SCIENTIFIC OPINION

Scientific Opinion on the safety of caffeine[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2,3]

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ABSTRACT

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies was asked to deliver a scientific opinion on the safety of caffeine, providing advice on caffeine intakes, from all dietary sources that do not give rise to concerns about adverse health effects for the general healthy population and subgroups thereof. Possible interactions between caffeine and other constituents of so-called "energy drinks", alcohol, *p*-synephrine and physical exercise should also be addressed. Single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) do not give rise to safety concerns. The same amount does not give rise to safety concerns when consumed < 2 hours prior to intense physical exercise under normal environmental conditions. Other constituents of "energy drinks" at typical concentrations in such beverages (about 300–320, 4 000 and 2 400 mg/L of caffeine, taurine and D-glucurono-γ-lactone, respectively), as well as alcohol at doses up to about 0.65 g/kg bw, would not affect the safety of single doses of caffeine up to 200 mg. Habitual caffeine consumption up to 400 mg per day does not give rise to safety concerns for non-pregnant adults. Habitual caffeine consumption up to 200 mg per day by pregnant women does not give rise to safety concerns for the fetus. Single doses of caffeine and habitual caffeine intakes up to 200 mg consumed by lactating women do not give rise to safety concerns for breastfed infants. For children and adolescents, the information available is insufficient to derive a safe caffeine intake. The Panel considers 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 for these population subgroups.

KEY WORDS

caffeine, taurine, D-glucurono-γ-lactone, *p*-synephrine, alcohol, physical activity, "energy drinks"

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SUMMARY

Following a request from the European Commission, the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the safety of caffeine. Possible interactions between caffeine and other common constituents of so-called "energy drinks", alcohol, synephrine and physical exercise should also be addressed.

Caffeine is an alkaloid found in various plant constituents, such as coffee and cocoa beans, tea leaves, guarana berries and the kola nut, and has a long history of human consumption. It is an ingredient added to a variety of foods, e.g. baked goods, ice creams, soft candy, cola-type beverages. Caffeine is also an ingredient of so-called "energy drinks" and it is present in combination with synephrine in a number of food supplements marketed for weight loss and sports performance, among others. Some medicines and cosmetics also contain caffeine. "Energy drinks" most often contain combinations of caffeine, taurine and D-glucurono-γ-lactone, among other ingredients. Synephrine is a biogenic amine of the chemical group of phenylethanolamines/phenylpropanolamines. The protoalkaloid (–)-*p*-synephrine is naturally found in bitter orange fruit (*Citrus aurantium* L.) and other citrus fruits. The presence of (+)-*p*-synephrine or *m*-synephrine in food supplements containing *C. aurantium* extracts is indicative of adulteration. Only (–)-*p*-synephrine, the natural compound from *C. aurantium* extracts found in food supplements, is considered in this opinion (referred to as *p*-synephrine hereafter).

This opinion addresses possible adverse health effects of caffeine consumption from all dietary sources, including food supplements, in the general healthy population and in relevant specific subgroups of the general population (e.g. children, adolescents, adults, the elderly, pregnant and lactating women, subjects performing physical exercise). Whether other substances present in "energy drinks" (D-glucurono-γ-lactone and taurine), alcohol or *p*-synephrine may modify the possible adverse health effects of caffeine and/or the doses at which such adverse effects may occur is also addressed. It is outside the scope of the present opinion to address possible adverse health effects of caffeine given as medicine or administered via routes other than the oral route; in subgroups of the population selected on the basis of a disease condition or in sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions which may require individual advice; or in combination with medicines and/or drugs of abuse, or in combination with alcohol doses which, by themselves, pose a risk to health (e.g. during pregnancy, binge drinking). It is also outside the scope of this opinion to assess possible beneficial health effects of caffeine or of particular dietary sources of caffeine.

The Panel interprets the request from the European Commission as follows: (i) to provide advice on a daily intake of caffeine from all sources which, if consumed *ad libitum* and throughout the day for long periods of time, does not give rise to concerns about harmful effects to health for the healthy population, divided into various life-stage groups as appropriate; (ii) for the specific group of individuals performing physical activity, to advise on caffeine consumption (dose and timing) prior to physical activity which does not give rise to concerns about harmful effects to health for this population subgroup; and (iii) to advise on whether or not, and if so to what extent, the consumption of caffeine together with other food constituents (such as alcohol, substances found in energy drinks or *p*-synephrine) presents a health risk and if additional or different recommendations for caffeine intakes need to be provided, regarding either the dose of caffeine or the time interval between the consumption of caffeine and the aforementioned food constituents.

The EFSA Comprehensive European Food Consumption Database was used to calculate caffeine intake from food and beverages. It contains data from 39 surveys in 22 different European countries for a total of 66 531 participants. These surveys do not provide information about the consumption of caffeine-containing food supplements. The EFSA report on energy drinks was used to calculate caffeine intakes from "energy drinks" in a "single session" in adults, either alone or in combination with physical exercise.

Owing to the abundance of scientific literature available, previous risk assessments on the safety of caffeine consumption in humans conducted by authoritative bodies will be reviewed first to identify the major health concerns raised in relation to the consumption of caffeine, either alone or in combination with other components of "energy drinks", alcohol or *p*-synephrine, and the specific population subgroups which are relevant for the assessment.

The Panel reviewed the literature reporting on the effects of single and repeated doses of caffeine consumed within a day, either alone or in combination with other constituents of "energy drinks" and with *p*-synephrine, on cardiovascular outcomes, hydration and body temperature in adults, both at rest and in relation to physical exercise. The effects of single and repeated doses of caffeine consumed within a day on the central nervous system were assessed in adults (sleep, anxiety, perceived exertion during exercise and subjective perception of alcohol intoxication) and children (sleep, anxiety and behavioural changes). Adverse effects of longer-term and habitual caffeine consumption were evaluated in children in relation to behavioural changes and in pregnant women in relation to adverse birth weight-related outcomes (e.g. fetal growth retardation, small for gestational age) in the offspring. In adults, the adverse effects of habitual caffeine consumption, either alone or in combination with other constituents of "energy drinks" and with *p*-synephrine, were evaluated in relation to cardiovascular outcomes. The scientific publications identified almost exclusively reported no relationship or an inverse relationship between habitual caffeine intake and other adverse health effects.

The scientific assessment is based on human intervention and observational studies with adequate control for confounding variables, which have been conducted in healthy subjects at recruitment. Whenever available, human intervention studies and prospective cohort studies have been preferred over case–control and cross-sectional studies because of the lower risk of reverse causality and recall bias. Case reports of adverse events have not been considered for the scientific assessment. Systematic reviews and meta-analysis have been used to summarise the scientific evidence whenever available.

On the basis of the data available, the NDA Panel reached the following conclusions on caffeine intakes which do not give rise to safety concerns for specific groups of the general population.

Adults

Single doses of caffeine

Single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) from all sources do not give rise to safety concerns for the general healthy adult population. 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. No studies are available in pregnant women or middle-aged/elderly subjects undertaking intense physical exercise. 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.

Other common constituents of "energy drinks" at concentrations commonly present in such beverages (typically about 300–320, 4 000 and 2 400 mg/L of caffeine, taurine and D-glucurono-γ-lactone, respectively) would not affect the safety of single doses of caffeine up to 200 mg. 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, the central nervous system or hydration status. Alcohol consumption at doses up to about 0.65 g/kg bw, leading to a blood alcohol concentration of about 0.08 %, would not affect the safety of single doses of caffeine up to 200 mg from any dietary source, including "energy drinks". Up to these levels of intake, caffeine is unlikely to mask the subjective perception of alcohol intoxication.

The human intervention studies on which these conclusions are based were primarily conducted with caffeine supplements for most of the outcomes assessed (i.e. changes in myocardial blood flow, hydration status, body temperature, perceived exertion/effort during exercise, sleep). Changes in blood

pressure were assessed using caffeine supplements, coffee, tea and "energy drinks" as sources of caffeine, whereas the subjective perception of alcohol intoxication was tested using caffeine either from supplements or from "energy drinks".

The question of whether or not *p*-synephrine modifies the acute cardiovascular effects of single doses of caffeine has not been adequately investigated in humans, particularly if consumed shortly before intense physical exercise, and therefore no conclusions could be drawn.

About 6 % of the adult population may exceed 200 mg of caffeine in a single session of "energy drink" consumption, and about 4 % do so in connection with physical exercise. This information is not available for other sources of caffeine.

Habitual caffeine consumption

Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg bw per day for a 70-kg adult) consumed throughout the day do not give rise to safety concerns for healthy adults in the general population, except pregnant women (see below). No health concerns in relation to acute toxicity, bone status, cardiovascular health, cancer risk or male fertility have been raised by other bodies in previous assessments for this level of habitual caffeine consumption and no new data have become available on these or other clinical outcomes which could justify modifying these conclusions.

Other common constituents of "energy drinks" at the doses commonly present in such beverages and/or moderate habitual alcohol consumption would not affect the safety of habitual caffeine consumption up to 400 mg per day.

The question of whether or not *p*-synephrine modifies the acute cardiovascular effects of single doses of caffeine or the long-term effects of caffeine on the cardiovascular system has not been adequately investigated in humans and therefore no conclusions could be drawn.

In 7 out of 13 countries, the 95th percentile of daily caffeine intake from foods and beverages exceeded 400 mg. In these countries, the estimated proportion of the adult population exceeding daily intakes of 400 mg ranged from about 6 % to almost one-third (33 %), and coffee was the main source of caffeine. More accurate estimates of caffeine intakes within a given country could be obtained by using national caffeine occurrence data, if available.

Pregnant women

Single doses of caffeine

There are no studies on the health effects of single doses of caffeine consumed by pregnant women prior to intense physical exercise. With regard to the different kinetics of caffeine in this population subgroup, single doses of caffeine which are of no safety concern for non-pregnant adults do not apply to pregnant women performing physical exercise.

Habitual caffeine consumption

Caffeine intakes from all sources up to 200 mg per day consumed throughout the day by pregnant women in the general population do not give rise to safety concerns for the fetus. This conclusion is based on prospective cohort studies showing a dose-dependent positive association between caffeine intakes during pregnancy and the risk of adverse birth weight-related outcomes (i.e. fetal growth retardation, small for gestational age) in the offspring. In these studies, the contribution of "energy drinks" to total caffeine intake was low (about 2 %).

Data to characterise the risk of habitual caffeine consumption in this population subgroup are scarce.

Lactating women

Single doses of caffeine and habitual caffeine consumption

Single doses of caffeine up to 200 mg and habitual caffeine consumption at doses of 200 mg per day consumed by lactating women in the general population do not give rise to safety concerns for the breastfed infant. At these doses of caffeine, daily caffeine intakes by the breastfed infant would not exceed 0.3 mg/kg bw, which is 10-fold below the lowest dose of 3 mg/kg bw tested in a dose finding study and at which no adverse effects were observed in the majority of infants.

There are no data to characterise the risk of single doses of caffeine consumed by lactating women, and data on habitual caffeine consumption in this population subgroup are scarce.

Children and adolescents

The information available for this population subgroup on the relationship between caffeine intakes and health outcomes is insufficient to derive a safe level of caffeine intake.

Single doses of caffeine

Single doses of caffeine of no concern derived for adults (3 mg/kg bw per day) may also apply to children, considering that caffeine clearance in children and adolescents is at least that of adults, and that the limited studies available on the acute effects of caffeine on anxiety and behaviour in children and adolescents support this level of no concern. 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.

There are no data available to characterise the risk of single doses of caffeine from all sources consumed by children and adolescents. Estimates of the proportion of single days in which caffeine intake exceeds 3 mg/kg bw among all survey days using the EFSA Comprehensive Database were used as a conservative approximation.

The estimated 95th percentile of caffeine intake from foods and beverages on a single day exceeded 3 mg/kg bw in 6 out of 16 countries for adolescents (10 to < 18 years), in 9 out of 16 countries for children (3 to < 10 years) and in 3 out of 10 countries for toddlers (12 to < 36 months). The proportion of survey days in which the level was exceeded ranged from about 7 to 12 % in adolescents, from 6 to 15 % in children and from 7 to 37 % in toddlers in the aforementioned countries. Chocolate beverages were important contributors to total caffeine intakes in children and toddlers in most countries, and the use of a conservative caffeine value for this food category may have led to an overestimation of caffeine intakes in these age groups.

Habitual caffeine consumption

As caffeine clearance in children and adolescents is at least that of adults, the same levels of no safety concern derived for adults (i.e. 5.7 mg/kg bw) may also apply to children, unless there are data showing a higher sensitivity to the effects of caffeine in this age group (i.e. difference in pharmacodynamics). As only limited studies are available on the longer-term effects of caffeine on anxiety and behaviour in children and adolescents, there is substantial uncertainty regarding longer-term effects of habitual caffeine consumption in this age group. A level of no safety concern of 3 mg/kg bw per day (i.e. the level of no concern derived for single doses of caffeine for adults) is proposed for habitual caffeine consumption by children and adolescents. This approach is rather conservative in relation to the effects of caffeine on the cardiovascular system, but the limited studies available regarding the longer-term effects of caffeine on anxiety and behaviour in children and adolescents support the proposed caffeine intake level of no safety concern.

The estimated 95th percentile of daily caffeine intake from foods and beverages exceeded 3 mg/kg bw in 5 out of 13 countries for adolescents, in 6 out of 14 countries for children (3 to < 10 years) and in

1 out of 9 countries for toddlers (12 to < 36 months). The proportion of subjects exceeding that level of intake in the above-mentioned countries was about 5 to 10 % for adolescents, 6 to 13 % for children and about 6 % for toddlers. Chocolate beverages were important contributors to total caffeine intakes in children and toddlers in most countries, and the use of a conservative caffeine value for this food category may have led to an overestimation of caffeine intakes in these age groups.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Member States raised concerns in relation to the risk of adverse health effects as a result of the intake of caffeine from all sources, in relation to the safety of caffeine consumption in the general population and in specific target groups (e.g. adults performing physical activity of various intensities, individuals (including adolescents) consuming foodstuffs containing caffeine together with other food constituents such as alcohol or substances found in energy drinks, and in relation to the validity and appropriateness of the total daily intake for the general population proposed in the conditions of use for the claims by the Commission, i.e. 300 mg per day, which is based on the conclusions for pregnant women in the report of the Scientific Committee on Food of 1999 (SCF, 1999).

In its reports, the Scientific Committee on Food (1999, 2003) concluded *inter alia*, that *"the contribution of energy drinks to overall caffeine intake, even when combined with other caffeine containing beverages, was not a matter of concern for non-pregnant adults. For pregnant adults, the Committee concluded that while intakes of caffeine up to 300 mg per day appeared to be safe, the question of possible effects on pregnancy and the offspring at regular intakes above 300 mg per day remained open and therefore moderation of caffeine intake, from whatever source, was advisable during pregnancy."*

Belgium's Superior Health Council (SHC, 2012) recently assessed the use of caffeine in foodstuffs[4] in January 2012 and concluded that *"in healthy adults a maximal daily intake of 400 mg per day does not raise concerns for adverse health effects. For women of childbearing age a maximal daily intake of 300 mg, or even 200 mg, is recommended. For children prior to adolescence an acceptable maximal daily intake of 2.5 mg per kg body weight is advisable."* Another assessment conducted in December 2009 by the same risk assessment body on energy drinks[5] leads to the recommendation that *"regular or excessive consumption of energy drinks should be avoided while ensuring that the total daily intake of caffeine remains below 400 mg, or even 300 mg."* It was also advised *"to avoid consumption of energy drinks when consuming alcoholic beverages or during intense physical activity"*. Finally it was suggested that *"the consumption of energy drinks should be avoided during pregnancy, during breastfeeding, by children up to 16 years old and by people who are susceptible to caffeine."* It is noted that Belgium's recommendation on the upper intake limit of caffeine for the general population is also in line with Health Canada and the US Food and Drug Administration (FDA)[6] which confirmed that *"the general population of healthy adults is not at risk for potential adverse effects from caffeine if they limit their caffeine intake to 400 mg per day"*.

Similarly, the French Agency for Food Safety[7] concluded that *"it is not possible to rule out a possible risk related to consumption of foodstuffs containing caffeine on cardiovascular health in people performing intense physical activity: however, further evaluation on this is needed"*. According to the French Agency[8], *"current knowledge on the risks related to the consumption of energy drinks should, however, help to better understand the role of caffeine in the observed effects"*. Further cases of deleterious effects of caffeine consumption have been reported through the nutri-vigilance system for products containing caffeine.

Overall, at EU level to date, caffeine has only been assessed in the context of energy drinks but the safety of overall caffeine intake, from all sources, and acceptable use levels has not yet been assessed. In order to inform on-going discussions with Member States, the European Commission asks the

[4] Avis du conseil supérieur de la santé No 8689, "Utilisation de la caféine dans les denrées alimentaires", 11 January 2012. Available online: http://www.health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19076526_fr.pdf

[5] Avis du conseil supérieur de la santé No 8622, "Boissons énergisantes", 2 December 2009. Available online: http://www.health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/17982877_fr.pdf

[6] Health Canada, 2010. Available online: http://www.hc-sc.gc.ca/hl-vs./alt_formats/pdf/iyh-vs.v/food-aliment/caffeine-eng.pdf, US FDA letter to Senator Richard J. Durbin, 10 August 2012.

[7] Agence Française de Sécurité Sanitaire des Aliments.

[8] Afssa—Saisine No 2002-SA-0260, 5 May 2003; Afssa—Saisine No 2005-SA-0111, 30 January 2006; Afssa Saisine No 2006-SA-0236, 9 November 2006.

Authority to review the existing scientific data on the possible link between the intake of caffeine, from all sources, and adverse health effects.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002 the European Commission[9] asks EFSA to:

- Review the existing scientific data on the potential link between caffeine intakes, from all sources, and possible adverse health effects in the general population and as appropriate, in specific subgroups of the population, including but not limited to, individuals performing physical activity of various intensities, women of childbearing age, pregnant women, breastfeeding women, children and adolescents;

- Provide advice on a tolerable upper intake level (UL) for caffeine, from all sources, for the general population and as appropriate, for specific subgroups of the population, including but not limited to, individuals performing physical activity of various intensities, women of childbearing age, pregnant women, breastfeeding women, children and adolescents. For the specific group of individuals performing physical activity, advice should be provided on a safe/recommended timing of caffeine consumption prior to the physical activity.

- In the absence of tolerable upper intake level (UL), to provide advice on a daily intake of caffeine, from all sources, that does not give rise to concerns about harmful effects to health for the general population and as appropriate, for specific subgroups of the population.

- Advise whether, and the extent to which, the consumption of caffeine together with other food constituents, such as alcohol or substances found in energy drinks, could present a risk to health and for which additional or different recommendations should be provided. Advice should focus inter alia on: 1) a daily intake of caffeine when combined with other food constituents and 2) a recommended interval between caffeine and other food constituents' consumption to prevent possible interactions.

In a follow-up communication, the European Commission informed EFSA that a number of Member States have issued risk assessments or warnings in relation to "fat-burning" food supplements containing synephrine in combination with caffeine. In addition the European Commission referred to a number of Rapid Alert System for Food and Feed (RASFF) notifications on food supplements containing synephrine which often contain also caffeine. The European Commission and EFSA agreed that this mandate will also cover possible interactions between caffeine and synephrine and the safety of food products containing these two substances.

[9] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ. L 31, 1.2.2002. p. 1.

ASSESSMENT

1. Introduction and interpretation of the terms of reference

Chemically, caffeine (1,3,7-trimethylxanthine) is a stable, unionised alkaloid and one of several related methylxanthines. It is found in various plant constituents, such as coffee and cocoa beans, tea leaves, guarana berries and the kola nut, and has a long history of human consumption. It is an ingredient added to a variety of foods, e.g. baked goods, ice creams, soft candy, cola-type beverages. Caffeine is also an ingredient of so-called "energy drinks" and it is present in combination with synephrine in a number of food supplements marketed for weight loss and sports performance, among others. Some medicines and cosmetics also contain caffeine.

"Energy drinks" most often contain combinations of caffeine, taurine and D-glucurono-γ-lactone, among other ingredients.

Synephrine is a biogenic amine of the chemical group of phenylethanolamines/phenylpropanolamines. Amphetamine, ephedrine, octopamine, adrenaline, noradrenaline and dopamine belong to this group. Different isomers of synephrine have been identified in food supplements. The protoalkaloid (–)-*p*-synephrine is naturally found in bitter orange fruit (*Citrus aurantium* L.) and other citrus fruits. One litre of orange juice contains about 15–27 mg of (–)-*p*-synephrine (EFSA, 2009b). *C. aurantium* extract, most often standardised for (–)-*p*-synephrine at concentrations of 6–10 %, is the predominant ingredient used in synephrine-containing food supplements. The synthetic racemate of the optical isomers (–)-*p*-synephrine and (+)-*p*-synephrine and the synthetic *m*-isomer (*m*-synephrine or phenylephrine) are drugs which induce vasoconstriction of the arterial bed (O'Neil, 2008; Martindale et al., 2011; BfR, 2012; SLE, 2012). The presence of small amounts of (+)-*p*-synephrine or *m*-synephrine in food supplements containing *C. aurantium* extracts is indicative of adulteration. Only (–)-*p*-synephrine, the natural compound from *C. aurantium* extracts found in food supplements, will be considered in this opinion (for convenience, referred to as *p*-synephrine hereafter).

This opinion addresses possible adverse health effects of caffeine consumption:

- from all dietary sources, including food supplements, in the general healthy population and in relevant specific subgroups thereof (e.g. children, adolescents, adults, the elderly, pregnant and lactating women, subjects performing physical exercise);
- in combination with other substances present in "energy drinks" (D-glucurono-γ-lactone and taurine), alcohol or *p*-synephrine, i.e. whether or not these substances modify the possible adverse health effects of caffeine and/or the doses at which such adverse effects may occur.

It is outside the scope of the present opinion to address:

- possible adverse health effects of caffeine:
  - given as a medicine, or administered via routes other than the oral route (e.g. through the skin);
  - in subgroups of the population selected on the basis of a disease condition;
  - in combination with medicines and/or drugs of abuse;

  - in combination with alcohol at doses which, by themselves, pose a risk to health (e.g. during pregnancy, binge drinking[10]).

- possible adverse health effects of alcohol, *p*-synephrine or substances present in "energy drinks" other than caffeine (D-glucurono-γ-lactone and taurine), and/or the doses at which adverse effects may occur, when consumed on their own, rather than in combination with caffeine;
- possible adverse effects of the synthetic racemate of the optical isomers (–)-*p*-synephrine and (+)-*p*-synephrine or of the synthetic *m*-isomer (*m*-synephrine or phenylephrine);
- possible beneficial health effects of caffeine or of particular dietary sources of caffeine;
- possible beneficial or adverse health effects of components other than caffeine in foods and beverages which are common dietary sources of caffeine (e.g. coffee, tea, soft drinks other than "energy drinks", chocolate).

The Panel notes that the concept of a tolerable upper intake level (UL) was developed for essential nutrients and refers to the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. Decisions on whether or not any effect is adverse require expert judgement. Nutritional requirements need to be taken into consideration when setting ULs. The UL is not a recommended level of intake and does not refer to single dose or short-term intakes of a nutrient (SCF, 2000).

The derivation of ULs for the normal healthy population, divided into various life-stage groups, accounts for normally expected variability in sensitivity, but it excludes sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions. Including these sub-populations would result in ULs that are significantly lower than needed to protect most people against adverse effects of high intakes. Sub-populations needing special protection are better served through public health screening, health care providers, product labelling or other individualised strategies. The extent to which a sub-population becomes significant enough to be assumed to be representative of the general population is an area of judgement and of risk management (SCF, 2000).

The Panel notes that several characteristics of nutrients are shared with caffeine, which distinguish both caffeine and nutrients from hazardous food chemicals (e.g. contaminants). Caffeine has a long history of human consumption and data on health effects are available from studies in humans. However, caffeine is not an essential nutrient, and thus ULs cannot be derived. In addition, advice on the safe/recommended timing of caffeine consumption prior to physical activity cannot be provided by the derivation of an UL. In this context, the Panel interprets the request from the European Commission as follows:

- to provide advice on a daily intake of caffeine from all sources which, if consumed *ad libitum* and throughout the day for long periods of time, does not give rise to concerns about harmful effects to health for the healthy population, divided into various life-stage groups as appropriate, but excluding sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions;

[10] Defined as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 % or above. For the typical adult, this pattern corresponds to consuming, in about two hours, five or more drinks (male) or four or more drinks (female) in the United States (US) (where a "drink" is standardised to 14 g of pure alcohol), or about eight or more drinks (male) or six or more drinks (female) in most European Union (EU) countries, including the United Kingdom (UK) (where a "drink" is standardised to 8 g of pure alcohol).
http://www.publications.parliament.uk/pa/cm201012/cmselect/cmsctech/writev/1536/ag22.htm
http://www.cdc.gov/alcohol/fact-sheets/binge-drinking.htm

- for the specific group of individuals performing physical activity, to advise on caffeine consumption (dose and timing) prior to physical activity which does not give rise to concerns about harmful effects to health for this population subgroup; and
- to advise on whether or not, and if so to what extent, the consumption of caffeine together with other food constituents (such as alcohol, substances found in energy drinks or *p*-synephrine) presents a health risk and if additional or different recommendations for caffeine intakes need to be provided, regarding either the dose of caffeine or the time interval between the consumption of caffeine and the aforementioned food constituents.

Owing to the abundance of scientific literature available, previous risk assessments on the safety of caffeine consumption in humans conducted by authoritative bodies will be reviewed first in order to identify the major health concerns raised in relation to the consumption of caffeine, either alone or in combination with other components of "energy drinks", alcohol or *p*-synephrine, and the specific population subgroups which are relevant for the assessment.

2. Previous safety assessments

2.1. Caffeine

Safety assessments in relation to acute and chronic consumption of caffeine have been issued by a number of authoritative bodies around the world.

In 1983, the Scientific Committee on Food (SCF) noted that caffeine in comparatively high doses showed weak teratogenic effects (slight delays in the mineralisation of sternebrae) in experimental animals and mutagenic effects *in vitro*, but not *in vivo*. The SCF concluded that there was no evidence for concerns about carcinogenic, teratogenic or mutagenic effects of caffeine in humans at observed levels of intake (between 2.0 and 4.5 mg/kg body weight (bw) per day) and that human epidemiological studies provided no evidence for any association between coffee consumption and congenital defects (SCF, 1983).

In 1999, the SCF re-assessed the safety of caffeine by considering the contribution of "energy drinks" to caffeine intakes (SCF, 1999). In the absence of representative intake data for the European population, the SCF assumed that "energy drink" users would consume about 160 mg caffeine per day from this source (0.5 L; 320 mg caffeine/L). On the basis of a number of human observational studies, the SCF found that results were contradictory regarding the association between prenatal caffeine exposure and birth weight, and were inconsistent for pre-term delivery and congenital malformation. No clear association was established between caffeine intake in early pregnancy and spontaneous abortion or delayed conception; only one study showed an association between heavy caffeine intake in pregnancy and the risk of sudden infant death syndrome. The SCF concluded that, in general, maternal caffeine consumption during pregnancy did not appear to have any measurable adverse consequences for the human fetus at intakes up to 300 mg caffeine per day. Moderation of caffeine intakes from whatever source was advised for pregnant women. For children, the SCF considered seven publications reporting on intervention studies (Elkins et al., 1981; Rapoport et al., 1981a, 1984; Baer, 1987; Zahn and Rapoport, 1987; Leviton, 1992; Bernstein et al., 1994; Stein et al., 1996) conducted in pre-school and school children with caffeine doses up to 10 mg/kg bw (3, 5 or 10 mg/kg bw), either as a single dose or on a daily basis for periods of up to two weeks. In these studies, either no effect or small, inconsistent effects were noted on mood, behavioural, cognitive and motor functions. According to the SCF, "some of the studies indicated that a dose of 5 mg/kg bw increased arousal, irritability, nervousness or anxiety in some subjects, particularly if they were normally low consumers of caffeine".

A Food Standards Australia and New Zealand expert group (FSANZ, 2000), on the basis of available prospective cohort studies in humans, concluded that a causal relationship between habitual caffeine intakes from dietary sources and an increased risk of hypertension or cardiovascular disease (CVD) could not be established. FSANZ noted reports of increased anxiety levels in children (Bernstein et al.,

1994) at doses of 2.5 mg/kg bw per day and in adults (Nickell and Uhde, 1994) at doses of 3 mg/kg bw per day when caffeine was administered intravenously, corresponding to 95 mg per day for a mean body weight of 32 kg in children aged 5–12 years and to 210 mg per day for a mean body weight of 70 kg in adults. FSANZ also noted that doses of 100 mg of caffeine (1.4 mg/kg bw for a 70-kg adult) taken at bedtime had been reported to reduce the ability to sleep in adults (Landolt et al., 1995).

In 2004, the Nordic Working Group on Food Toxicology and Risk Evaluation (NNT) assessed possible adverse health effects of the consumption of caffeine (and other methylxanthines) during pregnancy (NNT, 2004). Like the SCF in 1999, the NNT concluded that, on the basis of virtually the same human observational studies, results were contradictory regarding the association between prenatal caffeine exposure and birth weight (including fetal growth retardation). If present, the Committee judged that the effect of high caffeine intakes on birth weight would be small and of low clinical relevance. No clear association was found between caffeine intake in early pregnancy and increased risk of pre-term delivery or congenital malformations, or between caffeine intake in childbearing age and delayed conception. Different from the SCF, and on the basis of additional prospective cohort studies, the NNT concluded that the relationship between high caffeine intakes and increased risk of spontaneous abortion was probable. Recommendations were given to reduce caffeine intakes during pregnancy (e.g. as the SCF or the Food and Drug Administration (FDA)), but no cut off value was advised.

Maximum daily caffeine intakes recommended by Health Canada in 2006 (Health Canada, 2006) for different population subgroups were based on a review of the literature published in 2003 (Nawrot et al., 2003). On the basis of the studies available at the time on the relationship between caffeine consumption and health outcomes in humans, the authors concluded that daily caffeine intakes of 400 mg were not associated with adverse health effects such as general toxicity, cardiovascular effects, changes in adult behaviour, increased incidence of cancer, effects on male fertility or bone status/calcium balance if calcium intakes are adequate. In a review of the available observational studies on caffeine consumption during pregnancy and the risk of spontaneous abortion, pre-term delivery, fetal growth, congenital malformations and post-natal development, it was concluded that caffeine intake for women who plan to become pregnant and during gestation should not exceed 300 mg per day. The publications reviewed concerning caffeine intakes in children mostly addressed the effects of caffeine on the central nervous system (CNS), and were those considered by the SCF (1999) together with three additional studies (Rapoport et al., 1981b; Hale et al., 1995; Davis and Osorio, 1998). The authors noted the small size of the studies available and the diversity of study designs. The authors also noted that the use of different endpoints or of different ways to assess similar endpoints hampered comparability among studies, and that most studies did not stratify children by their usual (pre-study) caffeine intake, a variable which could affect the way subjects respond to pre-study caffeine withdrawal and to additional caffeine intakes. Nevertheless, findings of altered behaviour, including anxiety, were noted in some studies to the lowest level of administered caffeine used (2.5 mg/kg bw). In the absence of more robust data associated with low levels of administered caffeine in this population subgroup, an upper intake of 2.5 mg/kg bw per day based on the study by Bernstein et al. (1994) was derived for children, considering that the nervous system in children is continually developing and the lack of available information on the longer-term effects of caffeine consumption in this population subgroup.

Based on the results from a prospective cohort study (CARE Study Group, 2008), the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded in 2008 that caffeine consumption during pregnancy was associated with an increased risk of fetal growth restriction (FGR), and that the risk at intakes < 200 mg per day may be low, even if a threshold level of caffeine intake below which there was no increased risk could not be identified (COT, 2008). Based on an extensive review of the literature, the COT also suggested a possible association between caffeine consumption and an increased risk of miscarriage, but considered that data on the relationship between caffeine consumption and other pregnancy outcomes (e.g. pre-term birth, congenital malformations) were inconclusive.

In 2008, the NNT focused on the safety of caffeine among children and adolescents in the Nordic countries (NNT, 2008). A no observed effect level (NOEL) of 0.3 mg/kg bw (Goldstein and Wallace, 1997) and a lowest observed adverse effect level (LOAEL) of 1.0–1.3 mg/kg bw (Bernstein et al., 2002; Heatherley et al., 2006) were established for tolerance development with withdrawal symptoms, whereas a LOAEL of 2.5 mg/kg bw (Bernstein et al., 1994) was established for anxiety and jitteriness. The NNT noted that the only study which assessed the relationship between habitual caffeine consumption and sleep patterns in adolescents (Pollak and Bright, 2003) did not allow conclusions to be drawn on a causal effect of caffeine on disturbed sleep (i.e. it was an observational study and reverse causality could not be excluded) and that no studies were available in children. The NNT concluded that there were no data to conclude that caffeine would not have the same sleep-depriving effect in children and adolescents as in adults, and that, in adults, doses less than 100 mg, equivalent to 1.4 mg/kg bw, did not seem to have an effect on sleep (Dorfman and Jarvik, 1970).

The Belgium Superior Health Council (SHC, 2012) based its recommendations on the assessments conducted by FSANZ (2000), Health Canada (Nawrot et al., 2003) and the COT (2008). The SHC considered that caffeine intakes of 5.7 mg/kg bw per day (400 mg per day for a 70-kg adult) were not linked to any adverse effects in relation to general toxicity, altered behaviour, decreased male fertility, CVD or cancer risk; recommended a maximum daily intake of caffeine of 2.5 mg/kg bw for children and adolescents based on the increased risk of anxiety and altered behaviour beyond this dose (Bernstein et al., 1994); and advised to women of childbearing age not to exceed 300 mg per day, or even 200 mg per day. The SHC noted a report (Nickell and Uhde, 1994) of increased anxiety levels in adults who received 3 mg/kg bw per day (210 mg per day for a 70-kg adult) of caffeine intravenously.

2.2. Caffeine in combination with other constituents of "energy drinks" and in combination with alcohol

A number of safety assessments have also been conducted in relation to the consumption of "energy drinks", which most often contain combinations of caffeine (typically 300–320 mg/L), taurine (about 4 000 mg/L) and D-glucurono-γ-lactone (about 2 400 mg/L) among other ingredients, and to the consumption of "energy drinks" or caffeine in combination with alcohol.

In 1999, the SCF (1999) considered that the contribution of "energy drinks" to caffeine intakes in non-pregnant adults was not of concern on the assumption that "energy drinks" would replace other caffeine sources, such as coffee or tea. For children, the SCF concluded that the consumption of 160 mg caffeine per day from 0.5 L of "energy drinks", equivalent to 5.3 mg/kg bw per day for a 10-year-old, 30-kg child, could result in transient behavioural changes, such as increased arousal, irritability, nervousness or anxiety, based on the studies referred to in Section 2.1.

In 2003, the SCF (2003) considered that it is unlikely that D-glucurono-γ-lactone would interact with caffeine, taurine, alcohol or the effects of exercise. Caffeine exerts stimulatory effects in the CNS and, although taurine generally acts as an inhibitory neuromodulator, the SCF could not rule out the possibility of stimulatory effects of caffeine and taurine on the CNS. This was based on a rat study showing a stimulatory action on locomotor activity after taurine consumption in all treated rat groups. Based on the antagonistic effects of caffeine and taurine on the cardiovascular system (CVS) observed *in vitro* in animal studies and in human studies conducted with either caffeine or taurine, the SCF considered that, if there are any cardiovascular interactions between caffeine and taurine, taurine might reduce the cardiovascular effects of caffeine. The SCF also noted the possibility of additive effects of taurine and caffeine on diuresis (acting via different mechanisms), which could be exacerbated by the consumption of alcohol and sweating during exercise. This could theoretically result in short-term dehydration, but no human studies investigating this possibility were available. The majority of studies suggested that caffeine would not exacerbate the adverse effects of alcohol on the CNS.

In 2009, the Panel on Food Additives and Nutrient Sources Added to Food (ANS Panel) concluded that exposure to taurine and D-glucurono-γ-lactone at levels commonly used in "energy drinks" was not of safety concern, even for consumers of high levels (EFSA (European Food Safety Authority),

2009). Similarly to the SCF (2003), the ANS Panel considered that it is unlikely that D-glucurono-γ-lactone would have any interaction with caffeine, taurine, alcohol or the effects of exercise. The ANS Panel concluded that additive interactions between taurine and caffeine on diuretic effects were unlikely, based on a human intervention study (Riesenhuber et al., 2006), and that a possible stimulatory effect from taurine on the CNS was improbable on the basis of a second rat study, from which a no observed adverse effect level (NOAEL) of 1 500 mg/kg bw per day was derived for behavioural effects.

In 2008, the Federal Institute for Risk Assessment (BfR) assessed the safety of "energy drinks" in view of case reports on fatalities following reported consumption of these beverages, either alone or in combination with alcohol, which implicated, primarily, the CVS and CNS (BfR, 2008). The BfR considered that adverse health effects upon consumption of large amounts of "energy drink" in combination with intense physical exercise or alcohol could not be ruled out, and advised children, pregnant women, lactating women or individuals who are "sensitive" to caffeine (i.e. with cardiac arrhythmias or mental disorders) not to consume "energy drinks", particularly in large amounts. Subsequently, the BfR (BfR, 2009) assessed health risks related to the consumption of "energy shots", which contain higher concentrations of caffeine and taurine than "energy drinks" (50–200 mg caffeine and taurine 200–1 000 mg per portion). The BfR stated that the consumption of "energy shots" poses no risk to health if consumed in accordance with the suggested daily intake levels of 50–200 mg caffeine.

In 2012, the UK COT (COT, 2012) assessed the health effects of consuming caffeine from all sources, including "energy drinks" in combination with alcohol. A number of human observational (mostly cross-sectional and retrospective) studies suggested that higher caffeine intakes were associated not only with higher alcohol intakes but also with use of other psychoactive substances. Similarly, high intakes of "energy drinks" were correlated with higher alcohol intakes in some individuals. However, the studies available did not allow conclusions to be drawn on "whether this is because consumption of energy drinks causes people to drink more alcohol, or because people who are inclined to more risky behaviour tend generally to consume larger quantities of psychoactive substances, including caffeine and alcohol". Results from controlled human intervention studies, systematically reviewed by Verster et al. (2012), were conflicting with respect to the effects of caffeine (1.1 to 5.6 mg/kg bw) on mental performance (e.g. motor reaction time, mean tracking performance and memory reaction time) and subjective perception of alcohol intoxication when consumed together with alcohol (0.18 to 1.07 g/kg bw). The COT concluded that the heterogeneity of methods and neurological endpoints in the intervention studies available prevented firm conclusions on whether or not caffeine counteracts the acute neurocognitive effects of alcohol, and that the available evidence did not support a toxicological or behavioural interaction between caffeine and alcohol. The COT also noted the limitations of the data available and the uncertainty linked to this statement.

