/kg bw (corresponding to about 200 mg in a 70 kg adult) from all sources, including energy drinks, is unlikely to mask the subjective perception of alcohol intoxication which could lead to increased risk-taking behaviour when alcohol is consumed at doses of about 0.65 g/kg bw (blood concentration of about 0.08 %). These alcohol doses "would not affect the safety of single doses of caffeine up to 200 mg". Higher doses of alcohol have not been systematically investigated.

ANSES (2013) reported three cases from the French Nutritional Vigilance Scheme on the association between intake of energy drinks in combination with alcohol on various psychobehavioural effects including sleep disorders and manifested with physical symptoms in two of the cases. Some of the effects described were visual hallucinations, disorientation, aggressiveness, night awakenings, tachycardia and vomiting. For two cases causality between intake of energy drinks/alcohol and the effects observed were considered "likely" and for one case causality was considered "very likely" (ANSES' assessment). One male, 28 years old (75 kg) experienced the adverse effects after intake of four cans of energy drink; a 23 year-old female drank three glasses and a 43-year old male (90 kg) drank 500 ml. Neither the exact volume nor the caffeine content of the intake, nor the alcohol amount were known.

3.7.3.1 Conclusion on psychobehavioural effects of energy drinks in combination with alcohol

The Panel cannot draw any conclusions based on the included RCT about psychobehavioural effects (including sleep disturbances) of the combination of energy drinks and alcohol ingestion. EFSA (2015) considers that caffeine doses up to 3 mg/kg bw (corresponding to 210 mg in a 70 kg adult) including from energy drinks, is unlikely to mask the subjective perception of alcohol intoxication which could lead to increased risk-taking behaviour when alcohol is consumed at doses of about 0.65 g/kg bw.

3.7.4 Psychobehavioural effects of caffeine alone

The included RCT referred to in this chapter is summarised per endpoint in Table 3.7-5 and referred to in Table 9, Chapter 15, Appendix: Weight of evidence.

Please see Chapter 3.7.1 for information on psychobehavioural effects of caffeine in general.

Single dose

In the included RCT by Rogers et al. (2013) of non to low consumers (<40 mg/day) and medium to high caffeine consumers (≥ 40 mg/day) received one dose of 100 mg caffeine followed by another of 150 mg, adding up to a total dose of about 3.6 mg/kg bw. The study subjects reported a significantly lower score on a sleepiness scale after caffeine exposure compared to placebo. However, the score difference was small.

Rogers et al. (2013) also investigated anxiety and jitteriness and detected a small, significant effect for non to low consumers, but no effect for medium to high consumers. Dodd et al. (2015) reported no mood effects (only an overall mood effect adding seven mood items) following ingestion of a single dose of caffeine of 1.1 mg/kg bw. Both studies were designed to reveal psychobehavioural effects of caffeine; however, both were considered non-informative.

Single doses of caffeine of about 100 mg (1.4 mg/kg bw) consumed by adults increased sleep latency and reduced sleep duration when intake was close to bedtime. Doses of < 100 mg did not have the same effect (EFSA, 2015).

EFSA (2015) did not find that three single doses of caffeine (2.5-10 mg/kg bw) showed an effect on most self-reported measures of anxiety in children. Few studies were available and study sizes were small. Furthermore, the testing tools used to assess anxiety and behavioural changes varied. The studies could not be used to derive single doses of caffeine of no concern for children or adolescents. Inter-individual variability in relation to habitual caffeine intakes has not been studied (EFSA, 2015).

3.7.4.1 Conclusion on psychobehavioural effects of caffeine alone

The Panel could not draw any conclusions with respect to sleepiness, anxiety/jitteriness or mood following ingestion of caffeine doses in the range 1.1-3.6 mg/kg bw due to the shortcomings of the included RCTs (Rogers et al., 2013; Dodd et al., 2015).

Single doses of caffeine of about 100 mg (1.4 mg/kg bw) consumed by adults have been shown to increase sleep latency and reduce sleep duration when intake was close to bedtime. In children, 3 mg/kg bw was considered by EFSA (2015) not to induce anxiety or behavioural changes.

EFSA (2015) notes that "regular consumption of caffeine up to about 3 mg/kg bw per day does not appear to induce behavioural changes in children and adolescents, whereas higher intakes (10 mg/kg bw per day) may increase anxiety and adversely affect behaviour and sleep in habitual low caffeine consumers. Children appear to develop tolerance to the central effects of caffeine at high habitual intakes (> 300 mg per day) and show withdrawal symptoms.

3.7.5 Psychobehavioural and other self-reported effects of caffeine in combination with physical activity

The included RCT referred to in this chapter is summarised per endpoint in Table 3.7-6 and referred to in Table 12, Chapter 15, Appendix: Weight of evidence.

Please see Chapter 3.7.1 for information on psychobehavioural effects of caffeine in general.

Single dose

One of the two included RCTs investigating caffeine exposure in combination with physical activity, Puente et al. (2017), reported that for the study subjects, who were experienced basketball players, the prevalence of insomnia more than doubled 24 h after the combined physical activity and caffeine exposure of 3 mg/kg bw compared to ingestion of placebo. On the other hand, Salinero et al. (2017) exposed the participants to a single dose of 3 mg/kg bw in combination with physical activity and did not observe a higher frequency of insomnia

relative to placebo. The evidence of association between caffeine exposure and the effects of insomnia was considered to be weak.

Salinero et al. (2017), in addition to insomnia, further reported on seven side effects, and found no increased frequency of, among others, gastrointestinal, muscular or psychobehavioural effects compared with placebo. Owing to the lack of effects and evidence rating, the study was considered non-informative.

Single doses of caffeine of about 100 mg (1.4 mg/kg bw) consumed by adults increased sleep latency and reduced sleep duration when intake was close to bedtime. Doses of < 100 mg did not have the same effect (EFSA, 2015).

3.7.5.1 Conclusion on psychobehavioural and other self-reported effects of caffeine in combination with physical activity

The effect of 3 mg/kg bw of caffeine combined with physical activity on insomnia/sleepiness could not be clearly demonstrated in the included RCTs (Puente et al., 2017; Salinero et al., 2017).

Single doses of caffeine of about 100 mg (1.4 mg/kg bw) consumed by adults have been shown to increase sleep latency and reduced sleep duration when intake was close to bedtime. In children, 3 mg/kg bw was considered by EFSA (2015) not to induce anxiety or behavioural changes.

3.8 Susceptible groups

The Panel uses the definition of vulnerable and susceptible groups by the Integrated Environmental Health Impact Assessment (IEHIAS). Three groups of individuals who were susceptible to the effect of caffeinated energy drinks and/or caffeine were identified in the included RCTs. These were subjects with familiar long QT syndrome and subjects with supraventricular tachycardia, who may experience risk of arrhythmias, among other adverse cardiovascular effects (Gray et al., 2017; Lemery et al., 2015). According to Flueck et al. (2016), "the influence of caffeine on the autonomic nervous system [in paraplegic and tetraplegic individuals] seems to depend on the level of lesion and the extent of the impairment" since the sympathetic nerves leave the spine between Th1 (thoracic vertebra number 1) and L2 (lumbar vertebra number 2). In paraplegic individuals sympathetic nerve activity is almost fully conserved, but tetraplegic individuals show inability to activate the sympathetic nervous system (Flueck et al., 2016). Furthermore, Temple et al. (2014) observed that boys (8-17 years) demonstrated a greater caffeine response than girls of the same age.

Other susceptible groups not addressed in the included RCTs are e.g. the unborn foetus, breastfed babies and children. The EFSA Panel (2015) considers "unborn children to be the most vulnerable group for adverse effects of caffeine among the general population". Individuals with genetic predispositions (polymorphism in the CYP1A2 gene) (see Chapter

2.2.4) may be more susceptible than individuals without the polymorphism; however, the EFSA Panel (2015) noted that "genetic polymorphisms for genes involved in caffeine metabolism may explain only a small proportion of the inter-individual variability in caffeine intake".

ANSES (2013) elaborates on genetic predispositions to ventricular arrhythmias "that can result in sudden or unexplained death". Factors underlying heart rhythm disorders can be e.g. electrolyte disorders, bradycardia, tachycardia, and exposure to substances that block ion channels (e.g. certain antihistamines and antipsychotics). Furthermore, the risk of arrhythmia is higher in women than in men.

3.9 Summary hazard identification and characterisation

3.9.1 Energy drinks

3.9.1.1 Safe levels of caffeine in energy drinks

EFSA (2015) concludes that common constituents of energy drinks at concentrations commonly present in such bevarages (typically about 300-320 mg/l caffeine; 4000 mg/l taurine; 2400 mg/l D-glucorono-γ-lactone) would not affect the safety of single doses of caffeine up to 200 mg (3 mg/kg bw per day in a 70 kg adult, which may also apply to children and adolescents). "Up to these levels of intake, other common constituents of "energy drinks" are not expected to adversely interact with caffeine on its effects on the cardiovascular system, on the central nervous system or hydration status".

Regarding the combination of energy drinks and alcohol, EFSA (2015) concludes that alcohol consumption at doses up to about 0.65 g/kg bw (blood alcohol concentration of about 0.08%) would not affect the safety of single doses of caffeine up to 200 mg from any dietary source, including energy drinks.

3.9.1.2 Cardiovascular effects: evaluation for toxicological reference point

An intake of energy drinks of 480 ml containing 240 mg caffeine (caffeine concentration 0.5 mg/ml), corresponding to a dose of 3.4 mg/kg bw (70 kg adult) or 3.9 - 7.2 mg/kg bw in children and adolescents (9-18 years), increased blood pressure (systolic and diastolic) by 6.6 and 4.2 mm Hg, respectively (Svatikova et al., 2015). Blood pressure was accompanied by an increase in noradrenaline.

The same study did not demonstrate an increase in heart rate, neither after energy drink intake alone nor in combination with a physical stress test. Electrophysiological parameters or incidents of arrhythmia were not investigated in this study. Further conclusions on the presence of cardiovascular effects from energy drink intake cannot be made.

The increase in blood pressure demonstrated in the study by Svatikova et al., (2015) will not be used as toxicological reference point in the risk characterisation due to the limitations of

this pilot study such as investigation of only one moderate dose, moderate study size, small age range and few cardiovascular parameters.

3.9.1.3 Psychobehavioural effects

No conclusion on safe volumes of energy drinks or their caffeine concentrations with respect to psychobehavioural effects can be drawn due to shortcomings of the included RCTs. Nevertheless, when an amount of 250 ml energy drink, representing a caffeine dose of 3 mg/kg bw, was combined with physical activity in young adults, insomnia was reported more frequently in the energy drink group relative to the placebo group (Lara et al., 2014). This observation was not repeated in another study by the same authors and under the same exposure conditions.

When energy drink consumption was combined with alcohol, no psychological or psychobehavioural effects were observed. The energy drink volume and caffeine concentrations were unknown (Peacock et al., 2014). Therefore, no conclusion can be drawn regarding the effects of the combined consumption of energy drinks and alcohol from the included RCTs. The conclusion from EFSA (2015) above regarding combined alcohol and caffeine intake from any source, including energy drinks, applies.

The included RCTs demonstrated that energy drinks containing a given concentration of caffeine did not induce any adverse effects other than those observed from similar concentrations of caffeine. However, the evidence of an association between energy drink intake and effect was weak in many of the studies; therefore, the confidence in the results is limited. The EFSA (2015) conclusion on caffeine in energy drinks applies (see "Safe levels of caffeine in energy drinks" above).

3.9.1.4 Conclusion hazard energy drinks

Included RCTs

An energy drink intake of 480 ml with a caffeine dose of 3.4 mg/kg bw (70 kg adult), corresponding to 3.9- 7.2 mg/kg bw in children and adolescents (9-18 years), increased blood pressure to about 5 mm Hg, but did not increase heart rate, neither when energy drink was consumed alone nor in combination with a physical stress test.

The Panel cannot conclude on adverse effects in studies of energy drink intake with caffeine doses lower than 3.4 mg/kg bw due to the low number of studies and the shortcomings associated with them.

The Panel cannot conclude on psychobehavioural effects of energy drinks. A tendency of increased occurrence of insomnia relative to placebo was found in one study in which the energy drink intake was 250 ml and the resulting caffeine concentration was 3 mg/kg bw; however, the finding was not repeated in a similar study.

The Panel cannot conclude on psychological or psychobehavioural effects of energy drink consumption combined with alcohol due to the low number of studies and associated shortcomings.

The Panel cannot conclude on adverse effects of energy drinks in combination with physical activity and related dehydration due to lack of effects and quality shortcomings. No studies addressing dehydration were included.

The effects of increased blood pressure following intake of 480 ml energy drink representing a dose of 3.4 mg caffeine/kg bw (Svatikova et al., 2015) will not be used as toxicological reference point in the risk characterization. Owing to certain limitations of the study, the Panel decided to include caffeine doses of no concern (EFSA, 2015) as toxicological reference points. The basis for this decision was two-fold: In the definition of energy drinks provided by the NFSA, caffeine is the only specified ingredient. Furthermore, considerable uncertainties are associated with determination of a reference point from effects of energy drinks, which contain a mixture of ingredients. None of the observed adverse effects in the included RCTs demonstrated that energy drinks containing a given concentration of caffeine induce any adverse effects other than those observed from similar concentrations of caffeine.

EFSA (2015) Scientific Opinion on the safety of caffeine

All toxicological reference points relevant to the risk characterisation of energy drinks containing caffeine stated in EFSA (2015) applies.

3.9.2 Caffeine

3.9.2.1 General adverse effects

Single doses

EFSA (2015) considers that single doses of caffeine from all sources that do not give rise to safety concerns for the general healthy population of adults, is up to 200 mg. This dose corresponds to about 3 mg/kg bw per day in a 70 kg adult. The same dose of 3 mg/kg bw may also apply to children and adolescents. The same amount of caffeine does not give rise to safety concerns when consumed less than two hours prior to intense physical exercise under normal environmental conditions.

Habitual consumption

EFSA (2015) states that doses up to 400 mg caffeine per day (5.7 mg caffeine/kg bw for a 70 kg adult) from all sources consumed throughout the day do not give rise to safety concerns for healthy adults in the general population, except pregnant women.

Doses up to 400 mg caffeine per day do not raise fasting blood pressure significantly after habituation to caffeine takes place. EFSA further notes that "changes in blood pressure induced by repeated intakes of caffeine at doses and time intervals which would not exceed the maximum plasma concentrations achieved with a single dose of 200 mg caffeine (about 3 mg/kg bw for 70 kg person) would be of low clinical relevance for healthy individuals in the general population under normal environmental conditions". Prospective cohort studies evaluated by EFSA (2015) "on the relationship between habitual caffeine intake and long-term changes in blood pressure and on the risk of incident hypertension are conflicting and difficult to interpret".

3.9.2.2 Effects on sleep

Single doses of 100 mg, corresponding to a dose of 1.4 mg/kg bw in adults is considered to increase sleep latency and reduce sleep duration in some individuals, particularly when consumed close to bedtime. The same dose of 1.4 mg/kg bw may also apply to children and adolescents (EFSA, 2015).

3.9.2.3 Caffeine doses leading to cardiovascular effects in the hazard characterisation compared with EFSA (2015) values

Single doses of caffeine below the dose of 200 mg (1-2 mg/kg bw) increased systolic and diastolic blood pressures slightly in children and adolescents 8-17 years; the mean values were in the range of about 0.5-2.5 mm Hg. No dose-response was observed. The same dose decreased heart rate by maximum 8 beats/min (Temple et al., 2014). Since the changes were small and seen after a single dose, the Panel has no concerns about this specific result. The Panel cannot conclude on the association between caffeine exposure and heart rate due to conflicting results and scarcity of high-quality studies.

3.9.2.4 Conclusion hazard caffeine

The effects on blood pressure and heart rate were small and likely of no biological relevance after intake of a single dose of 1-2 mg/kg bw of caffeine. The blood pressure increase was below or in the lower range of blood pressure increases reported previously for similar doses (see e.g. Chapter 3.5.3.1). Therefore, EFSA doses of no concern will be used in the risk characterisation. No effects of caffeine on psychobehavioural effects, such as insomnia, were observed. Therefore, the EFSA reference point will be used in the risk characterisation: Single doses corresponding to 1.4 mg/kg bw in adults is considered to increase sleep latency and reduce sleep duration in some individuals. The same dose may also apply to children and adolescents (EFSA, 2015).

3.9.3 Conclusion susceptible groups

Individuals who were identified as susceptible to the effect of caffeinated energy drinks and/or caffeine in the included RCTs were the following: Subjects with familiar long QT syndrome and with supraventricular tachycardia, who may experience risk of e.g. arrhythmias, in addition to paraplegic and tetraplegic individuals depending on the level of lesion and the extent of the impairment.

4 Energy drinks - consumption

4.1 Studies of energy drink consumption in children and adolescents in Norway

In the present risk assessment, data from several dietary assessment studies and life style surveys, which assessed energy drink consumption, conducted among children and adolescents in Norway, were included. The surveys were conducted in different age groups, with different methodologies. An overview of the studies is presented in Table 4.1-1.

Table 4.1-1 Overview of studies included in this assessment.

Study	Year	Age of participants, years	Response rate, %	Number of participants included	Method
UNGKOST 3	2015	8-9 and 12-13	54	1323	3-4 days web-based food diary
Norwegian Consumer Council	2018	10 - 18	28	962	Web-based questionnaire
MoBa study	2017-2018	13-15	30	15767	Web-based FFQ[1]
Ungdata study	2016-2018	13 - 18	67	44894	Web-based questionnaire

[1]FFQ: food frequency questionnaire

More detailed information on age subgroups and percentage of energy drink consumers are presented in Table 4.1-2. The Norwegian Consumer Council study (NCC study) was the only study designed specifically to assess the energy drink consumption (Forbrukerrådet, 2018). The other studies aimed to assess total diet (UNGKOST 3 and MoBa study), and life style factors (Ungdata, OsloMet) (Bakken, 2018; Hansen et al., 2016; MoBa, 2018), including energy drink consumption.

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

The Norwegian Consumer Council conducted, via Norstat (www.norstat.no), an online data collection among children and adolescents in June 2018. Members of the Norstat Respondent Panel were invited and received the survey. Children and adolescents 10 to 14 years of age

were contacted through their parents. Participants 15 to 18 years of age received invitation to participate in the survey directly (Forbrukerrådet, 2018).

Table 4.1-2 Overview of age groups, participants and energy drink consumers in the different studies.

Study	Age of participants, years	Number of participants included, n	Consumers of energy drinks, n (%)
UNGKOST 3			
4th grade	8-9	636	7 (1)
8th grade	12-13	687	30 (4)
Norwegian consumer council			
	10-12	265	49 (18)
	13-15	280	149 (53)
	16-18	417	291 (70)
MoBa study			
	13-15	15767	4700 (30)
Ungdata study			
8th to 10th grade	13-15	29344	14720 (50)
11th to 13th grade	16-18	15550	8562 (55)

The Norwegian Mother and Child Cohort Study (MoBa) is a study investigating causes of disease among mothers and children (MoBa, 2018). MoBa began to recruit pregnant women in 1999, and more than a number of 100 000 pregnancies was included. The MoBa cohort study conducted a follow up study in 2017-2018 in the now 13 to 15 years old adolescents, using an online food frequency questionnaire.

The Ungdata study is a national research collaboration lead by Oslo Metropolitan University (Oslo Met). The data collection is carried out among Norwegian adolescents annually, studying health and well-being. The questionnaire is filled in online by the participants during school hours. The data used in the present study were collected from adolescents in grades 8-10 including ages 13-15 years and grades 11-13 including ages 16-18 years. Due to the design of the Ungdata study, questions about energy drink consumption differed somewhat with regard to population subgroups in the study. Overall, 167859 student registered intake of energy drinks at some time (Ungdata1 Appendix 16), which corresponds to 67% of the study population. Furthermore, subgroups of the study population were presented with a second session of questions regarding both frequency of intake (Ungdata2 in Appendix 16) and amount of intake (Ungdata3 in Appendix 16). To be able to estimate daily intake, we used the data from Ungdata which included registration of both frequency and amount of intake. Thus, only data from 44894 students from the Ungdata survey, who had answered the second session of questions about both frequency (Ungdata2 in Appendix 16) and amount of intake (Ungdata3 in Appendix 16) were included in this risk assessment.

Data from the Ungdata study from Sykehuset Innlandet was also provided. However, participants in the study from Sykehuset Innlandet were all from the Ungdata study, and due

to partial data overlap with the Ungdata study, data from this study was not included in the risk assessment. The study from Sykehuset Innlandet had the same percentage of energy drink consumers as the Ungdata study (results not shown).

In addition to the lifestyle surveys and dietary assessment studies described in Table 4.1-1, the Norwegian Food and Vegetable Marketing Board (Opplysningskontoret for frukt og grønt and Opplysningskontorene for Landbruket) and the Norwegian Seafood Council provided data from a study assessing frequency of intake of food and beverages during the school day, including energy drinks. Because the survey only assessed food consumption during a limited time of day (when at school), and the fact that the amounts were not assessed, data from this study was not included in this risk assessment. Furthermore, the Panel investigated whether the UNG-HUNT3 survey had relevant data on energy drink consumption. However, questions about energy drink consumption were not included in the UNG-HUNT3 survey (https://www.ntnu.no/hunt/skjema). The UNG-HUNT4 survey includes one question about intake of energy drinks. This survey is however still ongoing (https://www.ntnu.no/hunt/skjema).

4.2 Estimates of energy drink consumption

With regard to intake estimations, the NFSA asked for three scenarios in the terms of reference; a) chronic mean consumption, b) chronic high consumption, and c) acute high consumption of energy drinks and caffeine among children and adolescents. Intakes of energy drinks were estimated based on data from Ungkost 3, the NCC study, the Ungdata study from Oslo Met and the MoBa cohort follow-up study (Table 4.2-1). Please see Appendix 16 for the questions and answer alternatives used in the studies.

The intake estimates were calculated by multiplying the reported frequency of consumption with the reported amounts consumed.

The distribution of the estimated intakes of energy drinks was skewed to the right in all populations investigated. Due to the skewed distributions, the Panel decided to use the median intakes as an estimate of chronic intake. High chronic intake was defined as the 95th percentile of the intake distributions. The panel decided to use the highest reported acute intake during 24 hours, measured in each study and age group, as acute high consumption. The reason for this was that even these highest amounts only cover one or a few drinking occasions, these were the highest reported intakes of energy drinks.

Table 4.2-1 Estimates of energy drink consumption in consumers only, from different studies and age groups, given in ml/day.

Study, and age groups	Consumers, number	Median chronic intake, ml/day	High chronic intake, 95 percentile, ml/day	Highest acute intake, ml/24 hours
Ungkost 3, 8-9 years	7	50	-	400[a]

Study, and age groups	Consumers, number	Median chronic intake, ml/day	High chronic intake, 95 percentile, ml/day	Highest acute intake, ml/24 hours
Ungkost 3, 12-13 years	30	81	418[b]	2000[a]
Norwegian Consumer Council 10-12 years	49	0.5	115[b]	1500[a]
Norwegian Consumer Council 13-15 years	149	35	320	6000[a]
Norwegian Consumer Council, 16-18 years	291	35	320	10000[a]
Ungdata study, 13-15 years	14720	17	330	2000[c]
Ungdata study, 16-18 years	8562	17	330	2000[c]
MoBa study, 13 years	4700	14	114	800[d]

[a] Reported maximum intake in 24 hours.
[b] 95 percentile is reported, however, the value is not statistically robust due to a small number of energy drink consumers in this age group.
[c] The maximum amount that the participants could select was the response option "Many cans equivalent to more than 1.5 liter". The value was thus estimated to be 2000 ml.
[d] The maximum amount that the participants could select was the response option "More than 3 glasses per day". The value was thus estimated to be 800 ml.

In the Ungdata study the maximum amount of energy drink that the participants could select was the response option "Many cans equivalent to more than 1.5 liter". For the Panel to be able to estimate a maximum intake from these data a value had to be estimated. The values were thus added 33% and estimated to be 2000 ml. The same was done for the MoBa study; the maximum amount of energy drink that the participants could select was the response option "More than 3 glasses per day". The amount of one glass was set at 200 ml and the value was added 33% and thus estimated to be 800 ml.

In the NCC study the participants were asked about their habitual intake and an additional specific question about the maximum number of cans they had drunk in 24 hours (NCC4 and NCC5, Appendix 16). Based on these questions we estimated the highest acute intake in the NCC study, shown in table 4.2-1.

In order to describe the variation of maximum intake of energy drinks between the consumers, table 4.2-2 presents the percentiles of the reported maximum intake during 24 hours, in the NCC study.

Table 4.2-2 The percentiles of reported maximum intakes during 24 hours in consumers, in the Norwegian Consumer Council study, ml/24 hours.

	Percentiles, ml/24 hours						
Age group, years	5	10	25	50	75	90	95
10-12 (n=49)	125	250	250	500	705	1000	1160

	Percentiles, ml/24 hours						
13-15 (n=149)	250	250	415	660	1000	1500	2750
16-18 (n=291)	250	250	500	1000	1500	2500	3500

In the NCC study, in age group 10-12 years, the number of consumers were only 49 and thus the percentiles presented for this age group in table 4.2-2 are not statistically robust. However, 6 participants (12 % of the consumers and 2 % of the total population) reported a maximum intake above 1L (range 1000 ml – 1500 ml). In addition, 14 participants (29% of the consumers and 6% of the total population) registered intakes of energy drink in the range 500 ml to 990 ml as their maximum intake during 24 hours.

In the NCC study, in the age group 13-15 years, 5 participants (3% of the consumers) reported maximum intake in the range from 3000 ml to 6000 ml, and 60 participants (40% of the consumers) reported intakes from 1000 ml to 2500 ml as their maximum intake during a 24 hour period.

Furthermore, in the age group 16-18 years, the highest intake was 10 l reported by one participant NCC study. However, 10 participants (3% of the consumers) reported maximum intakes from 5000 ml to 7500 ml, 13 participants (5% of the consumers) reported maximum intakes from 3000 ml to 4950 ml, and 75 participants (26% of the consumers) reported intakes between 1000 ml and 3000 ml as their maximum intake during a 24 hour period.

4.3 Summary

Four studies were included in this assessment regarding intake of energy drinks: Ungkost 3, the Norwegian Consumer Council study (NCC study), the MoBa follow up study and the UngData study from Oslo Met. The participants' age ranged from 8 to 18 years. The assessment method differed between the studies, but all have collected data on habitual intake of energy drinks, and two studies enabled specific estimations of maximum intake of energy drinks during a period of 24 hours.

The percentage of energy drink consumers in the four studies varied. In the age group 8 to 12 year old children the percentage of energy drink consumers ranged from 1% to 18%. In the age group 13 to 15 years, the percentage of energy consumers ranged from 30% to 53% and in the 16 to 18 year olds, the energy drink consumers constituted 55 to 70 % of the study participants.

Median chronic intake in consumers of energy drinks was in the range of less than 1 ml per day to 81 ml/day; high chronic intakes given as 95-percentile ranged from 114-418 ml/day. The highest acute intake was 10 l reported by one participant 16-18-year-old in the NCC study. Among 13-15-year-olds, data from the NCC study suggests that approximately 43% of the energy drink consumers have had an intake during 24 hours above 1000 ml. Among 16-18 year olds, 34 % of the consumers in the NCC study reported maximum intakes above 1000 ml during a 24 hour period.

5 Caffeine – exposure

In order to estimate the exposure to caffeine from energy drinks, estimates of total dietary exposure to caffeine in children and adolescents consuming energy drinks in Norway were needed, as well as concentrations of caffeine in dietary sources. To estimate total caffeine exposure from the diet, except energy drinks, consumption data from Ungkost 3 and the NCC study (Table 4.1-1) were used. The other studies in Table 4.1-1 did not provide the Panel with data on total diet or data on other relevant sources of caffeine, and were thus not included in these estimates.

The concentration of caffeine (mg/100g) in dietary sources were compiled from EFSA (2015) (Appendix 16). For those participants consuming energy drinks, the estimated exposures to caffeine from dietary sources with and without energy drinks are presented in Table 5-1.

Table 5-1 Estimates of caffeine exposure in energy drink consumers, mg caffeine/day.

	Excluding energy drinks		Including energy drinks[1]	
	mg/day		mg/day	
Study	Median	High intake, P95	Median	High intake, P95
Ungkost 3[2]				
8-9-year-olds (n=7)	1.1	-[a]	17.1	-[a]
12-13-year-olds (n=30)	5.8	57.1[b]	26.0	133[b]
Norwegian Consumer Council study[3]				
10-12-year-olds, (n=49)	8.4	267[b]	11.3	320[b]
13-15-year-olds, (n=149)	14.8	104	31.5	170
16-18-year-olds, (n=291)	23.5	174	41.9	205

[1] Estimated given that all energy drinks contain 32 mg caffeine per 100 ml

[2] In the Ungkost 3 study intakes of caffeine from soda beverages that could contain caffeine were not included, due to missing specifications whether the registered soda beverages were with or without caffeine.

[3] The NCC study did not assess total diet. Only beverages asked for in the Norwegian Consumer Council study were included (cocoa, cola, coffee, espresso, caffe latte, ice-coffee and tea).

[a] 95 percentile is not reported, due to small number of participants (n=7).

[b] 95 percentile is reported, however, the value is not statistically robust due to a small number of participants.

Note that in the Ungkost 3 study intakes of caffeine from soda beverages that could contain caffeine were not included, due to missing specifications whether the registered soda beverages were with or without caffeine. The NCC study did not assess total diet, therefore, only beverages (cocoa, Cola, black coffee, espresso, caffe latte, iced coffee, and black tea) reported in the Norwegian Consumer Council study were included in the estimations of caffeine exposure.

To calculate caffeine exposure per kg body weight per person, individual body weights were used for the Ungkost 3 study. If no body weights were available, a mean body weight of 32.9 kg for 4th graders, and 50.3 kg for 8th graders were imputed. The NCC study had no information on body weight, and therefore mean body weights were used obtained from the Ungkost 3 study and EFSA (2012): 32.9 kg for 10-12-year-olds (Ungkost 3, for 4th graders), 50.3 kg for 13-15-year-olds (Ungkost 3, for 8th graders), and 61.3 kg for 16-18-year-olds (EFSA, 2012). Estimated caffeine exposures in consumers of energy drinks, including and excluding caffeine from energy drinks, in mg/kg bw/day are presented in Table 5-2.

Table 5-2 Estimates of caffeine exposure in energy drink consumers, mg caffeine/kg bw per day.

	Excluding energy drinks		Including energy drinks[1]	
	mg/kg bw/day		mg/kg bw/day	
Study	Median	High intake, P95	Median	High intake, P95
Ungkost 3[2,3]				
8-9-year-olds (n=7)	0.04	-[a]	0.7	-[a]
12-13-year-olds (n=30)	0.1	0.9[b]	0.8	3.0[b]
Norwegian Consumer Council study [4,5]				
10-12-year-olds, (n=49)	0.3	8.1[b]	0.34	9.7[b]
13-15year-olds, (n=149)	0.3	2.1	0.63	3.4
16-18-year-olds, (n=291)	0.4	2.8	0.68	3.4

[1] Estimated given that all energy drinks contain 32 mg caffeine per 100 ml

[2] In the Ungkost 3 study intakes of caffeine from soda beverages that could contain caffeine were not included, due to missing specifications whether the registered soda beverages were with or without caffeine.

[3]For the Ungkost 3 study individual body weights were used.

[4] The NCC study did not assess total diet. Only beverages asked for in the Norwegian Consumer Council study were included (cocoa, cola, coffee, espresso, caffe latte, ice-coffee and tea).

[5] For the NCC study the following body weight were used: 32.9 kg for 10-12-year-olds (Ungkost 3, for 4th graders), 50.3 kg for 13-15-year-olds (Ungkost 3, for 8th graders), and 61.3 kg for 16-18-year-olds (EFSA, 2012).

[a] 95 percentile not reported, due to small number of participants (n=7).

[b] 95 percentile is reported, however, the value is not statistically robust due to a small number of participants.

The caffeine exposure estimates from the Ungkost 3 study included almost all dietary sources of caffeine, such as intakes from coffee, tea, cocoa, other milk-based drinks with chocolate, chocolate, and chocolate-containing cakes and biscuits. Intakes of soda beverages containing caffeine were not included, due to missing specifications whether the registered soda beverages were with or without caffeine. Therefore, total caffeine exposure estimates were underestimated in this population.

To investigate the potential exposure to caffeine from sodas, we used the data on intake of soda beverages in Ungkost 3. For 8-9-year-olds the median consumption was 50 ml/day

(average consumption was 96 ml/day, skewed distribution). If all these sodas had been caffeine-containing sodas containing 10.8 mg caffeine per 100 ml (EFSA, 2015), the extra caffeine exposure would have been estimated to 5.4 mg/day (median), and 10.4 mg/day (average value). Using an average bodyweight of 32.9 kg this would translate into an additional 0.16 and 0.32 mg caffeine/kg bw/day for median and average values, respectively for children 8-9 years of age. For 12-13-year-olds the median intake of sodas was 100 ml/day (average consumption was 161 ml/day, skewed distribution). If all these sodas had been caffeine-containing sodas containing 10.8 mg caffeine per 100 ml (EFSA, 2015), the extra caffeine exposure would have been 10.8 to 17.4 mg (median and average values) caffeine per day. Using an average bodyweight of 50.3 kg this would translate into an additional 0.21 and 0.35 mg caffeine/kg bw/day, median and average, respectively.

The caffeine exposure estimates from the NCC study included the following caffeine sources in addition to energy drinks: cocoa, Cola, black coffee, caffe latte, espresso, ice-coffee and black tea. Furthermore, only frequency of intake of these beverages was registered by the participants. Standard portion sizes/amounts were therefore applied to estimate intake in ml/day. Regarding other foods that may contain caffeine, the survey only asked about the frequency of intake of chocolate. Since portion sizes of chocolate can vary greatly, data on the intake of chocolate were not included in the total caffeine exposure estimates presented in Table 5-1. Thus, total exposure of caffeine in the NCC study was underestimated due to missing information about intake of foods containing caffeine such as chocolate, milk-based caffeine containing beverages other than cocoa, and cakes, biscuits and other products containing chocolate, tea or coffee.

None of the studies included assessment of other possible caffeine containing products such as supplements with caffeine, caffeine containing tablets or energy-shots. Thus, the estimates of caffeine intake may be underestimated with regard to these products.

From the Ungkost 3 study and the NCC study, caffeine intake could also be estimated for children and adolescents not consuming energy drinks. The intake of caffeine in children and adolescents with no intake of energy drinks is presented in Table 5-3.

