

DRAFT SCIENTIFIC OPINION

Scientific Opinion on the safety of caffeine¹

EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA)^{2, 3}

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ABSTRACT

Following a request from the European Commission, the EFSA Panel on Dietetic products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the safety of caffeine. Advice should be provided 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 for specific subgroups of the population. Possible interactions between caffeine and other constituents of so-called “energy drinks”, alcohol, synephrine and physical exercise should also be addressed. Single doses of caffeine up to 200 mg, corresponding to about 3 mg/kg bw for a 70-kg adult are unlikely to induce clinically relevant changes in blood pressure, myocardial blood flow, hydration status or body temperature, to reduce perceived exertion/effort during exercise or to mask the subjective perception of alcohol intoxication. Daily caffeine intakes from all sources up to 400 mg per day do not raise safety concerns for adults in the general population, except pregnant women. 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. Daily caffeine intakes from all sources up to 200 mg per day by pregnant women do not raise safety concerns for the fetus. For children and adolescents, the information available 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.

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KEY WORDS

caffeine, taurine, D-glucurono- γ -lactone, synephrine, alcohol, physical activity, “energy drinks”

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26 **SUMMARY**

27 Following a request from the European Commission, the EFSA Panel on Dietetic products, Nutrition
28 and Allergies (NDA) was asked to deliver a scientific opinion on the safety of caffeine. Possible
29 interactions between caffeine and other common constituents of the so-called “energy drinks”, alcohol,
30 synephrine and physical exercise should also be addressed.

31 Caffeine (1,3,7-trimethylxanthine) is a stable alkaloid and one of several related methylxanthines. It is
32 found in various plants such as coffee and cocoa beans, tea leaves, guarana berries and the kola nut, and
33 thus has a long history of human consumption. It is contained in ingredients added to a variety of foods,
34 e.g. baked goods, ice creams, soft candy, cola-type beverages. Caffeine is also an ingredient of “energy
35 drinks” and it is present in combination with synephrine in a number of food supplements marketed for
36 weight loss and sports performance, among others.

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

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

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

- 47 i) caffeine consumption during pregnancy and lactation, and adverse health effects in the fetus,
- 48 ii) acute and long-term effects of caffeine consumption on the central nervous system (e.g. sleep,
49 anxiety, behavioural changes) in adults, adolescents and children
- 50 iii) long-term adverse effects of caffeine consumption on the cardiovascular system in adults
- 51 iv) acute effects of caffeine consumption in “energy drinks” and risk of adverse health effects in
52 adolescents and adults involving the cardiovascular and central nervous systems, particularly
53 when consumed within short periods of time, at high doses, and in combination with alcohol
54 and/or physical exercise
- 55 v) acute effects of caffeine in combination with synephrine on the cardiovascular system.

56 The Panel reviewed the literature reporting on the effects of single and repeated doses of caffeine
57 consumed within a day, either alone or in combination with other constituents of “energy drinks” and
58 with synephrine, on cardiovascular outcomes, hydration and body temperature in adults, both at rest and
59 in relation to physical exercise. The effects of single and repeated doses of caffeine consumed within a
60 day on the central nervous system were assessed in adults (sleep, anxiety, perceived exertion during
61 exercise and subjective perception of alcohol intoxication) and children (sleep, anxiety and behavioural
62 changes). Adverse effects of longer-term and habitual caffeine consumption were evaluated in children
63 in relation to behavioural changes and in pregnant women in relation to adverse health outcomes for the
64 fetus (e.g. pre-term delivery, fetal growth retardation or small for gestational age, miscarriage or
65 spontaneous abortion, stillbirth). In adults, the adverse effects of habitual caffeine consumption, either
66 alone or in combination with other constituents of “energy drinks” and with synephrine, were evaluated
67 in relation to cardiovascular outcomes. The scientific publications identified almost exclusively reported
68 no relationship or an inverse relationship between caffeine intake and other adverse health effects.

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

75 On the basis of the data available, the NDA Panel reached the following conclusions on caffeine intakes
76 which do not raise safety concerns for specific groups of the general population:

77 **Adults**

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

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

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

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

92 In seven out of 13 countries, the 95th percentile of daily caffeine intake from all sources exceeded 400
93 mg. The estimated proportion of the adult population exceeding daily intakes of 400 mg ranged from
94 5.8 % to almost one third (32.9 %).

95 **Pregnant women**

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

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

100 **Lactating women**

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

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

105 **Children and adolescents**

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

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

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

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

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

124

125	TABLE OF CONTENTS	
126	Abstract	1
127	Summary	2
128	Table of contents	5
129	Background as provided by the European Commission.....	7
130	Terms of reference as provided by the European Commission.....	8
131	Assessment	9
132	1. Introduction	9
133	2. Previous safety assessments	9
134	2.1. Caffeine.....	9
135	2.2. Caffeine in combination with other constituents of “energy drinks” and in combination with	
136	alcohol	11
137	2.3. Caffeine in combination with synephrine	12
138	2.4. Summary of previous safety assessments	13
139	3. Dietary intakes	14
140	3.1. Dietary sources and occurrence data.....	14
141	3.2. Food consumption data.....	16
142	3.2.1. EFSA comprehensive European food consumption database	16
143	3.3. Dietary intake.....	17
144	3.3.1. Caffeine intake estimated from the EFSA comprehensive European food consumption	
145	database	17
146	3.3.1.1. Daily caffeine intake	17
147	3.3.1.2. Caffeine intake on a single day.....	20
148	3.3.2. Caffeine intake from “energy drinks” on a “single session” estimated from the EFSA	
149	report on “energy drinks”	21
150	3.3.3. Prevalence of “energy drink” consumption.....	22
151	3.3.3.1. EFSA comprehensive European food consumption database.....	22
152	3.3.3.2. EFSA report on “energy drinks”	22
153	3.4. Limitations of the available caffeine intake data and data gaps.....	23
154	4. Hazard identification	23
155	4.1. Absorption, distribution, metabolism, and excretion	23
156	4.1.1. Adults	23
157	4.1.2. Pregnant women	25
158	4.1.3. Fetus	26
159	4.1.4. Breast fed infants	26
160	4.1.5. Conclusions	26
161	4.2. Pharmacodynamic effects	26
162	4.3. Adverse effects of caffeine: methodological considerations.....	27
163	4.4. Adverse effects of a single dose and of repeated doses of caffeine consumed within a day	
164	4.4.1. Cardiovascular system.....	28
165	4.4.1.1. Blood pressure, endothelial function and arterial compliance	28
166	4.4.1.2. Myocardial blood flow.....	33
167	4.4.1.3. Cardiovascular disease risk.....	35
168	4.4.1.4. Conclusions on the cardiovascular system.....	37
169	4.4.2. Hydration status and body temperature	37
170	4.4.2.1. Conclusions on hydration status and body temperature.....	39
171	4.4.3. Central nervous system.....	39
172	4.4.3.1. Sleep, anxiety and behavioural changes	39
173	4.4.3.2. Perceived exertion during exercise	40
174	4.4.3.3. Subjective perception of alcohol intoxication.....	41
175	4.4.3.4. Conclusions on the central nervous system	42
176	4.5. Adverse effects of longer-term and habitual caffeine consumption	42
177	4.5.1. Central nervous system.....	43
178	4.5.2. Cardiovascular system.....	43

179	4.5.2.1.	Methodological considerations	43
180	4.5.2.2.	Blood pressure	44
181	4.5.2.3.	Hypertension	47
182	4.5.2.4.	Coronary heart disease	49
183	4.5.2.5.	Atrial fibrillation	52
184	4.5.2.6.	Heart failure	52
185	4.5.2.7.	Stroke	53
186	4.5.2.8.	Cardiovascular disease risk (all outcomes combined)	54
187	4.5.2.9.	Conclusions on the cardiovascular system.....	55
188	4.5.3.	Pregnancy outcomes	56
189	4.5.3.1.	Human intervention studies	56
190	4.5.3.2.	Prospective cohort studies.....	57
191	4.5.3.3.	Case-control and cross-sectional studies.....	60
192	4.5.3.4.	Conclusions on pregnancy outcomes.....	60
193	5.	Dose response assessment and derivation of intake levels of no concern	61
194	5.1.	Adults.....	61
195	5.2.	Pregnant women.....	62
196	5.3.	Lactating women.....	62
197	5.4.	Children and adolescents (1 year to < 18 years)	62
198	6.	Characterisation of the risk.....	63
199	6.1.	Adults.....	63
200	6.1.1.	Single dose / single session	63
201	6.1.2.	Daily caffeine intakes	63
202	6.2.	Pregnant women.....	63
203	6.3.	Lactating women.....	63
204	6.4.	Adolescents (10 to < 18 years).....	63
205	6.4.1.	Single dose / single session	63
206	6.4.2.	Daily caffeine intakes	63
207	6.5.	Children (3 to < 10 years)	64
208	6.5.1.	Single dose / single session / single days.....	64
209	6.5.2.	Daily caffeine intakes	64
210	6.6.	Toddlers (12 to < 36 months).....	64
211	6.6.1.	Single dose / single session / single days.....	64
212	6.6.2.	Daily caffeine intakes	64
213		Conclusions	64
214		References	66
215		Appendices	84
216	Appendix A.	Dietary surveys used for the assessment of caffeine intakes.....	84
217	Appendix B.	Daily caffeine intake by country survey and age class.....	85
218	Appendix C.	95th percentile of caffeine intake from all sources for “all days” and for	
219		“consumption days”	90
220	Appendix D.	Caffeine intake on a single day by country survey and age class.....	91
221	Appendix E.	Food sources contributing daily caffeine intake.....	96
222	Appendix F.	Human intervention studies on the vascular effects of a single dose and of repeated	
223		doses of caffeine consumed within a day.....	99
224	Appendix G.	Randomised, placebo controlled human intervention studies on the effect of single	
225		doses of synephrine on blood pressure	102
226	Appendix H.	Human intervention studies on the longer-term (≥7 days) effects of caffeine or	
227		coffee on blood pressure	103
228	Appendix I.	Meta-analyses of prospective cohort studies on the relationship between habitual	
229		caffeine consumption and cardiovascular disease risk.....	105
230		Abbreviations	111

232 **BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION**

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

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

248 Belgium’s Superior Health Council (SHC (2012) recently assessed the use of caffeine in foodstuffs⁴ in
 249 January 2012 and concluded that “*in health adults a maximal daily intake of 400 mg per day does not*
 250 *raise concerns for adverse health effects. For women of childbearing age a maximal daily intake of 300*
 251 *mg, or even 200 mg, is recommended. For children prior to adolescence an acceptable maximal daily*
 252 *intake of 2.5 mg per kg body weight is advisable.*” Another assessment conducted in December 2009 by
 253 the same risk assessment body on energy drinks⁵ leads to the recommendation that “*regular or*
 254 *excessive consumption of energy drinks should be avoided while ensuring that the total daily intake of*
 255 *caffeine remains below 400 mg, or even 300 mg.*” It was also advised “*to avoid consumption of energy*
 256 *drinks when consuming alcoholic beverages or during intense physical activity*”. Finally it was
 257 suggested that “*the consumption of energy drinks should be avoided during pregnancy, during*
 258 *breastfeeding, by children up to 16 years old and by people who are susceptible to caffeine.*” It is noted
 259 that Belgium’s recommendation on the upper intake limit of caffeine for the general population is also
 260 in line with Health Canada and the US Food and Drug Administration (FDA)⁶ which confirmed that
 261 “*the general population of health adults is not at risk for potential adverse effects from caffeine if they*
 262 *limit their caffeine intake to 400 mg per day*”.