In 2013, Health Canada assessed the health risks associated with the consumption of "energy drinks" in Canada (Rotstein et al., 2013). The hazard assessment was based on individual ingredients. Caffeine was identified as the ingredient with the greatest potential for intakes of possible health concern. On this basis, excess consumption of energy drinks would be expected to result in health consequences similar to those from excess exposure to caffeine. Health Canada considered that the potential for taurine and glucuronolactone to interact with caffeine and the health effects of excessive intake of taurine and glucuronolactone were unknown. The hazard assessment concluded that the general adult population could consume two servings of a typical energy drink per day with no health consequences. This conclusion was based on the safety of the non-caffeine ingredients of energy drinks at the level of consumption, and the fact that caffeine from other dietary sources in addition to that in two servings of energy drink would not pose a health hazard to the general adult population. The consumption of energy drinks by sub-populations, such as children, adolescents and pregnant women, should be limited to their recommended maximum daily intakes of caffeine, as recommended by Health Canada (see Section 2.1). Health Canada concluded that the evidence did not conclusively indicate a harmful toxicological interaction between "energy drinks" and alcohol.

The French Agency for Food, Environmental and Occupational Health and Safety (ANSES, 2013) analysed 212 cases of adverse effects reported through the French Nutritional Vigilance Scheme and considered that a causal relationship between the consumption of "energy drinks" and the reported adverse effects was very likely or likely in 25 cases (12 %) and possible in 54 cases (24 %). The main signs and symptoms identified implicated the CVS (e.g. heart failure, feelings of tightness or pain in the chest, tachycardia, high blood pressure) and the CNS (e.g. irritability, nervousness, anxiety, panic attacks, hallucinations, epilepsy). Although most adverse effects were attributed to the consumption of high doses of caffeine, ANSES suggested that taurine could have additional effects in raising blood pressure and inducing vasospasm of the coronary arteries. ANSES warned about the chronic consumption of caffeinated beverages, including "energy drinks", by certain subgroups of the population at higher risk of adverse effects, including pregnant (risk of impaired fetal growth) and lactating women (caffeine transferred to milk), children and adolescents (disruption of sleep patterns, risk of "addictive behaviour" later in life), "slow caffeine metabolisers" and subjects with cardiac, psychiatric or neurological disorders, kidney failure or severe liver diseases. ANSES also noted that additional risks could arise from the different pattern of consumption of "energy drinks" compared with other dietary sources of caffeine, e.g. very high acute intakes, concomitant alcohol use (increased risk of cardiac arrhythmias and masking of alcohol intoxication) and/or concomitant intense physical exercise (increased risk of cardiac events, dehydration and heat stroke). Similar concerns were raised by the Italian National Food Safety Committee in 2012 regarding the consumption of "energy drinks", particularly in combination with alcohol[11].

2.3. Caffeine in combination with *p*-synephrine

A number of authoritative bodies in different European Union (EU) Member States have conducted risk assessments (BfR, 2012; SLE, 2012) or issued warnings (Sundhedsstyrelsen, 2008; MHRA, 2012; Evira, 2013) in relation to *p*-synephrine-containing products intended for weight loss and improving sports performance which also contain caffeine. Concerns were raised on the basis of case reports and Rapid Alert System for Food and Feed (RASFF) notifications of adverse health effects.

The BfR (2012) reviewed human intervention studies investigating the acute effects of *p*-synephrine on blood pressure and heart rate, either alone (Min et al., 2005; Bui et al., 2006; Stohs et al., 2011) or in combination with caffeine (Haller et al., 2005b, 2008; Seifert et al., 2011). Based on these studies, the BfR concluded that single doses of *p*-synephrine > 27 mg can be expected to significantly increase blood pressure in humans, and that the effect may be observed at lower doses (of about 5 mg) in combination with caffeine. The BfR (2012) considered a daily intake of 6.7 mg *p*-synephrine from food supplements to be safe, on the assumption that total intakes of *p*-synephrine (from conventional foods and food supplements) would remain < 25.7 mg (95^{th} percentile of *p*-synephrine intake from conventional foods), even in consumers with high intakes from the diet. On the basis of these and other human intervention studies (Penzak et al., 2001), the Swedish National Food Agency (SLE, 2010) and (ANSES, 2014) concluded that the effects of single-ingredient preparations (*p*-synephrine) are seen from about 20 mg, that at 50 mg there is a clear effect on heart rate and systolic and diastolic blood pressure and that caffeine could potentiate the cardiovascular effects of synephrine. ANSES (2014) recommended not combining *p*-synephrine with caffeine, whereas (Health Canada, 2011) established a limit of 50 mg of synephrine in supplements as a single active ingredient for healthy adults and the combination of caffeine and *p*-synephrine at daily doses up to 320 mg and 40 mg, respectively.

2.4. Summary of previous safety assessments

2.4.1. Caffeine

Recommendations on maximum levels of caffeine consumption for different population subgroups have been derived by different national and international bodies taking into account a variety of health

[11] http://www.salute.gov.it/imgs/c_17_pubblicazioni_1790_allegato.pdf

outcomes. No health concerns in relation to acute toxicity, calcium balance (under adequate calcium intakes), cardiovascular health, cancer risk or male fertility have been raised for habitual caffeine intakes from all sources up to 400 mg per day in the general adult population. It has been noted, however, that single doses of 1.4 mg/kg bw and above, taken at bedtime, could impair sleep in some individuals (Landolt et al., 1995), and that single doses of 3 mg/kg bw and above could increase anxiety in some cases when caffeine is administered intravenously (Nickell and Uhde, 1994). Early recommendations for pregnant women and for women of childbearing age to not exceed 300 mg of caffeine per day are based on a number of cross-sectional and prospective cohort studies which assessed the relationship between habitual caffeine consumption and a variety of outcomes (e.g. spontaneous abortion, pre-term delivery, fetal growth, congenital malformations, post-natal development). A later evaluation advised against exceeding 200 mg of caffeine per day in the light of a new prospective cohort study, which identified FGR as the most sensitive adverse outcome of caffeine consumption during pregnancy (CARE Study Group, 2008). Recommendations on maximum daily intakes of caffeine in children have been based on its acute and short-term effects on the CNS. The SCF noted that, considering all the available human intervention studies conducted in this population subgroup, doses of 5 mg/kg bw of caffeine increased arousal, irritability, nervousness or anxiety in some subjects, particularly if they were normally consumers of low amounts of caffeine (SCF, 1999). Other bodies (FSANZ, 2000; Health Canada, 2006; NNT, 2008; SHC, 2012), however, have recommended that doses of 2.5 mg/kg bw per day not be exceeded, on the basis of a single study (Bernstein et al., 1994).

2.4.2. Caffeine in combination with other constituents of "energy drinks" and in combination with alcohol

Concerns have been raised in relation to the consumption of "energy drinks" and an increased risk of adverse health effects involving the CVS and the CNS from a number of case reports, particularly when they are consumed within short periods of time, at high doses and in combination with alcohol and/or physical exercise. Although it has been acknowledged that such adverse effects could be attributed to caffeine alone, additive and/or synergistic cardiovascular and psychological effects have been proposed for other components of "energy drinks" on various health outcomes, especially taurine. Concerns regarding the possibility of an interaction between caffeine and taurine regarding the stimulatory effect on the CNS based on a rat study were not confirmed in subsequent animal studies. Similarly, it was found that the theoretical additive diuretic effects of caffeine and taurine mentioned in previous assessments were unlikely, on the basis of a human intervention study designed to investigate that question (Riesenhuber et al., 2006). Interactions between caffeine and taurine on the CVS were found to be unlikely based on the antagonistic effects of caffeine and taurine observed *in vitro* in animal studies and in human studies conducted with either caffeine or taurine. Studies linking high levels of consumption of caffeine and "energy drinks" with high alcohol intakes, consumption of other psychotropic drugs and increased "risk-taking" behaviour were either cross-sectional or retrospective and did not allow a causal role to be attributed to either caffeine or "energy drinks" in this cluster. It was also found that alcohol consumption is unlikely to exacerbate the effects of caffeine on the CVS and/or the CNS. Concerns were, however, expressed regarding the antagonistic effects of caffeine and alcohol on the CNS, and the possibility that caffeine could mask the subjective perception of alcohol intoxication, leading to increased "risk-taking" behaviour. However, the human intervention studies that investigated this question were found to yield conflicting results (Verster et al., 2012).

2.4.3. Caffeine in combination with *p*-synephrine

Concerns related to the co-consumption of caffeine and *p*-synephrine arise from the potential synergistic effects of these two substances on the CVS, and particularly on blood pressure. On the basis of human intervention studies which have investigated the acute effects of *p*-synephrine on blood pressure and heart rate, either alone (Penzak et al., 2001; Min et al., 2005; Bui et al., 2006; Stohs et al., 2011) or in combination with caffeine (Haller et al., 2005b, 2008; Seifert et al., 2011), authoritative bodies came to the conclusion that doses of *p*-synephrine between 20 and 27 mg increase blood pressure, and that this effect is enhanced by the concomitant consumption of caffeine.

3. Dietary intakes

3.1. Dietary sources and occurrence data

The main sources of caffeine in the diet include coffee, tea, caffeinated soft drinks (including "energy drinks") and chocolate. Caffeine concentrations in these foods and beverages as reported in different publications and European dietary surveys are depicted in Table 1.

In order to calculate dietary intakes of caffeine, data from a survey conducted in the UK were used whenever available (Fitt et al., 2013). Information on caffeine concentrations of 400 samples of teas (e.g. loose leaves, bags, vending machines and instant tea) and coffees (e.g. filter coffee, vending machines, espresso and instant coffee) prepared at home, prepared in workplaces or purchased in retail settings was collected. In addition, the survey checked websites of manufacturers for information on product- and brand-specific caffeine levels and used analytical data from a UK survey of 162 samples from various types of caffeine- and other methylxanthine-containing products (Ministry of Agriculture, Fisheries and Food, 1998). For foods for which the survey did not report caffeine levels, an average of mean values reported in other representative original surveys was used, except for "energy drinks", for which the caffeine concentration (320 mg/L) of the most consumed brand was chosen. Products in which chocolate occurs as a minor constituent, e.g. "chocolate biscuits", were not considered because of their relatively low and highly variable caffeine levels.

The Panel notes that there were no major differences among surveys and publications from different countries regarding average caffeine levels in foods and beverages (Table 1). Average values reported in Table 1 were used to assess daily caffeine intakes and caffeine intakes on single days for all countries and surveys.

Variability in caffeine levels for different foods and beverages, in particular for coffee drinks, espresso coffee and tea, have been noticed within the same product and for the same country. The highly variable caffeine concentrations in coffee beverages depend on the manufacturing process, on the type of coffee beans used and on the type of preparation (e.g. drip coffee, espresso) (Waizenegger et al., 2011). Owing to personal choices, individual consumers might therefore have coffee beverages with lower or higher caffeine levels than those used in the present assessment. The use of an average concentration value has been adopted by the Panel to account for this variability.

Cocoa-based beverages are another food product that might present significant variability in caffeine levels because of the amount and type of cocoa present in the different brands. The distinction between "cocoa beverages based on cocoa powder" and "cocoa beverages based on cocoa-beverage preparation powder", the latter being consumed mainly by children and containing more sugar and significantly lower amounts of cocoa, was used to minimise this uncertainty. However, it is not possible to exclude that some of the brands of cocoa-beverage preparation powder consumed in particular by children contain lower levels of caffeine than those used in the present assessment. It is also possible that some of them are decaffeinated.

Table 1: Caffeine concentrations in food and beverages

Groups	Subgroups	Caffeine concentrations (mg/L or mg/kg)													
		Used in the intake assessment	**Fitt et al. (2013)**	**Waizenegger et al. (2011)**	**Heckman et al. (2010)**	**Mayo Clinic Staff (2013)**	**ANSES (2013)**	**Austria Rudolph et al. (2012)**	**Zucconi et al. (2013)**	**Belgium SHC (2012)**	**Denmark NNT (2008)**	**Finland NNT (2008)**	**Iceland NNT (2008)**	**Norway NNT (2008)**	**Sweden NNT (2008)**
Chocolate	Chocolate bar	111 [a]	111	–	–	–	–	–	180	–	–	–	–	–	
	Milk chocolate	168 [a]	168	–	–	–	–	–	183	–	–	–	–	–	150
	Chocolate snacks			–	–	–	–	–	180	–	–	–	–	–	
	Cocoa beverage based on cocoa powder [b]			–	–	–	–	–	150	–	20	–	20	–	15
	Cocoa beverage based on cocoa-beverage preparation powder	42 [c]	–												
	Dark chocolate	525 [a]	525		–	–	–	–	340	–	–	–	–	–	650
Coffee	Coffee drink	445 [a]	445	380 (30–1 780)	586 (450–882)	477 (114–840)	513 (175–1 244)	400 (197–804)	400	320	500	500	550	500	690
	Cappuccino	273 [d]	–	–	–	315	–	250 (194–310)	250	–	–	–	–	–	–
	Espresso coffee	1 340 [e]	–	–	1 411 (1 058–3 175)	1 897 (1 320–2 475)	713 (250–2 140)	–	1916	–	–	–	–	–	–
	Decaffeinated and imitations	21 [f]	–	–	22 (13–53)	29 (8–50)	21 (15–120)	–	11	–	–	–	–	–	–
	Instant coffee, ready to drink	445 [a]	445	210 (80–500)	410 (119–763)	477 (113–840)	484 (201–856)	300 (201–485)	400	320	500	500	550	500	690
Tea	Black tea	220 [a]	220	–	207 (110–485)	–	272 (90–500)	150 (122–183)	100	320	160	150	170	160	240
	Green tea	151 [a]	151	–	198 (132–220)	–									
	Tea (unspecified)	165 [a]	165	–	234 (176–529)	158 (59–256)									
	Tea, decaffeinated	25	–	–	–	25 (0–50)	–	–	25	–	–	–	–	–	–
Cola beverages (caffeinated)		108 [a]	108	–	127 (101–163)	104 (76–132)	97 (41–132)	–	–	79	130	130	130	130	130
"Energy drinks"		320 [g]	300	–	335 (317–353)	–	300 (120–320)	300 (267–665)	–	300	150	320	150	150	320

(a): Derived from Fitt et al. (2013).

(b): Cocoa beverage products have been prepared or recorded differently in the different dietary surveys. When needed, a correction factor equal to 60 has been applied to transform "cocoa powder" and "cocoa mass" into cocoa beverage (assuming that 60 g of cocoa beverage contains 1 g of cocoa powder).

(c): "Cocoa-beverage preparation powder" was assumed to contain only 25 % of the cocoa contained in "cocoa powder" and, consequently, 25 % caffeine.
(d): Mean value from Mayo Clinic Staff (2013) and Austria (Rudolph et al., 2012) (minimum and maximum).
(e): Mean value from Heckman et al. (2010), Mayo Clinic Staff (2013) and ANSES (2013).
(f): Derived from ANSES (2013).
(g): Caffeine concentration of the most consumed "energy drink" considered.
–, no value provided in the references.

3.2. Food consumption data

3.2.1. EFSA Comprehensive European Food Consumption Database

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database) provides a compilation of existing national information on food consumption at the individual level. It was first created in 2010 (EFSA, 2011a; Huybrechts et al., 2011; Merten et al., 2011) and then updated in 2014[12]. Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011b). For dietary surveys included in the 2010 release, which was based on the FoodEx classification, products coded as "carbohydrate-rich energy food products for sports people" or "carbohydrate–electrolyte solutions for sports people" at the third level of FoodEx within the first-level category of "Products for special nutritional use" were used to calculate caffeine consumption from "energy drinks". Even using this conservative approach, the contribution of "energy drinks" to total caffeine intakes was very low in all surveys published before 2000. The 17 surveys from 11 Member States added in 2014 used the FoodEx2 code classification, which allows accurate reporting of "energy drink" consumption (Appendix A).

The database used to calculate caffeine intake included surveys conducted between 2005 and 2012, with two exceptions (DIPP 2001–2009, Finland; VELS 2001–2002, Germany). The database contains data from 39 surveys conducted in 22 different European countries for a total of 66 531 participants (Appendix A). Data from 11 surveys were available for toddlers (≥ 12 months to < 36 months old), from 19 surveys for other children (≥ 36 months to < 10 years old), from 19 surveys for adolescents (≥ 10 years to < 18 years old), from 21 surveys for adults (≥ 18 years to < 65 years old), from 15 surveys for the elderly (≥ 65 years to < 75 years old) and from 13 surveys for the very elderly (≥ 75 years old). Two additional surveys provided information on specific population groups: pregnant women (Latvia) and lactating women (Greece).

In the above-mentioned surveys, consumption data were collected using single or repeated 24- or 48-hour dietary recalls or dietary records covering three to seven days per subject. Owing to the differences in the methods used for data collection, direct country-to-country comparisons must be taken with caution. These surveys do not provide information about the consumption of caffeine-containing food supplements.

3.2.2. EFSA report on "energy drinks"

In 2011, EFSA commissioned a study to gather data on the prevalence of "energy drink" consumption among adults, adolescents and children in Europe (Zucconi et al., 2013). This study also aimed at estimating intakes of "energy drink" ingredients, including caffeine, in "energy drink consumers", as well as the relative contribution of "energy drinks" to total caffeine intakes. "Energy drink consumers" were defined as subjects who had consumed at least one "energy drink" over the last year. Consumption of "energy drinks" on a "single session", defined as a period of time of about two hours (e.g. a "night out", a "study or sport session"), and consumption of "energy drinks" with alcohol or in relation to physical exercise in adolescents and adults was also investigated. The Panel notes, however, that a "night out", "study session" or "sport session" could last more than two hours, and it is not possible from the report to precisely define the time frame covered by a "single session". Consumption data were collected through a food frequency questionnaire (FFQ)-based survey, involving more than 52 000 participants from 16 different European Member States.

The Panel notes that this study provides useful information about the prevalence of "energy drink" consumption in Europe, the number of "energy drinks" (and the amount of their constituents, including caffeine) consumed in a "single session" and the prevalence of "energy drink" consumption in combination with physical activity. However, the Panel notes that: (i) "energy drink consumers" may not be representative of the general population with respect to caffeine intake from all sources;

[12] http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

(ii) FFQs specifically developed to assess consumption of specific foods tend to overestimate consumption of such foods; and (iii) the study contains information about the frequency of consumption of "energy drinks" in combination with alcohol, but not on the amount of alcohol consumed in combination with "energy drinks". Therefore, the Panel considered that this study could be used to calculate caffeine intakes from "energy drinks" in a "single session", either alone or in combination with physical exercise, but not to calculate total caffeine intakes from all sources or from sources other than "energy drinks".

3.3. Dietary intake

3.3.1. Caffeine intake estimated from the EFSA Comprehensive European Food Consumption Database

3.3.1.1. Daily caffeine intake

Daily caffeine intake for an individual was calculated by finding the sum of the intakes reported on all survey days during the survey period for that individual and dividing by the number of days. Only surveys which collected data for at least two days were used.

Individual daily caffeine intakes were used to estimate the mean and 95th percentile of daily caffeine intake from all sources and for each food group (chocolate, coffee, cola beverages, energy drinks and tea) for "all subjects" in a survey. Mean and 95th percentile daily caffeine intakes were also estimated for "consumers only" of each food group. Consumers were defined as subjects who had consumed a food product of the concerned food groups at least once within the survey period.

The mean and 95th percentile of daily caffeine intake for each age class and food group across different dietary surveys are given below for all subjects (Table 2) and for consumers of a caffeine-containing specific food group only (Table 3). Detailed information by country can be found in Appendix B.

Table 2: Daily caffeine intakes of all subjects by age class and food group across different dietary surveys

Age class	Food groups	Mean caffeine intake				95th percentile caffeine intake [a]			
		mg per day		mg/kg bw per day		mg per day		mg/kg bw per day	
		Min [b]	Max [b]	Min [b]	Max [b]	Min [b]	Max [b]	Min [b]	Max [b]
Toddlers (12 to < 36 months; 10 surveys)	Total intakes [c]	0.3	30.3	0.0	2.1	0.8	45.4	0.1	3.5
	Chocolate	0.3	30.3	0.0	2.1	0.7	23.9	0.1	1.8
	Coffee	0.0	1.9	0.0	0.2	–	–	–	–
	Cola beverages	0.0	8.5	0.0	0.6	–	–	–	–
	"Energy drinks"	0.0	0.0	0.0	0.0	–	–	–	–
	Tea	0.0	6.6	0.0	0.5	0.0	43.3	0.0	3.2
Other children (3 to < 10 years; 17 surveys)	Total intakes	3.5	47.1	0.2	2.0	19.8	102.6	1.2	4.6
	Chocolate	2.1	35.0	0.1	1.4	6.5	94.5	0.4	4.6
	Coffee	0.0	10.3	0.0	0.4	0.0	44.5	0.0	1.8
	Cola beverages	0.0	6.3	0.0	0.3	0.0	27.0	0.0	1.5
	"Energy drinks"	0.0	0.3	0.0	0.0	–	–	–	–
	Tea	0.0	31.8	0.0	1.3	0.0	70.1	0.0	2.8
Adolescents (10 to < 18 years; 16 surveys)	Total intakes	17.6	69.5	0.4	1.4	60.5	211.6	1.5	4.1
	Chocolate	2.8	35.1	0.1	0.7	9.8	129.8	0.2	2.9
	Coffee	0.5	22.0	0.0	0.4	0.0	133.5	0.0	2.1
	Cola beverages	0.0	26.5	0.0	0.4	0.0	106.9	0.0	1.7
	"Energy drinks" [d]	0.0	5.7	0.0	0.1	0.0	40.0	0.0	0.8
	Tea	0.0	36.3	0.0	0.8	0.0	122.2	0.0	2.4
Adults (18 to < 65 years; 16 surveys)	Total intakes	36.5	319.4	0.5	4.3	108.6	742.4	1.5	10.0
	Chocolate	1.9	9.5	0.0	0.1	8.9	50.4	0.1	0.8
	Coffee	20.9	280.7	0.3	3.7	72.1	737.4	1.0	9.7
	Cola beverages	0.0	18.0	0.0	0.3	0.0	80.5	0.0	1.2
	"Energy drinks" [e]	0.0	4.4	0.0	0.1	0.0	34.4	0.0	0.4
	Tea	0.5	88.6	0.0	1.2	0.0	247.0	0.0	3.4
Elderly (65 to < 75 years; 13 surveys)	Total intakes	22.6	362.1	0.3	4.8	96.3	715.7	1.5	10.4
	Chocolate	1.0	5.0	0.0	0.1	4.2	30.2	0.1	0.4
	Coffee	18.9	330.6	0.3	4.4	93.8	712.0	1.4	10.3
	Cola beverages	0.0	3.4	0.0	0.0	0.0	22.8	0.0	0.3
	"Energy drinks"	0.0	0.7	0.0	0.0	–	–	–	–
	Tea	1.4	124.0	0.0	1.7	14.9	297.4	0.2	4.0
Very elderly (≥ 75 years; 11 surveys)	Total intakes	21.8	416.8	0.3	6.0	174.0	454.5	2.3	6.1
	Chocolate	1.5	9.3	0.0	0.1	4.4	36.6	0.1	0.6
	Coffee	16.8	382.6	0.2	5.5	134.1	446.8	1.8	6.1
	Cola beverages	0.0	1.8	0.0	0.0	0.0	13.5	0.0	0.2
	"Energy drinks"	0.0	1.0	0.0	0.0	–	–	–	–
	Tea	0.8	125.7	0.0	1.8	47.7	283.3	0.7	4.2

(a): The 95th percentile estimates obtained from dietary surveys and age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011b) and consequently were not considered in this table ("–").

(b): Minimum (min) and maximum (max) means and 95th percentiles of those calculated from individual surveys for each age class.

(c): "Total intakes" are not derived by calculating the minimum and maximum values for the different food categories (values obtained from different subjects), but reflect the minimum and maximum intakes of caffeine from all sources for all subjects in the survey and age group across the different dietary surveys.

(d): Only one study (the Netherlands) with a sufficient number (≥ 60) of subjects who had consumed "energy drinks", was available to estimate a statistically robust 95th percentile.

(e): Only two studies (the Netherlands and Ireland) with a sufficient number (≥ 60) of subjects who had consumed "energy drinks", were available to estimate statistically robust 95th percentiles.

Table 3: Daily caffeine intakes from each food group by age class and food group for consumers of that food group only across different dietary surveys

Age class	Food groups	Mean caffeine intake				95th percentile caffeine intake [a]			
		mg per day		mg/kg bw per day		mg per day		mg/kg bw per day	
		Min [b]	Max [b]	Min [b]	Max [b]	Min [b]	Max [b]	Min [b]	Max [b]
Toddlers (12 to < 36 months; 10 surveys)	Chocolate	1.6	46.8	0.1	3.2	6.2	26.3	0.5	2.2
	Coffee	0.7	67.5	0.1	6.1	–	–	–	–
	Cola beverages	1.7	18.0	0.2	1.3	–	–	–	–
	"Energy drinks"	8.0	8.0	0.8	0.8	–	–	–	–
	Tea	6.8	24.8	0.5	1.9	20.6	61.9	1.7	5.1
Other children (3 to < 10 years; 17 surveys)	Chocolate	2.6	44.8	0.1	1.8	6.8	105.0	0.4	5.0
	Coffee	1.1	62.1	0.1	2.5	29.7	29.7	1.3	1.3
	Cola beverages	5.9	19.8	0.3	1.0	18.0	53.4	0.9	2.1
	"Energy drinks"	6.5	58.5	0.4	1.9	–	–	–	–
	Tea	9.5	38.1	0.4	1.4	26.0	98.8	0.8	3.8
Adolescents (10 to < 18 years; 16 surveys)	Chocolate	4.0	46.4	0.1	1.0	14.1	165.4	0.3	3.2
	Coffee	14.1	93.1	0.3	1.5	103.5	246.1	1.9	4.4
	Cola beverages	13.4	46.5	0.3	0.8	36.0	124.7	0.7	2.0
	"Energy drinks" [c]	29.0	90.1	0.6	1.4	145.6	145.6	2.9	2.9
	Tea	9.0	72.0	0.2	1.2	43.3	216.7	1.2	3.5
Adults (18 to < 65 years; 16 surveys)	Chocolate	3.8	24.9	0.1	0.4	15.1	84.0	0.2	1.3
	Coffee	32.9	347.0	0.5	4.6	80.1	775.6	1.2	10.2
	Cola beverages	12.0	45.8	0.2	0.7	32.8	121.8	0.5	1.7
	"Energy drinks" [d]	23.5	98.5	0.3	1.2	152.0	200.0	2.0	2.8
	Tea	6.6	111.0	0.1	1.5	41.3	264.0	0.7	3.6
Elderly (65 to < 75 years; 13 surveys)	Chocolate	4.1	13.7	0.1	0.2	7.9	60.5	0.1	0.7
	Coffee	36.5	339.3	0.5	4.5	224.7	712.0	3.3	10.3
	Cola beverages	5.9	30.1	0.1	0.4	95.2	95.2	1.1	1.1
	"Energy drinks"	32.0	132.8	0.4	1.6	–	–	–	–
	Tea	19.8	135.8	0.3	1.8	66.0	335.0	1.0	4.6
Very elderly (≥ 75 years; 11 surveys)	Chocolate	5.1	22.3	0.1	0.4	21.8	34.1	0.3	0.5
	Coffee	34.3	382.6	0.5	5.5	247.0	446.8	3.7	6.1
	Cola beverages	3.9	26.5	0.1	0.3	43.2	43.2	0.6	0.6
	"Energy drinks"	24.0	113.1	0.4	1.7	–	–	–	–
	Tea	19.0	130.8	0.2	1.9	55.0	283.5	0.9	4.2

(a): The 95th percentile estimates obtained from dietary surveys and age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011b) and consequently were not considered in this table ("–").

(b): Minimum (min) and maximum (max) means and 95th percentiles of those calculated from individual surveys for each age class. Total caffeine intakes cannot be calculated for "consumers only" by calculating the sum of caffeine consumption from coffee, tea, colas and energy drink, because these figures reflect the intakes of different subjects (consumers of the food group).

(c): Only one study (the Netherlands) with a sufficient number (≥ 60) of subjects who had consumed "energy drinks" was available to estimate a statistically robust 95th percentile.

(d): Only two studies (the Netherlands and Ireland) with a sufficient number (≥ 60) of subjects who had consumed "energy drinks" were available to estimate statistically robust 95th percentiles.

Adults, the elderly and the very elderly

Daily caffeine intake from all sources could be estimated for adults from 16 Member States. Means and 95th percentiles ranged from 37 to 319 mg and from 109 to 742 mg, respectively, among countries (Table 2, Appendix B).

In most surveys, coffee was the predominant source of caffeine for the adult population and contributed between 40 and 94 % to total caffeine intake. In Ireland and the UK, tea was the main source of caffeine, which contributed 59 and 57 %, respectively, to total caffeine consumption (Appendix E).

Considering caffeine intake in consumers of the different caffeine-containing food groups, coffee consumers had the highest 95th percentile of caffeine consumption per day (up to 776 mg of caffeine from coffee), followed by tea drinkers (up to 264 mg of caffeine from tea), "energy drink consumers" (up to 200 mg of caffeine from "energy drinks") and consumers of cola beverages (up to 122 mg of caffeine from cola drinks) (Table 3).

Daily intake estimates for the elderly and very elderly are of a similar magnitude, with a tendency for lower 95th percentiles. Cola beverages and energy drinks were negligible as sources of caffeine in these population groups in all surveys.

Pregnant women

Data on pregnant women are available for Latvia only (n = 1 002). The mean and the 95th percentile of the daily caffeine intake from all sources were 109 mg and 206 mg per day, respectively (Appendix B).

Lactating women

Data on lactating women are available from only a small survey in Greece (n = 65). The mean and the 95th percentile of the daily caffeine intake from all sources were 31 mg and 97 mg per day, respectively (Appendix B).

Adolescents

Daily caffeine intakes from all sources could be estimated for adolescents from 13 Member States. Means and 95th percentiles ranged from 18 to 70 mg and from 61 to 212 mg, respectively, among countries (Table 2, Appendix B). On a per kg bw per day basis, the mean intakes ranged from 0.4 to 1.4 mg/kg bw per day. The 95th percentile varied between 1.5 and 4.1 mg/kg bw per day (Appendix B).

There were large differences among countries regarding the contribution of different food sources to total caffeine intake (Appendix E). Chocolate was the main contributor to caffeine intake in six surveys, coffee was the main contributor in four surveys, cola beverages were the main contributors in three surveys and tea was the main contributor in two surveys. Differences between surveys regarding the contribution of different caffeine sources to total caffeine intakes could be explained, at least in part, by the different mean age of the adolescents studied in the different surveys and by dietary habits. The highest contribution to total caffeine intakes from "energy drinks" was found for adolescents in the UK (11 %), followed by those in the Netherlands (8.1 %) and Belgium (5.3 %). In only the first two was a specific code for "energy drinks" available in the database.

Toddlers and other children

For toddlers, 10 surveys were available. Mean daily intakes of caffeine ranged from 0 to 2.1 mg/kg bw per day (Table 2, Appendix B). The 95th percentile ranged from 0.1 to 3.5 mg/kg bw per day. Tea or chocolate was the main caffeine source in all surveys except for Belgium, where cola drinks contributed the most to total caffeine intake (58 %; Appendix E). Mean daily caffeine intake was 1.1 mg/kg bw per day in this country (Appendix B).

For children aged 3 to < 10 years, 17 surveys were available. Mean daily intake of caffeine from all sources ranged from 0.2 to 2.0 mg/kg bw per day. The 95th percentile ranged from 1.2 to 4.6 m/kg bw per day.

In most countries, "chocolate" (which also includes cocoa drinks) was the predominant source of caffeine for children aged 3 to 10 years, followed by tea and cola drinks (Appendix E). "Energy drinks" were a negligible source of caffeine for children up to 10 years of age in the surveys considered.

3.3.1.2. Caffeine intake on a single day

Ninety-fifth percentiles are also reported for total caffeine intakes on single survey days (considering all days available) and for caffeine intakes from a given caffeine source on single survey days on which that caffeine source was consumed (Appendices C and D).

Data from multiple survey days for the same individual are considered independently, and data from all surveys, including those with a single survey day per individual, have been included. The 95th percentiles of caffeine intake on a single day have been calculated to gather information on days of particularly high caffeine consumption, but these do not provide information about the proportion of subjects with high caffeine consumption days.

Adults, the elderly and the very elderly

For adults, the highest 95th percentile of caffeine intake on a single day was 809 mg (10.8 mg/kg bw) (Appendices C and D).

When considering only coffee consumption days, the highest 95th percentile of caffeine intake from coffee on a single day was 890 mg. The highest 95th percentiles of caffeine intake from "energy drinks", tea and cola on a single day were 330, 308 and 216 mg, respectively.

Adolescents

The highest 95th percentiles of caffeine intake on a single day in absolute values and on a per kg bw basis were 240 mg and 4.3 mg/kg bw, respectively (Appendices C and D).

When considering only coffee consumption days, the highest 95th percentile of caffeine intake from coffee on a single day was 445 mg (Appendix C). The highest 95th percentiles of caffeine intake from "energy drinks", tea, chocolate and cola were 330, 308, 253 and 142 mg, respectively. On a per kg bw basis, the highest 95th percentile of caffeine intake was from coffee (7.1 mg), followed by chocolate (5.4 mg), "energy drinks" (5.2 mg), tea (5.0 mg) and cola beverages (2.4 mg).

Toddlers and other children

For toddlers, the highest 95th percentile of caffeine intake per kg bw on a single day when considering all days recorded was 7.1 mg/kg bw (Appendices C and D). Sufficient ($n \geq 60$) days to obtain statistically robust 95th percentiles for toddlers regarding caffeine intakes from different sources on consumption days were available only for chocolate and tea, for which the highest values across Member States were estimated to be 5.3 and 9.6 mg/kg bw per day of caffeine, respectively (Appendix C).

For children aged 3 to 10 years, the highest 95th percentile of caffeine intake from all sources on a single day was estimated to be 5.7 mg/kg bw (Appendices C and E). When considering only days with consumption of the different food categories, the 95th percentile of caffeine intake from coffee provided the highest estimate (15 mg/kg bw per day), followed by chocolate (7.7 mg/kg bw per day) (Appendix C).

3.3.2. Caffeine intake from "energy drinks" in a "single session" estimated from the EFSA report on "energy drinks"

Table 4 summarises caffeine intakes from "energy drinks" consumed in a "single session" by adults and adolescents who were "energy drink consumers" (i.e. at least once in the previous year). The table also indicates the prevalence of subjects who declared that they consume three or more "energy drinks" per "single session". Data were available from 16 Member States (Zucconi et al., 2013).

Table 4: Caffeine intakes from "energy drinks" in a "single session" by "energy drink consumers" and prevalence of subjects consuming three or more cans of "energy drink" per single session

	Caffeine intake per single session [(a)]				Percentage of "energy drink consumers" consuming ≥ 3 cans per single session	Percentage of total respondents consuming ≥ 3 cans per single session
	Mean		95th percentile			
	mg	mg/kg bw	mg	mg/kg bw		
Adolescents (10–18 years)	176	2.9	450	7.2	24	16.3
Adults (18–65 years)	155	2.2	344	5.1	19	5.7

(a): "Single session" was defined as a period of time of a couple of hours (e.g. a night out, study session or sport session); not studied in children.

Adults

The mean and 95th percentile of caffeine intakes in a "single session" from "energy drinks" in adult "energy drink consumers" were 155 mg and 344 mg, respectively (Table 4). In this survey, 52, 29, 11, 5 and 3 % of "energy drink consumers" declared that they consume one, two, three, four and five or more cans of "energy drinks" within a "single session".

Adolescents

The mean and 95th percentile of caffeine intakes in a "single session" from "energy drinks" in adolescent "energy drink consumers" were 176 mg and 450 mg, respectively (Table 4). On a per kg bw basis, these intakes were estimated to be 2.9 and 7.2 mg, respectively. In this survey, 51, 25, 11, 6 and 7 % of "energy drink consumers" declared that they consume one, two, three, four and five or more cans of "energy drinks" within a "single session".

3.3.3. Prevalence of "energy drink" consumption

3.3.3.1. EFSA Comprehensive European Food Consumption Database

The prevalence of "energy drink consumers" (defined as subjects who consumed "energy drinks" at least on one day during the survey) among the 17 surveys introduced into the EFSA Comprehensive Database in 2014 using the FoodEx2 code for "energy drinks" was < 10 %. The highest prevalences of "energy drink consumers" were observed in adolescents (9 % in the Netherlands, 7 % in the UK and 5 % in Finland) and adults (8 % in Ireland, 4 % in the Netherlands and 3 % in the UK). In these surveys, the prevalence of "energy drink consumers" was most often zero and never exceeded 1 % in toddlers (five surveys), children aged 3–10 years (seven surveys), the elderly (10 surveys) and very elderly (eight surveys), lactating women (one survey) and pregnant women (one survey).

3.3.3.2. EFSA report on "energy drinks"

Table 5 provides an overview of the prevalence of "energy drink consumers" (defined as consumers of "energy drinks" on at least one occasion during the previous year) alone and in combination with physical activity.

Table 5: Prevalence (%) of "energy drink consumers" and of consumers of "energy drinks" in combination with physical activity expressed as minimum and maximum ranges among 16 Member States and as mean values for all surveys combined

	Children (3–10 years)			Adolescents (10–18 years)			Adults (18–65 years)		
	Mean	**Min**	**Max**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**
"Energy drink consumers" [(a)]	18	6	40	68	48	82 [(b)]	30	14	50
Consumers of energy drinks plus physical activity [(c)] among "energy drink consumers"	–	–	–	41	14	65	52	26	62
Consumers of ≥ 3 "energy drinks" plus physical activity among "energy drink consumers"	–	–	–	11	–	–	14	–	–
Consumers of "energy drinks" plus physical activity [(c)] among total respondents	–	–	–	28	–	–	16	–	–
Consumers of ≥ 3 "energy drinks" plus physical activity among total respondents	–	–	–	8	–	–	4	–	–

(a): Percentage of "energy drink consumers" among total respondents.
(b): The highest prevalence of "energy drink" consumption among total respondents was observed in Belgium (85 %), but these data were not considered owing to the small sample size available for that MS (sampling error of estimates exceeds 5 %).
(c): Percentage of subjects who declared that they usually consume "energy drinks" before/in association with/after sports activities. Children were not studied.
–, not available.