Table 5-3 Estimates of dietary caffeine exposure in non-consumers of energy drinks, in mg caffeine/day and mg caffeine/kg bw per day.

	mg/day		mg/kg bw per day	
Study	Median	P95	Median	P95
Ungkost 3[1,2]				
8-9-year-olds (n=629)	2.9	15.8	0.1	0.5
12-13-year-olds (n=657)	4.3	25.1	0.1	0.5
Norwegian Consumer Council study[3,4]				
10-12-year-olds, (n=216)	7	25	0.2	0.8
13-15-year-olds, (n=131)	7	51	0.1	1.0
16-18-year-olds, (n=126)	10	156	0.2	2.5

[1] In the Ungkost 3 study exposure of caffeine from soda beverages that could contain caffeine were not included, due to missing specifications whether the registered soda beverages were with or without caffeine.
[2] For the Ungkost 3 study individual body weights were used.
[3] The NCC study did not assess total diet. Only beverages asked for in NCC study were included (cocoa, Cola, black coffee, caffe latte, espresso, ice-coffee and black tea).
[4] For the NCC study the following body weight were used: 32.9 kg for 10-12-year-olds (Ungkost 3, for 4th graders), 50.3 kg for 13-15-year-olds (Ungkost 3, for 8th graders), and 61.3 kg for 16-18-year-olds (EFSA, 2012).

In this risk assessment the NFSA requested VKM to estimate caffeine exposure, if all consumed energy drinks contained 15, 32, 40 or 55 mg caffeine/100 ml. In Table 5-4 the caffeine exposure from energy drinks are presented, given the different caffeine concentrations as requested by the NFSA.

Table 5-4 Caffeine exposure from energy drinks alone, given different levels of caffeine in the energy drinks, mg caffeine/day.

Level of caffeine	Ungkost 3		Norwegian Consumer Council study		
	8-9 years (n=7)	12-13 years (n=30)	10-12 years (n=49)	13-15 years (n=149)	16-18 years (n=291)
15 mg/100 ml					
Median chronic intake	7.5	12.2	0.1	3.8	3.8
High chronic intake[1]	–[a]	62.6[b]	17.2[b]	48.0	48.0
Higest acute intake[2]	60	300	225	900	1500
32 mg/100 ml					
Median chronic intake	16.0	26.0	0.2	8.0	8.0
High chronic intake[1]	–[a]	134[b]	36.7[b]	102.4	102.4
Highest acute intake[2]	128	640	480	1920	3200
40 mg/100 ml					
Median chronic intake	20.0	32.5	0.2	10.0	10.0
High chronic intake[1]	–[a]	167[b]	45.9[b]	128.0	128.0
Highest acute intake[2]	160	800	600	2400	4000
55 mg/100 ml					
Median chronic intake	27.5	44.7	0.3	13.8	13.8
High chronic intake[1]	–[a]	230[b]	63.1[b]	176	176
Highest acute intake[2]	220	1100	825	3300	5500

[1] Based on 95-percentile from energy drink consumption.
[2] Based on reported maximum energy drink consumption in 24 hours.
[a] 95 percentile is not reported due to small number of participants (n=7).
[b] 95 percentile is reported, however, the value is not statistically robust due to a small number of energy drink consumers in this age group.

In Table 5-5 the exposure to caffeine from energy drinks only, are presented in mg/kg bodyweight per day, given different scenarios for caffeine concentrations: 15; 32; 40; 55 mg/100 ml.

Table 5-5 Caffeine exposure (mg/kg bw per day) from energy drinks alone by age groups and dietary survey/study, given different levels of caffeine in the energy drinks (mg/100 ml).

Level of caffeine	Ungkost 3[1]		Norwegian Consumer Council study[2]		
	8-9 years (n=7)	12-13 years (n=30)	10-12 years (n=49)	13-15 years (n=149)	16-18 years (n=291)
15 mg/100 ml					
Median chronic intake	0.3	0.2	0.0	0.1	0.1
High chronic intake[3]	–	1.3[a]	0.5[a]	1.0	0.8
Highest acute intake[4]	2.1	5.7	6.8	17.9	24.5
32 mg/100 ml					
Median chronic intake	0.6	0.5	0.0	0.2	0.1
High chronic intake[3]	–	2.7[a]	1.1[a]	2.0	1.7
Highest acute intake[4]	4.4	12.1	14.6	38.2	52.2
40 mg/100 ml					
Median chronic intake	0.8	0.7	0.4	0.7	0.8
High chronic intake[3]	–	3.4[a]	1.4[a]	3.9	3.8
Highest acute intake[4]	5.5	15.1	18.2	47.7	65.3
55 mg/100 ml					
Median chronic intake	1.1	0.9	0.4	0.7	0.8
High chronic intake[3]	–	4.7[a]	1.9[a]	4.8	4.6
Highest acute intake[4]	7.6	20.8	25.1	65.6	89.7

[1] For the Ungkost 3 study individual body weights were used.

[2] For the NCC study the following body weight were used: 32.9 kg for 10-12-year-olds (Ungkost 3, for 4th graders), 50.3 kg for 13-15-year-olds (Ungkost 3, for 8th graders), and 61.3 kg for 16-18-year-olds (EFSA, 2012).

[3]Based on 95-percentile energy drink consumption.

[4] Reported maximum exposure to caffeine from energy drinks in 24 hours.

[a] 95 percentile not reported, due to small number of participants (n=7).

[b] 95 percentile is reported, however, the value is not statistically robust due to a small number of

energy drink consumers in this age group.

Total caffeine exposure from food and beverages is the sum of caffeine from energy drinks and other dietary sources. Estimates of caffeine exposure from dietary sources are presented in Tables 5-1 and 5-3, for consumers and non-consumers of energy drinks, respectively. Table 5-6 presents the contributions, in absolute values and percentages, of caffeine from different dietary sources for the 12-13-year-olds in the Ungkost 3 study.

Table 5-6 Mean contribution of caffeine from diet, in absolute values (mg/day) and percentage, for all 12-13-year-olds in the Ungkost 3 study.

Dietary sources	Non-consumers of energy drinks (n=657) Contribution to caffeine exposure from diet[1] (mean exposure: 7.3 mg caffeine/day)		Consumers of energy drinks (n=30) Contribution to caffeine exposure from diet[1,2] (mean exposure: 48.4 mg caffeine/day)	
	mg caffeine/day	%	mg caffeine/day	%
Energy drinks	0	0	36.8	76
Milk products with cocoa	1.8	25	3.5	7
Coffee	0.7	10	0	0
Tea	2.0	27	3.8	8
Cake	0.8	11	1.4	3
Chocolate/sweets	1.8	25	2.9	6

[1] In the Ungkost 3 study, exposure of caffeine from soda beverages that could contain caffeine was not included, due to missing specifications whether the registered soda beverages were with or without caffeine.
[2] Estimated given that all energy drinks contain 32 mg caffeine per 100 ml

The contribution of caffeine from energy drinks in Ungkost 3 and NCC, is based on a caffeine concentration in energy drinks of 32 mg/100 ml. Note also, that for the risk characterisation, the median exposure values for each study and age group were used, while for contribution from food groups to caffeine intake, the mean values were used.

In the Ungkost 3 study, consumers of energy drinks in the age group 12-13-year-olds received their main caffeine exposure from energy drinks. The absolute exposure to caffeine from other dietary sources was higher for the consumers compared to the non-consumers of energy drink. The same pattern was seen in the NCC study (Table 5-7 to 5-9).

The caffeine contributions listed in Table 5-6 exclude caffeine contributions from soda beverages, due to missing specifications on caffeine content. The potential exposure to caffeine from sodas was estimated to average intakes of 10.4 and 17.8 mg caffeine per day in 8-9-year-olds and 12-13-year-olds, respectively, when assuming that all intakes of sodas were sodas containing 10.8 mg caffeine/100 ml. When considering the whole 12-13-year-

olds population in Ungkost 3 (n=687), the average intake of energy drinks was 5 ml per day, resulting in an average caffeine exposure of 1.6 mg per day. The potential exposure of 10.8 mg (median) to 17.8 mg (average) caffeine per day from sodas containing caffeine, are 6.8 to 11.1 times higher than the average exposure from energy drinks.

When calculating the contribution of caffeine from different dietary sources for all study participants including consumers and non-consumers of energy drinks, energy drinks contributed with less than 5% of the total caffeine exposure in the Ungkost 3 study.

Table 5-7 Mean contribution of caffeine from beverages, in absolute values (mg/day) and percentage, for all 10-12-year-olds in the Norwegian Consumer Council study.

Dietary sources	Non-consumers of energy drinks (n=216) Contribution to caffeine exposure from beverages (mean exposure: 8.5 mg caffeine/day)		Consumers of energy drinks[1] (n=49) Contribution to caffeine exposure from beverages (mean exposure: 44.7 mg caffeine/day)	
	mg caffeine/day	%	mg caffeine/day	%
Energy drinks	0	0	6.7	15
Cocoa	1.0	11	1.8	4
Cola drinks	5.1	61	9.4	21
Coffee	0.3	3	11.1	25
Espresso	0	0	4.8	11
Caffe latte	0.1	2	5.2	12
Ice-coffee	0.4	4	3.7	8
Tea	1.6	19	1.8	4

[1] Estimated given that all energy drinks contain 32 mg caffeine per 100 ml

To estimate both absolute exposure and percentage contribution from the different caffeine containing beverages included in the NCC study, mean values were used. Tables 5-7 to 5-9 show that consumers of energy drinks had a higher exposure from all other caffeine containing drinks, in all three age groups, compared to non-consumers. The percentage contribution of energy drinks to caffeine ranged from 15% to 48%, meaning that the combined exposure from other beverages were higher.

For the two youngest age groups of non-consumers of energy drink (Table 5-7 and 5-8), cola drinks gave the highest contribution to caffeine exposure, while coffee contributed most to caffeine exposure in the age group 16-18 years (Table 5-9). For consumers of energy drinks, coffee and cola contributed most to the caffeine exposure in the age group 10-12 years, while for the two oldest age groups energy drinks contributed most, followed by cola and coffee.

When calculating the contribution of caffeine from beverages asked for in the NCC study for all study participants including consumers and non-consumers of energy drinks, energy drinks contributed with 31% of the total caffeine exposure in the NCC study.

Table 5-8. Mean contribution of caffeine from beverages, in absolute values (mg/day) and percentage, for all 13-15-year-olds in the Norwegian Consumer Council study.

Dietary sources	Non-consumers of energy drinks (n=133) Contribution to caffeine exposure from beverages (mean exposure: 13.5 mg caffeine/day)		Consumers of energy drinks[1] (n=149) Contribution to caffeine exposure from beverages (mean exposure: 53.7 mg caffeine/day)	
	mg caffeine/day	%	mg caffeine/day	%
Energy drinks	0	0	25.8	48
Cocoa	0.9	7	1.1	2
Cola drinks	5.8	43	13.0	24
Coffee	1.7	13	3.5	7
Espresso	0.1	1	1.0	2
Caffe latte	0.6	5	3.1	6
Ice-coffee	1.6	12	3.4	6
Tea	2.8	21	2.8	5

[1] Estimated given that all energy drinks contain 32 mg caffeine per 100 ml

Table 5-9. Mean contribution of caffeine from beverages, in absolute values (mg/day) and percentage, for all 16-18-year-olds in the Norwegian Consumer Council study.

Dietary sources	Non-consumers of energy drinks (n=129) Contribution to caffeine exposure from beverages (mean exposure: 26.0 mg caffeine/day)		Consumers of energy drinks[1] (n=288) Contribution to caffeine exposure from beverages (mean exposure: 65.8 mg caffeine/day)	
	mg caffeine/day	%	mg caffeine/day	%
Energy drinks	0	0	24.2	37
Cocoa	0.7	3	0.9	1
Cola drinks	6.9	27	9.4	14
Coffee	10.5	40	15.6	24
Espresso	1.0	4	1.6	2
Caffe latte	1.4	5	3.8	6
Ice-coffee	2.0	8	5.4	8
Tea	3.5	14	4.7	7

[1] Estimated given that all energy drinks contain 32 mg caffeine per 100 ml

5.1 Summary

Two studies were included in this assessment of exposure to caffeine: Ungkost 3, and NCC study. The study design differed between the studies. Ungkost 3 was a dietary assessment study using a web-based food diary covering all food and drinks in 4 days, while the NCC study used a questionnaire with questions mainly about energy drinks. Dietary data in the

Ungkost 3 study enabled estimation of caffeine exposure from the whole diet, with the exception of sodas with caffeine, while in the NCC study the caffeine exposure could only be estimated from drinks with caffeine (coffee, tea, cocoa, and soda with caffeine).

Caffeine exposure from energy drinks alone, given a caffeine concentration of 32 mg/100 ml energy drink, varied from close to zero to 2.7 mg caffeine/kg bw/day for the median and high chronic exposure across all age groups. The highest acute exposure varied from 4.4 to 52.2 mg caffeine/kg bw day.

Consumers of energy drinks also had a higher exposure from other caffeine containing food and beverages. The percentage contribution of caffeine exposure from energy drinks was 76% in 12-13-year-old consumers of energy drink in the Ungkost 3 study, and ranged from 15% to 48% in the NCC study. When calculating the contribution of caffeine from different dietary sources for all study participants including consumers and non-consumers of energy drinks, energy drinks contributed with less than 5% of the total caffeine exposure in the Ungkost 3 study (not including cola drinks), and energy drinks contributed 31% of the caffeine exposure in the NCC study (only including beverages)The main caffeine sources in the Ungkost 3 study were beverages with cocoa, and chocolate, while in the NCC study cola and coffee in addition to energy drinks were the main caffeine source.

6 Risk characterisation

6.1 Risk characterisation – energy drinks

Due to lack of dose-response data, including doses relevant for high acute intake, and lack of toxicity data on chronic consumption of energy drinks, the Panel concludes that more data are needed to establish a reference point for energy drinks as such.

Since none of the observed adverse effects in the included RCTs demonstrated that energy drinks containing a given concentration of caffeine induced any adverse effects other than those observed from similar concentrations of caffeine, in line with EFSA (2015), the risk characterisation will be based on the caffeine doses of no concern established by EFSA et al., (2015) (Chapter 6.2).

6.2 Risk characterisation - caffeine

Reference points for caffeine toxicity

As reference points for caffeine toxicity, the Panel decided to use the caffeine doses of no concern established by EFSA et al., (2015); 3 mg/kg bw per day for toxicity such as cardiovascular and haematological, neurological and psycobehavioural effects (denoted "general adverse health effects" in the following), and 1.4 mg/kg bw per day for increased sleep latency and reduced sleep duration (denoted "sleep disturbances" in the following).

Caffeine exposure:

NFSA requested VKM to calculate caffeine exposure scenarios for combinations of consumption patterns and caffeine concentrations in energy drinks. The consumption patterns, as specified by NFSA, were median chronic intake, high chronic intake and high acute intake (Table 4.2-1). (Note that the Panel decided to report "highest acute intake rather than "high acute intake").The scenarios were based on energy drink consumption from surveys in Norway (Chapter 4) and the scenarios were based on the assumption that all energy drinks contain 15 mg caffeine/100 ml, 32 mg caffeine/100 ml, 40 mg caffeine/100 ml or 55 mg caffeine/100 ml (Tables 5-4 and 5-5). An overview of the surveys used is given in Table 4.1-2.

NFSA also requested VKM to estimate caffeine exposure from other food and beverages (coffee drinks and tea drinks, chocolate milk, cocoa, etc.) (Tables 5-1, 5-2, 5-3, 5-6, 5-7, 5-8 and 5-9).

6.2.1 Risk characterisation of caffeine exposure from energy drinks

The amount of energy drinks containing a specific caffeine concentration, that can be consumed per day by the different age groups without exceeding the reference points, assuming no other caffeine intake, is presented in Table 6.2.1-1.

Table 6.2.1-1. The amount of energy drinks (ml/day) that can be consumed, assuming no other caffeine intake, without exceeding the different reference points (in ml/day) by age groups and given caffeine concentrations (mg/100 ml energy drink). Estimated body weights (kg) for the age groups (years) 8-12, 13-15, and 16-18 were 32.9, 50.3, and 61.3, respectively. The reference points are 1.4 mg caffeine/kg bw per day for sleep disturbance and 3 mg caffeine/kg bw per day for general adverse health effects.

	Amount (ml) of energy drink equal to or not exceeding 1.4 mg caffeine/kg bw per day			Amount of energy drink (ml) equal to or not exceeding 3 mg caffeine/kg bw per day		
Age, years	8-12	13-15	16-18	8-12	13-15	16-18
Caffeine content						
15	307	469	572	658	1006	1226
32	144	220	268	308	472	575
40	115	176	215	247	377	460
55	84	128	156	179	274	334

6.2.1.1 Median chronic intake of energy drinks

For children aged 8-12 years, the estimated median chronic intake of energy drinks ranged from 0.5 to 50 ml per day. For adolescents aged 13-15 years and 16-18 years, the estimated median chronic intake ranged from 14 to 81 ml per day and from 17 to 35 ml per day, respectively (Table 4.2-1).

The median chronic intake for all age groups was below the reference points for all included concentrations of caffeine in energy drinks.

6.2.1.2 High chronic intake of energy drinks

- For the age group 8-12 years
    - The Panel cannot characterise the risk due to the small number of participants in the surveys consuming energy drinks (based on Ungkost 3).
    - The intake is below the reference points given a caffeine content of 15 or 32 mg/100 ml in all energy drinks (based on NCC).
    - The intake is above the reference point for sleep disturbance given a caffeine content of 40 or 55 mg/100 ml in all energy drink (based on NCC).
- For the age group 13-15 years
    - The intake is below the reference points given a caffeine content of 15, 32, 40 or 55 mg/100 ml in all energy drinks (based on MoBa).
    - The intake is below the reference points given a caffeine content of 15 mg/100 ml in all energy drinks (based on Ungkost 3, Ungdata and NCC).
    - The intake is above the reference point for sleep disturbance given a caffeine content of 32, 40 or 55 mg/100 ml in all energy drinks (based on Ungkost 3, NCC and Ungdata).

- The intake is above the reference point for sleep disturbance and general adverse health effects given a caffeine content of 40 mg/100 ml in all energy drinks (based on Ungkost 3) and given a caffeine content of 55 mg/100 ml in all energy drinks (based on Ungkost 3, NCC and Ungdata).

- For the age group 16-18 years
  - The intake is below the reference points given a caffeine content of 15 mg/100 ml in all energy drinks (based on NCC study and Ungdata study).
  - The intake is above the reference point for sleep disturbance for energy drinks given a caffeine content of 32, 40 or 55 mg/100 ml in all energy drinks (based on NCC and Ungdata).

For children aged 9-12 years, the high chronic intake of energy drinks reported in the NCC survey was 115 ml per day. For adolescents aged 13-15 years and 16-18 years, the estimated high chronic intake ranged from 114 to 418 ml per day and from 320 to 330 ml per day, respectively. Note that not all values are statistically robust due to a small number of energy drinks consumers in some age groups. An overview of the risk characterisation for the high chronic intake of energy drinks is given in Table 6.2.1.2-1, showing if the intake is below or above the reference points for sleep disturbance and general adverse health effects.

Table 6.2.1.2-1. Risk characterisation for high chronic intake (95 percentile) of energy drinks based on dietary surveys/studies. Exceedance of reference points is indicated per age group and for given caffeine concentrations in the energy drinks (mg/100 ml energy drink).

Age group (years)	Survey/study	15 mg	32 mg	40 mg	55 mg
8–12	Ungkost 3 (n=7)	CC	CC	CC	CC
	Norwegian Consumer Council study (n=49)	–	–	X[a]	X[a]
13–15	Ungkost 3 (n=30)	–	X[a]	XX[a]	XX[a]
	Norwegian Consumer Council study (n=149)	–	X	X	XX
	Ungdata study (n=14720)	–	X	X	XX
	MoBa (n=4700)	–	–	–	–
16–18	Norwegian Consumer Council study (n=291)	–	X	X	X
	Ungdata study (n=8562)	–	X	X	X

XX: Intake equal to or above the reference point for general adverse health effects (EFSA, 2015)
X: Intake equal to or above the reference point for sleep disturbance (EFSA, 2015)
–: Intake below the reference points
CC: Cannot conclude due to the small number of participants in the surveys consuming energy drinks
[a]: The 95 percentile is reported, however, the values are not statistically robust due to a small number of energy drink consumers in this age group.

6.2.1.3 Highest acute intake of energy drinks

- For the age group 8-12 years
    - The intake is above the reference point for sleep disturbance given a caffeine content of 15, 32, 40 or 55 mg/100 ml in all energy drinks (based on Ungkost 3).
    - The intake is above the reference point for sleep disturbance and general adverse health effects given a caffeine content of 32, 40 or 55 mg/100 ml in all energy drinks (based on the Ungkost 3 survey).
    - The intake is above the reference point for sleep disturbance and general adverse health effects given a caffeine content of 15, 32, 40 or 55 mg/100 ml in all energy drinks (based on the NCC survey).
- For the age groups 13-15 years
    - The intake is above the reference point for sleep disturbance and general adverse health effects given a caffeine content of 15, 32, 40 or 55 mg/100 ml in all energy drinks (based on MoBa, Ungkost 3, NCC and Ungdata).
- For the age group 16-18 years
    - The intake from all surveys were above the reference point for sleep disturbance and general adverse health effects given a caffeine content of 15, 32, 40 or 55 mg/100 ml in all energy drinks.

For children aged 8-12 years, the estimated highest acute intake of energy drinks ranged from 400 to 1500 ml. For adolescents aged 13-15 years and 16-18 years, the estimated highest acute intake ranged from 800 to 6000 ml and from 2000 to 10000 ml, respectively.

An overview of the risk characterisation for the highest acute intake of energy drinks is given in Table 6.2.1.3-1, showing if the intake is below or above the reference points for sleep disturbance or for general adverse health effects.

Table 6.2.1.3-1. Risk characterisation for the single highest acute intake reported (ml/24 hours) of energy drinks based on dietary surveys/studies. Exceedance of reference points is indicated per age group and for given caffeine concentrations in the energy drinks (mg/100 ml energy drink). For the total number of participants in each study, see Table 4.1-2.

Age group	Survey/study	15 mg	32 mg	40 mg	55 mg
8-12	Ungkost 3	X	XX	XX	XX
	Norwegian Consumer Council study	XX	XX	XX	XX
13-15	Ungkost 3	XX	XX	XX	XX
	Norwegian Consumer Council study	XX	XX	XX	XX
	Ungdata study	XX	XX	XX	XX
	MoBa	XX	XX	XX	XX
16-18	Norwegian Consumer Council study	XX	XX	XX	XX
	Ungdata study	XX	XX	XX	XX

XX: Intake equal to or above the reference point for general adverse health effects (EFSA, 2015)
X: Intake equal to or above the reference point for sleep disturbance (EFSA, 2015)

6.2.2 Risk characterisation of caffeine exposure from food and beverages

The caffeine exposure from foods and beverages was estimated for energy drink consumers (Table 5-2) and non-consumers (Table 5-3) using the Ungkost 3 study and the NCC study. From the Ungkost 3 study, intake of caffeine from foods and beverages, not including energy drinks and sodas, was estimated. From the NCC study, intake of caffeine from beverages, not including foods and energy drinks, was estimated.

For the age group 8-12 years

- With regard to intake from food and beverages, not including energy drinks and sodas (using Ungkost 3)
    - Median intake is below the reference points for caffeine toxicity for both consumers and non-consumers
    - High intake is below the reference points for caffeine toxicity for non-consumers. For consumers, this cannot be estimated due to the small number of participants in the surveys consuming energy drinks
- With regard to intake from beverages, not including energy drinks and food (using NCC)
    - Median intake is below the reference points for caffeine toxicity for both consumers and non-consumers
    - High intake is below the reference points for caffeine toxicity for non-consumers whereas it is above the reference point for general adverse health effects for consumers. Note that for consumers, the value for high intake is not statistically robust due to a small number of energy drink consumers in this age group

For the age group 13-15 years

- With regard to intake from food and beverages, not including energy drinks and sodas (using Ungkost 3)
    - Median and high intake is below the reference points for caffeine toxicity for both consumers and non-consumers
- With regard to intake from beverages, not including energy drinks and food (using NCC)
    - Median intake is below the reference points for caffeine toxicity for both consumers and non-consumers
    - High intake is below the reference points for caffeine toxicity for non-consumers whereas it is above the reference point for sleep disturbance for consumers

For the age group 16-18 years

- With regard to intake from food and beverages, this could not be estimated since this age group was not included in Ungkost 3

- With regard to intake from beverages, not including energy drinks and food (using NCC)
    - Median intake is below the reference points for caffeine toxicity for both consumers and non-consumers
    - High intake is above the reference point for sleep disturbance for non-consumers and consumers

An overview of the risk characterisation of caffeine from other food and beverages is given in Tables 6.2.4-1 (food and beverages not including energy drinks and sodas) and 6.2.4-2 (beverages, not including energy drinks and food).

Table 6.2.4-1. Risk characterisation (exceedance of reference points) for caffeine from food and beverages, from the Ungkost 3 study[1].

	Non-consumers		Consumers	
Age group	Median intake of foods and beverages	High intake of other foods and beverages	Median intake of other foods and beverages	High intake of other foods and beverages
8-9	–	–	–	CC
12-13	–	–	–	–[a]

CC: Cannot conclude due to the small number of participants in the surveys consuming energy drinks
–: Intake below the reference points
[1] In the Ungkost 3 study, intakes of caffeine from soda beverages that could contain caffeine were not included, due to missing specifications whether the registered soda beverages were with or without caffeine.
[a]: 95 percentile is reported, however, the value is not statistically robust due to a small number of energy drink consumers in this age group.

Table 6.2.4-2. Risk characterisation (exceedance of reference points) for caffeine from beverages, from the NCC study[1].

	Non-consumers		Consumers	
Age group	Median intake of beverages	High intake of beverages	Median intake of beverages	High intake of beverages
10-12	–	–	–	XX[a]
13-15	–	–	–	X
16-18	–	X	–	X

XX: Intake equal to or above the reference point for general adverse health effects (EFSA, 2015)
X: Intake equal to or above the reference point for sleep disturbance (EFSA, 2015)
–: Intake below the reference points
[1] The NCC study did not assess total diet. Only beverages asked for in the NCC study were included (cocoa, cola, coffee, espresso, caffe latte, ice–coffee and tea).
[a]: 95 percentile is reported, however, the value is not statistically robust due to a small number of energy drink consumers in this age group.

6.2.3 Risk characterisation of energy drinks combined with physical activity

Energy drink intake in combination with exercise did not increase heart rate. No other conclusion can be drawn with respect to adverse effects of energy drink consumption in conjunction with physical activity and any related dehydration.

6.2.4 Risk characterisation of energy drinks combined with alcohol

No conclusions can be drawn with respect to adverse effects of energy drink consumption combined with alcohol due to limited data.

6.3 Conclusion - risk characterisation of caffeine exposure from energy drinks and from other food and beverages

For the risk characterisation, the reference points for sleep disturbance and for general adverse health effects, such as cardiovascular and haematological, neurological and psychobehavioural effects, were used (EFSA, 2015).

6.3.1 Caffeine exposure with low or no risk

The median chronic intake of energy drinks is unlikely to cause any risk in any of the age groups studied.

The high chronic intake of energy drinks is unlikely to cause any risk in any of the age groups studied if all consumed energy drinks contain 15 mg caffeine/100 ml, and in the age groups 8-12 years if all consumed energy drinks contain 32 mg caffeine/100 ml.

For caffeine exposure from foods and beverages, not including energy drinks and soda, median and high intake for consumers and non-consumers of energy drinks in all age groups studied, is unlikely to cause any risk. Note that high exposure for consumers aged 8-9 cannot be estimated, and that for consumers aged 12-13, the value for high intake is not statistically robust due to a small number of energy drink consumers.

For caffeine exposure from beverages, not including energy drinks and food, median intake for consumers and non-consumers in all age groups and high intake for non-consumers of energy drinks aged 10-12 and 13-15, is unlikely to cause any risk.

6.3.2 Caffeine exposure that may represent a risk for sleep disturbance

A caffeine exposure that may represent a risk for general adverse health effects (Chapter 6.3.3) may also represent a risk for sleep disturbance.

In the age group 9-12 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 40 or 55 mg caffeine/100 ml. Note

that the value are not statistically robust due to a small number of energy drink consumers in this age group.

In the age group 13–15 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 32 mg caffeine/100 ml.

In the age group 16–18 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 32, 40 or 55 mg caffeine/100 ml.

For caffeine exposure from beverages, not including energy drinks or food, high intake for consumers aged 13–15 years and high intake for both consumers and non–consumers of energy drinks aged 16–18 years, may represent a risk for sleep disturbance.

6.3.3 Caffeine exposure that may represent a risk for general adverse health effects

In the age group 13–15, high chronic intake of energy drinks may represent a risk for general adverse health effects if all consumed energy drinks contain 40 or 55 mg caffeine/100 ml. Note that for energy drinks containing 40 mg caffeine/100 ml, the value is not statistically robust due to a small number of energy drink consumers in this age group.

The highest acute intake estimates of energy drinks, using caffeine concentrations of 15, 32, 40 or 55 mg caffeine/100 ml, may all represent a risk for general adverse health effects in all age groups.

For caffeine exposure from beverages, not including energy drinks or food, high intake in consumers aged 10–12 years may represent a risk for general adverse health effects. Note that for this group, the value for high intake is not statistically robust due to a small number of energy drink consumers.

6.3.4 An overview of the conclusions on energy drinks

An overview of the conclusions from the risk characterisation of caffeine exposure from energy drinks (Tables 6.2.1.2–1 and 6.2.1.3–1) is shown in Tables 6.3.4–1. When studies indicated exceedance of the two reference points for the same age group and caffeine concentration, the reference point representing the highest dose (i.e. 3 mg caffeine/kg bw per day) was presented in Table 6.3.4–1.

Table 6.3.4–1. Risk characterisation of caffeine exposure from different scenarios of energy drink intake by age groups and given caffeine concentrations (mg/100 ml energy drink). Exceedance of intake equal to or above the reference points is indicated for the relevant, *combined* dietary surveys/studies.

Age group, years	Surveys/studies	Intake scenario	15 mg	32 mg	40 mg	55 mg

Age group, years	Surveys/studies	Intake scenario	15 mg	32 mg	40 mg	55 mg
8-12	Ungkost 3 Norwegian Consumer Council study	Median chronic intake	–	–	–	–
	Norwegian Consumer Council study	High chronic intake	–	–	X[a]	X[a]
	Ungkost 3 Norwegian Consumer Council study	Highest acute intake	XX	XX	XX	XX
13-15	Ungdata study MoBa Ungkost 3 Norwegian Consumer Council study	Median chronic intake	–	–	–	–
	Ungdata study MoBa Ungkost 3 Norwegian Consumer Council study	High chronic intake	–	X	XX[a]	XX
	Ungdata study MoBa Ungkost 3 Norwegian Consumer Council study	Highest acute intake	XX	XX	XX	XX
16-18	Norwegian Consumer Council study Ungdata study	Median chronic intake	–	–	–	–
	Norwegian Consumer Council study Ungdata	High chronic intake	–	X	X	X
	Norwegian Consumer Council study Ungdata study	Highest acute intake	XX	XX	XX	XX

XX: Intake equal to or above the reference point for general adverse health effects (EFSA, 2015)
X: Intake equal to or above the reference point for sleep disturbance (EFSA, 2015)
–: Intake below the reference points
[a]: 95 percentile is reported, however, the value is not statistically robust due to a small number of energy drink consumers in this age group

7 Uncertainties

7.1 Uncertainty in hazard identification and characterisation

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

One of the 28 included RCTs investigated adverse health effects in children and adolescents. The risk assessments of EFSA (2015) and ANSES (2013) included few studies on these age groups. Therefore, although the assessment is for children and adolescents, it is based predominantly on data from studies on adults. Other endpoints than those described in the included RCTs might have been detected and/or addressed if more studies on children and adolescents had been found.

Several of the included RCTs did not report or reported insufficiently about various factors such as exposure conditions, proper controls, information of origin of the caffeine product used in the intervention, and the full ingredient list with concentrations in energy drinks.

Dose-response data lacked or were insufficient in the evaluated RCTs, including doses relevant for high acute intake, and few studies investigating each endpoint. There were no studies investigating chronic intake of energy drinks and chronic exposure to caffeine; therefore, conclusions related to chronic intake must be interpreted with caution.

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

In the WoE evaluation, uncertainty is associated with the assessment of the element "Large magnitude of effect (e.g. incidence, degrees of severity)". This element may be influenced by study group size and dose. Effect sizes should have been estimated at a standardised exposure, but this was not performed. However, group sizes were taken into consideration when these were small.

7.2 Uncertainty in the exposure assessment

All dietary assessment studies and lifestyle surveys using self-reported data are prone to measurement errors. The evaluations of uncertainties in the estimates of intake of energy drinks and exposure to caffeine are presented in Table 7.2-2, highlighting the main sources of uncertainty and indicating, if possible, whether the respective source of uncertainty might

have led to an over– or underestimation of the estimates of intake and exposures, and consequently the resulting risk characterisation (EFSA et al., 2018).

There were several recent studies exploring the energy drink consumption among Norwegian children and adolescents included in the present assessment. The studies differed in study population, study design, dietary assessment methods used, size and questions asked.

With regard to study populations, all of the included surveys were initially designed to be nationwide studies covering the age groups in question. This strengthens the data credibility. However, in all studies some invited subjects chose not to participate, and this introduces population bias and uncertainty. The response rates in the included surveys ranged from 28% to 67%. Only one of the studies, the NCC study, was designed with the main aim to investigate energy drink consumption and reasons for drinking energy drinks.

