1 **DRAFT SCIENTIFIC OPINION**

2 # Scientific Opinion on the safety of caffeine[1]

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

4 European Food Safety Authority (EFSA), Parma, Italy

5 ## ABSTRACT

6 Following a request from the European Commission, the EFSA Panel on Dietetic products, Nutrition and Allergies
7 (NDA) was asked to deliver a scientific opinion on the safety of caffeine. Advice should be provided on a daily
8 intake of caffeine, from all sources, that does not give rise to concerns about harmful effects to health for the
9 general population and for specific subgroups of the population. Possible interactions between caffeine and other
10 constituents of so-called "energy drinks", alcohol, synephrine and physical exercise should also be addressed.
11 Single doses of caffeine up to 200 mg, corresponding to about 3 mg/kg bw for a 70-kg adult are unlikely to induce
12 clinically relevant changes in blood pressure, myocardial blood flow, hydration status or body temperature, to
13 reduce perceived extertion/effort during exercise or to mask the subjective perception of alcohol intoxication.
14 Daily caffeine intakes from all sources up to 400 mg per day do not raise safety concerns for adults in the general
15 population, except pregnant women. Other common constituents of "energy drinks" (i.e. taurine, D-glucurono-γ-
16 lactone) or alcohol are unlikely to adversely interact with caffeine. The short- and long-term effects of co-
17 consumption of caffeine and synephrine on the cardiovascular system have not been adequately investigated in
18 humans. Daily caffeine intakes from all sources up to 200 mg per day by pregnant women do not raise safety
19 concerns for the fetus. For children and adolescents, the information available is insufficient to base a safe level of
20 caffeine intake. The Panel considers that caffeine intakes of no concern derived for acute consumption in adults
21 (3 mg/kg bw per day) may serve as a basis to derive daily caffeine intakes of no concern for children and
22 adolescents.

24 **KEY WORDS**

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

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SUMMARY

Following a request from the European Commission, the 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 the so-called "energy drinks", alcohol, synephrine and physical exercise should also be addressed.

Caffeine (1,3,7-trimethylxanthine) is a stable alkaloid and one of several related methylxanthines. It is found in various plants such as coffee and cocoa beans, tea leaves, guarana berries and the kola nut, and thus has a long history of human consumption. It is contained in ingredients added to a variety of foods, e.g. baked goods, ice creams, soft candy, cola-type beverages. Caffeine is also an ingredient of "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.

The EFSA Comprehensive European Food Consumption Database was used to calculate caffeine intake from all sources. 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" on a "single session", either alone or in combination with physical exercise.

Owing to the abundance of scientific literature available, previous risk assessments on the safety of caffeine were reviewed to identify the major health concerns raised in relation to caffeine consumption and the specific population subgroups which were relevant for the assessment.

Concerns have been raised in relation to caffeine consumption in the following circumstances and age groups:

i) caffeine consumption during pregnancy and lactation, and adverse health effects in the fetus,

ii) acute and long-term effects of caffeine consumption on the central nervous system (e.g. sleep, anxiety, behavioural changes) in adults, adolescents and children

iii) long-term adverse effects of caffeine consumption on the cardiovascular system in adults

iv) acute effects of caffeine consumption in "energy drinks" and risk of adverse health effects in adolescents and adults involving the cardiovascular and central nervous systems, particularly when consumed within short periods of time, at high doses, and in combination with alcohol and/or physical exercise

v) acute effects of caffeine in combination with synephrine on the cardiovascular system.

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 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 nevous 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 health outcomes for the fetus (e.g. pre-term delivery, fetal growth retardation or small for gestational age, miscarriage or spontaneous abortion, stillbirth). In adults, the adverse effects of habitual caffeine consumption, either alone or in combination with other constituents of "energy drinks" and with synephrine, were evaluated in relation to cardiovascular outcomes. The scientific publications identified almost exclusively reported no relationship or an inverse relationship between 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 due to 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 raise safety concerns for specific groups of the general population:

Adults

Single doses of caffeine up to 200 mg (about 3 mg/kg bw) from all sources do not raise safety concerns for the general adult population, even if consumed less than two hours prior to intense physical exercise under normal environmental conditions. No studies are available in pregnant women or middle age/elderly subjects undertaking intense physical exercise. Single doses of 100 mg (about 1.5 mg/kg bw) of caffeine may increase sleep latency and reduce sleep duration in some adult individuals, particularly when consumed close to bedtime.

Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg bw) do not raise safety concerns for adults in the general population, except pregnant women (see below).

Other common constituents of "energy drinks" (i.e. taurine, D-glucurono-γ-lactone) or alcohol are unlikely to adversely interact with caffeine. The short- and long-term effects of co-consumption of caffeine and synephrine on the cardiovascular system have not been adequately investigated in humans.

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

In seven out of 13 countries, the 95th percentile of daily caffeine intake from all sources exceeded 400 mg. The estimated proportion of the adult population exceeding daily intakes of 400 mg ranged from 5.8 % to almost one third (32.9 %).

Pregnant women

Caffeine intakes from all sources up to 200 mg per day by pregnant women in the general population do not raise safety concerns for the fetus. This is based on prospective cohort studies where the contribution of "energy drinks" to total caffeine intakes was low (about 2 %).

Data on daily caffeine intake in this population subgroup are scarce.

Lactating women

Single doses of caffeine up to 200 mg and caffeine doses of 400 mg per day (about to 5.7 mg/kg per day) consumed by lactating women in the general population do not raise safety concerns for the breastfed infant.

Data on daily caffeine intake in this population subgroup are scarce.

Children and adolescents

Owing to the limited information available for this population subgroup, caffeine intakes of no concern derived for acute consumption in adults (3 mg/kg bw per day) may serve as a basis to derive daily caffeine intakes of no concern for children and adolescents. As in adults, caffeine doses of about 1.5

mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents, particularly when consumed close to bedtime.

About 8 % of adolescents (10 to < 18 years) may consume more than 200 mg of caffeine from "energy drinks" on a single session in connexion with physical exercise. This information is not available for other sources of caffeine. In five out of 13 countries, the 95th percentile of caffeine intake from all sources exceeded 3 mg/kg bw per day. The percentage of adolescents exceeding that amount ranged from 5.2 to 10.0 %.

In children (3 to < 10 years), the 95th percentile of caffeine intake from all sources on a single day exceeded 3 mg/kg bw in nine out of 16 countries (6.2 % to 15.4 % of survey days). The proportion of children with daily caffeine intakes from all sources beyond 3 mg/kg bw ranged from 6.0 % to 12.6 % in the six out of 14 countries where the 95th percentile exceeded 3 mg/kg bw.

For toddlers (12 to < 36 months), the estimated 95th percentile of caffeine intake from all sources on a single day exceeded 3 mg/kg bw in three out of 10 countries (7.3 % to 36.7 % of survey days). Only in one out of nine countries the 95th percentile of daily caffeine intake from all sources exceeded 3 mg/kg bw (6 % of toddlers).

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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 concluded (1999), (2003) *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 health 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 health 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 superieur de la sante n° 8689,"Utilisation de la caféine dans les denrées alimentaires, 11 janvier 2012. Link: http://www.health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/19076526_fr.pdf

[5] Avis du conseil superieur de la sante ° 8622, « Boissons énergisantes », 2 décembre 2009. Link : http://www.health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/17982877_fr.pdf

[6] Health Canada, 2010: 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, August 10, 2012

[7] Agence Française de Sécurité Sanitaire des Aliments

[8] Afssa – Saisine n° 2002-SA-0260, 5 mai 2003; Afssa – Saisine n° 2005-SA-0111, 30 janvier 2006; Afssa Saisine n° 2006-SA-0236, 9 novembre 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] OJ. L 031, 01.02.2002. p.1

ASSESSMENT

1. Introduction

Chemically, caffeine (1,3,7-trimethylxanthine) is a stable, unionised alkaloid and one of several related methylxanthines. It is found in various plants such as coffee and cocoa beans, tea leaves, guarana berries and the kola nut, and thus 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.

This Opinion will address possible adverse health effects of caffeine consumption from all sources in the general healthy population and in relevant specific subgroups of the population. Whether the consumption of caffeine in combination with other substances present in "energy drinks" (D-glucurono-γ-lactone and taurine), alcohol, or synephrine, modifies the possible adverse health effects of caffeine and/or the doses at which adverse effects may occur will also be addressed.

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 and the specific population subgroups which are relevant for the assessment.

2. Previous safety assessments

2.1. Caffeine

Safety assessments in relation to the 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 mineralization of sternebrae) in experimental animals and mutagenic effects *in vitro*, but not *in vivo*. The SCF concluded that there was no evidence for concern over carcinogenic, teratogenic, or mutagenic effects of caffeine in man at observed levels of intake (between 2.0 and 4.5 mg/kg 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 drinks" 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 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 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; Rapoport et al., 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 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".

An 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 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, 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 70 kg in adults. FSANZ also noted that doses of 100 mg of caffeine (1.4 mg/kg bw per day in 70 kg adults) taken at bedtime had been reported to reduce the ability to sleep in adults (Landolt et al., 1995).

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 adequate intakes of calcium are being consumed. In a review of the available observational studies on caffeine consumption during pregnancy and 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 references (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). The COT also suggested a possible association between caffeine consumption and an increased risk for 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 Nordic Working Group on Food Toxicology and Risk Evaluation (NNT) focussed on the safety of caffeine among children and adolescents in the Nordic countries (NNT, 2008). A NOEL of 0.3 mg/kg bw (Goldstein and Wallace, 1997) and a 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 drawing conclusions on a causal effect of caffeine on disturbed sleep (i.e, observational study, 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 (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 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 per day (210 mg per day for 70 kg males) 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 4000 mg/L), and D-glucurono-γ-lactone (about 2400 mg/L) among other ingredients, and to the consumption of "energy drinks" or caffeine in combination with alcohol.

In 1999, the SCF (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 it unlikely that D-glucurono-γ-lactone would interact with caffeine, taurine, alcohol or the effects of exercise. Even if caffeine exerts stimulatory effects in the CNS and 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 high consumers (EFSA, 2009). Similarly to the SCF (2003), the ANS Panel considered it 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 NOAEL of 1500 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 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 drinks" 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 compared with "energy drinks" (50-200 mg caffeine and taurine 200-1000 mg per portion). BfR stated that consumption of "energy shots" pose 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 concluding 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 end-points in the intervention studies available prevented firm conclusions on whether caffeine counteracts the acute neuro-cognitive 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.

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 (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 to 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).

2.3. Caffeine in combination with synephrine

A number of authoritative bodies in different EU Member States have conducted risk assessments (BfR, 2012; SLE, 2012) or issued warnings (Sundhedsstyrelsen, 2008; MHRA, 2012; Evira, 2013) in relation to synephrine-containing products intended for weight loss and 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; Haller et al., 2008; Seifert et al., 2011). Based on these studies, the BfR concluded that single doses of 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 synephrine (from conventional foods and food supplements) would remain < 25.7 mg (95th percentile of synephrine intake from conventional foods) even in consumers with high intakes form diet. On the basis of these and other human intervention studies (Penzak et al., 2001), the Swedish National Food Agency (2012) 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 synepphrine. ANSES (2014) recommended not combining 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 synephrine at daily doses up to 320 mg and 40 mg, respectively.

2.4. Summary of previous safety assessments

Recommendations on maximum levels of caffeine consumption for different population sub-groups have been derived by different national and international bodies taking into account a variety of health 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 (Nickell and Uhde, 1994). Early recommendations for pregnant women and for women in child-bearing age advised not to exceed 300 mg of caffeine per day based on a number of cross-sectional and prospective cohort studies which assessed a variety of outcomes (e.g. spontaneous abortion, pre-term delivery, fetal growth, congenital malformations, post-natal development), whereas a later evaluation advised not exceeding 200 mg of caffeine per day in light of a new prospective cohort study (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 low consumers of caffeine (SCF, 1999). Other bodies (FSANZ, 2000; Health Canada, 2006; NNT, 2008; SHC, 2012), however, have recommended not to exceed 2.5 mg/kg bw per day on the basis of a single study (Bernstein et al., 1994).

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 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, the theoretical additive diuretic effects of caffeine and taurine mentioned in previous assessments were found 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 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 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 attributing a causal role to either caffeine or "energy drinks" in this cluster. Alcohol consumption was found unlikely to exacerbate the effects of caffeine on the CVS and/or the CNS. Concerns were rather 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 which investigated this question were found to yield conflicting results (Verster et al., 2012).

Finally, concerns related to the co-consumption of caffeine and 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; Haller et al., 2008; Seifert et al., 2011), authoritative bodies came to the conclusion that doses between 20 and 27 mg of synephrine 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, in worksplaces 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 methylxanthines-containing products (MAFF, 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 due to the relatively low and highly variable caffeine levels.

The Panel notes that there were no major differences among surveys and publications from different countries regarding caffeine levels in foods and beverages (Table 1).

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**	**(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**[(1)]	111	-	-	-	-	180	-	-	-	-	-	150
	Milk chocolate	**168**[(1)]	168	-	-	-	-	183	-	-	-	-	-	
	Chocolate snacks			-	-	-	-	180	-	-	-	-	-	
	Cocoa beverage [(2)]			-	-	-	-	150	-	20	-	20	-	15
	Dark chocolate	**525**[(1)]	525	-	-	-	-	340	-	-	-	-	-	650
Coffee	Coffee drink	**445**[(1)]	445	586 (450-882)	477 (114-840)	513 (175-1244)	400 (197-804)	400	320	500	500	550	500	690
	Cappuccino	**272**[(3)]	-	-	315 (315-315)	250	250 (194-310)	250	-	-	-	-	-	-
	Espresso coffee	**1340**[(4)]	-	1411 (1058-3175)	1897 (1320-2475)	713 (250-2140)	-	1916	-	-	-	-	-	-
	Decaffeinated and imitates	**21**[(5)]	-	22 (13-53)	29 (8-50)	21 (15-120)	-	11	-	-	-	-	-	-
	Instant coffee, ready to drink	**445**[(1)]	445	410 (119-763)	477 (113-840)	484 (201-856)	300 (201-485)	400	320	500	500	550	500	690
Tea	Black tea	**220**[(1)]	220	207 (110-485)	-	272 (90-500)	150 (122-183)	100	320	160	150	170	160	240
	Green tea	**151**[(1)]	151	198 (132-220)	-									
	Tea (unspecified)	**165**[(1)]	165	234 (176-529)	158 (59-256)									
	Tea, decaffeinated	**25**	-	-	25 (0-50)	-	-	25	-	-	-	-	-	-
Cola beverages (caffeinated)		**108**[(1)]	108	127 (101-163)	104 (76-132)	97 (41-132)	-		79	130	130	130	130	130
"Energy drinks"		**320** [(6)]	300	335 (317-353)	-	300 (120-320)	300 (267-665)		300	150	320	150	150	320

[(1)] derived from Fitt et al., 2013

[(2)] correction factors have been applied in order to consider differences with respect to the amount of cocoa, and consequently of caffeine, in cocoa beverages depending on how these products have been prepared or recorded in the different surveys (i.e. based on "cocoa beans and cocoa products", "fermented cocoa beans", "cocoa powder", "cocoa-beverage preparation powder" or "cocoa mass").