The Panel notes that the prevalence of "energy drink consumers" in this survey is considerably higher than that calculated from the EFSA's Comprehensive Database, mainly because of differences in the definition of "consumers" and in the methodology used to retrieve consumption data.

Adults

About 52 % of adult "energy drink consumers" (15 % of all respondents) declared that they usually consume "energy drinks" before/in association with/after sports activities (Table 5). According to this survey, 47, 26, 13, 9 and 5 % of this population declared that they consume one, two, three, four and five or more cans of "energy drinks" in relation to a single sport session.

Adolescents

About 41 % of adolescent "energy drink consumers" (about 28 % of all respondents) declared that they usually consume "energy drinks" in relation to sport activities (Table 5). In this survey, 48, 25, 13, 7 and 7 % of this population declared that they consume one, two, three, four and five or more cans of "energy drinks" in relation to a single sport session.

3.4. Limitations of the available caffeine intake data and data gaps

The surveys included in the EFSA Comprehensive Database vary considerably regarding several aspects, e.g. the methodology used to retrieve food consumption data (e.g. number of survey days, dietary recalls versus dietary records), the number of subjects and age range of the subjects included, the sampling year(s). Such differences do not allow direct between-country comparisons, and thus ranges of means and 95th percentiles across surveys should be interpreted with caution. Data are particularly scarce for pregnant and lactating women, and absent regarding the consumption of caffeine-containing supplements. The EFSA Comprehensive Database is useful to gather data on daily caffeine intakes from all sources from unselected populations and population subgroups, as well as on the contribution of different food groups to total caffeine intakes.

The EFSA "energy drink" report provides information about caffeine intakes by adolescents and adults from "energy drinks" on a "single session", also in relation to a "single session" of physical exercise. Although the time covered by the term "single session" is imprecise, these data give an idea

of the amounts of caffeine from "energy drinks" consumed as a single dose or during short periods of time. However, the same type of information is not available for consumers of other caffeine sources that may provide similar or higher doses of caffeine in short periods of time (e.g. coffee, caffeine supplements), or for other population subgroups (e.g. children, pregnant women).

4. Hazard identification

As indicated in the background provided by the European Commission and in Section 2.4 of this opinion, the health concerns expressed by national and international risk assessment bodies in relation to caffeine mostly refer to its effects on pregnancy outcomes, the cardiovascular system and the CNS. Concerns were also raised with respect to caffeine in so-called "energy drinks" (i.e. also containing taurine and D-glucurono-γ-lactone), particularly if combined with alcohol, and to food supplements containing caffeine and *p*-synephrine. As in previous risk assessments by, for example, the SCF and EU Member State Committees, the present opinion considers primarily human data and addresses specific subgroups of the population, such as pregnant and lactating women, children and subjects performing physical exercise.

4.1. Absorption, distribution, metabolism and excretion

4.1.1. Adults

In humans, caffeine is rapidly (t_{max} 30–120 minutes) and completely absorbed after oral intake (Blanchard and Sawers, 1983). Once absorbed, it freely crosses the blood–brain, placental and blood–testicular barriers (Weathersbee and Lodge, 1977; Arnaud, 1993). The volume of distribution is 0.671 L/kg bw (Abernethy and Todd, 1985).

The main route of metabolism in humans (70–80 %) is via N-3 demethylation to paraxanthine (also known as 1,7-dimethylxanthine or 17X) catalysed by cytochrome (CYP) 1A2 in the liver. Other primary metabolites are theophylline and theobromine. Activity of CYP1A2 accounts for about 95 % of caffeine clearance, a smaller proportion is metabolised by CYP3A4, xanthine oxidase and N-acetyltransferase 2 (Berthou et al., 1991; Miners and Birkett, 1996). Caffeine has a plasma half-life of about four hours with range of about two to eight hours (Knutti et al., 1981; Abernethy and Todd, 1985; Abernethy et al., 1985; Balogh et al., 1995). The kinetics of caffeine have been reported to be linear in doses up to 10 mg/kg bw (Bonati et al., 1982), whereas a later study claimed non-linearity beginning at doses as high as 500 mg, corresponding to about 7.1 mg/kg bw (Kaplan et al., 1997). Paraxanthine, theophylline and theobromine are further metabolised and then excreted in the urine.

Several studies investigated the effect of the genetic polymorphism of the CYP1A2 gene, smoking, coffee consumption, sex, pregnancy and oral contraceptives on caffeine metabolism and clearance.

CYP1A2 polymorphism has been reported to be a source of variability in the metabolism of caffeine between individuals measured by caffeine metabolites in urine (Rasmussen et al., 2002). These authors also found a higher CYP1A2 activity in smokers and men than in non-smokers and women, respectively. A lower CYP1A2 activity was found in women taking oral contraceptives. A single base change of A to C at position 734 within intron 1 of the CYP1A2 gene decreases inducibility of the enzyme (Sachse et al., 1999; Han et al., 2001). This polymorphism is also referred to as CYP1A2*1F or -163C>A (AA, AC, CC) genotypes (Cornelis et al., 2006; Djordjevic et al., 2010) or as single nucleotide polymorphism (SNP) "rs762551" registered in the SNP Database of the US National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP). The homozygote AA genotype has been considered by some authors as a "fast metaboliser", while the AC and CC genotypes were considered to be "slow metabolisers". In four publications, the combined prevalence of the "slow" CC and AC genotypes was reported to be between 52 and 60 %, whereas the "fast" AA genotype was reported to be between 48 and 40 % (Sachse et al., 1999; Han et al., 2001; Cornelis et al., 2006; Wang et al., 2012). Djordjevic et al. (2010) and Rodenburg et al. (2012) reported a higher prevalence for the AA genotype (61 % in Serbs; 54 % in Dutch).

Tantcheva-Poor et al. (1999) studied the effect of genetic (CYP1A2, sex) and lifestyle (coffee consumption, smoking, intake of oral contraceptives) factors of 786 individuals on the clearance of caffeine with a single saliva sample taken five to seven hours after a test dose of about 145 mg caffeine. Overall, the geometric mean (geometric standard deviation (SD)) of caffeine clearance was 1.34 mL/min/kg bw (1.65). Relevant factors influencing clearance were (i) daily coffee consumption, increasing clearance 1.45-fold per consumed litre; (ii) smoking, increasing clearance 1.22-fold, 1.47-fold, 1.66-fold and 1.72-fold for 1–5, 6–10, 11–20 and > 20 cigarettes smoked per day, respectively; (iii) oral contraceptives, reducing clearance by 0.72-fold; and (iv) female gender, reducing clearance by 0.90-fold. These covariates explained 37 % of overall variation in clearance. The clearance data did not indicate a relevant functional polymorphism for CYP1A2 activity when adjusted for covariate effects.

CYP1A2 enzyme induction and higher caffeine clearance in smokers have also been reported in other studies (Joeres et al., 1988; Ghotbi et al., 2007). Ghotbi et al. (2007) and Sachse et al. (1999) found significantly higher CYP1A2 activity in smokers of the CYP1A2 -163AA genotype ("fast") than in smokers of the ("slow") AC and CC genotypes. No difference was found in enzyme activity among the three genotypes in non-smokers in these two studies.

In addition, coffee consumption of more than two cups per day was significantly associated with higher CYP1A2 activity in non-smoking Swedes and Serbs, but only in the CYP1A2 -163AA genotype (Djordjevic et al., 2010). No increased CYP1A2 activity was found for coffee consumers of less than three cups of coffee per day, irrespective of this SNP, and for the "slow" CC and AC genotypes, irrespective of their coffee consumption.

More than 150 SNPs have been identified for CYP1A2 (dbSNP database: http://www.ncbi.nlm.nih.gov/SNP/) (Yang et al., 2010) with unknown functional relevance concerning caffeine metabolism.

In a study with eight healthy individuals, two subjects who were taking oral contraceptives had significantly longer caffeine half-lives (15.5 ± 0.3 hours versus 5.6 ± 1.7 hours) and lower values for oral clearance (0.34 ± 0.01 mL/min/kg bw versus 0.99 ± 0.41 mL/min per kg bw) than subjects who were not taking oral contraceptives (Haller et al., 2002). These results are consistent with earlier studies on the influence of sex steroids on caffeine metabolism (Rietveld et al., 1984; Abernethy and Todd, 1985; Balogh et al., 1995). In addition, severe liver disorders (Arnaud, 1993) and some drugs (Carrillo and Benitez, 2000) have been reported to cause a significant inhibition of CYP1A2 activity.

4.1.2. Pregnant women

During pregnancy, the half-life of caffeine increased in 15 pregnant women to a range of 6–16 hours and returned to a range of two to eight hours within 4 and 15 weeks after delivery (Knutti et al., 1982). The reported prolonged half-life for pregnant women is consistent with results from other studies. For the end of pregnancy, the half-life of caffeine in non-smoking women was reported to be 11.5 hours (Arnaud, 1993) and 18 hours (Aldridge et al., 1981). This observation can be explained by the interaction of caffeine with oestrogens and gestagens which have been shown to inhibit the activity of CYP1A2 (Rietveld et al., 1984; Abernethy et al., 1985; Balogh et al., 1995). Tracy et al. (2005) reported that CYP1A2 activity was significantly and progressively lower during pregnancy (–32.8 ± 22.8 % for weeks 14–18), (–48.1 ± 27 % for weeks 24–28) and (–65.2 ± 15.3 % for weeks 36–40) than during the postpartum period. Similar quantitative and progressive reductions of CYP1A2 activity during pregnancy have been reported (Tsutsumi et al., 2001). The Panel notes that 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. This would lead to higher blood concentrations of caffeine at the end of pregnancy than in the non-pregnant state if caffeine intake is kept constant during pregnancy.

4.1.3. Fetus

Caffeine readily crosses the placenta into the fetus. Amniotic fluid and maternal serum concentrations of caffeine are believed to be reliable indicators of fetal serum concentration. Given the prolonged half-life of caffeine during pregnancy and considering that neither the fetus nor the placenta can metabolise caffeine, fetuses of caffeine-consuming women are exposed to caffeine and its metabolites for a significantly prolonged time (Grosso et al., 2006).

4.1.4. Breastfed infants

In a study on 18 nursing mothers who abstained for 24 hours from eating and drinking caffeine-containing food, the concentration of caffeine was measured in plasma and milk two and four hours after the intake of caffeine from coffee (148 ± 48 mg). The average milk/maternal plasma ratio was 0.8 ± 0.07. Intake in the nursed infants (4 days to 19 weeks) was estimated to be between 0.03 and 0.2 mg/kg bw per day. In eight of the infants, the caffeine concentration was measured in their saliva, which is close to the non-protein bound fraction of caffeine in plasma (90 %). The concentration in the saliva of infants was 0.38 ± 0.2 mg/L, whereas the peak concentration in the plasma of the mothers was about 3 mg/L, thus indicating low intakes of the infants (Hildebrandt and Gundert-Remy, 1983).

In two studies (Steer et al., 2003, 2004), pre-term neonates were treated for extubation with caffeine doses of 3 mg/kg bw (n = 42), 5 mg/kg bw (n = 121), 15 mg/kg bw (n = 40) 20 mg/kg bw (n = 131) and 30 mg/kg bw (n = 45). Mean caffeine concentrations in the 3 mg/kg bw group, the 15 mg/kg bw group and the 30 mg/kg bw group were 6.7 mg/L, 31.4 mg/L and 59.9 mg/L, respectively. The observed side effects of caffeine administration were tachycardia (defined as heart rate > 200 bpm) and jitteriness. Tachycardia was observed in 1 out of 42 pre-term infants in the 3 mg/kg bw group, in 1 out of 121 infants in the 5 mg/kg bw group, in 5 out of 40 infants in the 15 mg/kg bw group, in 4 out of 131 infants in the 20 mg/kg bw group and in 8 out of 45 infants in the 30 mg/kg bw group. Jitteriness was observed in 1 out of 42 infants in the 3 mg/kg bw group, 2 out of 121 infants in the 5 mg/kg bw group, 1 out of 40 infants in the 15 mg/kg bw group, 2 out of 131 infants in the 20 mg/kg bw group and 0 out of 45 infants in the 30 mg/kg bw group. As pre-term neonates are considered an especially sensitive population subgroup, these results can be extrapolated to neonates and breastfed infants in general as the most conservative estimates of the prevalence of side effects.

The half-life of caffeine in neonates who have no CYP1A2 activity has been reported to range from 50 to 103 hours (Ginsberg et al., 2004; Grosso et al., 2006). However, the half-life of caffeine is rapidly reduced in the first months of life, decreasing to 14 hours at three to four months of age and to two to three hours at five to six months of age (Aranda et al., 1979). Caffeine's half-life appears to remain stable at about two to three hours 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 (NNT, 2008).

4.1.5. Conclusions

The Panel notes that several genetic and non-genetic factors have been reported to significantly affect caffeine metabolism by CYP1A2 for various population groups. Considering the reduced maternal clearance and prolonged half-life during pregnancy, and the fetus's exposure to maternal caffeine plasma levels, the Panel considers unborn children to be the most vulnerable group for adverse effects of caffeine among the general population.

4.2. Pharmacodynamic effects

The pharmacology of caffeine has been extensively studied. The effects of caffeine are predominantly related to its antagonistic activity at adenosine receptors. Of the four adenosine receptors (A_1, A_{2A}, A_{2B} and A_3), caffeine acts as an antagonist to adenosine A_1 and A_{2A} receptors that are expressed in the CNS, in particular at the basal ganglia, which are involved in motor activity. The psychomotor stimulant effect of caffeine is generated by affecting a particular group of projection neurons located in the striatum, the main receiving area of the basal ganglia expressing high levels of adenosine A_{2A}

receptors. Caffeine acts, at least in part, by facilitating dopamine D_2 receptor transmission. Its mechanism of action appears to be substantially different from that of "dopaminomimetic" psychostimulants, such as cocaine and amphetamine (Fisone et al., 2004; Ferre, 2008). Caffeine is also known as a non-specific phosphodiesterase inhibitor, with a K_i of 48 µM, corresponding to the peak concentration after a 450 mg dose (Aronsen et al., 2014).

The diuretic activity of caffeine can be explained by an interaction with the adenosine receptor A_1 in the kidney, leading to inhibition of renal re-absorption and causing diuresis and natriuresis (Rieg et al., 2005).

Tolerance to caffeine is observed after repeated administration. The mechanism is not well understood. It has been attributed to upregulation of adenosine receptors (Ammon, 1991). Fast tolerance development has been observed concerning the pressor effects of caffeine (Shi et al., 1993). Prolonged administration of an adenosine A_{2A} receptor antagonist does not induce tolerance to its motor stimulant effect, suggesting that caffeine tolerance may be dependent on blockade of A_1, rather than A_{2A}, receptors (Ferre, 2008). Tolerance in humans develops to some, but not to all, effects of caffeine and the development of tolerance is highly variable among the population (Fredholm et al., 1999). Tolerance to 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. It is uncertain if the development of tolerance may explain the difference in the sensitivity to the effects of coffee on sleep. Some authors consider that the difference instead reflects inter-individual variations in sensitivity to the effects of caffeine as well as intra-individual variability.

Symptoms such as headache, fatigue, decreased energy and activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability and being not clear headed are observed 12–24 hours after abstinence and this clinical situation is called caffeine withdrawal syndrome (Juliano and Griffiths, 2004).

Polymorphisms in adenosine receptors have also been described and for some effects of caffeine the effect size might be related to the polymorphic state (Alsene et al., 2003).

4.3. Adverse effects of caffeine: methodological considerations

In order to update the safety assessment of caffeine conducted in 1999 by the SCF (SCF, 1999), EFSA launched a procurement project (RC/EFSA/NUTRI/2013/01) to retrieve articles published from 1997 onwards which addressed the effects of caffeine consumption in humans on different health outcomes (Bull et al., 2014). Previous risk assessments by other bodies and spontaneous submissions from stakeholders were also considered by the Panel when retrieving articles published up to June 2014 which could be used as a source of data in the present assessment.

The Panel considers that human intervention studies and human observational studies (prospective cohort, case–control and cross-sectional studies) with adequate control for confounding variables and which have been conducted in healthy subjects at recruitment are appropriate for evaluating potential adverse effects of caffeine consumption in humans. Moreover, studies conducted in subjects selected on the basis of a disease condition (e.g. established CVD, neurological or psychiatric diseases, behavioural or sleep disorders, diabetes mellitus and other metabolic disorders, renal or hepatic insufficiency, open angle glaucoma) do not allow conclusions to be drawn on the safety of caffeine for the general healthy population or subgroups thereof. Whenever available, human intervention studies and prospective cohort studies were preferred over case–control and cross-sectional studies because of the lower risk of reverse causality and recall bias. The Panel also considers that case reports of adverse health events following consumption of caffeine-containing foods or beverages are useful to identify health concerns for further investigation. However, "cases" are, by definition, not representative of the general population or subgroups thereof and case reports generally provide insufficient information to conclude on the doses of caffeine which may be considered as safe for the general population or subgroups thereof (e.g. they do not provide sufficient information to allow a comparison between the

incidence of adverse events associated with the consumption of caffeine-containing products and the background incidence of such adverse events in the general population). For these reasons, case reports of adverse reactions following consumption of caffeine-containing foods or beverages, including "energy drinks", will not be considered in the derivation of caffeine levels of no concern. Whenever available, systematic reviews and meta-analyses were used to summarise the scientific evidence.

On the basis of the human studies identified, the Panel addressed possible adverse health effects of caffeine as a result of single doses (acute) or repeated doses within a day of longer-term consumption (single or repeated doses within a day consumed daily for ≥ 7 days, after caffeine habituation takes place, but for ≤ 1 month), and of habitual caffeine consumption (doses of caffeine consumed throughout the day for longer periods of time, usually months or years, *ad libitum*).

4.4. Adverse effects of a single dose and of repeated doses of caffeine consumed within a day

With few exceptions, the effects of a single dose and of repeated doses of caffeine consumed within a day from a variety of sources (including "energy drinks"), either alone or in combination with alcohol or *p*-synephrine, have been addressed in human intervention studies. Among the variety of outcomes investigated in these studies, the Panel focuses on the main health concerns expressed by other bodies in previous safety assessments, i.e. adverse effects of caffeine on the CVS and the CNS (also considering that the CVS and the CNS are the target organs for the acute effects of caffeine), and on water–electrolyte balance and body temperature, primarily in relation to physical exercise. Studies which did not report on safety outcomes (i.e. investigating the effects of caffeine on outcomes which were deemed to be beneficial for the target population recruited, such as attention, alertness or physical performance, and studies addressing the beneficial effects of caffeine in the treatment of various diseases) were not considered by the Panel in this assessment.

The Panel notes that an assessment of the health effects of components other than caffeine in foods and beverages which are common dietary sources of caffeine (e.g. coffee, tea, soft drinks other than "energy drinks", chocolate) is outside the scope of this opinion, and therefore human intervention studies which do not provide information about the effects of caffeine on the above-mentioned health outcomes (e.g. studies using caffeinated coffee/tea and caffeine as control; studies using different doses of decaffeinated coffee/tea with no caffeine group; uncontrolled studies with a caffeine group only) are not considered specifically.

4.4.1. Cardiovascular system

Early metabolic studies found that single caffeine doses of 200–250 mg acutely increase plasma renin activity, catecholamine concentrations and blood pressure (BP), and are able to induce cardiac (mostly atrial) arrhythmias in healthy, caffeine-naive subjects (Robertson et al., 1978; Dobmeyer et al., 1983). Possible mechanisms for the acute cardiovascular effects of caffeine include antagonistic effects on adenosine receptors, activation of the sympathetic nervous system (release of catecholamines from adrenal medulla), stimulation of the adrenal cortex (release of corticosteroids), renal effects (diuresis, natriuresis, activation of the renin–angiotensin–aldosterone system) and inhibition of phosphodiesterases (increase in cyclic nucleotides), although the contribution of each of these mechanisms to the acute cardiovascular effects of caffeine are unclear (Nurminen et al., 1999). It has been suggested that the acute effects of caffeine on the CVS may depend on the source of caffeine, the dose administered and caffeine plasma concentrations prior to caffeine administration.

4.4.1.1. Blood pressure, endothelial function and arterial compliance

Caffeine: single dose

Nurminen et al. (1999) reviewed 20 controlled human intervention studies in normotensive subjects and five intervention studies in hypertensive subjects which had investigated the effects of single doses of caffeine or caffeinated coffee on BP. A single dose of caffeine (200–250 mg, equivalent to two to three cups of coffee) was found to increase systolic blood pressure (SBP) by 3–14 mmHg and

diastolic blood pressure (DBP) by 4–13 mmHg in normotensive subjects. Lower doses of caffeine were not tested. Changes in BP paralleled changes in plasma concentrations of caffeine. BP started increasing 30 minutes after caffeine administration to reach a maximal effect at 60–120 minutes, and lasted for about two to four hours. The effect was more pronounced in older subjects, in caffeine abstainers, during "mental or physical stress" and in subjects with hypertension. In a more recent meta-analysis (Mesas et al., 2011) of five randomised control trials (RCTs) conducted in subjects with hypertension, single caffeine doses of 200 to 300 mg induced a mean increase in SBP and DBP of 8.1 mmHg (95 % confidence interval (CI) = 5.7–10.6 mmHg) and 5.7 mmHg (95 % CI = 4.1–7.4 mmHg), respectively, which was observed in the first 60 minutes after intake and persisted up to 180 minutes afterwards. The effect of caffeine on BP did not change with the dose (only 200 to 300 mg was tested), the time of caffeine abstinence before the trial (9–48 hours) or the use of antihypertensive medication.

The effects of a single dose of caffeine on arterial BP were investigated in 182 men stratified in five groups by their risk of hypertension (Hartley et al., 2000). The study sample included 73 men with optimal BP, 28 men with normal BP, 36 men with high–normal BP, 27 men with stage 1 hypertension on the basis of resting BP and 18 men with diagnosed hypertension from a hypertension clinic. BP was measured after 20 minutes of rest and 45 to 60 minutes after the oral administration of caffeine (3.3 mg/kg bw or a fixed dose of 250 mg for an average dose of 260 mg). Caffeine significantly raised both SBP and DBP in all groups. However, the strongest response to caffeine was observed among diagnosed men (mean increase in SBP of 10 mmHg), followed by the stage 1 and high–normal groups and then by the normal and optimal groups, with a change 1.5 times greater in diagnosed hypertensive individuals than in the group with optimal BP.

A number of controlled human intervention studies have been published on the effects of single caffeine doses (as supplements and in coffee, tea and "energy drinks") on functional vascular outcomes, including endothelial function, arterial compliance and BP, in healthy subjects. The main characteristics of these studies are summarised in Appendix F.

Acute increases in SBP, DBP or both, as well as in pulse pressure and mean arterial blood pressure (MABP), have been reported after single doses of caffeine ranging from 80 to 250 mg in coffee abstainers, in habitual caffeine consumers after 12–48 hours' withdrawal and after caffeine habituation (300–600 mg per day for six days) (Hodgson et al., 1999; Lane et al., 2002; Farag et al., 2005a, b, 2010; Arciero and Ormsbee, 2009; Worthley et al., 2010; Buscemi et al., 2011). The effect was inversely related to the level of physical activity in pre-menopausal women (Arciero and Ormsbee, 2009), and did not translate into acute adverse changes in left ventricular repolarisation (corrected QT interval (QTc)) (Buscemi et al., 2011).

In studies assessing endothelial function, compared with decaffeinated coffee, caffeinated coffee has been reported to significantly increase SBP (130 mg caffeine) and DBP (80 and 130 mg caffeine), as well as to decrease endothelium-dependent flow-mediated dilatation (FMD) in habitual moderate coffee consumers after 12–24 hours' caffeine withdrawal (Papamichael et al., 2005; Buscemi et al., 2010). A significant decrease in endothelial function (assessed by peripheral artery tomography) with concomitant increases in SBP and DBP was also reported after consumption of an "energy drink" containing 80 mg caffeine, 1 000 mg taurine and 600 mg D-glucurono-γ-lactone (Worthley et al., 2010). Whether or not this effect could be explained by its content of caffeine was not addressed (no caffeine group). Conversely, a significant increase in acetylcholine-mediated, endothelium-dependent forearm blood flow (measured by brachial impedance plethysmography), which was reversible with the infusion of a nitric oxide synthetase inhibitor, was reported for a caffeine dose of 300 mg, which also induced a significant increase in both SBP and DBP (Umemura et al., 2006).

All studies available in healthy individuals (Mahmud and Feely, 2001; Vlachopoulos et al., 2003, 2006; Hartley et al., 2004; Karatzis et al., 2005; Swampillai et al., 2006) reported a significant adverse effect of caffeine (in supplements, coffee or tea) at doses of 100–250 mg on one or more measures of arterial compliance (e.g. forward compression and expansion waves or pulse wave velocity as

measures of stiffness; augmentation index and augmented pressure as measures of wave reflections), denoting an increase in arterial stiffness, which was accompanied by a simultaneous increase in one or more measures of BP (e.g. radial, aortic or brachial SBP and DBP, pulse pressure, MABP). The methods used to assess arterial compliance and BP, the arterial segments assessed and the indices derived as outcome variables differed among studies. Similar effects of caffeine on arterial compliance were found in men and women, although different mechanisms (increase in peripheral resistance versus increase in stroke volume and cardiac output, respectively) were proposed for each sex (Hartley et al., 2004).

The clinical relevance of acute changes in endothelial function and arterial compliance following an intervention is unclear, particularly when simultaneous changes in BP occur (Anderson, 2006; McCall et al., 2011). Changes in BP, and therefore blood flow, are associated with changes in FMD and pulse-wave velocity (PWV), which do not necessarily reflect an adverse change in the endothelial function or sustained stiffness of the artery (McCall et al., 2011). The acute changes in endothelial function and arterial compliance following caffeine consumption are vascular phenomena concordant with the acute increase in BP, which can be predicted from arterial physiology. Unlike for BP (see Section 4.5.1.2), there are no studies available on the longer-term effects of habitual caffeine consumption on these endpoints.

Caffeine: repeated doses

Two studies (Lane et al., 2002; Farag et al., 2005b) have investigated the effects of repeated doses of caffeine consumed within a day on 12- to 18-hour ambulatory BP in healthy habitual caffeine consumers (Appendix F).

In a double-blind, randomised, placebo-controlled cross-over study (Lane et al., 2002), 47 healthy normotensive, non-smoking subjects (20 female) were given either placebo or two 250 mg doses of caffeine four hours apart (at 7.30–8.30 am and before 1.00 pm) on two separate trial days after an overnight fast. Ambulatory BP was monitored after the first caffeine dose until bedtime or 10.00 pm. Compared with placebo, caffeine significantly raised average SBP through the entire day by about 4 mmHg and DBP by about 3 mmHg, whereas heart rate (HR) decreased by 2 bpm, with no significant interaction between treatment and location (at work, at home). Urinary free adrenaline levels were 32 % higher with caffeine than with placebo, particularly at work.

In a second study with a double-blind, randomised, placebo-controlled cross-over design (Farag et al., 2005b), 85 healthy normotensive subjects (38 women) completed a four-week protocol. During each week, subjects consumed capsules containing 0, 100 or 200 mg of caffeine three times daily (daily doses of 0, 300 or 600 mg) for five days. On day 6, subjects consumed capsules at 9.00 am, 1.00 pm and 6.00 pm with either 0 or 250 mg caffeine after the placebo (P) maintenance dose and with 250 mg caffeine (C) after each caffeine maintenance dose (four interventions: P-P, P-C, C300-C and C600-C). Ambulatory BP was monitored on day 6 after the second caffeine dose until 7.00 am the following day. Subjects were dived into “high” and “low” tolerance groups on the basis of the median DBP response to the first two challenge caffeine doses (at 9.00 am and 1.00 pm) given after the highest caffeine maintenance dose (600 mg per day). The Panel notes that data were not analysed for all the study subjects combined. As expected, significant differences in daytime BP were observed across maintenance caffeine doses and tolerance groups. However, no significant week by tolerance group interactions were noted. Sleep BP also differed significantly across caffeine maintenance doses, but not between tolerance groups, with no significant week by tolerance group interactions for sleep SBP or DBP. Compared with P-P, daytime BP was significantly higher during P-C in both tolerance groups and during C300-C in the “low” tolerance group, with no differences during C600-C in either tolerance group or during 300-C in the “high” tolerance group. Similarly, sleep BP was significantly higher during P-C in both tolerance groups and during C300-C (only SBP) in the “low” tolerance group, with no differences during C600-C in either tolerance group or during C300-C in the “high” tolerance group.

These studies suggest that repeated doses of 250 mg caffeine taken four hours apart may induce a significant increase in daytime BP, that BP remains significantly elevated up to 9–12 hours after consumption of the last dose and that the effect, which depends on habitual caffeine consumption, is mostly observed after caffeine withdrawal. The Panel notes the high total caffeine intakes used in these studies (500–750 mg per day), that lower repeated doses of caffeine (< 250 mg) have not been tested and that the time between doses (four hours), about one half-life, is likely to induce an increase in plasma caffeine concentrations throughout the day.

Caffeine and physical exercise

Three randomised, placebo-controlled, human intervention studies assessed the effects of caffeine (4–6 mg/kg bw) ingested 45–60 minutes pre-exercise on BP before (n = 3), during (n = 2) and after (n = 2) resistance exercise in recreational resistance-trained, normotensive men (except for three women in Souza et al., 2014) who were habitual caffeine consumers after 48–72 hours of caffeine withdrawal (Astorino et al., 2007, 2013; Souza et al., 2014). The study by Astorino et al. (2013) included seven subjects with either high–normal or stage 1 hypertension, although the number of subjects with hypertension was not specified. Sample size ranged from 14 to 22. BP variables and exercise programmes varied among studies. In the study by Astorino et al. (2007), SBP, HR and rate-pressure product (but not DBP) significantly increased during exercise with caffeine and placebo and were significantly higher before and during exercise with caffeine than with placebo, but no time by treatment interaction was observed, suggesting an additive (but not synergistic) effect of caffeine and exercise on BP. In the study by Astorino et al. (2013), in which four resistance exercise protocols were tested, SBP significantly increased during all exercise protocols and significantly decreased post exercise with caffeine and placebo. SBP was significantly higher before and two hours after exercise with caffeine than with placebo, whereas HR and DBP were not different between treatments. SBP was higher with caffeine than with placebo during only one (out of four) type of exercise and in the "pre-hypertensive" group only. Souza et al. (2014) reported a significant decrease in SBP and MABP and a significant increase in HR after exercise with caffeine and placebo. DPB and HR (but not SPB) were significantly higher at rest with caffeine than with placebo, as was peripheral vascular resistance (SBP, DBP, HR, stroke volume or cardiac output) in the nine hours post exercise. The Panel considers that, although these studies have small sample sizes and are difficult to compare, they suggest an additive effect of caffeine and resistance training on BP during exercise, and that caffeine could attenuate the decrease in BP observed after resistance training.

Caffeine and other components of "energy drinks"

Two randomised cross-over studies (Worthley et al., 2010; Grasser et al., 2014) assessed the effects of two "energy drinks" containing caffeine, taurine and D-glucurono-γ-lactone on BP and endothelial function compared with the same volume of water. One study (Bischoff, 2013)[13] conducted at the University of Hohenheim and submitted to EFSA investigated the effects of an "energy drink" containing caffeine, taurine and D-glucurono-γ-lactone, with and without 75 g of alcohol, on multiple outcomes (including heart rate and BP) compared with the same volume of a caffeine-free soft drink. The Panel notes that these studies do not allow conclusions to be drawn on whether or not "energy drinks" have a BP-raising effect over and above what could be expected from their caffeine content.

One open-label, randomised, two-period cross-over study investigated the effects of a single dose of an "energy drink" on BP compared with caffeine alone (Franks et al., 2012). Twelve healthy, non-smoking, normotensive volunteers aged 18–45 years consumed one serving of "energy drink" (80 mg caffeine and 1 000 mg taurine per serving) four times at 8.00 am, 11.00 am, 3.00 pm and 7.00 pm, giving a total consumption of 320 mg caffeine and 4 000 mg of taurine. Subjects underwent the same protocol with caffeine alone (80 mg per serving in a similar volume) 4–30 days apart. The order of the intervention was randomised. During the interventions, 24-hour ambulatory BP was monitored. Data from nine subjects were available for analysis. The analysis showed that 24-hour SBP, DBP and mean

[13] http://download.ble.de/09HS022/09HS022_AB.pdf

arterial BP were significantly higher with the consumption of "energy drinks" than with the consumption of caffeine alone (by 5.8, 5.3 and 5.3 mmHg, respectively), whereas HR and nocturnal dipping (SBP and DBP) did not differ. The Panel considers that, although this study suggests a greater BP-raising effect associated with the consumption of "energy drinks" than with caffeine alone, the small number of subjects included in the study, the high dropout rate (25 %) and the absence of blinding all limit the conclusions which can be drawn in relation to the effects of "energy drink" components other than caffeine on BP.

The aforementioned study (Bischoff, 2013) contains information on a "pre-study" using a cross-over design conducted in 19 healthy subjects who received a single dose (1 000 mL) of a sports drink (control, free of caffeine, taurine or D-glucurono-γ-lactone), the sports drink plus taurine (4 000 mg), the sports drink plus caffeine (320 mg) and an "energy drink" (containing 4 000 mg of taurine, 320 mg of caffeine and 240 mg of D-glucurono-γ-lactone) on four separate occasions. The same preliminary testing was conducted in 19 other subjects using 750 mL (as a single dose) of the same beverages. A significant increase in SBP (by about 7–8 mmHg) was reported following consumption of the sports drink plus caffeine in both preliminary tests, whereas consumption of the other beverages did not increase SBP significantly. No significant changes in DBP were noted. The increase in SBP was significantly higher with the consumption of the sports drink plus caffeine than with the consumption of the control sports drink or the sports drink plus taurine, whereas no significant differences were observed compared with the "energy drink". The Panel notes that the acute consumption of an "energy drink" did not increase BP over and above what could be expected from its caffeine content in this study.

Caffeine and *p*-synephrine

p-Synephrine has direct stimulant effects on the sympathetic nervous system, primarily via the α_1- and β-adrenoreceptors. In contrast with ephedrine and amphetamines, which have known psycho-stimulating effects in the CNS, synephrine is more hydrophilic, which leads to a lower transit across the blood–brain barrier and consequently to lower, or no, CNS stimulation. Therefore, any additive or synergistic effects of *p*-synephrine when consumed in combination with caffeine should be expected in the CVS.

The effects of single doses of *p*-synephrine in food supplements containing *C. aurantium* extracts on BP have been investigated in a number of controlled human interventions as safety outcomes, which have been recently reviewed (Stohs et al., 2012). The main characteristics of these studies are summarised in Appendix G. Most studies used *C. aurantium* extracts only, and some used combinations of *C. aurantium*, guarana and/or green tea, among other botanical preparations, in which *p*-synephrine and caffeine were the main active ingredients (Haller et al., 2005a; Sale et al., 2006; Seifert et al., 2011). Studies with caffeinated coffee as the control (dose of caffeine not reported; Hoffman et al., 2006) or an unclear study design (Gougeon et al., 2005) will not be considered.

The studies are generally small and the results difficult to interpret. Significant increases in SBP and DBP were reported for *p*-synephrine from *C. aurantium* extracts when consumed at doses of 54 mg, but not at lower doses (13.5–50 mg). Significant increases in SBP and DBP were also reported for a combination of 5.5 mg *p*-synephrine and 5.7 mg octopamine and caffeine (239.2 mg), and a significant increase in DBP, but not in SPB, was observed with 21 mg *p*-synephrine and 304 mg caffeine. Conversely, no significant changes in BP were found with *p*-synephrine (12–13 mg) and lower doses of caffeine (150–176 mg). However, similar doses of caffeine, on their own, have been consistently reported to increase BP significantly in other studies (Appendix F). The Panel notes that none of the available studies has investigated the effects on BP of single doses of caffeine alone, of *p*-synephrine alone or of their combination. The Panel considers that, from the information available, no conclusions can be drawn on whether or not the simultaneous consumption of *p*-synephrine modulates the pressor effects of caffeine, and if so to what extent or at what doses this occurs.

Conclusions

The Panel notes that caffeine consumption acutely increases BP in virtually all adult population subgroups tested, regardless of baseline BP, regular caffeine consumption/time of caffeine withdrawal, age, sex or hormonal status. The effect was observed at single doses of caffeine ranging from 80 to 300 mg, although most studies tested doses of about 200–300 mg, which induced a mean increase in SBP of about 3–8 mmHg and in DBP of about 4–6 mmHg, with high inter-individual variability. The available data suggest that BP generally increases 30 minutes after caffeine consumption, reaches a peak after 60–90 minutes and returns to baseline after about two to four hours, which is consistent with the pharmacokinetics of caffeine. The effect may be more pronounced in subjects with high BP and after caffeine withdrawal. The dose range tested in the majority of studies is tight and the dose–response relationship has not been systematically assessed. The Panel also notes that repeated doses of caffeine (250 mg) taken four hours apart also induce an increase in BP (of about 3–4 mmHg) which may last up to 9–12 hours, particularly after caffeine withdrawal. The acute effects of lower caffeine doses and/or taken at longer time intervals on BP have not been tested in the studies available. High doses of caffeine (4–6 mg/kg bw, corresponding to about 280–420 mg for a 70-kg adult) ingested 45–60 minutes prior to exercise could add to the BP-raising effect of resistance training and attenuate the decrease in BP observed after resistance training. Lower caffeine doses were not tested. The studies available do not provide sufficient information to conclude on whether consumption of *p*-synephrine, or of substances commonly found in "energy drinks" other than caffeine, modifies the acute effects of caffeine on BP.

4.4.1.2. Myocardial blood flow

Caffeine (like other methylxanthines) is a non-selective competitive A_{2A} receptor antagonist which counteracts the vasodilator effect of adenosine and other A_{2A} receptor agonists in the coronary arteries, where the density of such receptors is particularly high. The cardiac hyperaemic response to physical exercise is primarily mediated by the endogenous production of adenosine by myocytes as a consequence of hypoxia, which induces vasodilation of the coronary arteries.