263 Similarly, the French Agency for Food Safety⁷ concluded that “*it is not possible to rule out a possible*
 264 *risk related to consumption of foodstuffs containing caffeine on cardiovascular health in people*
 265 *performing intense physical activity: however, further evaluation on this is needed*”. According to the
 266 French Agency⁸, “*current knowledge on the risks related to the consumption of energy drinks should,*
 267 *however, help to better understand the role of caffeine in the observed effects*”. Further cases of
 268 deleterious effects of caffeine consumption have been reported through the nutri-vigilance system for
 269 products containing caffeine.

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

⁴ Avis du conseil supérieur 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 supérieur de la sante n° 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.

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

275 **TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION**

276 In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002 the European Commission⁹ asks
277 EFSA to:

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

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

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

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

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

305

⁹ OJ. L 031, 01.02.2002. p.1

306 **ASSESSMENT**307 **1. Introduction**

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

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

319 Owing to the abundance of scientific literature available, previous risk assessments on the safety of
320 caffeine consumption in humans conducted by authoritative bodies will be reviewed first in order to
321 identify the major health concerns raised in relation to the consumption of caffeine and the specific
322 population subgroups which are relevant for the assessment.

323 **2. Previous safety assessments**324 **2.1. Caffeine**

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

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

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

352 An Food Standards Australia and New Zealand expert group (FSANZ, 2000), on the basis of available
353 prospective cohort studies in humans, concluded that a causal relationship between habitual caffeine
354 intakes from dietary sources and increased risk of hypertension or cardiovascular disease (CVD) could
355 not be established. FSANZ noted reports of increased anxiety levels in children (Bernstein et al., 1994)
356 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
357 day, corresponding to 95 mg per day for a mean body weight of 32 kg in children aged 5-12 years and
358 to 210 mg per day for a mean body weight 70 kg in adults. FSANZ also noted that doses of 100 mg of
359 caffeine (1.4 mg/kg bw per day in 70 kg adults) taken at bedtime had been reported to reduce the ability
360 to sleep in adults (Landolt et al., 1995).

361 Maximum daily caffeine intakes recommended by Health Canada in 2006 (Health Canada, 2006) for
362 different population subgroups were based on a review of the literature published in 2003 (Nawrot et al.,
363 2003). On the basis of the studies available at the time on the relationship between caffeine consumption
364 and health outcomes in humans, the authors concluded that daily caffeine intakes of 400 mg were not
365 associated with adverse health effects such as general toxicity, cardiovascular effects, changes in adult
366 behaviour, increased incidence of cancer, effects on male fertility, or bone status/calcium balance if
367 adequate intakes of calcium are being consumed. In a review of the available observational studies on
368 caffeine consumption during pregnancy and risk of spontaneous abortion, pre-term delivery, fetal
369 growth, congenital malformations and post-natal development, it was concluded that caffeine intake for
370 women who plan to become pregnant and during gestation should not exceed 300 mg per day. The
371 publications reviewed concerning caffeine intakes in children, mostly addressed the effects of caffeine
372 on the central nervous system (CNS), and were those considered by the SCF (1999) together with three
373 additional references (Rapoport et al., 1981b; Hale et al., 1995; Davis and Osorio, 1998). The authors
374 noted the small size of the studies available and the diversity of study designs. The authors also noted
375 that the use of different endpoints or of different ways to assess similar endpoints hampered
376 comparability among studies, and that most studies did not stratify children by their usual (pre-study)
377 caffeine intake, a variable which could affect the way subjects respond to pre-study caffeine withdrawal
378 and to additional caffeine intakes. Nevertheless, findings of altered behaviour, including anxiety, were
379 noted in some studies to the lowest level of administered caffeine used (2.5 mg/kg bw). In the absence
380 of more robust data associated with low levels of administered caffeine in this population subgroup, an
381 upper intake of 2.5 mg/kg bw per day based on the study by Bernstein et al. (1994) was derived for
382 children, considering that the nervous system in children is continually developing and the lack of
383 available information on the longer-term effects of caffeine consumption in this population subgroup.

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

392 In 2008, the Nordic Working Group on Food Toxicology and Risk Evaluation (NNT) focussed on the
393 safety of caffeine among children and adolescents in the Nordic countries (NNT, 2008). A NOEL of 0.3
394 mg/kg bw (Goldstein and Wallace, 1997) and a LOAEL of 1.0–1.3 mg/kg bw (Bernstein et al., 2002;
395 Heatherley et al., 2006) were established for tolerance development with withdrawal symptoms,
396 whereas a LOAEL of 2.5 mg/kg bw (Bernstein et al., 1994) was established for anxiety and jitteriness.
397 The NNT noted that the only study which assessed the relationship between habitual caffeine
398 consumption and sleep patterns in adolescents (Pollak and Bright, 2003) did not allow drawing
399 conclusions on a causal effect of caffeine on disturbed sleep (i.e. observational study, reverse causality
400 could not be excluded) and that no studies were available in children. The NNT concluded that there
401 were no data to conclude that caffeine would not have the same sleep-depriving effect in children and

402 adolescents as in adults, and that, in adults, doses less than 100 mg, equivalent to 1.4 mg/kg bw, did not
403 seem to have an effect on sleep (Dorfman and Jarvik, 1970).

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

413 **2.2. Caffeine in combination with other constituents of “energy drinks” and in combination**
414 **with alcohol**

415 A number of safety assessments have also been conducted in relation to the consumption of “energy
416 drinks”, which most often contain combinations of caffeine (typically 300-320 mg/L), taurine (about
417 4000 mg/L), and D-glucurono- γ -lactone (about 2400 mg/L) among other ingredients, and to the
418 consumption of “energy drinks” or caffeine in combination with alcohol.

419 In 1999, the SCF (SCF, 1999) considered that the contribution of “energy drinks” to caffeine intakes in
420 non-pregnant adults was not of concern on the assumption that “energy drinks” would replace other
421 caffeine sources, such as coffee or tea. For children, the SCF concluded that the consumption of 160 mg
422 caffeine per day from 0.5 L of “energy drinks”, equivalent to 5.3 mg/kg bw per day for a 10 year-old,
423 30-kg child, could result in transient behavioural changes, such as increased arousal, irritability,
424 nervousness or anxiety, based on the studies referred to in section 2.1.

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

438 In 2009, the Panel on Food Additives and Nutrient Sources Added to Food (ANS Panel) concluded that
439 exposure to taurine and D-glucurono- γ -lactone at levels commonly used in “energy drinks” was not of
440 safety concern even for high consumers (EFSA, 2009). Similarly to the SCF (2003), the ANS Panel
441 considered it unlikely that D-glucurono- γ -lactone would have any interaction with caffeine, taurine,
442 alcohol or the effects of exercise. The ANS Panel concluded that additive interactions between taurine
443 and caffeine on diuretic effects were unlikely based on a human intervention study (Riesenhuber et al.,
444 2006), and that a possible stimulatory effect from taurine on the CNS was improbable on the basis of a
445 second rat study, from which a NOAEL of 1500 mg/kg bw per day was derived for behavioural effects.

446 In 2008, the Federal Institute for risk assessment (BfR) assessed the safety of “energy drinks” in view of
447 case reports on fatalities following consumption of these beverages, either alone or in combination with
448 alcohol, which implicated primarily the CVS and CNS (BfR, 2008). The BfR considered that adverse
449 health effects upon consumption of large amounts of “energy drinks” in combination with intense

450 physical exercise or alcohol could not be ruled out and advised children, pregnant women, lactating
 451 women or individuals who are “sensitive” to caffeine (i.e., with cardiac arrhythmias or mental disorders)
 452 not to consume “energy drinks”, particularly in large amounts. Subsequently, the BfR (BfR, 2009)
 453 assessed health risks related to the consumption of “energy shots”, which contain higher concentrations
 454 of caffeine and taurine compared with “energy drinks” (50-200 mg caffeine and taurine 200-1000 mg
 455 per portion). BfR stated that consumption of “energy shots” pose no risk to health if consumed in
 456 accordance with the suggested daily intake levels of 50-200 mg caffeine.

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

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

492 **2.3. Caffeine in combination with synephrine**

493 A number of authoritative bodies in different EU Member States have conducted risk assessments (BfR,
 494 2012; SLE, 2012) or issued warnings (Sundhedsstyrelsen, 2008; MHRA, 2012; Evira, 2013) in relation
 495 to synephrine-containing products intended for weight loss and sports performance which also contain
 496 caffeine. Concerns were raised on the basis of case reports and Rapid Alert System for Food and Feed
 497 (RASFF) notifications of adverse health effects.