[(3)] mean value from Mayo, ANSES and Austria

[(4)] mean value from Heckman, Mayo and ANSES

[(5)] derived from ANSES

[(6)] caffeine concentration of the most consumed "energy drink" considered

- no value provided in the respective 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 individual level. It was first built in 2010 (EFSA, 2011b; Huybrechts et al., 2011; Merten et al., 2011) and then updated in 2014 (to be published in 2015). Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011a). 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 3rd 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 (MSs) added in 2014 used the FoodEx2 code classification, which allows accurate reporting of "energy drink" consumption.

The database used to calculate caffeine intake included the 17 surveys from 2014 and surveys conducted between 2005 and 2012, with two exceptions (DIPP 2001-2009, Finland; VELS 2001-2002, Germany). The database contains data from 39 surveys in 22 different European countries for a total of 66 531 participants (Appendix A). Data from eleven 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 21surveys for adults (≥ 18 years to < 65 years old), from 15 surveus 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 surveys above, consumption data were collected using single or repeated 24- or 48-hour dietary recalls or dietary records covering from 3 to 7 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"), as well as consumption of "energy drinks" together with alcohol or in relation to physical exercise in adolescents and adults, were also investigated. Consumption data were collected through a food frequency questionnaire (FFQ)-based survey, involving more than 52 000 participants from 16 different European MSs.

The Panel notes that this study provides useful information about the prevalence of "energy drink" consumption in Europe, the amount of "energy drinks" (and their constituents, including caffeine) consumed on 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; ii) FFQs specifically developed to assess consumption of specific foods tend to oveestimate 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 amounts of alcohol which were consumed in

combination with "energy drinks". Therefore, the Panel considered that this study could be used to calculate caffeine intakes from "energy drinks" on 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 adding the intake reported on each survey day 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 consumed a food product of the concerned food groups at least once within the survey period.

Means and 95th percentiles of daily caffeine intake by 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 intake for all subjects by age class and food group across different dietary surveys

Age class	Food groups	Mean caffeine intake				95th percentile caffeine intake[1]			
		mg per day		mg/kg bw per day		mg per day		mg/kg bw per day	
		Min[2]	Max[2]	Min[2]	Max[2]	Min[2]	Max[2]	Min[2]	Max[2]
Toddlers (12 to < 36 mon; 10 surveys)	**Total intakes**[3]	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 yrs; 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 yrs; 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"[4]	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 yrs; 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" (5)	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 yrs; 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 yrs; 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

(1) The 95th percentile estimates obtained from dietary surveys and age classes with less than 60 subjects may not be statistically robust (EFSA, 2011a) and were consequently not considered in this table (" - ").
(2) Minimum and maximum mean and 95th percentiles of those calculated from individual surveys for each age class.
(3) "Total intakes" are not derived by adding up the min and max 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 respective survey and age group across the different dietary surveys.
(4) Only one study (the Netherlands) with a sufficient number (≥ 60) of subjects who consumed "energy drinks" was available to estimate a statistically robust 95th percentile.
(5) Only two studies (the Netherlands and Ireland) with a sufficient number (≥ 60) of subjects who consumed "energy drinks" were available to estimate statistically robust 95th percentiles.

Table 3: Daily caffeine intake 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**(1)			
		mg per day		**mg/kg bw per day**		**mg per day**		**mg/kg bw per day**	
		Min(2)	Max(2)	Min(2)	Max(2)	Min(2)	Max(2)	Min(2)	Max(2)
Toddlers (12 to < 36 mon; 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 yrs; 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 yrs; 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"(3)	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 yrs; 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" (4)	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 yrs; 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 yrs; 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

(1) The 95th percentile estimates obtained from dietary surveys and age classes with less than 60 subjects may not be statistically robust (EFSA, 2011a) and were consequently not considered in this table (" - ").
(2) Minimum and maximum mean and 95th percentiles of those calculated from individual surveys for each age class. Total caffeine intakes cannot be calculated for "consumers only" by adding up caffeine consumption from coffee, tea, colas and energy drink, because these figures reflect the intakes of different subjects (consumers of the respective food group).
(3) Only one study (the Netherlands) with a sufficient number (≥ 60) of subjects who consumed "energy drinks" was available to estimate a statistically robust 95th percentile.
(4) Only two studies (the Netherlands and Ireland) with a sufficient number (≥ 60) of subjects who consumed "energy drinks" were available to estimate statistically robust 95th percentiles.

Adults, elderly and very elderly

Daily caffeine intake from all sources could be estimated for adults from 16 MSs. 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 United Kingdom, tea was the main source of caffeine, wich 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 to lower 95th percentiles. Cola beverages and energy drinks were negligible as a source of caffeine in these population groups in all surveys.

Pregnant women

Data on pregnant women are available only for Latvia (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 only from 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 MSs. 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 between 0.4 and 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 in four surveys, cola beverages in three surveys, and tea in two surveys. Differences among 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 the Netherlands (8.1 %) and Belgium (5.3 %). Only in the first two cases was a specific code for "energy drinks" available in the database.

Toddlers and other children

Ten surveys were available for tooddlers. Mean daily intake of caffeine ranged between zero and 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 were the main caffeine sources 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).

Seventeen surveys were available for children aged 3 to < 10 years. Mean daily intakes of caffeine from all sources ranged between 0.2 and 2.0 mg/kg bw per day. The 95th percentiles 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 the children population 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 (Appendix C, 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. 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, elderly and 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 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 in one 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 were 7.1 mg/kg bw (Appendix C and D). Sufficient (n ≥ 60) days to obtain statistically robust 95th percentiles for toddlers regarding caffeine intakes from different sources on consumption days were only available for chocolate and tea, for which the highest values across MSs were estimated at 5.3 and 9.6 mg/kg bw per day of caffeine, respectively (Appendix C).

For children from 3 to 10 years of age, the highest 95th percentile of caffeine intake form all sources on a single day was estimated at 5.7 mg/kg bw (Appendix 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" on a "single session" estimated from the EFSA report on "energy drinks"

Table 4 summarises caffeine intakes from "energy drinks" consumed on 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 prevelance of subjects who declared to consume ≥ 3 "energy drinks" per "single session". Data were available from 16 MSs (Zucconi et al., 2013).

Table 4: Caffeine intakes on a "single session" by "energy drink" consumers and prevalence of subjects consuming ≥ 3 cans of "energy drinks" per single session

	Caffeine intake per single session(1)				**% of "energy drink consumers" consuming ≥ 3 cans per single session**	**% of total respondents consuming ≥ 3 cans per single session**
	Mean		95th percentile			
	mg	mg/kg bw	mg	mg/kg bw		
Adolescents (10 - 18 yrs)	176	2.9	450	7.2	24	16.3
Adults (18 - 65 yrs)	155	2.2	344	5.1	19	5.7

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

Adults

The mean and 95th percentile of caffeine intake on 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 to consume 1, 2, 3, 4 and ≥ 5 cans of "energy drinks" within a "single session".

Adolescents

The mean and 95th percentile of caffeine intakes on 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 at 2.9 and 7.2 mg, respectively. In this survey, 51, 25, 11, 6 and 7 % of "energy drink consumers" declared to consume 1, 2, 3, 4 and ≥ 5 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 prevalence of "energy drink" consumers was observed in adolescents (9 % in the Netherlands, 7 % in UK and 5 % in Finland) and adults (8 % in Ireland, 4 % in the Netherlands and 3 % in UK). In these surveys, the prevalence of "energy drink" consumers was most often zero and never exceeded 1 % in toddlers (5 surveys), children aged 3-10 years (seven surveys), elderly (ten surveys) and very elderly (8 surveys), lactating women (1 survey) and pregnant women (1 survey).

3.3.3.2. EFSA report on "energy drinks"

Table 5 provides an overview on 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 yrs)			**Adolescents (10-18 yrs)**			**Adults (18-65 yrs)**		
	mean	**min**	**max**	**mean**	**min**	**max**	**mean**	**min**	**max**
"Energy drink" consumers [1]	18	6	40	68	48	82 [2]	30	14	50
Consumers of energy drinks plus physical activity[3] 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[3] among total respondents	-	-	-	28	-	-	16	-	-
Consumers of ≥ 3 "energy drinks" plus physical activity among total respondents	-	-	-	8	-	-	4	-	-

[1] Percentage of "energy drink" consumers among total respondents.
[2] The highest prevalence of "energy drink" consumption among total respondents was observed in Belgium (85 %), but these data was not considered due to the small sample size available for that MS (sampling error of estimates exceeds 5 %).
[3] Percentage of subjects who declared to usually consume "energy drinks" before/in association with/after sport activities. Children were not studied.
(-) Not available

The Panel notes that the prevalence of "energy drink consumers" in this 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 to usually consume "energy drinks" before/in association with/after sport activities (Table 4). According to this survey, 47, 26, 13, 9 and 5 % of this population declared to consume 1, 2, 3, 4 and ≥ 5 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 to usually consume "energy drinks" in relation to sport activities (Table 4). Forty-eight, 25, 13, 7 and 7 % of this population declared to consume 1, 2, 3, 4 and ≥ 5 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 into 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 vs. 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, 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 central nervous system. Concerns were also raised with respect to caffeine in the 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 synephrine. As in previous risk assessments by e.g. 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 (tmax 30-120 min) 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 4 hours with range of about 2 - 8 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 the dose range up to 10 mg/kg (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 metabolized 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 as compared to 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 "fast metaboliser" while the AC and CC genotypes were considered to be "slow metaboliser". In four publications, the combined prevalence for the "slow" CC and AC genotypes was reported between 52 and 60 % versus 48 and 40 % for the "fast" AA genotype (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 life-style (coffee consumption, smoking, intake of oral contraceptives) factors of 786 individuals on the clearance of caffeine with a single saliva sample taken 5-7 hours after a test dose of about 145 mg caffeine. Overall geometric mean (geometric SD) of caffeine clearance was 1.34 mL/min/kg bw (1.65). Relevant factors influencing clearance were 1. daily coffee consumption, increasing clearance 1.45-fold per consumed litre; 2. 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; 3. oral contraceptives, reducing clearance by 0.72-fold; 4. 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 been reported also 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.

Also 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 -163 AA genotype (Djordjevic et al., 2010). No increased CYP1A2 activity was found for coffee consumers of less than three cups of coffee per day, irrespectively of this SNP, and for the "slow" CC and AC genotypes, irrespectively of their coffee consumption.

More than 150 single nucleotide polymorphisms 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.

A few studies investigated whether 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, as compared to 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, USA, Iceland) found two sequence variants (one locus between CYP1A1 and CYP1A2 gene and one in the aryl hydrocarbon receptor gene) which were associated with a difference of 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.

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). Also severe liver disorders (Arnaud, 1993) and some drugs (Carrillo and Benitez, 2000) have been reported to cause a significant inhibition of the 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 2-8 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 estrogens and gestagens which have been shown to inhibit the activity of CYP 1A2 (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) as compared with the postpartum period. Similar quantitative and progressive reductions of CYP1A2 activity during pregnancy have been reported (Tsutsumi et al., 2001). The Panel notes that the 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 as compared to the non-pregnant state if caffeine intake is kept constant during pregnancy.

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 CYP1A1 and CYP1A2 gene region (rs2472297) and one near the aryl-hydrocarbon receptor (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 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 for 0.04-0.048 %, and the two combined for about 0.16-1.28 %.

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 fetus nor placenta can metabolise caffeine, fetus of caffeine consuming women are exposed to caffeine and its metabolites for a significantly prolonged time (Grosso et al., 2006).

4.1.4. Breast fed 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 2 and 4 hours after intake of caffeine from coffee (148 ± 48 mg). Milk/maternal plasma ratios averaged 0.8 ± 0.07. Intake in the nursed infants (4 days up 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 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; Steer et al., 2004), preterm 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 concentration in the 3 mg/kg 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/min) and jitteriness. Tachycardia was observed in 1 out of 42 pre-term infants in the 3 mg/kg bw group, in one out of 121 in the 5 mg/kg bw group, in five out of 40 in the 15 mg/kg bw group, in four out of 131 in the 20 mg/kg bw group, and in eight out of 45 in the 30 mg/kg bw group. The figures for jitteriness were one out of 42 in the 3 mg/kg bw group, two out of 121 in the 5 mg/kg bw group, one out of 40 in the 15 mg/kg bw group, two out of 131 in the 20 mg/kg bw group and zero out of 45 in the 30 mg/kg bw group. As preterm neonates are considered an especially sensitive population subgroup, the results can be extrapolated to neonates and breastfed infants in general as most conservative estimates for 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, going down to 14 hours at 3-4 months and to 2-3 hours at 5-6 months (Aranda et al., 1979). Caffeine's half-life appears to remain stable at about 2-3 hours during childhood, and to increase thereafter in adolescents and adults. Caffeine clearance from plasma has been estimated to be between 5 and 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 that significantly affect caffeine metabolism by CYP1A2 for various population groups. Considering the reduced maternal clearance and prolonged half-life during pregnancy and the fetus' exposure to maternal caffeine plasma levels, the Panel considers the unborn child 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 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).

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, raising the possibility that caffeine tolerance is 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 less release of adrenaline, noradrenaline, and renin than in the non-tolerant state. It is uncertain whether the development of tolerance may explain the difference in the sensitivity to the effects of coffee on sleep. Some authors consider that the difference rather 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 not clear headed are observed 12-24 h after abstinence and this clinical situation is called caffeine withdrawal syndrome (Juliano and Griffiths, 2004).

Polymorphism in adenosine receptors has 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 to retrieve 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 to evaluate potential adverse effects of caffeine consumption in humans, and that 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. Whenever available, human intervention studies and prospective cohort studies will be preferred over case control and cross-sectional studies due to the lower risk of reverse causality and recall bias. The Panel also considers that, although case reports of adverse events following consumption of caffeine-containing foods or beverages are useful to identify health

concerns for further investigation, they generally provide insufficient information to conclude on a factor or combination of factors which trigger the adverse event and/or the doses of caffeine which could be considered as safe/unsafe for the general healthy population. Whenever available, systematic reviews and meta-analyses will be used to summarise the scientific evidence.