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

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

Table 7.2-1. Qualitative evaluation of impacts of uncertainties on the estimation of energy drink intake and caffeine exposure

Source of uncertainty	Impact of uncertainties
Energy drinks intake	
Portion size Energy drinks comes in different cans from 250 ml to 500 ml. It is assumed that the most common way of drinking energy drinks is directly from the can, but it can also be poured into a glass. The impact of the portion size comes from its combination with frequency when estimating intake in ml/day. UNGKOST 3 – portion sizes for energy drinks were given in dl and number of glasses, within a range from 0.5 to several dl (no limit). Each drinking occasion was reported separately, the amount translated into grams and the portion size would thus vary according to intake. The uncertainty associated with the use of glasses as portion sizes ("1/4 glass", "½ glass" and so on) are judged somewhat larger than the use of cans as portion size, because the participants must translate the	–/+

Source of uncertainty	Impact of uncertainties
amount of a can (the natural unit of energy drinks) into the amount in a glass. The NCC study – The question about usual portion size had alternatives in cans: 0.5l, 0.33 l and 0.25 l. For some participants the can size may have varied between drinking occasions, and lead to uncertainty in estimated intake of energy drinks. MoBa study – portion size was included in the frequency question, with options from 0 to more than 3 glasses per day. The amount of energy drink was measured in glasses, and one glass was defined as 2–2.5 dl. The amount of one glass was set at 200 ml. The uncertainty associated with the use of glasses as portion sizes are judged somewhat larger than the use of cans as portion size because the participants must translate the amount of a can (the natural unit of energy drinks) into the amount in a glass. In addition, the definition of one glass as 2 – 2.5 dl introduces further uncertainties when estimating amount. When estimating maximum intake the response option was added 33% and thus estimated to be 800 ml. Ungdata study – included one question regarding usual portion size, with cans as unit. This is judged as a good estimate of usual portion sizes of energy drinks. – However, the response option "many cans equivalent to more than 1.5 litre", introduced uncertainty in the estimations of maximum amount. The values was thus added 33% and estimated to be 2000 ml.	–/+ –/+ • +
Chronic intake, median and high The concept of habitual consumption of foods and beverages that are seldom or only periodically consumed, and in varying amounts, may be extra challenging for children and adolescents. UNGKOST 3 For the 4th graders (8–9 year old children) the number of energy drink consumers was only 7. This is a low number to conclude on median chronic intake and the value is not statistically robust. Furthermore, the number of participants were too low for estimating the 95th percentile, defined as high chronic intake. In the age group 12–13 years the number of participants was low, resulting in an estimate of the high chronic intake (95 percentile of distribution) that was not statistically robust. The NCC study – the NCC study was designed for assessing energy drink consumption. Many questions about the same food group/ product in the same questionnaire/survey have been shown to lead to over–reporting of intake. –In the NCC study, in age group 10–12 years, the number of consumers were only 49 and thus the percentiles presented for this age group in table 4.2–2 are not statistically robust.	• + – –/+

Source of uncertainty	Impact of uncertainties
High acute intake High acute intakes of energy drinks are difficult to measure. High acute intakes are typically seldom occasions, and only a few subjects have the highest acute intakes. In this assessment high acute intake was defined as maximum intake during 24 hours. UNGKOST 3 – 4 days dietary record may cover too short a time period to get a reliable picture of seldom intake occasions, such as high acute intakes. The high acute intake is most likely underreported. The NCC study – this study included one question about the highest number of cans consumed during 24 hours. The highest number of cans was combined with the can size that the participant reported he/she used most frequently. For the participant with the highest reported acute intake, the most used can size was 500 ml, and with a reported maximum intake of 20 cans this gave a total acute intake of 10 litres (n=1). However, the can size used at that particular acute intake occasion may have been 250, or 330 ml instead of 500 ml. This uncertainty in the can size used at the maximum intake occasion is relevant for all the estimations of maximum intake in this study. MoBa study – in the MoBa study the highest portion size alternative was formulated as a frequency of "more than 3 glasses per day". The amount of one glass was set at 200 ml and the value was added 33% and thus estimated to be 800 ml. It is judged that this estimate is probably too low for some participants' high acute intake. Ungdata study – the highest portion size option was "many cans equivalent to more than 1.5 litre". To get a portion size for this response option, the former value was added 33% and estimated to be 2000 ml. It is judged that this portion size, given as the highest response option in the study may be too low for some participants.	 + –/• + •/+
Caffeine exposure	
Caffeine concentration levels used in this risk assessment are compiled from the EFSA report 2015. No chemical analyses have been made to measure caffeine concentrations in food and beverages in the Norwegian market. Therefore, uncertainties in caffeine concentrations in different food and beverages will influence the estimations of caffeine intake. Ungkost 3 – the Ungkost 3 study did not differentiate between intake of sodas with and without caffeine. Thus, the exposure of caffeine from caffeine–containing sodas is underestimated. The NCC study – the NCC study included questions about beverages with caffeine and	 + +

Source of uncertainty	Impact of uncertainties
chocolate, but did not include questions about other dietary sources of caffeine. This leads to underestimation of total dietary caffeine exposure. None of the studies included questions about intake of supplement containing caffeine, caffeine–containing effervescent tablet or "energy shots". Thus, the total estimates of caffeine exposure may be underestimated due to this. We do not have any information about the frequency of use of these products. The relative percentages of caffeine from different dietary sources are based only on the dietary sources available for this risk assessment. When new data emerge about the contribution of other dietary sources, the relative percentages from the dietary sources presented in Table 5–5 may change.	 + –/+
Self–reported data	
All self–reported data are prone to errors, both random and systematic. Self–reported data rely on the participant's memory, the ability to remember what you ate and/or drank during a certain time period and correctly translate this into frequencies and amounts. This may introduce uncertainties in the data. This study design also relies on the participants' ability to understand the questions as intended by those who design the assessment/survey. Social desirability may influence the participants to underestimate the intakes of foods and beverages perceived as "undesirable/unhealthy" and overestimate the intake of healthy foods and beverages. In the studies upon which this risk assessment is based, the effect of the social desirability may be both negative and positive, depending on the perspective of each individual participant. For example, intake of energy drinks may be a way to impress others, and an overreporting of high consumption of energy drinks cannot be ruled out. In the same way, if consumption of energy drinks is looked upon as unhealthy by the participants, they may underreport the intake.	–/+

8 Methodological considerations of weight of evidence

Note that bias related to funding/conflict of interest could just as well have been included in the RoB question number 7 (e.g. Table 3.1.2.3-1) as described in the introduction text for this particular question by OHAT (NTP, 2015b). However, as no element should downgrade the confidence twice, the Panel decided to include the element in question in the WoE rather than in the RoB evaluation, for clarity.

It is possible to reach a fairly high WoE confidence rating (such as +++) for individual studies that were rated as having a moderate or high concern for RoB (tiers 2 or 3) due to the upgrading criteria. This was the case for the studies by Temple et al. (2014) and Bloomer et al. (2015) which were rated as RoB tier 3, yet were rated as +++ and +++/++, respectively, in the WoE evaluation. This apparent discrepancy may occur as a result of the RoB criteria which can result in a low score if e.g. randomisation or blinding is not described (i.e. the authors could have forgotten to report it) or the results are not reported in an appropriate or adequate manner. Still, the exposure can be well described, the effects can be plausible, clear and consistent with those of other studies, and thereby these elements may upgrade the study. This combination of "poor" and "good" rating is a possible consequence when the method of OHAT (NTP, 2015a) is used.

The upgrading element "Large magnitude of effect (e.g. incidence, degrees of severity)" may be influenced by study group size and dose. Effect sizes should have been estimated at a standardised exposure; however, this was not performed. However, group sizes were taken into consideration under the downgrading element "Imprecision" when these were small (see e.g. Table 1 in Chapter 15 Appendix: Weight of evidence).

According to the OHAT Handbook (NTP, 2015a) the following statement is associated with the terms used to describe "Very low confidence (+)": "The true effect is highly likely to be different from the apparent relationship". This statement may give the impression that a true effect is different from the one observed. However, in the OHAT Handbook, an additional explanation is given in Figure 2: OHAT Framework for Systematic Review and Evidence Integration, Step 6, where for low or no evidence for a health effect, the evidence is termed "inadequate". Furthermore, it is stated that "… a conclusion of "Very Low Confidence" suggests that further research is very likely to have an impact on confidence in the apparent relationship".

Interpretation of downgrading the risk of bias in the WoE evaluation form was also taken from the OHAT Handbook (NTP, 2015a):

"Not serious concern": Plausible bias unlikely to seriously alter the results
"Serious concern": Plausible bias that raises some doubt about the results

"Very serious concern": Plausible bias that seriously weakens confidence in the results

Note that the wording may be misinterpreted as the terms all contain the word "concern". The tier 1 studies normally had no concern associated with risk of bias.

Concerning the overall confidence rating when no effect is present, it may be argued that e.g. the group sizes were too small or that the study authors may have investigated the wrong parameters, to mention a few. Furthermore, it may be argued that scoring "very likely" in the absence of an effect is the same as scoring "very unlikely" for the presence of a health effect. Notwithstanding the interesting argumentation, the evidence for reaching these two terms would be very different as "very likely" is only achievable for studies of high quality whereas the opposite is true for those graded "very unlikely". For instances, if authors have investigated an endpoint that was not observed, the risk assessors cannot upgrade the element "large effect"; however, if the study still receives a score of ++++, the study is probably so well conducted that it can be argued that it is likely that the finding of absence of a health effect is true. Group sizes were taken into consideration under the downgrading element "imprecision".

9 Summary, discussion and conclusions

The population groups included in the current assessment are children and adolescents (from 8 to18 years). Possible effects of energy drinks and caffeine in pregnant and lactating women, foetuses, and children aged 0 to <8 years are not included.

9.1 Hazard identification and characterisation

Literature

The hazard assessment is based on previous risk assessments, reports and RCTs published in the period January 2013 to November 2018 (energy drinks)/ October 2018 (caffeine). As RCTs were the only type of articles included in the present risk assessment, endpoints, hypotheses and mechanisms of action described in human studies other than RCTs, animal and *in vitro* studies were not assessed. With regard to the assessment of energy drinks, the included literature was retrieved according to the energy drink definition given by NFSA (see Terms of reference).

To identify relevant publications for answering the hazard identification and characterisation sub-questions for energy drinks and caffeine, literature searches were performed by an expert librarian. A full systematic assessment procedure was applied to the included RCTs. First, the publication selection was performed by two persons independently based on predefined inclusion/exclusion criteria. Next, risk of bias of the included RCTs was evaluated by two persons independently using the OHAT Risk of Bias Rating Tool (NTP, 2015b). Then, effects reported in each of the included RCTs were evaluated, by two persons independently, using a weight of evidence approach (Chapter 3.1.4 and NTP (2015a)). Finally, all studies investigating effects on a given outcome/endpoint were grouped, and the confidence in the total evidence for an effect/no effect on the specific endpoint was evaluated, again by two persons separately. The overall confidence in the evidence for each endpoint/group of endpoints was transformed to likelihood, and only effects/no effects of an endpoint that received a score of "likely/very likely" were used in the risk characterisation of the current assessment.

Cardiovascular effects, single doses

Consumption of a single dose of 480 ml energy drink containing caffeine equivalent to a dose of 3.4 mg/kg bw led to an increase in blood pressure of the same magnitude as described previously (EFSA, 2015) for similar caffeine doses. Single doses of caffeine equivalent to 1 mg/kg bw to 6.2 mg/kg bw increased systolic and diastolic blood pressures with 0.5-9 mm Hg and 1-9 mm Hg, respectively, for the healthy, general population (including children and adolescents 8-17 years).

The included RCTs did not report on changes in heart rate induced by energy drink consumption. Evidence on the effect of energy drink consumption on heart palpitations, which may be expressed as heart arrhythmias, was insufficient. Thus, the Panel cannot conclude with respect to the consumption of energy drinks and induction of heart rate changes, palpitations or arrhythmias.

A single dose of 1-2 mg caffeine/kg bw induced a small, but statistically significant reduction in heart rate in children and adolescents. This reduction was unlikely to be of any biological significance. The Panel cannot conclude on the association between caffeine exposure and heart rate or electrophysiological effects of single doses due to inadequate evidence for the effects. In addition, there is not sufficient information available to conclude about effects of caffeine on tidal volume or cerebrovascular effects.

Cardiovascular effects, repeated doses

The Panel did not identify any RCTs addressing cardiovascular effects induced by habitual consumption of energy drinks exceeding 7 days. Furthermore, the Panel cannot conclude on the association between caffeine exposure and heart rate or electrophysiological effects induced by habitual exposure up to 12 weeks due to inadequate evidence for the effects.

Based on the included RCTs, the Panel cannot draw any conclusions about the effect of habitual caffeine exposure on blood pressure.

Regarding habitual consumption in adults, doses up to 400 mg caffeine per day (5.7 mg caffeine/kg bw for a 70 kg adult) do not raise fasting blood pressure significantly after habituation to caffeine takes place (EFSA, 2015). EFSA further stated that changes in blood pressure induced by repeated intake of caffeine would be of low clinical relevance for healthy individuals. This applies only if the intakes would not exceed the maximum plasma concentrations that can be achieved with a single dose of 200 mg caffeine (about 3 mg/kg bw for 70 kg person).

Central nervous system effects

Based on the included RCTs, the Panel did not identify any psychobehavioural effects such as anxiety, jitteriness, nervousness or insomnia after consumption of single doses of energy drinks alone. The caffeine concentration in the energy drinks was equivalent to doses in the range of about 2-4 mg/kg bw, a range which covers the toxicological reference point of 1.4 mg caffeine/kg bw per day that increased sleep latency and reduced sleep duration (denoted "sleep disturbance in this chapter") in adults, adolescents and children (EFSA, 2015). Thus, such effects might have been expected from the caffeine doses in the energy drink intervention addressed in the RCTs.

Likewise, the Panel could not draw any conclusions with respect to sleep disturbances, anxiety, jitteriness or mood following ingestion of caffeine doses in a similar range as for the energy drinks, about 1-4 mg/kg bw, due to the shortcomings of the included RCTs.

EFSA (2015) considered that, in children, regular consumption of 3 mg caffeine/kg bw would not induce anxiety or behavioural changes. "Children appear to develop tolerance to the effects on the central nervous system at high habitual intakes of caffeine (> 300 mg per day) and show withdrawal symptoms" (EFSA, 2015).

Effects of energy drink/caffeine in combination with physical activity

In combination with physical activity, energy drink consumption was not associated with adverse health effects after the activity. The included RCTs neither addressed nor found adverse effects during physical activity. The overall evidence in the included RCTs was insufficient to conclude on an association between caffeine exposure (3-6 mg/kg bw) combined with physical activity and the endpoints blood pressure, heart rate and arrhythmia.

EFSA (2015) refers to studies suggesting an additive effect of caffeine and resistance training on blood pressure. It was speculated that caffeine could attenuate the decrease in blood pressure observed after the physical activity. The studies included in the EFSA evaluation used similar caffeine doses as in the included RCTs (4-6 mg/kg bw).

None of the included RCTs in the current assessment addressed dehydration related to physical activity. Doses up to 6 mg/kg bw "ingested one hour before and during prolonged endurance exercise in a hot environment did not affect body temperature or hydration status" (EFSA, 2015). This dose level is equivalent to the intervention doses used in one of the relevant included RCTs in the current evaluation. The effect of 3 mg caffeine/kg bw combined with physical activity on sleep disturbances could not be clearly demonstrated in the included RCTs.

Effects of energy drink/caffeine in combination with alcohol

The Panel cannot draw any conclusions about psychobehavioural effects including sleep disturbances due to the combination of energy drinks and alcohol consumption. Only one included RCT addressed this topic. EFSA considers that caffeine doses up to 3 mg/kg bw including that from energy drinks, is unlikely to mask the subjective perception of alcohol intoxication which could lead to increased risk-taking behaviour when alcohol is consumed at doses of about 0.65 g/kg bw (blood concentration of about 0.08%). Such alcohol doses would not affect the safety of single caffeine doses up to 200 mg.

Other effects

The Panel cannot conclude on glucose, insulin or cortisol levels after combined exposure to caffeine and physical activity as only one RCT with insufficient evidence was included.

Comparison of effects from energy drinks and caffeine

Moderate, single doses

The Panel did not observe that energy drinks induced any other adverse health effects or that the effects were expressed differently than those observed from similar concentrations

of caffeine alone. This observation supports the conclusion by EFSA (2015) that common constituents of energy drinks at concentrations commonly present in such beverages would not affect the safety of single doses of caffeine up to 200 mg (3 mg/kg bw per day in a 70 kg adult), a dose which may also apply to children and adolescents. According to EFSA (2015), energy drinks typically contain about 300-320 mg/l caffeine, 4000 mg/l taurine, and 2400 mg/l D-glucorono-γ-lactone. "Up to these levels of intake, other common constituents of "energy drinks" are not expected to adversely interact with caffeine on its effects on the cardiovascular system, on the central nervous system or hydration status" (EFSA, 2015).

High acute doses

Insufficient data were available to the Panel to conclude about type and magnitude of effects resulting from high acute intake of energy drinks. These effects may or may not be identical to those resulting from caffeine exposure of similar doses.

Choice of toxicological reference points

Due to lack of dose-response data, including doses relevant for high acute intake, and lack of toxicity data from chronic consumption of energy drinks, the Panel concludes that more data are needed to establish a reference point for energy drinks as such.

The included RCTs in this review did not demonstrate any additional adverse effects or effects that were expressed differently than those that could be attributed to the caffeine content of the energy drinks. This observation is in line with EFSA (2015). Therefore, the risk characterisation was based on the caffeine doses of no concern established by EFSA (2015) (Chapter 6.2). The observed effects of caffeine on blood pressure were within expected and previously described magnitudes. Therefore, the Panel applied the toxicological reference point set by EFSA (2015) of 3 mg/kg bw for general adverse health effects in the risk characterisation. Likewise, due to lack of evidence with respect to sleep disturbances, the Panel applied the toxicological reference point for sleep disturbance, 1.4 mg caffeine/kg bw, set by EFSA (2015).

9.2 Energy drink consumption

Regarding intake of energy drinks, the following four studies were included in this assessment: the Ungkost 3 study, the NCC study, the Norwegian Mother and Child Cohort follow up study and the Ungdata study. All of the included studies gave valuable input to the intake of energy drinks, and the Ungkost 3 study and the NCC study gave background data for estimates of caffeine exposure.

9.2.1 Energy drink consumption; habitual intakes

Median chronic intake in consumers of energy drinks were estimated to be in the range of less than 1 ml per day to 81 ml/day; high chronic intake given as 95-percentile ranged from 114 to 418 ml/day. The studies varied in design, use of assessment methods and population

size. However, the estimated intakes from the two largest studies, the NCC study and the Ungdata study were in partial and full agreement with regard to the median chronic and high chronic intakes in age groups 13 to 18 years. Both studies used questionnaires for data collection. The fact that two independent surveys found such similar results is evaluated as a strength. In the Ungkost 3 study, a 4-days food diary was used as dietary assessment method, which is adequate for estimating intake on group level and the distribution of intake. However, the intake of food and beverages that are seldom or infrequently consumed may be underestimated. Furthermore, with smaller study populations, such as in the Ungkost 3 study and in the subgroup of 10-12 year olds in the NCC study, estimations of intake varied more and were less statistically robust. These results should therefore be interpreted and used with caution.

9.2.2 Energy drink consumption; highest acute intakes

The highest acute intakes ranged from 400 ml among 8-9 year old children in the Ungkost study to 10 l reported by one participant (in the group 16-18 year old) in the NCC survey.

The highest reported intake in a study and age group during 24 hours, was set as highest acute intake of energy drinks. The Ungkost 3 study and the NCC survey were designed with response options that enabled reporting of maximum intakes during 24 hours. The Ungdata study and the MoBa follow up study were designed with maximum response options that resulted in approximations of maximum intake.

9.3 Caffeine - exposure

Regarding exposure to caffeine, two studies were included in this assessment: Ungkost 3, and NCC study. From the detailed dietary data in the Ungkost 3 study we were able to estimate caffeine exposure from the whole diet with the exception of sodas with caffeine. In the NCC study the caffeine exposure could only be estimated based on data from beverages with caffeine (coffee, tea, cocoa, and sodas with caffeine). Caffeine exposure from energy drinks alone, given a caffeine level of 32 mg/100 ml energy drink, varied from close to zero to 2.0 mg caffeine/kg bw/day for the median and high chronic exposure. The highest acute exposure varied from 4.4 to 52.2 mg caffeine/kg bw/day. In both studies we would expect some underestimations of total caffeine exposure due to missing data on sodas with caffeine (the Ungkost study), and other dietary sources (the NCC study).

The percentage contribution of caffeine exposure from energy drinks was 76% in 12-13-year-old consumers of energy drinks in the Ungkost 3 study. Note that this is based on 30 consumers of energy drinks of the 687 participants in Ungkost 3. When estimating the contribution of caffeine from different dietary sources, energy drinks contributed with less than 5% of the total caffeine exposure in the Ungkost 3 study, including both consumers and non-consumers of energy drinks. The results suggest that beverages with cocoa, and chocolate, were the main dietary sources of caffeine in this age group. We expect that sodas with caffeine also contributed to the exposure of caffeine in this study.

The NCC study showed differences both in absolute exposure and percentage contribution from the different caffeine containing beverages between non-consumers and consumers of energy drinks. Consumers of energy drinks had a higher exposure from all other caffeine containing drinks, in all three age groups, compared with non-consumers. For the consumers of energy drinks the percentage contribution of caffeine from energy drinks ranged from 15% to 48%. When estimating the contribution of caffeine from different beverages, energy drinks contributed with 31% of the caffeine exposure in the NCC study, including both consumers and non-consumers of energy drinks. The Panel expect that the rest of the diet also would contribute to the exposure to caffeine.

9.4 Risk characterisation

Few of the included RCTs investigated the effects of energy drinks with proper controls such as controls for the caffeine content or other ingredients. Furthermore, sufficient description of ingredients was often missing. Few studies investigated a dose-response relationship, and no studies included higher caffeine doses than about 6 mg/kg bw per day. Thus, no studies investigated caffeine exposures that were identified as "highest acute intake" in the surveys. Chronic intake of energy drinks was not addressed in any of the included RCTs, and only few studies had sufficiently large study groups. Therefore, no reference point for energy drinks was derived.

None of the included RCTs, as well as the risk assessment of EFSA, demonstrated that energy drinks induced other adverse health effects than did similar concentrations of caffeine. Furthermore, the observed effects of energy drinks were not differently expressed than those observed from similar concentrations of caffeine. Therefore, the caffeine doses of no concern established by EFSA (2015) were used in the risk characterisation as reference point for toxicity. The dose of 3 mg/kg bw per day is based on adverse health effects such as cardiovascular and haematological, neurological and psycobehavioural effects (denoted "general adverse health effects" in the current document). Furthermore, a caffeine dose of 1.4 mg/kg bw per day was used as reference point for increased sleep latency and reduced sleep duration (denoted "sleep disturbances" in the current document).

Although the target population group in the current risk assessment is children and adolescents, the reference points for caffeine toxicity are based predominantly on data from studies on adults. Only one of the included RCTs from the retrieved literature investigated adverse health effects in children and adolescents, and the assessments by EFSA (2015) and ANSES (2013) dealt with few studies on these age groups. However, since caffeine clearance from plasma has been estimated to be 5 to 20% faster in children than in adults (EFSA, 2015), the Panel decided, in accordance with EFSA (2015), that the reference points can be used in this risk characterisation of caffeine for children and adolescents age 9-18 years old.

According to ANSES (2013), adverse effects have been reported following consumption of highly variable amounts of energy drinks, suggesting greater susceptibility in some consumers. This observation is predominantly due to inter-individual variability in response

to caffeine. The variability is particularly related to individual genotypes, physiological or health status such as the presence of certain disorders, caffeine consumption habits, and co-exposures with e.g. tobacco and intake of medicines. Groups in the population that may be more susceptible to the adverse effects of energy drinks and caffeine, include individuals with predispositions, often undiagnosed, to certain heart conditions, e.g. congenital prolonged QT syndrome that may lead to arrhythmias and cardiac arrest. The prevalence of several underlying conditions that may lead to arrhythmias was reported by ANSES to be in the range of 1:10000 to 1:500. The Panel considers these groups as especially susceptible to high consumption of energy drinks and caffeine, and the reference point of 3 mg/kg bw/day established by EFSA does not necessarily protect these individuals.

According to EFSA (2015), tolerance to caffeine is observed after repeated administration. Tolerance develops to some caffeine effects but not to all, and the development of tolerance is highly variable among the population. Symptoms such as headache, fatigue, decreased energy and activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability and being not clear-headed are observed 12–24 h after abstinence. This clinical situation is called caffeine withdrawal syndrome. Withdrawal symptoms of caffeine was not investigated in any of the included RCT's.

The conclusions from the risk characterisation are summarized in Table 9.4-1 (caffeine exposure from energy drinks), Table 9.4-2 (caffeine exposure from food and beverages not including energy drinks and sodas), and Table 9.4-3 (caffeine exposure from beverages, not including energy drinks and food). Conclusions about caffeine exposures with no or low risk, with risk for sleep disturbance, and with risk for general adverse health effects, are presented in Chapters 9.4.1, 9.4.2 and 9.4.3, respectively.

Table 9.4-1. Risk characterisation of caffeine exposure from different scenarios of energy drink intake by age groups and given caffeine concentrations (mg/100 ml energy drink). Exceedance of intake equal to or above the reference points is indicated for the relevant, *combined* dietary surveys/studies.

Age group, years	Surveys	Intake	15 mg	32 mg	40 mg	55 mg
8-12	Ungkost 3 Norwegian Consumer Council study	Median chronic intake	–	–	–	–
	Norwegian Consumer Council study	High chronic intake	–	–	X[a]	X[a]
	Ungkost 3 Norwegian Consumer Council study	Highest acute intake	XX	XX	XX	XX
13-15	Ungdata study MoBa Ungkost 3 Norwegian Consumer Council study	Median chronic intake	–	–	–	–

Age group, years	Surveys	Intake	15 mg	32 mg	40 mg	55 mg
	Ungdata study MoBa Ungkost 3 Norwegian Consumer Council study	High chronic intake	–	X	XX[a]	XX
	Ungdata study MoBa Ungkost 3 Norwegian Consumer Council study	Highest acute intake	XX	XX	XX	XX
16-18	Norwegian Consumer Council study Ungdata study	Median chronic intake	–	–	–	–
	Norwegian Consumer Council study Ungdata	High chronic intake	–	X	X	X
	Norwegian Consumer Council study Ungdata study	Highest acute intake	XX	XX	XX	XX

XX: Intake equal to or above the reference point for general adverse health effects (EFSA, 2015)
X: Intake equal to or above the reference point for sleep disturbance (EFSA, 2015)
–: Intake below the reference points
[a]: 95 percentile is reported, however, the value is not statistically robust due to a small number of energy drink consumers in this age group

Table 9.4-2. Risk characterisation characterisation (exceedance of reference points) for caffeine from food and beverages, not including energy drinks and soda, from the Ungkost 3 study.

	Non-consumers		Consumers	
Age group	Median intake of foods and beverages)	High intake of other foods and beverages	Median intake of other foods and beverages	High intake of other foods and beverages
8-9	–	–	–	CC
12-13	–	–	–	–[a]

CC: Cannot conclude due to the small number of participants in the surveys consuming energy drinks
–: Intake below the reference points
[a]: 95 percentile is reported, however, the value is not statistically robust due to a small number of energy drink consumers in this age group

Table 9.4-3. Risk characterisation characterisation (exceedance of reference points) for caffeine from beverages, not including energy drinks and food, from the NCC study.

		Non-consumers		Consumers	
Age	Median intake of	High intake of	Median intake of		High intake of

group	beverages	beverages	beverages	beverages
10-12	–	–	–	XX[a]
13-15	–	–	–	X
16-18	–	X	–	X

XX: Intake equal to or above the reference point for general adverse health effects (EFSA, 2015)
X: Intake equal to or above the reference point for sleep disturbance (EFSA, 2015)
–: Intake below the reference points
[a]: 95 percentile is reported, however, the value is not statistically robust due to a small number of energy drink consumers in this age group

9.4.1 Caffeine exposure with no or low risk

The median chronic intake of energy drinks is unlikely to cause any risk in any of the age groups studied.

The high chronic intake of energy drinks is unlikely to cause any risk in any of the age groups studied if all consumed energy drinks contain 15 mg caffeine/100 ml, and in the age groups 8-12 years if all consumed energy drinks contain 32 mg caffeine/100 ml.

For caffeine exposure from foods and beverages, not including energy drinks and soda, median and high intake for consumers and non-consumers of energy drinks in all age groups studied, is unlikely to cause any risk. Note that high exposure for consumers aged 8-9 cannot be calculated, and that for consumers aged 12-13, the value for high intake is not statistically robust due to a small number of energy drink consumers.

For caffeine exposure from beverages, not including energy drinks and food, median intake for consumers and non-consumers in all age groups and high intake for non-consumers of energy drinks aged 10-12 and 13-15, is unlikely to cause any risk.

9.4.2 Caffeine exposure that may represent a risk for sleep disturbance

All caffeine exposure that may represent a risk for general adverse health effects (Chapter 9.4.3) may also represent a risk for sleep disturbance.

In the age group 9-12 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 40 or 55 mg caffeine/100 ml. Note that the value are not statistically robust due to a small number of energy drink consumers in this age group.

In the age group 13-15 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 32 mg caffeine/100 ml.

In the age group 16-18 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 32, 40 and 55 mg caffeine/100 ml.

For caffeine exposure from beverages, not including energy drinks or food, high intake for consumers aged 13-15 years and high intake for both consumers and non-consumers of energy drinks aged 16-18 years, may represent a risk for sleep disturbance.

9.4.3 Caffeine exposure that may represent a risk for general adverse health effects

In the age group 13-15, high chronic intake of energy drinks may represent a risk for general adverse health effects if all consumed energy drinks contain 40 or 55 mg caffeine/100 ml. Note that for energy drinks containing 40 mg caffeine/100 ml, the value is not statistically robust due to a small number of energy drink consumers in this age group.

The calculated highest acute intake estimates of energy drinks, using caffeine concentrations of 15, 32, 40 and 55 mg caffeine/100 ml, may all represent a risk for general adverse health effects in all age groups.

For caffeine exposure from beverages, not including energy drinks or food, high intake for consumers aged 10-12 years may represent a risk for general adverse health effects. Note that for this group, the value for high intake is not statistically robust due to a small number of energy drink consumers.

9.5 Other considerations

As commented in the Danish intake report (Christensen LM et al., 2014), "A high intake of soft drinks with added sugar increases the risk of overweight, type 2 diabetes, dental caries, and dental erosion". As with other acidic beverages such as fruit juices and sodas, the acidity of energy drinks may further contribute to dental erosion. If energy drinks are consumed in addition to juices and soft drinks, they may contribute to a higher intake of sugar.

9.6 Conclusions of the risk assessment of energy drinks and caffeine

Reference points for toxicity

Due to lack of dose-response data, including doses representing the highest acute intakes, and lack of toxicity data from chronic consumption of energy drinks, the Panel concludes that more data are needed to establish a reference point for energy drinks as such.

The Panel did not observe that energy drinks induced any other adverse health effects or that the effects were expressed differently than those that could be attributed to similar concentrations of caffeine alone. Therefore, as reference points for caffeine toxicity, the Panel decided to use the caffeine doses of no concern established by EFSA (2015); 3 mg/kg bw per day for toxicity such as cardiovascular and haematological, neurological and psycobehavioural effects (denoted "general adverse health effects" in the following), and 1.4

mg/kg bw per day for increased sleep latency and reduced sleep duration (denoted "sleep disturbances" in the following).

Contribution of caffeine from different dietary sources

Energy drinks contributed with less than 5% of the total caffeine exposure in the Ungkost 3 study. The data suggest that chocolate, beverages with cocoa, cakes with cocoa and tea are the main dietary sources of caffeine in the age groups 8-9 and 12-13 years (sodas was not included in this study).

Consumers of energy drinks had a higher total caffeine intake from other caffeine containing food and beverages included in the studies, in all three age groups, compared to non-consumers according to the NCC study and Ungkost 3.

Adverse health effects

Caffeine exposure with no or low risk

- The median chronic intake of energy drinks is unlikely to cause any risk in any of the age groups studied.
- The high chronic intake of energy drinks is unlikely to cause any risk in any of the age groups studied if all consumed energy drinks contain 15 mg caffeine/100 ml, and in the age groups 8-12 years if all consumed energy drinks contain 32 mg caffeine/100 ml.
- For caffeine exposure from foods and beverages, not including energy drinks and soda, median and high intake for consumers and non-consumers of energy drinks in all age groups studied, is unlikely to cause any risk. Note that high exposure for consumers aged 8-9 cannot be calculated, and that for consumers aged 12-13, the value for high intake is not statistically robust due to a small number of energy drink consumers.
- For caffeine exposure from beverages, not including energy drinks and food, median intake for consumers and non-consumers in all age groups and high intake for non-consumers of energy drinks aged 10-12 and 13-15, is unlikely to cause any risk.

Caffeine exposure that may represent a risk for sleep disturbance

- All caffeine exposure that may represent a risk for general adverse health effects may also represent a risk for sleep disturbance.
- In the age group 9-12 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 40 or 55 mg caffeine/100 ml. Note that the value are not statistically robust due to a small number of energy drink consumers in this age group.

- In the age group 13-15 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 32, 40 or 55 mg caffeine/100 ml.
- In the age group 16-18 years, high chronic intake of energy drinks may represent a risk for sleep disturbance if all consumed energy drinks contain 32, 40 or 55 mg caffeine/100 ml.

- For caffeine exposure from beverages, not including energy drinks or food, high intake for consumers aged 13-15 years and high intake for both consumers and non-consumers of energy drinks aged 16-18 years, may represent a risk for sleep disturbance.

Caffeine exposure that may represent a risk for general adverse health effects

- In the age group 13-15, high chronic intake of energy drinks may represent a risk for general adverse health effects if all consumed energy drinks contain 40 or 55 mg caffeine/100 ml. Note that for energy drinks containing 40 mg caffeine/100 ml, the value is not statistically robust due to a small number of energy drink consumers in this age group.
- The calculated highest acute intake estimates of energy drinks, using caffeine concentrations of 15, 32, 40 or 55 mg caffeine/100 ml in the scenario calculations, may all represent a risk for general adverse health effects in all age groups.

- For caffeine exposure from beverages, not including energy drinks or food, high intake for consumers aged 10-12 years may represent a risk for general adverse health effects. Note that for this group, the value for high intake is not statistically robust due to a small number of energy drink consumers.

Energy drinks combined with physical activity/dehydration

- Based on the included RCTs, energy drink consumption in combination with physical activity was not associated with adverse health effects *after* the activity. These studies either did not address or did not observe adverse effects *during* physical activity. None of the included RCTs in the current assessment addressed dehydration related to physical activity. According to EFSA (2015), "Doses up to 6 mg/kg bw ingested one hour before and during prolonged endurance exercise in a hot environment did not affect body temperature or hydration status".

Energy drinks combined with alcohol

- The Panel cannot draw any conclusions about central nervous system effects including sleep disturbances due to the combination of energy drinks and alcohol consumption. EFSA considers that caffeine doses up to 3 mg/kg bw including that from energy drinks, is unlikely to mask the subjective perception of alcohol

intoxication which could lead to increased risk-taking behaviour when alcohol is consumed at doses of about 0.65 g/kg bw (blood concentration of about 0.08%). Such alcohol doses would not affect the safety of single caffeine doses up to 200 mg.