498 The BfR (2012) reviewed human intervention studies investigating the acute effects of *p*-synephrine on
 499 blood pressure and heart rate, either alone (Min et al., 2005; Bui et al., 2006; Stohs et al., 2011) or in

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

514 2.4. Summary of previous safety assessments

515 Recommendations on maximum levels of caffeine consumption for different population sub-groups
 516 have been derived by different national and international bodies taking into account a variety of health
 517 outcomes. No health concerns in relation to acute toxicity, calcium balance (under adequate calcium
 518 intakes), cardiovascular health, cancer risk or male fertility have been raised for habitual caffeine
 519 intakes from all sources up to 400 mg per day in the general adult population. It has been noted,
 520 however, that single doses of 1.4 mg/kg bw and above, taken at bedtime, could impair sleep in some
 521 individuals (Landolt et al., 1995) and that single doses of 3 mg/kg bw and above could increase anxiety
 522 in some cases (Nickell and Uhde, 1994). Early recommendations for pregnant women and for women
 523 in child-bearing age advised not to exceed 300 mg of caffeine per day based on a number of cross-
 524 sectional and prospective cohort studies which assessed a variety of outcomes (e.g. spontaneous
 525 abortion, pre-term delivery, fetal growth, congenital malformations, post-natal development), whereas a
 526 later evaluation advised not exceeding 200 mg of caffeine per day in light of a new prospective cohort
 527 study (CARE Study Group, 2008). Recommendations on maximum daily intakes of caffeine in children
 528 have been based on its acute and short-term effects on the CNS. The SCF noted that, considering all the
 529 available human intervention studies conducted in this population subgroup, doses of 5 mg/kg bw of
 530 caffeine increased arousal, irritability, nervousness or anxiety in some subjects, particularly if they were
 531 normally low consumers of caffeine (SCF, 1999). Other bodies (FSANZ, 2000; Health Canada, 2006;
 532 NNT, 2008; SHC, 2012), however, have recommended not to exceed 2.5 mg/kg bw per day on the basis
 533 of a single study (Bernstein et al., 1994).

534 Concerns have been raised in relation to the consumption of “energy drinks” and an increased risk of
 535 adverse health effects involving the CVS and the CNS from a number of case reports, particularly when
 536 consumed within short periods of time, at high doses, and in combination with alcohol and/or physical
 537 exercise. Although it has been acknowledged that such adverse effects could be attributed to caffeine
 538 alone, additive and/or synergistic cardiovascular and psychological effects have been proposed for other
 539 components of “energy drinks” on various health outcomes, especially taurine. Concerns regarding the
 540 possibility of an interaction between caffeine and taurine regarding the stimulatory effect on the CNS
 541 based on a rat study were not confirmed in subsequent animal studies. Similarly, the theoretical additive
 542 diuretic effects of caffeine and taurine mentioned in previous assessments were found unlikely on the
 543 basis of a human intervention study designed to investigate that question (Riesenhuber et al., 2006).
 544 Interactions between caffeine and taurine on the CVS were found unlikely based on the antagonistic
 545 effects of caffeine and taurine observed *in vitro*, in animal studies, and in human studies conducted with
 546 either caffeine or taurine. Studies linking high consumption of caffeine and “energy drinks” with high
 547 alcohol intakes, consumption of other psychotropic drugs, and increased “risk-taking” behaviour were
 548 either cross-sectional or retrospective and did not allow attributing a causal role to either caffeine or
 549 “energy drinks” in this cluster. Alcohol consumption was found unlikely to exacerbate the effects of
 550 caffeine on the CVS and/or the CNS. Concerns were rather expressed regarding the antagonistic effects
 551 of caffeine and alcohol on the CNS, and the possibility that caffeine could mask the subjective

552 perception of alcohol intoxication, leading to increased “risk-taking” behaviour. However, the human
553 intervention studies which investigated this question were found to yield conflicting results (Verster et
554 al., 2012).

555 Finally, concerns related to the co-consumption of caffeine and synephrine arise from the potential
556 synergistic effects of these two substances on the CVS, and particularly on blood pressure. On the basis
557 of human intervention studies which have investigated the acute effects of *p*-synephrine on blood
558 pressure and heart rate, either alone (Penzak et al., 2001; Min et al., 2005; Bui et al., 2006; Stohs et al.,
559 2011) or in combination with caffeine (Haller et al., 2005b; Haller et al., 2008; Seifert et al., 2011),
560 authoritative bodies came to the conclusion that doses between 20 and 27 mg of synephrine increase
561 blood pressure, and that this effect is enhanced by the concomitant consumption of caffeine.

562 3. Dietary intakes

563 3.1. Dietary sources and occurrence data

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

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

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

580 Table 1: Caffeine concentrations in food and beverages

		Caffeine concentrations (mg/L or mg/kg)													
Groups	Subgroups	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	-	-	-	-	-	-	
	Milk chocolate			-	-	-	-	183	-	-	-	-	-	150	
	Chocolate snacks	168⁽¹⁾	168	-	-	-	-	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)	-	-	-	-	-	-	-	-	-	-	
	Green tea	151⁽¹⁾	151	198 (132-220)	-	272	150	100	320	160	150	170	160	240	
	Tea (unspecified)	165⁽¹⁾	165	234 (176-529)	158 (59-256)	(90-500)	(122-183)	-	-	-	-	-	-	-	
	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		

581 ⁽¹⁾ derived from Fitt et al., 2013
582 ⁽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
583 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”
584 or “cocoa mass”).
585 ⁽³⁾ mean value from Mayo, ANSES and Austria
586 ⁽⁴⁾ mean value from Heckman, Mayo and ANSES
587 ⁽⁵⁾ derived from ANSES
588 ⁽⁶⁾ caffeine concentration of the most consumed “energy drink” considered
589 - no value provided in the respective references

590 3.2. Food consumption data

591 3.2.1. EFSA comprehensive European food consumption database

592 The EFSA Comprehensive European Food Consumption Database (Comprehensive Database)
593 provides a compilation of existing national information on food consumption at individual level. It
594 was first built in 2010 (EFSA, 2011b; Huybrechts et al., 2011; Merten et al., 2011) and then updated in
595 2014 (to be published in 2015). Details on how the Comprehensive Database is used are published in
596 the Guidance of EFSA (EFSA, 2011a). For dietary surveys included in the 2010 release, which was
597 based on the FoodEx classification, products coded as “carbohydrate-rich energy food products for
598 sports people” or “carbohydrate-electrolyte solutions for sports people” at the 3rd level of FoodEx,
599 within the first level category of “Products for special nutritional use”, were used to calculate caffeine
600 consumption from “energy drinks”. Even using this conservative approach, the contribution of “energy
601 drinks” to total caffeine intakes was very low in all surveys published before 2000. The 17 surveys
602 from 11 Member States (MSs) added in 2014 used the FoodEx2 code classification, which allows
603 accurate reporting of “energy drink” consumption.

604 The database used to calculate caffeine intake included the 17 surveys from 2014 and surveys
605 conducted between 2005 and 2012, with two exceptions (DIPP 2001-2009, Finland; VELS 2001-2002,
606 Germany). The database contains data from 39 surveys in 22 different European countries for a total
607 of 66 531 participants (Appendix A). Data from eleven surveys were available for toddlers (≥ 12
608 months to < 36 months old), from 19 surveys for other children (≥ 36 months to < 10 years old), from
609 19 surveys for adolescents (≥ 10 years to < 18 years old), from 21 surveys for adults (≥ 18 years to $<$
610 65 years old), from 15 surveys for the elderly (≥ 65 years to < 75 years old) and from 13 surveys for
611 the very elderly (≥ 75 years old). Two additional surveys provided information on specific population
612 groups: pregnant women (Latvia) and lactating women (Greece).

613 In the surveys above, consumption data were collected using single or repeated 24- or 48-hour dietary
614 recalls or dietary records covering from 3 to 7 days per subject. Owing to the differences in the
615 methods used for data collection, direct country-to-country comparisons must be taken with caution.
616 These surveys do not provide information about the consumption of caffeine-containing food
617 supplements.

618 3.2.2. EFSA report on “energy drinks”

619 In 2011, EFSA commissioned a study to gather data on the prevalence of “energy drink” consumption
620 among adults, adolescents and children in Europe (Zucconi et al., 2013). This study also aimed at
621 estimating intakes of “energy drink” ingredients, including caffeine, in “energy drink consumers”, as
622 well as the relative contribution of “energy drinks” to total caffeine intakes. “Energy drink” consumers
623 were defined as subjects who had consumed at least one “energy drink” over the last year.
624 Consumption of “energy drinks” on a “single session”, defined as a period of time of about two hours
625 (e.g. a “night out”, a study or “sport session”), as well as consumption of “energy drinks” together
626 with alcohol or in relation to physical exercise in adolescents and adults, were also investigated.
627 Consumption data were collected through a food frequency questionnaire (FFQ)-based survey,
628 involving more than 52 000 participants from 16 different European MSs.

629 The Panel notes that this study provides useful information about the prevalence of “energy drink”
630 consumption in Europe, the amount of “energy drinks” (and their constituents, including caffeine)
631 consumed on a “single session” and the prevalence of “energy drink” consumption in combination
632 with physical activity. However, the Panel notes that: i) “energy drink consumers” may not be
633 representative of the general population with respect to caffeine intake from all sources; ii) FFQs
634 specifically developed to assess consumption of specific foods tend to overestimate consumption of
635 such foods; and iii) the study contains information about the frequency of consumption of “energy
636 drinks” in combination with alcohol, but not on the amounts of alcohol which were consumed in

637 combination with “energy drinks”. Therefore, the Panel considered that this study could be used to
 638 calculate caffeine intakes from “energy drinks” on a “single session”, either alone or in combination
 639 with physical exercise, but not to calculate total caffeine intakes from all sources or from sources other
 640 than “energy drinks”.

641 3.3. Dietary intake

642 3.3.1. Caffeine intake estimated from the EFSA comprehensive European food consumption 643 database

644 3.3.1.1. Daily caffeine intake

645 Daily caffeine intake for an individual was calculated by adding the intake reported on each survey
 646 day during the survey period for that individual and dividing by the number of days. Only surveys
 647 which collected data for at least two days were used.

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

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

656 Table 2: Daily caffeine intake for all subjects by age class and food group across different
 657 dietary surveys

Age class	Food groups	Mean caffeine intake				95 th 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
	Total intakes	22.6	362.1	0.3	4.8	96.3	715.7	1.5	10.4
Elderly (65 to < 75 yrs; 13 surveys)	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
	Total intakes	21.8	416.8	0.3	6.0	174.0	454.5	2.3	6.1
Very elderly (≥ 75 yrs; 11 surveys)	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

- 658 (1) The 95th percentile estimates obtained from dietary surveys and age classes with less than 60 subjects may not be
659 statistically robust (EFSA, 2011a) and were consequently not considered in this table (“-”).
- 660 (2) Minimum and maximum mean and 95th percentiles of those calculated from individual surveys for each age class.
- 661 (3) “Total intakes” are not derived by adding up the min and max values for the different food categories (values obtained
662 from different subjects), but reflect the minimum and maximum intakes of caffeine from all sources for all subjects in the
663 respective survey and age group across the different dietary surveys.
- 664 (4) Only one study (the Netherlands) with a sufficient number (≥ 60) of subjects who consumed “energy drinks” was
665 available to estimate a statistically robust 95th percentile.
- 666 (5) Only two studies (the Netherlands and Ireland) with a sufficient number (≥ 60) of subjects who consumed “energy
667 drinks” were available to estimate statistically robust 95th percentiles.
668

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

Age class	Food groups	Mean caffeine intake				95 th 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

671 (1) The 95th percentile estimates obtained from dietary surveys and age classes with less than 60 subjects may not be
672 statistically robust (EFSA, 2011a) and were consequently not considered in this table (“-”).