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 (i.e., including „energy drinks"), either alone or in combination with alcohol or synephrine, have been addressed in human intervention studies. Among the variety of outcomes investigated in these studies, the Panel focuses on adverse effects of caffeine on the CVS and the CNS as the main health concerns expressed by other bodies in previous safety assessments (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. 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, like attention, alertness or physical performance, and studies addressing the beneficial effects of caffeine in the treatment of various diseases) are 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, and are able to induce cardiac (mostly atrial) arrhythmias in healthy, caffeine naïve 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 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 CV 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, on the dose administered, and on 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 mm Hg and diastolic blood pressure (DBP) by 4-13 mm Hg in normotensive subjects. Lower doses of caffeine were not tested. Changes in BP paralleled changes in plasma concentrations of caffeine. BP started increasing 30 min after caffeine administration to reach a maximal effect at 60-120 min, which lasted for about 2-4 h. 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 mm Hg (95 % CI: 5.7, 10.6 mm Hg) and 5.7 mm Hg (95 % CI: 4.1, 7.4 mm Hg), respectively, which was observed in the first 60 min after intake and persisted up to 180 min afterwards. The effect of caffeine on BP did not change with the dose (only 200 to 300 mg were tested), with the time of caffeine abstinence before the trial (9-48 h), or with 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 with normal BP, 36 with high-normal BP, 27 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 at 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 mm Hg), followed by the stage 1 and high-normal groups and then by the normal and optimal groups, with a difference of 1.5 times greater change in diagnosed hypertensives than in the group with optimal BP.

A number of controlled human intervention studies have been published thereafter on the effects of single caffeine doses (as supplements, 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 80-250 mg in coffee abstainers, in habitual caffeine consumers after 12-48 h 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; Farag et al., 2005b; Arciero and Ormsbee, 2009; Farag et al., 2010; 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 (QTc) (Buscemi et al., 2011).

In studies assessing endothelial function, compared to 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 dilation (FMD) in habitual moderate coffee consumers after 12-24 h 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, 1000 mg taurine and 600 mg D-glucurono-γ-lactone (Worthley et al., 2010). Whether 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 (NOs) 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; Hartley et al., 2004; Karatzis et al., 2005; Swampillai et al., 2006; Vlachopoulos 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, mean arterial blood pressure). The methods used to assess arterial compliance and BP, the arterial segments assessed, and the indexes 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 vs. 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 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, randomized, 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 4 hours apart (at 7.30-8.30 am and < 1 pm) on two separate trial days after an overnight fast. Ambulatory BP was monitored after the first caffeine dose until bedtime or 10 pm. Compared with placebo, caffeine significantly raised average SBP through the entire day by about 4 mm Hg and DBP by about 3 mm Hg, whereas HR decreased by 2 bpm, with no significant interaction between treatment and location (at work, at home). Urinary free epinephrine levels were 32 % higher with caffeine than with placebo, particularly at work.

In a second study with double-blind, randomized, 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 5 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 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 × tolerance group interactions were noted. The sleep BP also differed significantly across caffeine maintenance doses, but not between tolerance groups, with no significant week × tolerance group interactions for sleep SBP or DBP. Compared to 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 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 or during 300-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 following 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 (4 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 min 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 h of caffeine withdrawal (Astorino et al., 2007 and 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 programs 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 x 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 2-h after exercise with caffeine than with placebo, whereas HR and DBP were not different between treatments. SBP was only higher with caffeine than with placebo during one (out of four) type of exercise and only in the "pre-hypertensive" group. Souza et al. (2014) reported a significant decrease in SBP and MABP and a significant increase in HR after exercise for caffeine and placebo. DPB and HR (but not SPB) were significantly higher at rest with caffeine than with placebo, as well as peripheral vascular resistance (SBP, DBP, HR, stroke volume or cardiac output) in the nine hours post-exercise. The Panel considers that, although these studies are small and 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 two "energy drinks" containing caffeine, taurine, and D-glucurono-γ-lactone on BP and endothelial function as compared to the same volume of water. One unpublished study (Bischoff, 2013) 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) as compared to the same volume of a caffeine-free soft drink. The Panel notes that these studies do not allow conclusions on whether "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 as compared to caffeine alone (Franks et al., 2012). Twelve healthy, nonsmoking, normotensive volunteers aged 18-45 years consumed one serving of "energy drinks" (80 mg caffeine and 1000 mg taurine per serving) four times, at 8 am, 11 am, 3 pm and 7 pm, totalling 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. 24-h SBP, DBP and mean arterial BP were significantly higher with consumption of the "energy drinks" than with consumption of caffeine alone (by 5.8, 5.3 and 5.3 mm Hg, respectively), whereas HR and nocturnal dipping (SBP and DBP) did not differ. The Panel considers that, although this study suggests a bigger BP-raising effect associated with the consumption of "energy drinks" as compared to caffeine alone, the small number of subjects included in the study,

the high dropout rate (25 %), and the absence of blinding limit the conclusions which can be drawn in relation to the effects of "energy drinks" components other than caffeine on BP.

The afore-mentioned unpublished 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 sport drink (control, free of caffeine, taurine or D-glucurono-γ-lactone), the sport drink plus taurine (4 000 mg), the sport drink plus caffeine (320 mg) and of an "energy drink" (containing 4 000 mg of taurine, 320 mg of caffeine and 240 mg of D-glucurono-γ-lactone. The same preliminary testing was conducted in 19 other subjects using 750 mL (as single dose) of the same beverages. A significant increase in SBP (by about 7-8 mm Hg) was reported following consumption of the sport 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 sport 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 to 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 synephrine

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). *Citrus 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 these drugs in food supplements containing *C. aurantium* extracts is indicative of adulteration. Only (-)-*p*-synephrine (or synephrine thereafter) from *C. aurantium* extracts in food supplements will be considered in this Opinion.

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, if any, CNS stimulation. Therefore, any additive or synergistic effects of synephrine when consumed in combination with caffeine should be expected in the CVS.

The effects of single doses of 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 synephrine and caffeine were the main active ingredients (Haller et al., 2005a; Sale et al., 2006; Seifert et al., 2011). Studies having caffeinated coffee as 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. A significant increase in SBP and DBP was reported for synephrine from *C. aurantium* extracts when consumed at 54 mg, but not at lower doses (13.5-50 mg). A significant increase in SBP and DBP was also reported for a combination of 5.5 mg 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 synephrine and 304 mg caffeine. Conversely, no significant changes in BP were found with 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 of single doses of caffeine alone, of synephrine alone, and of their combination, on BP. The Panel considers that, from the information available, no conclusions can be drawn on whether the simultaneous consumption of synephrine modulates the pressor effects of caffeine, to which extent, or at which doses.

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 80-300 mg, although most studies tested doses of about 200-300 mg, which induced a mean increase in SBP of about 3-8 mm Hg and in DBP of about 4-6 mm Hg, with high inter-individual variability. The available data suggest that BP generally increases at 30 min after caffeine consumption, reaches a peak at 60-90 min, and returns to baseline at about 2-4 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 formally 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 mm Hg) 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 min 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 synephrine, or of substances commonly found in "energy drinks" other than caffeine, modify the acute effects of caffeine on BP.

4.4.1.2. Myocardial blood flow

Caffeine (in common with 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 blow during exercise (Higgins and Babu, 2013).

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

^{15}O-labeled H_2O 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 (7 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 was considered for power calculations. In 10 subjects (mean age, 27 ± 6 years), MBF was measured at rest and after a 5-min 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 min later. Caffeine did not affect resting MBF but induced a significant decrease in exercise-induced hyperemic MBF (2.51 ± 0.58 mL/min per g tissue vs. 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 vs. 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 vs. 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 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 are 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 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 in either group. Exercise-induced hyperaemic MBF and MFR significantly decreased 50 min after caffeine ingestion as compared to 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-labeled H_2O 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, randomized, placebo-controlled cross-over study (Gaemperli et al., 2008). A total of 41 healthy volunteers (15 female) aged ≥ 18 years, nonsmokers, 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 h. MBF was measured each day 2 hours after capsule ingestion at rest and after and intravenous administration of regadenoson. The MBF (mean ± SEM) was not significantly different between caffeine and placebo at rest (1.13 ± 0.04 mL/min per g vs. 1.06 ± 0.05 mL/min per g) and stress (2.98 ± 0.14 mL/min per g vs. 3.05 ± 0.14 mL/min/g), as was not MFR (2.75 ± 0.16 vs. 2.97 ± 0.16). The data show with 1-sided 95 % confidence that any MFR

reduction associated with caffeine intake was < 20 %. However, a similar study using regadenoson-stress 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 above could significantly counteract the vasodilator effect 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 1-2 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 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 sudden cardiac death (SCD), myocardial infarction (MI), and ischemic stroke, has been investigated using case-crossover study designs. Control information for each case is based on his/her past exposure experience, and a self-matched analysis was conducted (Maclure, 1991).

One 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 of 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 mailing one questionnaire to the family members of the deceased and one to the attending physician. Cases were those who died of SCD within 1 hour after coffee consumption or within 2 hours after ingesting alcohol; controls were those who died in the hours when they were not exposed to coffee or alcohol. The relative risk of dying within exposed hours in comparison to non-exposed hours was the parameter estimated for each risk factor. On average, each subject had 2.8 risk factors for ischemic heart disease. The estimated RR of dying during 1 hour after coffee consumption was 1.73 (95 % CI=1.13-2.65), and 3.00 (95 % CI=1.61-5.68) within 2 hours after alcohol consumption. Alcohol drinking did not appear to influence the risk in coffee drinkers.

In another study (Baylin et al., 2006), 503 first incident cases of nonfatal 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 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 nonfatal MI recruited, complete and consistent information was available for 503 cases regarding intake of coffee during the 24 hours and days before the event and regarding habitual intake of coffee. Most patients reported drinking 2–3 cups of coffee per day and only 37 (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, 80 had at least 1 cup of coffee in the hour before the onset of MI (69 had 1 cup of coffee, nine had 2 cups, and one had 3 cups). The RR for MI in the hour after taking 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 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 1 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 (2–3 cups per day; n = 280) had a RR of 1.60 (1.16–2.21), and heavy drinkers (4 or more cups per day; n = 120) had a RR of 1.06 (0.69–1.63; p = 0.006, test for interaction). This was the only variable significantly modifying the risk, whereas age, sex or physical activity, history of diabetes, hypercholesterolemia, hypertension, smoking status, or having at least three (n = 101) or less than three of these risk factors for disease did not.

In the Stroke Onset Study, the relationship between coffee and alcohol consumption and the onset of ischemic stroke was reported in two publications (Mostofsky et al., 2010a; Mostofsky et al., 2010b). Between January 2001 and November 2006, 390 subjects (209 men, 181 women) were interviewed a median of three days (range 0-14) after acute ischemic stroke. Subjects were asked about caffeinated coffee and alcohol intake the year prior to the stroke, and consumers were asked about the frequency of consumption and the last time 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 was compared with his or her usual frequency of consumption in the prior year. Of the 390 subjects, 304 (78 %) drank coffee in the prior year, 232 within 24 hours and 35 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 and 14 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 relative risk (RR) of stroke in the hour after consuming coffee was 2.0 (95 % CI, 1.4 to 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 to 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 ischemic stroke in the hour after coffee consumption was only apparent among those consuming ≤ 1 cup per day but not for patients who consumed coffee more regularly (p for trend = 0.002). Relative risks 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 to 4.0; p = 0.002) within one hour and 1.6 (95 % CI, 1.0 to 2.5; p = 0.05) in the second hour after alcohol use compared with periods of non use. The RR and 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 Panel notes that these three case-crossover 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. Although not formally tested, co-consumption of caffeine and alcohol does not appear to modify the risk. 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 sub-group analyses conducted to explore modifying factors (e.g., influence of other risk factors for the event, like 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 1-2 hours pre-exercise significantly increases BP during resistance training in caffeine-naïve subjects as well as in habitual coffee consumers upon 24-48 h of caffeine withdrawal. A single dose of 200 mg of caffeine also decreases myocardial blood flow if consumed approximately one hour prior to endurance exercise (i.e. when the BP-raising effect of caffeine reaches its peak). Whereas such changes could increase the risk of acute cardiovascular events in subjects with an increased risk for CVD (e.g. with underlying hypertension and/or advanced atherosclerosis), the Panel considers them 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. Consumption of alcohol in combination with caffeine does not appear to modify the CVD risk. The studies available do not provide sufficient information to conclude on whether co-consumption of 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 the healthy 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) did not lead to significant changes in body mass, urine osmolality, urine specific gravity, urine color, 24-h urine volume, 24-h Na^+ and K^+ excretion, 24-h creatinine, blood urea nitrogen, serum Na^+ and K^+, serum osmolality, hematocrit, or total plasma protein compared to placebo (Armstrong et al., 2005).

It has been suggested, however, that acute consumption of caffeine 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. Acute caffeine intake at doses of about 100-600 mg prior to exercise did, however, not lead to a significant increase in urinary volume, significantly different water retention during dehydration, or induce adverse water-electrolyte imbalances compared to water or placebo, particularly in habitual caffeine consumers (Armstrong, 2002).

A number of studies have investigated the acute effects of caffeine at doses 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-randomized cross-over study (Kim et al., 2011), 13 male student, non-habitual caffeine consumers, who followed daily aerobic training, completed two experimental trials (i.e., running for 30 min at 60 % of VO_2max) in thermo-neutral conditions (24 ^oC, 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 min before the test. Core (tympanic) and skin temperature were measured after caffeine consumption at rest, pre-exercise (40 min after caffeine/placebo consumption) and post-exercise (after 30 min 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 compared to water, whereas tympanic body temperature only increased significantly pre-exercise (by 0.12 °C). After caffeine consumption, sweating rate was significantly higher and the onset of sweating significantly delayed during exercise.