Susceptible groups

Relevant groups in the population that may be more susceptible to the adverse effects of energy drinks and caffeine, include individuals with predispositions to certain heart conditions, such as congenital prolonged QT syndrome. The Panel concludes that the reference point of 3 mg/kg bw per day, established by EFSA, may not necessarily protect individuals with predispositions to certain heart conditions.

10 Data gaps

High quality RCTs are scarce on children and adolescents in general and specifically with respect to diverse ethnicities and differences between genders. There are few studies investigating the effects of energy drinks with proper caffeine exposure controls, ingredient controls and description of ingredients. Dose-response is seldom studied, including doses that represent the highest acute intake in the dietary surveys. Sufficiently large study groups are lacking in several studies. This knowledge is important for the derivation of a more certain reference point, and for the evaluation of adverse effects of energy drinks versus adverse effects of caffeine alone. With such knowledge, a reference point for energy drinks for children and adolescents could be determined, and the uncertainty in the hazard characterisation and the conclusions would be reduced.

Few studies on energy drinks combined with alcohol have an alcohol control. This is needed to pinpoint possible adverse effects caused by the combination of energy drinks and alcohol, and not caused by alcohol alone.

Studies of energy drinks in combination with physical activity are needed to address possible adverse health effects that may occur during and after this intervention, especially with respect to dehydration and cardiovascular effects.

There are few studies available addressing chronic intake of energy drinks and chronic exposure to caffeine. This is needed for the evaluation of adverse effects of energy drinks versus adverse effects of caffeine alone to reduce the uncertainty in the conclusions on chronic consumption.

None of the included RCTs addressed dehydration as an effect of energy drink consumption or caffeine exposure in association with physical activity or alone. It is not clear whether the lack of reporting of dehydration effects was due to the fact that the participants did not experience it, that the question was not addressed or that the authors were not concerned about this potential endpoint.

Future studies on caffeine exposure in children should be designed to include enough consumers of energy drink to enable estimations of intakes that are statistically robust. Since there are few consumers of energy drink in the age group 9 to 13 years, there is a need for larger studies to get a sufficient number of energy drink consumers to calculate high chronic intake of energy drinks. Also, surveys in children 8-15 years of age should include assessment methods that can estimate both frequency of intake and amount per intake. To be able to get a better picture of maximum intakes, the high end answer alternatives of energy drinks should preferably be more specific.

Furthermore, there is a need for more specific estimations of caffeine from other dietary sources, both food, beverages and supplements. To do this it is necessary to compile high quality food composition data on caffeine in foods and beverages.

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12 Appendix: Literature search

12.1 Literature search energy drinks

The total result (after removal of duplicates) was 1719.

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to October 30, 2018>
Date: 31.10.2018
Result: 793

#	Searches	Results
1	Energy Drinks/	598
2	("energy drink*" or "energy shot*" or "red bull" or (battery adj drink*) or monster or rockstar or "Full Throttle" or "NOS energy" or "VPX Redline" or "Speed Stack" or "Cocaine energy drink" or "XS Energy" or "5-Hour Energy" or "DynaPep" or "Spike Shooter" or "Bang energy").tw,kw.	2107
3	1 or 2	2201
4	exp Exercise/ or (exercis* or sport* or athlet* or endurance or performance or behaviour or behavior or attention or psych* or alcohol* or neurologic* or gastroenterologic* or muscul* or haematologic* or cardio* or fertility or reproductive or interaction or "birth defect*").tw.	4663175
5	(adverse effect* or adverse event*).fs,tw,kw.	1772968
6	"dose response".tw.	63239
7	health hazard/ or ((health adj2 hazard*) or (harmful adj2 effect*1) or health harm* or (health adj2 risk*) or harm*).tw.	198391
8	((adverse adj2 effect*1) or (adverse adj2 event*) or (adverse adj2 reaction*) or side-effect* or side effect*).tw.	533187
9	risk assessment/ or ((risk adj2 assess*) or (safety adj2 assess*)).tw.	305972
10	risk factor/ or risk factor*.tw.	1001304
11	(negative health* or negative effect*1 or negative impact*).tw.	69204
12	toxicity/ or (toxicity or (toxic adj effect*1)).tw.	364362
13	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	7263356
14	3 and 13	1202

15	animal/ not (animal/ and human/)	4476868
16	14 not 15	1153
17	limit 16 to yr="2013 -Current"	793

Embase <1974 to 2018 October 30>
Date: 11.10.2017
Result: 1183

#	Searches	Results
1	Energy Drinks/	1544
2	("energy drink*" or "energy shot*" or "red bull" or (battery adj drink*) or monster or rockstar or "Full Throttle" or "NOS energy" or "VPX Redline" or "Speed Stack" or "Cocaine energy drink" or "XS Energy" or "5-Hour Energy" or "DynaPep" or "Spike Shooter" or "Bang energy").tw,kw.	2559
3	1 or 2	2864
4	exp Exercise/ or (exercis* or sport* or athlet* or endurance or performance or behaviour or behavior or attention or psych* or alcohol* or neurologic* or gastroenterologic* or muscul* or haematologic* or cardio* or fertility or reproductive or interaction or "birth defect*").tw.	5775152
5	*adverse event/ or (adverse effect* or adverse event*).fs,tw,kw.	416890
6	"dose response".tw.	76558
7	health hazard/ or ((health adj2 hazard*) or (harmful adj2 effect*1) or health harm* or (health adj2 risk*) or harm*).tw.	266223
8	((adverse adj2 effect*1) or (adverse adj2 event*) or (adverse adj2 reaction*) or side-effect* or side effect*).tw.	799773
9	risk assessment/ or ((risk adj2 assess*) or (safety adj2 assess*)).tw.	557327
10	risk factor/ or risk factor*.tw.	1171120
11	(negative health* or negative effect*1 or negative impact*).tw.	89872
12	toxicity/ or (toxicity or (toxic adj effect*1)).tw.	516772
13	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	7939940
14	3 and 13	1693
15	animal/ not (animal/ and human/)	1014193
16	14 not 15	1681
17	limit 16 to yr="2013 -Current"	1183

Web of Science
Date: 31.10.2018
Result: 749

Set	Results	Search
#16	752	#12 NOT #13 **Refined by:** [excluding] **WEB OF SCIENCE CATEGORIES:** (ENGINEERING ENVIRONMENTAL OR ENGINEERING INDUSTRIAL OR MATERIALS SCIENCE MULTIDISCIPLINARY OR CRIMINOLOGY PENOLOGY OR HISTORY OR PHILOSOPHY OR HISTORY PHILOSOPHY OF SCIENCE OR LANGUAGE LINGUISTICS OR FOOD SCIENCE TECHNOLOGY OR LITERATURE ROMANCE OR COMMUNICATION OR PHYSICS APPLIED OR ELECTROCHEMISTRY OR ENERGY FUELS OR ENGINEERING CIVIL OR RELIGION OR EDUCATION EDUCATIONAL RESEARCH OR FILM RADIO TELEVISION OR VETERINARY SCIENCES OR COMPUTER SCIENCE INFORMATION SYSTEMS OR ECONOMICS OR HUMANITIES MULTIDISCIPLINARY OR ART OR GENETICS HEREDITY OR ENGINEERING CHEMICAL OR GREEN SUSTAINABLE SCIENCE TECHNOLOGY OR EDUCATION SCIENTIFIC DISCIPLINES OR INSTRUMENTS INSTRUMENTATION OR LITERATURE GERMAN DUTCH SCANDINAVIAN OR LITERATURE OR MANAGEMENT OR METALLURGY METALLURGICAL ENGINEERING OR THEATER OR ZOOLOGY OR BUSINESS OR WATER RESOURCES OR LAW OR COMPUTER SCIENCE INTERDISCIPLINARY APPLICATIONS OR AGRICULTURE DAIRY ANIMAL SCIENCE) AND [excluding] **WEB OF SCIENCE CATEGORIES:** (PHYSICS FLUIDS PLASMAS OR TRANSPORTATION OR TRANSPORTATION SCIENCE TECHNOLOGY OR COMPUTER SCIENCE ARTIFICIAL INTELLIGENCE OR COMPUTER SCIENCE CYBERNETICS OR COMPUTER SCIENCE SOFTWARE ENGINEERING OR ENGINEERING MECHANICAL OR ETHNIC STUDIES OR INFORMATION SCIENCE LIBRARY SCIENCE OR LITERARY REVIEWS OR LITERARY THEORY CRITICISM OR LITERATURE AMERICAN OR LITERATURE BRITISH ISLES OR LITERATURE SLAVIC OR BUSINESS FINANCE OR CLASSICS OR FAMILY STUDIES OR MEDIEVAL RENAISSANCE STUDIES OR NANOSCIENCE NANOTECHNOLOGY) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#15	772	#12 NOT #13 **Refined by:** [excluding] **WEB OF SCIENCE CATEGORIES:** (ENGINEERING ENVIRONMENTAL OR ENGINEERING INDUSTRIAL OR MATERIALS SCIENCE MULTIDISCIPLINARY OR CRIMINOLOGY PENOLOGY OR HISTORY OR PHILOSOPHY OR HISTORY PHILOSOPHY OF SCIENCE OR LANGUAGE LINGUISTICS OR FOOD SCIENCE TECHNOLOGY OR LITERATURE ROMANCE OR COMMUNICATION OR PHYSICS APPLIED OR ELECTROCHEMISTRY OR ENERGY FUELS OR ENGINEERING CIVIL OR RELIGION OR EDUCATION EDUCATIONAL RESEARCH OR FILM RADIO TELEVISION OR VETERINARY SCIENCES OR COMPUTER SCIENCE INFORMATION SYSTEMS OR ECONOMICS OR HUMANITIES

		MULTIDISCIPLINARY OR ART OR GENETICS HEREDITY OR ENGINEERING CHEMICAL OR GREEN SUSTAINABLE SCIENCE TECHNOLOGY OR EDUCATION SCIENTIFIC DISCIPLINES OR INSTRUMENTS INSTRUMENTATION OR LITERATURE GERMAN DUTCH SCANDINAVIAN OR LITERATURE OR MANAGEMENT OR METALLURGY METALLURGICAL ENGINEERING OR THEATER OR ZOOLOGY OR BUSINESS OR WATER RESOURCES OR LAW OR COMPUTER SCIENCE INTERDISCIPLINARY APPLICATIONS OR AGRICULTURE DAIRY ANIMAL SCIENCE) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#14	991	#12 NOT #13 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#13	2 842 749	TS=((rat* OR mouse OR mice)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#12	1 350	#11 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#11	4 234 819	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#10	180 840	TS=((toxicity OR (toxic NEAR effect*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#9	62 540	TS=(("negative health*" OR "negative effect*" OR "negative impact*")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#8	295 636	TS=(("risk factor*")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#7	88 265	TS=(("risk assessment" OR (risk NEAR/2 assess*) OR (safety NEAR/2 assess*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#6	145 306	TS= (((adverse NEAR/2 effect*) OR (adverse NEAR/2 event*) OR (adverse NEAR/2 reaction*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#5	29 967	TS=(("health harm*" OR (health NEAR/2 risk*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#4	11 071	TS=(("health hazard" OR (health NEAR/2 hazard*) OR (harmful NEAR/2 effect*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#3	185 863	TS=(("adverse event*" OR "adverse effect*" OR "dose response" OR "side effect*" or "side-effect*")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-*

		2018
#2	3 743 041	TS= ((exercis* OR sport* OR athlet* OR endurance OR performance OR behaviour OR behavior OR attention OR psych* OR alcohol* OR neurologic* OR gastroenterologic* OR muscul* OR haematologic* OR cardio* OR fertility OR reproductive OR interaction OR "birth defect*")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
#1	2 970	TS=(("energy drink*" OR "energy shot*" OR "red bull" OR monster OR rockstar OR "Full Throttle" OR "NOS energy" OR "VPX Redline" OR "Speed Stack" OR "Cocaine energy drink" OR "XS Energy" OR "5-Hour Energy" OR "DynaPep" OR "Spike Shooter" OR "Bang energy" OR battery NEAR Drink)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*

12.2 Literature search caffeine

The total result (after removal of duplicates) was 7301.

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to November 02, 2018>
Date: 6.11.2018
Result: 2938

#	Searches	Results
1	*CAFFEINE/	12211
2	(caffein* or coffein*).fs,tw,kw.	27624
3	58-08-2.tw,kw.	6
4	1 or 2 or 3	28616
5	exp Exercise/ or (exercis* or sport* or athlet* or endurance or performance or behaviour or behavior or attention or psych* or alcohol* or neurologic* or gastroenterologic* or muscul* or haematologic* or cardio* or fertility or reproductive or interaction or "birth defect*").tw.	4659694
6	(adverse effect* or adverse event*).fs,tw,kw.	1773156
7	"dose response".tw.	63214
8	health hazard/ or ((health adj2 hazard*) or (harmful adj2 effect*1) or health harm* or (health adj2 risk*) or harm*).tw.	198193

9	((adverse adj2 effect*1) or (adverse adj2 event*) or (adverse adj2 reaction*) or side-effect* or side effect*).tw.	532546
10	risk assessment/ or ((risk adj2 assess*) or (safety adj2 assess*)).tw.	305901
11	risk factor/ or risk factor*.tw.	1000918
12	(negative health* or negative effect*1 or negative impact*).tw.	69095
13	toxicity/ or (toxicity or (toxic adj effect*1)).tw.	363977
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	7259031
15	4 and 14	11966
16	animal/ not (animal/ and human/)	4477980
17	15 not 16	9258
18	limit 17 to yr="2013 -Current"	2947
19	remove duplicates from 18	2938

Embase <1974 to 2018 November 02>
Date: 6.11.2018
Result: 4626

#	Searches	Results
1	*CAFFEINE/	19667
2	(caffein* or coffein*).fs,tw,kw.	33132
3	58-08-2.tw,kw.	6
4	1 or 2 or 3	37945
5	exp Exercise/ or (exercis* or sport* or athlet* or endurance or performance or behaviour or behavior or attention or psych* or alcohol* or neurologic* or gastroenterologic* or muscul* or haematologic* or cardio* or fertility or reproductive or interaction or "birth defect*").tw.	5783936
6	*adverse event/ or (adverse effect* or adverse event*).fs,tw,kw.	417698
7	"dose response".tw.	76608

8	health hazard/ or ((health adj2 hazard*) or (harmful adj2 effect*1) or health harm* or (health adj2 risk*) or harm*).tw.	266763
9	((adverse adj2 effect*1) or (adverse adj2 event*) or (adverse adj2 reaction*) or side-effect* or side effect*).tw.	801011
10	risk assessment/ or ((risk adj2 assess*) or (safety adj2 assess*)).tw.	558290
11	risk factor/ or risk factor*.tw.	1173217
12	(negative health* or negative effect*1 or negative impact*).tw.	90053
13	toxicity/ or (toxicity or (toxic adj effect*1)).tw.	517282
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	7952021
15	4 and 14	15001
16	animal/ not (animal/ and human/)	1014644
17	15 not 16	14685
18	limit 17 to yr="2013 -Current"	4756
19	remove duplicates from 18	4626

Web of Science
Date: 6.11.2018
Result: 1939

#15	1939	#12 NOT #13 **Refined by:** [excluding] **WEB OF SCIENCE CATEGORIES:** (WATER RESOURCES OR GENETICS HEREDITY OR EDUCATION SCIENTIFIC DISCIPLINES OR FOOD SCIENCE TECHNOLOGY OR CHEMISTRY ANALYTICAL OR ENGINEERING CIVIL OR PHYSICS APPLIED OR CHEMISTRY MULTIDISCIPLINARY OR PLANT SCIENCES OR MARINE FRESHWATER BIOLOGY OR ENTOMOLOGY OR MULTIDISCIPLINARY SCIENCES OR GREEN SUSTAINABLE SCIENCE TECHNOLOGY OR PHYSICS ATOMIC MOLECULAR CHEMICAL OR MATERIALS SCIENCE BIOMATERIALS OR CHEMISTRY PHYSICAL OR ZOOLOGY OR INSTRUMENTS INSTRUMENTATION OR AGRONOMY OR CHEMISTRY APPLIED OR NANOSCIENCE NANOTECHNOLOGY OR ENGINEERING CHEMICAL OR TRANSPORTATION OR CHEMISTRY ORGANIC OR VETERINARY SCIENCES OR ENGINEERING ENVIRONMENTAL OR EDUCATION EDUCATIONAL RESEARCH OR ELECTROCHEMISTRY OR RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAGING OR METEOROLOGY ATMOSPHERIC SCIENCES OR MATERIALS SCIENCE MULTIDISCIPLINARY OR CHEMISTRY INORGANIC NUCLEAR) AND

		[excluding] **WEB OF SCIENCE CATEGORIES:** (ETHICS OR LAW OR MANAGEMENT OR AGRICULTURE DAIRY ANIMAL SCIENCE OR AUDIOLOGY SPEECH LANGUAGE PATHOLOGY OR COMPUTER SCIENCE INTERDISCIPLINARY APPLICATIONS OR ENGINEERING MECHANICAL OR MATERIALS SCIENCE PAPER WOOD OR MUSIC OR ARCHAEOLOGY OR BUSINESS FINANCE OR COMMUNICATION OR COMPUTER SCIENCE ARTIFICIAL INTELLIGENCE OR COMPUTER SCIENCE HARDWARE ARCHITECTURE) AND [excluding] **WEB OF SCIENCE CATEGORIES:** (BUSINESS OR COMPUTER SCIENCE INFORMATION SYSTEMS OR CRIMINOLOGY PENOLOGY OR ECONOMICS OR EDUCATION SPECIAL OR ENGINEERING AEROSPACE OR ENGINEERING BIOMEDICAL OR ENGINEERING ELECTRICAL ELECTRONIC OR ENVIRONMENTAL STUDIES OR FORESTRY OR GEOGRAPHY OR LINGUISTICS OR MATERIALS SCIENCE CERAMICS OR PARASITOLOGY) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
14	3 012	#12 NOT #13 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
13	2 847 173	TS=((rat* OR mouse OR mice)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
12	5 045	#11 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
11	4 212 927	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
10	168 433	TS=(toxicity OR (toxic NEAR effect*1)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
9	26 315	TS=("negative health*" OR "negative effect*1" OR "negative impact*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
8	296 135	TS=("risk factor*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
7	88 369	TS=("risk assessment" OR (risk NEAR/2 assess*) OR (safety NEAR/2 assess*)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
6	88 295	TS= ((adverse NEAR/2 effect*1) OR (adverse NEAR/2 event*) OR (adverse NEAR/2 reaction*)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
5	29 993	TS=("health harm*" OR (health NEAR/2 risk*)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
4	4 407	TS=("health hazard" OR (health NEAR/2 hazard*) OR (harmful NEAR/2 effect*1)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
3	186 152	TS=("adverse event*" OR "adverse effect*" OR "dose response" OR "side effect*" or "side-effect*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
2	3 784 987	TS= (exercis* OR sport* OR athlet* OR endurance OR performance OR behaviour OR behavior OR attention OR psych* OR alcohol* OR neurologic* OR gastroenterologic* OR muscul* OR haematologic* OR cardio* OR fertility OR reproductive OR interaction OR "birth defect*") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*
1	8 956	TS=(caffein* OR coffein* OR "58-08-2") *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=2013-2018*

Scopus
Date: 6.11.2018
Result: 3115

```
( ( ( TITLE-ABS-KEY ( ( caffein* OR coffein* OR "58-08-2" ) ) )
AND ( ( TITLE-
ABS_KEY ( ( exercis* OR sport* OR athlet* OR endurance OR performance OR beha
viour OR behavior OR attention OR psych* OR alcohol* OR neurologic* OR gastroe
nterologic* OR muscul* OR haematologic* OR cardio* ) ) ) OR ( TITLE-ABS-
KEY ( ( fertility OR reproductive OR interaction OR "birth defect*" ) ) ) OR ( TITLE-
ABS-KEY ( "dose response" ) ) OR ( TITLE-ABS-
KEY ( ( ( health W/2 hazard* ) OR ( harmful W/2 effect* ) OR health AND harm* OR
 ( health W/2 risk* ) OR harm* ) ) ) OR ( TITLE-ABS-KEY ( ( "risk
assessment" OR ( risk W/2 assess* ) OR ( safety W/2 assess* ) ) ) ) OR ( TITLE-ABS-
KEY ( ( adverse W/2 effect* ) OR ( adverse W/2 event* ) OR ( adverse W/2 reaction* )
 OR side-effect* OR "side effect*" ) ) OR ( TITLE-ABS-KEY ( "negative
health*" OR "negative effect*" OR "negative impact*" ) ) OR ( TITLE-ABS-
KEY ( toxicity OR ( toxic W/10 effect* ) ) ) ) )
AND NOT ( TITLE-ABS-KEY ( rat* OR mouse OR mice ) ) )
AND ( PUBYEAR > 2012 )
AND ( EXCLUDE ( SUBJAREA , "CHEM" ) OR EXCLUDE ( SUBJAREA , "ENVI" )
OR EXCLUDE ( SUBJAREA , "CENG" ) OR EXCLUDE ( SUBJAREA , "ENGI" ) OR
EXCLUDE ( SUBJAREA , "PHYS" ) OR EXCLUDE ( SUBJAREA , "MATE" ) OR EX
CLUDE ( SUBJAREA , "COMP" ) OR EXCLUDE ( SUBJAREA , "MULT" ) OR EXCL
UDE ( SUBJAREA , "ARTS" ) OR EXCLUDE ( SUBJAREA , "MATH" ) OR EXCLUD
E ( SUBJAREA , "EART" ) OR EXCLUDE ( SUBJAREA , "BUSI" ) OR EXCLUDE ( S
UBJAREA , "ENER" ) OR EXCLUDE ( SUBJAREA , "DECI" ) OR EXCLUDE ( SUBJ
AREA , "VETE" ) OR EXCLUDE ( SUBJAREA , "ECON" ) )
```

13 Appendix: Data extraction

13.1 Data extraction energy drinks

Study ID a. Reference b. Health outcome(s)	a. Brothers et al. (2017) b. Cardiovascular
Funding a. Funding source(s) b. Reported conflict of interest	a. Beverage Research Consultants, LLC b. Authors declared no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover with four arms b. Double-blinded c. No information d. No information

Subjects a. Number of participants in the study (invited, accepted, dropout, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. Protocol 1 and 2: 15 recruited, dropouts not reported. b. Not reported c. Not reported d. Protocol 1: 8 M/7 F; protocol 2: 9 M/6 F e. No information f. Protocol 1 and 2: 27±4 years (mean±SD). g. No information h. No information i. Normotensive, non-smoking j. Not reported k. It was reported that subjects did not take medications, were free of any known cardiovascular, cerebrovascular, metabolic or neurological diseases.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Protocol 1: energy drink, energy drink, coffee or water. Protocol 2: energy drink (16 oz), energy drink (24 oz), 1 packet of coffee or water Protocol 1 and 2, test substance form: beverages b. Protocol 1: energy drink (Monster, 2 mg/kg caffeine), energy drink (Monster, 3 mg/kg caffeine), coffee (Keurig K-Cup Starbuck Breakfast Blend coffee, 2mg/kg caffeine) or 250 ml water. Protocol 2: 16 oz(~473 ml) can of energy drink (Monster), 24 oz (~946 ml) can of energy drink (Monster), 1 packet of coffee (Keurig K-Cup Starbucks Breakfast Blend), and a 250-ml bottle of water c. Crossover design, with a minimum 4 day wash-out period: subjects consumed one of the above mentioned drinks. The participants were instructed to finish the beverage within 20 minutes. After the beverage consumption, the participants ate a light meal (6-inch subway sandwich of their choice) with 8 oz (~237 ml) of water. All trials were conducted in the morning following an overnight fast (at least 12 Subjects refrained from strenuous exercise and caffeinated or alcoholic beverages before each data collection trial (at least 72 h). Subjects were asked to keep a log of food intake on the day prior to the first experimental trial

	and repeat this diet on the day prior to each subsequent experimental trial.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Instrumentation for each aim was identical. All data were collected in the upright seated position. Subjects were instrumented with a 12-lead electrocardiogram (ECG, QT interval, the QT interval (ms) was corrected for heart rate using the Bazzett formula) for continuous measurement of cardiac rhythms and heart rate (beats per min) from an electrocardiogram. A blood pressure (mm Hg) cuff was placed on the left arm, and intermittent blood pressure measurements were obtained by auscultation of the brachial artery via electrosphygmomanometry. Mean arterial blood pressure (MAP) was calculated as one-third pulse pressure plus diastolic blood pressure. All of the collected ECG strips, for both protocols, were subsequently analysed by a board-certified cardiologist using the standard techniques. b. At baseline, 30 min post beverage consumption and then at 60 min intervals until 6.5 h post beverage consumption.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No b. Baseline hemodynamic data (i.e. HR, MAP and QTc,) during each study visit were compared using a oneway repeated-measures analysis of variance (ANOVA) with the factors of beverage (low dose or 16 oz Monster, medium dose or 24 oz Monster, coffee, water). Also, for each protocol the effect of beverage consumption was analysed using a twoway repeated-measures ANOVA with main effect of beverage and time (BL and measures obtained postbeverage consumption). Significant differences were accepted at $P<0.05$. c. Diastolic blood pressure and mean blood pressure were slightly elevated in Protocol 1 ($P<0.05$, main effect of time) at 6.5 h port beverage consumption, the response was similar for all four beverages ($P<0.05$). In both protocol 1 and 2, heart rate was reduced during the 6.5 h period postbeverage consumption ($p<0.05$), however, this response was similar between the four beverages. No other significant findings.

Study ID a. Reference b. Health outcome(s)	a. Fletcher et al. (2017) b. Cardiovascular effects
Funding a. Funding source(s) b. Reported conflict of interest	a. Funding was provided by the Clinical Investigations Facility at Travis Air Force Base, CA b. None reported
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover, two arms b. Double-blind. No further information. c. Randomization using a computer-generated randomization code d. Recruitment of participants between 2013 and 2014
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health stauts of participants j. Inclusion/exclusion criteria k. Other	a. 18 participants. Participants were recruited via email and flyers b. 100% completion rate c. 27 were assessed for eligibility, nine were excluded d. 12 M/6 F e. USA f. Between 18 and 40 years (26.7±4.0 years) g. Eleven identified as white, three as Asian, two as Hispanic, one as black, and one undisclosed h. Nine were regular coffee drinkers (≥1 cup of coffee per day), five were occasional drinkers, and four reported no coffee consumption. Four reported regular energy drink use (≥1 can per day), five reported occasional energy drink use, and nine reported no energy drink use. i. Healthy j. Participants were excluded if they had a current or previous diagnosis of abnormal heart rhythm, a BP >140/ 90 mm Hg, any comorbid medical conditions, history of substance abuse, renal or hepatic dysfunction, concurrent use of drugs or over-the-counter products that may interact with study drinks or affect ECG or BP parameters (excluding oral contraceptives), or were pregnant or lactating.

	k. All recruited from a US Air Force Base installation. Participants were required to fast for 12 hours, and abstain from any caffeinated products 48 hrs prior to each study day and throughout the 24-hr follow-up period
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Energy drink and caffeinated drink (control). b. Participants consumed 946 ml energy drink/946 ml caffeinated drink. Caffeine content was 320 mg (both drinks; two cans with 320 mg caffeine each). The energy drink contained 108 g of sugar, vitamin B2, vitamin B3, vitamin B6, and vitamin B12, and a proprietary energy blend of taurine, panax ginseng extract, L-carnitine, caffeine (320 mg), glucuronolactone, inositol, guarana extract, and maltodextrin. The caffeinated control drink contained caffeine (320 mg), 40 mL of lime juice, and 140 mL of cherry syrup in carbonated water. All study drinks were presented in identical containers and were consumed over a 45-minute period c. Minimum a 6 day washout period between the two treatments
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Corrected, QTc, and uncorrected QT interval, PR interval, QRS duration, heart rate, peripheral and central systolic and diastolic blood pressures, augmentation index (AI) were measured. A 12-lead ECG was obtained with the participant in the supine position. The machine was calibrated to a 1-mV/cm standardization with a paper speed of 25 mm/s. Peripheral BP measurements were obtained in duplicate after a 5-minute rest using a standard automated vital signs monitor. Central BP measurements were obtained using the SphygmoCor PWA system. SphygmoCor is a validated system that uses applanation tonometry to noninvasively translate a radial pressure waveform taken at the wrist to an aortic pressure waveform. Applanation tonometry required operator proficiency and only those with an operator index of 70% or greater were included. AI was corrected to a HR of 75 beats per minute. Due to the possibility of circadian rhythm changes, the start time for each patient was approximately the same on the 2 study days (maximum difference ≤80 minutes). Participants were asked to describe any adverse events they were experiencing at each time point. b. Measurements were obtained at baseline, and 1, 2, 4, 6, and 24 hrs post drink consumption. Adverse effects were reported throughout the 24-hr monitoring period.

Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. 18 participants were needed to detect a between-group difference of 10 ms and assuming an SD of 14 ms (2-sided α=5% and 80% power). b. The time-matched changes from baseline were compared between the energy drink and control arms using the Wilcoxon signed rank test. All data were reported as mean SD unless otherwise stated. Intention-to-treat analysis using the last-observation-carried-forward methodology was performed to account for the missing values. Data imputation was performed for less than 4% of central BP parameters. The time-matched, baseline-adjusted changes were compared c. -The change in corrected QT interval from baseline in the energy drink arm was significantly higher than the caffeine arm at 2 hrs (0.44±18.4 ms versus -10.4±14.8 ms, respectively; P=0.02). The QTc changes were not different at other time points. -Both the energy drink and caffeine arms raised systolic BP in a similar fashion initially, the systolic BP was significantly higher at 6 hrs when compared with the caffeine arm (4.72±4.67 mm Hg versus 0.83±6.09 mm Hg, respectively; P=0.01). -Post energy drink, augmentation index was lower than caffeine at 6 hrs. Adverse effects were experienced by 15 participants during the energy drink arm and by 13 participants during the caffeine control arm. Adverse events included anxiety, difficulty in falling asleep, dizziness, dyspepsia/upset stomach, epistaxis, headache, jitteriness, nausea, palpitations, and shortness of breath. There were no discernible pattern and none of the adverse events caused a discontinuation in the study participation.

Study ID a. Reference b. Health outcome(s)	a. Garcia et al. (2017) b. Cardiovascular effects; psychobehavioural effects

Funding a. Funding source b. Reported conflict of interest	a. Universidad Tecnológica de Pereira (financial support) b. Reported no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT parallell design with four groups b. Double blinding (participant and examiner) c. Participants were randomised to intervention group (method not reported) d. Participants were enrolled for the 2014 academic year
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. Eighty participants were recruited and included in the study b. 100% c. No explicit information (80 subjects were randomised in four groups. «Eight sessions were programmed, and ten subjects were evaluated in each session») d. 50 M/30 F e. Colombia f. Mean age of 21±1 yr g. No information h. No information on confounders. i. Healthy participants. j. Inclusion: being an enrolled medical student older than 18 years of age. Exclusion: Students with a previous diagnosis of mitral valve prolapse, epilepsy, migraine or hypertension as well as subjects with previous adverse reactions to energy drinks or no previous energy drink consumption history. k. -
Intervention/exposure a. Test substance and control b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean,	a. Three commercial energy drinks (no trade names reported) and carbonated water as control b. Energy drink A, B and C contained 149.5 mg, 147.2 mg and 155 mg caffeine, respectively. One energy drink container (460 ml) was consumed per person. The three different beverages had different sugar content (23 g, 49.6 g and 52.8 g in A, B and C, respectively. A contained no taurine, B and C contained 1.84 g and 1.95 g taurin, respectively. A contained vitamins A, B3-

standard deviation, median, percentiles, minimum/maximum) c. Intervention design	B12 and C; B contained vitamins B3, B5, B6, B12; C contained vitamins B2, B5, B6 and B12 (no concentrations) and all contained other undetermined components. Energy drinks had similar level of carbonation. No confirmation of energy drink content. c. Subjects consumed one of four intervention beverages. The beverage containers were covered with foil to avoid identification by colour or appearance. Subjects were instructed to comply with a 12-h fast, and none of the subjects consumed tobacco, alcohol, caffeine or energy drinks for at least 48 h prior to the tests to avoid interference with the effects of energy drink components; beverage consumption time was 5 min.
Endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Systolic blood pressure (palpatory), diastolic blood pressure (auscultatory) (both mm Hg)(subjects in sitting position and the arm located at the level of the heart; all measurements were performed using an aneroid sphygmomanometer). Heart rate (bpm), P wave length, QRS complex length (ms), T wave (mV), ST segment magnitude and length, PR interval length (ms), QTc (ms)(electrocardiography; subjects in supine position; 1 mV and 25 mm/s; a trace of DII derivation measured). Cortisol levels (μG/dL)(1 ml saliva; stored at -20°C until analysis with ELISA kit). Physiological stress (state-trait anxiety inventory (STAI) using only the anxiety part of the questionnaire). Haemoglobin oxygen saturation (%)(fingertip pulse oximeter). Breath rate (%) (auscultation of the right pulmonary base with a stethoscope) b. Baseline parameters obtained prior to intervention intake; blood pressure determined after 30 min and all test were repeated after 1 h.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. A Student's t test assessed each variable to establish the statistical significance of basal compared to post-energy drink exposure individually. A repeated measures ANOVA and Dunnett's multi comparison test were used to compare all the variables together. For salivary cortisol concentrations, a Mann–Whitney test, Kruskal–Wallis test and Dunn's multi-comparison test were employed. A mixed-model ANOVA test was employed to assess the pre- versus post-energy drink consumption values of each variable as the within-subject factor and the energy drink group as the between-subject factor. A two-level analysis (each energy drink vs. control) and a four-level analysis (all energy drinks vs. control) were performed. The data analyzed met all the criteria for the mixed-model ANOVA. To assess the differences between the percentage of change in each variable, a Student's test was employed. A p-value ≤ 0.05 was considered significant for all tests. c. Thirty-minute post-intervention systolic blood pressure increased significantly in the energy drinks A and C groups. The energy drink B group exhibited a diminution of the percentage of

	the 1-h post-intervention systolic blood pressure increase, an increase of 1-h diastolic blood pressure and QTc (corrected QT) shortening. Heart rate showed an increase in the percent change in the A and C groups. Cortisol salivary levels increased in the B group. The anxiety test score decreased in the C group. No other significant findings. Subjects did not report adverse effects during or after intervention time.