673 (2) Minimum and maximum mean and 95th percentiles of those calculated from individual surveys for each age class. Total
674 caffeine intakes cannot be calculated for “consumers only” by adding up caffeine consumption from coffee, tea, colas and
675 energy drink, because these figures reflect the intakes of different subjects (consumers of the respective food group).

676 (3) Only one study (the Netherlands) with a sufficient number (≥ 60) of subjects who consumed “energy drinks” was available
677 to estimate a statistically robust 95th percentile.

678 (4) Only two studies (the Netherlands and Ireland) with a sufficient number (≥ 60) of subjects who consumed “energy drinks”
679 were available to estimate statistically robust 95th percentiles.
680

681 *Adults, elderly and very elderly*

682 Daily caffeine intake from all sources could be estimated for adults from 16 MSs. Means and 95th
683 percentiles ranged from 37 to 319 mg and from 109 to 742 mg, respectively, among countries (Table
684 2, Appendix B).

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

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

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

697 *Pregnant women*

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

701 *Lactating women*

702 Data on lactating women are available only from a small survey in Greece (n = 65). The mean and the
703 95th percentile of the daily caffeine intake from all sources were 31 mg and 97 mg per day,
704 respectively (Appendix B).

705 *Adolescents*

706 Daily caffeine intakes from all sources could be estimated for adolescents from 13 MSs. Means and
 707 95th percentiles ranged from 18 to 70 mg and from 61 to 212 mg, respectively, among countries (Table
 708 2, Appendix B). On a per kg bw per day basis, the mean intakes ranged between 0.4 and 1.4 mg/kg bw
 709 per day. The 95th percentile varied between 1.5 and 4.1 mg/kg bw per day (Appendix B).

710 There were large differences among countries regarding the contribution of different food sources to
 711 total caffeine intake (Appendix E). Chocolate was the main contributor to caffeine intake in six
 712 surveys, coffee in four surveys, cola beverages in three surveys, and tea in two surveys. Differences
 713 among surveys regarding the contribution of different caffeine sources to total caffeine intakes could
 714 be explained, at least in part, by the different mean age of the adolescents studied in the different
 715 surveys and by dietary habits. The highest contribution to total caffeine intakes from “energy drinks”
 716 was found for adolescents in the UK (11 %), followed by the Netherlands (8.1 %) and Belgium (5.3
 717 %). Only in the first two cases was a specific code for “energy drinks” available in the database.

718 *Toddlers and other children*

719 Ten surveys were available for toddlers. Mean daily intake of caffeine ranged between zero and 2.1
 720 mg/kg bw per day (Table 2, Appendix B). The 95th percentile ranged from 0.1 to 3.5 mg/kg bw per
 721 day. Tea or chocolate were the main caffeine sources in all surveys except for Belgium, where cola
 722 drinks contributed the most to total caffeine intake (58 %; Appendix E). Mean daily caffeine intake
 723 was 1.1 mg/kg bw per day in this country (Appendix B).

724 Seventeen surveys were available for children aged 3 to < 10 years. Mean daily intakes of caffeine
 725 from all sources ranged between 0.2 and 2.0 mg/kg bw per day. The 95th percentiles ranged from 1.2
 726 to 4.6 mg/kg bw per day.

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

731 3.3.1.2. Caffeine intake on a single day

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

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

740 *Adults, elderly and very elderly*

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

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

746 *Adolescents*

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

749 When considering only coffee consumption days, the highest 95th percentile of caffeine intake from
750 coffee in one day was 445 mg (Appendix C). The highest 95th percentiles of caffeine intake from
751 “energy drinks”, tea, chocolate and cola were 330, 308, 253 and 142 mg, respectively. On a per kg bw
752 basis, the highest 95th percentile of caffeine intake was from coffee (7.1 mg), followed by chocolate
753 (5.4 mg), “energy drinks” (5.2 mg), tea (5.0 mg), and cola beverages (2.4 mg).

754 *Toddlers and other children*

755 For toddlers, the highest 95th percentile of caffeine intake per kg bw on a single day when considering
756 all days recorded were 7.1 mg/kg bw (Appendix C and D). Sufficient (n ≥ 60) days to obtain
757 statistically robust 95th percentiles for toddlers regarding caffeine intakes from different sources on
758 consumption days were only available for chocolate and tea, for which the highest values across MSs
759 were estimated at 5.3 and 9.6 mg/kg bw per day of caffeine, respectively (Appendix C).

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

765 **3.3.2. Caffeine intake from “energy drinks” on a “single session” estimated from the EFSA**
766 **report on “energy drinks”**

767 Table 4 summarises caffeine intakes from “energy drinks” consumed on a “single session” by adults
768 and adolescents who were “energy drink consumers” (i.e at least once in the previous year). The table
769 also indicates the prevalence of subjects who declared to consume ≥ 3 “energy drinks” per “single
770 session”. Data were available from 16 MSs (Zucconi et al., 2013).

771 Table 4: Caffeine intakes on a “single session” by “energy drink” consumers and prevalence of
772 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		95 th 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

773 ⁽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
774 in children.

775 *Adults*

776 The mean and 95th percentile of caffeine intake on a “single session” from “energy drinks” in adult
777 “energy drink consumers” were 155 mg and 344 mg, respectively (Table 4). In this survey, 52, 29, 11,
778 5 and 3 % of “energy drink consumers” declared to consume 1, 2, 3, 4 and ≥ 5 cans of “energy drinks”
779 within a “single session”.

780 *Adolescents*

781 The mean and 95th percentile of caffeine intakes on a “single session” from “energy drinks” in
 782 adolescent “energy drink consumers” were 176 mg and 450 mg, respectively (Table 4). On a per kg
 783 bw basis, these intakes were estimated at 2.9 and 7.2 mg, respectively. In this survey, 51, 25, 11, 6 and
 784 7 % of “energy drink consumers” declared to consume 1, 2, 3, 4 and ≥ 5 cans of “energy drinks”
 785 within a “single session”.

786 **3.3.3. Prevalence of “energy drink” consumption**

787 3.3.3.1. EFSA comprehensive European food consumption database

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

796 3.3.3.2. EFSA report on “energy drinks”

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

800 Table 5: Prevalence (%) of “energy drink consumers” and of consumers of “energy drinks” in
 801 combination with physical activity expressed as minimum and maximum ranges among 16
 802 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	-	-

803 ⁽¹⁾ Percentage of “energy drink” consumers among total respondents.

804 ⁽²⁾ The highest prevalence of “energy drink” consumption among total respondents was observed in Belgium (85 %), but
 805 these data was not considered due to the small sample size available for that MS (sampling error of estimates exceeds 5
 806 %).

807 ⁽³⁾ Percentage of subjects who declared to usually consume “energy drinks” before/in association with/after sport activities.
 808 Children were not studied.

809 (-) Not available

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

813 *Adults*

814 About 52 % of adult “energy drink consumers” (15 % of all respondents) declared to usually consume
 815 “energy drinks” before/in association with/after sport activities (Table 4). According to this survey, 47,
 816 26, 13, 9 and 5 % of this population declared to consume 1, 2, 3, 4 and ≥ 5 cans of “energy drinks” in
 817 relation to a single sport session.

818 *Adolescents*

819 About 41 % of adolescent “energy drink” consumers (about 28 % of all respondents) declared to
 820 usually consume “energy drinks” in relation to sport activities (Table 4). Forty-eight, 25, 13, 7 and 7
 821 % of this population declared to consume 1, 2, 3, 4 and ≥ 5 cans of “energy drinks” in relation to a
 822 single sport session.

823 **3.4. Limitations of the available caffeine intake data and data gaps**

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

833 The EFSA “energy drink” report provides information about caffeine intakes by adolescents and
 834 adults from “energy drinks” on a “single session”, also in relation to a “single session” of physical
 835 exercise. Although the time covered by the term “single session” is imprecise, these data give an idea
 836 of the amounts of caffeine from “energy drinks” consumed as a single dose or during short periods of
 837 time. However, the same type of information is not available for consumers of other caffeine sources
 838 that may provide similar or higher doses of caffeine in short periods of time (e.g. coffee, caffeine
 839 supplements), or for other population subgroups (e.g. children, pregnant women).

840 **4. Hazard identification**

841 As indicated in the background provided by the European Commission, the health concerns expressed
 842 by national and international risk assessment bodies in relation to caffeine mostly refer to its effects on
 843 pregnancy outcomes, the cardiovascular system and central nervous system. Concerns were also raised
 844 with respect to caffeine in the so-called “energy drinks” (i.e., also containing taurine and D-glucuron-
 845 γ -lactone), particularly if combined with alcohol, and to food supplements containing caffeine and
 846 synephrine. As in previous risk assessments by e.g. the SCF and EU Member State Committees, the
 847 present opinion considers primarily human data and addresses specific subgroups of the population,
 848 such as pregnant and lactating women, children and subjects performing physical exercise.

849 **4.1. Absorption, distribution, metabolism, and excretion**

850 **4.1.1. Adults**

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

855 The main route of metabolism in humans (70-80 %) is via N-3 demethylation to paraxanthine also
 856 known as 1,7-dimethylxanthine or 17X catalysed by cytochrome (CYP) 1A2 in the liver. Other
 857 primary metabolites are theophylline and theobromine. Activity of CYP1A2 accounts for about 95 %
 858 of caffeine clearance, a smaller proportion is metabolised by CYP3A4, xanthine oxidase and N-
 859 acetyltransferase 2 (Berthou et al., 1991; Miners and Birkett, 1996). Caffeine has a plasma half-life of
 860 about 4 hours with range of about 2 - 8 hours (Knutti et al., 1981; Abernethy and Todd, 1985;
 861 Abernethy et al., 1985; Balogh et al., 1995). The kinetics of caffeine have been reported to be linear in
 862 the dose range up to 10 mg/kg (Bonati et al., 1982) whereas a later study claimed non-linearity
 863 beginning at doses as high as 500 mg, corresponding to about 7.1 mg/kg bw (Kaplan et al., 1997).
 864 Paraxanthine, theophylline and theobromine are further metabolized and then excreted in the urine.