In another double-blind, randomized cross-over study (Del Coso et al., 2008), seven endurance-trained cyclists pedalled for 120 min at 63 % of VO_{2max} in a hot-dry environment (36 ^{o}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 min 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 raise 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 those 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 per cent of VO_2max) in a hot environment (31 ^{o}C, 70 % relative humidity) but received regular hydration (3 mL of cool water/kg bw every 20 min) 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-randomized 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 1 h prior to exercise, which consisted of cycling for 60 min at 55 % of W_{max}, immediately before a time trial to measure performance. Compared to placebo, caffeine significantly increased core (rectal) temperature during exercise 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 to placebo, acute doses of 9 mg/kg bw caffeine consumed after 4 days of caffeine abstinence also showed to increase core (rectal) body temperature (by 0.20-0.30 °C), but not skin temperature, in 10 healthy men performing 30-min of cycle ergometry at 50 % VO_2 peak followed by a 15-min performance time trial at 40 ^{o}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, mean body temperature was significantly higher (by 0.27 ^{o}C) one hour after caffeine consumption compared to placebo only at the begining of the exercise (cycling for 30 min at 50 % of VO_2 peak in a 40 °C, 25 % relative humidity environment) in another study using the same caffeine dose, 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 (each 750 mL of fluid) containing: a) 80 mg caffeine and 1 g taurine per 250 mL; b) 80 mg caffeine per 250 mL, c) 1 g taurine per 250 mL, and d) neither caffeine nor taurine. Caffeine significantly increased urinary output and natriuresis, whereas taurine had no effect on either outcome 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 to placebo. The Panel also notes that higher doses of caffeine (6 mg/kg bw equivalent to 420 mg for a 70-kg adult) ingested about one hour prior to prolonged endurance exercise in a hot environment do not affect body temperature or hydration status beyond what could be expected from the testing conditions, and that changes in body temperature and hydration status under these conditions are of no health concern if fluid losses can be timely replaced.

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 (1.5 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 in 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 non-habitual caffeine consumers (FSANZ, 2000; Nawrot et al., 2003; Childs and de Wit, 2006; NNT, 2008; SHC, 2012). Polymorphisms of the adenosine receptor gene $ADORA_{2A}$ have been suggested to account for part of the inter-individual variability observed in the anxiogenic response to caffeine (Childs et al., 2008; Rogers et al., 2010).

Children and adolescents

A number of human intervention studies (Elkins et al., 1981; Rapoport et al., 1981b; (Rapoport et al., 1984); Leviton, 1992; Baer, 1987; Bernstein et al., 1994; (Rapoport et al., 1981b; 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 been alredy considered by other assessment bodies. No new studies have become available since then in this population sub-group.

Stein et al. (1996) searched for human studies reporting the effects of caffeine on cognitive, behavioral, sleep, or psychological effects which included a caffeine comparison (either placebo, alternate drug treatment, baseline, or matched control group). Nine studies were indentified, of which five were in children with attention-deficit hyperactivity disorders (ADHD) and four 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, stomachache, nausea, chest pain, heart pounding, feeling flush, feeling faint, feeling

nervous/jittery, increased diuresis, difficulty sleeping) one hour after caffeine administration. Items were rated on a 3-point scale. Nine items of behaviour (fidgety, distractible, tense, hypoactive, pressured speech, physical complaints, euphoria-elation, and nervous habits and manierisms) from a Psychiatric Rating Scale were rated on a 7-point scale by a research assistant. No significant differences in self-reported side effects were observed in children for any caffeine dose compared to 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 compared to the 3 mg/kg bw. 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 body weight) on self-reported anxiety in 21 children (mean age 10.6 ± 1.3) 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 was the child at the time of testing (anxiety state) and 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 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. The Panel also notes that single doses of caffeine of 3 and 10 mg/kg bw (Rapoport et al., 1981b) had no effect on nine investigator-rated items of behaviour, and that a dose-response relationship was observed only for one out of the 11 self-reported side effects tested ("feeling nervous/jittery").

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, 2011).

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 to placebo, caffeine significantly reduced RPE during exercise (in 20 out of the 22 studies) by 5.6 % (95 % CI -4.5 to -6.7). 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 mg/kg bw to 10 mg per 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). Since 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 owing to 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 in caffeine consumers which 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 min before performing a rugby test consisting of seven circuits in each of two 40-min halves with a 10-min half-time rest (Stuart et al., 2005). The development of fatigue during the test was significantly reduced after caffeine consumption compared to placebo.

In the health claim opinion (EFSA, 2011c), 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 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 under the assumption that the perception of fatigue is a physiological mechanism leading to the spontaneous ending of physical activities that, due to their high intensity, extended duration, or both, may compromise the cardiovascular and/or the musculoskeletal systems. The Panel notes that single doses of caffeine which have been observed to reduce the rated perceived exertion/effort during exercise (≥ 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 considered by the UK COT (Verster et al., 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 beverages (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 meet these criteria (Fillmore and Vogel-Sprott, 1999; Fillmore et al., 2002; Marczinski and Fillmore, 2006; Howland et al., 2011; Marczinski et al., 2011; Marczinski et al., 2012; Heinz et al., 2013; Marczinski 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, producing peak blood alcohol concentrations (BAC) 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 source of caffeine. Three had a cross-over and six 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 a 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 targeted 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 source 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) had 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 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 an 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 per day (3 mg/kg/bw for a 70-kg adult) do not appear to induce anxiety in unselected adult subjects from the general population, to reduce the perceived exertion/effort during exercise when consumed one hour prior to exercise after 12-24 hours of caffeine withdrawal, or to 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 1.5 mg/kg bw) 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 cardiovasculat system 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 risk of chronic diseases (e.g., CVD, cancer, diabetes mellitus type II, Parkinson disease, Alzheimer disease, bone fractures), adverse pregnancy outcomes, male fertility, and birth defects (neural tube defects, oral clefts), mostly comes 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 on adverse pregnancy outcomes (e.g. pre-term delivery, fetal growth retardation or small for gestational age, 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; Rapoport et al., 1984; Baer, 1987; Halle et al., 1995).

In the study by Halle et al. (1995), 18 adolescents (11-15 years) underwent six independent randomised, double-blind, placebo-controlled, trials. On each trial, participants were given a noncaffeinated and a caffeinated soft drink (providing 33 mg of caffeine) in a 2-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 et al. (1987), six 5-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, parents/teachers ratings of childrens 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 sudy, (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. Collectivelly, 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 are small and heterogeneous in design, and that doses between 3 mg/kg bw per day 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 risk of a number of CVD-related outcomes, including incident hypertension, (fatal, non-fatal, total) CHD, (total, non-fatal) MI, (total, fatal and non-fatal) stroke (all types, haemorrhagic, ischemic), 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 of case-control and prospective cohort studies have consistently reported positive associations between habitual consumption of caffeine-containing foods and beverages (mostly coffee) and 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 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 CVD-related outcomes in one or more of these studies. In some, tea has been assessed but only used as confounding variable 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 are not tabled, 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 lower amounts of 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 W et al., 2009; Zhang WL et al., 2009b) 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 had 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 in the US (Klag et al., 2002), and one in Australia (Jenner et al., 1988). Sample size varied from 340 to 5 189 subjects and follow-up between six 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: whereas 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 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 not 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 ≥ 6 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 during ≥ 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 heart rate (HR). Studies using co-interventions (e.g. caffeine plus epinephrine) 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 (7 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 (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 mL to 1 235 mL, which corresponds to a caffeine dose of 225-798 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 either received 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 mm Hg for systolic BP (median 122 mm Hg) and from 65 to 94 mm Hg for diastolic BP (median 74 mm Hg). 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 mm Hg for systolic BP and from -2.4 to 5.0 mm Hg for diastolic BP. Combining all caffeine and coffee studies, SBP significantly increased by 2.04 mm Hg (95 % CI, 1.10– 2.99) for systolic and DBP 0.73 mm Hg (95 % CI, 0.14–1.31). After excluding nine coffee trials with an open design, changes in SBP were 2.81 mm Hg (1.08–4.53) and in DBP were 1.17 mm Hg (0.54–1.81). 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 ≥ 130/85 mm Hg), baseline caffeine intake (< 400 or ≥ 400 mg per day), and caffeine dose (< or ≥ the median intake of 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 SPB and DBP for coffee (18 strata) were and 1.22 mm Hg (0.52, 1.92) and 0.49 mm Hg (–0.06, 1.04), and for caffeine (7 strata) were 4.16 mm Hg (2.13, 6.20) and 2.41 mm Hg (0.98, 3.84). Caffeine from any source at doses ≥ 410 mg per day significantly increased SPB (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, 1.78; change in DBP = mean - 0.52, 95 % CI = - 1.62, 0.57). Caffeine significantly increases 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*, or 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 control were excluded. Of the 10 RCTs included (**Appendix H**), six 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 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 as compared to 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 mm Hg (95 % CI –2.46 to 1.36) and of DBP was –0.45mm Hg (95 % CI –1.52 to 0.61). 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 duration 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 mm Hg (95 % CI, 1.0 to 3.7) for SBP and 1.2 mm Hg for DBP (95 % CI, 0.4 to 2.1). Duration of run-in and coffee dose significantly modified the effect of coffee on BP. Studies with the shorter run-in and the highest doses of coffee showed the biggest effect on BP. A significant effect of caffeinated coffee on BP was only observed by pooling studies using ≥ 5 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-h ambulatory SBP and DBP in 13 subjects with high-normal systolic and diastolic BP in a cross-over design. Changes in 24-h ambulatory BP did not differ significantly among interventions of 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 synephrine

The majority of human intervention studies available which have investigated the health effects of daily consumption (> 7 days) of 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 synephrine (in two doses of 49 mg each) for 60 days (Kaats et al., 2013) and in one study using a combination of 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 to placebo. The Panel notes that these studies provide no information on

whether the co-consumption of synephrine may modify 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 consumption of 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 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 hypertensives at baseline (Palatini, 2007) and the second recruited both normotensives and untreated hypertensives (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 only assessed intake of caffeinated coffee (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 %) in Finland at the time (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 the meta-analyses data from original studies were categorised into four categories of coffee consumption: reference (< 1 cup per day), low (1–3 cups per day), moderate (3–5 or 3-6 cups per day), and high (> 5 or > 6 cups per day). In the meta-analysis by Zhang et al. (2011), the group consuming > 0-3 cups per day was used as reference category for the study by (Uiterwaal et al., 2007) instead of coffee abstainers due to the low number of the latter, and the group consuming 3-6 cups per day as the second category. For the study by Palatini et al. (2007), the group consuming > 3 cups per day (highest category) was taken as the high category and the group of 1-3 cups per day 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 (1–3 cups per day), 1.07 (0.96, 1.20) for the moderate category (3–5 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 3 cups per day (RR for the comparison of 3 with 0 cups per day: 1.07; 95 % CI: 0.97, 1.20) and decreasing with higher intake (RR for the comparison of 6 with 0 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 > 0-3 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 to 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 as compared to no consumption, with no significant difference in risk among categories of coffee intake (0, 1-3, and > 3 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 C/C or C/A allele (59 %) of the CYP1A2 gene, but not in carriers of the fast A/A allele, suggesting that the risk of developing hypertension associated with caffeine consumption may depend on the genetic background. However, these two studies enrolled exclusively subjects with never treated stage 1 hypertension at baseline (incidence of hypertension requiring medication of 50.7 % in the 6-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: 0–1 cup per day, 2–3 cups per day, 4–5 cups per day, 6–7 cups per day, and > 8 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 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 > 0-3 cups per day was taken as reference, higher coffee intake was not associated with an increased risk of hypertension, whereas coffee abstainers showed a decreased risk compared to 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). Food frequency questionnaires 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 1991, 1995, and 1999 for NHS II (25 to 42 years) 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 %) in NHS II. In both cohorts, no linear association between caffeine consumption and 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 mg per day 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 quartile (608.1 mg per day 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), but not of decaffeinated coffee (p for trend = 0.08 and 0.67 in NHS I and NHS II, respectively), and risk of hypertension was observed in both cohorts. 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 inverse 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-shape relationship between total caffeine intake calculated 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 to women with very low (about 15-20 mg per day) or high (about 600 mg per day) intake. 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 risk of incident hypertension is conflicting. An increased risk for any level of intake, an inverse U-shape relationship and no relationship have 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 7402 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 in the United States, and three 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, 0 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, 5 cups per day). A significant heterogeneity between studies was found for the second and third categories. In the dose-response analysis, a nonlinear ($p < 0.001$) 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 8 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 (1-2 cups per day), 1.05 (95 % CI 0.90-1.22) for the second category (3-4 cups per day), and 1.16 (95 % CI 0.95-1.41) for the third category (> 4 cups per day), as compared to the reference category (none or < 1 cup per day). Sensitivity analyses removing for each category the studies contributing more for heterogeneity gave similar results. Stratified

analyses by region (US and Europe), publication year (before or after the median, 1995), fatal *vs* non-fatal events, and number of years if 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 only had two categories of coffee consumption, if subjects had type 2 diabetes or CVD at baseline, or if only caffeine intake (and not coffee) were reported. A total of 21 independent prospective cohort studies (20 publications) were included in the analysis, eight 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: light (reference), US studies, ≤ 1 cup per day; European studies, ≤ 2 cups per day; moderate: US studies, 1–3 cups per day, European studies, 3–4 cups per day; heavy: US studies 4–5 cups per day, European studies, 5–6 cups per day; and very heavy level: US studies, ≥ 6 cups per day; European study, ≥ 7 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, respectively. Stratified analyses by sex, region, study quality, 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 on or before 1995, reported a positive association between coffee consumption and risk of CHD, including fatal and non-fatal coronary artery disease, fatal ischemic heart disease, and fatal and non- fatal MI. The risk increased significantly at 1-4 cups per day (Murray et al., 1981), ≥ 3 cups per day (Lindsted et al., 1992), 3-4 cups per day (Klag et al., 1994); 4-6 cups per day (Klatsky et al., 1990); for non-fatal MI, but not for other coronary cases), 5-6 cups per day (Stensvold and Tverdal, 1995), ≥ 6 cups per day (LeGrady et al., 1987). In the study by Tverdal et al. (1990), only ≥9 cups per day were compared to < 1 cup. In the study by Happonen et al. (2004), the reference category was 376 to 813 mL per day of coffee, and thus does not allow concluding on the amount of coffee associated with an increased risk compared to 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), which 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 users. 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 (≤ 1 cup, 2-3 cups and ≥ 4 cups per day compared to 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, 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 nonfatal MI and 724 fatal cases of