Physical exercise protocols are used to induce maximal vasodilation of the coronary arteries in nuclear stress myocardial perfusion imaging tests (MPI) for the diagnosis of (and risk stratification of patients with) coronary artery disease (CAD). When adequate exercise workloads cannot be achieved, non-selective (i.e. adenosine, dipyridamole) and selective (i.e. regadenoson) agonists of the A_{2A} receptor are used. The consumption of caffeine (and other methylxanthines) has been contraindicated 24 hours before vasodilator MPI tests (Henzlova et al., 2006) because it attenuates the coronary hyperaemia induced by adenosine and dipyridamole in a dose-dependent manner.

A recent narrative review summarises the mechanisms by which caffeine could reduce myocardial blood flow (MBF) during exercise (Higgins and Babu, 2013).

Few studies have investigated the effects of single doses of caffeine on MBF at rest and under stress (hyperaemic MBF), and on the myocardial blood flow reserve (MFR) calculated as the difference between MBF at rest and under stress, using nuclear imaging techniques. These studies have been conducted in young healthy subjects or in patients with CAD. Physical exercise protocols and regadenoson have been used as stressors to induce maximal coronary vasodilation.

^{15}O-labelled water and positron emission tomography (PET) were used to assess the effects of caffeine on resting and exercise-induced hyperaemic MBF and the resulting MFR in conditions of normoxia and hypoxia (to simulate CAD states of oxygen deprivation) in 18 (seven female) healthy habitual coffee drinkers after 36 hours of caffeine withdrawal (Namdar et al., 2006). A minimum clinically relevant difference in coronary resistance of 20 % between baseline and caffeine consumption was considered for power calculations. In 10 subjects (mean age 27 ± 6 years), MBF was measured at rest and after a five-minute supine bicycle exercise of increasing intensity after the target workload was achieved at normoxia, corresponding to environmental conditions at 4 500 m above sea level. Then subjects consumed a 200-mg caffeine tablet and the same measurements were repeated 50 minutes

later. Caffeine did not affect resting MBF but induced a significant decrease in exercise-induced hyperaemic MBF (2.51 ± 0.58 mL/min per g tissue versus 2.15 ± 0.47 mL/min per g tissue; $p < 0.05$), leading to a decrease in MFR of 22 % (2.53 ± 0.69 to 1.90 ± 0.49 mL/min per g tissue; $p < 0.01$). In eight subjects (mean age 29 ± 4 years), MBF was measured following the same protocol as above but in conditions of hypoxia, simulating an altitude of 4 500 m by inhalation of a mixture of 12.5 % oxygen. Caffeine significantly increased resting MBF (1.71 ± 0.41 mL/min per g tissue versus 2.22 ± 0.49 mL/min per g tissue; $p < 0.001$) and significantly decreased exercise-induced hyperaemic MBF (5.15 ± 0.79 mL/min per g tissue versus 3.98 ± 0.83 mL/min per g tissue; $p < 0.005$), leading to a decrease in MFR of 39 % (3.13 ± 0.60 to 1.87 ± 0.45; $p < 0.005$). The Panel notes that the decrease in MFR in healthy subjects following consumption of 200 mg of caffeine under normal environmental conditions was not considered clinically relevant by the authors for that population group. The Panel also notes that the effect could be considered clinically relevant for healthy subjects under extreme environmental conditions where oxygen partial pressure in the air is low (e.g. high altitude).

The effects of caffeine on resting and exercise-induced hyperaemic MBF and the resulting MFR in conditions of normoxia were also assessed in 15 patients with CAD and 15 age-matched healthy controls by the same research group using an identical protocol and the same dose of caffeine (200 mg) (Namdar et al., 2009). Subjects refrained from caffeine for 24 hours prior to the tests. A minimum clinically relevant difference in hyperaemic MBF of 20 % between baseline and caffeine was considered for power calculations. Resting MBF was not significantly affected by caffeine consumption in either group. Exercise-induced hyperaemic MBF and MFR significantly decreased 50 minutes after caffeine ingestion compared with baseline measurements without caffeine. MFR significantly decreased in healthy subjects by 14 % ($p < 0.05$) and in CAD patients by 18 % ($p < 0.05$) in remote segments and by 25 % ($p < 0.01$) in stenotic segments. The Panel notes that the decrease in MFR in healthy subjects following consumption of 200 mg of caffeine was not considered clinically relevant by the authors for that population group under normal environmental conditions.

The Panel notes that the order in which resting and exercise-induced MBF were measured in relation to caffeine consumption was not randomised in these studies, so that caffeine measurements were always performed following an exercise test whereas non-caffeine measurements were not, and thus the physiological condition of the subjects in relation to the outcome variables tested may not have been comparable.

^{15}O-labelled water and PET were also used to assess the effects of caffeine on resting and regadenoson-induced hyperaemic MBF, and the resulting MFR, in a double-blind, randomised, placebo-controlled cross-over study (Gaemperli et al., 2008). A total of 41 healthy volunteers (15 female) aged ≥ 18 years who were non-smokers and regular coffee drinkers received, in a blinded fashion, either a 200 mg caffeine capsule on day 1 and placebo on day 2 (2–14 days washout) or the inverse after refraining from methylxanthine-containing products for at least 24 hours. MBF was measured each day two hours after capsule ingestion at rest and after intravenous administration of regadenoson. The MBF (mean ± standard error of the mean (SEM)) was not significantly different between caffeine and placebo at rest (1.13 ± 0.04 mL/min per g versus 1.06 ± 0.05 mL/min per g) or under stress (2.98 ± 0.14 mL/min per g versus 3.05 ± 0.14 mL/min per g). There was no difference in MFR between caffeine and placebo (2.75 ± 0.16 mL/min per g versus 2.97 ± 0.16 mL/min per g). The data show with one-sided 95 % confidence that any MFR reduction associated with caffeine intake was < 20 %. However, a similar study using regadenoson stress- single-photon emission computed tomography (SPECT) MPI in patients with CAD showed that doses of caffeine of 200 mg and 400 mg significantly decreased the number of cardiac segments with reversible vascularisation defects, suggesting that caffeine at doses of 200 mg or greater could significantly counteract the vasodilator effect of regadenoson in the coronary arteries in these patients (Tejani et al., 2014).

The Panel notes that caffeine antagonises the vasodilator effect of adenosine and other A_{2A} receptor agonists in the coronary arteries in a dose-dependent manner and this effect leads to a reduction of MBF and MFR during intense physical exercise, primarily in subjects with CAD, but also in healthy subjects to some degree. However, on the basis of the data available, the Panel considers that caffeine

at doses of 200 mg consumed one to two hours prior to exercise does not induce clinically relevant reductions of the coronary flow reserve in healthy adult subjects under normal environmental conditions. The Panel notes that the effect of higher doses of caffeine has not been tested.

4.4.1.3. Cardiovascular disease risk

There is marked diurnal variation in the onset time of cardiovascular events, with a peak in the early morning, which parallels the significant diurnal variation in BP observed in hypertensive subjects, with a decrease during sleep and a surge in the morning (Kario, 2010). It has been hypothesised that the morning surge in BP could trigger cardiovascular events in subjects with underlying atherosclerosis. Similarly, it has been hypothesised that the transient increase in BP induced by acute caffeine intake could increase the risk of cardiovascular events in the first hour after consumption, when BP reaches its peak.

The effect of transient exposure to coffee on the risk of onset of acute cardiovascular events, including myocardial infarction (MI) and ischaemic stroke, has been investigated using case cross-over study designs (Baylin et al., 2006; Mostofsky et al., 2010a, b). Control information for each case was based on the subject's past exposure experience, and a self-matched analysis was conducted (Maclure, 1991). The effect of transient exposure to coffee on the risk of onset of sudden cardiac death (SCD) was also investigated in a case–control study (Selb Semerl and Selb, 2004).

In one study (Baylin et al., 2006), 530 first incident cases of non-fatal MI between 1994 and 1998 were recruited in Costa Rica. Information on habitual coffee intake was retrieved by a FFQ, which showed high correlation with seven 24-hour recalls for caffeine intake (0.83) and took into account serving size and type of coffee as well as nine possible frequencies of consumption. Intake of coffee during the time prior to the MI was collected by asking "when was the last time you had coffee before your heart attack?" The number of cups consumed was also recorded. The median time between hospital discharge and data collection was 11 days, with most people (82 %) completing the interview within two weeks after discharge. Out of the 530 incident cases of non-fatal MI recruited, complete and consistent information was available for 503 cases regarding intake of coffee during the 24 hours before the event and regarding habitual intake of coffee. Most patients reported drinking two to three cups of coffee per day and only 37 patients (7 %) reported no intake of coffee. All coffee consumed was caffeinated coffee; 93 % of respondents reported drinking filtered coffee.

A hazard period of one hour was selected based on the absorption and bioavailability of caffeine in blood. Of the 503 patients for which complete data on coffee intake was available, 80 had at least one cup of coffee in the hour before the onset of MI (69 had one cup, nine had two cups and two had three cups). The relative risk (RR) of MI in the hour after drinking coffee was 1.49 (95 % CI = 1.17–1.89). The RR after coffee intake was not significantly increased when two or three hours were selected as the hazard period, suggesting that the risk dropped to basal conditions between one and two hours after drinking coffee. When stratifying by usual intake of coffee, patients with light/occasional intake of coffee (up to one cup per day; n = 66) had a RR of MI in the hour after taking coffee of 4.14 (95 % CI = 2.03– 8.42), those with moderate consumption of coffee (two to three cups per day; n = 280) had a RR of 1.60 (95 % CI = 1.16–2.21), and heavy drinkers (four or more cups per day; n = 120) had a RR of 1.06 (95 % CI = 0.69–1.63; p = 0.006, test for interaction). This was the only variable that significantly modified the risk; age, sex or physical activity, history of diabetes, hypercholesterolaemia, hypertension, smoking status or having at least three (n = 101) or less than three of these risk factors for disease did not significantly modify the risk.

In the Stroke Onset Study, the relationship between coffee and alcohol consumption and the onset of ischaemic stroke was reported in two publications (Mostofsky et al., 2010 a, b). Between January 2001 and November 2006, 390 subjects (209 men, 181 women) were interviewed a median of three days (range 0–14) after acute ischaemic stroke. Subjects were asked about their caffeinated coffee and alcohol intake the year prior to the stroke, and consumers were asked about the frequency of consumption and the last time that they consumed coffee or alcohol before the event. The same

questions were asked for caffeinated tea and cola. Each subject's coffee consumption in the hour before stroke symptoms occurred was compared with his or her usual frequency of consumption in the prior year. Of the 390 subjects, 304 (78 %) drank coffee in the year prior to stroke, 232 drank coffee within 24 hours of the stroke and 35 drank coffee within one hour of stroke onset; of the 248 subjects who drank alcohol in the previous year, 169 subjects reported alcohol exposure during the week before stroke, 104 subjects drank alcohol within 24 hours of the stroke and 14 drank coffee within one hour of stroke onset. Of the 35 people exposed to coffee in the hour prior to stroke onset, three were also exposed to vigorous physical activity, one experienced feelings of anger, one smoked a cigarette and one drank an alcoholic beverage. Of the 14 people exposed to alcohol in the hour before stroke onset, four were also exposed to vigorous physical activity and one drank coffee.

The RR of stroke in the hour after consuming coffee was 2.0 (95 % CI = 1.4–2.8; $p < 0.001$). There was no apparent increase in risk in the hour following consumption of caffeinated tea (RR = 0.9; 95 % CI = 0.4–2.0; $p = 0.85$) or cola (RR = 1.0; 95 % CI = 0.4–2.4; $p = 0.95$), possibly because of the lower caffeine content of these beverages or their lower consumption. The association between ischaemic stroke in the hour after coffee consumption was apparent only among those consuming at most one cup per day but not for patients who consumed coffee more regularly (p for trend = 0.002). RRs were similar when the sample was restricted to those who were not simultaneously exposed to other potential triggers (such as vigorous physical activity, feelings of anger, smoking of a cigarette, drinking an alcoholic beverage) and the results remained significant after stratifying by time of day. The risk of stroke onset was 2.3-fold higher (95 % CI = 1.4–4.0; $p = 0.002$) within one hour of stroke and RR was 1.6 (95 % CI = 1.0–2.5; $p = 0.05$) in the second hour after alcohol use compared with periods of non-use. The RR returned to baseline thereafter. Results remained similar when analyses were limited to subjects with no prior MI (n = 283) or were conducted excluding the 75 people exposed to any potential stroke trigger in the hour preceding stroke onset.

The case–control study (Selb Semerl and Selb, 2004) was conducted in Slovenia among the 309 out-of-hospital SCD victims who died in the period from January 2000 to March 2001 in that country (253 men and 56 women, median age at death 57.1 and 57.7 years, respectively). Information on exposure to coffee and alcohol, as well as on lifestyle, health and several socio-demographic variables, were obtained by posting one questionnaire to the family members of the deceased and one to the attending physician. Cases were those who died of SCD within one hour after coffee consumption or within two hours after ingesting alcohol; controls were those who died in the hours when they were not exposed to coffee or alcohol. The RR of dying within exposed hours compared with in non-exposed hours was the parameter estimated for each risk factor. On average, each subject had 2.8 risk factors for ischaemic heart disease. The estimated RR of dying within one hour after coffee consumption was 1.73 (95 % CI = 1.13–2.65) and was 3.00 (95 % CI = 1.61–5.68) within two hours after alcohol consumption. Alcohol drinking did not appear to influence the risk in coffee drinkers.

The Panel notes that these studies suggest an increased risk of acute cardiovascular events in the hour following consumption of caffeinated coffee, particularly in subjects with low habitual coffee intake. The Panel also notes that these studies conducted in subjects with an established (fatal or non-fatal) cardiovascular event included few cases, which may limit the value of the sensitivity and subgroup analyses conducted to explore modifying factors (e.g. influence of other risk factors of the event, such as disease conditions or physical activity prior to the event), and do not provide information about the risk of acute cardiovascular events following caffeine consumption in the general population, or on the dose of caffeine which could trigger such events.

4.4.1.4. Conclusions on the cardiovascular system

A single dose of 200 mg of caffeine consumed one to two hours pre-exercise significantly increases BP during resistance training in caffeine-naive subjects as well as in habitual coffee consumers after 24–48 hours of caffeine withdrawal. A single dose of 200 mg of caffeine also decreases MBF if consumed approximately one hour prior to endurance exercise (i.e. when the BP-raising effect of caffeine reaches its peak). Although such changes could increase the risk of acute cardiovascular

events in subjects with an increased risk of CVD (e.g. with underlying hypertension and/or advanced atherosclerosis), the Panel considers the effect to be of low clinical relevance for healthy individuals in the general population under normal environmental conditions. Although not formally tested, the Panel considers that changes in BP and MBF 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 of caffeine would also be of low clinical relevance for healthy individuals in the general population under normal environmental conditions. The studies available do not provide sufficient information to conclude on whether co-consumption of *p*-synephrine or of substances commonly found in "energy drinks" other than caffeine may affect the risk associated with caffeine consumption alone.

4.4.2. Hydration status and body temperature

Caffeine

It is well established that caffeine has a diuretic effect (SCF, 1983; EFSA, 2009). However, any diuretic effects resulting from chronic caffeine consumption are unlikely to have adverse health consequences for healthy individuals in the general population. In addition, 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 body mass, urine osmolality, urine specific gravity, urine colour, 24-hour urine volume, 24-hour Na^+ and K^+ excretion, 24-hour creatinine, blood urea nitrogen, serum Na^+ and K^+, serum osmolality, haematocrit or total plasma protein compared with placebo (Armstrong et al., 2005). Similar results were obtained in two studies with a similar design conduced in healthy males, in which 5 mg/kg bw of caffeine were consumed daily for four consecutive days by low habitual caffeine consumers (< 100 mg/day) (Silva et al., 2013) and 4 mg/kg bw per day of caffeine from coffee were consumed for three consecutive days by habitual coffee consumers (three to six cups of coffee per day) (Killer et al., 2014).

It has been suggested, however, that single doses of caffeine consumed prior to exercise, and particularly at high temperatures, could increase body temperature and sweating as well as diuresis, leading to water–electrolyte imbalances which may pose a risk to health. Single doses of caffeine of about 100–600 mg consumed prior to exercise, however, did not lead to a significant increase in urinary volume or a significantly different water retention during dehydration, and did not induce adverse water–electrolyte imbalances compared with water or placebo, particularly in habitual caffeine consumers (Armstrong, 2002).

A number of studies have investigated the effects of single doses of caffeine of 3–9 mg/kg bw on hydration status and/or body temperature before and during endurance exercise under different conditions of temperature and humidity.

In a double-blind randomised cross-over study (Kim et al., 2011), 13 male students who were non-habitual caffeine consumers, who followed daily aerobic training, completed two experimental trials (i.e. running for 30 minutes at 60 % of VO_{2max}) in thermo-neutral conditions (24 °C, 40 % relative humidity) one week apart, in which they received caffeine (3 mg/kg bw and 200 mL of water) or water only (200 mL) 40 minutes before the test. Core (tympanic) and skin temperature were measured after caffeine consumption at rest, pre-exercise (40 minutes after caffeine/placebo consumption) and post exercise (after 30 minutes of running at 60 % VO_{2max}). Mean body temperature (calculated from tympanic and skin temperatures) was significantly higher in pre- (by 0.08 °C) and post exercise (by 0.14 °C) following caffeine consumption than following water consumption, whereas tympanic body temperature increased significantly pre-exercise only (by 0.12 °C). After caffeine consumption, sweating rate was significantly higher and the onset of sweating was significantly delayed during exercise.

In a double-blind, randomised cross-over study (Millard-Stafford et al., 2007) which used higher doses of caffeine, 16 cyclists completed three trials consisting of cycling for 120 minutes at 60–75 % VO_{2max}

followed by 15 minutes of maximal effort cycling at 28.5 °C and 60 % relative humidity. During each trial, subjects consumed either placebo (artificially sweetened water), a carbohydrate–electrolyte drink (CE) containing 6 % carbohydrates or a carbohydrate–electrolyte drink containing 7 % carbohydrates and 46 mg/L carnitine, 1.92 mg/L taurine and 195 mg/L caffeine (CAF + CE). Total caffeine intake during the trial was 5.3 mg/kg bw. No significant differences among trials were found regarding measures of hydration status, relative dehydration, fluid retention, urine output or sweat rate. Exercise intensity during the last 15 minutes was significantly higher in the CAF + CE trials than in the CE or placebo trials, which is consistent with a higher increase in heart rate. Rectal temperature in the CAF + CE trials was significantly higher than in the placebo trials (by 0.19 to 0.29 °C) after 60 minutes, but was significantly higher than in the CE trials only in the last 15 minutes, which is consistent with a higher relative exercise intensity for the CAF + CE trial. The Panel notes that this study does not show a clinically significant effect of caffeine on core (rectal) temperature or hydration status at doses of 5.3 mg/kg bw consumed during physical exercise and hot and humid conditions.

In another double-blind, randomised cross-over study (Del Coso et al., 2008), seven endurance-trained cyclists pedalled for 120 minutes at 63 % of VO_{2max} in a hot-dry environment (36 °C, 29 % humidity) under six different testing conditions: no fluid, water (WAT) to replace 97 % fluid losses, the same volume of a 6 % carbohydrate–electrolyte solution (CES) or each of these treatments along with caffeine at 6 mg/kg bw. Caffeine or placebo capsules were ingested about 50 minutes prior to the trial. Core (rectal) temperature and serum osmolality as an indicator of fluid balance were measured throughout the six trials. Rehydration with WAT or CES, with or without caffeine, prevented the significant losses of body fluid, the increase in serum osmolality and the significant rise in core temperature observed with no fluid replacement, with or without caffeine. No significant differences in fluid losses, serum osmolality or core temperature were observed between the WAT and CES groups with caffeine and without caffeine. This is consistent with the results from a more recent study (Ping et al., 2010) conducted in nine male recreational runners (normally non-caffeine users) who consumed caffeine (5 mg/kg bw) one hour prior to a running exercise (at 70 % of VO_{2max}) in a hot environment (31 °C, 70 % relative humidity) but received regular hydration (3 mL of cool water/kg bw every 20 minutes) during the trial. No significant differences in core temperature were observed between the caffeine and placebo conditions.

The same dose of caffeine (6 mg/kg bw) was tested by Roelands et al. (2011) in a double-blind randomised cross-over study, in which eight healthy trained male cyclists who were habitual "mild" caffeine consumers completed two experimental trials (at 30 °C). Subjects ingested either placebo or caffeine one hour prior to exercise, which consisted of cycling for 60 minutes at 55 % of W_{max} immediately before a time trial to measure performance. Compared with placebo, caffeine significantly increased core (rectal) temperature during exercise by up to about 0.5 °C, whereas it had no significant effect on skin temperature, heart rate, loss of body mass or sweat rate.

Compared with placebo, single doses of 9 mg/kg bw caffeine consumed after four days of caffeine abstinence also increased core (rectal) body temperature (by 0.20–0.30 °C), but not skin temperature, in 10 healthy men performing 30 minutes of cycle ergometry at 50 % VO_{2peak} followed by a 15-minute performance time trial at 40 °C and 20–30 % relative humidity (Cheuvront et al., 2009). "Caffeine sensitive" and heavy caffeine drinkers (> 400 mg per day) were excluded from this study. Conversely, in another study using the same caffeine dose, mean body temperature was significantly higher (by 0.27 °C) one hour after caffeine consumption than with placebo only at the beginning of the exercise (cycling for 30 minutes at 50 % of VO_{2peak} in a 40 °C and 25 % relative humidity environment), whereas no differences between caffeine and placebo were observed with respect to core, skin or mean temperature during exercise (Ely et al., 2011).

Caffeine in combination with taurine

The acute diuretic effects of caffeine do not appear to be modified by the concomitant ingestion of taurine or by any other component of "energy drinks" (EFSA, 2009).

In a human intervention study (Riesenhuber et al., 2006), 12 participants received, in a random order, each of four different test drinks at weekly intervals in a blinded fashion (750 mL of each fluid) containing: (i) 80 mg caffeine and 1 g taurine per 250 mL, (ii) 80 mg caffeine per 250 mL, (iii) 1 g taurine per 250 mL and (iv) neither caffeine nor taurine. Caffeine significantly increased urinary output and natriuresis, whereas taurine had no effect on either of these outcomes and did not appear to modify the diuretic effects of caffeine when administered simultaneously.

4.4.2.1. Conclusions on hydration status and body temperature

The Panel notes that caffeine at doses of 3 mg/kg bw (equivalent to 210 mg for a 70-kg adult) ingested about one hour prior to endurance exercise appear to induce only a modest increase in body temperature compared with placebo. The Panel also notes that higher doses of caffeine (5–6 mg/kg bw) ingested one hour before and during prolonged endurance exercise in a hot environment do not affect body temperature or hydration status significantly beyond what could be expected from the testing conditions.

4.4.3. Central nervous system

4.4.3.1. Sleep, anxiety and behavioural changes

Adults

In adults, single doses of caffeine of about 100 mg (1.4 mg/kg bw per day in a 70-kg adult) have been shown to increase sleep latency and reduce sleep duration when consumed close to bedtime (Landolt et al., 1995), whereas doses < 100 mg do not appear to have such an effect on sleep (Dorfman and Jarvik, 1970).

Higher doses (≥ 400–500 mg) consumed either on a single occasion or within short periods of time have been reported to increase anxiety upon oral consumption, mostly in patients with psychiatric anxiety disorders, but also in healthy adults, particularly if they are non-habitual caffeine consumers (FSANZ, 2000; Nawrot et al., 2003; Childs and de Wit, 2006; NNT, 2008; SHC, 2012). The study by Nickell and Uhde (1994) has been referred to by other bodies (FSANZ, 2000; SHC, 2012) to conclude that lower doses of caffeine (3 mg/kg bw) could increase anxiety in adult subjects. The Panel notes that Nickell and Uhde (1994) investigated the effects of caffeine (3, 5 and 7 mg/kg bw) versus placebo given intravenously in 10 subjects, who experienced olfactory hallucinations immediately following intravenous caffeine infusion. The Panel considers that this route of administration is not appropriate to investigate the effects of oral caffeine consumption on anxiety.

Polymorphisms of the adenosine receptor gene $ADORA_{2A}$ have been suggested as the cause of some of the inter-individual variability observed in the anxiogenic response to caffeine (Childs et al., 2008; Rogers et al., 2010) and in the effects of caffeine on sleep (Retey et al., 2007; Byrne et al., 2012).

Children and adolescents

A number of human intervention studies (Elkins et al., 1981; Rapoport et al., 1981a, b, 1984; Baer, 1987; Leviton, 1992; Bernstein et al., 1994; Hale et al., 1995; Davis and Osorio, 1998) and a systematic review and meta-analysis of human studies (Stein et al., 1996) which investigated the effects of caffeine on behaviour in children and adolescents have already been considered by other assessment bodies. No new studies have become available since then in this population subgroup.

Stein et al. (1996) searched for human studies reporting cognitive, behavioural, sleep or psychological effects of caffeine that included a caffeine comparison (either placebo, alternative drug treatment, baseline or matched control group). Nine studies were identified, of which five were in children with attention deficit hyperactivity disorders (ADHD) and four were in healthy children. The Panel considers that results obtained in children with ADHD cannot be extrapolated to children in the general population and will not be further considered in this opinion (e.g. Leviton, 1992).

Of the studies mentioned above, only two (three publications) have assesed the effects of single doses of caffeine in healthy children (Elkins et al., 1981; Rapoport et al., 1981b; Bernstein et al., 1994). Both studies investigated two caffeine doses using randomised, placebo-controlled cross-over designs.

The behavioural and cognitive effects of single doses of caffeine (3 and 10 mg/kg bw) were investigated in 19 prepubertal boys (mean age 10.6 ± 2.5 years) and 20 young men (mean age 21.7 ± 3.4 years) (Elkins et al., 1981; Rapoport et al., 1981b). Children were not recruited on the basis of their habitual caffeine consumption, which was on average 125 ± 160 mg per day. Subjects were asked to complete the anxiety scale "What I think I feel" and an 11-item caffeine side-effect questionnaire (headache, stomach ache, nausea, chest pain, heart pounding, feeling flush, feeling faint, feeling nervous, feeling jittery, increased diuresis, difficulty sleeping) one hour after caffeine administration. Items were rated on a three-point scale. Nine items of behaviour (fidgety, distractible, tense, hypoactive, pressured speech, physical complaints, euphoria-elation, nervous habits, and mannerisms) from a Psychiatric Rating Scale were rated (on a seven-point scale) by a research assistant. No significant differences in self-reported side effects were observed in children for any caffeine dose compared with placebo, with the exception of feeling "nervous/jittery". Scores for this side effect were significantly higher for the 3 mg/kg bw dose than for placebo, and for the 10 mg/kg bw dose than for the 3 mg/kg bw dose. No significant differences in self-rated anxiety or investigator-rated items of behaviour were found between placebo and caffeine at any dose.

The study by Berstein et al. (1994) investigated the effects of two single doses of caffeine (2.5 and 5 mg/kg bw) on self-reported anxiety in 21 children (mean age 10.6 ± 1.3 years) after 12–15 hours of abstinence from caffeine. Self-reported anxiety was evaluated using the Visual Analogue Scale for Anxiety Revised (VAA-R), which assessed how anxious the child was at the time of testing (anxiety state) and how anxious the child was most of the time (anxiety trait); the State-Trait Anxiety Inventory for Children (STAIC), which assessed anxiety trait and anxiety state; and the Revised Children's Manifest Anxiety Scale (RCMAS). Caffeine intake was not significantly associated with any of these measures of self-reported anxiety, whereas a significant linear association was reported between caffeine concentrations in saliva and the anxiety state item in the VAA-R scale only. The Panel notes that caffeine intakes were not significantly associated with anxiety, and that caffeine concentrations in saliva were generally not associated with self-reported measures of anxiety in this study. The Panel also notes that the above-mentioned tools to assess self-reported anxiety have been developed to discriminate between children with high and low anxiety levels, rather than to assess changes in anxiety.

The Panel notes that these studies (Elkins et al., 1981; Rapoport et al., 1981b; Bernstein et al., 1994) do not show an effect of single doses of caffeine ranging from 2.5 to 10 mg/kg bw on most self-reported measures of anxiety in children. However, the Panel also notes the scarcity of studies available and the low number of children enrolled, as well as the heterogeneity of the studies regarding the testing conditions (e.g. with respect to the tools used to assess anxiety and behavioural changes, and to the caffeine status before testing), which hampers the comparability of the results. The Panel considers that the results of these studies cannot be used on their own to derive single doses of caffeine of no concern for children or adolescents.

4.4.3.2. Perceived exertion during exercise

In 2011, health claims on caffeine and endurance capacity, endurance performance and reduction in the rated perceived exertion/effort during exercise were evaluated by the NDA Panel with a positive outcome. The conditions of use for these claims were that caffeine should be consumed one hour prior to exercise at doses of 3 mg/kg bw for claims on endurance capacity and performance and of 4 mg/kg bw for claims on reduction in the rated perceived exertion/effort during exercise (EFSA NDA Panel, 2011a). The target population was adults performing endurance exercise.

The scientific substantiation of the claim on the reduction in the rated perceived exertion/effort during exercise was based on a meta-analysis of 22 laboratory-based, double-blind, fully randomised (and

mostly cross-over), placebo-controlled intervention studies which examined the effects of caffeine ingestion on ratings of perceived exertion (RPE) during exercise (Doherty and Smith, 2005). Compared with placebo, caffeine significantly reduced RPE during exercise (in 20 out of the 22 studies) by 5.6 % (95 % CI = –6.7 to –4.5 %). RPE could account for 29 % of the variance in the improved exercise performance (based on 16 studies where changes in exercise performance were tested). This analysis comprised studies from 1975 to 2004, representing over 200 subjects (74 % men) who were 20 to 35 years of age, ranging from physically active individuals to extremely well-trained elite athletes, and included both habitual caffeine users and non-users (half of the studies did not provide information on coffee use). The protocols varied, including work intensities from 50 % to 125 % (mean = 80 %) of VO_{2max}. The caffeine doses ranged from 4 to 10 mg/kg bw (median 6 mg/kg bw) and were typically given one hour before the start of the exercise test after a period of caffeine withdrawal. The caffeine abstinence of the subjects varied from 12 to 240 hours (median = 24 hours). As only the effect-size difference between caffeine and placebo was calculated in the meta-analysis, it was unclear whether the between-group difference observed was a result of an increased perception of fatigue due to caffeine deprivation, to a decreased perception of fatigue due to caffeine consumption or both. The effect of a single dose of caffeine on fatigue perception in either caffeine abstainers or caffeine consumers who are not caffeine deprived was not investigated.

These conclusions were supported by the results of a double-blind, cross-over, placebo-controlled intervention study published after the meta-analysis by Doherty and Smith (2005), where nine competitive male rugby players ingested either caffeine (6 mg/kg bw) or placebo (dextrose) 70 minutes before performing a rugby test consisting of seven circuits in each of two 40-minute halves with a 10-minute half-time rest (Stuart et al., 2005). The development of fatigue during the test was significantly reduced after caffeine consumption compared with placebo.

In the health claim opinion (EFSA NDA Panel, 2011b), a reduction in the rated perceived exertion/effort during exercise was considered by the Panel as a plausible mechanism by which single doses of caffeine administered after at least 12–24 hours of caffeine deprivation could increase endurance capacity and performance. In this context, the Panel considered this to be a beneficial physiological effect for adults performing endurance exercise willing to obtain such an effect.

In the context of this opinion, however, a reduction in the perceived exertion/effort during exercise can be considered a potential adverse health effect for the general population (not limited to adults performing endurance exercise willing to obtain such an effect) under the assumption that the perception of fatigue is a physiological mechanism leading to the spontaneous ending of physical activities that, because of their high intensity, extended duration or both, may compromise the cardiovascular and/or musculoskeletal systems. The Panel notes that single doses of caffeine which have been observed to reduce the rated perceived exertion/effort during exercise ($\geq$ 4 mg/kg bw) are equivalent to 280 mg of caffeine for a 70-kg adult.

4.4.3.3. Subjective perception of alcohol intoxication

It has been suggested that consumption of caffeinated beverages (including “energy drinks”) together with alcohol may “mask” or alter the subjective perception of alcohol intoxication, which could increase the likelihood of engaging in potentially dangerous activities while intoxicated (i.e. risk-taking behaviour).

In addition to the review of the literature (Verster et al., 2012) considered by the UK COT (COT, 2012), a recent systematic review and meta-analysis of RCTs, which includes all the studies identified by Verster et al. (2012), has addressed this question (Benson et al., 2014). Studies were included if they had assessed the effects of alcohol with and without any type of caffeinated beverage (including, but not limited to, “energy drinks”) on a direct measure of subjective intoxication and provided enough data to be included in a meta-analysis. Of the 16 publications identified by the literature search, nine met these criteria (Fillmore and Vogel-Sprott, 1999; Fillmore et al., 2002; Marczinski and Fillmore, 2006; Howland et al., 2011; Marczinski et al., 2011, 2012, 2013; Heinz et al., 2013; Peacock

et al., 2013). Alcohol doses were typically 0.65 g/kg bw (in six studies) and ranged from 0.29 to 1.068 g/kg bw, typically producing peak blood alcohol concentrations (BAC) between 0.068 and 0.088 % (in seven studies) and ranging from 0.032 to 0.12 %. Caffeine doses ranged from 0.6 to 5.5 mg/kg bw. Four studies used "energy drinks" as a source of caffeine. Three had a cross-over design and six had a parallel design. Sample size (per arm) varied between 7 and 74 subjects. Subjective intoxication was measured using the Beverage Rating Scale (BRS) in six studies, a self-estimate BAC in one study, a Subjective Intoxication Scale (SIS) in one study and a "feel any effects" visual analogue scale (VAS) in one study. A meta-analysis of all studies combined showed no masking effect of caffeine when combined with alcohol relative to alcohol alone on direct measures of subjective intoxication. The only individual study reporting a significant masking effect of caffeine was Heinz et al. (2013), which had the biggest sample size (BAC 0.088 %, caffeine 5.0 mg/kg bw for females and 5.5 mg/kg bw for males). Marczinski and Fillmore (2006) reported no masking effect of caffeine at the highest caffeine dose tested (4 mg/kg bw), whereas Howland et al. (2011), who tested the highest dose of alcohol (target BAC 0.12 %) and caffeine (5.0 mg/kg bw) in heavy alcohol drinkers and used the second biggest sample (n = 35 alcohol plus caffeine, n = 28 caffeine) showed no significant masking effect of caffeine.

Seven studies addressing the research question were excluded from the meta-analysis because they did not address subjective intoxication directly (Liguori and Robinson, 2001; Ferreira et al., 2006; Alford et al., 2012) or the publication did not contain sufficient detail to calculate the effect size for pooling in a meta-analysis (Rush et al., 1989; Azcona et al., 1995; Marczinski and Fillmore, 2003; Attwood et al., 2012). Doses of alcohol had a target BAC between 0.03 and 0.10 % and caffeine doses were between 1.14 and 7 mg/kg bw (80–500 mg). Two studies used "energy drinks" as sources of caffeine. No significant differences between the alcohol and the alcohol plus caffeine groups were reported in these studies in relation to direct or indirect measures of subjective intoxication.

Another systematic review (Peacock et al., 2013) restricted the question to the consumption of alcohol together with "energy drinks" (rather than with caffeine from any source) and addressed a wide variety of (physiological and psychological) outcomes, mostly using cross-sectional studies. All of the RCTs on the combination of "energy drinks" with caffeine reviewed in this publication were already considered in the systematic review by Benson et al. (2014).

The Panel considers that caffeine consumed at doses up to 3 mg/kg bw (corresponding to 210 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. Higher doses of alcohol have not been systematically investigated.

4.4.3.4. Conclusions on the central nervous system

Single doses of caffeine up to about 200 mg (3 mg/kg/bw for a 70-kg adult) do not appear to induce anxiety in unselected adult subjects from the general population, reduce the perceived exertion/effort during exercise when consumed one hour prior to exercise after 12–24 hours of caffeine withdrawal or alter the subjective perception of alcohol intoxication when alcohol is consumed at doses of about 0.65 g/kg bw. In children, similar single doses of caffeine on a weight basis (3 mg/kg bw) do not appear to induce anxiety or behavioural changes, although inter-individual variability in relation to habitual caffeine intakes has not been studied. The Panel notes that 100 mg of caffeine (about 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.

4.5. Adverse effects of longer-term and habitual caffeine consumption

Adverse effects of daily caffeine consumption over longer periods of time (> 7 days) on the CNS and the CVS have been reported in human intervention studies. These concern sustained changes in BP and children's behaviour.

Data on the relationship between habitual consumption of caffeine in foods and beverages and the risk of chronic diseases (e.g. CVD, cancer, type 2 diabetes mellitus, Parkinson disease, Alzheimer disease, bone fractures), adverse pregnancy outcomes, male fertility and birth defects (neural tube defects, oral clefts) mostly come from human observational studies. With the exception of CVD risk and adverse pregnancy outcomes, the scientific publications identified almost exclusively reported no relationship or an inverse relationship between caffeine intake and adverse health effects in relation to these outcomes. Therefore, the Panel will focus on CVD risk and adverse pregnancy outcomes (e.g. pre-term delivery, FGR or SGA, miscarriage or spontaneous abortion, stillbirth) to assess the safety of habitual caffeine consumption in adults.

4.5.1. Central nervous system

In adults, tolerance to the anxiogenic effect of caffeine develops with frequent consumption, even in genetically susceptible individuals (Rogers et al., 2010).

In children, four studies have investigated the effects of caffeine consumed for longer periods of time (up to two weeks) using randomised, placebo-controlled, parallel or cross-over designs (Rapoport et al., 1981a, 1984; Baer, 1987; Hale et al., 1995).

In the study by Hale et al. (1995), 18 adolescents (11–15 years of age) underwent six independent randomised, double-blind, placebo-controlled trials. In each trial, participants were given a non-caffeinated and a caffeinated soft drink (providing 33 mg of caffeine) in a two-day cross-over, followed by two days in which subjects were given concurrent access to the two drinks, which were consumed *ad libitum*. No behavioural symptoms were reported by any participant. Average caffeine intake among the four subjects who tended to select caffeinated soft drinks repeatedly was 167 mg per day (about 3.3 mg/kg bw per day).

In the placebo-controlled, cross-over study by Baer (1987), six five-year-old children were administered daily a caffeine-free or a caffeinated soft drink (providing 1.6–2.5 mg/kg bw of caffeine per day) for two weeks, at the end of which the drink conditions were reversed. No consistent effects on behavioural outcomes such as off-task behaviour or motor activity were noted. Anxiety was not assessed.