Study ID a. Reference b. Health outcome(s)	a. Gray et al. (2017) b. Cardiovascular
Funding a. Funding source(s) b. Reported conflict of interest	a. The study was supported by a Heart Foundation Vanguard Grant (#100601) b. The authors reported no relationships that could be a conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover, two arms b. Double-blind (participants, investigators). QT measurements were performed by blinded cardiologists. c. No method reported d. Participants were recruited from 2014-2016

Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 24 b. 100% c. 24 subjects participated in both arms d. 11 M/13 F e. Australia f. Mean age was 29± 9 years g. Not reported h. Not applicable i. The participants were patients with a familial long QT syndrome (LQTS). 20/24 participants were on beta-blocker therapy j. No information k. Eighty-four patients were eligible for the study of whom 49 were geographically located to present for two 90-min study visits. Participants were approached until the sample size was reached. 67% of the patients had a daily caffeine intake of ≤2 drinks.
Intervention/exposure a. Test substance and control b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Energy drink (ED; Red Bull Sugar-free) and control drink (CD) b. Energy drink (160 mg caffeine + 2000 mg taurine in 500 mL)/control drink (cordial-based, no caffeine or taurine in 500 mL) c. Participants were administered one half the drink volume at zero time and the other half at the 30 min time points. At least one week washout period between ED and CD (or vice versa). Participants were instructed to be caffeine-free (list was provided) for 48 hr and alcohol-free for 24 hr prior to the study. The investigators were blinded to the allocation of the drinks which were prepared in identical opaque bottles by an independent research assistant.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Corrected QT interval (QTc) (ms) (Standard 12-lead electrocardiograms (ECG) and signal averaged ECG (SAECG) and changes in systolic and diastolic blood pressure (mm Hg) (no measurement information). The QT measurements were performed by two cardiologists and corrected using Bazett's formula. b. In a 90 min period after drinking the test substance. Serial (ECG) and blood pressures at every 10 min between t=0 and t =90 min. SAECG at t=0, 30, 60 and 90 min. Bloods (serum caffeine and taurine) at t=0, 30, 60 and 90 min.

Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Yes b. Intention to treat statistical analyses were carried out. Continuous variables were assessed between the two groups using two-sample paired t-tests. Categorical variables were compared using chi-square and Fisher's exact tests. Significance was set at a two-sided p value of 0.05. c. The systolic and diastolic blood pressure significantly increased with ED compared to CD (peak change 7 ± 16 mm Hg vs 1 ± 16 mm Hg, 6% vs 0.8%, and 8±10 vs 2± 9 mmHg, 11 % vs 3 % respectively). These changes correlated with significant increases in serum caffeine (14.6±11.3 vs 0.5±0.1 µmol/L) and serum taurine (737±199 vs -59±22 µmol/L). There were three patients with dangerous QTc prolongation of ≥50 ms following energy drink consumption, all with documented family history of sudden cardiac death

Study ID a. Reference b. Health outcome(s)	a. Shah et al. (2016a) b. Cardiovascular effects
Funding a. Funding source(s) b. Reported conflict of interest	a. Funded by the Clinical Investigations Facility (Travis AFB, California) and University of the Pacific (Stockton, California). b. No information
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with two arms b. Double blinded. Test substance prepared in identical looking bottles when not in the presence of a study team member. c. No information d. No information
Subjects	a. 26 b. No information on dropouts (26 completed the trial).

a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health stauts of participants j. Inclusion/exclusion criteria k. Other	c. 26. All participants included in each arm. d. 20 M/6 F e. USA f. 28±6 year g. 20 white, two black, two Asian, two Hispanic h. Not applicable. i. Healthy subjects. j. Inclusion: healthy volunteers between 18 and 40 years of age with no premorbid conditions Exclusion: Blood pressure assessment and ECG evaluation at baseline used to exclude subjects with previously undiagnosed hypertension or rhythm disturbance (Blood pressure≥140/80 mm Hg; QT interval>440 ms). Use of medication known to interact with study drinks or affecting any hemodynamic or ECG parameters. k. Active duty personnel. Five subjects were caffeine abstainers and 21 subjects were caffeine users.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. 5-Hour ENERGY Lemon Lime flavor (2 fluid ounce (~59 ml) shot) or placebo (24 ml filtered water, 15 ml reconstituted lime juice, 20 ml cherry flavour syrup). According to the manufacturer, 5-Hour ENERGY contains 200 mg of caffeine. b. Twice daily (morning and afternoon) for 7 days during each phase. There is no information on the exact measure of caffeine content in the energy drink, but it is only stated that the 5-Hour ENERGY product contains an energy blend (1870 mg) consisting of taurine, glucuronolactone, malic acid, N-actyl L-tyrosine, L-phenylalanine, caffeine and citicoline. c. Subjects were asked to abstain from all energy drinks for 1 week before randomization and during the study period. Caffeine consumption was not permitted beginning 48 h before end point assessment days (days 1, 7, 15 and 31). Washout period: 7 days

Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Systolic and diastolic blood pressure (mm Hg) using a standard calibrated automated devise with subjects in a upright position (duplicated and averaged) Heart rate (beats/min), PR interval (ms), QRS duration (ms), QT interval (ms) using a 12-lead ECG. QT interval was corrected (QTc) using the Bazzett's formula. b. Baseline, 1, 3 and 5 h on the first and seventh day in the morning
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Performed. Based on estimates from previous studies, to detect a difference of 4-6 mm Hg in systolic blood pressure (assuming SD=8 mm Hg, alpha of 0.05, power of 80%), a sample size of 16-34 subjects would be needed. b. Paired students *t* test comparing the two arms at each time-point (time matched) along with descriptive reporting of data. P≤0.05 was considered statistically significant. Intention to treat analysis was performed and reported. Maximum post-dosing values were compared. c. After a single energy shot: Post-systolic blood pressure significantly elevated at 3 and 5 hrs after energy drink compared to placebo (125±10 vs 119±9 mm Hg and 124±9 vs 118±10 mm Hg, respectively). Post-diastolic blood pressure significantly elevated at 1 and 5 hrs after energy drink compared to placebo (81±8 vs 77±6 mm Hg and 79±7 vs 75±7 mm Hg, respectively). No other significant differences were found either after a single shot or during the whole phase. All subjects consumed the study drinks except for 1 subject who missed the 2 doses on day 6 during their energy drink phase.

Study ID a. Reference b. Health outcome(s)	a. Shah et al. (2016b) b. Cardiovascular effects
Funding a. Funding source(s) b. Reported conflict of interest	a. This study was funded by a University of the Pacific, Eberhardt Research Fellowship grant without any additional role in the study. b. Authors declared no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover, three arms b. Double-blinded (participants, investigators) c. Computer generated code d. Not reported

Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 35 individuals assessed for eligibility, 30 included, 27 completed the study b. 90% of the participants in each arm were included in analysis (one participant in each arm withdrew participation) c. 27 subjects participated in all arms d. 20 M/7 F e. USA f. Mean±SD: 21.6±2.58 years g. 20 were identified as Asian, three as Hispanic, three as Caucasian, and one as Native American. h. Not applicable i. Healthy with no comorbid conditions j. Healthy volunteers between the ages of 18 and 40 were eligible for enrollment. Subjects were excluded if pregnant, had a baseline QTc >440 ms, blood pressure over 140/90 mm Hg, any baseline ECG abnormality or taking daily prescription or over-the-counter medications. k. Participants were recruited from a University campus. Nine patients were regular coffee drinkers (≥1 cup of coffee/day), 16 occasional consumers, and 2 drank no coffee. Two patients reported regular baseline energy drink intake (≥1 can/day), 15 occasionally consumed energy drinks, and 10 reported none or extremely rare usage.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Energy drinks, *Panax ginseng* drink and placebo drink. b. The energy drink: two 16 oz (~473 ml in each) containers of a popular energy drink (commercially obtained; reported to contain 4000 mg of taurine, 800 mg of *P. ginseng*, and an energy blend of L-carnitine, glucose, caffeine (320 mg), guarana, inositol, glucuronolactone, maltodextrin amongst other vitamins and elements). The ginseng drink: 800 mg of *P. ginseng* in 70 ml of cherry syrup, 20 ml of lime juice and 410 ml of carbonated water. The placebo drink: 70 ml of cherry syrup, 20 ml of limejuice and 410 ml of carbonated water. c. All drinks were packaged in identical looking containers prepared within 24 h of administration. There was a 6 day washout period between study phases. To account for circadian rhythm changes, subjects started at approximately the same time on study days. Subjects were required to refrain from consuming any caffeinated products 72 h before each study phase. Blinding and randomization were performed by a non-study investigator who had no interaction with the investigators or subjects other than providing a blinded study drink.

Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Primary endpoints were QTc interval and systolic blood pressure (SBP). Secondary endpoints included QT interval (uncorrected), PR interval, QRS duration, heart rate (HR), and diastolic blood pressure (DBP). Electrocardiographies (ECGs) were performed in triplicate at each time point approximately 60 s apart. The machine calculated HR (beats/min), PR interval (ms), QRS duration (ms), QT interval (ms), and QTc (ms) interval. Blood pressure (mm Hg) was obtained using an automated device. Two measurements were taken 2 min apart. b. All endpoints were assessed at baseline, 1, 2, 3.5, and 5.5 h post initial drink consumption.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Yes b. A two-way analysis of variance (ANOVA) was performed utilizing a significance level of 0.10 to allow post-hoc pair-wise comparisons. The students t-test with Bonferroni correction was utilized with a p-value <0.033 considered statistically significant. When appropriate, intention-to-treat analysis was performed using the last observation carried forward for missing data. A post-dosing maximum regardless of time was also evaluated. Most data were reported as mean ± standard deviation or mean ± standard error. Missing data was imputed for less than 2% of ECG and BP endpoints when subjects did not return timely for scheduled measurements. c. The QTc interval was significantly increased for energy drinks compared to placebo at 2 h post-study drink consumption. The PR interval was significantly different at 1 and 2 h post-study drink consumption. The PR interval was significantly decreased at 1 h comparing the energy drink and the placebo arm. A significant decrease was evident between the energy drink and *P. ginseng* arms at 1 and 2 h. A significant increase in SBP between the energy drink and placebo arms was seen at 2 h post-drink consumption. No other comparisons were significantly different.

Study ID a. Reference b. Health outcome(s)	a. Grasser et al. (2015) b. Cardiovascular, hemodynamic, cerebrovascular

Funding a. Funding source(s) b. Reported conflict of interest	a. Research relating to this study was funded partially by the SNF (SNF number: 122554) b. Declared no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT with a crossover design with two arms b. No participant blinding of test substance. c. No information d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 20 b. No information on dropouts c. 20, all participants included in each arm d. 10 M/10 F e. Switzerland f. 19-29 years (22.1±0.5) g. No information h. Not applicable i. Healthy subjects not taking medications affecting cardiovascular or autonomic regulation. j. No description given k. Daily caffeine intake before start of the study was estimated (based on a questionnaire) to be 1-4 drinks/day.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles,	a. Red Bull (114 mg caffeine, 1420 mg taurine, 84.2 mg glucuronolactone, 39.1 g sucrose and glucose) or tap water b. 355 ml fluid. One dose over a period of 4 minutes. c. All participants fasted for ≥12 hrs and were requested to avoid alcohol or caffeine at least 24 hrs before the test.

minimum/maximum) c. Intervention design	
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Cardiovascular and electrocardiographic recordings using a Task Force Monitor. Cardiac interval, systolic blood pressure (BP) (mm Hg), diastolic BP (mm Hg), cerebral blood flow velocity (cm/s), and stroke volume (mL) were measured. Heart rate (beats/min), cardiac output (L/min) and mean BP (mm Hg) were calculated Cerebral blood flow velocity using transcranial Doppler ultrasonography. Beat-to-beat values of systolic, diastolic, and mean velocity were recorded and merged real time with the Task Force Monitor to allow synchronous cardiovascular and cerebrovascular recordings Cognitive effects: Compromising a total of 60 unique calculations Rating of perceived stress using a standard 5-point Likert scale. b. Cardiovascular effects: A baseline recording was made after attaining cardiovascular stability before start of each experiment and 80 minutes after drinking the test substance. Mental arithmetic task for 5 minutes followed by 5 minutes recovery period: after the cardiovascular recordings 80 min after drinking the test substance. Five seconds interval between each calculation. Beat-to-beat values of cardiac interval, systolic blood pressure (BP), diastolic BP, cerebral blood flow velocity, and stroke volume were averaged over the 20 minutes predrink baseline period and minute by minute starting 5 min before (postdrink baseline), during (mental task for 5 min) and after the mental stress (recovery for 5 min)
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. Two-way ANOVA for repeated measures with time and treatment as within-subject factors. Effects of each drink over time were analysed by comparing values at each time point of the mental task and recovery period with the average postdrink baseline values recorded during the 5 min immediately before the mental task using repeated measures analysis of variance with Dunnett's multiple comparison post hoc testing. Changes between postdrink baseline, mental task, and recovery were evaluated using

	repeated measures analysis of variance with Newman-Keuls post hoc testing. A Wilcoxon matched pairs test was used to elicit differences in mistakes and stress perception in response to the drink. Level of statistical significance was set at $p<0.05$. c. Red Bull elevated significantly systolic and diastolic BP, heart rate, cardiac output, double product, cerebrovascular resistance, and decreased cerebral blood low velocity flow over the postdrink period. In comparison, water had no significant effects on systolic and diastolic blood pressures or heart rate. Mental stress 80 min after ingestion: Red Bull decreased total peripheral resistance (-1.58 mm Hg min/L) For the other test parameters, Red Bull or water invoked similar responses. Total peripheral resistance decreased similarly with Red Bull (-1.58 mm Hg min/L) and water (-1.73 mm Hg min/L) in response to mental stress. Ingestion of Red Bull and water did not influence stroke volume in response to mental stress. Overall, the combination of Red Bull ingestion and mental stress application 80 minutes later caused total increases in systolic BP of +10.2 mm Hg, diastolic BP of +7.3 mm Hg, heart rate +19.7 beats/min, cardiac output of +1.6 L/min, double product of +3,137 mm Hg beats/min, and cerebrovascular resistance index of +0.32 mm Hg cm/s, whereas a decrease was found for cerebral blood flow velocity of -7.1 cm/s and total peripheral resistance of -2.3 mm Hg min/L Cardiac output (+0.01 vs +0.37 L/min) and stroke volume (+0.5 vs +5.7 ml) were significantly higher in the 5 minute recovery period compared with postdrink values before the mental task after ingestion of water, whereas ingestion of Red Bull increased stroke volume only (-0.4 vs +2.9 ml). Moreover, water ingestion significantly decreased total peripheral resistance (+0.14 vs -0.59 mm Hg min/L) in the recovery period compared with postdrink values before the mental task. No significant differences between the drinks were found for a total count of mistakes and for stress perception during the mental task.

Study ID a. Reference b. Health outcome(s)	a. Lara et al. (2015) b. Cardiovascular, psychobehavioural and muscular effects
Funding a. Funding source(s) b. Reported conflict of interest	a. No funding. The energy drinks were provided by Fure® (ProEnergetics, Spain) b. No information.
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with two arms b. Double-blind. No information on blinding of examiners/assessors. c. No information d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. Fourteen volunteered to participate, all completed the study b. 100% c. Fourteen participants in both study arms d. 14 M e. Spain f. 25.3 (SD 1.1) yr g. No information h. No explicit information regarding confounding. i. Competitive sprint swimmers j. Inclusion criteria: obtained the qualifying standards for the 2013 National Spanish Championship in 50 m swimming competitions, had swimming experience of at least 5 yr and had trained at least 6 d/wk during the previous year. Exclusion: no explicit information k. Participants were light caffeine consumers (less than one can of soda or energy drink per day), had no previous history of cardiopulmonary diseases and had no musculoskeletal injuries in the previous 3 months.
Intervention/exposure	a. Powdered, caffeine-containing energy drink in water (Fure®, ProEnergetics) and placebo energy drink.

a. Test substance and control b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	b. Energy drink powder dissolved in 250 ml tap water individually made to provide the dose per bodyweight (3 mg/kg bw). The placebo energy drink contained no caffeine. Both intervention beverages contained in addition to the caffeine equal amounts of taurine (18.7 mg/kg), sodium bicarbonate (4.7 mg/kg), L-carnitine (1.9 mg/kg), and carbohydrate (6.6 mg/kg), and had the same taste. c. The beverages were given in coded, opaque bottles. Investigators supervised that participants drank only from their own bottle. Washout period: 7 d. Participants were encouraged to refrain from all dietary sources of caffeine, alcohol or stimulants for the duration of the study. Before a period of 24 h of each experimental trial, the participants mimicked their habitual routines before competition: refrained from strenuous exercise and adopted a precompetition food and fluid regimen. On the day of the experimental trials, they had breakfast and rested 4h prior to arrival of the study site. Beverages were ingested 60 min before onset of experimental trials (physical exercise). Food and fluid diaries were obtained and analysed to ensure compliance. The swimmers were encouraged to avoid medications or nutritional supplements for the duration of the study.
endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Maximum heart rate (beats/min) measured by a heart rate monitor. Side effects (headache, abdominal/gut discomfort, muscle soreness, tachycardia/heart palpitations, insomnia, increased anxiety) were surveyed by use of a yes/no scale. b. Heart rate was measured during a swim ergometer test approximately 1 h post-intervention. The survey (see a)) was to be filled out approximately 24 h after the intervention and the following exercise.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. Normality was tested for each variable with the Shapiro–Wilk test. All the variables included was normally distributed (P>0·05). Differences between the caffeinated v. placebo energy drink in the variables obtained once in each experimental trial (e.g. subjective feelings) were determined using paired t tests. Differences between the caffeinated v. placebo energy drink in the variables obtained twice or more in each experimental trial (e.g. heart rate) were determined by two-way ANOVA (beverage × time) with repeated measures. After a significant F test (Geisser–Greenhouse correction for the assumption of sphericity), differences between means were identified using Tukey's HSD post hoc. Differences on side effects after beverage intake was analysed using the McNemar test. The results are presented as mean ± SD (n =

	14), P<0.05. c. There were no significant differences between energy drink with and without caffeine with respect to maximum heart rate or self-reported adverse effects.

Study ID a. Reference b. Health outcome(s)	a. Svatikova et al. (2015) b. Cardiovascular and metabolic effects
Funding a. Funding source(s) b. Reported conflict of interest	a. The research was supported by grant M01-RR00585 from The Mayo Foundation and grant UL1 TR000135 from the National Center for Advancing Translational Sciences, National Institutes of Health. b. Authors declared no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with two arms b. Double-blind, participants and study investigators. c. Randomisation was computer-generated using a randomised block design, with a block size of six. Experimental session was conducted in random order. d. Data were collected at the Mayo Clinical Research Unit between August and November 2013

Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. Twenty-five; one person did not attend one study day b. 100% in one arm; 96% in the other c. Twenty-five in one arm, twenty-four in the other d. 14 M/11 F e. USA f. Mean age: 29 years (95% CI, 26-31 years) g. No information h. No information i. Healthy, free of known disease. j. Inclusion: Adults 18 years of age and older, healthy subjects without known cardiovascular disease and thyroid disease, subjects who are on no medications (except oral contraceptive pill), nonsmokers, no prior history of caffeine sensitivity or allergy. Exclusion: Subjects with known cardiovascular or thyroid disease, subjects currently taking medications other than oral contraceptive pill, smokers, prior history of caffeine sensitivity or allergy, pregnancy k. Participants gave a medical history interview and answered three questionnaires (on cardiovascular health, diet and caffeine intake) prior to intervention, and had a pregnancy test taken.
Intervention/exposure a. Test substance and control b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Rockstar energy drink and placebo beverage (HyVee fruit punch) as control b. The 480 ml Rockstar energy drink contained 240 mg caffeine, 2000 mg taurine, extracts of guarana seed, ginseng root, and milk thistle (260 cal; 0 g fat; 62 g carbohydrate, 0 g protein). The 480 ml placebo beverage lacked caffeine and the other above-mentioned ingredients (240 cal; 0 g fat; 62 g carbohydrate, 2 g protein). Serum levels of caffeine were measured (µg/mL). Caffeine levels remained unchanged after the placebo drink. c. Washout-period: minimum 24 h, maximum 2 wk. Participants were fasting and abstained from caffeine and alcohol 24 hrs prior to each study day. Intervention beverages were given immediately after baseline recordings. The beverage was consumed within 5 min. Blinding was maintained until analysis of data. The energy drink and control beverage (fruit punch) were similar in taste, texture and colour and were given in identical cups. Physical, mental and cold stress tests were performed following intake of intervention beverage.

endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Serum levels of plasma glucose (mg/dL) and norepinephrine (pg/mL) (blood samples; peripheral IV catheter; supine rest); blood pressure (mm Hg) and heart rate (beats/min) (blood pressure cuff) b. Blood test, blood pressure and heart rate were obtained at baseline and 30 min after drink ingestion. Blood pressure and heart rate were taken at regular intervals.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Yes b. Results are reported as means and 95% confidence intervals. A 2 × 2 mixed-model analysis of variance was applied to continuous variables. Changes were compared between groups using a 2-sample t test. Two-sided statistical significance was defined as $P < 0.05$. c. Caffeine levels increased significantly after energy drink consumption. The mean norepinephrine level increased significantly more after consumption of the energy drink than after placebo (change rate: 73.6% [95% CI, 53.9%-93.2%] vs 30.9% [95% CI, 11.3%-50.6%], respectively. When participants were at rest: Consumption of the energy drink elicited a 6.2%(95% CI, 4.5% to 7.8%) increase in systolic blood pressure (from 108.4 mm Hg to 115.0 mm Hg) vs a 3.1% (95% CI, 1.5% to 4.7%) increase with the placebo drink (from 108.3 mm Hg to 111.6 mm Hg). Diastolic blood pressure increased by 6.8% (95% CI, 4.1% to 9.6%) vs 0% (95% CI, −2.8% to 2.8%) with placebo. Mean blood pressure increased after consumption of the energy drink by 6.4% (95% CI, 4.3% to 8.6%) from 74.2 mm Hg to 78.9 mm Hg vs by 1.0% (95%CI, −1.2% to 3.2%) with the placebo drink (from 74.9 mm Hg to 75.4 mm Hg) (all results: $p<0.05$).

Study ID a. Reference b. Health outcome(s)	a. Grasser et al. (2014) b. Cardiovascular, hemodynamic, cerebrovascular effects and microvascular endothelial function

Funding a. Funding source(s) b. Reported conflict of interest	a. Research related to this paper was funded in part by the Swiss National Science Foundation (Project 3200B0122554 to JPM) b. The study authors declare no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover, two arms b. Non-blinded ingestion c. Randomization was performed using a random sequence generator where the session order was determined for 25 test subjects before the study. Test subjects were not allowed to know the order of their sessions until they had their first drink. d. Not reported
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 25 participants b. No information on dropouts c. 25 d. 13 M/12 F e. Switzerland f. 20–31 years (mean 22.5 ± 0.6 years) g. Not reported h. Not applicable i. Healthy j. Exclusion criteria included those with a BMI greater than 30 kg m^{-2}, competition athletes and individuals with a daily exercise workload exceeding 60 min per day. k. None of the subjects had any diseases or were taking any medication affecting cardiovascular or autonomic regulation and none reported caffeine intake in excess of 150 mg daily from food and beverages. Based on a questionnaire, 15 subjects were low caffeine users with an estimated daily intake of approximately 60 mg, while 10 subjects were caffeine naïve. The questionnaire included coffee and energy drink consumption. Participants were non-obese. All were recruited from a local university student population and their friends.
Intervention/exposure a. Test substance and control b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles,	a. Energy drink, and tap water as control b. Energy drink (Red Bull, RB; degased); 355 mL, containing caffeine (114 mg), taurine (1420 mg), glucuronolactone (84.2 mg), sucrose and glucose (39.1 g). Tap water (355 mL) at room temperature. c. Two experimental sessions on separate days, each session separated at least by 2 days. All participants were studied in the morning after an overnight (12 h) fast, and they were

minimum/maximum) c. Intervention design	requested to avoid alcohol or caffeine for at least 24 h prior to the test. All experiments took place in a quiet, temperature-controlled (20–22 °C) laboratory and started between 08.00 and 09.00 a.m. Intake time: 4 min. Participants were requested to avoid alcohol or caffeine for at least 24 h prior to the test.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Beat-to-beat blood pressure (beats/min) measurements, impedance cardiography and transcranial Doppler measurements, and endothelial function test (AU). Prior to cardiovascular monitoring subjects were asked to empty their bladders if necessary and to sit in a comfortable armchair. Cardiovascular recordings were performed using a Task Force Monitor (TFM). Continuous blood pressure (BP) (mm Hg) was monitored using the Penaz principle from either the index or middle finger of the right hand and was calibrated to oscillometric brachial BP measurements on the contralateral arm. Impedance cardiography measurements, in which the changes in thoracic impedance were converted to reflect changes in thoracic fluid content/volume over time, were performed. For transcranial Doppler measurements, cerebral blood flow velocity (cm s^{-1}) was measured using transcranial Doppler ultrasonography. Beat-to-beat values of systolic, diastolic and mean velocity were recorded and merged real-time with the TFM. Expiratory air was sampled via a nasal cannula, and end-tidal CO_2 (mm Hg) measured by infrared absorption (Datex)). Microvascular endothelial function was assessed noninvasively in the finger skin microcirculation by a combination of iontophoresis and laser Doppler flowmetry using a standard protocol. b. Beat-to-beat blood pressure (beats/min) measurements, impedance cardiography and transcranial Doppler measurements were performed for at least 20 min baseline and for 2 h post-intervention. Following a variable period for reaching cardiovascular and metabolic stability (at least 30 min), the microvascular function test was performed (about 30 min). A baseline recording was made for 20 min, and the test was repeated after 2 h of post-drink cardiovascular recording.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No b. Statistical analysis was performed by two-way ANOVA for repeated measures with time and treatment (drink type) as within-subject factors. Where significant differences were found, the effects of each drink over time were analysed by comparing values at each timepoint over the post-drink period with the basal values recorded during the 20 min immediately before drinking using one-way ANOVA with Dunnett's multiple comparison test or the Friedman test with Dunn's post hoc testing. Variables were tested for normality using the D'Agostino &

	Pearson omnibus normality test. A paired t test or Wilcoxon matched pairs test was used to compare the post drink effect between the drinks. A Friedman test with Dunn's multiple comparison post hoc analysis was used to compare vasodilatory responses before and after drug administration. All reported p values are two-sided. For all tests, significance was set at $p \leq 0.05$. All values were reported as mean ± SE. c. Red Bull (RB) consumption led to: - Increased systolic and diastolic blood pressure (SBP, DBP): SBP peak was 5.2 ± 1.0 mm Hg at around 70 min; DBP peak was 6.1 ± 1.1 mm Hg at around 90 min. Compared to the water load the RB drink resulted in significantly higher values for SBP (3.3 ± 1.0 vs. 0.3 ± 0.7 mm Hg) and DBP (4.1 ± 0.7 vs. 1.3 ± 0.4 mm Hg) when values were averaged over 120 min post-drink. -Increased mean arterial blood pressure (MAP) compared to water between 40 and 120 min post-intervention (peak at about 90 min (5.7 ± 1.0 mm Hg)). -Increased cardiac output (CO). MAP and CO responses to RB drink were significantly higher with RB than water, namely 3.8 ± 0.7 vs. 1.0 ± 0.5 mm Hg for MAP and 0.20 ± 0.05 vs. 0.04 ± 0.03 L min^{-1} for CO. - Increased cerebrovascular resistance and breathing frequency. - Decreased cerebral blood flow velocity ($p<0.005$) and end-tidal carbon dioxide. - Increased response to acetylcholine-mediated vasodilation (66 ± 10 vs. 117 ± 18 AU) in comparison with the response to the water load. -The change in heart rate during the measurement time was significantly higher for RB than water. -Increased double product (reflecting myocardial load) (391 ± 94 vs. -75 ± 65 mm Hg beats min^{-1}) compared to water, with a peak around 90 min (737 ± 130 mm Hg beats min^{-1}). -Declined cerebral blood flow velocity (CBFV) and a gradually increased cerebrovascular resistance (CVRI). Immediately after ingestion of RB, the CBFV started to decline with a negative peak (-8.2 ± 1.0 cm s^{-1}) around 70 min. CVRI rose gradually above baseline levels, peaking around 90 min (0.22 ± 0.03 mmHg s cm^{-1}). Ingestion of water also decreased CBFV and increased CVRI significantly over time. When values were averaged over 120 min post-drink for CBFV: -7.4 ± 0.9 vs. -2.2 ± 0.6 cm s-1; and CVRI: 0.16 ± 0.02 vs. 0.05 ± 0.02 mm

	Hg s cm^{-1}. -The data on changes in BF and end-tidal CO_2 ($etCO_2$) showed that after an initial stable period for 20 min, $etCO_2$ started to decline and BF to increase in response to RB (but not with water), with a peak for $etCO_2$ around 50 min (-1.4 ± 0.3 mm Hg) and for BF around 30 min (1.8 ± 0.4 breaths min^{-1}). Subsequently, whereas $etCO_2$ in response to RB returned slowly toward the baseline levels, BF remained elevated above baseline levels even at the end of the test, i.e., at 120 min post-drink. Average values over the post-drink study time indicate significant differences with RB compared to water both for $etCO_2$ (-0.7 ± 0.2 vs. 0.4 ± 0.2 mm Hg) and BF (1.28 ± 0.25 vs. -0.24 ± 0.23 breaths min^{-1}) No other comparisons were significantly different.

Study ID a. Reference b. Health outcome(s)	a. Lara et al. (2014) b. Cardiovascular, psychobehavioural
Funding a. Funding source(s) b. Reported conflict of interest	a. The study was supported by a grant from Camilo Jose Cela University b. Declared no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with two arms b. Double-blinded. Test solutions prepared in opaque plastic bottles given an alphanumeric code assigned to each trial to blind participants and investigators. c. No information d. No information

Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 22 recruited. Two drop outs due to injury. Data from two goalkeepers not included in the analysis. b. 90% c. 18 in each crossover arm d. 18 F e. Spain f. 21±2 years g. No information h. No information i. No information j. Not stated. Soccer players from the same team. k. All participants were light caffeine consumers.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Energy drink with or without 3 mg/ kg bw caffeine b. Caffeine drink: Commercially available powdered caffeine-containing energy drink (Fure®, ProEnergetics) dissolved in 250 ml tap water. Placebo: Identical drink with no caffeine provided by the energy drink manufacturer. No information on analysis of caffeine contents, but the two powders are produced by the same manufacturer. Caffeine content was 173 ±23 mg. The energy drink formulae included taurine (18.7 mg/kg), sodium bicarbonate (4.7 mg/kg) and of L-carnitine (1.9 mg/kg), and these substances were ingested in identical proportions in the two experimental trials. c. One week washout-period. Encouraged to refrain from all dietary sources of caffeine (coffee, cola drinks, chocolate, etc.) and alcohol 48 hrs before testing. Adopted a similar diet and fluid intake regime the day before each trial. At the trial day, participants were encouraged to have a pre-competition meal 3 h before start of the trial. No strenuous exercise the day before each trial. Test-drink were distributed before start of the exercise. Before starting a standardized warm-up followed by a performance test (maximal countermovement jump test and a 7x30 min maximal running speed test with 30 s of active recovery between repetitions) just 60 min

	after the end of beverage intake. 15 min after soccer-specific testing, players completed a 2x40 min simulated soccer game. In each team, a similar number of field players received the energy drink or placebo. Players could drink water *ad libitum* from individually labelled bottles.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Participants wore a GPS/HR device and a heart rate belt attached to their chest to measure maximal running speed and distance covered at sprint velocity during the stimulated match. Body weight measured (nude) Collection of urine samples Water-intake during the trial Sweat rate estimated from body mass change, total fluid intake and experimental trial duration. Questionnaire on their sensation of power, endurance and perceived exertion during the soccer game. Survey on sleep quality, nervousness, gastrointestinal problems and other discomforts (yes/no scale) previously used to assess side effects derived from energy drink ingestion. b. Urine samples: before start, 30-60 minutes after the exercise Bodyweight: before and after each trial Questionnaire: just after the game Survey: the following morning
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Not performed b. Two-way ANOVA (beverage x repetition) with repeated measures. After a significant *F* test, differences between means were identified using Bonferroni adjustment. Paired *t* tests used for several outcomes. Differences on side effects analysed using the McNemar test. Significance level set at $p<0.05$. c. Results related to possible adverse effects are included in the data extraction Compared to placebo caffeine: Maximal and average heart rate during the game: No significant differences A tendency that caffeine increased insomnia ($p=0.09$). No statistically significant differences for the other reported side effects

Study ID a. Reference b. Health outcome(s)	a. Peacock et al. (2014) b. Cardiovascular, psychological and muscular effects. All effects were self-reported
Funding a. Funding source(s) b. Reported conflict of interest	a. Funding for this study was provided by the Alcohol, Tobacco & other Drug Council (Tas) Inc. Placebo samples were provided by Red Bull GmbH, Austria. These parties had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. b. Not reported by the authors
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover, 4 arms b. Single-blinded. Data collectors, participants, and data analysts were blind to energy drink (ED) administration; only participants and data analysts were blind to alcohol administration c. Not reported. d. Not reported
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria	a. 28 b. Two participants had missing Profile of Mood States (POMS) and Somatic Symptom Scale (SSS) data (N = 26) and one participant had missing Beverage Rating Scale (BRS) data (N = 27) due to technical malfunction. c. All subjects participated in each arm d. 14 M/14 F e. Australia f. Mean ± SD: 19.5 ± 1.8, range 18-25 years g. Not reported h. Not applicable i. Not reported j. Volunteers who scored 16 or higher on the Alcohol Use Disorders Identification Test were excluded. k. The sample consisted of participants that self-reported no: (i) significant physical or psychiatric

k. Other	history, (ii) current pregnancy or lactation and (iii) regular current tobacco, medication, or illicit drug use. Participants were informed they may receive alcohol (maximum of six standard alcoholic drinks) and ED (maximum of three standard 250 mL EDs). Recruitment occurred via public advertisements at the University of Tasmania. Participants were reimbursed. Participants consisted of regular caffeine, alcohol, and energy drink (ED) consumers.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Red Bull energy drink, alcohol, energy drink + alcohol, placebo b. Energy drink (3.57 mL/kg bw), alcohol (Smirnoff Red Label® vodka (0.5 g/kg bw), energy drink (3.57 mL/kg bw) + alcohol (0.5 g/kg bw), placebo (placebo alcohol dose was achieved by floating 5 ml vodka on each beverage portion, with a light alcohol mist sprayed on the inner container; placebo ED dose was 3.57 mL/kg Red Bull® minus caffeine, taurine, glucuronolactone, inositol, and B vitamin complex content; sugar content was identical for active and placebo beverages (27 g/250 mL)). The alcohol dose was decreased to 85% for females. c. Participants attended a 90-min familiarisation session where they completed screening measures, were weighed for substance administration purposes, and familiarised with the experimental procedure. Participants then attended four 180-min experimental sessions conducted between 09.30 and 19.00 and separated by a minimum of two and maximum of 10 days. Participants were required to fast for 4 h (excluding consumption of a standard breakfast bar 90 min prior to session commencement) and abstain from caffeine for 8 h, from alcohol and prescription medication for 24 h prior to each session, and from illicit drugs for the duration of participation. Following completion of baseline POMS and SSS measures, participants were administered the beverage in two portions served in opaque lidded cups, consuming each portion within a 5-min period. At the conclusion of the session, participants received a detoxification meal and remained at leisure in the laboratory until recording two BrAC measurements of .030% or less over 15 min
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Participants independently completed the POMS (perceived current psychological state) and an SSS (20-100 mm visual analogue scale). The POMS was used to assess perceived current psychological state. Likert scale was used to assess current mood (0-4). The SSS was used to assess current perceived physiological state. BRS was used to assess perceived alcohol and ED intake and confirm successful placebo manipulation. Breath alcohol concentrate (BrAC)(%) was investigated using an Alcolizer HH-2 unit. All self-report data were collected via computerised survey software to minimise experimenter bias. Electroencephalographic data were collected. b. At baseline, 30 and 125 min after beverage administration. Post-drink administration of the

	POMS and SSS occurred 30 min and 125 min after initiation of beverage consumption, with the BRS administered at the later time point. BrAC was also tested at these points. Participants completed several cognitive tasks, and ECG were collected, in the interval between the post-drink assessments.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Not reported b. Psychological outcome: Two participants had missing POMS and SSS data (N = 26) and one participant had missing BRS data (N = 27) due to technical malfunction. POMS subscale and Total Mood Disturbance scores and SSS item ratings were calculated as the change from baseline at each time point (30 and 125 min post-beverage administration) and analysed using 2 (Alcohol: Active, Placebo) x 2 (ED: Active, Placebo) ANOVAs, with Bonferroni-adjusted follow-up paired sample t-tests. Effect size was calculated using Hedges' g. To enhance clarity, effects of moderate magnitude (g ≥0.50) are discussed where p < 0.100. c. -A significant Alcohol x ED interaction was observed at 30 min for muscular tension, F(1,25) = 8.052, with moderate magnitude decreases in muscular tension ratings in the ED and alcohol conditions relative to the placebo condition. - A significantly lower tension-anxiety score was found for ED F(1,25) = 5.649, p = 0.025, g= 0.40, relative to placebo ED at 125 min. -A trend towards a significant alcohol x ED interaction was shown at 30 min o for heart palpitation ratings, F(1,25) = 3.453, p = .075; follow-up comparisons showed a moderate magnitude decrease in ratings which trended towards significance in the alcohol relative to AmED (p = .100, g = 0.50) and placebo (p = .080, g = 0.51) conditions. No other significant findings related to energy drink or energy drink + alcohol were observed.