CHD) among men and 2 254 cases (1 561 nonfatal 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 (<1/mo, 1/mo–4 per week, 5–7 per week, 2–3 per day, 4–5 per day, ≥ 6 per day) were 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) and chocolate snacks, consumption of all caffeinated beverages combined, and 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 normotensives 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 risk of sudden cardiac death (SCD). FFQs were completed at baseline and at 3 years. A total of 239 women experienced SCD after an average of 11 years of follow-up. Compared with very light alcohol intake (0.1–5 g per day), no alcohol intake, moderate alcohol intake (15–30 g per day), and heavy alcohol intake (> 30 g/d) were not associated with risk of SCD, 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 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 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) may modify the association between coffee consumption and 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. Fifty-five percent 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 nonfatal MI associated with the consumption of < 1, 1, 2 - 3, and ≥ 4 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 x coffee interaction). In sensitivity analysis stratified by age and smoking status, a significant gene x coffee interaction (p=0.003) was observed only among the younger participants (< 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 x 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 polymorphism modified the association between coffee consumption and risk of MI, although a significant coffee x 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 or the hypothesis 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 ≤ 4 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 4-5 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 3-4 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 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 *vs* caffeine from all sources, caffeine dose, or duration of follow-up. An inverse relationship was found between habitual caffeine intake and 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 stroke 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 was in 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 in women, and two included both sexes. A nonlinear association between coffee consumption and heart failure risk (p for nonlinearity = 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 to 0.99) for 1 to 2 servings per day, 0.93 (0.86 to 0.99) for 2 to 3 servings per day, 0.90 (0.82 to 0.99) for 3 to 4 servings per day, 0.89 (0.81 to 0.99) for 4 to 5 servings per day, 0.91 (0.83 to 1.01) for 5 to 6 servings per day, 0.93 (0.85 to 1.02) for 6 to 7 servings per day, 0.95 (0.87 to 1.05) for 7 to 8 servings per day, 0.97 (0.89 to 1.07) for 8 to 9 servings per day, 0.99 (0.90 to 1.10) for 9 to 10 servings per day, 1.01 (0.90 to 1.14) for 10 to 11 servings per day, and 1.03 (0.89 to 1.19) for 11 servings per day. With the exception of the study by Mukamal et al. (2009), which was conducted in subjects with 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 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 nonlinear ($p < 0.001$) association between coffee consumption and CHD risk with significant trend ($p < 0.001$) and non-significant heterogeneity ($p = 0.07$) was reported. Coffee consumption was inversely associated with the risk of stroke up to about 4 cups per day. No association was observed between coffee consumption and risk of stroke 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 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 nonlinear inverse association between coffee consumption and stroke risk was observed (p for nonlinearity = 0.005). Compared with no coffee consumption, the pooled relative risks of total stroke were 0.92 (95 % CI: 0.89, 0.96) for 1 cup of coffee per day, 0.86 (95 % CI: 0.78, 0.94) for 2 cups per day, 0.83 (95 % CI: 0.74, 0.92) for 3-4 cups per day, 0.87 (95 % CI: 0.77, 0.97) for 6 cups per day, and 0.93 (95 % CI: 0.79, 1.08) for 8 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- < 5 cups per day, 0.87 (95 % CI: 0.75, 1.02) for 5 – < 7 cups per day, and 0.93 (95 % CI: 0.76, 1.12) for ≥ 7 cups per day. In stratified analyses by sex (men, 5 studies; women, 5 studies; both sexes, 4 studies), geographical region (Europe, 7 studies; US, 2 studies; Japan, 2 studies), duration of follow-up (≤ 10 years, 4 studies; > 10 years, 7 studies), or stroke type (ischemic, 4 studies; haemorrhagic, 4 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 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 3 cups per day compared to 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 age (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), a caffeine content of 80 mg per 100 mL of coffee and of 26 mg per 100 mL of tea was 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 ischemic or haemorrhagic stroke. In the study by Lopez-Garcia et al. (2009), consumption of caffeinated beverages (cups) of < 1/month, 1/month–4/week, 5–7/week, 2–3 per day, and ≥ 4 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, 0 cups per day), the relative risk (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, 5 cups per day) category. No significant interactions were found between coffee intake and baseline hypertension or MI of the study population, smoking status, publication year, study quality score, dietary assessment method (24-hour diet recall/diet record/food frequency questionnaire versus other methods), stroke versus CHD as the outcome, country (US, Europe, Japan), sex, and type of coffee (caffeinated coffee or decaffeinated coffee) when the analyses were stratified for these variables. 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 6 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 Examination Survey III (NHAES III) reported no association between coffee consumption and CVD mortality (including stroke, congestive heart failure and ischemia-related

mortality) in multivariate analysis adjusted for confounding variables at any level of intake among 8 608 subjects >45 years of age.

4.5.2.9. Conclusions on the cardiovascular system

Data from RCTs suggests 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. Equal number of studies reporting positive, negative and no association between habitual caffeinated coffee consumption and long-term changes in BP are available. Whereas 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-shape 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 mostly 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, arrythmias-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 only been reported for CHD (but not for stroke, AF, or heart failure) in 8 out of the 56 studies reviewed, only six 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 ≤ 4 cups per day (one for ≥ 3 cups per day, one for ≥ 3-4 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 which have investigated all sources of caffeine. In addition, the individual studies and meta-analysis available which have 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 for up to 3-5 cups per day and no increased risk thereafter compared to 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 due to 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 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 it is poorly metabolised by the fetus (Aldridge et al., 1979; Aldridge et al., 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, small for gestational age), fetal death-related outcomes (miscarriage or spontaneous abortion, stillbirth), and infant death. Pre-term delivery, FGR and small for gestational age (SGA) are associated with increased risk of perinatal morbidity and mortality. FGR 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 and conducted four years apart (Jahanfar and Sharifah, 2009; Jahanfar and Jaafar, 2013), identified only one human intervention study which addressed this question (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 from either those booked for delivery at a 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 mailed questionnaire at 16 weeks of pregnancy and by a telephone interview at about 12 weeks of pregnancy, respectively. Eligibility criteria included regular consumption of at least three cups of coffee per day and no history of a low birthweight baby (< 2 500 g), preterm 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 or 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 (according to manufacturer), 100 mg for other caffeinated coffees, 50 mg for tea, and of 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 calculated 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 (IQR) was 317 mg (229-461 mg) 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 BMI 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) 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 birthweight.

4.5.3.2. Prospective cohort studies

Five prospective cohort studies have investigated the relationship between maternal intake of caffeine from caffeinated beverages and pregnancy (fetal and neonatal) outcomes, including 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. 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 for birth weight and related outcomes.

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 %) 18-45 years old living in the UK were recruited between 8 and 12 weeks 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 the period 13-28 weeks of pregnancy and the third covered the period 29-40 weeks of pregnancy. The prevalence of FGR in the cohort was 343/2635 (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 relation 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 odds ratio of having a baby with FGR were 1.2 (95 % CI, 0.9 to 1.6) for intakes of 100-199 mg per day, 1.5 (1.1 to 2.1) for intakes of 200-299 mg per day, and 1.4 (1.0 to 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 relations 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 to women consuming <100 mg per day of caffeine, ORs were 2.2 (95 % CI: 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 birthweight- 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 for spontaneous preterm delivery (PTD), 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 definitions. Caffeine intake in the first 4-5 months of pregnancy was assessed using a semi-quantitative FFQ at week 22 of pregnancy, which was validated using 4-day weighed food dairies. 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 was almost doubled (14 012 women, 24 %) and the median caffeine intake had decreased to 44 mg per day (13 to 104 mg per day). At gestational week 30, the median caffeine intake had increased again to 62 mg per day (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 a 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 birthweight. An additional 100 mg total caffeine per day was associated with a 21 to 28 g birthweight decrease, depending on the growth curve. There were 1 451 cases of spontaneous PTD (240 early spontaneous PTDs, between weeks 22 and 33 + 6 days, and 1 211 late spontaneous PTDs, 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 PTD, whereas black tea caffeine was associated with increased risk of early spontaneous PTD (OR 1.61, 95 % CI 1.10 to 2.35, p = 0.01). Total and coffee caffeine intake was 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 analysis 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 odds ratios for SGA consistently increased in the three models of SGA from the third sixtile upwards compared with the reference category. Categorising caffeine intake according to current Nordic (up to 200 mg per day) and WHO 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) compared to 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 birthweight-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 relationship between coffee and fetal death was investigated in a cohort of 88 482 Danish pregnant women who agreed to have a telephone interview at 16 weeks of gestation (Bech et al., 2005). Women were asked about the number of cups of coffee, tea or cola they had per day, and about potential confounding variables that could affect the outcome of interest. Fetal death was defined as defined as either miscarriage (gestational age < 196 days) or stillbirth (gestational age ≥ 196 days) and did not include intra-partum death. Coffee intake was considered as a categorical variable (0, 0.5–3, 4–7, and > 8 cups per day) and as a continuous variable (number of cups per day) in a test for trend. Although almost all caffeine intake came from coffee, data were also analysed according to caffeine intake by using average levels of 100 mg of caffeine for a cup of coffee and 50 mg for a cup of tea.

There were 1 102 fetal deaths. A total of 49 042 (55.4 %) women did not report drinking coffee during pregnancy; 27 803 women (31.4 %) drank ½–3 cups per day, 8 619 women (9.7 %) drank 4–7 cups per day, and 3 018 women (3.4 %) drank > 8 cups per day. The adjusted hazard ratios for fetal death associated with coffee consumption of 0.5-3, 4-7, and ≥ 8 cups of coffee per day were 1.03 (95 % CI: 0.89, 1.19), 1.33 (95 % CI: 1.08, 1.63), and 1.59 (95 % CI: 1.19, 2.13), respectively, relative to no coffee consumption. The risk increased with increasing coffee intake (p for trend = 0.001), with no statistically significant departure from linearity. No statistically significant interaction between coffee consumption and fetal death during specific periods of gestation was found. The increased risk of fetal death for coffee intakes ≥ 4 cups per day (about 400 mg caffeine) was similar in smokers and non-smokers, and in alcohol drinkers and non-alcohol drinkers, and the association did not change when caffeine intake from tea and coffee were considered. The risk of stillbirth due to placental dysfunction was increased among consumers of ≥ 4 cups of coffee per day (hazard ratio = 2.27, 95 % CI: 1.21, 4.28), but not the risk of stillbirth for other causes. The Panel notes that this study shows a dose-dependent positive association between caffeine intake at week 16 of pregnancy and fetal death-related outcomes (miscarriage and stillbirth), that the risk becomes significant at caffeine intakes of about ≥ 400 mg per day, and that stillbirth associated to higher caffeine intake was mostly due to placental dysfunction.

Weng et al. (2008) conducted a population-based prospective cohort study in 1 063 pregnant women living in the US in order to examine whether the risk of miscarriage was associated with caffeine consumption during pregnancy after controlling for pregnancy-related symptoms. Information on "caffeine" consumption during pregnancy was obtained during an in-person interview conducted soon after a woman's pregnancy was confirmed (the median gestational age at interview was 71 days). Women were asked to report their intake of beverages since their last menstrual period and whether patterns of consumption had changed since becoming pregnant. Sources of caffeine included caffeinated or decaffeinated coffee and tea, caffeinated soft drinks, and hot chocolate. Conversion factors to estimate the amount of caffeine intake were, for every 150 mL of a beverage, 100 mg for caffeinated coffee, 2 mg for decaffeinated coffee, 39 mg for caffeinated tea, 15 mg for caffeinated soda, and 2 mg for hot chocolate. Miscarriage was defined as spontaneous abortion at ≤ 20 weeks of pregnancy. The 63 % of total caffeine consumed was from coffee. Coffee was the only source of caffeine for 152 women (19 %), whereas 293 women (36.7 %) consumed caffeine only from sources other than coffee and 351 women (43.9 %) from coffee and non coffee sources. Overall 172 of women (16.18 %) miscarried. Whereas 264 women (25 %) reported no consumption of any caffeine-containing beverages during pregnancy, 635 women (60 %) reported 0-200 mg of caffeine intake per day, and 164 women (15 %) > 200 mg. After adjusting for potential confounders, the hazard ratio of miscarriage was 1.42 (95 % CI, 0.93 to 2.15) and 2.23 (95 % CI, 1.34 to 3.69) for daily caffeine consumption of 0-200 mg and > 200 mg, respectively (p for trend < 0.01), compared to the reference category (no caffeine consumption). Stratified analyses by sources of caffeine did not change the

association. The Panel notes that this study shows an increased risk of fetal death-related outcomes (miscarriage) associated with caffeine intake at doses > 200 mg per day in early pregnancy, regardless of the source.

The relationship between caffeine intake before and during pregnancy and the risk of miscarriage (≤ 20 weeks of pregnancy) and stillbirth (> 20 weeks of pregnancy) was also investigated in a prospective cohort study (Fenster et al., 1997) of 5 144 pregnant women living in the US. Women were asked to quantify (cups/cans per day) their daily consumption of decaffeinated coffee and caffeinated beverages (coffee, tea, soft drinks) in the week before a computer-assisted telephone interview, which took place between 4 and 13 weeks of pregnancy (mean 8 weeks), and during the week around their last menstrual period. Caffeine consumption was calculated assuming a content of 107 mg and 34 mg in a cup of coffee and a cup of tea, respectively, and of 47 mg in a can of soft drink.

There were 499 cases of miscarriage and 32 stillbirths. About 74 % of women reported caffeine consumption before pregnancy but only 50 % during pregnancy. About 13 % of women reported caffeine consumption > 300 mg per day before pregnancy, but only 4 % during pregnancy. Caffeine consumption and consumption of any type of caffeinated beverages, either before pregnancy or in the first trimester of pregnancy, were not associated with an increased risk of miscarriage. The adjusted OR for caffeine intake > 300 mg per day was 1.3 (95 % CI = 0.8, 2.1). Conversely, consumption of > 3 cups of decaffeinated coffee per day in the third trimester of pregnancy was associated with an increased risk of miscarriage (OR = 1.52, 95 % CI = 0.85, 2.72). Data on caffeine intake in relation to the risk of stillbirth was not reported. The Panel notes that this study shows no association between caffeine intake in early pregnancy and risk of fetal death-related outcomes (miscarriage).

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 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) is less consistent (COT, 2008), as observed in the prospective cohort studies described above.

Some of these studies have investigated whether 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 the prospective cohort studies available (CARE Study Group, 2008; Sengpiel et al., 2013) show a dose-dependent positive association between caffeine intake during pregnancy and risk of adverse birth weight-related outcomes (i.e, FGR, SGA). The relationship between caffeine consumption during pregnancy and other pregnancy outcomes (e.g., in relation to length of gestation or fetal death) is less consistent. The Panel also notes that the relationship between caffeine intakes and adverse birthweight-related outcomes is observed at all levels of intake, with no threshold below which the relationship is not observed. However, the Panel considers the risk to become 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) and 7 % (in combination with sugar-containing soft drinks) to caffeine intake in the two studies reporting on this source (CARE Study Group, 2008) and (Sengpiel et al., 2013), respectively).

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 question are lacking.

5. DOSE RESPONSE ASSESSMENT AND DERIVATION OF INTAKE LEVELS OF NO CONCERN

5.1. Adults

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 blood pressure, myocardial blood flow, 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, and even in hot environments as long as body fluids are timely replaced. This applies to non-habitual caffeine consumers, to caffeine-deprived subjects and to habitual caffeine consumers. The Panel notes that this may not be the case when caffeine is consumed prior to physical exercise under unusual environmental conditions (e.g. high altitude). The Panel also notes that no studies are available in pregnant women or middle age/elderly subjects undertaking intense physical exercise.