Two studies by the same authors have investigated daily caffeine consumption (10 mg/kg bw per day) for two weeks in relation to self-reported anxiety, parent/teacher ratings of children's behaviour and side effects in prepubertal children (mean age about 10 years, age range 6–13 years). These studies were either planned (Rapoport et al., 1984) or analysed considering habitual caffeine intakes and used a randomised, double-blind, placebo-controlled cross-over design. In the first study (Rapoport et al., 1981a), data from 19 children were analysed depending on whether they were "low" (< 50 mg per day) or "high" (> 300 mg per day) caffeine consumers. In the second study, 19 "high" habitual caffeine consumers (> 500 mg per day) and 19 "low" habitual caffeine consumers (< 50 mg per day) matched by age, gender and teacher were recruited and separately randomised. Collectively, these two studies provide evidence that "high" habitual caffeine consumers (and their parents) tend to report more side effects during the caffeine withdrawal period, whereas the reverse is observed in "low" caffeine consumers, suggesting the development of tolerance and withdrawal symptoms in "high" habitual consumers.

The Panel 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. The Panel 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.

4.5.2. Cardiovascular system

4.5.2.1. Methodological considerations

There is a wealth of human prospective cohort studies which have investigated the relationship between caffeine-containing foods and beverages (e.g. coffee, tea, soft drinks, chocolate) and the risk of a number of CVD-related outcomes, including incident hypertension (fatal, non-fatal, total), coronary heart disease (CHD) (total, non-fatal), MI (total, fatal and non-fatal), stroke (all types, haemorrhagic, ischaemic), arrhythmias (mostly atrial fibrillation) and total CVD risk. There is also a wealth of meta-analyses published in relation to these outcomes which will be used to summarise the evidence available.

Case–control and cross-sectional studies will not be considered specifically in this section. Previous meta-analyses have consistently reported positive associations between habitual consumption of caffeine-containing foods and beverages (mostly coffee) and the risk of CVD from case–control studies, but not from prospective cohort studies (Greenland, 1993; Kawachi et al., 1994; Sofi et al., 2007). Possible explanations for this discrepancy include recall bias for exposure in cases (over-reporting), low caffeine consumption in controls recruited from inpatients with chronic conditions, differences in outcome measures (case–control studies usually report on non-fatal events only) and lack or inappropriate control for confounding variables in case–control studies (Wilhelmsen et al., 1977; Kawachi et al., 1994; Sofi et al., 2007).

The prospective cohort studies available are heterogeneous with respect to the exposure used as an independent variable. Coffee (unspecified), caffeinated coffee, decaffeinated coffee, tea (unspecified), green tea, oolong tea, black tea (sugar-containing and sugar-free), caffeinated soft drinks and chocolate, as well as caffeine from all sources, have been investigated in relation to CVD-related outcomes in one or more of these studies. In some, tea has been assessed but used as a confounding variable only to adjust models on coffee.

Appendix I provides an overview of the prospective cohort studies considered in the most recently published systematic reviews and meta-analyses which have investigated the association between habitual consumption of coffee or caffeine from all sources and CVD-related outcomes. Meta-analyses of prospective cohort studies investigating only tea in relation to CVD-related outcomes do not appear in the table, but will be discussed in the sections below where appropriate. Individual prospective cohort studies investigating only tea in relation to CVD-related outcomes will not be considered specifically because tea contains less caffeine than coffee, coffee is the major source of caffeine for adults in the majority of European countries and caffeine intakes in countries where tea is the major source of caffeine are generally lower than caffeine intakes in "coffee-drinking" countries (see Section 3 on dietary intake).

Although some of the meta-analyses in Appendix I occasionally include one or more prospective cohort studies where the study population has been selected on the basis of a disease condition or a risk factor for disease (hypertension, previous MI, type 2 diabetes mellitus), the vast majority of the studies included were conducted in unselected samples from the general population. Individual studies (Martin et al., 1988; Hakim et al., 1998; Bidel et al., 2006; Palatini, 2007; Silletta et al., 2007; Mukamal et al., 2009; Zhang et al., 2009a, b) and meta-analyses (Mesas et al., 2011) focusing on particular population subgroups with a disease condition or a risk factor for disease will not be considered specifically.

4.5.2.2. Blood pressure

Caffeine

Prospective cohort studies

A systematic review (Zhang et al., 2011) identified four prospective cohort studies which investigated the association between coffee drinking and long-term changes in BP measured in fasting conditions. Two were conducted in the Netherlands (Uiterwaal et al., 2007; Driessen et al., 2009), one was conducted in the US (Klag et al., 2002) and one was conducted in Australia (Jenner et al., 1988). Sample size varied from 340 to 5 189 subjects and follow-up varied between 6 and 33 years. Data from these studies could not be pooled in a meta-analysis because different BP variables were used as outcomes (e.g. residuals of BP, mean arterial BP, SBP and DBP) and the results were mixed: although the Australian study found a negative association between coffee drinking and long-term changes in BP, the Dutch studies found no association and the US study found a positive association. An additional prospective cohort study published thereafter (Giggey et al., 2011) investigated the relationship between habitual caffeinated coffee consumption and long-term changes in resting BP and pulse pressure in 2 442 participants (865 women and 1 577 men) from the Baltimore Longitudinal Study of Aging. In men, significant quadratic (non-linear) interactions were observed between coffee consumption, age and time since baseline on SBP and pulse pressure, but these were not observed in women. The models predicted an increase in SBP and pulse pressure with age which, beyond 70 years, would be potentiated by the intake of six or more cups of coffee per day. The Panel notes that the results from prospective cohort studies on the association between habitual caffeine consumption and long-term changes in BP are mixed.

Randomised controlled trials lasting ≥ 7 days

Three meta-analyses of RCTs (Jee et al., 1999; Noordzij et al., 2005; Steffen et al., 2012) have investigated the effects of caffeine or coffee consumption for ≥ 7 days (after habituation to caffeine takes place) on fasting BP in unselected populations. The characteristics of the studies included in each meta-analysis are summarised in Appendix H.

Noordzij et al. (2005) selected RCTs in humans that had investigated the effects of caffeinated coffee or caffeine consumption for ≥ 7 days on fasting BP and HR. Studies using co-interventions (e.g. caffeine plus adrenaline) which did not allow conclusions on caffeine or coffee were excluded. The meta-analysis included 11 trials on coffee (18 strata) and five trials on caffeine (seven strata) published between 1984 and 2000, which varied in sample size from 10 to 123 participants (median: 45) for a total of 1 010 subjects, of which ≥ 50 % were men in 17 strata. All trials were in adults (aged 23 to 77 years) and lasted 7 to 84 days (median: 42 days). Six strata (24 %) included study populations with high–normal BP or hypertension, with two strata having subjects on antihypertensive treatment. The coffee trials were conducted using instant coffee (n = 8), filtered coffee (n = 7), boiled coffee (n = 2) or coffee that was boiled and subsequently filtered (n = 1). Daily coffee dose in active treatment groups varied from 450 to 1 235 mL, which corresponds to a caffeine dose of 225 to 798 mg per day (one cup of coffee was assumed to contain 150 mL and 90 mg of caffeine when not reported in the original publication). In caffeine trials, caffeine was administered in tablets at doses ranging from 295 to 750 mg per day. In coffee and caffeine trials combined, the median caffeine dose was 410 mg per day. The control groups of coffee trials received either no coffee (11 strata) or decaffeinated coffee (seven strata). In the caffeine trials, all control groups received placebo tablets.

Average pre-treatment BP ranged from 109 to 143 mmHg for SBP (median 122 mmHg) and from 65 to 94 mmHg for DBP (median 74 mmHg). Mean pre-treatment HR ranged from 61 to 78 bpm (median 71 bpm). Net BP changes in coffee and caffeine trials ranged from –1.6 to 12.0 mmHg for SBP and from –2.4 to 5.0 mmHg for DBP. Combining all caffeine and coffee studies, SBP significantly increased by 2.04 mmHg (95 % CI = 1.10–2.99 mmHg) and DBP significantly increased by 0.73 mmHg (95 % CI = 0.14–1.31 mmHg). After excluding nine coffee trials with an open design, changes in SBP were 2.81 mmHg (95 % CI = 1.08–4.53 mmHg) and in DBP were 1.17 mmHg (95 %

CI = 0.54–1.81 mmHg). HR did not change significantly. In stratified analyses adjusted for type of intervention (coffee or caffeine), age (< 40 or ≥ 40 years), sex (proportion of males < 50 % or ≥ 50 %), baseline BP (< 130/85 or ≥ 130/8 mmHg), baseline caffeine intake (< 400 or ≥ 400 mg per day) and caffeine dose (median intake < 410 or ≥ 410 mg per day in all the coffee and caffeine studies combined), except when used as stratification factor, the type of intervention, sex and caffeine dose significantly affected changes in BP, whereas age, baseline BP, baseline caffeine intake and study duration (< 6 weeks or ≥ 6 weeks) did not. Changes (mean and 95 % CI) in SBP and DBP for coffee (18 strata) were 1.22 mmHg (0.52–1.92 mmHg) and 0.49 mmHg (–0.06 to 1.04 mmHg), and for caffeine (seven strata) were 4.16 mmHg (2.13–6.20 mmHg) and 2.41 mmHg (0.98–3.84 mmHg). Caffeine from any source at doses ≥ 410 mg per day significantly increased SBP (mean 2.98, 95 % CI = 2.15–3.80) and DBP (mean 1.96, 95 % CI = 1.19–2.73), whereas caffeine doses < 410 mg per day did not (change in SBP = mean 0.72, 95 % CI = –0.35 to 1.78; change in DBP = mean –0.52, 95 % CI = –1.62 to 0.57). Caffeine significantly increased SBP and DBP in studies with a majority of women (n = 8), but not in those with a majority of men (n = 17). The Panel notes that this meta-analysis shows a sustained BP-raising effect of continuous (≥ 7 days) caffeine consumption at doses of about 400 mg per day, but not at lower doses.

The meta-analysis by Steffen et al. (2012) aimed to assess the effects of daily coffee consumption (> 7 days) on fasting BP. The effects of caffeine *per se*, and the effects of caffeine in coffee, were not assessed. The search targeted RCTs which included an intervention group that consumed coffee and a control group that consumed either no coffee or less coffee, which lasted > 7 days to eliminate any acute pressor effect of coffee. Studies (or intervention arms within a study) which used decaffeinated coffee as the control were excluded. Of the 10 RCTs included (Appendix H), 6 had been considered in the meta-analysis by Noordzij et al. (2005). Five studies had a parallel design and five had a cross-over design, and the duration of the intervention was between 2 and 11 weeks. Seven trials included two strata and six used the same control group to compare the two interventions. Of these, only one intervention group with coffee was selected for inclusion in the meta-analysis, giving preference to the most common types of coffee consumed (caffeinated, filtered), so that only the effects of caffeinated coffee compared with no coffee were explored in the meta-analysis. Most of the study populations were healthy, normotensive individuals. Coffee consumption varied between trials and ranged from three to over six cups daily. Only four trials used a standard amount of coffee in the intervention, whereas the other trials defined a minimum amount of consumption, but no maximum. The pooled weighted difference in mean change of SBP was –0.55 mmHg (95 % CI = –2.46 to 1.36 mmHg) and of DBP was –0.45 mmHg (95 % CI = –1.52 to 0.61 mmHg). Heterogeneity in the pooled SBP (I_2 = 72 %) and DBP (I_2 = 41 %) analysis was explored by considering type of coffee, sex and pre-study BP in subgroup analyses, but no significant interactions were found. The Panel notes that this meta-analysis does not show a significant increase in fasting BP following consumption of caffeinated coffee for > 7 days at doses of about three to six cups per day.

A previous meta-analysis of RCTs on the effects of caffeinated coffee on fasting BP (Jee et al., 1999) included nine studies with durations of the intervention ranging between 2 and 11 weeks. Eight had been considered by Noordzij et al. (2005) and four by Steffen et al. (2012). The overall pooled estimates of treatment effect associated with coffee drinking were 2.4 mmHg (95 % CI = 1.0–3.7 mmHg) for SBP and 1.2 mmHg for DBP (95 % CI = 0.4–2.1 mmHg). Duration of run-in and coffee dose significantly modified the effect of coffee on BP. Studies with shorter run-ins and the highest doses of coffee showed the biggest effect on BP. A significant effect of caffeinated coffee on BP was observed only by pooling studies using five or more cups of coffee, but not in studies using ≤ 4.5 cups.

One study not included in the meta-analyses above (Hodgson et al., 1999) assessed the effects of consuming 250 mg of caffeine in hot water, black tea or green tea (five cups per day) for seven days on 24-hour ambulatory SBP and DBP in 13 subjects with high–normal SBP and DBP in a cross-over design. Changes in 24-hour ambulatory BP did not differ significantly among interventions with respect to baseline. Consistent with the finding by Noordzij et al. (2005), this study suggests that

caffeine intake for one week at doses of 250 mg per day (< 400 mg per day) does not increase fasting BP significantly, regardless of the caffeine source.

Caffeine and *p*-synephrine

The majority of human intervention studies available which have investigated the effects of daily consumption (> 7 days) of *p*-synephrine in food supplements containing *C. aurantium* extracts have addressed energy metabolism, body weight and body composition as measures of efficacy (reviewed in Stohs et al. (2012)). Cardiovascular outcomes (SBP, DBP, HR) have only been evaluated in one study using 98 mg per day of *p*-synephrine (in two doses of 49 mg each) for 60 days (Kaats et al., 2013) and in one study using a combination of *p*-synephrine (10 mg per day) and caffeine (400 mg per day) for 14 days (Kalman et al., 2002). None of these studies found a significant effect of the intervention on BP compared with placebo. The Panel notes that these studies provide no information on whether or not the co-consumption of *p*-synephrine modifies the effects of daily caffeine consumption on fasting BP.

The Panel notes that caffeine intakes at doses of about 400 mg per day did not raise fasting BP significantly after caffeine habituation in human intervention studies. The studies available do not provide sufficient information to conclude on whether or not consumption of *p*-synephrine modifies the effects of daily caffeine consumption on fasting BP.

4.5.2.3. Hypertension

Two systematic reviews and meta-analyses of prospective cohort studies have addressed the association between coffee consumption and the risk of incident hypertension (Zhang et al., 2011; Steffen et al., 2012). They considered the same six cohort studies reported in five publications (Appendix I), which included a total of 172 567 participants and 37 135 incident cases of hypertension. Mean follow-up ranged from 6.4 to 33 years. Three studies reported in two publications were conducted in the US (Klag et al., 2002; Winkelmayer et al., 2005) and three were conducted in Europe: one in Finland (Hu et al., 2007), one in Italy (Palatini et al., 2007) and one in the Netherlands (Uiterwaal et al., 2007).

Two studies used drug-treated hypertension as the outcome: one recruited only untreated hypertensive individuals at baseline (Palatini, 2007) and the second recruited both normotensive individuals and untreated hypertensive individuals (Hu et al., 2007). The remaining studies were conducted in normotensive individuals at baseline and used either diagnosis of hypertension or drug treatment for hypertension at follow-up as the outcome (Klag et al., 2002; Winkelmayer et al., 2005; Uiterwaal et al., 2007). Two studies assessed the intake of caffeinated coffee only (Klag et al., 2002; Palatini et al., 2007); the Finnish study did not discriminate between caffeinated and decaffeinated coffee, but the use of the latter was very low (about 0.8 %) (Hu et al., 2007); one study assessed both caffeinated and decaffeinated coffee (Uiterwaal et al., 2007); and two studies reported in one publication (Winkelmayer et al., 2005) assessed caffeine intake from all sources, including caffeinated and decaffeinated coffee. Both meta-analyses assessed the relationship between habitual consumption of (any) coffee and incident hypertension, and stratified analyses by type of coffee were not possible with the data available.

In both of the meta-analyses, data from original studies were grouped into four categories of coffee consumption: reference (less than one cup per day), low (one to three cups per day), moderate (three to five or three to six cups per day) and high (five or more or six or more cups per day). In the meta-analysis by Zhang et al. (2011), the group consuming more than zero to three cups per day was used as a reference category for the study by Uiterwaal et al. (2007) instead of coffee abstainers because of the low number of coffee abstainers, and the group consuming three to six cups per day was used as the second category. For the study by Palatini et al. (2007), the group consuming three or more cups per day (highest category) was taken as the high category and the group consuming one to three cups per day was used as the low category. Compared with the reference category, the pooled RRs (95 % CI) for hypertension were 1.09 (1.01–1.18) for the low category (one to three cups per day), 1.07

(0.96–1.20) for the moderate category (three to five cups per day) and 1.08 (0.96–1.21) for the highest category. In a dose–response meta-analysis, the best-fitting model showed an inverse "J-shaped" curve (p for quadratic term < 0.001), with the risk of hypertension increasing up to three cups per day (RR for the comparison of three cups with zero cups per day: 1.07, 95 % CI = 0.97–1.20) and decreasing with higher intake (RR for the comparison of six cups with zero cups per day: 0.99, 95 % CI = 0.89–1.10). The Panel notes that the risk of hypertension did not increase significantly at any dose of coffee consumption in this dose–response analysis. In the meta-analysis by Steffen et al. (2012), the study by Uiterwaal et al. (2007) was excluded from the combined analysis because it used more than zero to three cups of coffee per day as the reference category. Coffee drinking was not significantly associated with an increased risk of hypertension at any category of coffee intake compared with the reference category.

Among the individual studies considered, the study by Palatini et al. (2007) reported an increased risk of developing sustained hypertension associated with caffeinated coffee consumption compared with no consumption, with no significant difference in risk among categories of coffee intake (zero, one to three and three or more cups per day). A subsequent study by the same authors (Palatini et al., 2009) reported an increased risk of developing sustained hypertension requiring pharmacological treatment with increasing caffeinated coffee consumption in carriers of the slow CC or CA allele (59 %) of the CYP1A2 gene, but not in carriers of the fast AA allele, suggesting that the risk of developing hypertension associated with caffeine consumption may depend on the genetic background. However, these two studies exclusively enrolled subjects with never-treated stage 1 hypertension at baseline (incidence of hypertension requiring medication of 50.7 % in the six-year follow-up) and do not provide information about the general (unselected) adult population. Caffeinated coffee drinking was also positively associated with initiation of antihypertensive treatment (p for trend = 0.024 across categories of coffee intake: zero to one cup per day, two to three cups per day, four to five cups per day, six to seven cups per day and eight or more cups per day) in the study by Hu et al. (2007), which enrolled never-treated hypertensive and normotensive subjects, but the association was no longer significant when baseline BP was considered in the analysis. No association between caffeinated coffee consumption and the risk of incident hypertension was observed after adjusting for confounding variables in the study by Klag et al. (2002) in normotensive young males. In the study by Uiterwaal et al. (2007), where the category of more than zero to three cups per day was taken as the reference, higher coffee intake was not associated with an increased risk of hypertension, whereas coffee abstainers showed a decreased risk compared with the reference category. The Panel notes the low number of coffee abstainers included in the study and the low number of incident cases of hypertension in this group. The Panel also notes that the interaction between coffee intake and sex on the incidence of hypertension was not statistically significant, and thus subgroup analyses by sex were not statistically justified.

In the Nurses' Health Studies (NHSs) I and II of 155 594 US women free from physician-diagnosed hypertension were followed up over 12 years (Winkelmayer et al., 2005). FFQs were used to measure dietary intake and were completed in 1990, 1994 and 1998 for NHS I (30 to 55 years of age at recruitment) and in 1991, 1995 and 1999 for NHS II (25 to 42 years of age) and referred to the previous year. Relevant beverages included on the questionnaire were low-calorie and regular cola drinks, and caffeinated and decaffeinated tea and coffee. Caffeine content was assumed to be 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or bottle of cola beverage and 7 mg per serving of chocolate candy. A total of 19 541 (32 %) incident cases of physician-diagnosed hypertension were reported in NHS I and 13 536 (14.3 %) cases were reported in NHS II. In both cohorts, no linear association between caffeine consumption and the risk of incident hypertension was observed after multivariate adjustment. Using categorical analysis, an inverse U-shaped association between caffeine consumption and incident hypertension was found. Compared with participants in the lowest quintile of caffeine consumption (mean intakes 14.8 and 19.6 mg per day), those in the third quintile (209.3 and 174.7 mg per day) had a significant 14 % and 15 % increased risk of hypertension in NHS I and NHS II, respectively, whereas no increased risk was observed in the highest quintile (608.1 and 597.4 mg per day). In multivariate models including beverage type, rather than actual caffeine intake, significant inverse associations between intake of caffeinated coffee (p for trend = 0.02 and 0.03 in

NHS I and NHS II, respectively) and the risk of hypertension was observed in both cohorts, but an association was not found with decaffeinated coffee (p for trend = 0.08 and 0.67 in NHS I and NHS II, respectively). A significant association between caffeinated tea intake and incident hypertension was found in the cohort of younger women in NHS II (p for trend = 0.01), but not in NHS I (p for trend = 0.79). A significant positive association between the intake of sugar-containing (p for trend = 0.03 and < 0.001 in NHS I and NHS II, respectively) and sugar-free (p for trend = 0.03 and < 0.001 in NHS I and NHS II, respectively) caffeinated cola drinks and incident hypertension was observed in both cohorts. The Panel notes that this study shows an inverse U-shaped relationship between total caffeine intake from dietary sources and incident hypertension. An increased risk of hypertension was reported for women with mean caffeine intake of about 200 mg per day compared with women with very low (about 15–20 mg per day) or high (about 600 mg per day) intakes. The Panel also notes that different types of caffeinated beverages were differently associated with the risk of incident hypertension. Whereas caffeinated (but not decaffeinated) coffee was inversely associated with the risk of hypertension, caffeinated tea (in one cohort) and cola beverages (in both cohorts) were directly associated with that risk.

The Panel notes that BP values are used for CVD risk stratification and as a therapeutic target in prevention studies, and that hypertension is an independent risk factor for CVD, including CHD and stroke, so that studies on the relationship between caffeine intake and risk of CVD may help to define habitual caffeine intakes which pose no concern in relation to the CVS. The Panel also notes that data from prospective cohort studies on the relationship between habitual caffeine intake and the risk of incident hypertension are conflicting. An increased risk at any level of intake, an inverse U-shaped relationship and no relationship have all been reported in the individual studies, whereas the meta-analyses which combined data from all the studies available do not find an increased risk of hypertension at any level of caffeine intake. Although it has been suggested that polymorphisms of the CYP1A2 gene may affect the risk of hypertension associated with caffeine consumption and explain in part the different findings among studies, this hypothesis has not been tested prospectively in unselected populations.

4.5.2.4. Coronary heart disease

The dose–response meta-analysis by Ding et al. (2014) assessed prospective cohort studies on the relationship between coffee consumption and CVD risk (i.e. CHD, stroke, heart failure, CVD mortality). The 36 studies included (Appendix I) comprised ≈1 283 685 study participants and 47 779 CVD cases, including 28 347 CHD cases, 12 030 stroke cases and 7 402 other CVD cases. Duration of follow-up for incident CVD ranged from 6 to 44 years, with a median follow-up of 10 years. Twenty-one studies were conducted in Europe, 12 were conducted in the US and three were conducted in Japan. Nine studies assessed the association of caffeinated coffee consumption with CVD risk, and four studies assessed the association of decaffeinated coffee consumption with CVD risk. The outcome in 17 studies was risk of stroke, whereas the outcome in 22 studies was risk of CHD.

Compared with the lowest category of coffee consumption (median zero cups per day), the RRs of CHD were 0.89 (95 % CI = 0.85–0.94) for the first category (median 1.5 cups per day), 0.90 (95 % CI = 0.84–0.97) for the second category (median 3.5 cups per day) and 0.93 (95 % CI = 0.84–1.02) for the third category of coffee consumption (median five cups per day). A significant heterogeneity between studies was found for the second and third categories. In the dose–response analysis, a non-linear (p < 0.001) association between coffee consumption and CHD risk with significant trend (p < 0.001) and significant heterogeneity (p = 0.001) was reported. Coffee consumption was inversely associated with the risk of CVD up to eight cups per day. No association was observed between coffee consumption and CHD risk at higher intake. Caffeinated and decaffeinated coffee were not analysed separately for this outcome.

Two meta-analyses of prospective cohort studies have specifically addressed the association between coffee consumption and CHD risk (Sofi et al., 2007; Wu et al., 2009).

Sofi et al. (2007) searched for articles published between 1966 and April 2006 and included 10 independent prospective cohort studies (nine publications) with a total of 403 631 participants that were followed for between 3 and 44 years. Studies were excluded if they included a category other than that of very low consumption as a reference, if subjects were selected on the basis of a disease condition (hypertension), if categories of coffee consumption were not reported or if only decaffeinated coffee was studied. The cumulative RR for all cohort studies was 1.04 (95 % CI = 0.90–1.19) for the first category of coffee consumption (one to two cups per day), 1.05 (95 % CI = 0.90–1.22) for the second category (three to four cups per day) and 1.16 (95 % CI = 0.95–1.41) for the third category (four or more cups per day) compared with the reference category (none or less than one cup per day). Sensitivity analyses removing for each category the studies contributing more to heterogeneity gave similar results. Stratified analyses by region (US and Europe), publication year (before or after the median of 1995), fatal versus non-fatal events and number of years of follow-up (more or less than the median of 15 years) showed that only the publication year had an influence on the outcome (i.e. coffee consumption was associated with an increased risk of CHD in studies published before or in 1995 but not in studies published after 1995).

In the meta-analysis by Wu et al. (2009), the literature search was limited to articles in English published between 1966 and 2008. Studies were excluded if they had only two categories of coffee consumption, if subjects had type 2 diabetes or CVD at baseline or if only caffeine intake (and not coffee) was reported. A total of 21 independent prospective cohort studies (20 publications) were included in the analysis, 8 of which had already been considered by Sofi et al. (2007). The 21 studies included 433 054 participants and 17 149 cases. Categories of coffee consumption were defined as follows:

i. light (reference): US studies, one or less cups per day; European studies, two or less cups per day;
ii. moderate: US studies, one to three cups per day; European studies, three to four cups per day;
iii. heavy: US studies four to five cups per day; European studies, five to six cups per day; and
iv. very heavy: US studies, six or more cups per day; European study, seven or more cups per day.

The pooled RRs of CHD for all studies combined were 0.96 (95 % CI = 0.87–1.06) for the moderate, 1.04 (95 % CI = 0.92–1.17) for the heavy and 1.07 (95 % CI = 0.87–1.32) for the very heavy categories of coffee consumption. Stratified analyses by sex, region, study quality and duration of follow-up and adjustment for confounding variables did not affect the results significantly.

Among the 56 prospective cohort studies included in the meta-analyses above, eight studies, seven of which were published in or before 1995, reported a positive association between coffee consumption and the risk of CHD, including fatal and non-fatal CAD, fatal ischaemic heart disease and fatal and non-fatal MI. The risk increased significantly at one to four cups per day (Murray et al., 1981), three or more cups per day (Lindsted et al., 1992), three to four cups per day (Klag et al., 1994), four to six cups per day for non-fatal MI but not for other coronary cases (Klatsky et al., 1990), five to six cups per day (Stensvold and Tverdal, 1995), and six or more cups per day (LeGrady et al., 1987). In the study by Tverdal et al. (1990), only nine or more cups per day were compared with less than one cup. In the study by Happonen et al. (2004), the reference category was 376 to 813 mL per day of coffee, and thus did not allow conclusions to be drawn on the amount of coffee associated with an increased risk compared with no coffee consumption. Two studies (Murray et al., 1981; Stensvold and Tverdal, 1995) were not adjusted for any confounding variable. All these studies investigated coffee except Klatsky et al. (1990), who also investigated tea and found no increased risk of CHD in relation to tea consumption.

Four studies investigated the relationship between total caffeine intake (from various sources) and risk of CHD.

Grobbee et al. (1990) assessed caffeine intake from coffee, brownies, candies, chocolate and chocolate cookies, cocoa, cola beverages and tea in 45 589 men participating in the US Health Professionals Follow-up Study. Mean caffeine intakes were 236.7 mg per day in the sample, 52.6 mg per day in non-coffee consumers, 268.6 mg per day in consumers of any coffee, 312.3 mg per day in caffeinated coffee consumers and 211.1 mg per day in decaffeinated coffee consumers. The risk of CHD (total, non-fatal MI and fatal CHD), coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA), stroke or total CVD did not increase significantly across categories of caffeinated or decaffeinated coffee consumption (one or less cup, two to three cups and four or more cups per day compared with none) or of total caffeine intake (quintiles: 0–74 mg per day, 74–148 mg per day, 149–285 mg per day, 286–491 mg per day and 492–1 796 mg per day), except for a significant p per tend (0.04) for an increased risk of CABG and PTCA in the highest category of decaffeinated coffee consumption.

The publication by Lopez-Garcia et al. (2006) reports on two independent cohorts: the Health Professionals Follow-up Study (44 005 men) and the Nurses' Health Study (84 488 women). Documented events were 2 173 incident cases of CHD (1 449 non-fatal MI and 724 fatal cases of CHD) among men and 2 254 cases (1 561 non-fatal MI and 693 fatal cases of CHD) among women. Total caffeine intake was estimated from caffeinated beverages (coffee, tea, soft drinks) and chocolate candies. Total caffeine intake from all sources across categories of coffee consumption (in cups: < one per month, one per month to four per week, five to seven per week, two to three per day, four to five per day, six or more per day) were 51, 91, 194, 418, 691 and 885 mg per day in men and 118, 134, 218, 418, 751 and 881 mg per day in women, respectively. After adjustment for confounders, neither coffee nor total caffeine intake were significantly associated with the risk of CHD in either men or women. The results did not change when only the most recent information on coffee consumption before the event was considered in the analyses to assess short-term effects. Stratification by smoking status, alcohol consumption, history of type 2 diabetes mellitus and body mass index gave similar results.

Using data from 6 594 men and women participating in the first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-Up Study (NHEFS), Greenberg et al. (2008) studied the relationship between caffeine intake from caffeinated beverages (ground and instant caffeinated coffee, tea, cola drinks), chocolate snacks and all caffeinated beverages combined, and the risk of CHD, stroke and total CVD. Analyses were given for subjects < 65 years and ≥ 65 years of age separately, and were also stratified by history of hypertension. The risk of CHD, stroke and total CVD did not increase significantly across categories of total caffeine intake (> 30, 30–100, 100–350 and ≥ 350 mg per day) or of caffeinated beverages consumed (< 0.5, 0.5 to < 2, 2 to < 4 and ≥ 4 servings per day). The risk of CVD and CHD mortality significantly decreased across categories of caffeine and caffeinated beverages consumption in subjects ≥ 65 years of age, in normotensive individuals and in subjects with untreated (stage 1) hypertension, whereas consumption of decaffeinated beverages did not affect the risk.

One prospective study not included in the meta-analyses above (Bertoia et al., 2013) used data from 93 676 postmenopausal women who participated in the Women's Health Initiative Observational Study to assess the association between habitual alcohol and caffeine consumption and the risk of SCD. FFQs were completed at baseline and after three years. A total of 239 women experienced SCD after an average of 11 years of follow-up. No alcohol intake, moderate alcohol intake (15–30 g per day) and heavy alcohol intake (> 30 g per day) were not associated with risk of SCD compared with very light alcohol intake (0.1–5 g per day), whereas light alcohol intake (one drink or 5.1–15 g per day) was associated with a reduced risk of SCD only when recent alcohol exposure was used in the model. No association between total caffeine, caffeinated (regular) coffee, decaffeinated coffee or caffeinated tea and the risk of SCD was found. Caffeine analyses were not adjusted for alcohol and vice versa and alcohol–caffeine interactions were not addressed because no correlation between alcohol intake and caffeine intake (r = 0.08) was found in this population.

One case–control study aimed to determine whether or not polymorphisms of the CYP1A2 gene (Cornelis et al., 2006) and polymorphisms of the adenosine receptor gene ADORA2A, the serotonin receptor gene HTR2A and the dopamine receptor gene DRD2 (DaCosta, 2011) modify the association between coffee consumption and the risk of acute non-fatal MI. Cases (n = 2 014) and population-based controls (n = 2 014) living in Costa Rica matched for age, sex and area of residence were genotyped (CYP1A2 gene) and answered a FFQ to assess coffee intake. In total, 55 % of cases (n = 1 114) and 54 % of controls (n = 1 082) were carriers of the slow *1F allele, for which the multivariate-adjusted odds ratios (ORs) and 95 % CIs for non-fatal MI associated with the consumption of less than one, one, two to three and four or more cups of coffee per day were 1.00 (reference), 0.99 (0.69–1.44), 1.36 (1.01–1.83) and 1.64 (1.14–2.34), respectively. Corresponding ORs (95 % CIs) for individuals with the rapid *1A/*1A genotype were 1.00, 0.75 (0.51–1.12), 0.78 (0.56–1.09) and 0.99 (0.66–1.48) (p = 0.04 for gene by coffee interaction). In sensitivity analysis stratified by age and smoking status, a significant gene by coffee interaction (p = 0.003) was observed among the younger participants only (< 59 years, the median age of the sample). An increased risk of non-fatal MI with increasing coffee consumption in carriers of the slow *1F allele was also observed among non-smokers, although the gene by coffee interaction did not reach significance in either smokers or non-smokers. The DRD2 genotype was associated with caffeine consumption among non-smokers and the slow *1F allele carriers of the CYP1A2 gene. HTR2A genotype was associated with caffeine consumption among non-smokers and subjects with the ADORA2A TT genotype. Neither of the polymorphisms modified the association between coffee consumption and the risk of MI, although a significant coffee by HTR2A interaction was seen among subjects with the slow *1F allele. The Panel notes that, although this case–control study suggests that polymorphisms of the CYP1A2 gene may affect the risk of MI in relation to caffeine consumption, which may be further affected by polymorphisms of the serotonin receptor gene HTR2A, the results have not yet been replicated and the hypothesis has not been tested in prospective cohort studies.

The Panel notes that three meta-analyses and the vast majority of the 56 prospective cohort studies included in these review publications reported no increased risk of CHD associated with habitual coffee consumption at any level of intake. The Panel also notes that almost no study reported an increased risk of CHD associated with habitual coffee consumption of four or less cups per day, corresponding to about 400 mg per day of caffeine, which may be an underestimation of total caffeine intake considering that other sources of caffeine were not taken into account in the majority of the studies (e.g. mean caffeine intake from all sources in the category of subjects drinking four to five cups of coffee per day were 751 mg per day in the study by Lopez-Garcia et al. (2006), and 286–491 mg per day in subjects drinking three to four cups of coffee per day in the study by Grobbee et al. (1990)).

4.5.2.5. Atrial fibrillation

Two systematic reviews and meta-analyses of prospective cohort studies have specifically addressed the association between habitual caffeine consumption and risk of atrial fibrillation (AF) (Caldeira et al., 2013; Cheng et al., 2014). Both considered the same six prospective cohorts (Appendix I), which included a total of 228 465 adult participants (mean age 51–62 years) and 4 261 cases of AF during a mean follow-up between 4 and 25.2 years. The meta-analysis by Caldeira et al. (2013) used, in addition, data from one case–control study (Mattioli et al., 2005).

Three prospective cohort studies (two in the US and one in Denmark) assessed caffeine from all sources (i.e. coffee, tea, soft drinks, chocolate) and three assessed coffee as a source of caffeine. To calculate caffeine intake in the coffee studies, it was assumed in both meta-analyses that a cup of coffee contained 140 mg of caffeine in Sweden (two studies) and 85 mg in the US (one study). Caldeira et al. (2013) assumed 50 mg of caffeine per cup of coffee in the Italian case–control study (Mattioli et al., 2005). There was no significant association between caffeine exposure and AF risk in primary or subgroup analyses, considering age, sex, race, study quality, caffeine from coffee versus caffeine from all sources, caffeine dose or duration of follow-up. An inverse relationship was found between habitual caffeine intake and the risk of AF in a dose–response analysis (Cheng et al., 2014).

Incidence of AF decreased by 6 % (RR = 0.94, 95 % CI = 0.90–0.99) for every 300 mg per day increment in habitual caffeine intake up to about 1 000 mg per day. No single prospective cohort study reported an increased risk of AF associated with habitual caffeine or coffee consumption.

The Panel notes that habitual caffeine consumption from all sources up to about 1 000 mg per day was not significantly associated with an increased risk of AF in these two meta-analyses. The Panel also notes that no single prospective cohort study reported an increased risk of AF associated with habitual caffeine consumption.

4.5.2.6. Heart failure

A systematic review and a dose–response meta-analysis of prospective studies assessed the relationship between habitual caffeinated coffee consumption and the risk of heart failure (Mostofsky et al., 2012). The meta-analysis selected five independent prospective studies published between 2001 and 2011, which included, combined, 6 522 heart failure events among 140 220 participants. Four studies were conducted in Sweden (Wilhelmsen et al., 2001b; Ahmed et al., 2009; Mukamal et al., 2009; Levitan et al., 2011), where a standard cup of coffee is 150 mL, and one was conducted in Finland (Wang et al., 2011), where a serving was defined as 100 mL. Three of the studies consisted of participants with no history of MI, one study consisted of patients with MI and one included separate analyses for people with and without a history of diabetes or MI. Two studies were in men, one was in women and two included both sexes. A non-linear association between coffee consumption and heart failure risk was found (p for non-linearity = 0.02; p for overall significance of curve = 0.02). Compared with no coffee consumption, the pooled RR (95 % CI) for heart failure was 0.96 (0.90–0.99) for 1 to 2 servings per day, 0.93 (0.86–0.99) for 2 to 3 servings per day, 0.90 (0.82–0.99) for 3 to 4 servings per day, 0.89 (0.81–0.99) for 4 to 5 servings per day, 0.91 (0.83–1.01) for 5 to 6 servings per day, 0.93 (0.85–1.02) for 6 to 7 servings per day, 0.95 (0.87–1.05) for 7 to 8 servings per day, 0.97 (0.89–1.07) for 8 to 9 servings per day, 0.99 (0.90–1.10) for 9 to 10 servings per day, 1.01 (0.90–1.14) for 10 to 11 servings per day and 1.03 (0.89–1.19) for 11 servings per day. With the exception of the study by Mukamal et al. (2009), which was conducted in subjects with a history of MI, the only source of caffeine studied was coffee.

The Panel notes that coffee intake up to 11 cups per day, corresponding to about 1 100 mg of caffeine, were not significantly associated with an increased risk of heart failure in this meta-analysis. The Panel also notes that no single prospective cohort study reported an increased risk of heart failure associated with habitual coffee consumption.