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

867 CYP1A2 polymorphism has been reported to be a source of variability in the metabolism of caffeine
 868 between individuals measured by caffeine metabolites in urine (Rasmussen et al., 2002). These authors
 869 also found a higher CYP1A2 activity in smokers and men as compared to non smokers and women,
 870 respectively. A lower CYP1A2 activity was found in women taking oral contraceptives. A single base
 871 change of A to C, at position 734 within intron 1 of the CYP1A2 gene decreases inducibility of the
 872 enzyme (Sachse et al., 1999; Han et al., 2001). This polymorphism is also referred to as CYP1A2*1F
 873 or -163C>A (AA, AC, CC) genotypes (Cornelis et al., 2006; Djordjevic et al., 2010) or as single
 874 nucleotide polymorphism (SNP) "rs762551" registered in the SNP Database of the US National
 875 Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/SNP>). The homozygote AA
 876 genotype has been considered by some authors as "fast metaboliser" while the AC and CC genotypes
 877 were considered to be "slow metaboliser". In four publications, the combined prevalence for the
 878 "slow" CC and AC genotypes was reported between 52 and 60 % versus 48 and 40 % for the "fast"
 879 AA genotype (Sachse et al., 1999; Han et al., 2001; Cornelis et al., 2006; Wang et al., 2012).
 880 Djordjevic et al. (2010) and Rodenburg et al. (2012) reported a higher prevalence for the AA genotype
 881 (61 % in Serbs; 54 % in Dutch).

882 Tantcheva-Poor et al. (1999) studied the effect of genetic (CYP1A2, sex) and life-style (coffee
 883 consumption, smoking, intake of oral contraceptives) factors of 786 individuals on the clearance of
 884 caffeine with a single saliva sample taken 5-7 hours after a test dose of about 145 mg caffeine. Overall
 885 geometric mean (geometric SD) of caffeine clearance was 1.34 mL/min/kg bw (1.65). Relevant factors
 886 influencing clearance were 1. daily coffee consumption, increasing clearance 1.45-fold per consumed
 887 litre; 2. smoking, increasing clearance 1.22-fold, 1.47-fold, 1.66-fold, and 1.72-fold for 1-5, 6-10, 11-
 888 20, and > 20 cigarettes smoked per day, respectively; 3. oral contraceptives, reducing clearance by
 889 0.72-fold; 4. female gender, reducing clearance by 0.90-fold. These covariates explained 37 % of
 890 overall variation in clearance. The clearance data did not indicate a relevant functional polymorphism
 891 for CYP1A2 activity when adjusted for covariate effects.

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

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

902 More than 150 single nucleotide polymorphisms have been identified for CYP1A2 (dbSNP database:
903 <http://www.ncbi.nlm.nih.gov/SNP/>)(Yang et al., 2010) with unknown functional relevance concerning
904 caffeine metabolism.

905 A few studies investigated whether genetic polymorphisms have an effect on caffeine consumption.
906 Rodenburg et al. (2012) studied the effect of this CYP1A2-163C>A polymorphism on coffee and tea
907 intake in 6 689 subjects in the Netherlands. Hetero- and homozygote “slow” metabolisers (AC/CC)
908 consumed 0.19 and 0.34 cups of coffee per day less, respectively, as compared to subjects of the “fast”
909 AA genotype ($p < 0.0005$); no difference was found for tea consumers. Cornelis et al. (2006) found no
910 statistically significant effect of this SNP on habitual caffeine consumption in 2 735 subjects. A meta-
911 analysis of four genome wide association studies of coffee consumption (in the Netherlands, Germany,
912 USA, Iceland) found two sequence variants (one locus between CYP1A1 and CYP1A2 gene and one
913 in the aryl hydrocarbon receptor gene) which were associated with a difference of coffee consumption
914 (Sulem et al., 2011). The difference was about 0.2 cups of coffee per day. No significant effect of the
915 CYP1A2-163C>A polymorphism on coffee consumption was found in this meta-analysis.

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

923 **4.1.2. Pregnant women**

924 During pregnancy, the half-life of caffeine increased in 15 pregnant women to a range of 6-16 hours
925 and returned to a range of 2-8 hours within 4 and 15 weeks after delivery (Knutti et al., 1982). The
926 reported prolonged half-life for pregnant women is consistent with results from other studies. For the
927 end of pregnancy, the half-life of caffeine in non-smoking women was reported to be 11.5 hours
928 (Arnaud, 1993) and 18 hours (Aldridge et al., 1981). This observation can be explained by the
929 interaction of caffeine with estrogens and gestagens which have been shown to inhibit the activity of
930 CYP 1A2 (Rietveld et al., 1984; Abernethy et al., 1985; Balogh et al., 1995). Tracy et al. (2005)
931 reported that CYP1A2 activity was significantly and progressively lower during pregnancy ($-32.8 \% \pm$
932 22.8% for weeks 14-18), ($-48.1 \% \pm 27 \%$ for weeks 24-28) and ($-65.2 \% \pm 15.3 \%$ for weeks 36 - 40)
933 as compared with the postpartum period. Similar quantitative and progressive reductions of CYP1A2
934 activity during pregnancy have been reported (Tsutsumi et al., 2001). The Panel notes that the
935 CYP1A2 activity is reduced during pregnancy and hence, the half-life of caffeine is increased. At the
936 end of pregnancy, the half-life of caffeine is three to four times longer than in the non-pregnant state.
937 This would lead to higher blood concentrations of caffeine at the end of pregnancy as compared to the
938 non-pregnant state if caffeine intake is kept constant during pregnancy.

939 One recent study (McMahon et al., 2014) assessed the allelic variation in two genetic loci which have
940 been associated with habitual caffeine consumption, one in CYP1A1 and CYP1A2 gene region
941 (rs2472297) and one near the aryl-hydrocarbon receptor (AHR) gene (rs6968865), and its contribution
942 to the inter-individual variability in habitual caffeine intake in a sample of pregnant women who
943 participated in the Avon Longitudinal Study of Parents and Children (ALSPAC). Genetic and data on
944 self-reported coffee, tea and cola consumption (including consumption of decaffeinated drinks) at
945 multiple time points (8, 18 and 32 weeks gestation and 2, 47, 85, 97 and 145 months after delivery)
946 were available from between 4 460 and 7 520 women. Caffeine intake generally increased across time
947 points. Cola contributed to about 4-11 % of caffeine intake. Both genotypes were individually
948 associated with total caffeine consumption and with the consumption of caffeinated drinks (coffee and
949 tea) at all time points, but not with the consumption of decaffeinated drinks. However, the proportion
950 of phenotypic variance (i.e. observed variability in caffeine intake) explained by these two genotypes

951 was small: CYP1A1 accounted for 0.15-0.88 %, AHR for 0.04-0.048 %, and the two combined for
952 about 0.16-1.28 %.

953 **4.1.3. Fetus**

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

959 **4.1.4. Breast fed infants**

960 In a study on 18 nursing mothers who abstained for 24 hours from eating and drinking caffeine
961 containing food, the concentration of caffeine was measured in plasma and milk 2 and 4 hours after
962 intake of caffeine from coffee (148 ± 48 mg). Milk/maternal plasma ratios averaged 0.8 ± 0.07 . Intake
963 in the nursed infants (4 days up to 19 weeks) was estimated to be between 0.03 and 0.2 mg/kg bw per
964 day. In eight of the infants, the caffeine concentration was measured in their saliva which is close to
965 the non- protein bound fraction of caffeine in plasma (90 %). The concentration in saliva of infants
966 was 0.38 ± 0.2 mg/L whereas the peak concentration in the plasma of the mothers was about 3 mg/L,
967 thus indicating low intakes of the infants (Hildebrandt and Gundert-Remy, 1983).

968 In two studies (Steer et al., 2003; Steer et al., 2004), preterm neonates were treated for extubation with
969 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
970 (n = 131) and 30 mg/kg bw (n = 45). Mean caffeine concentration in the 3 mg/kg group, the 15 mg/kg
971 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
972 observed side effects of caffeine administration were tachycardia (defined as heart rate > 200/min) and
973 jitteriness. Tachycardia was observed in 1 out of 42 pre-term infants in the 3 mg/kg bw group, in one
974 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
975 the 20 mg/kg bw group, and in eight out of 45 in the 30 mg/kg bw group. The figures for jitteriness
976 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
977 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
978 bw group. As preterm neonates are considered an especially sensitive population subgroup, the results
979 can be extrapolated to neonates and breastfed infants in general as most conservative estimates for the
980 prevalence of side effects.

981 The half-life of caffeine in neonates who have no CYP1A2 activity has been reported to range from 50
982 to 103 hours (Ginsberg et al., 2004; Grosso et al., 2006). However, the half-life of caffeine is rapidly
983 reduced, in the first months of life, going down to 14 hours at 3-4 months and to 2-3 hours at 5-6
984 months (Aranda et al., 1979). Caffeine's half-life appears to remain stable at about 2-3 hours during
985 childhood, and to increase thereafter in adolescents and adults. Caffeine clearance from plasma has
986 been estimated to be between 5 and 20 % faster in children than in adults (NNT, 2008).

987 **4.1.5. Conclusions**

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

993 **4.2. Pharmacodynamic effects**

994 The pharmacology of caffeine has been extensively studied. The effects of caffeine are predominantly
995 related to its antagonistic activity at adenosine receptors. Of the four adenosine receptors (A₁, A_{2A}, A_{2B}

996 and A₃), caffeine acts as an antagonist to adenosine A₁ and A_{2A} receptors that are expressed in the
 997 CNS, in particular at basal ganglia, which are involved in motor activity. The psychomotor stimulant
 998 effect of caffeine is generated by affecting a particular group of projection neurons located in the
 999 striatum, the main receiving area of the basal ganglia expressing high levels of adenosine A_{2A}
 1000 receptors. Caffeine acts, at least in part, by facilitating dopamine D₂ receptor transmission. Its
 1001 mechanism of action appears to be substantially different from that of ‘dopaminomimetic’
 1002 psychostimulants, such as cocaine and amphetamine (Fisone et al., 2004; Ferre, 2008).

1003 The diuretic activity of caffeine can be explained by an interaction with the adenosine receptor A₁ in
 1004 the kidney, leading to inhibition of renal re-absorption and causing diuresis and natriuresis (Rieg et al.,
 1005 2005).