Single doses of caffeine up to 200 mg (about 3 mg/kg bw) 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 the musculoskeletal systems.

Single doses of caffeine up to 200 mg (about 3 mg/kg bw) 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 Panel notes that 100 mg (about 1.5 mg/kg bw) of caffeine may increase sleep latency and reduce sleep duration in some adult individuals, particularly when consumed close to bedtime.

The Panel considers that other common constituents of "energy drinks" (i.e. taurine, D-glucurono-γ-lactone) or alcohol are unlikely to adversely interact with caffeine in relation to these outcomes at the dose levels reported in the studies reviewed. The Panel also considers that the short-term effects of co-consumption of caffeine and synephrine on the cardiovascular system have not been adequately investigated in humans, particularly when consumed shortly before intense physical exercise.

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 raise safety concerns for adults in the general population should take into account the half-life of caffeine (mean 4 hours, range 2-8 hours) so as not to exceed the maximum plasma concentrations achieved with an acute 200 mg dose.

Caffeine intakes from all sources up to 400 mg per day (corresponding to about 5.7 mg/kg bw for a 70 kg adult) do not raise safety concerns for adults in the general population, except 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.

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 in the market) or unknown. However, the Panel considers that other common constituents of "energy drinks" (e.g. taurine, D-glucurono-γ-lactone) or alcohol are unlikely to adversely interact with caffeine in relation to these outcomes. The Panel also considers that the long-term effects of co-consumption of caffeine and synephrine on the cardiovascular system have not been adequately investigated in humans.

5.2. Pregnant women

Caffeine intakes from all sources up to 200 mg per day by pregnant women in the general population do not raise 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 risk of adverse birthweight-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 birthweight-related outcomes. However, given the consistency of the association, the dose-response relationship observed in the studies available, 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 the studies available, 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

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

Repeated doses of caffeine consumed by lactating women in the general population which do not raise safety concerns for the breastfed infant should take into account the half-life of caffeine (mean 4 hours, range 2-8 hours) in women and the longer half-life in infants. In this context, doses of 400 mg per day (corresponding to 5.7 mg/kg bw per day) consumed by lactating women do not raise safety concerns for the beastfed infant.

5.4. Children and adolescents (1 year 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 base a safe level of caffeine intake.

The Panel considers that caffeine intakes of no concern derived for acute consumption in adults (3 mg/kg bw per day) may serve as a basis to derive daily caffeine intakes of no concern for children and adolescents. The Panel notes that the caffeine clearance in children and adolescents is at least that of adults, if not faster, and that the limited studies available on the acute and longer-term effects of caffeine on anxiety and behaviour in children and adolescents support this level of no concern. The Panel also notes that, as in adults, caffeine doses of about 1.5 mg/kg bw may increase sleep latency

and reduce sleep duration in some children and adolescents, particularly when consumed close to bedtime.

6. Characterisation of the risk

6.1. Adults

6.1.1. Single dose / single session

There are no data available to estimate single doses of caffeine intake. The EFSA energy drink report, however, provides information to estimate caffeine intakes from "energy drinks" at "single sessions", defined as periods of time of a couple of hours, also in connexion 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 14 % of adult "energy drink" consumers and about 4 % of the total adult population may exceed caffeine intakes of 200 mg on a single sports session (Table 4).

6.1.2. Daily caffeine intakes

For seven out of 13 MSs, estimates of the 95th percentile of daily caffeine intake from all sources exceeded 400 mg. In these countries, the estimated proportion of the adult population exceeding daily intakes of 400 mg ranged from 5.8 % to almost one third (32.9 %) (Appendix B).

6.2. Pregnant women

The mean and the 95th percentile of the daily caffeine intakes from all sources 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 in this population subgroup (Appendix B).

6.3. Lactating women

The mean and the 95th percentile of the daily caffeine intakes from all sources 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 in this population subgroup (Appendix B).

6.4. Adolescents (10 to < 18 years)

6.4.1. Single dose / single session

Like for adults, there are no data available to estimate single doses of caffeine by adolescents. The EFSA energy drink report can be used to estimate caffeine intakes from "energy drinks" at "single sessions", also in connection with physical exercise, in absolute amounts, but not on a kg bw basis.

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 11 % of adolescent "energy drink" consumers and about 8 % of all adolescents may exceed caffeine intakes of 200 mg on a single sport session (Table 4).

6.4.2. Daily caffeine intakes

For five out of 13 MSs, the 95th percentile of caffeine intake from all sources 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 all sources ranged from 5.2 % to 10 % (Appendix B). The mean age of the adolescents studied in the surveys of these five countries ranged from 13 years to 16 years.

6.5. Children (3 to < 10 years)

6.5.1. Single dose / single session / single days

There are no data available to estimate caffeine intakes at single doses or at single sessions in children. In the absence of such data, estimates on the proportion of single days in which caffeine intake exceeds 3 mg/kg bw among all survey days may serve as a conservative approximation.

For nine out of 16 MSs the estimated 95th percentile of caffeine intake from all sources on a single day exceeded 3 mg/kg bw. The proportion of days on which daily intakes of caffeine from all sources exceeds 3 mg/kg bw ranges from 6.2 % to 15.4 % (Appendix D).

6.5.2. Daily caffeine intakes

For six out of 14 Member States the estimates for the 95th percentile of mean 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 all sources range from 6.0 % to 12.6 % (Appendix B).

6.6. Toddlers (12 to < 36 months)

6.6.1. Single dose / single session / single days

There are no data available to estimate single doses of caffeine or caffeine consumed at single sessions for toddlers. In the absence of such data, estimates on the proportion of single days with caffeine intakes exceeding 3 mg/kg bw among all survey days may serve as conservative approximation.

For three out of ten MSs 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 7.3 % to 36.7 % (Appendix D).

6.6.2. Daily caffeine intakes

Only for one out of nine MS the 95th percentile of caffeine intake from all sources exceeds 3 mg/kg bw per day. About 6 % of the toddlers had a daily consumption > 3 mg/kg bw in that country (Appendix B).

CONCLUSIONS

Adults

Single doses of caffeine up to 200 mg (about 3 mg/kg bw) from all sources do not raise safety concerns for the general adult population. The same amount of caffeine does not raise 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 age/elderly subjects undertaking intense physical exercise. Single doses of 100 mg (about 1.5 mg/kg bw) of caffeine may increase sleep latency and reduce sleep duration in some adult individuals, particularly when consumed close to bedtime.

Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg bw per day) do not raise safety concerns for adults in the general population, except pregnant women (see below).

Other common constituents of “energy drinks” (i.e. taurine, D-glucurono-γ-lactone) or alcohol are unlikely to adversely interact with caffeine. The short- and long-term effects of co-consumption of caffeine and synephrine on the cardiovascular system have not been adequately investigated in humans.

About 4 % of the adult population may exceed 200 mg of caffeine on a single session of "energy drink" consumption in connexion with physical exercise. This information is not available for other sources of caffeine.

In seven out of 13 countries, the 95th percentile of daily caffeine intake from all sources exceeded 400 mg. The estimated proportion of the adult population exceeding daily intakes of 400 mg in these countries ranged from 5.8 to almost one third (32.9 %).

Pregnant women

Caffeine intakes from all sources up to 200 mg per day by pregnant women in the general population do not raise safety concerns for the fetus. This is based on prospective cohort studies where the contribution of "energy drinks" to total caffeine intakes was low (about 2 %).

Data on daily caffeine intake in this population subgroup is scarce.

Lactating women

Single doses of caffeine up to 200 mg and caffeine doses of 400 mg per day (about 5.7 mg/kg per day) consumed by lactating women in the general population do not raise safety concerns for the beastfed infant.

Data on daily caffeine intake in this population subgroup is scarce.

Children and adolescents

Owing to the limited information available for this population subgroup, caffeine intakes of no concern derived for acute consumption in adults (3 mg/kg bw per day) may serve as a basis to derive daily caffeine intakes of no concern for children and adolescents. As in adults, caffeine doses of about 1.5 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents, particularly when consumed close to bedtime.

About 8 % of the adolescent population (10 to < 18 years) may consume more than 200 mg of caffeine from "energy drinks" on a single session in connexion with physical exercise. This information is not available for other sources of caffeine. In five out of 13 countries, the 95th percentile of caffeine intake from all sources exceeded 3 mg/kg bw per day, ranging from 5.2 to 10 % the percentage of adolescents exceeding that amount.

In children (3 to < 10 years), the 95th percentile of caffeine intake from all sources on a single day exceeded 3 mg/kg bw in nine out of 16 countries (6.2 to 15.4 % of survey days). The proportion of children with daily caffeine intakes from all sources beyond 3 mg/kg bw ranged from 6.0 % to 12.6 % in the six out of 14 countries where the 95th percentile exceeded 3 mg/kg bw.

For toddlers (12 to < 36 months), the estimated 95th percentile of caffeine intake from all sources on a single day exceeded 3 mg/kg bw in three out of 10 countries (7 to 37 % of survey days). Only in one out of nine countries the 95th percentile of daily caffeine intake from all sources exceeded 3 mg/kg bw (6 % of toddlers).

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3587 **APPENDICES**

3588 **Appendix A. Dietary surveys used for the assessment of caffeine intakes**

Country	Survey 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	2002-2002	3	36/108	625/1875	-	-	-	-
Belgium	Diet National 2004	2004	2	-	-	576/1187 *(16a)*	1292/2648	511/1045	704/1408
Bulgaria	NSFIN	2004	1			-/162	-/691	-/151	-/200
Bulgaria	NUTRICHILD	2007	2	428/856	433/867	-	-	-	-
Cyprus	Childhealth	2003	3	-	-	303/909 *(13a)*	-	-	-
Czech Republic	SISP04	2003-2004	2	-	389/778	298/596 *(13a)*	1666/3332	-	-
Denmark	DANSDA 2005-08	2005-2008	7	-	298/2085	377/2622 *(13a)*	1739/12127	274/1916	12/84
Denmark	IAT 2006 07	2006-2007	7	917/6388	-	-	-	-	-
Estonia	NDS 1997	1997	1				-/1866	-	-
Finland	DIPP 2001 2009	2001-2009	3	500/1500	750/2250	-	-	-	-
Finland	NWSSP07 08	2007-2008	4	-	-	306/1186 *(13a)*	-	-	-
Finland	FINDIET2012	2012	2	-	-	-	1295/2590	413/826	-
France	INCA2	2007	7	-	482/3315	973/6728 *(14a)*	2276/15727	264/1824	84/571
Germany	VELS	2001-2002	6	348/1947	293/1610	-	-	-	-
Germany	EsKiMo	2006	3	-	835/2498	393/1179 *(11a)*	-	-	-
Germany	National Nutrition Survey II	2007	2	-	-	1011/2022 *(16a)*	10419/20838	2006/4012	490/980
Greece	Regional Crete	2004-2005	3		838/2508	-	-	-	-
Greece	DIET LACTATION GR	2005-2007	3	-	-	-	65/350	-	-
Hungary	National Repr Surv	2003	3	-	-	-	1074/3222	206/618	80/240
Ireland	NANS 2012	2008-2010	4	-	-	-	1274/5096	149/596	77/308
Italy	INRAN SCAI 2005 06	2005-2006	3	36/108	193/579	247/741	2313/6939	290/870	228/684

						(14a)			
Latvia	EFSA TEST	2008	2		187/377	453/979 *(14a)*	1271/2655	-	-
Latvia	FC PREGNANTWOMEN 2011	2011	2	-	-	-	1002/2005	-	-
Netherlands	VCP kids	2006-2007	3	322/644	957/1914	-	-	-	-
Netherlands	VCPBasis AVL2007 2010	2007-2010	2	-	447/894	1142/2284 *(14a)*	2057/4114	173/346	
Netherlands	VCP-Elderly	2010-2012	2	-	-	-	-	289/578	450/900
Poland	IZZ FAO 2000	2000	1	-/79	-/409	-/666 *(14a)*	-/2527	-/329	-/124
Romania	Dieta Pilot Children	2012	1	-	-/205	-/567 *(14a)*	-	-	-
Romania	Dieta Pilot Adults	2012	7	-	-	-	1254/8770	83/581	45/315
Slovakia	SK MON 2008	2008	1	-	-	-	2761	-	-
Slovenia	CRP 2008	2007-2008	1	-	-	-	407	-	-
Spain	enKid	1998-2000	2	17/34	156/312	209/418 *(12a)*	-	-	-
Spain	AESAN	1999-2001	3	-	-	-	410/828	-	-
Spain	NUT INK05	2004-2005	2		399/798	651/1302 *(14a)*	-	-	-
Spain	AESAN FIAB	2009	3	-	-	86/226 *(17a)*	981/2748	-	-
Sweden	NFA	2003	4	-	1473/5875	1018/4047 *(12a)*	-	-	-
Sweden	Riksmaten 2010	2010-2011	4	-	-	-	1430/5680	295/1167	72/288
United Kingdom	NDNS-RollingProgrammeYears1-3	2008-2011	4	185/737	651/2595	666/2653 *(14a)*	1266/5040	166/662	139/552
United Kingdom	DNSIYC 2011	2011	4	1314/5217	-	-	-	-	-

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

Age class	Country	Survey	Number of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95[(1)]	Mean	P95[(1)]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)

Age class	Country	Survey	Number of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95[1]	Mean	P95[1]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
Toddlers (12 to < 36 mon) 10 surveys	Belgium	Regional Flanders	36	14.8	-	1.1	-	8.3	n.a. [2]
	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 ProgrammeYears 1-3	185	4.9	30.6	0.4	2.2	2.2	n.a.
		DNSIYC 2011	1314	2.0	7.8	0.2	0.7	1.8	n.a.
Other children (3 to < 10 yrs) 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. [2]
	Sweden	NFA	1473	9.9	37.3	0.4	1.4	0.6	n.a.