4.5.2.7. Stroke

In the dose–response meta-analysis by Ding et al. (2014), the risk of stroke was assessed in 17 studies. Compared with the lowest category of coffee consumption, the RRs of stroke were 0.89 (95 % CI = 0.84–0.94) for the first category, 0.80 (95 % CI = 0.75–0.86) for the second category and 0.95 (95 % CI = 0.84–1.07) for the highest category of coffee consumption. No significant heterogeneity between studies was found for any category of coffee consumption. In the dose–response analysis, a non-linear ($p < 0.001$) association between coffee consumption and CHD risk with significant trend ($p < 0.001$) and non-significant heterogeneity ($p = 0.07$) was reported. Coffee consumption up to about four cups per day was inversely associated with the risk of stroke. No association was observed between coffee consumption of higher intakes and the risk of stroke. Caffeinated and decaffeinated coffee were not analysed separately for this outcome.

Two meta-analyses of prospective cohort studies have specifically addressed the association between coffee consumption and the risk of stroke (Larsson and Orsini, 2011; Kim et al., 2012).

The meta-analysis by Larsson and Orsini (2011) searched for prospective cohort studies published between 1966 and 2011 which reported the risk of stroke for three or more categories of coffee consumption. The meta-analysis included 11 prospective studies, with 479 689 participants and 10 003 cases of stroke. A non-linear inverse association between coffee consumption and stroke risk was

observed (p for non-linearity = 0.005). Compared with no coffee consumption, the pooled RRs of total stroke were 0.92 (95 % CI = 0.89–0.96) for one cup of coffee per day, 0.86 (95 % CI = 0.78–0.94) for two cups per day, 0.83 (95 % CI = 0.74–0.92) for three to four cups per day, 0.87 (95 % CI = 0.77–0.97) for six cups per day and 0.93 (95 % CI = 0.79–1.08) for eight cups per day. When the RRs for comparable categories of coffee consumption were pooled, the RRs of stroke were 0.88 (95 % CI = 0.86–0.90) for < 3 cups per day, 0.88 (95 % CI = 0.77–1.01) for 3 to < 5 cups per day, 0.87 (95 % CI = 0.75–1.02) for 5 to < 7 cups per day and 0.93 (95 % CI = 0.76–1.12) for ≥ 7 cups per day. In stratified analyses by sex (men, five studies; women, five studies; both sexes, four studies), geographical region (Europe, seven studies; US, two studies; Japan, two studies), duration of follow-up (≤ 10 years, four studies; > 10 years, seven studies) or stroke type (ischaemic, four studies; haemorrhagic, four studies), coffee consumption was not associated with an increased risk of stroke in any strata. Similar results were obtained in the meta-analysis by Kim et al. (2012), in which the literature search was limited to articles in English published between 2001 and July 2011. The meta-analysis included nine prospective cohort studies, six of which had also been considered by Larsson and Orsini (2011). One meta-analysis (Arab et al., 2009) of prospective cohort studies which assessed the relationship between green and black tea consumption and the risk of stroke and included data from nine individual studies involving 4 378 strokes among 194 965 individuals in total found similar results. The risk of stroke was assessed for three cups per day compared with low intake or no tea.

Among the prospective cohort studies included in the meta-analyses above, none reported a positive association (increased risk) between coffee consumption and the risk of stroke of any type. The only exception was the study by Hakim et al. (1998), which was conducted in a population of middle-aged (45–68 years) men with hypertension at baseline and it is not considered by the Panel as pertinent to this evaluation.

Four studies investigated the relationship between total caffeine intake (from various sources) and risk of stroke.

In addition to the studies by Grobbee et al. (1990) and Greenberg et al. (2007) described above in relation to CHD risk, two studies investigated the relationship between total caffeine intake from coffee and tea (Larsson et al., 2008), or from coffee, tea, caffeinated soft drinks and chocolate candy (Lopez-Garcia et al., 2009), and the risk of stroke. In the study by Larsson et al. (2008), caffeine contents of 80 mg per 100 mL of coffee and of 26 mg per 100 mL of tea were assumed to calculate total caffeine intake. Median caffeine intake was 186 mg per day. Consumption of caffeinated coffee, caffeinated tea or total caffeine (from coffee and tea) was not associated with an increased risk of ischaemic or haemorrhagic stroke. In the study by Lopez-Garcia et al. (2009), consumption of caffeinated beverages (cups) of less than one cup per month, one cup per month to four cups per week, five to seven cups per week, two to three cups per day and four or more cups per day corresponded to median total caffeine intakes of 71, 191, 318, 423 and 687 mg per day. Total caffeine intake, consumption of caffeinated beverages (tea, caffeinated soft drink and caffeinated coffee) and consumption of decaffeinated coffee were not significantly associated with an increased risk of stroke.

The Panel notes that coffee intake up to 8–11 cups per day, corresponding to about 800–1 100 mg of caffeine per day, were not significantly associated with an increased risk of stroke in the meta-analyses considered. The Panel also notes that no single prospective cohort study reported an increased risk of stroke associated with habitual coffee or tea consumption in the general adult population.

4.5.2.8. Cardiovascular disease risk (all outcomes combined)

In the dose–response meta-analysis by Ding et al. (2014), compared with the lowest category of coffee consumption (median zero cups per day), the RR (mean, 95 % CI) of CVD (all outcomes combined) was 0.89 (0.84–0.94) for the first category (median 1.5 cups per day), 0.85 (0.80–0.90) for the second category (median 3.5 cups per day) and 0.95 (0.87–1.03) for the third (highest) category (median five cups per day). No significant interactions were found between coffee intake and baseline hypertension or MI when the analyses were stratified for the following variables: smoking status, publication year,

study quality score, dietary assessment method (24-hour diet recall/diet record/FFQ versus other methods), stroke versus CHD as the outcome, country (US, Europe, Japan), sex and type of coffee (caffeinated coffee or decaffeinated coffee). Compared with the lowest category of coffee consumption, the RRs (mean, 95 % CI) for caffeinated (11 comparisons) and decaffeinated (five comparisons) coffee consumption were 0.89 (0.81–0.91) and 0.99 (0.93–1.05) for the first category, 0.83 (0.79–0.88) and 0.98 (0.87–1.15) for the second category and 0.91 (0.81–1.03) and 1.00 (0.88–1.14) and third category, respectively. In the dose–response analysis, coffee consumption was inversely associated with the risk of CVD up to six cups per day. No association was observed between coffee consumption and CVD risk at higher intake.

An additional prospective cohort study published thereafter (Loomba et al., 2014) using data from the US National Health and Nutrition Examination Survey III (NHANES III) reported no association between coffee consumption and CVD mortality (including stroke, congestive heart failure and ischaemia-related mortality) in multivariate analysis adjusted for confounding variables at any level of intake among 8 608 subjects > 45 years of age.

A few studies investigated whether or not genetic polymorphisms have an effect on caffeine consumption. Rodenburg et al. (2012) studied the effect of this CYP1A2-163C>A polymorphism on coffee and tea intake in 6 689 subjects in the Netherlands. Hetero- and homozygote "slow" metabolisers (AC/CC) consumed 0.19 and 0.34 cups of coffee per day less, respectively, than subjects of the "fast" AA genotype ($p < 0.0005$); no difference was found for tea consumers. Cornelis et al. (2006) found no statistically significant effect of this SNP on habitual caffeine consumption in 2 735 subjects. A meta-analysis of four genome-wide association studies of coffee consumption (in the Netherlands, Germany, US and Iceland) found two sequence variants (one locus between CYP1A1 and CYP1A2 gene and one in the aryl-hydrocarbon receptor (AHR) gene) which were associated with a difference in coffee consumption (Sulem et al., 2011). The difference was about 0.2 cups of coffee per day. No significant effect of the CYP1A2-163C>A polymorphism on coffee consumption was found in this meta-analysis. The Panel notes that genetic polymorphisms for genes involved in caffeine metabolism may explain only a small proportion of the inter-individual variability in caffeine intake.

4.5.2.9. Conclusions on the cardiovascular system

Data from RCTs suggest that caffeine intake (from coffee or supplements) at doses ≤ 400 mg per day does not raise fasting BP significantly after caffeine habituation takes place. Prospective cohort studies on the relationship between habitual caffeine intake and long-term changes in BP and on the risk of incident hypertension are conflicting and difficult to interpret. An equal number of studies reporting positive, negative and no association between habitual caffeinated coffee consumption and long-term changes in BP are available. Although meta-analyses combining data form all the prospective studies available do not find an increased risk of hypertension at any level of caffeine intake, an increased risk for any level of intake, an inverse U-shaped relationship and no relationship have been reported in the individual studies.

Hypertension is an established risk factor for CVD, and in particular for stroke, CHD and heart failure. A wealth of prospective cohort studies investigating the relationship between caffeinated coffee consumption (the type of coffee most often consumed and the main source of caffeine intake in most European populations) and the risk of total CVD and CVD subtypes (fatal and non-fatal CHD including MI and SCD, stroke and stroke subtypes, arrhythmias (mostly AF)), as well as systematic reviews and dose–response meta-analyses summarising their results, are available. Habitual caffeinated coffee consumption has not been associated with an increased risk of total CVD or CVD subtypes in the general adult population at any level of intake in any summary publication. Among the individual studies, a positive association between habitual caffeinated coffee consumption and CVD risk has been reported only for CHD (but not for stroke, AF or heart failure) in 8 out of the 56 studies reviewed, only 6 of which had any type of adjustment for confounding variables. Of these, only two reported an increased risk of CHD associated with habitual coffee consumption of four or less cups per

day (one for three or more cups per day, one for three to four cups per day), corresponding to about 400 mg per day of caffeine, which may be an underestimation of total caffeine intake considering that other sources of caffeine were not taken into account in these studies.

It has been suggested that certain substances in coffee (and tea) other than caffeine may decrease the risk of CVD and thus counteract any adverse effects of caffeine in the CVS which may become evident if the same amounts of caffeine are consumed from other sources (e.g. supplements, caffeinated soft drinks, "energy drinks"). However, total caffeine intake was not associated with an increased CVD risk in any of the studies that investigated all sources of caffeine. In addition, the individual studies and meta-analysis available that investigated the relationship between the consumption of caffeinated and decaffeinated beverages and CVD risk separately have reported either no association for any type of beverage (caffeinated or decaffeinated) or a J-shaped relationship (decreased risk of up to three to five cups per day and no increased risk thereafter compared with low or no consumption) for caffeinated beverages (mostly coffee, but also tea), which was not observed for decaffeinated beverages (mostly coffee, no change in risk across levels of intake). Although no firm conclusions can be drawn from these observations because of the low intake and/or low percentage of consumers of decaffeinated beverages and of caffeinated beverages other than coffee (except in the US) in these studies, the Panel considers that, on the basis of the data available, habitual caffeine intake up to about 400 mg per day from all sources does not increase the risk of CVD in the general adult population.

Some case–control and one prospective cohort study in hypertensive subjects suggest that polymorphisms of genes involved in caffeine metabolism could affect the relationship between caffeine intakes and CVD-related outcomes. The Panel notes that genetic polymorphisms for genes involved in caffeine metabolism may explain only a small proportion of the inter-individual variability in caffeine intake, and that there is no evidence that such polymorphisms influence the risk of CVD-related outcomes in the general population, although prospective cohort or human intervention studies investigating this hypothesis are currently not available for any subgroup of the general population. The Panel also notes that, considering that the distribution of "fast" and "slow" caffeine metabolisers in the general population is roughly 50:50, both phenotypes may have been equally represented in the human studies considered.

The vast majority of prospective cohort studies assessed habitual alcohol intake (alcohol consumers were not excluded) and used this variable to adjust multivariate models, rather than to explore interactions between alcohol and coffee or caffeine intake on CHD risk. In addition, the intervention study which assessed the effect of coffee on longer-term BP in habitual alcohol drinkers did not control for (or report on) caffeine intake. Despite the scarcity of data available on the combined effects of habitual caffeine and alcohol consumption on CVD risk, the Panel considers that habitual caffeine intake up to about 400 mg per day from all sources does not increase the risk of CVD in habitual alcohol drinkers from the general adult population.

4.5.3. Pregnancy outcomes

Different mechanisms have been proposed by which caffeine consumption during pregnancy could adversely affect fetal development. Caffeine is rapidly absorbed, passes freely across the placenta and is poorly metabolised by the fetus (Aldridge et al., 1979, 1981). By increasing the levels of circulating catecholamines, caffeine could induce uteroplacental vasoconstriction and fetal hypoxia (Kirkinen et al., 1983), as well as impair normal cell development by increasing cellular cyclic adenosine monophosphate (Weathersbee and Lodge, 1977).

Pregnancy outcomes that have been investigated in relation to the potential adverse health effects of caffeine consumption during pregnancy include length of gestation and related outcomes (e.g. pre-term delivery), birth weight and related outcomes (e.g. FGR, SGA), fetal death-related outcomes (miscarriage or spontaneous abortion, stillbirth) and infant death. The Panel focuses on birth weight-related outcomes (e.g. FGR, SGA), as these have been identified in previous assessments (COT, 2012)

as the most sensitive to the potential adverse health effects of caffeine consumption during pregnancy. FGR and SGA are associated with increased risk of perinatal morbidity and mortality. FGR has been found to be correlated with increased risk of metabolic diseases later in life.

4.5.3.1. Human intervention studies

Two Cochrane systematic reviews addressing the effects of maternal caffeine consumption during pregnancy on fetal, neonatal and/or pregnancy outcomes, conducted four years apart (Jahanfar and Sharifah, 2009; Jahanfar and Jaafar, 2013), identified only one human intervention study which addressed this topic (Bech et al., 2007). No other human intervention studies have been identified by the Panel.

In a double-blind RCT, 1 207 Danish women who were less than 20 weeks' pregnant were recruited either from those booked for delivery at Aarhus University Hospital or from a national birth cohort (Bech et al., 2007). Data on inclusion and exclusion criteria (pre-enrolment) were retrieved through a postal questionnaire at 16 weeks of pregnancy and by a telephone interview at about 12 weeks of pregnancy. Eligibility criteria included regular consumption of at least three cups of coffee per day and no history of a low birth weight baby (< 2 500 g), pre-term delivery, kidney diseases, epilepsy, diabetes or metabolic disorders. Eligible women were randomised to receive caffeinated instant coffee (n = 568) or decaffeinated instant coffee (n = 629) in identical boxes provided by the same manufacturer and were asked to replace their regular coffee with that provided, but were not advised on how much to drink and were not asked to avoid regular coffee offered by others or intake of other caffeinated beverages such as tea, cocoa or cola. Women were interviewed about daily consumption of the study coffee, of other caffeinated beverages (coffee, tea, cola or cocoa) and smoking status at weeks 20, 25 and 34 of gestation and at week 4 after the expected date of delivery. Caffeine intake from all sources during the study in both groups were calculated from data collected during the interviews, assuming a caffeine content per cup of 65 mg and 0 mg for caffeinated and decaffeinated study coffees, respectively (according to manufacturer), 100 mg for other caffeinated coffees, 50 mg for tea, and 5 mg and 20 mg per glass (2 dL) of drinking chocolate and cola drinks, respectively. Assuming a standard deviation of birth weight of 500 g, a sample size of 800 women was needed to detect a difference in birth weight of at least 100 g with 80 % power at a 5 % two-sided significance.

Total median daily caffeine intake (interquartile range (IQR)) was 317 mg (229–461 mg) and 117 mg (56–228 mg) in the caffeinated and decaffeinated coffee groups, respectively. Data on birth weight and length of gestation were obtained for 1 150 and 1 153 live-born singletons, respectively. The adjusted difference in length of gestation between the decaffeinated and caffeinated coffee groups was –1.31 days (–2.87 to 0.25). After adjustment for length of gestation, parity, pre-pregnancy body mass index and smoking at baseline, the mean birth weight of babies born to women in the decaffeinated coffee group was 16 g (95 % CI = –40 to 73 g), which was higher than those born to women in the caffeinated group. The Panel notes that this study did not report an effect of decreasing caffeine consumption from about 300 mg per day to about 100 mg per day in the last four months of pregnancy on length of gestation or birth weight.

4.5.3.2. Prospective cohort studies

Three prospective cohort studies have investigated the relationship between maternal intake of caffeine from caffeinated beverages and pregnancy and birth weight-related outcomes (i.e. FGR, SGA). In these studies, statistical analyses have been adjusted for a number of potentially confounding variables, including alcohol drinking and smoking during pregnancy, parity and socio-economic status. Maternal age, height and weight, maternal education, the baby's sex, length of gestation, outcome of previous pregnancies and occasionally pregnancy-related symptoms (e.g. nausea, vomiting) were also generally considered.

The CARE Study Group examined the relationship between maternal caffeine intake and birth weight, FGR (primary outcome, defined as birth weight < 10^{th} centile on a customised centile chart), late miscarriage (spontaneous pregnancy loss between 12 and 24 weeks), pre-term delivery (delivery at

< 37 completed weeks) and stillbirth (CARE Study Group, 2008; Greenwood et al., 2010). A total of 2 635 low-risk pregnant women (out of the 13 071 invited: 20 %) aged 18–45 years living in the UK were recruited between weeks 8 and 12 of pregnancy. Caffeine intakes were estimated using a validated questionnaire designed to record habitual caffeine intake before and during pregnancy from all sources, including over-the-counter medications. The questionnaire was administered three times: the first at recruitment, when women were asked to recall caffeine intake from 4 weeks before pregnancy to 8–12 weeks of pregnancy; the second covered weeks 13–28 of pregnancy; and the third covered weeks 29–40 of pregnancy. The prevalence of FGR in the cohort was 343 out of 2 635 (13 %). The women's mean caffeine intake during pregnancy was 159 mg per day, which decreased from 238 mg per day before pregnancy to 139 mg per day between weeks 5 and 12 of pregnancy, remained almost unchanged during the second trimester and gradually increased to 153 mg per day in the third trimester. The main sources of caffeine were tea (62 %), coffee (14 %), cola drinks (12 %), chocolate (8 %) and soft drinks (2 %). Hot chocolate, "energy drinks" and alcoholic drinks contributed 2, 1 and < 1 % to caffeine intake, respectively.

After adjustment for confounding variables, the relationship between total caffeine intake in pregnancy and FGR showed a significant trend with increasing caffeine intake (p for trend = 0.02). Compared with caffeine intake of < 100 mg/day, the ORs (95 % CI) of having a baby with FGR were 1.2 (0.9–1.6) for intakes of 100–199 mg per day, 1.5 (1.1–2.1) for intakes of 200–299 mg per day and 1.4 (1.0–2.0) for intakes of ≥ 300 mg per day. Caffeine consumption of > 200 mg per day during pregnancy was associated with a reduction in birth weight of about 60–70 g, with a significant trend for greater reduction in birth weight with higher caffeine intake (p = 0.004). These relationships were consistent across all three trimesters. When caffeine intake was analysed as a continuous variable, the risk of FGR increased exponentially up to 30 mg per day and linearly thereafter, and no threshold was identified (CARE Study Group, 2008). The association between caffeine intake and FGR did not appear to be mediated by nausea and vomiting during pregnancy (Boylan et al., 2013). Caffeine intake was also associated with an increased risk of late miscarriage or stillbirth (Greenwood et al., 2010). Compared with women consuming < 100 mg per day of caffeine, ORs (95 % CI) were 2.2 (0.7–7.1) for 100–199 mg per day, 1.7 (0.4–7.1) for 200–299 mg per day and 5.1 (1.6–16.4) for ≥ 300 mg per day (p per trend = 0.004).

The Panel notes that this study shows a dose-dependent positive association between caffeine intake during pregnancy and adverse birth weight- and fetal death-related outcomes, and that the risk becomes significant at caffeine doses ≥ 200 mg per day for FGR and at ≥ 300 mg per day for late miscarriage or stillbirth.

The association between maternal caffeine intake from different sources (coffee, black tea, cola, "energy drinks", chocolate milk) and gestational length, the risk of spontaneous pre-term delivery, birth weight and the risk of a baby being SGA was investigated in 59 123 Norwegian women with uncomplicated pregnancies giving birth to a live singleton (Sengpiel et al., 2013). SGA was diagnosed using three different growth curves and two definitions: < –2 SD or < 10th percentile of the growth curve distribution. Caffeine intake in the first four to five months of pregnancy was assessed using a semi-quantitative FFQ at week 22 of pregnancy, which was validated using four-day weighed food diaries. The way in which coffee was prepared was considered in calculating caffeine intake from this source. At weeks 15–17 and 30 of pregnancy, women also reported their current and pre-pregnancy consumption of coffee, tea and caffeinated soft drinks in cups or glasses per day. Coffee (56 %), black tea (22 %), sugar-containing soft drinks including "energy drinks" (7 %), sugar-free soft drinks (7 %) and chocolate (7 %) accounted for > 98 % of caffeine intake, although predominant sources of caffeine varied across quartiles of caffeine intake (chocolate in the first, black tea in the second and third and coffee in the fourth quartile). Self-reported pre-pregnancy median intake of caffeine from coffee, black tea and soft drinks was 126 mg per day (IQR 40 to 254 mg per day) for all 59 123 women, including 7 406 (12.5 %) women who did not consume any caffeine at all. At gestational week 17, the number of non-consumers almost doubled (14 012 women: 24 %) and the median caffeine intake had decreased to 44 mg per day (IQR 13 to 104 mg per day). At gestational week 30,

the median caffeine intake had increased again to 62 mg per day (IQR 21 to 130 mg per day) and 9 792 (16.5 %) women remained non-consumers.

When caffeine intake and intake of caffeinated beverages were analysed as continuous variables, and after adjusting for confounding variables, total caffeine and coffee caffeine were significantly associated with increased gestational length. Conversely, total caffeine and soft drink caffeine were significantly associated with decreased gestational length in non-coffee drinkers, whereas no association was found with black tea or chocolate caffeine. Total caffeine and caffeine intake from the individual sources were significantly associated with lower birth weight. An additional 100 mg total caffeine per day was associated with a 21- to 28-g birth weight decrease, depending on the growth curve. There were 1 451 cases of spontaneous pre-term delivery (240 early spontaneous pre-term deliveries, between weeks 22 and 33 + 6 days, and 1 211 late spontaneous pre-term deliveries, between weeks 34 and 36 + 6 days). There was no significant association between total or coffee caffeine intake and the odds for overall, early or late spontaneous pre-term delivery, whereas black tea caffeine was associated with increased risk of early spontaneous pre-term delivery (OR 1.61, 95 % CI = 1.10–2.35, p = 0.01). Total and coffee caffeine intakes were significantly associated with higher odds for SGA in all three SGA models, and with soft drink and black tea caffeine in two SGA models. All these associations remained when only non-smokers were considered (n = 54 136) in the analyses. The analyses were also conducted with caffeine intake as a categorical variable (six categories) to test threshold effects (0 to 14.6, reference; 14.6 to 32.1; 32.1 to 57.3; 57.3 to 96.0; 96.0 to 163.8; > 163.8 mg per day). The ORs for SGA consistently increased in the three models of SGA from the third of the six categories upwards compared with the reference category. Categorising caffeine intake based on current Nordic (up to 200 mg per day) and World Health Organization recommendations (up to 300 mg per day), women with a daily caffeine intake of 51 to 200 mg per day (43.5 %), of 200 to 300 mg (7.7 %) and of > 300 mg (3.3 %) had significantly higher odds for SGA (1.09 to 1.18, 1.27 to 1.62 and 1.62 to 1.66, respectively, depending on the SGA definition) than the lowest (0 to 50 mg per day) reference category. The Panel notes that this study shows a dose-dependent positive association between caffeine intake during pregnancy and adverse birth weight-related outcomes. The risk becomes statistically significant at caffeine doses > 50 mg per day but increases notably at > 200 mg per day. The Panel also notes that the relationship between caffeine intake and outcomes related to the length of gestation is inconsistent.

The third study (Bakker et al., 2010) was conducted in 7 346 pregnant women participating in a population-based prospective cohort study from early pregnancy onwards in the Netherlands (2001–2005). Fetal growth characteristics were assessed by ultrasound in the first, second and third trimesters. SGA at birth was defined as a gestational age-adjusted birth weight below the fifth percentile in the study cohort (< −1.81 SD score for boys and −1.73 SD score for girls). Caffeine intake from coffee and tea in the first (gestational age < 18.0 weeks), second (gestational age 18.0–24.9 weeks) and third (gestational age ≥ 25.0 weeks) trimesters of pregnancy was assessed by postal questionnaires. Intakes of caffeinated and decaffeinated coffee and tea were converted to caffeine units, each unit of caffeine intake reflecting caffeine exposure based on one cup (90 mg caffeine) of caffeinated coffee. Total caffeine intake was subsequently categorised as < 2, 2–3.9, 4–5.9 and ≥ 6 units per day for statistical analysis. No clear dose–response associations were found for caffeine intakes during pregnancy and fetal growth. Mothers who consumed ≥ 6 caffeine units per day had a smaller first-trimester fetal crown–rump length, smaller third-trimester femur length and impaired fetal weight and length growth than those who consumed no caffeine. Caffeine intake was positively associated with the risks of delivering an SGA child. Compared with mothers who consumed < 2 units caffeine per day, the adjusted ORs were 1.38 (95 % CI = 1.08–1.76), 1.50 (95 % CI = 0.96–2.36) and 1.87 (95 % CI = 0.84–4.15) for mothers consuming 2–3.9, 4–5.9 and ≥ 6 units caffeine per day, respectively (p trend < 0.01). The Panel notes that this study did not assess caffeine intake during pregnancy from all dietary sources. The Panel also notes that the reference category includes women with caffeine intakes up to 180 mg per day from tea and coffee, and that this categorisation does not allow the low end of the caffeine consumption curve to be explored in relation to the outcomes investigated.

One recent study (McMahon et al., 2014) assessed the allelic variation in two genetic loci which have been associated with habitual caffeine consumption, one in the CYP1A1 and CYP1A2 gene region (rs2472297) and one near the AHR gene (rs6968865), and its contribution to the inter-individual variability in habitual caffeine intake in a sample of pregnant women who participated in the Avon Longitudinal Study of Parents and Children (ALSPAC). Genetic information and data on self-reported coffee, tea and cola consumption (including consumption of decaffeinated drinks) at multiple time points (8, 18 and 32 weeks' gestation and 2, 47, 85, 97 and 145 months after delivery) were available from between 4 460 and 7 520 women. Caffeine intake generally increased across time points. Cola contributed to about 4–11 % of caffeine intake. Both genotypes were individually associated with total caffeine consumption and with the consumption of caffeinated drinks (coffee and tea) at all time points, but not with the consumption of decaffeinated drinks. However, the proportion of phenotypic variance (i.e. observed variability in caffeine intake) explained by these two genotypes was small: CYP1A1 accounted for 0.15–0.88 %, AHR accounted for 0.04–0.048 % and the two combined accounted for about 0.16–1.28 %. Whether or not the allelic variation in these two genetic loci influences the risk of adverse birth weight-related outcomes associated with caffeine consumption during pregnancy has not been investigated prospectively (e.g. using Mendelian randomisation).

4.5.3.3. Case–control and cross-sectional studies

The available case–control and cross-sectional studies on the relationship between caffeine consumption and pregnancy-related outcomes published up to 2008 have been thoroughly reviewed in previous assessments (COT, 2008). Overall, the results from these studies support a positive association between caffeine intake and the risk of adverse birth weight-related outcomes, whereas the relationship between caffeine consumption during pregnancy and other pregnancy outcomes (e.g. in relation to length of gestation or fetal death) was less consistent (COT, 2008), as observed in the prospective cohort studies described above.

Some of these studies have investigated whether or not the association between caffeine intake and adverse pregnancy outcomes could be modulated by differences in the activity of enzymes involved in the metabolism of caffeine, such as xanthine oxidase or N-acetyltransferase, or by genetic polymorphisms of the CYP1A2, CYP1B1 and CYP2E1 genes (Fenster et al., 1998; Signorello et al., 2001; Karypidis et al., 2006; Infante-Rivard, 2007). However, the results from these studies are not consistent, and whether genetic polymorphisms and/or phenotypic differences in the activity of enzymes involved in caffeine metabolism modify the relationship between caffeine intakes and adverse pregnancy-related outcomes has not been investigated in prospective studies.

4.5.3.4. Conclusions on pregnancy outcomes

The Panel notes that two prospective cohort studies (CARE Study Group, 2008; Sengpiel et al., 2013) show a dose-dependent positive association between caffeine intake during pregnancy from all dietary sources and the risk of adverse birth weight-related outcomes (i.e. FGR, SGA). The Panel also notes that the relationship between caffeine intakes and adverse birth weight-related outcomes is observed at all levels of intake, with no threshold below which the relationship is not observed. However, the Panel considers that the risk becomes clinically relevant at daily doses of about 200 mg of caffeine from all sources. In addition, the Panel also notes that pregnant women tend to reduce (pre-pregnancy) consumption of caffeine, and that decreasing caffeine intake from about 300 mg per day to about 100 mg per day in the third trimester of pregnancy does not decrease the risk, as observed in one human intervention study (Bech et al., 2007). Major sources of caffeine in the studies reviewed were coffee and tea, followed by soft drinks (including cola drinks) and chocolate. "Energy drinks" contributed 2 % (alone) (CARE Study Group, 2008) and 7 % (in combination with sugar-containing soft drinks) (Sengpiel et al., 2013) to caffeine intake in the two studies reporting on this source.

Genetic polymorphisms for genes involved in caffeine metabolism have been shown to explain only a small proportion of the inter-individual variability in caffeine intake during and after pregnancy (McMahon et al., 2014), and there is no evidence that such polymorphisms influence the risk of

adverse birth weight-related outcomes significantly, although prospective studies investigating this topic are lacking.

5. Dose–response assessment and derivation of intake levels of no concern

Consistent with the Panel's interpretation of the terms of reference (Section 1), this section addresses the derivation of caffeine intake levels of no concern for:

i. habitual caffeine consumption (i.e. a daily intake of caffeine from all sources which, if consumed *ad libitum* and throughout the day for long periods of time, does not give rise to concerns about harmful effects to health for the normal healthy population, divided into various life-stage groups as appropriate, but excluding sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other considerations);

ii. single doses of caffeine consumed prior to physical activity;

iii. caffeine (single doses and habitual consumption) consumed in combination with other common constituents of "energy drinks" (i.e. taurine, D-glucurono-γ-lactone) and/or with alcohol, or in combination with *p*-synephrine.

5.1. Adults

5.1.1. Single doses of caffeine

To provide advice on caffeine consumption (dose and timing) prior to physical activity that does not give rise to safety concerns, the Panel considers that clinically relevant changes in MBF are the appropriate health outcome on which to base such advice.

Single doses of caffeine up to 200 mg, corresponding to about 3 mg/kg bw for a 70-kg adult, or the same amount consumed within a short period of time, are unlikely to induce clinically relevant changes in MBF in the general healthy adult population, either at rest or when consumed less than two hours prior to intense physical exercise, under normal environmental conditions. The Panel notes that this may not be the case when caffeine is consumed prior to physical exercise under unusual environmental conditions (e.g. very high altitude). The Panel also notes that no studies are available in pregnant women or middle-aged/elderly subjects undertaking intense physical exercise. As only single doses of caffeine of 200 mg have been tested in relation to this outcome, a dose–response relationship cannot be derived on the basis of the data available.

Single doses of caffeine up to 200 mg are also unlikely to induce clinically relevant changes in blood pressure, hydration status or body temperature. This is the case both at rest or when consumed less than two hours prior to intense physical exercise under normal environmental conditions. This applies to non-habitual caffeine consumers, to caffeine-deprived subjects and to habitual caffeine consumers.

Single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) are unlikely to reduce the perceived exertion/effort during exercise. Higher doses could lead to prolonged physical exercise that might compromise the cardiovascular and/or musculoskeletal systems.

Single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) are also unlikely to mask the subjective perception of alcohol intoxication when alcohol is consumed at doses up to about 0.65 g/kg bw.

The human intervention studies on which these conclusions are based (Section 4.4) were primarily conducted with caffeine supplements for most of the outcomes assessed (i.e. changes in MBF, hydration status, body temperature, perceived exertion/effort during exercise, sleep). Changes in BP were assessed using caffeine supplements, coffee, tea and "energy drinks" as sources of caffeine, whereas the subjective perception of alcohol intoxication was tested using caffeine either from supplements or from "energy drinks".

The Panel notes that 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.

5.1.2. Single doses of caffeine in combination with other common constituents of "energy drinks", alcohol and *p*-synephrine

Other common constituents of "energy drinks" at concentrations commonly present in such beverages (typically about 300–320, 4 000 and 2 400 mg/L of caffeine, taurine and D-glucurono-γ-lactone, respectively) would not affect the safety of single doses of caffeine up to 200 mg. 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 CVS, the CNS or hydration status.

Alcohol consumption at doses up to about 0.65 g/kg bw, leading to a BAC 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". Up to these levels of intake, caffeine is unlikely to mask the subjective perception of alcohol intoxication.

The Panel also considers that the question of whether or not *p*-synephrine modifies the acute cardiovascular effects of single doses of caffeine has not been adequately investigated in humans, particularly if consumed shortly before intense physical exercise, and therefore no conclusions could be drawn.

5.1.3. Repeated doses of caffeine within a day

The Panel notes the absence of data for repeated caffeine doses in relation to the majority of health outcomes discussed for single doses of caffeine. However, the Panel considers that repeated doses of caffeine which do not give rise to safety concerns for non-pregnant adults in the general population should take into account the half-life of caffeine (mean four hours, range two to eight hours) so as not to exceed the maximum plasma concentrations achieved with a single 200 mg dose.

5.1.4. Habitual caffeine consumption

Caffeine intakes from all sources up to 400 mg per day (corresponding to about 5.7 mg/kg bw for a 70-kg adult) consumed throughout the day do not give rise to safety concerns for healthy adults in the general population, except for pregnant women (see Section 5.2). No health concerns in relation to acute toxicity, bone status, cardiovascular health, cancer risk or male fertility have been raised by other bodies in previous assessments for this level of habitual caffeine consumption and no new data have become available on these or other clinical outcomes which could justify modifying these conclusions.

5.1.5. Habitual caffeine consumption in combination with other common constituents of "energy drinks", alcohol and *p*-synephrine

The Panel notes that, in the prospective cohort studies considered in relation to CVD risk, the consumption of "energy drinks" was zero (i.e. studies which collected intake data before "energy drinks" appeared on the market) or unknown. However, based on the data available regarding the acute effects of caffeine in combination with other common constituents of "energy drinks" on the CVS, the Panel considers that such constituents at the doses commonly present in "energy drinks" (typically about 300–320, 4 000 and 2 400 mg/L of caffeine, taurine and D-glucurono-γ-lactone, respectively) would not affect the safety of habitual caffeine consumption up to 400 mg per day. In addition, the Panel considers that moderate habitual alcohol consumption would not affect the safety of habitual caffeine consumption up to 400 mg per day.

The Panel considers that the question of whether or not *p*-synephrine modifies the long-term effects of caffeine on the cardiovascular system has not been adequately investigated in humans, and therefore no conclusions could be drawn.

5.2. Pregnant women

5.2.1. Single doses of caffeine

There are no studies on the health effects of single doses of caffeine consumed by pregnant women prior to intense physical exercise. Taking into account the different kinetics of caffeine in this population subgroup, the Panel considers that single doses of caffeine which are of no safety concern for non-pregnant adults may not apply to pregnant women performing physical exercise.

5.2.2. Habitual caffeine consumption

Caffeine intakes from all sources up to 200 mg per day consumed throughout the day by pregnant women in the general population do not give rise to safety concerns for the fetus. This conclusion is based on two prospective cohort studies (CARE Study Group, 2008; Sengpiel et al., 2013) showing a dose-dependent positive association between caffeine intakes during pregnancy and the risk of adverse birth weight-related outcomes (i.e. FGR, SGA). The association between caffeine intakes and other adverse pregnancy-related outcomes is less consistent.

The Panel notes that prospective cohort studies cannot provide evidence for a causal association between caffeine and adverse birth weight-related outcomes. However, given the consistency of the association, the dose–response relationship observed in these studies and the plausibility of the proposed mode of action by which caffeine could affect fetal development, the Panel assumes that the relationship is causal in the context of this safety assessment. In these studies, the contribution of "energy drinks" to total caffeine intake was low (about 2 % when considered alone, about 7 % in combination with sugar-containing soft drinks).

5.3. Lactating women

5.3.1. Single doses of caffeine

Single doses of caffeine up to 200 mg consumed by lactating women in the general population do not give rise to safety concerns for the breastfed infant. Daily caffeine intakes by the breastfed infant would not exceed 0.3 mg/kg bw (Hildebrandt and Gundert-Remy, 1983), which is 10-fold below the lowest dose of 3 mg/kg bw tested in a dose finding study (Steer et al., 2003). For this dose, only 1 out of 42 pre-term infants showed tachycardia and jittering, and only tachycardia (with no jittering) was observed in 8 out of 45 infants at doses 100-fold higher (30 mg/kg bw).

5.3.2. Repeated doses of caffeine within a day and habitual caffeine consumption

Repeated doses of caffeine consumed by lactating women in the general population which do not give rise to safety concerns for the breastfed infant should take into account the half-life of caffeine (mean four hours, range two to eight hours) in women and the longer half-life in infants (i.e. 50–103 hours in neonates with no CYP1A2 activity, about 14 hours at three to four months of age). In this context, the Panel considers that doses of 200 mg per day from all sources consumed throughout the day by lactating women do not give rise to safety concerns for the breastfed infant.

5.4. Children and adolescents (1 to < 18 years)

The Panel notes that the information available for this population subgroup on the relationship between caffeine intakes and health outcomes is insufficient to derive a safe level of caffeine intake.

5.4.1. Single doses of caffeine

The Panel considers that single doses of caffeine of no concern derived for adults (3 mg/kg bw per day) may also apply to children, considering that caffeine clearance in children and adolescents is at least that of adults, and that the limited studies available on the acute effects of caffeine on anxiety and behaviour in children and adolescents support this level of no concern.

The Panel notes 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.

5.4.2. Habitual caffeine consumption

As mentioned above, caffeine clearance in children and adolescents is at least that of adults. Therefore, the same levels of no concern derived for adults (i.e. 5.7 mg/kg bw for a 70-kg adult) may also apply to children, unless there are data showing a higher sensitivity to the effects of caffeine of this age group (i.e. difference in pharmacodynamics). As only limited studies are available on the longer-term effects of caffeine on anxiety and behaviour in children and adolescents, there is substantial uncertainty regarding longer-term effects of habitual caffeine consumption in this age group. The Panel, therefore, considers a level of no safety concern for habitual caffeine consumption by children and adolescents of 3 mg/kg bw per day (i.e. the level of no safety concern derived for single doses of caffeine for adults) as appropriate. The Panel notes that this approach is rather conservative in relation to the effects of caffeine on the CVS, but the limited studies available regarding the longer-term effects of caffeine on anxiety and behaviour in children and adolescents support this caffeine intake level of no safety concern.