1006 Tolerance to caffeine is observed after repeated administration. The mechanism is not well
 1007 understood. It has been attributed to upregulation of adenosine receptors (Ammon, 1991). Fast
 1008 tolerance development has been observed concerning the pressor effects of caffeine (Shi et al., 1993).
 1009 Prolonged administration of an adenosine A_{2A} receptor antagonist does not induce tolerance to its
 1010 motor stimulant effect, raising the possibility that caffeine tolerance is dependent on blockade of A₁,
 1011 rather than A_{2A}, receptors (Ferre, 2008). Tolerance in humans develops to some, but not to all effects
 1012 of caffeine and the development of tolerance is highly variable among the population (Fredholm et al.,
 1013 1999). Tolerance to the effects of caffeine on blood pressure and heart rate usually develops within a
 1014 couple of days and it is accompanied by less release of adrenaline, noradrenaline, and renin than in the
 1015 non-tolerant state. It is uncertain whether the development of tolerance may explain the difference in
 1016 the sensitivity to the effects of coffee on sleep. Some authors consider that the difference rather
 1017 reflects inter-individual variations in sensitivity to the effects of caffeine as well as intra-individual
 1018 variability.

1019 Symptoms such as headache, fatigue, decreased energy and activeness, decreased alertness,
 1020 drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and not
 1021 clear headed are observed 12-24 h after abstinence and this clinical situation is called caffeine
 1022 withdrawal syndrome (Juliano and Griffiths, 2004).

1023 Polymorphism in adenosine receptors has also been described and for some effects of caffeine the
 1024 effect size might be related to the polymorphic state (Alsene et al., 2003).

1025 **4.3. Adverse effects of caffeine: methodological considerations**

1026 In order to update the safety assessment of caffeine conducted in 1999 by the SCF (SCF, 1999), EFSA
 1027 launched a procurement project (RC/EFSA/NUTRI/2013/01) to retrieve articles published from 1997
 1028 onwards which addressed the effects of caffeine consumption in humans on different health outcomes
 1029 (Bull et al., 2014). Previous risk assessments by other bodies and spontaneous submissions from
 1030 stakeholders were also considered by the Panel to retrieve articles published up to June 2014 which
 1031 could be used as a source of data in the present assessment.

1032 The Panel considers that human intervention studies and human observational studies (prospective
 1033 cohort, case control and cross-sectional studies) with adequate control for confounding variables and
 1034 which have been conducted in healthy subjects at recruitment are appropriate to evaluate potential
 1035 adverse effects of caffeine consumption in humans, and that studies conducted in subjects selected on
 1036 the basis of a disease condition (e.g. established CVD, neurological or psychiatric diseases,
 1037 behavioural or sleep disorders, diabetes mellitus and other metabolic disorders, renal or hepatic
 1038 insufficiency, open angle glaucoma) do not allow conclusions to be drawn on the safety of caffeine for
 1039 the general healthy population. Whenever available, human intervention studies and prospective
 1040 cohort studies will be preferred over case control and cross-sectional studies due to the lower risk of
 1041 reverse causality and recall bias. The Panel also considers that, although case reports of adverse events
 1042 following consumption of caffeine-containing foods or beverages are useful to identify health

1043 concerns for further investigation, they generally provide insufficient information to conclude on a
 1044 factor or combination of factors which trigger the adverse event and/or the doses of caffeine which
 1045 could be considered as safe/unsafe for the general healthy population. Whenever available, systematic
 1046 reviews and meta-analyses will be used to summarise the scientific evidence.

1047 **4.4. Adverse effects of a single dose and of repeated doses of caffeine consumed within a day**

1048 With few exceptions, the effects of a single dose and of repeated doses of caffeine consumed within a
 1049 day from a variety of sources (i.e., including „energy drinks”), either alone or in combination with
 1050 alcohol or synephrine, have been addressed in human intervention studies. Among the variety of
 1051 outcomes investigated in these studies, the Panel focuses on adverse effects of caffeine on the CVS
 1052 and the CNS as the main health concerns expressed by other bodies in previous safety assessments
 1053 (also considering that the CVS and the CNS are the target organs for the acute effects of caffeine), and
 1054 on water-electrolyte balance and body temperature. Studies which did not report on safety outcomes
 1055 (i.e. investigating the effects of caffeine on outcomes which were deemed to be beneficial for the
 1056 target population recruited, like attention, alertness or physical performance, and studies addressing
 1057 the beneficial effects of caffeine in the treatment of various diseases) are not considered by the Panel
 1058 in this assessment.

1059 The Panel notes that an assessment of the health effects of components other than caffeine in foods
 1060 and beverages which are common dietary sources of caffeine (e.g., coffee, tea, soft drinks other than
 1061 “energy drinks”, chocolate) is outside the scope of this opinion, and therefore human intervention
 1062 studies which do not provide information about the effects of caffeine on the above-mentioned health
 1063 outcomes (e.g. studies using caffeinated coffee/tea and caffeine as control; studies using different
 1064 doses of decaffeinated coffee/tea with no caffeine group; uncontrolled studies with a caffeine group
 1065 only) are not considered specifically.

1066 **4.4.1. Cardiovascular system**

1067 Early metabolic studies found that single caffeine doses of 200-250 mg acutely increase plasma renin
 1068 activity, catecholamine concentrations, and blood pressure, and are able to induce cardiac (mostly
 1069 atrial) arrhythmias in healthy, caffeine naïve subjects (Robertson et al., 1978; Dobmeyer et al., 1983).
 1070 Possible mechanisms for the acute cardiovascular effects of caffeine include antagonistic effects on
 1071 adenosine receptors, activation of the sympathetic nervous system (release of catecholamines from
 1072 adrenal medulla), stimulation of adrenal cortex (release of corticosteroids), renal effects (diuresis,
 1073 natriuresis, activation of the renin-angiotensin-aldosterone system), and inhibition of
 1074 phosphodiesterases (increase in cyclic nucleotides), although the contribution of each of these
 1075 mechanisms to the acute CV effects of caffeine are unclear (Nurminen et al., 1999). It has been
 1076 suggested that the acute effects of caffeine on the CVS may depend on the source of caffeine, on the
 1077 dose administered, and on caffeine plasma concentrations prior to caffeine administration.

1078 4.4.1.1. Blood pressure, endothelial function and arterial compliance

1079 *Caffeine: single dose*

1080 Nurminen et al. (1999) reviewed 20 controlled human intervention studies in normotensive subjects
 1081 and five intervention studies in hypertensive subjects which had investigated the effects of single
 1082 doses of caffeine or caffeinated coffee on BP. A single dose of caffeine (200 - 250 mg, equivalent to
 1083 two to three cups of coffee) was found to increase systolic blood pressure (SBP) by 3-14 mm Hg and
 1084 diastolic blood pressure (DBP) by 4-13 mm Hg in normotensive subjects. Lower doses of caffeine
 1085 were not tested. Changes in BP paralleled changes in plasma concentrations of caffeine. BP started
 1086 increasing 30 min after caffeine administration to reach a maximal effect at 60-120 min, which lasted
 1087 for about 2-4 h. The effect was more pronounced in older subjects, in caffeine abstainers, during
 1088 “mental or physical stress”, and in subjects with hypertension. In a more recent meta-analysis (Mesas
 1089 et al., 2011) of five randomised control trials (RCTs) conducted in subjects with hypertension, single

1090 caffeine doses of 200 to 300 mg induced a mean increase in SBP and DBP of 8.1 mm Hg (95 % CI:
 1091 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
 1092 first 60 min after intake and persisted up to 180 min afterwards. The effect of caffeine on BP did not
 1093 change with the dose (only 200 to 300 mg were tested), with the time of caffeine abstinence before the
 1094 trial (9-48 h), or with the use of antihypertensive medication.

1095 The effects of a single dose of caffeine on arterial BP were investigated in 182 men stratified in five
 1096 groups by their risk of hypertension (Hartley et al., 2000). The study sample included 73 men with
 1097 optimal BP, 28 with normal BP, 36 with high-normal BP, 27 with stage 1 hypertension on the basis of
 1098 resting BP, and 18 men with diagnosed hypertension from a hypertension clinic. BP was measured
 1099 after 20 minutes of rest and at 45 to 60 minutes after the oral administration of caffeine (3.3 mg/kg bw
 1100 or a fixed dose of 250 mg for an average dose of 260 mg). Caffeine significantly raised both SBP and
 1101 DBP in all groups. However, the strongest response to caffeine was observed among diagnosed men
 1102 (mean increase in SBP of 10 mm Hg), followed by the stage 1 and high-normal groups and then by the
 1103 normal and optimal groups, with a difference of 1.5 times greater change in diagnosed hypertensives
 1104 than in the group with optimal BP.

1105 A number of controlled human intervention studies have been published thereafter on the effects of
 1106 single caffeine doses (as supplements, in coffee, tea, and “energy drinks”) on functional vascular
 1107 outcomes, including endothelial function, arterial compliance and BP, in healthy subjects. The main
 1108 characteristics of these studies are summarised in **Appendix F**.

1109 Acute increases in SBP, DBP, or both, as well as in pulse pressure and mean arterial blood pressure
 1110 (MABP), have been reported after single doses of caffeine ranging from 80-250 mg in coffee
 1111 abstainers, in habitual caffeine consumers after 12-48 h withdrawal, and after caffeine habituation
 1112 (300-600 mg per day for six days) (Hodgson et al., 1999; Lane et al., 2002; Farag et al., 2005a; Farag
 1113 et al., 2005b; Arciero and Ormsbee, 2009; Farag et al., 2010; Worthley et al., 2010; Buscemi et al.,
 1114 2011). The effect was inversely related to the level of physical activity in pre-menopausal women
 1115 (Arciero and Ormsbee, 2009), and did not translate into acute adverse changes in left ventricular
 1116 repolarisation (QTc) (Buscemi et al., 2011).

1117 In studies assessing endothelial function, compared to decaffeinated coffee, caffeinated coffee has
 1118 been reported to significantly increase SBP (130 mg caffeine) and DBP (80 and 130 mg caffeine), as
 1119 well as to decrease endothelium-dependent flow-mediated dilation (FMD) in habitual moderate coffee
 1120 consumers after 12-24 h caffeine withdrawal (Papamichael et al., 2005; Buscemi et al., 2010). A
 1121 significant decrease in endothelial function (assessed by peripheral artery tomography) with
 1122 concomitant increases in SBP and DBP was also reported after consumption of an “energy drink”
 1123 containing 80 mg caffeine, 1000 mg taurine and 600 mg D-glucurono-γ-lactone (Worthley et al.,
 1124 2010). Whether this effect could be explained by its content of caffeine was not addressed (no caffeine
 1125 group). Conversely, a significant increase in acetylcholine-mediated, endothelium-dependent forearm
 1126 blood flow (measured by brachial impedance plethysmography), which was reversible with the
 1127 infusion of a nitric oxide synthetase (NOs) inhibitor, was reported for a caffeine dose of 300 mg,
 1128 which also induced a significant increase in both SBP and DBP (Umemura et al., 2006).