Age class	Country	Survey	Number of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95[1]	Mean	P95[1]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
	United Kingdom	NDNS-Rolling Programme Years 1-3	651	9.9	46.9	0.4	1.8	1.4	n.a.
Adolescents (10 to < 18 yrs) 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	1142	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	1018	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 yrs) 16 surveys	Belgium	Diet National 2004	1292	191.9	543.3	2.7	7.6	n.a.	10.4 (9.1)
	Czech Republic	SISP04	1666	124.8	269.7	1.7	3.8	n.a.	1.2 (0.7)
	Denmark	DANSDA 2005-2008	1739	319.4	742.4	4.3	10.0	n.a.	32.9 (29.1)
	Finland	FINDIET2012	1295	236.0	538.5	3.1	6.9	n.a.	13.4 (10.6)
	France	INCA2	2276	154.5	414.0	2.3	6.4	n.a.	5.8 (6.7)
	Germany	National Nutrition Survey II	10419	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[3]
	Hungary	National Repr Surv	1074	103.0	268.1	1.5	3.8	n.a.	1.4 (1.7)
	Ireland	NANS 2012	1274	149.0	346.2	2.0	4.7	n.a.	3.0 (2.7)
	Italy	INRAN SCAI 2005-2006	2313	139.3	323.1	2.1	4.8	n.a.	2.1 (2.8)

Age class	Country	Survey	Number of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95[1]	Mean	P95[1]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
	Latvia	EFSA TEST	1271	149.4	310.4	2.0	4.4	n.a.	1.6 (1.3)
		Pregnant Women 2011	1002	108.6	205.7	1.6	3.0	n.a.	6.5[3]
	Netherlands	VCP Basis AVL2007-2010	2057	258.5	589.2	3.3	7.7	n.a.	17.6 (13.3)
	Romania	Dieta Pilot Adults	1254	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	1430	205.3	482.2	2.8	6.7	n.a.	9.0 (8.0)
	United Kingdom	NDNS-Rolling Programme Years 1-3	1266	138.2	318.4	1.8	4.4	n.a.	2.4 (2.4)
Elderly (65 to < 75 yrs) 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	2006	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 yrs) 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)

Age class	Country	Survey	Number of subjects	Caffeine intake				% of subjects with a mean daily intake of	
				mg per day		mg/kg bw per day			
				Mean	P95[1]	Mean	P95[1]	> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
	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)
	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)

(1) The 95th percentile estimates obtained on dietary surveys/age classes with less than 60 subjects may not be statistically robust (EFSA, 2011b) and were consequently not considered (" - ").
(2) n.a. = not applicable
(3) % 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(1) (all days)				95th percentile caffeine intake(1) (consumption days)			
		mg per day		mg per day		mg per day		mg per day	
		Min(2)	Max(2)	Min(2)	Max(2)	Min(2)	Max(2)	Min(2)	Max(2)
Toddlers (12 to < 36 mon; 11 surveys)	**Total intakes**	0.0	82.5	0.0	7.1	(3)	(3)	(3)	(3)
	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 yrs; 19 surveys)	**Total intakes**	0.0	130.1	0.0	5.7	(3)	(3)	(3)	(3)
	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 yrs; 19 surveys)	**Total intakes**	0.0	239.8	0.0	4.3	(3)	(3)	(3)	(3)
	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 yrs; 24 surveys)	**Total intakes**	0.0	809.3	0.0	10.8	(3)	(3)	(3)	(3)
	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 yrs; 15 surveys)	**Total intakes**	0.0	784.3	0.0	10.7	(3)	(3)	(3)	(3)
	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 yrs; 13 surveys)	**Total intakes**	0.0	801.0	0.0	13.1	(3)	(3)	(3)	(3)
	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

(1) The 95th percentile estimates obtained on dietary surveys/age classes with less than 60 days may not be statistically robust (EFSA, 2011a) and were consequently not considered (" - ") in this table.

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

(3) Please note that "total intakes" are not derived by adding up the min and max values for the different food categories, but that "total intakes" reflect the min and max intakes for total caffeine from all sources for all days among the respective survey. (Adding up the min and max values for the different food categories, is not an appropriate approach because these values represent intakes at different days, thus would unrealistically overestimate high consumption at single days).

3604 **Appendix D. Caffeine intake on a single day by country survey and age class**

Age class	Country	Survey	Number of days	95th caffeine intake(1)		% 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 (12 to < 36 mon) 11 surveys	Belgium	Regional Flanders	108	53.1	4.3	10.2	n.a.(1)
	Bulgaria	NUTRICHILD	856	22.1	1.9	1.4	n.a.
	Denmark	IAT 2006 07	6388	17.1	1.4	1.0	n.a.
	Finland	DIPP 2001 2009	1500	0.5	0.1	0.1	n.a.
	Germany	VELS	1947	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	5217	5.5	0.6	1.6	n.a.
Other children (3 to < 10 yrs) 19 surveys	Belgium	Regional Flanders	1875	48.6	2.8	4.1	n.a.
	Bulgaria	NUTRICHILD	867	21.6	1.3	2.4	n.a.
	Czech Republic	SISP04	778	99.0	4.6	15.4	n.a.
	Denmark	DANSDA 2005-08	2085	58.5	2.2	2.3	n.a.
	Finland	DIPP 2001 2009	2250	114.1	5.7	12.3	n.a.
	France	INCA2	3315	75.6	3.3	6.7	n.a.
	Germany	EsKiMo	2498	69.8	2.6	4.0	n.a.
		VELS	1610	51.7	3.0	5.0	n.a.
	Greece	Regional Crete	2508	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	1914	63.3	3.2	6.2	n.a.
		VCP Basis AVL2007 2010	894	104.9	3.7	7.6	n.a.

Age class	Country	Survey	Number of days	95th caffeine intake(1)		% 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)
	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	5875	54.0	2.0	1.8	n.a.
	United Kingdom	NDNS-Rolling Programme Years 1-3	2595	51.8	2.2	2.0	n.a.
Adolescents (10 to < 18 yrs) 19 surveys	Belgium	Diet National 2004	1187	216.0	3.5	7.2	0.0
	Bulgaria	NSFIN	162	93.1	1.8	3.1	0.0
	Cyprus	Childhealth	909	141.9	3.0	5.1	0.0
	Czech Republic	SISP04	596	131.5	2.9	4.2	0.0
	Denmark	DANSDA 2005-08	2622	116.8	2.3	2.6	0.0
	Finland	NWSSP07 08	1186	219.2	4.1	11.0	0.0
	France	INCA2	6728	115.3	2.3	2.8	0.0
	Germany	National Nutrition Survey II	2022	239.8	3.8	7.7	0.0
		EsKiMo	1179	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	2284	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	1302	123.0	2.3	2.2	0.0
	Sweden	NFA	4047	77.9	2.0	1.7	0.0
	United Kingdom	NDNS-Rolling Programme Years 1-3	2653	155.0	2.5	4.0	0.0

Age class	Country	Survey	Number of days	95th caffeine intake(1)		% 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)
Adults (18 to < 65 yrs) 24 surveys	Austria	ASNS	2123	356.0	5.4	n.a.	3.4 (4.1)
	Belgium	Diet National 2004	2648	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	3332	298.0	4.2	n.a.	1.9 (1.9)
	Denmark	DANSDA 2005-08	12127	809.3	10.8	n.a.	31.8 (29.6)
	Estonia	NDS 1997	1866	311.5	4.6	n.a.	1.9 (2.7)
	Finland	FINDIET2012	2590	538.5	7.0	n.a.	14.1 (11.9)
	France	INCA2	15727	445.0	6.7	n.a.	6.6 (7.8)
	Germany	National Nutrition Survey II	20838	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	3222	270.1	4.2	n.a.	1.3 (1.9)
	Ireland	NANS 2012	5096	378.4	5.1	n.a.	4.5 (3.7)
	Italy	INRAN SCAI 2005 06	6939	325.7	5.1	n.a.	3.2 (3.6)
	Latvia	EFSA TEST	2655	338.2	4.8	n.a.	2.3 (2.2)
		FC Pregnant Women 2011	2005	221.8	3.3	n.a.	0.0[c]
	Netherlands	VCP Basis AVL2007 2010	4114	622.5	8.1	n.a.	19.0 (14.7)
	Poland	IZZ FAO 2000	2527	347.3	5.5	n.a.	2.4 (4.0)
	Romania	Dieta Pilot Adults	8770	122.4	1.8	n.a.	0.2 (0.2)
	Slovakia	SK MON 2008	2761	305.0	4.4	n.a.	1.8 (1.6)
	Slovenia	CRP 2008	407	211.9	3.2	n.a.	1.0 (1.2)
	Spain	AESAN	828	155.7	2.3	n.a.	0.4 (0.5)
		AESAN FIAB	2748	178.1	2.8	n.a.	1.5 (1.5)
	Sweden	Riksmaten 2010	5680	535.1	7.2	n.a.	11.2 (9.6)
	United Kingdom	NDNS-Rolling Programme Years 1-3	5040	353.2	4.9	n.a.	3.5 (3.1)
Elderly (65 to < 75 yrs)	Belgium	Diet National 2004	1045	511.8	6.9	n.a.	11.0 (10)
	Bulgaria	NSFIN	151	89.0	1.2	n.a.	0.0 (0.0)

Age class	Country	Survey	Number of days	95th caffeine intake(1)		% 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)
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	1824	335.5	4.7	n.a.	2.4 (2.6)
	Germany	National Nutrition Survey II	4012	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	1167	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 (≥ 75 yrs) 13 surveys	Belgium	Diet National 2004	1448	445.0	6.6	n.a.	8.1 (8.1)
	Bulgaria	NSFIN	200	66.8	0.9	n.a.	0.0 (0.0)
	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)

(1) The 95th percentile estimates obtained on dietary surveys/age classes with less than 60 days may not be statistically robust (EFSA, 2011a) and were consequently not considered (“ - ”).
(2) n.a. = not applicable for the respective population group
(3) % exceeding 200 mg/kg bw per day

3608 **Appendix E. Food sources contributing daily caffeine intake**

Population Group	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Coffee	Tea	Chocolate	Cola beverages	Energy Drinks
Toddlers (12 to < 36 mon)	Belgium	Regional Flanders	12.7	0.0	29.6	57.7	0.0
	Bulgaria	NUTRICHILD	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	0.0	53.6	37.6	8.8	0.0
	Netherlands	VCP kids	2.6	73.2	20.3	3.9	0.0
	Spain	enKid	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 Years1-3	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 yrs)	Belgium	Regional Flanders	19.8	7.5	20.4	52.1	0.2
	Bulgaria	NUTRICHILD	0.0	6.9	77.6	15.5	0.0
	Czech Rep.	SISP04	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	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	1.8	3.7	85.1	9.3	0.0
	Italy	INRAN SCAI 2005 06	39.9	19.1	32.8	8.1	0.0
	Latvia	EFSA TEST	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	2.4	64.9	18.3	14.4	0.0
	Spain	NUT INK05	1.8	0.2	90.9	7.1	0.0
		enKid	2.1	0.0	97.9	0.0	0.0
	Sweden	NFA	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 yrs)	Belgium	Diet National 2004	24.2	16.9	14.8	38.8	5.3
	Cyprus	Childhealth	53.2	9.2	37.6	0.0	0.0
	Czech Rep.	SISP04	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	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	33.3	33.1	16.3	17.3	0.0
	Italy	INRAN SCAI 2005 06	42.1	22.6	20.2	14.4	0.7
	Latvia	EFSA TEST	32.4	53.4	11.5	2.3	0.3
	Netherlands	VCPBasis AVL2007 2010	13.9	42.8	12.3	22.9	8.1

Population Group	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Coffee	Tea	Chocolate	Cola beverages	Energy Drinks
	Spain	AESAN FIAB	41.1	1.0	41.9	15.9	0.0
		NUT INK05	17.4	1.5	64.5	16.5	0.0
		enKid	8.2	0.0	91.8	0.0	0.0
	Sweden	NFA	2.7	20.7	33.0	42.1	1.6
	United Kingdom	NDNS-Rolling Programme Years1-3	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 yrs)	Belgium	Diet National 2004	81.3	5.8	2.9	9.4	0.7
	Czech Rep.	SISP04	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	80.5	13.3	3.2	3.0	0.0
	Germany	National Nutrition Survey II	84.1	10.9	1.8	3.1	0.0
	Hungary	National Repr Surv	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	91.4	5.0	2.0	1.5	0.1
	Latvia	EFSA TEST	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	40.5	20.7	16.5	18.1	4.2
		AESAN FIAB	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 Years1-3	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 yrs)	Belgium	Diet National 2004	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	78.9	19.1	1.5	0.5	0.0
	Germany	National Nutrition Survey II	86.5	12.1	0.8	0.5	0.0
	Hungary	National Repr Surv	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	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 Years1-3	32.6	64.9	1.3	0.8	0.4
	Median		**84**	**12**	**1**	**1**	**0**
	Range		**(24-97)**	**(2-74)**	**(0-10)**	**(0-1)**	**(0)**

Population Group	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Coffee	Tea	Chocolate	Cola beverages	Energy Drinks
Very elderly (≥ 75 yrs)	Belgium	Diet National 2004	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	81.3	11.0	7.4	0.4	0.0
	Germany	National Nutrition Survey II	84.8	13.8	1.2	0.1	0.0
	Hungary	National Repr Surv	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	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-RollingProgrammeYears1-3	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)**

3609

3610 **Appendix F. Human intervention studies on the vascular effects of a single dose and of repeated doses of caffeine consumed**
3611 **within a day**

3612

								Outcomes			
Study	**Design**	**Subjects, habitual daily consumption**	**Run-in[1]**	**n (I/C) [c]**	**Intervention**	**Caffeine (mg)**	**Control**	**Arterial stiffness**	**Endothelial function**	**BP**	**Other**
Single doses of caffeine											
Vlachopoulos et al. (2003)	rdb-X	Healthy, >100 mg caffeine	12h	20	Caffeine	250	Placebo	PWV, AI	-	Radial, aortic and pulse BP	-
Hartley et al. (2004) Women	rdb-P	Healthy, 50-700 mg caffeine	14h	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	12h	27 (17,10)	Caffeine	100	Water	FCW, FEW, WR, WS	-	Brachial BP	-
Umemura et al. (2006)	rdb-P	Healthy, non habitual caffeine consumers	24h	20 (10,10)	Caffeine	300	Placebo	-	FBF	Brachial BP	-
Astorino et al. (2007)	rdb-X	Resistance trained, 0-600 mg caffeine per day	48h	22	Caffeine	6 mg/kg bw	Placebo	-	-	Brachial BP, MABP, RPP	-
Arciero and Ormsbee (2009) pre-menopausal	rdb-X	Healthy, <400 mg caffeine	48h	10	Caffeine	5 mg/kg FFM (208-270 mg)	Placebo (lactose)	-	-	Brachial BP	-
Arciero and Ormsbee (2009) post-menopausal				10							
Farag et al. (2010)	rdb-X	Healthy, 3-4 cups coffee	6d[3]	165	Caffeine	250	Placebo	-	-	Brachial BP	-

								Outcomes			
Study	**Design**	**Subjects, habitual daily consumption**	**Run-in[1]**	**n (I/C) [c]**	**Intervention**	**Caffeine (mg)**	**Control**	**Arterial stiffness**	**Endothelial function**	**BP**	**Other**
Mahmud and Feely (2001)	rdb-X	Healthy, NR	12h	7	Coffee	150	DC	PWV, AI	-	Brachial BP	-
Papamichael et al. (2005)	rsb-X	Healthy, 1-2 cups coffee	12-24h	17	Coffee	80	DC	-	FMD (brachial artery)	Brachial BP	-
Buscemi et al. (2010)	rdb-X	Healthy, ≤2 cups coffee	24h	20	Coffee	130	Decaffeinated coffee	-	FMD (brachial artery)	Brachial BP	-
Buscemi et al. (2011)	rdb-X	Healthy, ≤2 cups coffee	24h	40	Coffee	130	Decaffeinated coffee	-	-	Brachial BP	QT, QTc
Hodgson et al. (1999)	rsb-X	Healthy, NR	24h	20	Caffeine Black tea Green tea	180	Water	-	-	Brachial BP	-
Vlachopoulos et al. (2006) black tea	rsb-X	Healthy, NR	12h	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	12h	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	12h	47	Caffeine	250 +250 4h apart	Placebo	-	-	Day ambulatory BP	-
Farag et al. (2005a); Farag et al. (2005b)	rdb-X	Healthy, 50-700 mg caffeine	5d[2]	85	Caffeine	250 x 3, 4h 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; HR= heart rate; MABP = mean arterial blood pressure; nr-P = non-randomised, parallel; NR = not reported; PWV= pulse wave velocity; rdb-X = randomised, doble-blind, cross-over; rdb-P = randomised, doble-blind, parallel; rsb-X = randomised, single-blind, cross-over; RPP = rate-pressure product; WR = wave reflections; WS = wave speed.