Study ID a. Reference b. Health outcome(s)	a. Phan and Shah (2014) b. Cardiovascular and psychobehavioural effects

Funding a. Funding source(s) b. Reported conflict of interest	a. University of the Pacific Internal Seed Grant b. None reported
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with two arms b. Double-blind (indirectly reported that participants were blinded, no further information on examiners/assessors). c. No information d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. Ten participants included and completed. b. 100% c. Ten participants in each study arm d. 2 M/8 F e. USA f. Age range: 18-40 yr and mean age: 23±1.83 yr g. Asian: 8; Caucasian: 1; African American: 1 h. No explicit information on confounding. i. Healthy (not confirmed), non-smokers j. Inclusion: not specified. Exclusion: Peripheral blood pressures of 140/80 mm Hg or greater, presence of comorbid conditions, use of any prescription or over-the counter drugs, self-reported allergy to the energy shot or any of its components, or participation in previous energy-drink studies conducted at the same university centre, pregnancy or planning to become pregnant. k. Nine participants were self-reported coffee abstainers (caffeine-naïve), and one participant reported drinking three cups of coffee/day.

Intervention/exposure a. Test substance and control b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Caffeinated and noncaffeinated energy shot (both «5-hr Energy»). b. The caffeinated energy shot contained 215 mg caffeine and the noncaffeinated contained 6 mg caffeine. Beverage liquid amount was not reported. Caffeine content was according to a web-page video from Consumer Reports, 2012. c. Washout-period: 6 d minimum. Outer packaging of intervention product was removed.
Endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Peripheral systolic blood pressure (SBP), peripheral diastolic blood pressure (DBP), peripheral pressure (PP), central SBP, DBP and PP (all mm Hg), heart rate (Beats/min), augmentation pressure, augmentation index (Aix) (%), P1 height (mm Hg), PP amplification ratio, ejection duration (ED) (ms), and the Buckberg Subendocardial Viability Ratio (SEVR) (%). Peripheral blood pressure was measured using a standard automated blood pressure device. Central hemodynamic parameters were assessed with the SphygmoCor PWA system (a validated system that uses applanation tonometry to noninvasively translate a radial pressure waveform taken at the wrist to an aortic pressure waveform). After a 10-minute seated resting period, two peripheral blood pressure measurements separated by 2 minutes were averaged and imputed into the PWA software followed by applanation tonometry for collection of central hemodynamic parameters. Each reading is associated with an operator index score, which assesses the quality of the recordings. Recordings were conducted multiple times, and scores with the highest operator index were selected for data analysis. Aix, augmentation pressure, and ejection duration were corrected by a heart rate of 75 beats/min. b. All endpoints were measured at baseline and at 1 and 3 hr after consuming the energy shot.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No b. A paired student's t test between the two study arms was performed for all continuous data, $p \leq 0.05$. Change from baseline was calculated and compared between the two intervention arms. Data are expressed as mean ± standard deviation. An intention-to treat analysis was performed using the last observation carried forward methodology for missing data. c. Peripheral PP and P1 height at baseline were significantly greater in the noncaffeinated arm than in the caffeinated arm, and baseline SEVR was significantly greater in the caffeinated arm. Peripheral SBP increased significantly with the caffeinated energy shot compared with the noncaffeinated (change from baseline: 8.30 ± 4.19 mm Hg and -0.20±5.55, respectively)

	at 3 hrs. Central SBP increased significantly with the caffeinated energy shot compared with the noncaffeinated (change from baseline: 8.00 ± 4.03 mm Hg and 1.50 ± 6.57, respectively) at 3 hrs. Peripheral and central PP were significantly higher with the caffeinated energy shot compared with noncaffeinated 1 hr after consumption. At 3 hrs after caffeinated energy shot consumption, peripheral PP was significantly higher with central PP trending similarly (p=0.061). The P1 height was significantly higher with the caffeinated shot compared with the noncaffeinated shot at both 1 and 3 hrs (p<0.05). Two subjects felt palpitations and another one experienced dizziness with the caffeinated energy shot. One subject had a headache after consumption of the noncaffeinated energy shot. There were no other significant effects.

Study ID a. Reference b. Health outcome(s)	a. Salinero et al. (2014) b. Psychobehavioural, gastrointestinal and muscular effects
Funding a. Funding source(s) b. Reported conflict of interest	a. The study received no specific grant from any funding agency b. Authors declared no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover with two arms b. Double-blinded, both subjects and investigators. c. Each participant was assigned with a number (alphanumeric code) by an experimenter who did not take part in the experiment. Odd numbers received the caffeinated energy drink and placebo beverage order while even numbers received the placebo beverage and caffeinated energy drink order. d. No information

Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 98 recruited (athletes from different sport disciplines). 8 drop outs. b. 92% c. 90 subjects participated in each arm d. 53 M/37 F e. Spain f. f.: M: 25.0±6.2; F: 23.2±4.5 (years, mean±SD) g. No information h. No information i. Athletes, non-smoking, not under medical treatment j. No information k. All subjects were experienced and trained athletes and competed at the national or regional level with more than 8 years of training experience, and over 5 h of weekly training. All subjects were light caffeine consumers (<60 mg/d, approximately 1 cup of coffee).
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Beverages: Caffeinated energy drink+physical activity or non-caffeinated energy drink+physical activity b. A single dose, caffeinated energy drink: 3 mg/kg bw. The two experimental drinks had a similar taste and appearance and they only differed in the amount of caffeine they contained. The energy drinks also contained taurine (18.7 mg/kg), sodium bicarbonate (4.7 mg/kg), L-carnitine (1.9 mg/kg) and maltodextrin (6.6 mg/kg). c. Crossover design, with one week wash-out period: subjects ingested either a powdered caffeine-containing energy drink (3 mg/kg bw) (Fure®; Pro-Energetics) dissolved in 250 ml of tap water or the same amount of energy drink but with no caffeine content (placebo; 0 mg/kg). Beverages were provided in opaque plastic bottles to avoid identification. An alphanumeric code was assigned to each trial to blind participants and investigators to the beverage tested. The experimental beverages were ingested 60 min before the onset of the experimental trials to allow for complete caffeine absorption. Subjects completed a specific sport session, including a standardised warm-up and a simulated competition.

	Both experimental trials were performed at the same time of the day to avoid the effects of circadian rhythms in the studied variables. The day before, participants refrained from strenuous exercise and adopted a similar diet and fluid intake regimen. Participants were encouraged to withdraw from all dietary sources of caffeine (coffee, cola drinks, chocolate, etc.) and alcohol 48 h before testing. In addition, participants were instructed to have a light meal at least 2 h before the onset of the experimental trials.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Self-reported psycho-behavioural effects: headache and activeness, sleep quality including insomnia, fatigue and nervousness. Self-reported gastrointestinal and muscular effects (muscular pain). b. The participants were provided with a survey to be filled out before going to sleep about side-effects they had perceived in the hrs after the drink ingestion on a yes/no scale. In the following morning after the ingestion of the energy drinks, participants were asked about sleep quality (e.g. insomnia) on a yes/no scale and about perceived fatigue on a 1- to 10-point scale. Before going to sleep on the day of testing and in the morning after (sleep quality, fatigue).
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Yes, difference in self-reported nervousness and gastrointestinal side effects. b. Differences in the 1- to 10-point scale were analysed using the Wilcoxon signed-rank test. Effect size was calculated (Cohen's d) for each item. Results of qualitative data (e.g. side effects) are presented as percentages. Differences in side effects after beverage intake was analysed using the McNemar test. Sex influences on the tested variables were verified by using a general linear model and a two-way repeated-measures ANOVA (beverage × sex). The criterion for statistical significance in all these tests was set at P=0.05. Participants that did not complete the study were left out of the statistical analysis. c. The caffeinated energy drink produced a higher prevalence of side effects such as insomnia (31.2 v. 10.4 %; P=0.001), nervousness (13.2 v. 0%; P=0.002) and activeness (16.9 v. 3.9%; P=0·007) than the non-caffeinated energy drink.

Study ID a. Reference b. Health outcome(s)	a. Kurtz et al. (2013) b. Cardiovascular, psycobehavioral effects
Funding a. Funding source(s) b. Reported conflict of interest	a. University of the Pacific Internal Seed Grant b. No information
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover with two arms b. Double-blinded c. Automated computer-generated code was used to randomize the order. d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. N=20, no drop-outs (from University campus) b. 100% c. 20 subjects participated in each arm d. 10 M/10 F e. USA f. 23.30±2.67 yr g. Eighteen were Asian, two were Caucasian h. No information i. Healthy j. Inclusion criteria: between the ages of 18 and 40 years, healthy, had no comorbid conditions, and willing to sign the informed consent document. Exclusion criteria: blood pressure >140/90 mm Hg, current use of prescription or over-the-counter products, allergy to 5-hr Energy products, pregnancy, and use of any energy drink or energy shot within the previous 7 days. k. Previous use of caffeinated beverages: six subjects reported 0 cups/day, five subjects reported <1 cup/day, 9 reported >1 cup/day. No subjects were smokers.

Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Caffeinated energy shot or non-caffeinated energy shot b. 5-hr caffeinated energy shot (the caffeine concentration was reported to be anywhere between 138– 215 mg/1.9–fluid ounce bottle) or 5-hr non-caffeinated energy shot (6 mg of caffeine). The non-caffeinated energy shot did not contain niacin or citicoline which was present in the caffeinated energy shot. Volume: 1.93 ounces (approximately 57 ml). c. Participants were randomized to receive caffeinated or decaffeinated energy shot. There was a minimum 6 day washout period and then the subjects received the alternate energy shot. Participants were instructed not to consume any caffeinated products during the 48 hrs before assessment days and no energy drinks or shots throughout the study period. During the washout period, subjects could proceed with normal daily activities without any restrictions. Subjects were asked to guess which version they had received based on taste. All energy shots were obtained through a random vendor by using Amazon.com, and the outer plastic packaging was removed to yield a matching blinded product.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Measured parameters: Heart rate (beats per min), systolic and diastolic blood pressures (mm Hg), and self-reported adverse effects. Blood pressure and heart rate were measured by using a calibrated, automated blood pressure machine. For blood pressure the average of two measurements was used. Adverse effects were evaluated at each visit by verbally asking subjects if they were experiencing any unpleasant feelings or symptoms. b. At baseline and 1, 3, and 5 hrs after consumption of the energy shot.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Yes, based on a change of 4±4 mm Hg (mean±SD) in systolic blood pressure. b. Intent-to-treat analysis. Analysis of variance with Bonferroni post hoc t test for pairwise comparisons. The maximum effect regardless of time was also compared with baseline by using a paired Student t test. All data are reported as mean±standard deviation or mean±standard error. c. Mean changes in systolic blood pressure between the caffeinated arm and the decaffeinated arm at the 1- and 3-hr time points were significantly increased compared with baseline (mean±SD 6.08±7.71 mm Hg at 1 hr [p=0.001] vs 3.33±6.99 mm Hg at 3 hrs [p=0.042]). Similarly, mean diastolic blood pressure changes between the caffeinated arm and the decaffeinated arm were significantly increased at the 1- and 3- hr time points compared with

	baseline (mean±SD 5.18±8.38 mm Hg at 1 hr [p=0.007] and 5.43±7.21 mm Hg at 3 hrs [p=0.005]).

13.2 Data extraction caffeine

Study ID a. Reference b. Health outcome(s)	a. Puente et al, 2017 b. Cardiovascular and psychobehavioural effects
Funding a. Funding source(s) b. Reported conflict of interest	a. Vice-Rectorate of Research and Science of the Camilo José Cela University (BEYDEF and CAFEGEN projects). b. The authors declare no conflict of interest. The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with two arms b. Double-blinding (participants and researchers. c. An alphanumeric code was assigned to each trial. The order of the experimental trials was set so that all the players from the same basketball team received the same treatment (caffeine or placebo). d. No information

Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. Twenty participants were recruited and completed. b. 100% c. Twenty subjects were included in each arm. d. 10 M/10 F e. Spain f. Males: 27.1 ±4.0 yr; females: 27.9 ± 6.1 yr g. No information h. No information i. Well-trained, in good health (physical examination 1 wk prior to trial) j. Exclusion criteria: Previous history of cardiopulmonary diseases, taking medications or sympathetic stimulants during the experiment or having suffered a musculoskeletal injury in the 3 months prior to the competition. Inclusion: not specifically reported k. Volunteers, experienced basketball players, from two different basketball teams. The females were professional basketball players and the men were semiprofessional. Players had at least 10 years basketball experience and had trained for approximately 2 h/day, 5 days/week during the previous year. Players had no, and were not taking, medications during the duration of the investigation. All participants were non-smokers and light-caffeine consumers (<100 mg/day). All female participants that took part in this investigation were tested during the luteal phase of their menstrual cycle.
Intervention/exposure a. Test substance and control b. lemerEstimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Caffeine and placebo (cellulose) control. b. 3 mg caffeine/kg bw (weights ±50 g) or placebo was taken orally as one capsule. Caffeine exposure for women: 191.3 ±76.7 mg; men: 268.4 ± 40.6 mg. Caffeine purity was 99%. c. Each participant took part in two trials under the same experimental conditions. Washout period: 1 wk. The experimental testing was carried out at the same time of day. The capsule was ingested 60 min before the onset of the experimental trials and were opaque and unidentifiable. The capsules were prepared by an investigator who did not take part in the experimental trials, who assigned an alphanumeric code to each trial to blind participants and researchers to the substance ingested by each team. This code was unveiled after the analysis of the variables. After 60 min, participants performed various basketball performance skill tests and participated in a 20 min simulated basketball game.

	The participants were encouraged by the investigators to abstain from caffeine ingestion in any form (coffee, cola, energy drinks) during the investigation. The day before each experimental trial, participants refrained from strenuous exercise and adopted a similar diet and fluid intake regimen. Their habitual pre-competition meal was taken at least 3 h before the onset of the experimental trials, with proportions of 60/16/24% for carbohydrate/protein/fat.
Endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Heart rate (beats/min)(heart rate/GPS/accelerometer device and heart rate monitor); self-reported insomnia and other various self-reported side effects (yes/no scale) b. Heart rate was measured during a 20 min simulated basketball match, which took place after a 60 min post-ingestion period and pre-match exercise. A questionnaire on psychobehavioural effects (self-reported) was filled out later the same day.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. The Shapiro–Wilk test was used to test the normality of each variable ($p > 0.05$). Student's t-test for dependent variables was used to establish the differences in the variables normally distributed between the caffeine and placebo. The McNemar test was used to detect differences in the frequencies of side effects reported after the ingestion of each treatment. The magnitude of Cohen's effect size was calculated and interpreted using the following scale: Trivial (0–0.19), small (0.20–0.49), medium (0.50–0.79) and large (0.80 and greater). The results are presented as m deviation and $p < 0.05$. The 95% confidence interval for the mean difference (95% CI) between placebo and caffeine was also calculated. c. In comparison to placebo, caffeine intake significantly increased prevalence of self-reported insomnia (19.0 vs. 54.4%; $p = 0.041$) during the 24 h following the match. No other significant effects were noted.

Study ID a. Reference b. Health outcome(s)	a. Salinero et al. (2017) b. Ergogenic effects

Funding a. Funding source(s) b. Reported conflict of interest	a. Camilo Jose Cela University b. Declared no conflict of interest
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with two arms b. Double-blinded. An alphanumeric code was assigned to each trial to blind participants and investigators to the substance tested in each session. The code was unveiled after the analysis of the variables. c. Order of test substance was randomised and counterbalanced. d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health stauts of participants j. Inclusion/exclusion criteria k. Other	a. 21 b. No information on drop-outs c. 21 participants in each of the arms d. 14M/7F e. Spain f. 28.9±7.3 years/29.3±7.7 (information given in Materials & Methods and Abstract, respectively) g. No information h. Not applicable i. Healthy subjects with no physical limitations or musculoskeletal injuries affecting the results of the study. Subjects underwent a routine physical examination to ensure that they were in good health. Women were always tested in the luteal phase j. No information k. None-smokers. Light caffeine consumers (<60 mg/day)
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles,	a. 3 mg caffeine/kg body mass (207±30 mg) or placebo (cellulose) b. Identical opaque capsules ingested with 200 ml of water. The capsule was ingested 60 minutes before onset of each experimental trial. Caffeine content in test substances not analysed and the caffeine product and placebo were purchased from a different suppliers.

minimum/maximum) c. Intervention design	c. After a standardized warm-up, participants performed a familiarisation session with all tests included. The day before familiarisation test and between pre-experimental and experimental periods, participants were encouraged to avoid strenuous exercise and caffeine ingestion in any form (e.g. coffee, cola, energy drinks, etc.). Compliance obtained by exercise and dietary records. At both experimental trials, participants arrived at the laboratory in the afternoon and ingested the capsule assigned for the trial. Afterwards, participants rested supine for 60 min to allow for caffeine absorption. One week washout-period.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Body weight (nude) Visual attention test: simple reaction time and error cognitive processes. Wingate test (cycle ergometer test) Second-by-second and peak power output was calculated and registered throughout the test. Calculation of a fatigue index. Perceptual evaluation and side effects: ad hoc questionnaire including queries about their self-perceived exertion and muscle power during the Wingate test. Questionnaire previously used to assess the perceptible side effects including information on sleep quality, prevalence of gastrointestinal problems, muscular pain and headache, and self-perception of nervousness or increased activeness. b. Visual attention test: 60 minutes after ingestion. Wingate test: after the visual attention test (?). Perceptual evaluation: 10 minutes after the Wingate test. Questionnaire on side effects: The following morning.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. Paired *t* test to test for differences between experimental conditions (caffeine vs placebo), including all participants as a whole group. A non-parametric test for dichotomous variables and related samples (McNemar test) to analyse side effects c. Visual attention test: No significant differences Wingate test: Caffeine increased the mean power output and peak power (p=0.01). No other significant differences.

	Perceptual evaluation: No significant differences. Side-effects: No significant differences.

Study ID a. Reference b. Health outcome(s)	a. Flueck et al. (2016) b. Cardiovascular and metabolic? effects
Funding a. Funding source(s) b. Reported conflict of interest	a. The authors received no specific funding for this work b. The authors declared that no competing interests exist
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover, 2 arms b. Double-blind. Neither the head of study, nor participants or staff knew the assignment of interventions during the study phase. The blinding process was done by the Clinical Trial Unit where the key for trial assignment was stored. c. Randomization was applied using a data management software (SecuTrial) which randomized trials automatically. Randomization of treatment sequence with a fixed block size of 5 and stratified by group was applied d. Data were collected between the July 2014 and January 2015
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable)	a. 39 men recruited, 7 were excluded (not meeting the inclusion criteria/declined to participate), 4 were excluded from analysis (technical reasons). 28 completed (12 able-bodied, 9 paraplegic and 7 tetraplegic participants) b. 71.2 % completion rate

b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	c. Per arm: 16 caffeine/16 placebo; 16 placebo/16 caffeine d. 28 M e. Switzerland f. Median (range): 32 (25-52) years g. Not reported h. All participants had spinal cord injury (12 able-bodied, 9 paraplegic and 7 tetraplegic participants). Respiration seemed to influence heart rate variability (caffeine induces bronchodilation). Breathing was standardized through metronomic breathing strategy, tidal volume was not standardized. i. Healthy j. Inclusion criteria: Healthy, non-smoking, men, between 18 and 60 years old. They had to be physically active for a minimum of three times 45 minutes per week. All participants with a spinal cord injury were motor and sensory complete lesioned. Participants with a paraplegia showed a lesion level below Th10 and participants with a tetraplegia a lesion level between C5 and C7. Drugs affecting the cardiovascular function were not allowed whereas the intake of any other drugs was kept constant throughout the trials. Participants suffering from diabetes were excluded from study participation k. All participants were habitual caffeine consumers with a daily caffeine intake of 250 mg [2 min; 600 max] for able-bodied, 250 mg [32 min; 440 max] for paraplegic and 200 mg [72 min; 420 max] for tetraplegic participants. During the testing phase, participants followed their habitual training patterns and did not increase or decrease training volume. Light training sessions were performed the last two days prior the trial. Participants didn`t drink any alcohol 24 hrs before the test session. They abstained from caffeine on the test day. The diet during the study phase was self-selected and ad libitum. Participants were asked to eat breakfast exactly 2 hrs before the start of the measurements and to replicate the meal on the second trial. A nutrition and exercise protocol was filled out together with the participant before the start of the test session to check if the participants followed these instructions. Participants were asked to sleep at least seven hrs the two nights before the measurements. They were excluded from data analysis if they violated any of these conditions. All tests were performed in a laboratory where temperature (22°C) and

	humidity (40%) were kept constant. The two tests were performed at least 2 days and at most 2 weeks apart from each other at the same time of the day.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design d. Co-exposure description (if applicable)	a. Caffeine/placebo b. Caffeine: 5.8 to 6.2 mg/kg body mass Caffeine as well as placebo were ingested in form of gelatin capsules either containing 50 or 100 mg. Placebo capsules were filled with a sugar alcohol (mannitol), which was not expected to have any further effects on performance. The caffeine capsules were filled with pure caffeine powder. Placebo and caffeine capsules were not distinguishable from each other due to equal colour, size and taste. The dosage for each participant was calculated by multiplying body mass with 6 which equates a dosage of 6 mg caffeine per kg body mass. As only 50 and 100 mg capsules were available, the dosages were then rounded up or down resulting in an actual dose varying from 5.8 to 6.2 mg/kg body mass. The number of capsules was kept identical in the placebo trial. c. Wash out period between the two tests ranged from at least 2 days to at most two weeks d. Drugs affecting the cardiovascular function were not allowed whereas the intake of any other drugs was kept constant through the trials
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Heart rate variability parameters, blood pressure and tidal volume in paraplegic and tetraplegic participants were compared to able-bodied participants. Metronomic breathing was applied (0.25 Hz) and tidal volume was recorded during heart rate variability assessment. Blood pressure, plasma caffeine and epinephrine concentrations were analyzed pre and post ingestion. Heart rate variability assessment consisted out of 6 min measurement in supine position and another 6 min in sitting position. Paced breathing (15 breaths per min, 0.25 Hz) was applied provided through and audio recording for standardization purposes. The sitting position was achieved passively by increasing the backrest up to 60°. All tetraplegic participants were able to stabilize their upper body by themselves while sitting. The R-peak to R-peak intervals were recorded using a heart rate monitor. Any signals interfering with the analysis were removed using an appropriate artefact correction factor. Blood pressure was recorded at the left arm in the 9th minute of each 10 min resting period during the first and the second HRV measurement using an

	automated blood pressure monitor. Blood samples were taken subsequently after the HRV measurements from the antecubital vein. Caffeine, epinephrine and norepinephrine concentrations were determined using high performance liquid chromatography. Gastrointenstinal side effects were reported b. Heart rate variability (HRV) parameters were assessed before and after ingestion of the test substance (after ingestion, there was a 40 min break providing enough time for absorption)
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. A two-sided power analysis was performed. Applying a significance level of 0.05, a power of 0.8, a standard deviation of 5 Watt and an effect size of 1 resulted in an actual power of 0.84 and a total sample size of 9 participants per group. An additional over-recruitment by approximately 20% was anticipated in order to take possible drop-outs into account. b. Data were tested for normal distribution using the Q-Q-plot, the Kolmogorov-Smirnov and the Shapiro-Wilk test. Results are presented as median [minimum;maximum] as data was not normally distributed. Statistical significance level was set at 0.05. To determine differences in parameters between pre and post supplement ingestion or between placebo and caffeine trials within the same group, the Wilcoxon signed-rank test was applied. The Kruskal-Wallis test was used to find any differences between the three groups whereas significant differences were then located using the Mann-Whitney-U test as a post hoc analysis. Bonferroni corrections were applied, where multiple testing with the Mann-Whitney-U test was done and the statistical significance level was then set to 0.0166. Spearman correlation was applied to find any relationship between habitual caffeine consumption and different parameter outcomes. Data were presented as the p-value and the Spearman correlation coefficient c. Most parameters of heart rate variability did not significantly change post caffeine ingestion compared to placebo. Comparing the change in tidal volume in supine position from pre to post ingestion in the placebo compared to the caffeine trial, only able-bodied participants showed a significant increase. Caffeine ingestion resulted in: Increased systolic and diastolic blood pressure in able-bodied and tetraplegic patients, Systolic and diastolic blood pressure increased by ~9 and ~8 mm Hg respectively after the ingestion of caffeine in able-bodied participants. Tetraplegic participants showed an increase of ~19 and ~27 mmHg in systolic and diastolic blood pressure.

	Difference in tidal volume (pre- vs post-) was higher after caffeine than placebo ingestion in able-bodied participants, Plasma caffeine concentrations were significantly increased post caffeine ingestion in all three groups of participants Plasma epinephrine concentrations increased significantly in able-bodied and paraplegic

Study ID a. Reference b. Health outcome(s)	a. Bloomer et al. (2015) b. Cardiovascular, respiratory effects, metabolic effects, haematology
Funding a. Funding source(s) b. Reported conflict of interest	a. USPlabs, LLC, and the University of Memphis. b. First author has been a consultant for, and/or principal investigator on research studies funded by, various dietary supplement companies.
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT with four parallel groups b. Double-blinded. No further information. c. No information d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls	a. 51 recurited (by informal word of mouth conversations, e-mail communications, and recruitment flyers posted on campus). 3 drop-outs. 48 participants included. b. 94% c. 12 participants in each group d. 51 M e. USA f. Placebo: 23.4±2.7; caffeine: 26.3±5.3; higenamine: 23.7±3.7; higenamine+caffeine+yohimbe bark extract (HCY): 24.3±4.3 (years, mean±SD)

d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	g. No information h. No information i. Not current smokers and in good overall health. j. Participants without a history of of cardiovascular, neurological, or metabolic disorders (e.g. hypertension, seizures, and diabetes). k. Originally 51 men were recruited. Following the drop-out of three people, three additional subjects were enrolled to fill the slots of these subjects. Reported daily caffeine consumption (median): placebo-group: 2 cups; caffeine-group: 3 cups.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Placebo (cellulose), caffeine, higenamine, or higenamine + caffeine + yohimbe bark extract. b. Placebo (cellulose), caffeine, higenamine (50 mg per capsule), or higenamine (50 mg per capsule) + caffeine (125 mg per capsule) + yohimbe bark extract (3.5 mg per capsule). Day 1-3: 1 capsule, 125 mg caffeine per day; day 4 until the end of 8 weeks: 1-3 capsules, 125-475 mg caffeine per day. c. 8 weeks intervention. On day 1-3: one capsule within 1 h of waking; day 4 until the end of 8 weeks: 1-3 capsules daily. One capsule within 1 h of waking and a second capsule 6-8 h after. The participants could choose to ingest a third capsule (together with the first capsule) or to ingest only one capsule per day. Subjects were instructed to maintain their normal diet throughout the study period and not to ingest capsules within 8 h of bedtime. Subjects were advised not to consume caffeinated beverages such as "energy drinks", coffee, tea, or soda during the study period and not to use other dietary supplements containing caffeine or other stimulants. Subjects were asked to maintain their usual physical activity patterns during the entire course of the study but to avoid strenuous physical activity for the 48 h prior to each test day. No instruction was provided regarding whether the capsules needed to be ingested before or after meals.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Hematology: Complete blood count, lipid panel, metabolic panel. Urinalysis with microscopic examination. Respiratory rate (in 60 s, breaths per minute) was counted by observation. Heart rate (in 60 s, beats per minute) was counted by palpation of the radial artery. Blood pressure (mm Hg) was measured by two trained technicians using a stethoscope and cuff.

	Self-reported adverse effects were recorded. B. Before supplementation, after 4 and 8 weeks.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. Four (condition/treatment) by three (time) analysis of variance. Tukey's post hoc testing used as needed. Statistical significance set at $p \leq 0.05$. Results presented as mean±SEM, with the exception of subject characteristics (mean±SD). c. No significant findings. Self-reported adverse effects: One subject assigned to the caffeine condition experienced a rash on both arms on the 5th day of treatment. One subject assigned to the higenamine+caffeine (125 mg per capsule) + yohimbe bark extract reported a lack of appetite, a rapid heart rate, difficulty falling asleep at night, and bad dreams within the first few days of treatment. The subject indicated that he accidentally consumed double the dosage (two capsules instead of one) that was indicated.

Study ID a. Reference b. Health outcome(s)	a. Bunsawat et al. (2015) b. Cardiovascular effects
Funding a. Funding source(s) b. Reported conflict of interest	a. No specific grant from any funding agency in the public, commercial, or not-for-profit sectors b. None declared

Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover study with two arms b. Double-blinding, no further information on blinding procedure c. Not reported d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 18 b. No information on dropouts c. All participants included in each arm. d. 10M/8F e. USA f. 26±1 years g. No information h. All participants were recruited from the general population of the University of Illinois at Chicago i. Healthy volunteers j. Exclusion criteria: cardiovascular diseases, hypertension, metabolic disorders, orthopaedic conditions, tobacco use, caffeinated beverage consumption of greater than the equivalent of three cups of coffee per day (285 mg), use of multi-vitamins and medications of any kind (incl. over-the-counter NSAIDS). k. No information
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Placebo and caffeine (400 mg) b. One pill taken orally. Caffeine and placebo pills looked similar. No analytical data regarding measurements of caffeine levels in the pills is reported. c. Participants abstained from caffeinated and alcoholic beverages, food and strenuous exercise for at least 12 hrs before each testing session. Washout-period: at least 48 hrs. Females were tested during the first 7 days of their menstrual cycle to control for the effects of sex hormones on heart rate variability (HRV). All testing sessions were conducted at the same time of day. Treadmill exercise 45 minutes after ingestion of test pill.

Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Continuous 5-minute recording of ECG obtained in supine position: heart rate (HR), corrected QT interval (QTc) using the Bazett's correction formula. Heart rate variability (HRV) was analysed in the frequency domaine. Respiration was paced with a metronome at 12 breath-s/min. Beat-to-beat arterial blood pressure (BP) recorded for 5 minutes. Maximum oxygen consumption (VO_{2max}) determined by means of a continuous incremental treadmill exercise until volitional exhaustion. Heart rate recovery (HRR; Index of autonomic function and cardiovascular fitness), As%HRR (from HR_{max} and HR-1 and HR-2 after exercise termination) b. Baseline, 5, 15, and 30 minutes post-exercise HRV were collected 5 minutes post-exercise to allow for steady HRs
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. Student's paired *t* test to compare baseline differences between the placebo and caffeine trials 2x3 ANOVA with repeated measures (trial by time) conducted on HRV, BP and QTc variables. Appropriate post-hoc tests were conducted where a significant interaction was detected. c. HR_{max}, HR-2, VO_{2max}, time to exhaustion significantly higher in the caffeine trial at all time points ($p<0.05$) (Placebo vs caffeine: HR_{max} 189±2 vs 192±2; VO_{2max} 45.2±2.3 vs 46.5±2.4; time to exhaustion 12.8±0.7 vs 13.3±0.7) During recovery: absolute HR higher in the caffeine trial at all time points ($p<0.05$). Compared to baseline, mean arterial pressure and diastolic blood pressure increased in the caffeine trial at all recovery time points ($p<0.05$). QTc increased from baseline at all time point in both trials, with greater increases in the caffeine trial ($p<0.05$). No other significant findings with regard to differences between caffeine and placebo were observed.