1129 All studies available in healthy individuals (Mahmud and Feely, 2001; Vlachopoulos et al., 2003;
 1130 Hartley et al., 2004; Karatzis et al., 2005; Swampillai et al., 2006; Vlachopoulos et al., 2006) reported
 1131 a significant adverse effect of caffeine (in supplements, coffee or tea) at doses of 100-250 mg on one
 1132 or more measures of arterial compliance (e.g., forward compression and expansion waves or pulse
 1133 wave velocity as measures of stiffness; augmentation index and augmented pressure as measures of
 1134 wave reflections), denoting an increase in arterial stiffness, which was accompanied by a simultaneous
 1135 increase in one or more measures of BP (e.g., radial, aortic or brachial SBP and DBP, pulse pressure,
 1136 mean arterial blood pressure). The methods used to assess arterial compliance and BP, the arterial
 1137 segments assessed, and the indexes derived as outcome variables, differed among studies. Similar

1138 effects of caffeine on arterial compliance were found in men and women, although different
 1139 mechanisms (increase in peripheral resistance vs. increase in stroke volume and cardiac output,
 1140 respectively) were proposed for each sex (Hartley et al., 2004).

1141 The clinical relevance of acute changes in endothelial function and arterial compliance following an
 1142 intervention is unclear, particularly when simultaneous changes in BP occur (Anderson, 2006; McCall
 1143 et al., 2011). Changes in BP, and therefore blood flow, are associated with changes in FMD and PWV
 1144 which do not necessarily reflect an adverse change in the endothelial function or sustained stiffness of
 1145 the artery (McCall et al., 2011). The acute changes in endothelial function and arterial compliance
 1146 following caffeine consumption are vascular phenomena concordant with the acute increase in BP,
 1147 which can be predicted from arterial physiology. Unlike for BP (see section 4.5.1.2), there are no
 1148 studies available on the longer-term effects of habitual caffeine consumption on these endpoints.

1149 ***Caffeine: repeated doses***

1150 Two studies (Lane et al., 2002; Farag et al., 2005b) have investigated the effects of repeated doses of
 1151 caffeine consumed within a day on 12 to 18-hour ambulatory BP in healthy habitual caffeine
 1152 consumers (**Appendix F**).

1153 In a double-blind, randomized, placebo-controlled cross-over study (Lane et al., 2002), 47 healthy
 1154 normotensive, non-smoking subjects (20 female) were given either placebo or two 250 mg doses of
 1155 caffeine 4 hours apart (at 7.30-8.30 am and < 1 pm) on two separate trial days after an overnight fast.
 1156 Ambulatory BP was monitored after the first caffeine dose until bedtime or 10 pm. Compared with
 1157 placebo, caffeine significantly raised average SBP through the entire day by about 4 mm Hg and DBP
 1158 by about 3 mm Hg, whereas HR decreased by 2 bpm, with no significant interaction between
 1159 treatment and location (at work, at home). Urinary free epinephrine levels were 32 % higher with
 1160 caffeine than with placebo, particularly at work.

1161 In a second study with double-blind, randomized, placebo-controlled cross-over design (Farag et al.,
 1162 2005b), 85 healthy normotensive subjects (38 women) completed a four-week protocol. During each
 1163 week, subjects consumed capsules containing 0, 100, or 200 mg of caffeine three times daily (daily
 1164 doses of 0, 300 or 600 mg) for 5 days. On day 6, subjects consumed capsules at 9:00 am, 1:00 pm and
 1165 6:00 pm with either 0 or 250 mg caffeine after the placebo (P) maintenance dose and with 250 mg
 1166 caffeine (C) after each caffeine maintenance dose (four interventions: P-P, P-C, C300-C, and C600-C).
 1167 Ambulatory BP was monitored on day 6 after the second caffeine dose until 7 am the following day.
 1168 Subjects were divided into “high” and “low” tolerance groups on the basis of the median DBP response
 1169 to the first two challenge caffeine doses (at 9:00 am and 1:00 pm) given after the highest caffeine
 1170 maintenance dose (600 mg per day). The Panel notes that data were not analysed for all the study
 1171 subjects combined. As expected, significant differences in daytime BP were observed across
 1172 maintenance caffeine doses and tolerance groups. However, no significant week × tolerance group
 1173 interactions were noted. The sleep BP also differed significantly across caffeine maintenance doses,
 1174 but not between tolerance groups, with no significant week × tolerance group interactions for sleep
 1175 SBP or DBP. Compared to P-P, daytime BP was significantly higher during P-C in both tolerance
 1176 groups and during C300-C in the “low” tolerance group, with no differences during C600-C in either
 1177 tolerance or during 300-C in the “high” tolerance group. Similarly, sleep BP was significantly higher
 1178 during P-C in both tolerance groups and during C300-C (only SBP) in the “low” tolerance group, with
 1179 no differences during C600-C in either tolerance or during 300-C in the “high” tolerance group.

1180 These studies suggest that repeated doses of 250 mg caffeine taken four hours apart may induce a
 1181 significant increase in daytime BP, that BP remains significantly elevated up to 9-12 hours following
 1182 consumption of the last dose, and that the effect, which depends on habitual caffeine consumption, is
 1183 mostly observed after caffeine withdrawal. The Panel notes the high total caffeine intakes used in
 1184 these studies (500-750 mg per day), that lower repeated doses of caffeine (< 250 mg) have not been

1185 tested, and that the time between doses (4 hours), about one half-life, is likely to induce an increase in
 1186 plasma caffeine concentrations throughout the day.

1187 ***Caffeine and physical exercise***

1188 Three randomised, placebo-controlled, human intervention studies assessed the effects of caffeine (4-6
 1189 mg/kg bw) ingested 45-60 min pre-exercise on BP before (n=3), during (n=2) and after (n=2)
 1190 resistance exercise in recreational resistance-trained, normotensive men (except for three women in
 1191 Souza et al., 2014) who were habitual caffeine consumers after 48-72 h of caffeine withdrawal
 1192 (Astorino et al., 2007 and 2013; Souza et al., 2014). The study by Astorino et al. (2013) included
 1193 seven subjects with either high-normal or stage 1 hypertension, although the number of subjects with
 1194 hypertension was not specified. Sample size ranged from 14 to 22. BP variables and exercise programs
 1195 varied among studies. In the study by Astorino et al. (2007), SBP, HR and rate-pressure product (but
 1196 not DBP) significantly increased during exercise with caffeine and placebo and were significantly
 1197 higher before and during exercise with caffeine than with placebo, but no time x treatment interaction
 1198 was observed, suggesting an additive (but not synergistic) effect of caffeine and exercise on BP. In the
 1199 study by Astorino et al. (2013), in which four resistance exercise protocols were tested, SBP
 1200 significantly increased during all exercise protocols and significantly decreased post-exercise with
 1201 caffeine and placebo. SBP was significantly higher before and 2-h after exercise with caffeine than
 1202 with placebo, whereas HR and DBP were not different between treatments. SBP was only higher with
 1203 caffeine than with placebo during one (out of four) type of exercise and only in the “pre-hypertensive”
 1204 group. Souza et al. (2014) reported a significant decrease in SBP and MABP and a significant increase
 1205 in HR after exercise for caffeine and placebo. DPB and HR (but not SPB) were significantly higher at
 1206 rest with caffeine than with placebo, as well as peripheral vascular resistance (SBP, DBP, HR, stroke
 1207 volume or cardiac output) in the nine hours post-exercise. The Panel considers that, although these
 1208 studies are small and difficult to compare, they suggest an additive effect of caffeine and resistance
 1209 training on BP during exercise, and that caffeine could attenuate the decrease in BP observed after
 1210 resistance training.

1211 ***Caffeine and other components of “energy drinks”***

1212 Two randomised cross-over studies (Worthley et al., 2010; Grasser et al., 2014) assessed the effects
 1213 two “energy drinks” containing caffeine, taurine, and D-glucurono- γ -lactone on BP and endothelial
 1214 function as compared to the same volume of water. One unpublished study (Bischoff, 2013) conducted
 1215 at the University of Hohenheim and submitted to EFSA investigated the effects of an “energy drink”
 1216 containing caffeine, taurine, and D-glucurono- γ -lactone, with and without 75 g of alcohol, on multiple
 1217 outcomes (including heart rate and BP) as compared to the same volume of a caffeine-free soft drink.
 1218 The Panel notes that these studies do not allow conclusions on whether “energy drinks” have a BP-
 1219 raising effect over and above what could be expected from their caffeine content.

1220
 1221 One open-label, randomised, two-period cross-over study investigated the effects of a single dose of
 1222 an “energy drink” on BP as compared to caffeine alone (Franks et al., 2012). Twelve healthy,
 1223 nonsmoking, normotensive volunteers aged 18-45 years consumed one serving of “energy drinks”
 1224 (80 mg caffeine and 1000 mg taurine per serving) four times, at 8 am, 11 am, 3 pm and 7 pm, totalling
 1225 320 mg caffeine and 4 000 mg of taurine. Subjects underwent the same protocol with caffeine alone
 1226 (80 mg per serving in a similar volume) 4-30 days apart. The order of the intervention was
 1227 randomised. During the interventions, 24-hour ambulatory BP was monitored. Data from nine subjects
 1228 were available for analysis. 24-h SBP, DBP and mean arterial BP were significantly higher with
 1229 consumption of the “energy drinks” than with consumption of caffeine alone (by 5.8, 5.3 and 5.3 mm
 1230 Hg, respectively), whereas HR and nocturnal dipping (SBP and DBP) did not differ. The Panel
 1231 considers that, although this study suggests a bigger BP-raising effect associated with the consumption
 1232 of “energy drinks” as compared to caffeine alone, the small number of subjects included in the study,

1233 the high dropout rate (25 %), and the absence of blinding limit the conclusions which can be drawn in
 1234 relation to the effects of “energy drinks” components other than caffeine on BP.