6. Characterisation of the risk

Daily caffeine intake from foods and beverages obtained from the EFSA Comprehensive Database was used to characterise the risk of habitual caffeine consumption. The Panel notes that the surveys considered did not report on the consumption of caffeine from food supplements, and that there are no data on the frequency and quantity of consumption of caffeine from this source in Europe in different subgroups of the population.

6.1. Adults

6.1.1. Single doses of caffeine

There are no data available to characterise the risk of single doses of caffeine consumed by adults in relation to physical exercise. The EFSA energy drink report, however, provides information to estimate caffeine intakes from "energy drinks" in "single sessions", defined as periods of time of a couple of hours, and in connection with physical exercise.

Considering the most common concentration of caffeine in "energy drinks" (320 mg/L) and the most common format (250 mL/can), it can be estimated that about 19 % of adult "energy drink consumers" and about 6 % of the total adult population may exceed caffeine intakes of 200 mg from "energy drinks" in a "single session" (Table 4), and that 14 % of adult "energy drink consumers" and 4 % of the total adult population may do so in relation to physical exercise (Table 5).

On the one hand, the Panel notes that this information is not available for other sources of caffeine, or for caffeine from all sources, including food supplements, and thus the percentage of adults exceeding 200 mg caffeine in a single sports session may be underestimated. On the other hand, caffeine intakes of no concern up to 200 mg refer to single doses of caffeine, whereas "a single sports session" may be extended for longer periods of time (e.g. a couple of hours or more), and the percentage of subjects exceeding 200 mg caffeine from "energy drinks" consumed as single doses in relation to physical exercise may have been overestimated.

6.1.2. Habitual caffeine consumption

For 7 out of 13 Member States, estimates of the 95th percentile of daily caffeine intake from foods and beverages exceeded 400 mg. In these countries, the estimated proportion of the adult population exceeding daily intakes of 400 mg ranged from about 6 % to almost one-third (32.9 %) (Appendix B).

The Panel notes that coffee was the main source of dietary caffeine in the seven countries for which the 95th percentile of daily caffeine intake exceeded 400 mg, and that the use of a mean value for the caffeine content in coffee on a volume basis may not accurately reflect caffeine intakes in all countries. More accurate estimates of caffeine intakes within a given country could be obtained by using national caffeine occurrence data, if available.

6.2. Pregnant women

6.2.1. Single doses of caffeine

There are no data to characterise the risk of single doses of caffeine consumed by pregnant women.

6.2.2. Habitual caffeine consumption

The mean and the 95th percentile of the daily caffeine intakes from foods and beverages in the only survey available were 109 mg and 206 mg per day, respectively. About 6.5 % of the women in that survey (n = 1 002) had daily caffeine intakes > 200 mg per day. The Panel notes the limited caffeine intake data available for this population subgroup (Appendix B).

6.3. Lactating women

6.3.1. Single doses of caffeine

There are no data to characterise the risk of single doses of caffeine consumed by lactating women.

6.3.2. Habitual caffeine consumption

The mean and the 95th percentile of the daily caffeine intakes from food and beverages in the only survey available were 31 mg and 97 mg per day, respectively, which are well below 200 mg. No women in that small survey (n = 65) consumed more than 400 mg of caffeine per day. The Panel notes the limited intake data available for this population subgroup (Appendix B).

6.4. Adolescents (10 to < 18 years)

6.4.1. Single doses of caffeine

Like for adults, there are no data available to characterise the risk of single doses of caffeine from all sources consumed by adolescents in relation to physical exercise. In the absence of such data, estimates of the proportion of single days in which caffeine intake exceeds 3 mg/kg bw among all survey days using the EFSA Comprehensive Database may serve as a conservative approximation.

For 6 out of 16 Member States, the estimated 95th percentile of caffeine intake from foods and beverages on a single day exceeded 3 mg/kg bw. The proportion of days on which daily intakes of caffeine from food and beverages exceeds 3 mg/kg bw in these countries ranges from about 7% to about 12 % (Appendix D).

6.4.2. Habitual caffeine consumption

For 5 out of 13 Member States, the 95th percentile of caffeine intake from food and beverages exceeded 3 mg/kg bw per day. In these countries, the estimated proportion of the adolescent population exceeding caffeine intakes of 3 mg/kg bw per day from food and beverages ranged from 5 to 10 % (Appendix B). The mean age of the adolescents studied in the surveys of these five countries ranged from 13 to 16 years.

6.5. Children (3 to < 10 years)

6.5.1. Single doses of caffeine

There are no data available to characterise the risk of single doses of caffeine consumed by children. Like for adolescents, estimates of the proportion of single days in which caffeine intake exceeds 3 mg/kg bw among all survey days using the EFSA Comprehensive Database may serve as a conservative approximation.

For 9 out of 16 Member States, the estimated 95th percentile of caffeine intake from food and beverages on a single day exceeded 3 mg/kg bw. The proportion of days on which daily intakes of caffeine from food and beverages exceeds 3 mg/kg bw in these countries ranges from about 6 % to about 15 % (Appendix D).

6.5.2. Habitual caffeine consumption

For 6 out of 14 Member States the estimates of the 95th percentile of daily caffeine intake from all sources exceeds 3 mg/kg bw. The estimated proportion of children with intakes exceeding 3 mg/kg bw per day of caffeine from foods and beverages in these countries ranged from 6 % to about 13 % (Appendix B).

The Panel notes that chocolate beverages were important contributors to total caffeine intakes in this age group in most countries, and that the use of a conservative caffeine value for this food category may have led to an overestimation of caffeine intakes in children.

6.6. Toddlers (12 to < 36 months)

6.6.1. Single doses of caffeine

There are no data available to characterise the risk of single doses of caffeine consumed by toddlers. In the absence of such data, estimates of the proportion of single days with caffeine intakes exceeding 3 mg/kg bw among all survey days using the EFSA Comprehensive Database may serve as a conservative approximation.

For 3 out of 10 Member States, the estimated 95th percentile of caffeine intake from all sources on a single day exceeded 3 mg/kg bw. The proportion of days in which daily intakes of caffeine from all sources exceeds 3 mg/kg bw ranges from 7 % to 37 % (Appendix D).

6.6.2. Habitual caffeine consumption

For only one out of nine Member States did the 95th percentile of caffeine intake from all sources exceed 3 mg/kg bw per day. About 6 % of the toddlers had a daily consumption > 3 mg/kg bw in that country (Appendix B).

The Panel notes that chocolate beverages were important contributors to total caffeine intakes in this age group in most countries, and that the use of a conservative caffeine value for this food category may have led to an overestimation of caffeine intakes in toddlers.

CONCLUSIONS

On the basis of the data available, the NDA Panel reached the following conclusions on caffeine intakes which do not give rise to safety concerns for specific groups of the general population. In line with the interpretation of the terms of reference, these conclusions do not apply to subgroups of the population selected on the basis of a disease condition or to sub-populations with extreme and distinct vulnerabilities due to genetic predisposition or other conditions which may require individual advice.

Adults

Single doses of caffeine

Single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) from all sources do not give rise to safety concerns for the general healthy adult population. 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. No studies are available in pregnant women or middle-aged/elderly subjects undertaking intense physical exercise. 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.

Other common constituents of "energy drinks" at concentrations commonly present in such beverages (typically about 300–320, 4 000 and 2 400 mg/L of caffeine, taurine and D-glucurono-γ-lactone, respectively) would not affect the safety of single doses of caffeine up to 200 mg. 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 CVS, the CNS or hydration status. Alcohol consumption at doses up to about 0.65 g/kg bw, leading to a BAC 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". Up to these levels of intake, caffeine is unlikely to mask the subjective perception of alcohol intoxication.

The human intervention studies on which these conclusions are based (see Section 4.4) were primarily conducted with caffeine supplements for most of the outcomes assessed (i.e. changes in MBF, hydration status, body temperature, perceived exertion/effort during exercise, sleep). Changes in BP were assessed using caffeine supplements, coffee, tea and "energy drinks" as sources of caffeine, whereas the subjective perception of alcohol intoxication was tested using caffeine either from supplements or from "energy drinks".

The question of whether or not *p*-synephrine modifies the acute cardiovascular effects of single doses of caffeine has not been adequately investigated in humans, particularly if consumed shortly before intense physical exercise, and therefore no conclusions could be drawn.

About 6 % of the adult population may exceed 200 mg of caffeine in a single session of "energy drink" consumption, and about 4 % do so in connection with physical exercise. This information is not available for other sources of caffeine.

Habitual caffeine consumption

Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg bw per day for a 70-kg adult) consumed throughout the day do not give rise to safety concerns for healthy adults in the general population, except pregnant women (see below). No health concerns in relation to acute toxicity, bone status, cardiovascular health, cancer risk or male fertility have been raised by other bodies in previous assessments for this level of habitual caffeine consumption and no new data have become available on these or other clinical outcomes which could justify modifying these conclusions.

Other common constituents of "energy drinks" at the doses commonly present in such beverages and/or moderate habitual alcohol consumption would not affect the safety of habitual caffeine consumption up to 400 mg per day.

The question of whether or not *p*-synephrine modifies the acute cardiovascular effects of single doses of caffeine or the long-term effects of caffeine on the cardiovascular system has not been adequately investigated in humans and therefore no conclusions could be drawn.

In 7 out of 13 countries, the 95th percentile of daily caffeine intake from foods and beverages exceeded 400 mg. In these countries, the estimated proportion of the adult population exceeding daily intakes of 400 mg ranged from 6 % to almost one-third, and coffee was the main source of caffeine. More accurate estimates of caffeine intakes within a given country could be obtained by using national caffeine occurrence data, if available.

Pregnant women

Single doses of caffeine

There are no studies on the health effects of single doses of caffeine consumed by pregnant women prior to intense physical exercise. With regard to the different kinetics of caffeine in this population subgroup, single doses of caffeine which are of no safety concern for non-pregnant adults may not apply to pregnant women performing physical exercise.

Habitual caffeine consumption

Caffeine intakes from all sources up to 200 mg per day consumed throughout the day by pregnant women in the general population do not give rise to safety concerns for the fetus. This conclusion is based on prospective cohort studies showing a dose-dependent positive association between caffeine intakes during pregnancy and the risk of adverse birth weight-related outcomes (i.e. FGR, SGA) in the offspring. In these studies, the contribution of "energy drinks" to total caffeine intake was low (about 2 %).

Data to characterise the risk of habitual caffeine consumption in this population subgroup are scarce.

Lactating women

Single doses of caffeine and habitual caffeine consumption

Single doses of caffeine up to 200 mg and habitual caffeine consumption at doses of 200 mg per day consumed by lactating women in the general population do not give rise to safety concerns for the breastfed infant. At these doses of caffeine, daily caffeine intakes by the breastfed infant would not exceed 0.3 mg/kg bw, which is 10-fold below the lowest dose of 3 mg/kg bw tested in a dose finding study and at which no adverse effects were observed in the majority of infants.

There are no data to characterise the risk of single doses of caffeine consumed by lactating women, and data on habitual caffeine consumption in this population subgroup are scarce.

Children and adolescents

The information available for this population subgroup on the relationship between caffeine intakes and health outcomes is insufficient to derive a safe level of caffeine intake.

Single doses of caffeine

Single doses of caffeine of no concern derived for adults (3 mg/kg bw per day for a 70-kg adult) may also apply to children, considering that caffeine clearance in children and adolescents is at least that of adults, and that the limited studies available on the acute effects of caffeine on anxiety and behaviour in children and adolescents support this level of no concern. 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.

There are no data available to characterise the risk of single doses of caffeine from all sources consumed by children and adolescents. Estimates of the proportion of single days in which caffeine intake exceeds 3 mg/kg bw among all survey days using the EFSA Comprehensive Database were used as a conservative approximation.

The estimated 95th percentile of caffeine intake from foods and beverages on a single day exceeded 3 mg/kg bw in 6 out of 16 countries for adolescents (10 to < 18 years), in 9 out of 16 countries for children (3 to < 10 years) and in 3 out of 10 countries for toddlers (12 to < 36 months). The proportion of survey days in which the level was exceeded ranged from 7.2 to 11.8 % in adolescents, from about 6 to 15 % in children and from 7 to 37 % in toddlers in the aforementioned countries. Chocolate beverages were important contributors to total caffeine intakes in children and toddlers in most countries, and the use of a conservative caffeine value for this food category may have led to an overestimation of caffeine intakes in these age groups.

Habitual caffeine consumption

As caffeine clearance in children and adolescents is at least that of adults, the same levels of no safety concern derived for adults (i.e. 5.7 mg/kg bw) may also apply to children, unless there are data showing a higher sensitivity to the effects of caffeine in this age group (i.e. difference in pharmacodynamics). As only limited studies are available on the longer-term effects of caffeine on anxiety and behaviour in children and adolescents, there is substantial uncertainty regarding longer-term effects of habitual caffeine consumption in this age group. A level of no safety concern of 3 mg/kg bw per day (i.e. the level of no concern derived for single doses of caffeine for adults) is proposed for habitual caffeine consumption by children and adolescents. This approach is rather conservative in relation to the effects of caffeine on the CVS, but the limited studies available regarding the longer-term effects of caffeine on anxiety and behaviour in children and adolescents support the proposed caffeine intake level of no safety concern.

The estimated 95th percentile of daily caffeine intake from foods and beverages exceeded 3 mg/kg bw in 5 out of 13 countries for adolescents, in 6 out of 14 countries for children (3 to < 10 years) and in 1 out of 9 countries for toddlers (12 to < 36 months). The proportion of subjects exceeding that level of intake in the above-mentioned countries was about 5 to 10 % for adolescents, 6 to 13 % for children and about 6 % for toddlers. Chocolate beverages were important contributors to total caffeine intakes in children and toddlers in most countries, and the use of a conservative caffeine value for this food category may have led to an overestimation of caffeine intakes in these age groups.

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APPENDICES

Appendix A. Dietary surveys used for the assessment of caffeine intakes

Country	Survey name/acronym	Survey period	No of days per subject	No of subjects/No of days				
				Toddlers	Other children	Adolescents *(mean age)*	Adults	Elderly	Very elderly
Belgium	Regional Flanders [a]	2002–2002	3	36/108	625/1 875	–	–	–	–
Belgium	Diet National 2004 [a]	2004	2	–	–	576/1 187 *(16 years)*	1 292/2 648	511/1 045	704/1 408
Bulgaria	NSFIN [a]	2004	1			–/162	–/691	–/151	–/200
Bulgaria	NUTRICHILD [a]	2007	2	428/856	433/867	–	–	–	–
Cyprus	Childhealth [a]	2003	3	–	–	303/909 *(13 years)*	–	–	–
Czech Republic	SISP04 [a]	2003–2004	2	–	389/778	298/596 *(13 years)*	1 666/3 332	–	–
Denmark	DANSDA 2005–08 [b]	2005–2008	7	–	298/2 085	377/2 622 *(13 years)*	1 739/12 127	274/1 916	12/84
Denmark	IAT 2006–07 [b]	2006–2007	7	917/6 388	–	–	–	–	–
Estonia	NDS 1997 [a]	1997	1			–	–/1866	–	–
Finland	DIPP 2001–2009 [b]	2001–2009	3	500/1 500	750/2 250	–	–	–	–
Finland	NWSSP07–08 [b]	2007–2008	4	–	–	306/1 186 *(13 years)*	–	–	–
Finland	FINDIET2012 [b]	2012	2	–	–	–	1 295/2 590	413/826	–
France	INCA2 [a]	2007	7	–	482/3 315	973/6 728 *(14 years)*	2 276/15 727	264/1 824	84/571
Germany	VELS [b]	2001–2002	6	348/1 947	293/1 610	–	–	–	–
Germany	EsKiMo [b]	2006	3	–	835/2 498	393/1 179 *(11 years)*	–	–	–
Germany	National Nutrition Survey II [a]	2007	2	–	–	1 011/2 022 *(16 years)*	10 419/20 838	2 006/4 012	490/980
Greece	Regional Crete [a]	2004–2005	3	–	838/2 508	–	–	–	–
Greece	DIET LACTATION GR [b]	2005–2007	3	–	–	–	65/350	–	–
Hungary	National Repr Surv [a]	2003	3	–	–	–	1 074/3 222	206/618	80/240
Ireland	NANS 2012 [b]	2008–2010	4	–	–	–	1 274/5 096	149/596	77/308

Country	Survey name/acronym	Survey period	No of days per subject	No of subjects/No of days					
				Toddlers	Other children	Adolescents *(mean age)*	Adults	Elderly	Very elderly
Italy	INRAN SCAI 2005–2006 [(a)]	2005–2006	3	36/108	193/579	247/741 *(14 years)*	2 313/6 939	290/870	228/684
Latvia	EFSA TEST [(a)]	2008	2		187/377	453/979 *(14 years)*	1 271/2 655	–	–
Latvia	FC PREGNANTWOMEN 2011 [(b)]	2011	2	–	–	–	1 002/2 005	–	–
Netherlands	VCP kids [(a)]	2006–2007	3	322/644	957/1 914	–	–	–	–
Netherlands	VCPBasis AVL2007–2010 [(b)]	2007–2010	2	–	447/894	1 142/2 284 *(14 years)*	2 057/4 114	173/346	
Netherlands	VCP-Elderly [(b)]	2010–2012	2	–	–	–	–	289/578	450/900
Poland	IZZ FAO 2000 [(a)]	2000	1	–/79	–/409	–/666 *(14 years)*	–/2 527	–/329	–/124
Romania	Dieta Pilot Children [(b)]	2012	1	–	–/205	–/567 *(14 years)*	–	–	–
Romania	Dieta Pilot Adults [(b)]	2012	7	–	–	–	1 254/8 770	83/581	45/315
Slovakia	SK MON 2008 [(a)]	2008	1	–	–	–	2 761	–	–
Slovenia	CRP 2008 [(a)]	2007–2008	1	–	–	–	407	–	–
Spain	enKid [(a)]	1998–2000	2	17/34	156/312	209/418 *(12 years)*	–	–	–
Spain	AESAN [(a)]	1999–2001	3	–	–	–	410/828	–	–
Spain	NUT INK05 [(a)]	2004–2005	2	–	399/798	651/1 302 *(14 years)*	–	–	–
Spain	AESAN FIAB [(a)]	2009	3	–	–	86/226 *(17 years)*	981/2 748	–	–
Sweden	NFA [(a)]	2003	4	–	1473/5 875	1 018/4 047 *(12 years)*	–	–	–
Sweden	Riksmaten 2010 [(b)]	2010–2011	4	–	–	–	1 430/5 680	295/1 167	72/288
United Kingdom	NDNS Rolling Programme Years 1–3 [(b)]	2008–2011	4	185/737	651/2 595	666/2 653 *(14 years)*	1 266/5 040	166/662	139/552
United Kingdom	DNSIYC 2011 [(b)]	2011	4	1 314/5 217	–	–	–	–	–

(a): Dietary surveys included in the 2010 release of the EFSA Comprehensive European Food Consumption Database (FoodEx classification).
(b): Dietary surveys added to the EFSA Comprehensive European Food Consumption Database for the 2014 release (FoodEx2 classification).

Appendix B. Daily caffeine intake by country survey and age class

Age class	Country	Survey	No of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95 [a]	Mean	P95 [a]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
Toddlers (12 to < 36 months) 10 surveys	Belgium	Regional Flanders	36	14.8	–	1.1	–	8.3	n.a. [b]
	Bulgaria	NUTRICHILD	428	3.0	16.6	0.3	1.4	0.5	n.a.
	Denmark	IAT 2006–2007	917	3.4	11.2	0.3	0.9	0.4	n.a.
	Finland	DIPP 2001–2009	500	0.3	0.8	0.0	0.1	0.0	n.a.
	Germany	VELS	348	5.9	27.3	0.5	2.2	3.2	n.a.
	Italy	INRAN SCAI 2005–2006	36	3.6	–	0.3	–	2.8	n.a.
	Netherlands	VCP kids	322	9.1	45.4	0.7	3.5	5.9	n.a.
	Spain	enKid	17	30.3	–	2.1	–	17.6	n.a.
	United Kingdom	NDNS Rolling Programme Years 1–3	185	4.9	30.6	0.4	2.2	2.2	n.a.
		DNSIYC 2011	1 314	2.0	7.8	0.2	0.7	1.8	n.a.
Other children (3 to < 10 years) 17 surveys	Belgium	Regional Flanders	625	10.4	37.8	0.6	2.3	2.9	n.a.
	Bulgaria	NUTRICHILD	433	3.5	19.8	0.2	1.2	1.4	n.a.
	Czech Republic	SISP04	389	47.1	93.5	2.0	4.0	12.9	n.a.
	Denmark	DANSDA 2005–2008	298	15.6	41.7	0.6	1.5	0.3	n.a.
	Finland	DIPP 2001–2009	750	20.7	87.1	1.1	4.4	11.1	n.a.
	France	INCA2	482	21.0	60.6	1.0	2.8	4.6	n.a.
	Germany	EsKiMo	835	17.2	54.8	0.6	2.1	1.9	n.a.
		VELS	293	13.5	47.4	0.8	2.6	3.4	n.a.
	Greece	Regional Crete	838	8.9	34.2	0.4	1.6	1.4	n.a.
	Italy	INRAN SCAI 2005–2006	193	25.8	77.9	1.1	4.3	5.7	n.a.
	Latvia	EFSA TEST	187	45.1	102.6	1.5	4.0	9.6	n.a.
	Netherlands	VCP kids	957	14.8	57.6	0.7	2.8	4.6	n.a.
		VCPBasis AVL2007–2010	447	25.8	96.4	0.9	3.6	6.0	n.a.
	Spain	enKid	156	35.8	94.5	1.4	4.6	11.5	n.a.
		NUT INK05	399	29.0	77.0	1.1	3.0	4.5	n.a. [b]
	Sweden	NFA	1473	9.9	37.3	0.4	1.4	0.6	n.a.
	United Kingdom	NDNS Rolling Programme Years 1–3	651	9.9	46.9	0.4	1.8	1.4	n.a.

Age class	Country	Survey	No of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95 [a]	Mean	P95 [a]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
Adolescents (10 to < 18 years) 16 surveys	Belgium	Diet National 2004	576	68.3	190.8	1.1	3.0	5.2	0.7 (1.2)
	Cyprus	Childhealth	303	38.2	133.5	0.7	2.4	3.0	0.0 (0.0)
	Czech Republic	SISP04	298	50.1	119.8	1.1	2.4	4.0	0.3 (0.3)
	Denmark	DANSDA 2005–2008	377	30.8	92.8	0.6	1.6	1.3	0.3 (0.3)
	Finland	NWSSP07–08	306	52.1	172.9	1.0	3.4	6.9	0.0 (1.0)
	France	INCA2	973	30.5	95.4	0.6	1.9	1.7	0.0 (0.2)
	Germany	National Nutrition Survey II	1011	59.4	208.1	1.0	3.5	6.6	0.6 (1.1)
		EsKiMo	393	22.0	68.9	0.6	1.8	1.5	0.0 (0.3)
	Italy	INRAN SCAI 2005–2006	247	43.5	136.7	0.8	2.3	2.8	0.0 (0.0)
	Latvia	EFSA TEST	453	67.8	152.7	1.4	3.1	5.3	0.2 (0.9)
	Netherlands	VCP Basis AVL2007–2010	1 142	69.5	211.6	1.3	4.1	10.0	0.5 (1.6)
	Spain	AESAN FIAB	86	40.3	114.3	0.7	2.3	2.3	0.0 (1.2)
		enKid	209	38.2	105.0	0.8	2.4	2.9	0.0 (1.0)
		NUT INK05	651	47.8	109.2	0.9	2.2	2.0	0.3 (0.3)
	Sweden	NFA	1 018	17.6	60.5	0.4	1.5	0.5	0.0 (0.1)
	United Kingdom	NDNS Rolling Programme Years 1–3	666	37.0	126.4	0.7	2.2	2.4	0.0 (0.2)
Adults (18 to < 65 years) 16 surveys	Belgium	Diet National 2004	1 292	191.9	543.3	2.7	7.6	n.a.	10.4 (9.1)
	Czech Republic	SISP04	1 666	124.8	269.7	1.7	3.8	n.a.	1.2 (0.7)
	Denmark	DANSDA 2005–2008	1 739	319.4	742.4	4.3	10.0	n.a.	32.9 (29.1)
	Finland	FINDIET2012	1 295	236.0	538.5	3.1	6.9	n.a.	13.4 (10.6)
	France	INCA2	2 276	154.5	414.0	2.3	6.4	n.a.	5.8 (6.7)
	Germany	National Nutrition Survey II	10 419	238.0	538.7	3.2	7.3	n.a.	14.6 (11.8)
	Greece	Diet Lactation Gr	65	31.3	97.4	0.5	1.6	n.a.	0.0 [c]
	Hungary	National Repr Surv	1 074	103.0	268.1	1.5	3.8	n.a.	1.4 (1.7)
	Ireland	NANS 2012	1 274	149.0	346.2	2.0	4.7	n.a.	3.0 (2.7)
	Italy	INRAN SCAI 2005–2006	2 313	139.3	323.1	2.1	4.8	n.a.	2.1 (2.8)
	Latvia	EFSA TEST	1 271	149.4	310.4	2.0	4.4	n.a.	1.6 (1.3)
		Pregnant Women 2011	1 002	108.6	205.7	1.6	3.0	n.a.	6.5 [c]

Age class	Country	Survey	No of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95 [(a)]	Mean	P95 [(a)]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
	Netherlands	VCP Basis AVL2007–2010	2 057	258.5	589.2	3.3	7.7	n.a.	17.6 (13.3)
	Romania	Dieta Pilot Adults	1 254	36.5	108.6	0.5	1.5	n.a.	0.1 (0.1)
	Spain	AESAN	410	51.6	157.2	0.7	2.2	n.a.	0.2 (0.2)
	Spain	AESAN FIAB	981	66.8	156.0	1.0	2.6	n.a.	1.5 (1.7)
	Sweden	Riksmaten 2010	1 430	205.3	482.2	2.8	6.7	n.a.	9.0 (8.0)
	United Kingdom	NDNS Rolling Programme Years 1–3	1 266	138.2	318.4	1.8	4.4	n.a.	2.4 (2.4)
Elderly (65 to < 75 years) 13 surveys	Belgium	Diet National 2004	511	216.3	472.8	3.0	6.5	n.a.	9.6 (8.2)
	Denmark	DANSDA 2005–2008	274	362.1	715.7	4.8	10.4	n.a.	34.7 (29.9)
	Finland	FINDIET2012	413	214.2	416.1	2.8	5.9	n.a.	6.3 (5.6)
	France	INCA2	264	130.1	309.1	1.9	4.4	n.a.	2.3 (2.3)
	Germany	National Nutrition Survey II	2 006	241.4	486.4	3.2	6.3	n.a.	10.4 (7.7)
	Hungary	National Repr Surv	206	75.2	178.7	1.0	2.3	n.a.	1.0 (0.0)
	Ireland	NANS 2012	149	167.3	348.5	2.3	5.1	n.a.	2.0 (3.4)
	Italy	INRAN SCAI 2005–2006	290	122.7	321.7	1.7	4.6	n.a.	2.1 (2.4)
	Netherlands	VCPBasis AVL2007–2010	173	280.4	548.2	3.7	7.6	n.a.	17.3 (15.0)
	Netherlands	VCP-Elderly	289	265.7	470.4	3.4	6.0	n.a.	12.5 (6.9)
	Romania	Dieta Pilot Adults	83	22.6	96.3	0.3	1.5	n.a.	0.0 (0.0)
	Sweden	Riksmaten 2010	295	222.2	445.0	3.0	6.4	n.a.	7.1 (6.1)
	United Kingdom	NDNS Rolling Programme Years 1–3	166	164.9	377.0	2.1	5.3	n.a.	4.2 (3.0)
Very elderly (≥ 75 years) 11 surveys	Belgium	Diet National 2004	704	197.5	422.8	2.9	6.1	n.a.	6.8 (7.2)
	Denmark	DANSDA 2005–08	12	416.8	–	6.0	–	n.a.	41.7 (58.3)
	France	INCA2	84	108.2	271.5	1.5	3.8	n.a.	2.4 (2.4)
	Germany	National Nutrition Survey II	490	208.2	397.9	2.8	5.2	n.a.	4.9 (3.5)
	Hungary	National Repr Surv	80	68.6	174.0	1.0	2.3	n.a.	1.3 (1.3)
	Ireland	NANS 2012	77	160.2	291.9	2.4	5.9	n.a.	2.6 (5.2)
	Italy	INRAN SCAI 2005–2006	228	101.4	262.6	1.5	4.2	n.a.	1.8 (1.3)
	Netherlands	VCP-Elderly	450	239.2	454.5	3.2	5.9	n.a.	9.8 (6.2)
	Romania	Dieta Pilot Adults	45	21.8	–	0.3	–	n.a.	0.0 (0.0)

Age class	Country	Survey	No of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95 [(a)]	Mean	P95 [(a)]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
	Sweden	Riksmaten 2010	72	194.3	446.8	2.7	6.1	n.a.	8.3 (6.9)
	United Kingdom	NDNS Rolling Programme Years 1–3	139	151.9	303.5	2.2	4.7	n.a.	0.7 (0.7)

(a): The 95th percentile estimates based on dietary surveys/age classes with fewer than 60 subjects may not be statistically robust (EFSA, 2011b) and consequently were not considered ("–").
(b): n.a. = not applicable.
(c): % exceeding 200 mg/kg bw per day.

Appendix C. 95th percentile of caffeine intake from all sources for "all days" and for "consumption days"

Age class	Food groups	95th percentile caffeine intake [a] (all days)				95th percentile caffeine intake [a] (consumption days)			
		mg per day		mg per day		mg per day		mg per day	
		Min. [b]	Max. [b]	Min. [b]	Max. [b]	Min. [b]	Max. [b]	Min. [b]	Max. [b]
Toddlers (12 to < 36 months) 11 surveys	**Total intakes** [c]	0.0	82.5	0.0	7.1	[d]	[d]	[d]	[d]
	Chocolate	0.4	25.2	0.0	1.8	8.4	60.5	0.6	5.3
	Coffee	0.0	5.6	0.0	0.4	–	–	–	–
	Cola beverages	0.0	48.6	0.0	3.2	–	–	–	–
	"Energy drinks"	–	–	–	–	–	–	–	–
	Tea	0.0	82.5	0.0	7.1	27.6	110.0	2.6	9.6
Other children (3 to < 10 years) 19 surveys	**Total intakes**	0.0	130.1	0.0	5.7	[d]	[d]	[d]	[d]
	Chocolate	7.7	126.0	0.4	5.4	9.5	136.1	0.6	7.7
	Coffee	0.0	71.2	0.0	2.2	44.5	385.6	2.4	15.1
	Cola beverages	0.0	37.3	0.0	1.8	35.6	75.6	1.7	3.2
	"Energy drinks"	–	–	–	–	–	–	–	–
	Tea	0.0	123.8	0.0	5.3	66.0	132.0	2.5	5.4
Adolescents (10 to < 18 years) 19 surveys	**Total intakes**	0.0	239.8	0.0	4.3	[d]	[d]	[d]	[d]
	Chocolate	8.4	169.1	0.1	3.3	33.6	253.6	0.7	5.4
	Coffee	0.0	133.5	0.0	2.7	138.0	445.0	2.4	7.1
	Cola beverages	0.0	108.0	0.0	1.8	64.8	142.6	1.5	2.4
	"Energy drinks"	–	–	–	–	240.0	329.6	4.4	5.2
	Tea	0.0	148.5	0.0	3.2	69.3	308.0	1.8	5.0
Adults (18 to < 65 years) 24 surveys	**Total intakes**	0.0	809.3	0.0	10.8	[d]	[d]	[d]	[d]
	Chocolate	1.7	50.4	0.0	0.9	33.6	151.2	0.5	2.3
	Coffee	66.6	801.0	1.0	10.5	106.8	890.0	1.5	11.4
	Cola beverages	0.0	89.6	0.0	1.3	54.0	216.0	0.9	2.3
	"Energy drinks"	–	–	–	–	320.0	330.2	4.2	5.3
	Tea	0.0	264.0	0.0	3.6	41.3	308.0	0.9	4.4
Elderly (65 to < 75 years) 15 surveys	**Total intakes**	0.0	784.3	0.0	10.7	[d]	[d]	[d]	[d]
	Chocolate	0.0	30.2	0.0	0.4	23.6	121.0	0.3	1.6
	Coffee	89.0	756.5	1.2	10.3	111.3	801.0	1.7	10.6
	Cola beverages	0.0	26.1	0.0	0.3	54.4	108.0	0.7	1.5
	"Energy drinks"	–	–	–	–	–	–	–	–
	Tea	0.0	316.8	0.0	4.2	99.0	338.8	1.2	4.3
Very elderly (≥ 75 years) 13 surveys	**Total intakes**	0.0	801.0	0.0	13.1	[d]	[d]	[d]	[d]
	Chocolate	1.1	35.5	0.0	0.6	37.8	504.0	0.5	8.1
	Coffee	66.8	801.0	0.9	10.5	144.6	801.0	2.1	10.5
	Cola beverages	0.0	16.2	0.0	0.2	81.0	81.0	1.1	1.1
	"Energy drinks"	–	–	–	–	–	–	–	–
	Tea	0.0	288.2	0.0	4.1	66.0	312.4	1.1	4.2

(a): The 95th percentile estimates based on dietary surveys/age classes with fewer than 60 days of data may not be statistically robust (EFSA, 2011b) and consequently were not considered ("–") in this table.

(b): Minimum and maximum 95th percentile across the correspondent statistic calculated for each age class and dietary survey.

(c): Please note that "total intakes" are not derived by summing the minimum and maximum values for the different food categories, but reflect the minimum and maximum total caffeine intakes from all sources for all days in that survey.

(d): Minimum and maximum total caffeine intakes on consumption days cannot be calculated because the value would depend on the food group which is used to define a consumption day.