Study ID a. Reference b. Health outcome(s)	a. Dodd et al. (2015) b. Cardiovascular and psychobehavioural effects
Funding a. Funding source(s) b. Reported conflict of interest	a. No information b. No information
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with four arms b. Double-blinding. Participants were blinded to treatment, a third party administrated test substances. c. Latin square and random allocation to treatment order for each group (habitual and non-habitual caffeine consumers). d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. Twenty-four participants were recruited b. 100% c. Twenty-four; 12 habitual and 12 non-habitual caffeine consumers. All participants were included in each arm. d. 10 M/14 F (each group: 5 M/7 F) e. UK f. Habitual group: 23.3, SD 3.65 year; non-habitual group: 20.4, SD 1.88 yr. g. No information h. No information i. In good health j. Recruited to take part in the study were non-smoking volunteers in good health not currently taking any dietary supplements or medication (including the contraceptive pill), were not colour-blind and did not have a history of head trauma, learning difficulties, ADHD, neurological, vascular or psychiatric illness. k. Habitual caffeine intake and source were assessed via questionnaire. Habitual consumers reported drinking between 163 mg and 432 mg caffeine per day (mean 252.2, SD 74.3). Nonhabitual consumers reported drinking between 0 and 56 mg caffeine per day (mean 16.7, SD 15.6). Habitual consumers reported consuming between 1 and 6 cups of tea per day (mean 3.50, SD 1.46) and nonhabitual consumers reported consuming between 0 and 2 per week

	(mean 0.45, SD 0.62).
Intervention/exposure a. Test substance and control b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Caffeine, L-theanine, and placebo control (content was not reported). b. 75 mg caffeine, 50 mg L-theanine, 75 mg caffeine and 50 mg of L-theanine in combination, or placebo. Intervention substances were taken orally as two capsules at four study visits. The caffeine powder was pharmaceutical grade. Salivary caffeine levels were measured. c. Five study visits including baseline. Washout-period: at least 48 h and maximum 7 days between study visits. Participants fasted for 12 h prior to study visit (drinking water was permitted). A third party prepared and coded intervention capsules.
Endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Mood measures (caffeine research visual analogue scales (VAS) of mood); brain blood flow changes expressed as oxygenated(oxy)/deoxygenated (deoxy) haemoglobin (Hb)(µmol/L) (near-infrared spectroscopy (NIRS)); blood pressure (mm Hg); heart rate (bpm) (blood pressure monitoring device; Boso-Medicus Prestige) b. Blood pressure and heart rate were taken (following a 5 min seated rest) at each visit upon arrival and following 80 min post-dose. Brain blood flow changes were recorded from a time point 20 min prior to treatment baseline, and until 80 min post-treatment, including an 8 min rest period. Heart rate, blood pressure and VAS were measured before and after the end of the brain blood flow changes measurements.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No Information b. To assess differences in mood, blood pressure and heart rate prior to treatment, two-way repeated measures ANOVAs were conducted (treatment×consumer status) on baseline data with Bonferroni-corrected pairwise comparisons of any significant differences. A two-way mixed ANOVA was conducted (treatment×time) on pre- and post-caffeine and combination saliva samples. NIRS data from both channels were analysed by three-way mixed ANOVA (epoch×treatment×consumer status). Significant treatment-related interactions were further investigated by a priori planned comparisons where each active treatment was compared to placebo at each epoch utilising t tests calculated with the mean squares error from the ANOVA (Keppel 1991).In order to reduce the potential for type I errors, only those planned comparisons associated with a statistically significant difference on the initial ANOVA are reported. Subjective mood, heart rate and blood pressure data were analysed using a model which included the

	respective baseline as a time variant covariate, and fixed effects terms entered into the model were treatment, consumer, treatment*consumer and baseline value. Significant effects or interactions ($p<0.05$) were further explored with Bonferroni-corrected pairwise comparisons. c. Mean salivary caffeine was significantly higher than baseline values following caffeine treatments. Mean change in oxy-Hb was reduced during most time points of the first half of the post-dose period following caffeine as compared to placebo. Nonhabitual consumers had significantly higher deoxy-Hb throughout the absorption following caffeine as compared to placebo (dispersion measure not given for the above results). Significantly higher values were found for overall mood ratings (self-reported) following caffeine compared to placebo (mean±SEM, $p<0.05$). Systolic and diastolic blood pressure were significantly increased after (caffeine) treatment (mean±SEM, $p<0.05$). No other significant findings.

Study ID a. Reference b. Health outcome(s)	a. Lemery et al. (2015) b. Cardiovascular
Funding a. Funding source(s) b. Reported conflict of interest	a. No information b. None reported
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT with two parallel groups b. No information c. A computer-generated randomization table was used for randomization d. No information

Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 80 recruited (participants had symptomatic supraventricular tachycardia and were scheduled to undergo radiofrequency ablation). No drop-outs. b. 100% c. 40 participants in each group d. 31 M/49 F; placebo: 12 M/28 F; caffeine: 19 M/21 F e. Canada f. Placebo: 49 (median); caffeine: 50 (median) (years) g. No information h. No information i. Participants had supraventricular tachycardia j. Exclusion criteria: Intolerance to caffeinated beverages, use of medications that may react with caffeine through the cytochrome P450 1A2 pathway (CYP1A2), and pregnancy. k. 15/80 pasalarticipants reported that they had a previous possible relation between caffeine intake and occurrence of palpitations or tachycardia. A history of smoking was documented in 13/80 patients (16%), including 5 patients in the caffeine group and 8 patients in the placebo group.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Tablets: placebo or caffeine (5 mg/kg). b. Measured caffeine levels in blood (median): caffeine group, 7.4 µg/mL; placebo, 0.15 µg/mL. c. Single dose study: immediately prior to entering the electrophysiology laboratory, patients received oral tablets of caffeine or placebo, consisting of 5 mg/kg.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Electrophysical measurements: blood pressure (mm Hg), heart rate (beats per min), intracardiac measurements (milliseconds), refractory period, atrioventricular node conduction. Method: Catheters were introduced from the right femoral vein and the right internal jugular vein under fluoroscopic guidance to the high RA, right ventricle apex, antrioventricular node, and coronary sinus. Programmed electrical stimulation was performed at twice diastolic threshold according to standard protocol at 600 and 500 milliseconds, and when needed at

	400 milliseconds. Sinus node recovery times were obtained following pacing from the high right atrium. This was followed by determination of the effective refractory period of the right ventricle, and 1:1 conduction retrograde over the atrioventricular node, and when present of the fast pathway, slow pathway, and accessory pathway. The same protocol was then followed to determine the ERP and 1:1 conduction when pacing from the high RA and distal coronary sinus. Finally, rapid atrial pacing to 2:1 atrial capture or to 250 milliseconds was performed. b. Parameters were measured after ingestion of placebo or caffeine. Baseline variables of blood pressure, heart rate, and intracardiac measurements were obtained while the patient was resting in the supine position prior to performing intracardiac stimulation.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. Yes, 10% reduction in refractory period b. Study groups were compared using the Mann-Whitney U test for continuous outcomes and Fisher's exact test for categorical outcomes. A regression analysis was conducted to assess the relationship between caffeine and ERP. A 2-sided P value of less than 0.05 was considered to indicate statistical significance. c. Caffeine was associated with a significant increase in resting systolic and diastolic blood pressures as compared with placebo. Systolic blood pressure (median, interquartile range): caffeine, 143, 128-165; placebo, 132, 114-150. Diastolic blood pressure (median, interquartile range): caffeine, 83, 77-94; placebo, 74, 69-86. No other significant findings.

Study ID a. Reference b. Health outcome(s)	a. Wu (2015) b. Metabolic effects
Funding a. Funding source(s) b. Reported conflict of interest	a. Supported by a grant from National Science Council (Taiwan) b. None reported.

Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover with four arms b. The subjects were randomized in a counterbalanced order. Method not described. c. No information d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 12 recruited (college students). Drop-outs not reported b. Not reported c. 12 in each arm d. 12 M e. Taiwan f. 20.8±1.1 (years, mean±SD) g. No information h. No information i. Healthy j. No information k. k. Subjects reported low caffeine consumption (<100 mg/day) and no hypersensitivity to caffeine. Subjects had at least six months experience in performing resistance exercise (at least three days per week in the six-month period before the study).
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Caffeine or placebo b. A single dose, 2, 4 or 6 mg/kg bw anhydrous caffeine or placebo (methyl cellulose) c. Crossover design, with 7 day wash-out period: subjects ingested either 6 mg/kg caffeine, 4 mg/kg caffeine, 2 mg/kg caffeine or placebo. One hr after ingestion of the capsule, the subjects performed resistance exercise; 2 exercises, 3 sets of 10 repetitions at 75% of repetition maximum test (performed prior to ingestion of test substance). All intervention capsules were similar looking. All subjects were required to consume the same dinner on the day prior to each trial. In additon, subjects were required to fasting 12 h and abstain from intense exercise in the 72 h before each trial. The subjects filled out a 24 h dietary log to assess the caffeine intake.

	Subjects were instructed to refrain from ingestion of dietary caffeine, such as coffee, tea, chocolate, caffeine-containing beverages and alcohol throughout the study period. Physical activity (resistance exercise)
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Venous blood samples of serum glucose (mmol/L), insulin (pmol/L) and cortisol (nmol/L). b. Samples were drawn prior to caffeine ingestion (baseline), immediately prior to performed resistance exercise (pre-exercise; 60 min post-ingestion), and 0, 15 and 30 min after exercise (post-exercise; 100, 115 and 130 min post-ingestion).
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No b. A 4 (treatment) x 5 (time) analysis of variance (ANOVA) with repeated measure was used to analyze hormonal and blood variable data. Tukey`s post hoc test was used for pairwise comparisons. Statistical significance was set at $P \leq 0.05$. c. A single dose of 6 mg/kg bw caffeine significantly increased cortisol levels both pre- and post-exercise compared with placebo. A single dose of 6 and 4 mg/kg bw caffeine, decreased insulin concentrations at 0 and 15 minutes after the exercise (100 and 115 min post-ingestion). Increased glucose concentrations were observed following 4 and 6 mg/ kg bw caffeine at pre-exercise (60 min post-ingestion) and immediately after the restistance exercise (100 min post-ingestion).

Study ID a. Reference b. Health outcome(s)	a. Souza et al. (2014) b. Cardiovascular effects
Funding a. Funding source(s) b. Reported conflict of interest	a. No information b. None reported

Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, crossover with two arms b. No information c. No information d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 15 recruited. All subjects completed both conditions. b. 100% c. 15 in each arm d. 12 M/3 F e. Brazil f. 21.3 ± 2.1 years g. No information h. No information i. Healthy j. No information k. All subjects were non-smokers, light caffeine habituated (<250 ml of black coffee by day). All subjects had recreational resistance training experience, were non-hypertensive (blood pressure lower than 140/90 mm Hg), had no orthopedic problems, and used no substances or medications with cardiovascular effects.
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Placebo+physical activity or caffeine+physical activity b. Caffeine arm: 4 mg/kg bw, placebo: talc c. Crossover design, with a minimum 72 h wash-out period: subjects ingested either a capsule containing 4 mg caffeine per kg of body weight or a placebo capsule. Subjects then underwent a resistance exercise session consisting of three sets of 10 repetitions each. Subjects were instructed not to drink any caffeinated beverages, perform strenuous physical exertion, or consume alcohol for 72 hrs before the start of data collection and throughout the experiment. Participants were told that both capsules contained caffeine.

Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Measured cardiovascular parameters: Systolic (SBP), diastolic (DBP) and mean (MAP) blood pressures (mm Hg) (by an automatic device, not specified; by beat-to-beat measurements, Finometer PRO, Finapres Medical Systems; monitoring device, SpaceLabs 90207), heart rate (HR, beats per min), stroke volume (SV, ml), cardiac output (CO, L per min) and peripheral vascular resistance (PVR, mm Hg min/L) (by beat-to-beat measurements). b. At baseline: resting SBP, DBP and MAP assessment 45 min after caffeine/placebo ingestion: resting SBP, DBP, MAP, HR, SV, CO and PVR assessment 15 min after exercise session: SBP, DBP, MAP, HR, SV, CO and PVR assessment For 9 hrs following exercise, measurements were taken every 30 minutes: SBP, DBP and MAP assessment.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. Mauchly's test was applied to confirm the sphericity of the data. For those cases in which sphericity was not preserved, the authors employed the Greenhouse–Geisser correction. The comparison of resting variables before and after the intake of caffeine or placebo was performed using a two-way analysis of variance (ANOVA). The same statistical procedures were used for comparison of the caffeine/placebo conditions at the post-exercise time point (i.e. 15 minutes after exercise) as well as the mean values during the 9 hrs of ambulatory monitoring. Tukey's post-hoc tests were utilized when necessary. To analyze the period of ambulatory monitoring, multiple comparisons were performed using a repeated measures ANOVA, followed by Bonferroni post-hoc tests, when necessary, to identify the differences. The significance was set at $p < 0.05$. Comparison between different time points, caffeine Caffeine increased ($p < 0.05$) pre-exercise (rest) DBP and MAP. Following caffeine supplementation, decreases in ($p < 0.05$) SBP, MAP, and PVR between the pre- and post-exercise time points were observed. The mean values for SBP, DBP and MAP during the 9 h of post-exercise monitoring were increased ($p < 0.05$) for the caffeine. Comparison between placebo and caffeine: At 9 h post-exercise, significant differences were shown between the caffeine and placebo conditions for SBP, DBP and MAP ($p < 0.05$).

	c. 45 minutes after ingestion of caffeine or placebo (pre-exercise) and fifteen minutes after the end of the exercise (post-exercise): The comparison between the caffeine and placebo conditions showed a significant difference in DBP and MAP for the caffeine condition pre-exercise, as well as a significant increase in PVR for the caffeine condition post-exercise ($p<0.05$).

Study ID a. Reference b. Health outcome(s)	a. Temple et al. (2014) b. Cardiovascular and psychobehavioural effects
Funding a. Funding source(s) b. Reported conflict of interest	a. This study was funded by a grant from the National Institute on Drug Abuse (RO1 DA030386) to Dr Temple. Funded by the National Institutes of Health (NIH) b. None to disclose
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT crossover design with three arms (two age groups) b. Double-blind (participants, no further information) c. Random number table (order of caffeine administration) d. Study was conducted between August 2011 and October 2012
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country)	a. 101 participants recruited; 96 completed (five participants removed due to missing data /not meeting Tanner requirements) b. 95% c. All (101) participants were included in each arm d. 54 M/47 F (52 M/44 F completed) e. USA f. Prepubertal M: 8.62+/-0.12; postpubertal M: 16.08+/- 0.12; prepubertal F: 8.38+/-0.12; postpubertal F: 15.75+/-0.14 (mean+/SEM, yr)

f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	g. Asian: two; black/African American: 16; white: 74; other: one (no difference between gender or pubertal group) h. Confounders not reported. One participant was taking an inhaled steroid with potential effects on heart rate and blood pressure i. No specific information reported (13 were using medications) j. Eligibility for the study: not smoking, having previous experience with caffeine without adverse reactions, not using hormone-based contraceptives and/or not being pregnant, not taking any medications affecting caffeine metabolism, willingness to abstain from regular caffeine use. k. Socieconomic status between participants varied: primarily white, middle class and with well-educated parents.
Intervention/exposure a. Test substance and control b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Caffeine or placebo b. Fluid portions of 300 ml lemon-lime flavoured soda, orange juice or lemonade containing either placebo or caffeine (1 or 2 mg/kg liquid). Average body weight all participants was approximately 50 kg (prepubertal group: 33 kg and postpubertal group: 69 kg). c. Caffeine or placebo was consumed at each of six laboratory visits, three visits during 1 wk with the remaining three visits occurring 2 wk later. Participants were asked to abstain from all soda and caffeine-containing products for 24 hrs before their appointment times, as well as from all food and drink other than water for 2 h before their appointments. Participants provided 24-h food and activity recall at each visit. Thirteen participants were taking medications; 1 participant was taking an inhaled steroid
Endpoint assessment c. Parameters measured and methods used d. Measurement time points	a. Heart rate (beats/min) and blood pressure (mm Hg) (heart rate and blood pressure monitor while seated in upright position); psychobehavioural parameters (Behavioural Checlist) b. Heart rate/blood pressure at each visit: baseline measurements at 20-30 min after arrival; every 10 min for 1 h. Psychobehavioural parameters: at each visit prior to intervention at baseline and after 60 min

Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. Gender and pubertal group differences in participant characteristics were analyzed by using either an analysis of variance or x2 analyses for categorical. Data did not differ as a function of visit for prepubertal boys and girls and postpubertal boys, and the data from the same-dose sessions were averaged. The pattern of diastolic and systolic blood pressure and heart rate were analysed by using mixed-effects regression models with gender and pubertal group as the time-invariant predictors, time and caffeine dose as time-variant predictors, and average daily caffeine use and baseline blood pressure and heart rate as covariates. Unstructured models were used with the intercept, identifier (ID), and time treated as random variables. Model selection was done with the Akaike information criteria. Behavioral checklist variables were analyzed by using a mixed repeated-measures analysis of covariance with gender and pubertal group as between-subject variables, caffeine dose and pre/post as within-subject variables, and average daily caffeine use as a covariate. c. 1-mg/kg and 2-mg/kg caffeine (in soda) doses reduced heart rate (z =22.71) significantly compared with placebo, (z = 22.1 and 22.7, respectively). The reduction in heart rate was significantly larger for males than females (z = 1.98) among postpubertal participants. Males had a greater response to caffeine than females (z =22.6). 1-mg/kg and 2-mg/kg caffeine doses increased systolic blood pressure compared with placebo (z = 2.1). The increase in systolic blood pressure was significantly higher among females among postpubertal participants (z= 2.2) (mean±SEM, $p<0.05$). For the diastolic blood pressure there was a significant interaction between gender and caffeine dose in postpubertal participants with females having a larger increase than males). For postpubertal females, there was a significant interaction between caffeine dose and menstrual cycle on heart rate, diastolic blood pressure and systolic blood pressure (mean±SEM, $p<0.05$). For the self-reported adverse effect behavioural parameters there was an interaction between caffeine dose and pre/post caffeine administration for "falling asleep", "ringing in ears", "stomach ache", "sleepy", "tired", "queasy" and "sweaty". No other significant differences.

Study ID a. Reference b. Health outcome(s)	a. Bloomer et al. (2013) b. Cardiovascular effects, haematology, metabolic effects
Funding a. Funding source(s) b. Reported conflict of interest	a. USPlabs LLC and University of Memphis b. First author has been a Consultant for and/or PI on research studies funded by various dietary supplement companies
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, parallel design with four groups b. Double blinded. The study sponsor retained the blinding code until study completion. c. No information on randomization method. d. No information
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health stauts of participants j. Inclusion/exclusion criteria k. Other	a. 66 recruited (by informal word of mouth conversations, formal presentations, online postings, recruitment flyers posted on and off campus). 16 dropouts (missed an assessment day, ceased their participation due to time constraints). 50 participants included. b. 76% c. Placebo n=11, Caffeine n=14, 1,3-dimethylamylamine (DMAA) n=13, Caffeine n=12 d. 50 M e. USA f. Years, mean±SEM: Placebo: 23.1±1.5; Caffeine: 23.0±1.1; DMAA: 23.1±1.8; Caffeine+DMAA: 23.6±1.8 g. No information h. No information i. Not current smokers, all considered to be in good overall health. j. Participants did not have a history of cardiovascular, neurological, or metabolic disorders (e.g. hypertension, seizures, diabetes). k. Participants were regular consumers of stimulants (e.g. caffeine) such as beverages or nutritional supplements, who did not report a history of adverse reactions to caffeine/other stimulants. Compensation ($200) after completion.

Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design	a. Placebo (cellulose), caffeine (250 mg), DMAA (50 mg) or caffeine (250 mg)+DMAA (50 mg). All conditions were produced under standard good manufacturing practices by a dietary supplement contract manufacturer. Quality assurance procedures confirmed the purity and potency of each condition. b. Week 1: 250 mg caffeine per day; Week 2-12: 2x250 mg caffeine per day. c. 12 weeks intervention. One capsule per day the first week. Weeks 2-12: Two capsules per day (one upon rising in the morning, one capsule 4-6 hrs later). Last capsule consumed on the day prior to the final test day. No capsules were consumed before assessments were performed on the mornings of test days. Maintaining normal diet throughout the study period, but no consumption of caffeinated beverages (e.g. energy drinks, coffee, tea, soda). Advised not to use supplements containing caffeine or other stimulants. An 8-hr overnight fast before test days. Participants asked to refrain from strenuous physical activity for 48 hrs prior to each test day. Capsule counts of returned bottles allowed for calculation of compliance to intake. Preparations produced under standard good manufacturing practices by a dietary supplement contract manufacturer. Quality assurance procedures confirmed the purity and potency of each substance. No analytical data on purity and composition are shown.
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Serology: Complete blood count, metabolic panel, lipid panel, CRP, cardiac tropinin I, malondialdehyde, oxidation protein products, Trolox Equivalent Antioxidation Capacity. Urinalaysis with microscopic examination. ECG (12-lead) using automated procedures. Counting of respiratory rate (60 s) by simple observation. Blood pressure using a stethoscope and cuff. Body mass and body composition via dual energy x-ray absorptiometry using a 4-min fan array. Participants recorded intake of food and beverages during 72 hrs prior to each test day. Records reviewed for accuracy, analysed using Food Processor SQL. b. Before supplementation (Pre), week 6 and 12.

Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No information b. 4 (condition/treatment) by 3 (time) analysis of variance. Tukey's post hoc testing used as needed. Statistical significance set at $p \leq 0.05$). Results presented as mean±SEM. c. None reported a significant adverse event. No differences in compliance to capsule intake. Results only for placebo vs caffeine are listed below. Urine analyses: pH: time effect week 6 < Pre No other significant findings. Serology: Advanced oxidation protein products (AOPP): caffeine > placebo ($p=0.005$) Potassium: caffeine>placebo ($p=0.003$) CO_2: time effect week 12 > week 6 ($p=0.02$) No other significant findings. Cardiovascular effects: No significant findings. Diet: No significant findings.

Study ID a. Reference b. Health outcome(s)	a. Rogers et al. (2013) b. Psychobehavioural effects
Funding a. Funding source(s) b. Reported conflict of interest	a. Funded by a grant (BBS/B/ 01855) from the UK Biotechnology and Biological Sciences Research Council b. One author has received grants to support research on caffeine from GlaxoSmithKline

Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	a. RCT, parallel design, medium-high and non-low caffeine consumers b. Double-blinded (each treatment was double-blindly administered) c. Not reported d. Not reported
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	a. 369; 212 medium-high caffeine consumers and 157 non-low caffeine consumers. 'Non-low' and 'medium-high' caffeine consumers was defined as caffeine intake of <40 and ≥40 mg/day, respectively (salivary caffeine concentration confirmed their caffeine consumer status) b. Not reported c. 369/369 d. 'Non-low': 85 F/72 M. 'Medium-high': 109 F/103 M e. UK f. Age between 18 and 62 years. For 'non-low' and 'medium-high' caffeine consumers, age (mean ± SD) were 31.7±12.1 and 33.8±12.7 years g. Not reported h. Not applicable i. Not reported j. Not reported k. Participants were non- or light smokers (≤5 cigarettes or equivalent a day). Smoking was not permitted during the test day until after the participants left the laboratory. A caffeine questionnaire measured the frequency of participants' consumption of caffeine-containing products during the week preceding testing. Caffeine intake was calculated from consumption frequency using information from various sources on the caffeine content of these products (teas, coffees, colas, etc.)
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean,	a. Caffeine or placebo. b. Caffeine (100 mg, then 150 mg anhydrous powder) or placebo (cornflour). Each treatment was administered in a single, white cellulose capsule, identical in appearance, and swallowed with 50 ml of room temperature water. c. The first treatment was given at 11:15 AM and the second at 12:45 PM. Participants were

standard deviation, median, percentiles, minimum/maximum) c. Intervention design	instructed to abstain from caffeine consumption from at least 7:00 PM of the previous evening, and they left at 4:15 PM. (a light lunch was served at 12:50 AM)
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	a. Anxiety, jitteriness, sleepiness. Sleepiness and anxiety/jitteriness were self-reported. b. Participants completed testing a total of four times: before treatment (baseline, starting at 10:30 AM), starting at 45 min after the first dose of caffeine or placebo and starting at 60 and 135 min after the second dose of caffeine or placebo.
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	a. No b. Data were analysed primarily using analysis of variance (ANOVA). Data from measures taken before administration of caffeine or placebo (pre-treatment baseline) were analysed for effects of consumer status (non-low versus medium-high consumers). Post-treatment data were analysed for the effects of caffeine (caffeine versus placebo) and consumer status. Only the results from measures taken after the administration of the second dose of caffeine (means of the data from the third and fourth repeats of the task battery) were reported in detail. Block (four levels) was additionally included as a repeated measures factor (Greenhouse–Geisser correction applied) in the analysis of the data from the simple reaction time task. For the post-treatment data, multiple paired comparisons were made using Tukey's honestly significant difference test (Ferguson and Takane 1989). In further analyses of the effects of caffeine, pre-treatment baseline scores were included as a covariate. Because their scores for a majority of variables differed or tended to differ at baseline, these particular analyses were carried out separately for non-low and medium-high consumers (the purpose was to control for baseline differences within consumer status groups, not between these groups). Gender was included as a fixed factor, and age and smoking status were included as covariates in all of the above analyses. Standard multiple linear regression was used to examine the contributions of the effects of caffeine on mental alertness and tapping speed to its effect on simple reaction time. The contributions of caffeine's effects on sleepiness and anxiety/jitteriness to its effect on mental alertness were examined for only those participants who received caffeine and separately for non-low and medium-high caffeine consumers. Alpha was set at 0.05 (two-tail). c. Caffeine withdrawal was associated with some detrimental effects at 10:30 AM, and more severe effects, including greater sleepiness, lower mental alertness, and poorer performance on simple

	reaction time, choice reaction time and recognition memory tasks, later in the afternoon. Caffeine improved these measures in medium-high consumers but, apart from decreasing sleepiness, had little effect on them in non-low consumers.

14 Appendix: Risk of bias

The criteria for the answer options to the RoB questions were described in OHAT Risk of Bias Rating Tool for Human and Animal Studies (NTP, 2015b). The project group designed criteria that were appropriate for the included RCT articles for question number 5: "Can we be confident in the exposure characterisation". The criteria were different for energy drink consumption and caffeine exposure. For the included articles on energy drink consumption the criteria for the following response options were:

- Definitely low risk of bias (++): The content and amount of all ingredients must be stated including the amount of carbohydrates
- Probably low risk of bias (+): The content of all ingredients and amount of at least caffeine must be stated
- Probably high risk of bias/not reported (NR) (–): The content of caffeine was not stated
- Definitely high risk of bias (– –): The amount of caffeine was not stated and/or the amount of energy drink to be consumed (study volume) was not stated

For the included articles on caffeine exposure the criteria for the following response options for RoB question number 5 were:

- Definitely low risk of bias (++): Purity confirmed as >99% (supplier documentation of purity), supplier is known AND direct evidence that exposure was consistently administrated (same method and time-frame) across treatment groups
- Probably low risk of bias (+): Pharmacy made the capsules AND/OR Good Manufacturing Practice was used AND supplier of chemical is known AND indirect evidence that exposure was consistently administrated (same method and time-frame) across treatment groups
- Probably high risk of bias/not reported (NR) (–): No information about quality of preparation of caffeine AND/OR chemical form of caffeine (e.g. anhydrous) OR insufficient information about the validity of the exposure assessment method, but no evidence for concern (NR)
- Definitely high risk of bias (– –): No information about the above AND no supplier information OR direct evidence that exposure was assessed using poorly validated methods.

14.1 Risk of bias of energy drink consumption article

Brothers et al. (2017)		
Number	Question	Rating (++,+,–,––)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	–
3	Were research personnel blinded to the study group during the study?	–(NR)

Brothers et al. (2017)		
4	Were outcome data complete without attrition or exclusion from analysis?	–
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	– –
7	Were all measured outcomes reported?	– –
8	Where there no other potential threats to internal validity?	+
Conclusion		TIER 3

Fletcher et al. (2017)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	+
3	Were research personnel blinded to the study group during the study?	+
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	–
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	+
Conclusion		TIER 2

Garcia et al. (2017)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	–
3	Were research personnel blinded to the study group during the study?	–
4	Were outcome data complete without attrition or exclusion from analysis?	– (NR)
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	–
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 3

Gray et al. (2017)		
Number	Question	Rating (++,+,–,—)

1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	–
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	++
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	+
Conclusion		TIER 2

Shah et al. (2016a)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	–(NR)
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)? 1) objectivity of outcome assessment 2) consistency in measurement of outcome 3) blinding of the outcome assessors	+
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity? Statistics, recruitment method	–
Conclusion		TIER 2

Shah et al. (2016b)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	–
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	++

Shah et al. (2016b)		
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	+
Conclusion		TIER 2

Grasser et al. (2015)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	—
3	Were research personnel blinded to the study group during the study?	—
4	Were outcome data complete without attrition or exclusion from analysis?	–(NR)
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)? 1) objectivity of outcome assessment 2) consistency in measurement of outcome 3) blinding of the outcome assessors	–
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity? Statistics, recruitment method	–
Conclusion		TIER 3

Lara et al. (2015)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	+
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	++
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	+
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity	–

Lara et al. (2015)	
Conclusion	TIER 1

Svatikova et al. (2015)		
Number	Question	Rating (++,+,–,––)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	++
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	++
Conclusion		TIER 1

Grasser et al. (2014)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	—
3	Were research personnel blinded to the study group during the study?	–(NR)
4	Were outcome data complete without attrition or exclusion from analysis?	–(NR)
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	–
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 3

Lara et al. (2014)		
Number	Question	Rating (++,+,–,––)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	++

Lara et al. (2014)		
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)? 1) objectivity of outcome assessment 2) consistency in measurement of outcome 3) blinding of the outcome assessors	+
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity? Statistics, recruitment method	+
Conclusion		TIER 1

Peacock et al. (2014)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	+
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	–
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	+
7	Were all measured outcomes reported?	+
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 2

Phan and Shah (2014)		
Number	Question	Rating (++,+,–,––)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	–(NR)
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	—
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	–(NR)
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 3

Salinero et al. (2014)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	+
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	+
Conclusion		TIER 1

Kurtz et al. (2013)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	+
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	—
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	–
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 3

14.2 Risk of bias of caffeine articles

Puente et al. (2017)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	–
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	++

Puente et al. (2017)		
5	Can we be confident in the exposure characterization?	++
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	+
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	+
Conclusion		TIER 2

Salinero et al. (2017)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	–(NR)
5	Can we be confident in the exposure characterization?	–(NR)
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)? 1) objectivity of outcome assessment 2) consistency in measurement of outcome 3) blinding of the outcome assessors	++
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity? Statistics, recruitment method	–
Conclusion		TIER 2

Flueck et al. (2016)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	++
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	++
Conclusion		TIER 1

Bloomer et al. (2015)

Bloomer et al. (2015)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	+
3	Were the research personnel blinded to the study group during the study?	–(NR)
4	Were outcome data complete without attrition or exclusion from analysis?	–
5	Can we be confident in the exposure characterization?	– –
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	++
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 3

Bunsawat et al. (2015)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	+
3	Were research personnel blinded to the study group during the study?	–(NR)
4	Were outcome data complete without attrition or exclusion from analysis?	–(NR)
5	Can we be confident in the exposure characterization?	–(NR)
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)? 1) objectivity of outcome assessment 2) consistency in measurement of outcome 3) blinding of the outcome assessors	–(NR)
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity? Statistics, recruitment method	+
Conclusion		TIER 3

Dodd et al. (2015)		
Number	Question	Rating (++, +, –, – –)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	++

Dodd et al. (2015)		
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	+
5	Can we be confident in the exposure characterization?	-
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	+
7	Were all measured outcomes reported?	++
8	Were there no other potential threats to internal validity?	-
Conclusion		TIER 2

Lemery et al. (2015)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	–(NR)
3	Were research personnel blinded to the study group during the study?	–(NR)
4	Were outcome data complete without attrition or exclusion from analysis?	+
5	Can we be confident in the exposure characterization?	–
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	–(NR)
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	+
Conclusion		TIER 3

Wu (2015)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	–(NR)
3	Were research personnel blinded to the study group during the study?	–(NR)
4	Were outcome data complete without attrition or exclusion from analysis?	–(NR)

Wu (2015)		
5	Can we be confident in the exposure characterization?	– –
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	+
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 3

Souza et al. (2014)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Was allocation to study groups adequately concealed?	–(NR)
3	Were subjects blinded to the study group during the study?	–(NR)
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	–
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	– –
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	+
Conclusion		TIER 3

Temple et al. (2014)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	++
2	Were subjects blinded to the study group during the study?	+
3	Were research personnel blinded to the study group during the study?	+
4	Were outcome data complete without attrition or exclusion from analysis?	++
5	Can we be confident in the exposure characterization?	—
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	+
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 3

Bloomer et al. (2013)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	–
5	Can we be confident in the exposure characterization?	+
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)? 1) objectivity of outcome assessment 2) consistency in measurement of outcome 3) blinding of the outcome assessors	+
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity? Statistics, recruitment method	–
Conclusion		TIER 2

Rogers et al. (2013)		
Number	Question	Rating (++,+,–,—)
1	Was administered dose or exposure level adequately randomized?	+
2	Were subjects blinded to the study group during the study?	++
3	Were research personnel blinded to the study group during the study?	++
4	Were outcome data complete without attrition or exclusion from analysis?	–(NR)
5	Can we be confident in the exposure characterization?	–(NR)
6	Can we be confident in the outcome assessment (including blinding of outcome assessors)?	–
7	Were all measured outcomes reported?	++
8	Where there no other potential threats to internal validity?	–
Conclusion		TIER 3

15 Appendix: Weight of evidence

15.1 Energy drinks and caffeine - Weight of evidence (WoE)

Table 1. Weighting the body of evidence; Cardiovascular and various physiological effects of energy drinks.