[1] Refers to the time of abstinence from caffeine before testing, unless otherwise noted

[2] Subjects consumed 0, 300 or 600 mg of caffeine (in three divided daily doses) per day for 5 days before testing

[3] Subjects consumed 80 mg of caffeine three times per day for 6 days before testing

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

Study	Design[1]	Run-in[2]	Duration	n	Synephrine (mg)	Caffeine (mg)	Δ SBP (mm Hg)	Δ DBP (mm Hg)
Penzak Penzak et al. (2001) et al., 2001	rol-X	8h[3]	13h	12	13.5	-	NS	NS
Min Min et al. (2005) et al., 2005	rdb-X	12 h	8h	18	27	-	NS	NS
Haller et al. (2005a)	rdb-X	24 h	6h	10	46.9	-	NS	NS
Haller et al. (2005a)	rdb-X	24 h	6h	10	5.5 + 5.7[4]	239.2	+9.6 ± 6.2 *	+9.1 ± 7.8 *
Bui et al. (2006)	rdb-X	10h	6h	15	54	-	+7.3 ± 4.6 *	+2.6 ± 3.8 *
Sale et al. (2006)	rdb-X	48 h	7h	10	12	150	NS	NS
Haller et al. (2008)	rdb-X	24 h	2h	10	21	304	NS	+8.7 ± 3.8*
Seifert et al. (2011)	rdb-X	24h[5]	24h	23	13	176	NS	NS
Stohs et al. (2011)	rdb-P	8-10h	2h	10[6]	50	-	NS	NS

NR= not reported; NS = non significant; rdb-X = randomised, doble-blind, cross-over; rdb-P = randomised, doble-blind, parallel; rol-X = randomised, open-label, cross-over.

[1] All studies had a double-blind cross-over design and used placebo capsules as control except Penzak et al., (2001), which was an open-label study and used orange juice as intervention and water as placebo, and Soths et al., (2011), which was a double-blind parallel study.

[2] Refers to the time of abstinence from caffeine before testing, unless otherwise noted

[3] Subjects consumed 13.5 mg of synephrine 8 h before testing.

[4] Doses refer to synephrine + octopamine

[5] 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

[6] Refers to the number of subjects per arm

* Statistically significant

3634 **Appendix H. Human intervention studies on the longer-term (≥7 days) effects of caffeine or coffee on blood pressure**

3635

	Design	Sex	n (I/C) [d]	I/C	Coffee (cups per day)	Coffee (ml per day)	Caffeine (mg per day)	Duration[e] (weeks)
Studies with caffeine								
Arciero et al. (1998)[a]	X-db	M	10	Caffeine/placebo	-	-	295	4
Bak and Grobbee (1991)[a]	P-db	M/F	62 (32/30)	Caffeine+D/placebo	-	-	375	7
James (1994)[a]	X-db	M/F	36	Caffeine/placebo	-	-	336-410[1]	1
Robertson et al. (1984)[a]	P-db	M/F	17 (9/8)	Caffeine/placebo	-	-	750	12
Watson et al. (2000)[a]	X-db	M/F	34	Caffeine/placebo	-	-	400	12
Studies with coffee								
Agudelo et al. (2008)[b]	P-open	M/F	116 (29, 29, 29/30)	F/N	2, 4, 6	300, 600, 900[2]	180, 360, 540[3]	6
Ammon et al. (1983)[c]	X-db	M	8	I/D	8	1200[2]	720[3]	4
Bak and Grobbee (1990)[a,b,c]	P-open	M/F	111 (77/34)	B, F/N	4-6	700	469	9
Burr et al. (1989)[a,b, c]	X-open	M/F	54	I/D, N	≥5	1235	741	4
van Dusseldorp et al. (1989)[a,c]	X-db	M/F	45	F/D	5	750[2]	435[3]	6
van Dusseldorp et al. (1991)[a,b,c]	P-open	M/F	64 (43/21)	B (+ F)/N	6	900	(774-798)	11
Eggertsen et al. (1993)[a,c]	X-db	M/F	23	I/D	3-4	525[2]	263[3]	2
Funatsu et al. (2005)[b]	X-open	M	42	F/N	3.4	510[2]	306[3]	4
Hofer and Battig (1994)[a]	P-open	M/F	120 (80, 40)	I/D	-	998	335	1
MacDonald et al. (1991)[a,b,c]	X-open	M/F	50	I/D, N	>3	450[2]	225	2
Rakic et al. (1999)[a,b]	P-open	M/F	27 (14/13)	I/N	5	750[2]	300	2
Rosmarin et al. (1990)[a,b,c]	X-open	M	21	F/N	3.6	540[2]	270[3]	8

	Design	Sex	n (I/C) [d]	I/C	Coffee (cups per day)	Coffee (ml per day)	Caffeine (mg per day)	Duration[e] (weeks)
Strandhagen and Thelle (2003)[b]	X-open[f]	M/F	121	F/N	4	600[2]	360[3]	4
Superko Superko et al. (1991)[a,b]	P-open	M	181 (123/58)	F/D, N	4.5	1067	615	8
Superko et al. (1994)[a,c]	P-open	M	150 (100, 50)	F/D, N	4.5	1067	615	8

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

3646 **Appendix I. Meta-analyses of prospective cohort studies on the relationship between habitual caffeine consumption and**
3647 **cardiovascular disease risk**

				Meta-analyses									
				Ding et al., 2014	**Cheng et al., 2014**	**Caldeira et al., 2013**[1]	**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	**Country**	**Sex**	**Outcomes**										
Wilhelmsen et al. (1977) *	SE	M	nf-MI	X	-	-	-	-	-	-	-	X	-
Murray et al. (1981)	USA	M	f-IHD	-	-	-	-	-	-	-	-	X	-
Jacobsen et al. (1986)	NO	M/F		-	-	-	-	-	-	-	-	X	-
LaCroix et al. (1986)	USA	M/F	CHD	-	-	-	-	-	-	-	-	-	X
LeGrady et al. (1987) *Chicago Western Electric Company Study*	USA	M	f-CHD f-Stroke	X	-	-	-	-	-	-	-	X	-
Yano K et al. (1987)	USA	M	f-CHD nf-MI	-	-	-	-	-	-	-	-	X	-
Martin et al. (1988) *Hypertension Detection and Follow-up Program*	USA	M/F	f-CHD f-Stroke	X	-	-	-	-	-	-	-	X	-
Wilson et al., 1989	USA	M/F	CVD	-	-	-	-	-	-	-	-	X	-
Grobbee et al. (1990) *Health Professionals Follow-up Study*	USA	M	CVD CHD MI Stroke	X	-	-	-	-	X	-	-	-	-
Klatsky et al. (1990)**	USA	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	-

				Meta-analyses									
				Ding et al., 2014	**Cheng et al., 2014**	**Caldeira et al., 2013**[1]	**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	**Country**	**Sex**	**Outcomes**										
Lindsted et al. (1992)	USA	M	f-CVD	X	-	-	-	-	-	-	-	X	X
			f-IHD										
Klatsky et al. (1993)	USA	M/F	f-CHD	-	-	-	-	-	-	-	-	-	X
Klag et al. (1994)	USA	M	CHD	X	-	-	-	-	-	-	-	X	X
			MI										
Gyntelberg et al. (1995)	DK	M	nf-IHD	X	-	-	-	-	-	-	-	X	X
Copenhagen Male Study													
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*	USA	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	X	-	-	-	-	-	-	-	X	-
			nf-MI										
Wilhelmsen et al. (2001b); Wilhelmsen et al. (2001a) *Multifactor Primary Prevention Study*	SE	M	HF, AF	-	X	X	X	-	-	-	-	-	-
Klag et al. (2002)	USA	M	HT	-	-	-	-	-	-	X	X	-	-
John Hopkins Precursors													

				Meta-analyses									
				Ding et al., 2014	**Cheng et al., 2014**	**Caldeira et al., 2013**[1]	**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	**Country**	**Sex**	**Outcomes**										
Study													
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)	DK	M/F	AF	-	X	X	-	-	-	-	-	-	-
Danish Diet, Cancer, and Health Study													
Winkelmayer et al. (2005) *Nurses' Health Study I and II*	USA	F	HT	-	-	-	-	-	-	X	X	-	-
Bidel et al. (2006)	FI	M/F	f-CVD f-CHD f-Stroke	X	-	-	-	-	X	-	-	-	-
Andersen et al. (2006) *Iowa Women's Health Study*	USA	F	f-CVD	X	-	-	-	-	-	-	-	X	X
Lopez-Garcia et al. (2006)	USA	M/F	CHD f-CHD nf-MI	X	-	-	-	-	-	-	-	X	X
Health Professionals Follow-up Study													
Nurses' Health Study													
Greenberg et al. (2007)	USA	M/F	f-CVD f-CHD f-Stroke	X	-	-	-	-	-	-	-	-	-
NHANES I-NHEFS													
Hu et al. (2007)	FI	M/F	HT	-	-	-	-	-	-	X	X	-	-
Palatini et al. (2007)	Italy	M/F	HT	-	-	-	-	-	-	X	X	-	-

				Meta-analyses									
				Ding et al., 2014	**Cheng et al., 2014**	**Caldeira et al., 2013**[1]	**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	**Country**	**Sex**	**Outcomes**										
HARVEST study													
Rosner et al. (2007)	SE	F	MI	-	-	-	-	-	-	-	-	X	-
Swedish Mammography Cohort													
Silletta et al. (2007) *GISSI-Prevention Trial*	IT	M/F	CV death nf-MI nf-stroke	X	-	-	-	X	X	-	-	-	-
Uiterwaal et al. (2007)	DK	M/F	HT	-	-	-	-	-	-	X	X	-	-
Doetinchem Cohort Study													
Greenberg et al., 2008 *Framingham Heart Study*	USA	M/F	CVD CHD Stroke	X	-	-	-	X	-	-	-	-	-
Happonen et al. (2008)	FI	M/F	f-CVD	X	-	-	-	-	-	-	-	-	-
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)	USA	F	Stroke	X	-	-	-	X	X	-	-	-	-
Nurses' Health Study													
Mukamal et al. (2009) *Stockholm Heart Epidemiology Program-*	SE	M/F	HF, AF, Stroke f-MI	X	X	X	X	X	X	-	-	-	-
Zhang WL et al. (2009b,	USA	M/F	CVD CHD		-	-	-	X	-	-	-	-	-

				Meta-analyses									
				Ding et al., 2014	**Cheng et al., 2014**	**Caldeira et al., 2013**[1]	**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	**Country**	**Sex**	**Outcomes**										
2009a)			f-CHD nf-MI Stroke										
Conen et al. (2010) *Women' Health Study*	USA	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*	USA	M/F	AF	-	X	X	-	-	-	-	-	-	-
Sugiyama et al. (2010)	JPN	M/F	f-CVD f-CHD f-Stroke	X	-	-	-	-	X	-	-	-	-
Klatsky et al. (2011)	USA	M/F	AF, other arrythmias	-	X	X	-	-	-	-	-	-	-
Larsson et al. (2011) Levitan et al. (2011) *Swedish Mammography Cohort*	SE	F	HF Stroke	X	-	-	X	X	X	-	-	-	-
Mineharu et al., 2011	JPN	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*	USA	M/F	CHD	X	-	-	-	-	-	-	-	-	-

				Meta-analyses									
				Ding et al., 2014	**Cheng et al., 2014**	**Caldeira et al., 2013**[1]	**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	**Country**	**Sex**	**Outcomes**										
Health–AARP Diet and Health Study			Stroke										
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)	JPN	M/F	CVD CHD Stroke	X	-	-	-	-	-	-	-	-	-

* Prospective cohort and case-control study; ** nested case-control study; *** prospective case-control study

[1] Also includes a case-control study (Mattioli et al., 2005)

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

ABBREVIATIONS

ADHD	Attention-deficit hyperactivity disorder
AF	Atrial fibrillation
AHR	Aryl-hydrocarbon receptor
ALSPAC	Avon Longitudinal Study of Parents and Children
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
BMI	Body mass index
BP	Blood pressure
bw	Body weight
CABG	Coronary-artery bypass grafting
CAD	Coronary arterial disease
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
CNS	Central nervous system
CVS	Cardiovascular system
DBP	Diastolic blood pressure
FDA	US Food and Drug Administration
FFQ	Food frequency questionnaire
FGR	Fetal growth retardation
FMD	Flow-mediated vasodilation
FSANZ	Food Standards Australia and New Zealand
HR	Heart rate
IQR	Interquartile range
MABP	Mean arterial blood pressure
MBF	Myocardial blood flow
MFR	Myocardial blood flow reserve
MI	Myocardial infarction

3685	MS	Member state
3686	OR	Odds ratio
3687	PET	Positron emission tomography
3688	PTCA	Percutaneous transluminal coronary angioplasty
3689	PTD	Pre-term delivery
3690	PWV	Pulse-wave velocity
3691	RASFF	Rapid alert system for food and feed
3692	RCT	Randomised controlled trial
3693	RR	Relative risk
3694	SBP	Systolic blood pressure
3695	SCD	Sudden cardiac death
3696	SCF	Scientific committee on food
3697	SGA	Small for gestational age
3698	SHC	Belgium's Superior Health Council
3699	UL	Upper tolerable level of intake
3700	US	United states
3701	WHO	World health organisation