Appendix D. Caffeine intake on a single day by country survey and age class

Age class	Country	Survey	No of days	95th percentile caffeine intake [a]		% of days with an intake of	
				mg per day	mg/kg bw per day	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
Toddlers	Belgium	Regional Flanders	108	53.1	4.3	10.2	n.a. [b]
(12 to < 36 months)	Bulgaria	NUTRICHILD	856	22.1	1.9	1.4	n.a.
11 surveys	Denmark	IAT 2006–07	6 388	17.1	1.4	1.0	n.a.
	Finland	DIPP 2001–2009	1 500	0.5	0.1	0.1	n.a.
	Germany	VELS	1 947	27.7	2.2	3.0	n.a.
	Italy	INRAN SCAI 2005–06	108	24.8	2.0	3.7	n.a.
	Netherlands	VCP kids	644	47.1	3.6	7.3	n.a.
	Poland	IZZ FAO 2000	79	82.5	7.1	36.7	n.a.
	Spain	enKid	34	–	–	23.5	n.a.
	United Kingdom	NDNS Rolling Programme Years 1–3	737	33.7	2.6	3.7	n.a.
		DNSIYC 2011	5 217	5.5	0.6	1.6	n.a.
Other children	Belgium	Regional Flanders	1 875	48.6	2.8	4.1	n.a.
(3 to < 10 years)	Bulgaria	NUTRICHILD	867	21.6	1.3	2.4	n.a.
19 surveys	Czech Republic	SISP04	778	99.0	4.6	15.4	n.a.
	Denmark	DANSDA 2005–08	2 085	58.5	2.2	2.3	n.a.
	Finland	DIPP 2001 2009	2 250	114.1	5.7	12.3	n.a.
	France	INCA2	3 315	75.6	3.3	6.7	n.a.
	Germany	EsKiMo	2 498	69.8	2.6	4.0	n.a.
		VELS	1 610	51.7	3.0	5.0	n.a.
	Greece	Regional Crete	2 508	37.8	1.7	1.4	n.a.
	Italy	INRAN SCAI 2005–06	579	99.0	4.3	8.1	n.a.
	Latvia	EFSA TEST	377	118.8	4.3	11.4	n.a.
	Netherlands	VCP kids	1 914	63.3	3.2	6.2	n.a.
		VCP Basis AVL2007–2010	894	104.9	3.7	7.6	n.a.
	Poland	IZZ FAO 2000	409	130.1	5.7	35.9	n.a.
	Romania	Dieta Pilot Children	205	126.0	3.8	6.8	n.a.
	Spain	enKid	312	105.0	4.4	14.1	n.a.
		NUT INK05	798	87.4	3.2	6.0	n.a.
	Sweden	NFA	5 875	54.0	2.0	1.8	n.a.
	United Kingdom	NDNS Rolling Programme Years 1–3	2 595	51.8	2.2	2.0	n.a.
Adolescents	Belgium	Diet National 2004	1 187	216.0	3.5	7.2	0.0
(10 to < 18 years)	Bulgaria	NSFIN	162	93.1	1.8	3.1	0.0
19 surveys	Cyprus	Childhealth	909	141.9	3.0	5.1	0.0
	Czech Republic	SISP04	596	131.5	2.9	4.2	0.0

Age class	Country	Survey	No of days	95th percentile caffeine intake [a] mg per day	mg/kg bw per day	% of days with an intake of > 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
	Denmark	DANSDA 2005–08	2 622	116.8	2.3	2.6	0.0
	Finland	NWSSP07–08	1 186	219.2	4.1	11.0	0.0
	France	INCA2	6 728	115.3	2.3	2.8	0.0
	Germany	National Nutrition Survey II	2 022	239.8	3.8	7.7	0.0
		EsKiMo	1 179	89.4	2.4	3.1	0.0
	Italy	INRAN SCAI 2005–06	741	156.3	2.7	4.3	0.0
	Latvia	EFSA TEST	949	177.7	3.5	8.0	0.0
	Netherlands	VCP Basis AVL2007–2010	2 284	235.6	4.3	11.8	0.0
	Poland	IZZ FAO 2000	666	170.8	3.9	11.0	0.0
	Romania	Dieta Pilot Children	567	89.0	1.8	1.9	0.0
	Spain	AESAN FIAB	226	122.8	2.3	2.2	0.0
		enKid	418	126.0	2.6	3.1	0.0
		NUT INK05	1 302	123.0	2.3	2.2	0.0
	Sweden	NFA	4 047	77.9	2.0	1.7	0.0
	United Kingdom	NDNS Rolling Programme Years 1–3	2 653	155.0	2.5	4.0	0.0
Adults (18 to < 65 years) 24 surveys	Austria	ASNS	2 123	356.0	5.4	n.a.	3.4 (4.1)
	Belgium	Diet National 2004	2 648	538.7	7.7	n.a.	11.0 (10.1)
	Bulgaria	NSFIN	691	155.1	2.4	n.a.	0.3 (0.3)
	Czech Republic	SISP04	3 332	298.0	4.2	n.a.	1.9 (1.9)
	Denmark	DANSDA 2005–08	12 127	809.3	10.8	n.a.	31.8 (29.6)
	Estonia	NDS 1997	1 866	311.5	4.6	n.a.	1.9 (2.7)
	Finland	FINDIET2012	2 590	538.5	7.0	n.a.	14.1 (11.9)
	France	INCA2	15 727	445.0	6.7	n.a.	6.6 (7.8)
	Germany	National Nutrition Survey II	20 838	561.7	7.7	n.a.	16.9 (13.4)
	Greece	Diet Lactation GR	350	114.9	1.8	n.a.	0.0
	Hungary	National Repr Surv	3 222	270.1	4.2	n.a.	1.3 (1.9)
	Ireland	NANS 2012	5 096	378.4	5.1	n.a.	4.5 (3.7)
	Italy	INRAN SCAI 2005–06	6 939	325.7	5.1	n.a.	3.2 (3.6)
	Latvia	EFSA TEST	2 655	338.2	4.8	n.a.	2.3 (2.2)
		FC Pregnant Women 2011	2 005	221.8	3.3	n.a.	0.0 [c]
	Netherlands	VCP Basis AVL2007– 2010	4 114	622.5	8.1	n.a.	19.0 (14.7)
	Poland	IZZ FAO 2000	2 527	347.3	5.5	n.a.	2.4 (4.0)
	Romania	Dieta Pilot Adults	8 770	122.4	1.8	n.a.	0.2 (0.2)
	Slovakia	SK MON 2008	2 761	305.0	4.4	n.a.	1.8 (1.6)
	Slovenia	CRP 2008	407	211.9	3.2	n.a.	1.0 (1.2)

Age class	Country	Survey	No of days	95th percentile caffeine intake (a) mg per day	mg/kg bw per day	% of days with an intake of > 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
	Spain	AESAN	828	155.7	2.3	n.a.	0.4 (0.5)
		AESAN FIAB	2 748	178.1	2.8	n.a.	1.5 (1.5)
	Sweden	Riksmaten 2010	5 680	535.1	7.2	n.a.	11.2 (9.6)
	United Kingdom	NDNS Rolling Programme Years 1–3	5 040	353.2	4.9	n.a.	3.5 (3.1)
Elderly	Belgium	Diet National 2004	1 045	511.8	6.9	n.a.	11.0 (10)
(65 to < 75 years)	Bulgaria	NSFIN	151	89.0	1.2	n.a.	0.0 (0.0)
15 surveys	Denmark	DANSDA 2005–08	1916	784.3	10.7	n.a.	35.0 (31.8)
	Finland	FINDIET2012	826	440.6	5.9	n.a.	6.9 (5.7)
	France	INCA2	1 824	335.5	4.7	n.a.	2.4 (2.6)
	Germany	National Nutrition Survey II	4 012	507.3	6.6	n.a.	12.8 (9.3)
	Hungary	National Repr Surv	618	201.1	2.7	n.a.	1.5 (0.5)
	Ireland	NANS 2012	596	385.2	5.5	n.a.	3.9 (4.5)
	Italy	INRAN SCAI 2005–06	870	338.3	4.6	n.a.	3.1 (2.4)
	Netherlands	VCP Basis AVL2007–2010	346	557.6	7.6	n.a.	18.8 (17.3)
		VCP-Elderly	578	481.3	6.2	n.a.	13.3 (8.7)
	Poland	IZZ FAO 2000	329	301.3	4.3	n.a.	0.9 (0.9)
	Romania	Dieta Pilot Adults	581	111.3	1.6	n.a.	0.0 (0.0)
	Sweden	Riksmaten 2010	1 167	479.9	6.4	n.a.	9.4 (7.5)
	United Kingdom	NDNS Rolling Programme Years 1–3	662	396.7	5.4	n.a.	5.0 (3.9)
Very elderly	Belgium	Diet National 2004	1 448	445.0	6.6	n.a.	8.1 (8.1)
(≥ 75 years)	Bulgaria	NSFIN	200	66.8	0.9	n.a.	0.0 (0.0)
13 surveys	Denmark	DANSDA 2005–08	84	801.0	13.1	n.a.	45.2 (46.2)
	France	INCA2	571	319.2	4.4	n.a.	2.6 (2.8)
	Germany	National Nutrition Survey II	980	422.8	5.7	n.a.	7.8 (4.9)
	Hungary	National Repr Surv	240	191.3	2.9	n.a.	1.3 (0.8)
	Ireland	NANS 2012	308	313.9	5.7	n.a.	2.9 (5.2)
	Italy	INRAN SCAI 2005–06	684	274.8	4.3	n.a.	1.9 (2.2)
	Netherlands	VCP-Elderly	900	472.6	6.3	n.a.	11.0 (7.9)
	Poland	IZZ FAO 2000	124	250.3	3.8	n.a.	0.0 (0.8)
	Romania	Dieta Pilot Adults	315	102.7	1.5	n.a.	0.0 (0.0)
	Sweden	Riksmaten 2010	288	465.5	6.4	n.a.	7.6 (5.6)
	United Kingdom	NDNS Rolling Programme	552	338.2	4.7	n.a.	1.8 (2.0)

(a): The 95th percentile estimates based on dietary surveys/age classes with fewer than 60 days of data may not be statistically robust (EFSA, 2011b) and consequently were not considered (–).
(b): n.a. = not applicable for the population group.
(c): % exceeding 200 mg/kg bw per day.

Appendix E. Food sources contributing to daily caffeine intake

Age class	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Coffee	Tea	Chocolate	Cola beverages	Energy Drinks [b]
Toddlers (12 to < 36 months)	Belgium	Regional Flanders [a]	12.7	0.0	29.6	57.7	0.0
	Bulgaria	NUTRICHILD [a]	0.0	49.2	49.9	0.9	0.0
	Denmark	IAT 2006–07	0.9	32.3	66.9	0.0	0.0
	Finland	DIPP 2001–2009	6.2	0.0	89.9	3.9	0.0
	Germany	VELS	0.3	13.0	84.5	2.3	0.0
	Italy	INRAN SCAI 2005–06 [a]	0.0	53.6	37.6	8.8	0.0
	Netherlands	VCP kids [a]	2.6	73.2	20.3	3.9	0.0
	Spain	enKid [a]	0.0	0.0	100.0	0.0	0.0
	United Kingdom	DNSIYC 2011	0.3	35.8	63.0	0.6	0.3
		NDNS Rolling Programme Years 1–3	0.1	76.4	17.5	6.0	0.0
	Median		0	34	56	3	0
	Range		(0–13)	(0–73)	(20–100)	(0–58)	(0)
Other children (3 to < 10 years)	Belgium	Regional Flanders [a]	19.8	7.5	20.4	52.1	0.2
	Bulgaria	NUTRICHILD [a]	0.0	6.9	77.6	15.5	0.0
	Czech Republic	SISP04 [a]	5.4	67.6	27.0	0.0	0.0
	Denmark	DANSDA 2005–08	2.7	14.9	42.2	40.2	0.0
	Finland	DIPP 2001–2009	3.2	0.7	89.3	6.8	0.0
	France	INCA2 [a]	6.6	7.8	68.5	17.1	0.0
	Germany	EsKiMo	2.1	32.2	55.6	9.6	0.6
		VELS	0.2	12.3	85.3	2.2	0.0
	Greece	Regional Crete [a]	1.8	3.7	85.1	9.3	0.0
	Italy	INRAN SCAI 2005–06 [a]	39.9	19.1	32.8	8.1	0.0
	Latvia	EFSA TEST [a]	15.0	64.2	18.8	2.0	0.0
	Netherlands	VCPBasis AVL2007–2010	2.5	55.7	21.3	19.2	1.3
		VCP kids [a]	2.4	64.9	18.3	14.4	0.0
	Spain	NUT INK05 [a]	1.8	0.2	90.9	7.1	0.0
		enKid [a]	2.1	0.0	97.9	0.0	0.0
	Sweden	NFA [a]	2.3	12.6	39.0	45.4	0.7
	United Kingdom	NDNS Rolling Programme Years1–3	2.3	46.9	21.1	27.0	2.7
	Median		2	13	42	10	0
	Range		(0–40)	(0–68)	(18–98)	(0–52)	(0–3)
Adolescents (10 to < 18 years)	Belgium	Diet National 2004 [a]	24.2	16.9	14.8	38.8	5.3
	Cyprus	Childhealth [a]	53.2	9.2	37.6	0.0	0.0
	Czech Republic	SISP04 [a]	14.4	65.3	20.3	0.0	0.0
	Denmark	DANSDA 2005–08	17.6	25.1	24.4	32.9	0.0
	Finland	NWSSP07–08	19.7	2.1	61.3	13.3	3.6
	France	INCA2 [a]	22.8	15.6	39.4	22.2	0.0
	Germany	EsKiMo	2.6	34.0	42.7	19.7	0.9
		National Nutrition Survey II [a]	33.3	33.1	16.3	17.3	0.0
	Italy	INRAN SCAI 2005–06 [a]	42.1	22.6	20.2	14.4	0.7
	Latvia	EFSA TEST [a]	32.4	53.4	11.5	2.3	0.3

Age class	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Coffee	Tea	Chocolate	Cola beverages	Energy Drinks [b]
	Netherlands	VCPBasis AVL2007–2010	13.9	42.8	12.3	22.9	8.1
	Spain	AESAN FIAB [a]	41.1	1.0	41.9	15.9	0.0
		NUT INK05 [a]	17.4	1.5	64.5	16.5	0.0
		enKid [a]	8.2	0.0	91.8	0.0	0.0
	Sweden	NFA [a]	2.7	20.7	33.0	42.1	1.6
	United Kingdom	NDNS Rolling Programme Years 1–3	10.2	39.2	7.5	32.7	10.5
	Median		19	22	29	17	0
	Range		(3–53)	(1–65)	(8–92)	(0–42)	(0–13)
Adults (18 to ≤ 65 years)	Belgium	Diet National 2004 [a]	81.3	5.8	2.9	9.4	0.7
	Czech Republic	SISP04 [a]	71.5	25.9	2.6	0.0	0.0
	Denmark	DANSDA 2005–08	87.9	8.1	2.0	2.0	0.0
	Finland	FINDIET2012	93.8	2.5	2.0	1.0	0.6
	France	INCA2 [a]	80.5	13.3	3.2	3.0	0.0
	Germany	National Nutrition Survey II [a]	84.1	10.9	1.8	3.1	0.0
	Hungary	National Repr Surv [a]	57.0	29.8	8.5	4.7	0.0
	Ireland	NANS 2012	32.5	59.4	1.3	3.9	3.0
	Italy	INRAN SCAI 2005–06 [a]	91.4	5.0	2.0	1.5	0.1
	Latvia	EFSA TEST [a]	75.0	22.1	2.2	0.6	0.1
	Netherlands	VCPBasis AVL2007–2010	70.1	20.7	1.7	6.1	1.3
	Romania	Dieta Pilot Adults	82.6	2.1	12.0	3.0	0.3
	Spain	AESAN [a]	40.5	20.7	16.5	18.1	4.2
		AESAN FIAB [a]	76.2	0.7	14.1	8.7	0.3
	Sweden	Riksmaten 2010	85.0	11.3	0.9	2.5	0.3
	United Kingdom	NDNS Rolling Programme Years 1–3	34.2	56.5	1.4	6.7	1.2
	Median		78	12	2	3	0
	Range		(33–94)	(1–59)	(1–17)	(0–18)	(0–4)
	Greece	Diet Lactation Gr	69	4.2	20	7.0	0.0
	Latvia	FC Pregnant Women 2011	42	52	5.9	0.4	0.0
Elderly (65 to < 75 years)	Belgium	Diet National 2004 [a]	92.9	4.2	1.6	1.1	0.2
	Denmark	DANSDA 2005–08	91.3	7.0	1.4	0.3	0.0
	Finland	FINDIET2012	97.2	1.7	1.0	0.1	0.0
	France	INCA2 [a]	78.9	19.1	1.5	0.5	0.0
	Germany	National Nutrition Survey II [a]	86.5	12.1	0.8	0.5	0.0
	Hungary	National Repr Surv [a]	58.5	35.2	5.3	1.0	0.0
	Ireland	NANS 2012	23.5	74.1	1.6	0.8	0.0
	Italy	INRAN SCAI 2005–06 [a]	92.3	6.6	0.8	0.2	0.0
	Netherlands	VCP-Elderly	73.1	25.1	1.1	0.7	0.0
		VCPBasis AVL2007–2010	79.5	18.6	0.6	1.2	0.0
	Romania	Dieta Pilot Adults	83.6	6.3	10.0	0.0	0.0
	Sweden	Riksmaten 2010	88.9	10.1	0.6	0.4	0.0
	United Kingdom	NDNS Rolling Programme Years 1–3	32.6	64.9	1.3	0.8	0.4

Age class	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Coffee	Tea	Chocolate	Cola beverages	Energy Drinks [b]
	Median		84	12	1	1	0
	Range		(24–97)	(2–74)	(0–10)	(0–1)	(0)
Very elderly (≥ 75 years)	Belgium	Diet National 2004 [a]	93.1	4.9	1.1	0.9	0.0
	Denmark	DANSDA 2005–08	91.8	5.9	2.2	0.1	0.0
	France	INCA2 [a]	81.3	11.0	7.4	0.4	0.0
	Germany	National Nutrition Survey II [a]	84.8	13.8	1.2	0.1	0.0
	Hungary	National Repr Surv [a]	41.9	50.6	7.3	0.3	0.0
	Ireland	NANS 2012	20.3	78.5	1.2	0.0	0.0
	Italy	INRAN SCAI 2005–06 [a]	88.3	9.0	1.5	0.2	1.0
	Netherlands	VCP-Elderly	66.4	31.6	1.5	0.5	0.1
	Romania	Dieta Pilot Adults	77.0	3.9	17.9	1.2	0.0
	Sweden	Riksmaten 2010	89.0	10.2	0.8	0.0	0.0
	United Kingdom	NDNS Rolling Programme Years 1–3	27.9	68.1	3.3	0.5	0.2
	Median		81	11	2	0	0
	Range		(28–93)	(4–79)	(1–18)	(0–1)	(0–1)

(a): Dietary surveys included in the 2010 release of the EFSA Comprehensive European Food Consumption Database (FoodEx classification).

(b): For dietary surveys included in the 2010 release of the EFSA Comprehensive European Food Consumption Database (FoodEx classification), products coded as "carbohydrate-rich energy food products for sports people" or "carbohydrate–electrolyte solutions for sports people" at the third level of FoodEx, within the first-level category of "Products for special nutritional use", were used to calculate caffeine consumption from "energy drinks" and their contribution to total caffeine intake.

Appendix F. Human intervention studies on the vascular effects of a single dose and of repeated doses of caffeine consumed within a day

Study	Design	Subjects, habitual daily consumption	Run-in period [a]	n (I/C) [b]	Intervention	Caffeine (mg)	Control	Outcomes			
								Arterial stiffness	Endothelial function	BP	Other
Single doses of caffeine											
Vlachopoulos et al. (2003)	rdb-X	Healthy, > 100 mg caffeine	12 h	20	Caffeine	250	Placebo	PWV, AI	–	Radial, aortic and pulse BP	–
Hartley et al. (2004): Women	rdb-P	Healthy, 50–700 mg caffeine	14 h	42 (21/21)	Caffeine	3.3 mg/kg bw	Placebo	Peripheral resistance, arterial compliance	–	Brachial BP, MABP, pulse pressure	Stroke volume, cardiac output
Hartley et al. (2004): Men	rdb-P			35 (16/19)							
Swampillai et al. (2006)	nr-P	Healthy, > 100 mg caffeine	12 h	27 (17/10)	Caffeine	100	Water	FCW, FEW, WR, WS	–	Brachial BP	–
Umemura et al. (2006)	rdb-P	Healthy, non-habitual caffeine consumers	24 h	20 (10/10)	Caffeine	300	Placebo	–	FBF	Brachial BP	–
Astorino et al. (2007)	rdb-X	Resistance trained, 0–600 mg caffeine per day	48 h	22	Caffeine	6 mg/kg bw	Placebo	–	–	Brachial BP, MABP, RPP	–
Arciero and Ormsbee (2009): pre-menopausal	rdb-X	Healthy, < 400 mg caffeine	48 h	10	Caffeine	5 mg/kg FFM 208–270	Placebo (lactose)	–	–	Brachial BP	–
Arciero and Ormsbee (2009): post-menopausal				10							
Farag et al. (2010)	rdb-X	Healthy, 3–4 cups coffee	6 d [c]	165	Caffeine	250	Placebo	–	–	Brachial BP	–
Mahmud and Feely (2001)	rdb-X	Healthy, NR	12 h	7	Coffee	150	DC	PWV, AI	–	Brachial BP	–

Study	Design	Subjects, habitual daily consumption	Run-in period [a]	n (I/C) [b]	Intervention	Caffeine (mg)	Control	Outcomes			
								Arterial stiffness	Endothelial function	BP	Other
Papamichael et al. (2005)	rsb-X	Healthy, 1–2 cups coffee	12–24 h	17	Coffee	80	DC	–	FMD (brachial artery)	Brachial BP	–
Buscemi et al. (2010)	rdb-X	Healthy, ≤ 2 cups coffee	24 h	20	Coffee	130	Decaffeinated coffee	–	FMD (brachial artery)	Brachial BP	–
Buscemi et al. (2011)	rdb-X	Healthy, ≤ 2 cups coffee	24 h	40	Coffee	130	Decaffeinated coffee	–	–	Brachial BP	QT, QTc
Hodgson et al. (1999)	rsb-X	Healthy, NR	24 h	20	Caffeine Black tea Green tea	180	Water	–	–	Brachial BP	-
Vlachopoulos et al. (2006) black tea	rsb-X	Healthy, NR	12 h	16	Black tea Caffeine	175 175	Water	PWV, WR (AI, AP)	–	Radial and aortic BP, pulse pressure	–
Vlachopoulos et al. (2006) green tea	rsb-X	Healthy, NR	12 h	13	Green tea Caffeine	125 125	Water	PWV, WR (AI, AP)	–	Radial and aortic BP, pulse pressure	–
Repeated doses of caffeine consumed within a day											
Lane et al. (2002)	rdb-X	Healthy, 2–7 cups coffee	12 h	47	Caffeine	250 + 250 4 h apart	Placebo	–	–	Day ambulatory BP	–
Farag et al. (2005a, b)	rdb-X	Healthy, 50–700 mg caffeine	5 d [d]	85	Caffeine	250 × 3, 4 h apart	Placebo (lactose)	–	–	Brachial BP	–

AI = augmentation index; AP = augmented pressure; BP = blood pressure; DC = decaffeinated coffee; FCW = forward compression wave; FEW = forward expansion wave; FFM = fat-free mass; HR = heart rate; MABP = mean arterial blood pressure; nr-P = non-randomised, parallel; NR = not reported; PWV = pulse wave velocity; QT = QT interval; QTc = corrected QT interval; rdb-X = randomised, double-blind, cross-over; rdb-P = randomised, double-blind, parallel; rsb-X = randomised, single-blind, cross-over; RPP = rate–pressure product; WR = wave reflections; WS = wave speed.

(a): Refers to the time of abstinence from caffeine before testing, unless otherwise noted.

(b): Number of participants (intervention/control). Only one number is given for cross-over designs, in which subjects act as their own controls.

(c): Subjects consumed 80 mg of caffeine three times per day for six days before testing.

(d): Subjects consumed 0, 300 or 600 mg of caffeine (in three divided daily doses) per day for five days before testing.

Appendix G. Randomised, placebo-controlled human intervention studies on the effect of single doses of synephrine on blood pressure

Study	Design [a]	Run-in period [b]	Duration	n	Synephrine (mg)	Caffeine (mg)	Δ SBP (mmHg)	Δ DBP (mmHg)
Penzak et al. (2001)	rol-X	8 h [c]	13 h	12	13.5	–	NS	NS
Min et al. (2005)	rdb-X	12 h	8 h	18	27	–	NS	NS
Haller et al. (2005a)	rdb-X	24 h	6 h	10	46.9	–	NS	NS
Haller et al. (2005a)	rdb-X	24 h	6 h	10	5.5 + 5.7 [d]	239.2	+9.6 ± 6.2*	+9.1 ± 7.8*
Bui et al. (2006)	rdb-X	10 h	6 h	15	54	–	+7.3 ± 4.6*	+2.6 ± 3.8*
Sale et al. (2006)	rdb-X	48 h	7 h	10	12	150	NS	NS
Haller et al. (2008)	rdb-X	24 h	2 h	10	21	304	NS	+8.7 ± 3.8*
Seifert et al. (2011)	rdb-X	24 h [e]	24 h	23	13	176	NS	NS
Stohs et al. (2011)	rdb-P	8–10 h	2 h	10 [f]	50	–	NS	NS

NR= not reported; NS = non-significant; rdb-X = randomised, double-blind, cross-over; rdb-P = randomised, double-blind, parallel; rol-X = randomised, open-label, cross-over.
(a): All studies had a double-blind cross-over design and used placebo capsules as control, except the study by Penzak et al. (2001), which was an open-label study and used orange juice as intervention and water as placebo, and that of Soths et al. (2011), which was a double-blind parallel study.
(b): Refers to the time of abstinence from caffeine before testing, unless otherwise noted
(c): Subjects consumed 13.5 mg of synephrine eight hours before testing.
(d): Doses refer to synephrine + octopamine.
(e): Subjects consumed three capsules (one capsule per meal) containing 13 mg synephrine and 176 mg caffeine (39 mg synephrine and 528 mg caffeine) the day before testing.
(f): Refers to the number of subjects per arm.
*Statistically significant.

Appendix H. Human intervention studies on the longer-term (≥ 7 days) effects of caffeine or coffee on blood pressure

	Design	Sex	n (I/C) [a]	I, C	Coffee (cups per day)	Coffee (ml per day)	Caffeine (mg per day)	Duration [b] (weeks)
Studies with caffeine								
Arciero et al. (1998) [c]	rdb-X	M	10	Caffeine, placebo	–	–	295	4
Bak and Grobbee (1991) [a]	rdb-P	M/F	62 (32/30)	Caffeine + D, placebo	–	–	375	7
James (1994) [c]	rdb-X	M/F	36	Caffeine, placebo	–	–	336–410 [d]	1
Robertson et al. (1984) [a]	rdb-P	M/F	17 (9/8)	Caffeine, placebo	–	–	750	12
Watson et al. (2000) [c]	rdb-X	M/F	34	Caffeine, placebo	–	–	400	12
Studies with coffee								
Agudelo et al. (2008) [e]	rol-P	M/F	116 (29/29/ 29/30)	F, N	2, 4, 6	300, 600, 900 [f]	180, 360, 540 [g]	6
Ammon et al. (1983) [h]	rdb-X	M	8	In, D	8	1200 [f]	720 [g]	4
Bak and Grobbee (1990) [c] [e] [h]	rol-P	M/F	111 (77/34)	B, F or N	4–6	700	469	9
Burr et al. (1989) [c] [e] [h]	rol-X	M/F	54	In or D, N	≥ 5	1235	741	4
van Dusseldorp et al. (1989) [c] [h]	rdb-X	M/F	45	F, D	5	750 [f]	435 [g]	6
van Dusseldorp et al. (1991) [c] [e] [h]	rol-P	M/F	64 (43/21)	B (+F), N	6	900	(774–798)	11
Eggertsen et al. (1993) [c] [h]	rdb-X	M/F	23	In, D	3–4	525 [f]	263 [g]	2
Funatsu et al. (2005) [e]	rol-X	M	42	F, N	3.4	510 [f]	306 [g]	4
Hofer and Battig (1994) [c]	rol-P	M/F	120 (80,/40)	In, D	–	998	335	1

	Design	Sex	n (I/C) [a]	I, C	Coffee (cups per day)	Coffee (ml per day)	Caffeine (mg per day)	Duration [b] (weeks)
MacDonald et al. (1991) [c] [e] [h]	rol-X	M/F	50	In or D, N	> 3	450 [f]	225	2
Rakic et al. (1999) [c] [e]	rol-P	M/F	27 (14/13)	In, N	5	750 [f]	300	2
Rosmarin et al. (1990) [c] [e] [h]	rol-X	M	21	F, N	3.6	540 [f]	270 [g]	8
Strandhagen and Thelle (2003) [e]	rol-X [i]	M/F	121	F, N	4	600 [f]	360 [g]	4
Superko et al. (1991) [c] [e]	rol-P	M	181 (123/58)	F or D, N	4.5	1 067	615	8
Superko et al. (1994) [c] [h]	rol-P	M	150 (100/50)	F or D, N	4.5	1 067	615	8

B = boiled coffee; C = control; D = decaffeinated coffee; F = females; I = intervention; In = instant coffee; M = males; N = no coffee; rdb-P = randomised, double-blind, parallel; rdb-X = randomised, double-blind, cross-over; rol-P= randomised, open-label, parallel; rol-X = randomised, open-label, cross-over

(a): Number of participants (intervention/control). Only one number is given for cross-over designs, in which subjects act as their own controls.
(b): Duration of the intervention.
(c): Included in Noordzij et al. (2005).
(d): Estimated from caffeine dose given in mg per day (about 5.25 mg/kg bw) assuming a mean body weight of 78 kg for males and of 64 kg for females.
(e): Included in Steffen et al. (2012).
(f): Estimated assuming that one cup of coffee corresponds to 150 ml.
(g): Estimated assuming that one cup of coffee corresponds to 90 mg of caffeine.
(h): Included in Jee et al. (1999).
(i): Study not randomised. All subjects received no coffee/coffee in the same sequence.

Appendix I. Meta-analyses of prospective cohort studies on the relationship between habitual caffeine consumption and cardiovascular disease risk

				Meta-analyses									
				Ding et al. (2014)	Cheng et al. (2014)	Caldeira et al. (2013) [(a)]	Motofsky et al. (2012)	Kim et al. (2012)	Larsson and Orsini (2011)	Steffen et al. (2012)	Zang et al. (2011)	Wu et al. (2009)	Sofi et al. (2007)
Outcomes				**CVD, CHD, stroke**	**AF**	**AF**	**HF**	**Stroke**	**Stroke**	**HT**	**HT**	**CHD**	**CHD**
Individual studies	**C**	**Sex**	**Outcomes**										
Wilhelmsen et al. (1977)*	SE	M	nf-MI	X	–	–	–	–	–	–	–	X	–
Murray et al. (1981)	US	M	f-IHD	–	–	–	–	–	–	–	–	X	–
Jacobsen et al. (1986)	NO	M/F	CHD	–	–	–	–	–	–	–	–	X	–
LaCroix et al. (1986)	US	M/F	CHD	–	–	–	–	–	–	–	–	–	X
LeGrady et al. (1987) *Chicago Western Electric Company Study*	US	M	f-CHD f-Stroke	X	–	–	–	–	–	–	–	X	–
Yano et al. (1987)	US	M	f-CHD nf-MI	–	–	–	–	–	–	–	–	X	–
Martin et al. (1988) *Hypertension Detection and Follow-up Program*	US	M/F	f-CHD f-Stroke	X	–	–	–	–	–	–	–	X	–
Wilson et al. (1989)	US	M/F	CVD	–	–	–	–	–	–	–	–	X	–
Grobbee et al. (1990) *Health Professionals Follow-up Study*	US	M	CVD CHD MI Stroke	X	–	–	–	–	X	–	–	–	–
Klatsky et al. (1990)**	US	M/F	nf-CHD nf-MI	X	–	–	–	–	–	–	–	X	X
Tverdal et al. (1990)	NO	M/F	f-CHD	X	–	–	–	–	–	–	–	–	–
Rosengren and Wilhelmsen (1991) *Primary Prevention Study*	SE	M	nf-MI f-CHD	X	–	–	–	–	–	–	–	X	–
Lindsted et al. (1992)	US	M	f-CVD f-IHD	X	–	–	–	–	–	–	–	X	X
Klatsky et al. (1993)	US	M/F	f-CHD	–	–	–	–	–	–	–	–	–	X

				Meta-analyses									
				Ding et al. (2014)	Cheng et al. (2014)	Caldeira et al. (2013) [(a)]	Motofsky et al. (2012)	Kim et al. (2012)	Larsson and Orsini (2011)	Steffen et al. (2012)	Zang et al. (2011)	Wu et al. (2009)	Sofi et al. (2007)
Outcomes				**CVD, CHD, stroke**	**AF**	**AF**	**HF**	**Stroke**	**Stroke**	**HT**	**HT**	**CHD**	**CHD**
Individual studies	**C**	**Sex**	**Outcomes**										
Klag et al. (1994)	US	M	CHD, MI	X	–	–	–	–	–	–	–	X	X
Gyntelberg et al. (1995) *Copenhagen Male Study*	DK	M	nf-IHD	X	–	–	–	–	–	–	–	X	X
Stensvold and Tverdal (1995)	NO	M/F	nf-MI	–	–	–	–	–	–	–	–	X	–
Hart and Smith (1997)	UK	M	f-CHD	X	–	–	–	–	–	–	–	X	X
Hakim et al. (1998) *Honolulu Heart Program*	US	M	Stroke subtypes	X	–	–	–	–	–	–	–	–	–
Woodward and Tunstall-Pedoe (1999), *Scottish Heart Health Study*	UK	M/F	CHD	X	–	–	–	–	–	–	–	X	–
Kleemola et al. (2000)	FI	M/F	f-CHD nf-MI	X	–	–	–	–	–	–	–	X	–
Wilhelmsen et al. (2001a, b), *Multifactor Primary Prevention Study*	SE	M	HF, AF	–	X	X	X	–	–	–	–	–	–
Klag et al. (2002), *Johns Hopkins Precursors Study*	US	M	HT	–	–	–	–	–	–	X	X	–	–
Jazbec et al. (2003)	HR	M/F	f-CVD	X	–	–	–	–	–	–	–	–	–
Happonen et al. (2004) *Kuopio Ischaemic Heart Disease Risk Factor Study*	FI	M	f-CHD nf-MI	X	–	–	–	–	–	–	–	X	–
Frost and Vestergaard (2005), *Danish Diet, Cancer, and Health Study*	DK	M/F	AF	–	X	X	–	–	–	–	–	–	–
Winkelmayer et al. (2005) *Nurses' Health Study I, II*	US	F	HT	–	–	–	–	–	–	X	X	–	–

				Meta-analyses									
				Ding et al. (2014)	Cheng et al. (2014)	Caldeira et al. (2013) [(a)]	Motofsky et al. (2012)	Kim et al. (2012)	Larsson and Orsini (2011)	Steffen et al. (2012)	Zang et al. (2011)	Wu et al. (2009)	Sofi et al. (2007)
Outcomes				**CVD, CHD, stroke**	**AF**	**AF**	**HF**	**Stroke**	**Stroke**	**HT**	**HT**	**CHD**	**CHD**
Individual studies	**C**	**Sex**	**Outcomes**										
Bidel et al. (2006)	FI	M/F	f-CVD f-CHD f-Stroke	X	–	–	–	–	X	–	–	–	–
Andersen et al. (2006) *Iowa Women's Health Study*	US	F	f-CVD	X	–	–	–	–	–	–	–	X	X
Lopez-Garcia et al. (2006) *Health Professionals Follow-up Study* *Nurses' Health Study*	US	M/F	CHD f-CHD nf-MI	X	–	–	–	–	–	–	–	X	X
Greenberg et al. (2007) *NHANES I-NHEFS*	US	M/F	f-CVD f-CHD f-Stroke	X	–	–	–	–	–	–	–	–	–
Hu et al. (2007)	FI	M/F	HT	–	–	–	–	–	–	X	X	–	–
Palatini et al. (2007) *HARVEST study*	IT	M/F	HT	–	–	–	–	–	–	X	X	–	–
Rosner et al. (2007) *Swedish Mammography Cohort*	SE	F	MI	–	–	–	–	–	–	–	–	X	–
Silletta et al. (2007) *GISSI-Prevention Trial*	IT	M/F	CV death nf-MI nf-stroke	X	–	–	–	X	X	–	–	–	–
Uiterwaal et al. (2007) *Doetinchem Cohort Study*	DK	M/F	HT	–	–	–	–	–	–	X	X	–	–
Greenberg et al. (2008) *Framingham Heart Study*	US	M/F	CVD, CHD Stroke	X	–	–	–	X	–	–	–	–	–
Happonen et al. (2008)	FI	M/F	f-CVD	X	–	–	–	–	–	–	–	–	–

				Meta-analyses									
				Ding et al. (2014)	Cheng et al. (2014)	Caldeira et al. (2013) [(a)]	Motofsky et al. (2012)	Kim et al. (2012)	Larsson and Orsini (2011)	Steffen et al. (2012)	Zang et al. (2011)	Wu et al. (2009)	Sofi et al. (2007)
Outcomes				**CVD, CHD, stroke**	**AF**	**AF**	**HF**	**Stroke**	**Stroke**	**HT**	**HT**	**CHD**	**CHD**
Individual studies	**C**	**Sex**	**Outcomes**										
Larsson et al. (2008) *Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study*	FI	M	Stroke	X	–	–	–	X	X	–	–	–	–
Ahmed et al. (2009) *Cohort of Swedish Men*	SE	M	HF	X	–	–	X	–		–	–	–	–
Lopez-Garcia et al. (2009) *Nurses' Health Study*	US	F	Stroke	X	–	–	–	X	X	–	–	–	–
Mukamal et al. (2009) *Stockholm Heart Epidemiology Program*	SE	M/F	HF, AF Stroke f-MI	X	X	X	X	X	X	–	–	–	–
Zhang et al. (2009, a, b)	US	M/F	CVD, CHD f-CHD nf-MI Stroke		–	–	–	X	–	–	–	–	–
Conen et al. (2010) *Women's Health Study*	US	F	AF		X	X	–	–	–	–	–	–	–
de Koning Gans et al. (2010), *EPIC-NL*	NL	M/F	CHD Stroke	X	–	–	–	X	X	–	–	–	–
Leurs et al. (2010)*** *The Netherlands Cohort Study*	NL	M/F	f-CHD f-Stroke	X	–	–	–	–	X	–	–	–	–
Shen et al. (2011) *Framingham Heart Study*	US	M/F	AF	–	X	X	–	–	–	–	–	–	–
Sugiyama et al. (2010)	JP	M/F	f-CVD, f-CHD f-Stroke	X	–	–	–	–	X	–	–	–	–
Klatsky et al. (2011)	US	M/F	AF, other arrhythmias	–	X	X	–	–	–	–	–	–	–

				Meta-analyses									
				Ding et al. (2014)	Cheng et al. (2014)	Caldeira et al. (2013) [(a)]	Motofsky et al. (2012)	Kim et al. (2012)	Larsson and Orsini (2011)	Steffen et al. (2012)	Zang et al. (2011)	Wu et al. (2009)	Sofi et al. (2007)
Outcomes				**CVD, CHD, stroke**	**AF**	**AF**	**HF**	**Stroke**	**Stroke**	**HT**	**HT**	**CHD**	**CHD**
Individual studies	**C**	**Sex**	**Outcomes**										
Larsson et al. (2011), Levitan et al. (2011) *Swedish Mammography Cohort*	SE	F	HF Stroke	X	–	–	X	X	X	–	–	–	–
Mineharu et al. (2011)	JP	M/F	f-CHD f-Stroke	X	–	–	–	–	X	–	–	–	–
Wang et al. (2011) *FINRISK study*	FI	M/F	HF	–	–	–	X	–	–	–	–	–	–
Freedman et al. (2012), *National Institutes of Health–AARP Diet and Health Study*	US	M/F	CHD Stroke	X	–	–	–	–	–	–	–	–	–
Floegel et al. (2012) *EPIC-Germany*	DE	M/F	CVD, MI Stroke	X	–	–	–	–	–	–	–	–	–
Rautiainen et al. (2012), *Swedish Mammography Cohort*	SE	F	MI	X	–	–	–	–	–	–	–	–	–
Kokubo et al. (2013)	JP	M/F	CVD, CHD Stroke	X	–	–	–	–	–	–	–	–	–

AF = atrial fibrillation; CHD = coronary heart disease; CVD = cardiovascular disease; CSD = Caffeinated soft drinks; EPIC = European Prospective Investigation into Cancer and Nutrition; f- = fatal; F = females; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; HF = heart failure; HT = hypertension; M = males; MI = myocardial infarction; nf- = non-fatal; NHANES I- NHEFS = National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study; SHEEP = Stockholm Heart Epidemiology Program.
*Prospective cohort and case–control study; **nested case–control study; ***prospective case–control study.
(a): Also includes a case–control study (Mattioli et al., 2005).

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
AF	atrial fibrillation
AHR	aryl-hydrocarbon receptor
ANS	EFSA Panel on Food Additives and Nutrient Sources Added to Food
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
BAC	blood alcohol concentration
BfR	Federal Institute for Risk Assessment
BP	blood pressure
bw	body weight
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
COT	UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
CVD	cardiovascular disease
CNS	central nervous system
CVS	cardiovascular system
CYP	cytochrome
DBP	diastolic blood pressure
FDA	US Food and Drug Administration
FFQ	food frequency questionnaire
FGR	fetal growth retardation
FMD	flow-mediated dilation
FSANZ	Food Standards Australia and New Zealand
HR	heart rate
IQR	interquartile range
LOAEL	lowest observed adverse effect level

MABP	mean arterial blood pressure
MBF	myocardial blood flow
MFR	myocardial blood flow reserve
MI	myocardial infarction
MPI	myocardial perfusion imaging
MS	Member State
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NNT	Nordic Working Group on Food Toxicology and Risk Evaluation
OR	odds ratio
PET	positron emission tomography
PTCA	percutaneous transluminal coronary angioplasty
PWV	pulse-wave velocity
RASFF	Rapid Alert System for Food and Feed
RCT	randomised controlled trial
RPE	ratings of perceived exertion
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SCF	Scientific Committee on Food
SGA	small for gestational age
SHC	Belgium's Superior Health Council
SNP	single nucleotide polymorphism
SPECT	single-photon emission computed tomography
UL	upper tolerable level of intake