Energy drinks: Cardiovascular and other physiological effects									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/ COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency (for final rating only)	
1 Brothers 2017 Initial rating +++ It is questionable whether water is a relevant comparator	3: Very serious concern	Very serious concern Beverage Research Consultants, LLC	Not serious concern	Serious concern	No No reported effect between treatment and control group in any of the two protocols	No No effect of increased dose of energy drink	No Crossover study		+

2 Fletcher 2017 Initial rating ++++	2: Serious concern	Not serious concern	Not serious concern	Serious concern	Small increase in SBP and DBP, within the normal range. No effect in HR Small increase in QT were observed for treatment group at 2 h post–drink compared to control group. However, this could be caused by a drop in QT in the control group for this time point. No difference for other time points	No Only one study group/dose tested	No Crossover study		++

3 Garcia et al 2017 Initial rating +++ It is questionable whether water is a relevant comparator.	3: Very serious concern	Not serious concern	Serious concern All energy drinks had approximately the same caffeine content. Energy drink B and C were similar in content of sugar, taurine and vitamins. Energy drink A had lower sugar content and no taurine. Overall, the same significant effects were found for drink A and C. Based on the content of the drinks, it is more likely that the effects would be similar for drinks B and C.	Serious concern The test is with three different energy drinks, with variations in content. Unclear if the groups are large enough to detect difference in exposure.	No In general, small and inconsistent effects within normal range.	No Impossible to evaluate. Caffeine: one dose	Yes probably Not reported		+

4 Grasser et al 2015 Initial rating +++ It is questionable whether water is a relevant comparator.	3: Very serious concern	Not serious concern	Not serious concern	Serious concern Short ingestion period (5 min).	No No effects on SBP, DBP or HR from treatment versus control.	No Only one study group/dose tested	No Crossover study		+/++
5 Grasser et al 2014 Initial rating +++ It is questionable whether water is a relevant comparator.	3: Very serious concern Study subjects and personnel were not blinded to treatment. Attrition or exclusion from analysis were not given	Not serious concern	Not serious concern	Serious concern Short ingestion period (5 min).	Small increase in SBP, DBP and mean arterial blood pressure, within the normal range. Also moderate increase in heart rate and cardiac output in treated group compared to control.	No Only one study group/dose tested	No Crossover study		+/++

6 Gray Initial rating +++ The content of the control drink was not described.	2: Serious concern	Not serious concern	Not serious concern	Serious concern	Small increase in SBP and DBP between treated and control group. No effect in the QTc measurements between treated and control group, except for 3 participants. Question the relevance of the study group to the general population	No Only one study group/dose tested	No Crossover study		++

7 Kurtz et al 2013 Initial rating +++ Lack of controlled exposure conditions	3: Very serious concern	Not serious concern	Not serious concern	Very serious concern Not possible to evaluate sufficient group size, since exposure conditions were uncertain. Relatively high variability in measurements. Caffeine content in test group was not specified.	Small increase in blood pressure parameters such as SBP and DBP, within the normal range.	No Only one study group/dose tested	No Crossover study		+

8 Phan and Shah 2014 +++ Lack of controlled exposure conditions	3: Very serious concern	Not serious concern	Not serious concern	Very serious concern Small test group (n=10). Beverage liquid amount was not reported. There were statistically significant differences in baseline values for treated and control group for several parameters.	Small increase in blood pressure parameters such as SBP, central SBP and central and peripheral pulse pressure. No effect on heart rate or other cardiovascular parameters.	No Only one study group/dose tested	No Crossover study		+

9 Shah et al 2016A Initial rating ++++	2: Serious concern	Not serious concern	Not serious concern	Serious concern The test group got energy drink with described content, while the control group got carbonated drink with lime juice and cherry syrup. Nutritional content was not further described.	Day 1: Small increase in SBP and DBP No effect on HR, QT, QRS or PR–interval. Day 7: No effect on any parameters	No Only one study group/dose tested	No Crossover study		++

10 Shah et al 2016B Initial rating ++++	2: Serious concern	Not serious concern	Serious concern The QTc measurements show increase after 2 and 5.5 hrs, but no increase after 1 and 3.5 hrs.	Serious concern The test group got energy drink with described content, while the control group got carbonated drink with lime juice and cherry syrup. Nutritional content was not further described. High variability in QTc measurements	Small increase in SBP measurements after 2 h between treatment and control. Small/moderate increase in QTc measurements in treatment group compared to control after 2 h, but inconsistent results. No effect on heart rate	No Only one study group/dose tested	No Crossover study		+/++
11 Svatikova et al 2015 Initial rating ++++	1: Not serious concern	Not serious concern	Not serious concern	Not serious concern	Small increase in SBP and DBP measurements between treatment and control. No effect on heart rate	No Only one study group/dose tested	No Crossover study		++++

12 Peacock et al 2014 ++++	2: Serious concern	Very serious concern	Not serious concern	Not serious concern Self–reported effects	Heart palpitations: no effect Other physiological outcomes: no effect All outcomes were self–reported	No, only one dose	No		+++/++

All studies (initial **rating ≥** +++)	Major influence on RoB comes from lack of exposure control, lack of proper blinding of study subjects or personnel and lack of description of randomization method. Less important was the lack of information on attrition or exclusion from analysis	2/14 studies had concern regarding industry funding. No concern regarding other conflict of interest	Consistent increase in blood pressure parameters across studies. Inconsistent results on heart arrhythmia and heart rate across studies	Generally lack of control of exposure condition in control groups. Moderately sized test groups in most studies. Nutritional content was often not describes. Baseline values were different between treatment and control group. Question the use of water as a comparator to energy drink.	Generally small or no effects.	Most studies have only one study group, and therefore dose–response are not possible to assess. One study with low quality had three study groups with energy drinks, but no dose response was observed.	No	The study groups were consistent, and contained mostly healthy adult individuals. One exception with study participants with familial long QT syndrome (LQTS).	<u>Energy drink versus water</u>: Blood pressure (increase): unlikely Heart rate (increase): unlikely <u>Energy drink versus sugar/juice/de–caffeinated control</u>: Blood pressure (increase): Likely Heart arrhythmia (no effect): inadequate Heart rate (no effect): Very likely <u>Energy drink versus caffeine control (one study only)</u>: Blood pressure (increase): As likely as not/unlikely Heart arrhythmia (small increase, but drop in control): inadequate Heart rate (no effect): Inadequate

Table 2. Weighting the body of evidence; Metabolic effects of energy drinks. * Metabolic effects: as described in the study in question

Energy drinks: Metabolic effects									
		Elements triggering downgrading			Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency	
1 Svatikova et al 2015 Initial rating ++++	1: Not serious concern	Not serious concern	Not serious concern	Not serious concern	Moderate effect Increase in norepinephrine in treatment group (73.6%, 249.8 pg/ml) compared to control (30.9%, 178 pg/ml).	No Only one study group/dose tested	No Crossover study		++++
All studies (initial **rating ≥** ++++)	Not serious concern	Not serious concern	Not serious concern	Not serious concern		No Only one study group/dose tested	No	Not applicable (one study)	Norepinephrine increase: Very likely (in line with increase in blood pressure)

Table 3. Weighting the body of evidence; Psychobehavioural effects of energy drinks.

Energy drinks: Psychobehavioural effects									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/ COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency	
1 Kurtz et al 2013 +++ Lack of controlled exposure conditions	3: Very serious concern	Not serious concern	Serious concern The type of reported psychobehavioural effects were different in the treated versus control groups and were inconsistent.	Serious concern Moderate size of study group. Self–reported data on psychobehavioural effects. Relatively high variability in measurements. Caffeine content in test group not specified.	No effect The participants were asked about events such as headache, jitteriness, nausea and sleepiness. No difference were found between treated and control group	No Only one study group/dose tested	No Crossover study	Not applicable	+
2 Phan and Shah 2014 +++ Lack of controlled exposure	3: Very serious concern	Not serious concern	Serious concern Few and no consistency in the reported results	Serious concern Small test group (n=10). Beverage liquid amount was not reported. There were statistically significant differences in	No effect No clear differences between treated and control group	No Only one study group/dose tested	No Crossover study	Not applicable	+

conditions				baseline values of treated and control group for several parameters. The method for registration of psychobehavioural effects was not reported.					
3 Peacock et al 2014 ++++	2: Serious concern	Very serious concern	Not serious concern	Not serious concern Self–reported data on psychological effects.	Psychological outcomes: no effects	No, one dose only	No Crossover study	Not applicable	+++/++
All studies (initial rating = +++)	Study blinding, exposure control and outcome assessment were inadequate.	1/3 studies had serious concern with funding bias	Inconsistency in outcome	Imprecision in exposure between treatment and control, and method for registration of psychobehavioural effects was not reported.	No effects between treatment and control groups	No Only one study group/dose tested	No	Consistent within university recruitment populations of young adults	Inadequate (no effect)

Table 4. Weighting the body of evidence; Cardiovascular effects of energy drinks combined with physical activity

Energy drinks + exercise: Cardiovascular effects									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency	
Lara et al 2014 Initial rating ++++	1: Not serious concern	Not serious concern	Not serious concern	Not serious concern	No effect between treatment and control regarding HR during exercise	No Only one study group/dose tested	No Crossover study	Not applicable	++++
Lara et al 2015 Initial rating ++++	1: Not serious concern	Serious concern Energy drinks provided by industry	Not serious concern	Not serious concern	No effect on peak HR or heart palpitations	No Only one study group/dose tested	No Crossover study	Not applicable	+++
Svatikova et al 2015 Initial rating ++++	1: Not serious concern	Not concern	Not serious concern	Not serious concern	No effect on SBP, DBP, MBP or HR of treatment during physical stress test	No Only one study group/dose tested	Not applicable	No Crossover study	++++

All studies (initial rating = ++++)	No description of randomization and some weaknesses in exposure characterisation and outcome assessment	One study got the energy drinks from industry	No serious concern	Final rating	No description of randomization and some weaknesses in exposure characterisation and outcome assessment	One study got the energy drinks from industry	No	Consistency across the three studies	Heart palp: inadequate evidence Blood pressure: very likely no health effect Heart rate: very likely no health effect

Table 5. Weighting the body of evidence; Psychobehavioural effects of energy drinks combined with physical activity

Energy drinks + exercise: Psychobehavioural effects									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/ COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency	
1 Lara et al 2014 Initial rating ++++	1: Not serious concern	Not concern	Not serious concern	Not serious concern	Moderate effect of treatment on insomnia, but not possible to evaluate the statistical significance of this finding. Placebo group reported higher effect on headache and gut discomfort.	No Only one study group/dose tested	No Crossover study	Not applicable	++++
2 Lara et al 2015 Initial rating ++++	1: Not serious concern	Serious concern Energy drinks provided by industry	Not serious concern	No serious concern	No effect on insomnia, gut discomfort Placebo group had higher anxiety, but not statistically significant	No Only one study group/dose tested	No Crossover study	Not applicable	+++
3 Salinero et al 2014 Initial	1: Not serious concern	Not concern	Not serious concern	No serious concern .	Small effect of treatment on nervousness, insomnia and fatigue (females	No Only one study group/dose	No Crossover study	Not applicable	++++

rating ++++					only), but not possible to evaluate statistical significance No effect of treatment on headache, irritability and gut discomfort	tested			
All studies (initial rating = ++++)	No serious concern	Energy drinks provided by industry in one study	No serious concern	No serious concern	Some very small effects, but not possible to evaluate statistical significance.	No Only one study group/dose tested	No	Small non–significant effects and inconsistent between the studies.	Insomnia: No significant effects Nervousness: No significant effects Headache, anxiety, irritability, gut discomfort: no effect

Table 6. Weighting the body of evidence; Physiological and psychological effects of energy drinks combined with alcohol.

Energy drink + alcohol: Physiological and psychological effects									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/ COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency (for final rating only)	
Peacock et al 2014 ++++	2: Serious concern	Very serious concern	Not serious concern	Serious concern. Comparison difficult due to insufficient description of combined alchohol/ energy drink Self–reported data Moderate size of study group	Muscular tension reduction: small effect Self–reported psychological outcomes: no effects	No, only one dose	No		++

All studies (initial **rating ≥** +++)	Bias in exposure characterisation	Products received from industry	Consistent results	Comparison difficult due to insufficient description of combined alchohol/ energy drink	No or small effects of energy drink and alcohol combined compared with placebo	No dose–response	No	Not applicable (one study)	Final rating: <u>Muscular tension reduction:++</u> Unlikely <u>Other psychological outcomes: ++</u> Inadequate

Table 7. Weighting the body of evidence; Cardio–, cerebrovascular and cardiorespiratory effects of caffeine

Caffeine: Cardio–, cerebrovascular and cardiorespiratory effects									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/ COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency	
Bloomer 2013 Initial rating ++++	2: Serious concern	Very serious concern	Not serious concern, but difficult to interpret due to the large amount of endpoints combined with lack of correction for multiple comparisons	Not serious concern.	Cardiovascular: no effect Respiratory rate: no effect	No (not reported)	No (parallel design) Caffeine induces bronchodilation, however, no effect on respiratory rate was seen		++

Bloomer 2015 Initial rating +++ Variable dosing	3: Very serious concern	Very serious concern	Not serious concern, but difficult to interpret due to the large amount of endpoints combined with lack of correction for multiple comparisons. Baseline differences for several conditions.	Not serious concern.	Cardiovascular: no effect Respiratory rate: no effect	No (not reported)	No (parallel design) Caffeine induces bronchodilation, however, no effect on respiratory rate was seen		+

Dodd 2015 Initial rating ++++	2: Serious concern	Not serious concern. No information on COI	Not serious concern.	Not serious concern.	Cardiovascular: Significant increase in SBP (4 mm Hg) and DBP (8 mm Hg) Low/moderate Heart rate: No effect Cerebrovascular: Reduced mean change in oxygenated Hb during first 18 min post–dose. Increase in change in deoxygenated Hb following caffeine treatment (non–consumers) Level is that of neuronal activation during behavioural test tasks. Low effect	No (one dose).	No, crossover design		+++

Flueck 2016 Initial rating ++++	1: Not serious concern	Not serious concern	Not serious concern	Not serious concern	Note: Effects in tetra– and paraplegic are not necessarily relevant for the general population SBP and DBP: Significant increase in able–bodied (9 and 8 mm Hg) and tetraplegic (19 and 27 mm Hg) subjects, not sign. increase in placebo–group. Increase was less than BP range at baseline for able–bodied. Moderate effect for able–bodied; high effect for tetraplegic. Heart rate variability parameters: no effect Tidal volume: Sign. increase in able–bodied/ paraplegic. Health effect or normal physiologic response (<25% night variation)	No (one dose)	Large effect despite confounding and measures taken Authors reported that respiration could have confounded results as it influenced heart rate variability		++++

Lemery 2015 Initial rating ++++	3: Very serious concern	Not serious concern No information on COI	Not serious concern	Serious concern. Unknown placebo content.	Note: In patients with supraventricular tachycardia. Not relevant for the general population. Resting SBP and DBP: Sign. increase after caffeine (143 mm Hg) compared with placebo (132 mm Hg). Difference is less than the interquartile ranges. Change from baseline not given. Moderate effect Heart rate: no effect Inducibility/cycle length of tachycardia: no effect	No (one dose)	No information		+++/++

Temple 2014 Initial rating ++++	3: Very serious concern	Not serious concern	Not serious concern	Not serious concern.	Change in SBP: sign. increase (both doses) compared with placebo (max ~3 mm Hg). Low effect Change in DBP: sign. increase (both doses) compared with placebo (max ~3 mm Hg). Low effect Heart rate: sign. reduction in heart rate (both doses) compared with placebo (max. 8 beats/min). Low effect Boys had greater response to caffeine than girls	No (two doses)	No, crossover		+++

All studies (initial **rating ≥** +++)	Major influence on RoB comes from lack of exposure control and proper blinding. Less important was the lack of information on randomisation method, attrition or exclusion from analysis, inadequate statistics and recruitment method	Two of six studies have funding bias	Consistent increase in blood pressure parameters across studies. Consistent none or low effect on heart rate across studies	Generally adequately difference between treatment and control	Low to moderate increase in blood pressure for the general population, no effect on heart rate in adults, moderate decrease in 8–17– year–olds (one study). Cannot conclude about remaining endpoints due to the small number of studies.	No dose–response in the few relevant studies	Seldom applicable due to mostly crossover design, however (one study, not general population).	Mostly consistent across healthy adults, including patients with tachycardia. Tetraplegic subjects were less influenced by caffeine, and girls less than boys. Variation across menstrual cycle.	Final rating: <u>Blood pressure:</u> +++ (increase) Likely <u>Heart rate</u>:+++ (no effect/small decrease) Inadequate <u>Respiratory rate</u>: ++ (no effect)Inadequate <u>Cerebrovascular (blood oxygenation):</u> +++ (very low effect) Inadequate Tidal volume: ++++ (normal phys. effect?) Very likely no health effect Inducibility/cycle length of tachycardia:+++/++ (no effect) Inadequate

Table 8. Weighting the body of evidence; Oxidative stress, and haematological and metabolic effects of caffeine. * Metabolic effects: as described in the study in question

Caffeine: Oxidative stress, and haematological and metabolic effects									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/ COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency	
Bloomer 2015 Initial rating +++ Variable dosing	3: Very serious concern	Very serious concern	Not serious concern	Not serious concern	Haematology: no effect Metabolic effects*: no effect	No (not reported)	No information		+
Bloomer 2013 ++++	2: Serious concern	Very serious concern	Not serious concern	Not serious concern	Haematology: no effect Metabolic effects*: significantly higher potassium values for caffeine compared to placebo group (within normal range). Low effect	No (not reported)	No information		++/+++

					Advanced oxidation protein products: Significantly higher level for caffeine compared to placebo. Low biological sifgnificance				
Flueck 2016 Initial rating ++++	Not serious concern	Not serious concern	Not serious concern	Not serious concern	Note: Effects in paraplegics are not necessarily relevant for the general population Epinephrine: significant (3–fold) increase in plasma concentration in able–bodied and paraplegic after caffeine ingestion (no change in corresponding placebo groups) (within normal physiological variations)	No (one dose)	No information		++++

All studies (initial r**ating ≥** +++)	Variable bias from none to uncertainty in exposure control, blinding and statistical analysis	Two of three studies had funding bias	No consistency concern	Test substance and placebo were adequately different	No effect or low (within normal physiological variations)	No evidence for dose–response	No	Haematological and metabolic values were consistent for adult men (Epinephrine: one study)	Final rating: <u>Haematology</u>:++ Inadequate <u>Metabolic effects</u>*:++ Inadequate <u>Advanced oxidation protein products</u>: ++ Unlikely

Table 9. Weighting the body of evidence; Psychobehavioural effects of caffeine.

Caffeine: Psychobehavioural effects									
	Elements triggering downgrading				Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/ COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency	
Dodd 2015 Initial rating ++++	2: Serious concern	Not serious concern. No information on COI	Serious concern. Mostly not significant mood effects (one of seven parameters), except on overall mood	Not serious concern.	Mood: No effects on individual parameters	No	No		+++/++
Rogers 2013 ++++	3: Very serious concern	Very serious concern Conflict of interest	Serious concern Sleepiness and anxiety/jitteriness did not vary consistently among non–low and medium–high consumers	Not serious concern	Sleepiness: Small reduction in test score Anxiety/jitteriness: Small or no increase	No	No		++

All studies (initial **rating ≥** +++)	Bias in exposure characterisation and outcome. Less important are recruitments methods and statistics	One of two studies reported receiving grants from pharmaceutical industry	Not consistent within studies	Not serious concern	Small or no effect	No dose–response can be established	No	Lack of or low effects despite different intake groups: One study compared non–low and medium–high (< or > 40 mg caffeine/day). The other compared habitual (up to 432 mg/day) and nonhabitual (<56 mg/day)	Final rating: <u>Mood:</u> +++/++ (no effect) Inadequate <u>Sleepiness:</u> ++ (low effect) Unlikely/inadequate <u>Anxiety/jitteriness</u>: ++ (low effect) Unlikely/inadequate

Table 10. Weighting the body of evidence; Cardiovascular effects of caffeine and physical activity

Caffeine + physical activity: Cardiovascular effects									
		Elements triggering downgrading			Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/ COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency (for final rating only)	
Puente 2017 Initial rating ++++	2: Serious concern	Not serious concern	Not serious concern	Not serious concern	No effect of caffeine supplement prior to physical activity on heart rate.	No	No		+++

Souza 2014 Initial rating ++++	3: Very serious concern	Not serious concern	Serious concern Unexplained decrease in blood pressure in the placebo group between resting values and pre–exercise.	Not serious concern	No Small increase in blood pressure pre– and post–exercise. There was a difference in 10 mm Hg between resting blood pressure (diastolic and systolic), however, variation within the groups were up to 9 mm Hg. No difference in heart rate between caffeine and placebo.	No	No		++

Bunsawat 2015 Initial rating +++ All participants received equal amounts of caffeine with no adjustment for body weight.	3: Very serious concern	Not serious concern	Not serious concern	Not serious concern	Not large effects During recovery, heart rate, QTc and blood pressure were slightly elevated with caffeine compared to placebo The differences between caffeine and placebo were in the same range as variability (standard error)	No	No		+

All studies (initial **rating ≥** + + +)	Major influence on RoB comes from lack of information on randomization method and blinding. There were also bias in exposure characterisation and outcome. Less important are recruitments methods and statistics.			Not serious concern. Identical capsules were used. Intervention capsules contained caffeine, whereas placebo did not contain caffeine.	No large effects	No dose–response can be established Only one caffeine dose tested.	All studies used crossover design	Consistent increase in blood pressure parameters across studies. Inconsistent results on heart rate across studies No effect on arrhythmia	<u>Caffeine + versus placebo, post–exercise</u>: Blood pressure: Unlikely (2 studies: small increase; 1 study: not assessed) Heart rate: Inadequate (2 studies: no effect; 1 study: small increase) Arrhythmia: Inadequate (1 study: small increase) <u>Caffeine versus placebo capsule, pre–exercise:</u> Blood pressure: Unlikely (1 study: small increase; 2 studies: not assessed) Heart rate: Inadequate (2 studies: no difference; 1 study: not assessed)

Table 11. Weighting the body of evidence; Metabolic effects of caffeine and physical activity

Caffeine + physical activity: Metabolic effects									
		Elements triggering downgrading			Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding/COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency (for final rating only)	
Wu 2015 Initial rating ++++	3: Very serious concern	Not serious concern	Not serious concern	Not serious concern	Small increase in cortisol and glucose levels. Small decrease in insulin response	No	No		++
All studies (initial **rating ≥** +++)	Inadequate reporting of blinding, randomization, recruitment methods.			Identical capsules; control capsule did not contain caffeine and intervention capsules contained either 2, 4 or 6 mg caffeine/kg bw. Small number of subjects and power analysis not performed.	No large effects	No clear dose response	Crossover study		Metabolic effects: Unlikely (1 study: small increase)

Table 12. Weighting the body of evidence; Psychobehavioural, insomnia, gastrointestinal and muscular effects of caffeine and physical activity

Caffeine + physical activity: Psychobehavioural, insomnia, gastrointestinal and muscular effects									
		Elements triggering downgrading			Elements triggering upgrading				Rating of individual study
Reference Initial rating	Risk of bias (tiers 1–3)	Funding / COI bias	Unexplained inconsistency	Imprecision	Large effect	Dose–response relationship	Residual confounding	Consistency (for final rating only)	
Puente 2017 Initial rating ++++	2: Serious concern	Not serious concern	Not serious concern	Not serious concern	Moderate effect Self–reported insomnia increased from 19 to 54.4% following a single dose of 3 mg/kg bw caffeine (p= 0.041)	No	No		++++
Salinero 2017 Initial rating ++++	2: Serious concern	Not serious concern	Not serious concern	Not serious concern	No effect on side–effects; sleep quality /insomnia, nervousness, muscular pain, headache, gastrointestinal effects.	No	No		+++

All studies (initial rating = ++++)	Lack of information on randomization, attrition or exclusion from analysis and inadequate information on caffeine			Not serious concern. Identical capsules were used. Intevention capsules contained caffeine, whereas placebo did not contain caffeine.	Moderate effect of insomnia in one study, no difference in another study. No difference in psychobehavioral, muscular and gastrointestinal effects.	No dose–response can be established Only one caffeine dose tested.	All studies used crossover design	Inconsistent results across studies.	Insomnia/sleep quality: As likely as not (1 study: moderate increase, 1 study: no difference) Muscular effects: Inadequate (1 study: no difference) Gastrointestinal effects: Inadequate (1 study: no difference) Psychobehavioral effects: Inadequate (1 study: no difference)

16 Appendix: Exposure

16.1 Energy drink consumption – questions and answer alternatives

In this appendix we present the questions and answer alternatives from the surveys using questionnaires for data collection, used in the present risk opinion. The questions were translated into English.

16.1.1 Norwegian Consumer Council study (NCC study)

NCC1

Question: "Do you sometimes drink energy drinks with caffeine (for example Battery, Burn, Red Bull, Monster or similar)?"

Answer alternatives: "Yes"; "No"; "I do not know what it is".

NCC2

Question: "Which energy drinks do you drink?"

Answer alternatives: "Battery energy drink"; "Burn energy drink"; "Mad-Croc energy drink"; "Monster energy drink"; "Nocco energy drink"; "Powerking energy drink"; "Red Bull energy drink"; "Other energy drinks, please fill in" (open ended alternative); "Do not know/do not remember".

NCC3

Question: "How often do you drink energy drinks?"

Answer alternatives: "Many times per day"; "Every day"; "3-6 times each week"; "1-2 times each week"; "1-2 times per month"; "I have only drunken energy drink a few times"; "Do not know".

NCC4

Question: "When you drink energy drinks, how much do you usually drink?"

Answer alternatives: "0.5 liter"; "0.33 liter"; "0.25 liter"

NCC5

Question: "What is the highest number of cans you have drunk during 24 hours?"

No answers alternatives, open ended question to be filled in.

NCC6

Question:"How often do you eat or drink the following:"

- "Chocolate"
- "Cocoa"
- "Cola"
- "Black coffee"
- "Espresso"
- "Caffe latte"
- "Iced coffee"
- "Black tea"

Answer alternatives for each food or beverage: "'"Many times per day"; "Once per day"; "3 to 6 times each week"; "1 to 2 times each week"; "1 to 3 times per month"; "I have only drunken energy drink a few times"; "Never"; "Do not know".

16.1.2 Ungdata study, Oslo Metropolitan University

Ungdata1

Question: "How often do you eat or drink any of the items in the list below?"

Answer alternatives: many different foods and beverages, one item read: "Energy drinks (Red Bull, Battery or similar)?". The frequency alternatives were: "Never"; "Less than once per week"; "Once per week"; "2-3 times per week"; "4-6 times per week"; "Every day"; "Many times daily".

Ungdata2

Question: "How often do you drink energy drinks (for example Andrenaline, Battery, Burn, Monster, Red Bull, Urge, Intense)?"

Answer alternatives: "Never"; "Used to drink them but quit"; "Approximately once a month or less"; "Approximately every 14th day"; "1- 3 times per week"; "4-6 times per week"; "Daily".

Ungdata3

Question: "How much energy drink do you usually drink, when you do consume energy drinks?"

Answer alternatives: "1 small can (approx. 250 ml)"; "1 medium sized can (approx. 330 ml)"; "1 big can (approx. 500 ml)";"Many cans equivalent to approx. 1 liter"; "Many cans equivalent to approx. 1.5 liters"; "Many cans equivalent to more than 1.5 liter".

16.1.3 MoBa Cohort survey 2017-2018

MoBa1

Question: "What have you been drinking the last month?"

Answer alternatives: "Energy drinks (for example Red Bull, Battery and similar)".

For frequency of intake the questionnaire had the following options: "0 glasses per month"; "1-3 glasses per month"; "1 glass per week"; "2-6 glasses per week"; "1 glass per day"; "2-3 glasses per day"; "More than 3 glasses per day".

One glass was defined as "2-2.5 dl".

16.1.4 Caffeine concentrations in food and beverages

Table A16-1 lists all caffeine concentration levels used in this assessment. Ungkost 3 was a dietary study that cover the whole diet for four days. The caffeine content in food, beverages and recipes were calculated in KBS (Kostberegningssystemet, University of Oslo). All foods, beverages and recipes were calculated with the caffeine concentrations given in table A16-1. This means that for example bakery wares with chocolate or cocoa powder got a caffeine concentration. A total of 138 foods and recipes were given a caffeine concentration.

Table 16.1.4-1. Concentrations of caffeine used in the exposure assessment, from EFSA 2015 (Table 1, p 21).

	Caffeine concentrations mg/kg or mg/L
Cappuccino	273
Chocolate bar	111
Chocolate, milk	168
Cocoa beverages based on cocoa powder	168
Cocoa beverages based on instant powder	42
Cocoa powder	2000[a]
Coffee, black	445
Cola beverages	108
Dark chocolate	525
Espresso	1340
Ice coffee/caffe latte	144
Tea, drink	220

[a] value based on data from the USDA National Nutrient Database for Standard Reference Legacy Release, December 2018.

17 Appendix: Deviations from the protocol

The project group undertook all deviations during their work with the hazard evaluation and presented them to the Panel on the first following meeting for acceptance. All mention to the Protocol for the risk assessment of energy drinks and caffeine (VKM, 2018) will be denoted "Protocol" below and the Chapter numbers are those of this protocol.

17.1 Literature

The literature search was from January 2013, not May 2013 as stated in the protocol.

Due to the large amount of literature retrieved, the number of reviewers to screen titles and abstract and later, screening of full-text publications were increased from two to three to minimise the risk for overlooking a study to be included.

17.2 Inclusion/exclusion criteria

In addition to identifying studies on adverse effects, on the proposal of the project group, the Panel decided to include studies focusing on beneficial effects as well as these studies may contain mention of adverse effect as a secondary aim. Furthermore, effect regarded as beneficial may not be so in all population groups and may, dependent of magnitude, pose a hazard.

17.3 Data extractions forms

Following the project group's completion of initial data extraction exercises of the 28 included RCTs, the group slightly amended Table 3.2.5.1 of the Protocol (VKM, 2018) to optimise data extraction to adjust to the study type in question to aid in extracting the relevant information. The amended table is presented below (Table 17.3-1).

Table 17.3-1. Data extraction form used in the present assessment.

Study ID a. Reference b. Health outcome(s)	
Funding a. Funding source(s) b. Reported conflict of interest	

Study ID a. Reference b. Health outcome(s)	
Study design a. Study type (e.g. RCT, cohort, etc.) b. Type of blinding c. Method for randomization d. Year the study was conducted (start/stop)	
Subjects a. Number of participants in the study (invited, accepted, drop out, participating, included in follow-up if applicable) b. Completion rate c. Number of exposed/non-exposed subjects or number of cases/controls d. Sex (male/female) e. Geography (country) f. Age g. Ethnicity h. Confounders and other variables as reported i. Health status of participants j. Inclusion/exclusion criteria k. Other	
Intervention/exposure a. Test substance b. Estimated dietary exposure/intake (measures of variance as presented in paper such as mean, standard deviation, median, percentiles, minimum/maximum) c. Intervention design d. Co-exposure description (if applicable)	
Methods for endpoint assessment a. Parameters measured and methods used b. Measurement time points	
Statistical analysis a. Power analysis b. Statistical test c. Results and outcome assessment	

17.4 Risk of bias evaluation

Following risk of bias evaluation according to the Protocol, the project group found that the five questions that were constructed to answer any risk of bias in the extracted literature (Table 3.2.5.2 in VKM et al. (2018)) and the two additional aspects described (Chapter 3.2.5, (VKM et al., 2018)) were insufficient to properly evaluate risk of bias. The issues were related both to the number of questions and to lack of specificity to adequately evaluate the internal validity of the included literature. Therefore, the project group consulted previously defined rating questions (NTP, 2015b) and chose to include the questions specifically

pertaining to human controlled studies. The new questions included the specifically mentioned aspects outlined in the protocol (included in the new questions). Furthermore, the project group exchanged the response options presented by NTP (2015b) with those in Table 3.2.5-3 in the Protocol as the project group considered these evaluation criteria to be more specific and detailed than those in the above-mentioned table. Following a second risk of bias evaluation, the project group considered it more fair to tailor the response options (risk of bias rating) to specifically meet the demands of the assessment of energy drinks and caffeine. The project group went on to define response options to question number 5 (Tables 3.1.3-1 and 3.2.3-1): "Can we be confident in the exposure characterisation" (note: other bias related to exposure in addition to that specifically mentioned in the response options were included as well). The response options to this question is presented in Chapter 14 Appendix: Risk of bias.

Risk of bias evaluation to be integrated to classify the final rating in tiers from 1 to 4 corresponding to decreasing levels of risk of bias. The project group found that four tiers would be too compartmentalised and decided to adapt the tier approach outlined in the EFSA Protocol for assessment of BPA (EFSA et al., 2017) applying three tiers. These tiers correspond to decreasing levels of internal validity.

The project group performed initial exercises in tier classifications and adjusted the tier definitions to separate sufficiently the selected literature in justified classes of risk of bias. Following an evaluation of the initial risk of bias exercises, the tiers were defined as presented in Chapter 3.1.3.

The Protocol describes (3.2.5) how the rating of the risk of bias was to be integrated to classify the final rating in tiers from 1 to 4 corresponding to decreasing levels of risk of bias. The project group found that four tiers would be too compartmentalised and decided to adapt the tier approach outlined in the EFSA Protocol for assessment of BPA (EFSA et al., 2017) applying three tiers. These tiers correspond to decreasing levels of internal validity.

17.5 Weighting the body of evidence

The Protocol describes that one table of WoE would be used per endpoint for energy drinks, energy drinks in combination with alcohol, energy drinks in combination with physical exercise, and caffeine. To improve comparison of endpoints observed in the studies of energy drinks to those of caffeine, the project group decided to divide exposure in the same manner as for energy drinks to caffeine as well. This procedure resulted in two exposure groups per endpoint for caffeine: caffeine alone and caffeine in combination with exercise. To aid in the separation of weight of evidence of the included literature, the project group decided to adapt the initial confidence rating described in EFSA et al. (2017) (Chapter 8.2) modified to apply to human RCTs. The decision was made by the project group following an exercise in weight of evidence of one endpoint group observed in four articles. The initial rating criteria are described in Chapter 3.1.4 of this risk assessment. To further facilitate the confidence rating, the project group decided to apply the upgrading and downgrading

criteria written in the first row of Table 3.2.6-1 of the Protocol to the final rating of all studies combined under the endpoint in question. For each study, the criteria outlined in the first row of Table 10 in EFSA et al. 2017 were implemented (Table 3.1.4-1). In this way, the grading of confidence of each study could be done more specifically and with greater precision. To enable evidence rating of studies in which adverse effects were not observed, the project group decided to adapt the rating system of OHAT, (NTP, 2015a).

Weighting the body of evidence shows translation of confidence into evidence of health effect, and the translation of no effect was adapted in the current WoE. This implies that only high confidence in the body of evidence could be denoted "evidence of no health effect" whereas all other levels of confidence were denoted "inadequate evidence for health effect".

In Chapter 3 of the Protocol it was stated that dose-response would be performed for "very likely" and "likely" adverse effects. Dose-response was not observed in any study and the statement was modified to "Risk characterisation will be performed for "very likely" and "likely" adverse effects".

Due to the importance of the weight of evidence outcome for the hazard characterisation, the project group decided that three individual reviewers should perform the task of confidence rating. A fourth reviewer checked the step-by-step procedure and took part in discussions of disagreements until a consensus was reached.