1235 The afore-mentioned unpublished study (Bischoff, 2013) contains information on a “pre-study” using
 1236 a cross-over design conducted in 19 healthy subjects who received a single dose (1 000 mL) of a sport
 1237 drink (control, free of caffeine, taurine or D-glucurono- γ -lactone), the sport drink plus taurine
 1238 (4 000 mg), the sport drink plus caffeine (320 mg) and of an “energy drink” (containing 4 000 mg of
 1239 taurine, 320 mg of caffeine and 240 mg of D-glucurono- γ -lactone. The same preliminary testing was
 1240 conducted in 19 other subjects using 750 mL (as single dose) of the same beverages. A significant
 1241 increase in SBP (by about 7-8 mm Hg) was reported following consumption of the sport drink plus
 1242 caffeine in both preliminary tests, whereas consumption of the other beverages did not increase SBP
 1243 significantly. No significant changes in DBP were noted. The increase in SBP was significantly higher
 1244 with the consumption of the sport drink plus caffeine than with the consumption of the control sports
 1245 drink or the sports drink plus taurine, whereas no significant differences were observed compared to
 1246 the “energy drink”. The Panel notes that the acute consumption of an “energy drink” did not increase
 1247 BP over and above what could be expected from its caffeine content in this study.

1248 *Caffeine and synephrine*

1249 Synephrine is a biogenic amine of the chemical group of phenylethanolamines/phenylpropanolamines.
 1250 Amphetamine, ephedrine, octopamine, adrenaline, noradrenaline and dopamine belong to this group.
 1251 Different isomers of synephrine have been identified in food supplements. The protoalkaloid (-)-*p*-
 1252 synephrine is naturally found in bitter orange fruit (*Citrus aurantium L.*) and other citrus fruits. One
 1253 litre of orange juice contains about 15-27 mg of (-)-*p*-synephrine (EFSA, 2009b). *Citrus aurantium*
 1254 extract, most often standardised for (-)-*p*-synephrine at concentrations of 6-10 %, is the predominant
 1255 ingredient used in synephrine-containing food supplements. The synthetic racemate of the optical
 1256 isomers (-)-*p*-synephrine and (+)-*p*-synephrine and the synthetic *m*-isomer (*m*-synephrine or
 1257 phenylephrine) are drugs which induce vasoconstriction of the arterial bed (O’Neil, 2008; Martindale
 1258 et al., 2011; BfR, 2012; SLE, 2012). The presence of small amounts of these drugs in food
 1259 supplements containing *C. aurantium* extracts is indicative of adulteration. Only (-)-*p*-synephrine (or
 1260 synephrine thereafter) from *C. aurantium* extracts in food supplements will be considered in this
 1261 Opinion.

1262 Synephrine has direct stimulant effects on the sympathetic nervous system, primarily via the α_1 - and β -
 1263 adrenoreceptors. In contrast with ephedrine and amphetamines, which have known psycho-stimulating
 1264 effects in the CNS, synephrine is more hydrophilic, which leads to a lower transit across the blood-
 1265 brain barrier and consequently to lower, if any, CNS stimulation. Therefore, any additive or
 1266 synergistic effects of synephrine when consumed in combination with caffeine should be expected in
 1267 the CVS.

1268 The effects of single doses of synephrine in food supplements containing *C. aurantium* extracts on BP
 1269 have been investigated in a number of controlled human interventions as safety outcomes, which have
 1270 been recently reviewed (Stohs et al., 2012). The main characteristics of these studies are summarised
 1271 in **Appendix G**. Most studies used *C. aurantium* extracts only, and some used combinations of *C.*
 1272 *aurantium*, guarana and/or green tea, among other botanical preparations, in which synephrine and
 1273 caffeine were the main active ingredients (Haller et al., 2005a; Sale et al., 2006; Seifert et al., 2011).
 1274 Studies having caffeinated coffee as control (dose of caffeine not reported; Hoffman et al., 2006), or
 1275 an unclear study design (Gougeon et al., 2005) will not be considered.

1276 The studies are generally small and the results difficult to interpret. A significant increase in SBP and
 1277 DBP was reported for synephrine from *C. aurantium* extracts when consumed at 54 mg, but not at
 1278 lower doses (13.5-50 mg). A significant increase in SBP and DBP was also reported for a combination
 1279 of 5.5 mg synephrine and 5.7 mg octopamine and caffeine (239.2 mg), and a significant increase in

1280 DBP, but not in SPB, was observed with 21 mg synephrine and 304 mg caffeine. Conversely, no
 1281 significant changes in BP were found with synephrine (12-13 mg) and lower doses of caffeine (150-
 1282 176 mg). However, similar doses of caffeine, on their own, have been consistently reported to increase
 1283 BP significantly in other studies (**Appendix F**). The Panel notes that none of the available studies has
 1284 investigated the effects of single doses of caffeine alone, of synephrine alone, and of their
 1285 combination, on BP. The Panel considers that, from the information available, no conclusions can be
 1286 drawn on whether the simultaneous consumption of synephrine modulates the pressor effects of
 1287 caffeine, to which extent, or at which doses.

1288 *Conclusions*

1289 The Panel notes that caffeine consumption acutely increases BP in virtually all adult population
 1290 subgroups tested, regardless of baseline BP, regular caffeine consumption/time of caffeine withdrawal,
 1291 age, sex, or hormonal status. The effect was observed at single doses of caffeine ranging from 80-300
 1292 mg, although most studies tested doses of about 200-300 mg, which induced a mean increase in SBP
 1293 of about 3-8 mm Hg and in DBP of about 4-6 mm Hg, with high inter-individual variability. The
 1294 available data suggest that BP generally increases at 30 min after caffeine consumption, reaches a peak
 1295 at 60-90 min, and returns to baseline at about 2-4 hours, which is consistent with the pharmacokinetics
 1296 of caffeine. The effect may be more pronounced in subjects with high BP and after caffeine
 1297 withdrawal. The dose range tested in the majority of studies is tight and the dose-response relationship
 1298 has not been formally assessed. The Panel also notes that repeated doses of caffeine (250 mg) taken
 1299 four hours apart also induce an increase in BP (of about 3-4 mm Hg) which may last up to 9-12 hours,
 1300 particularly after caffeine withdrawal. The acute effects of lower caffeine doses and/or taken at longer
 1301 time intervals on BP have not been tested in the studies available. High doses of caffeine (4-6 mg/kg
 1302 bw, corresponding to about 280-420 mg for a 70-kg adult) ingested 45-60 min prior to exercise could
 1303 add to the BP-raising effect of resistance training and attenuate the decrease in BP observed after
 1304 resistance training. Lower caffeine doses were not tested. The studies available do not provide
 1305 sufficient information to conclude on whether consumption of synephrine, or of substances commonly
 1306 found in “energy drinks” other than caffeine, modify the acute effects of caffeine on BP.

1307 4.4.1.2. Myocardial blood flow

1308 Caffeine (in common with other methylxanthines) is a non-selective competitive A_{2A} receptor
 1309 antagonist which counteracts the vasodilator effect of adenosine and other A_{2A} receptor agonists in the
 1310 coronary arteries, where the density of such receptors is particularly high. The cardiac hyperaemic
 1311 response to physical exercise is primarily mediated by the endogenous production of adenosine by
 1312 myocytes as a consequence of hypoxia, which induces vasodilation of the coronary arteries.

1313 Physical exercise protocols are used to induce maximal vasodilation of the coronary arteries in nuclear
 1314 stress myocardial perfusion imaging tests (MPI) for the diagnosis of (and risk stratification of patients
 1315 with) coronary artery disease (CAD). When adequate exercise workloads cannot be achieved, non-
 1316 selective (i.e., adenosine, dipyridamole) and selective (i.e., regadenoson) agonists of the A_{2A} receptor
 1317 are used. The consumption of caffeine (and other methylxanthines) has been contraindicated 24 hours
 1318 before vasodilator MPI tests (Henzlova et al., 2006) because it attenuates the coronary hyperaemia
 1319 induced by adenosine and dipyridamole in a dose-dependent manner.

1320 A recent narrative review summarises the mechanisms by which caffeine could reduce myocardial
 1321 blood flow during exercise (Higgins and Babu, 2013).

1322 Few studies have investigated the effects of acute doses of caffeine on myocardial blood flow (MBF)
 1323 at rest and under stress (hyperaemic MBF), and on the myocardial blood flow reserve (MFR)
 1324 calculated as the difference of the above, using nuclear imaging techniques. These studies have been
 1325 conducted in young healthy subjects or in patients with CAD. Physical exercise protocols and
 1326 regadenoson have been used as stressors to induce maximal coronary vasodilation.

1327 ¹⁵O-labeled H₂O and positron emission tomography (PET) were used to assess the effects of caffeine
 1328 on resting and exercise-induced hyperaemic MBF and the resulting MFR in conditions of normoxia
 1329 and hypoxia (to simulate CAD states of oxygen deprivation) in 18 (7 female) healthy habitual coffee
 1330 drinkers after 36 hours of caffeine withdrawal (Namdar et al., 2006). A minimum clinically relevant
 1331 difference in coronary resistance of 20 % between baseline and caffeine was considered for power
 1332 calculations. In 10 subjects (mean age, 27 ± 6 years), MBF was measured at rest and after a 5-min
 1333 supine bicycle exercise of increasing intensity after the target workload was achieved at normoxia,
 1334 corresponding to environmental conditions at 4 500 m above sea level. Then subjects consumed a 200-
 1335 mg caffeine tablet and the same measurements were repeated 50 min later. Caffeine did not affect
 1336 resting MBF but induced a significant decrease in exercise-induced hyperemic MBF (2.51 ± 0.58
 1337 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
 1338 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
 1339 years), MBF was measured following the same protocol as above but in conditions of hypoxia,
 1340 simulating an altitude of 4 500 m by inhalation of a mixture of 12.5 % oxygen. Caffeine significantly
 1341 increased resting MBF (1.71 ± 0.41 mL/min per g tissue vs. 2.22 ± 0.49 mL/min per g tissue; p <
 1342 0.001) and significantly decreased exercise-induced hyperaemic MBF (5.15 ± 0.79 mL/min per g
 1343 tissue vs. 3.98 ± 0.83 mL/min per g tissue; p < 0.005), leading to a decrease in MFR of 39 % (3.13 ±
 1344 0.60 to 1.87 ± 0.45, p < 0.005). The Panel notes that the decrease in MFR in healthy subjects
 1345 following consumption 200 mg of caffeine under normal environmental conditions was not considered
 1346 clinically relevant by the authors for that population group. The Panel also notes that the effect could
 1347 be considered clinically relevant for healthy subjects under extreme environmental conditions where
 1348 oxygen partial pressure in the air are low (e.g. high altitude).

1349 The effects of caffeine on resting and exercise-induced hyperaemic MBF and the resulting MFR in
 1350 conditions of normoxia were also assessed in 15 patients with CAD and 15 age-matched healthy
 1351 controls by the same research group using an identical protocol and the same dose of caffeine
 1352 (200 mg) (Namdar et al., 2009). Subjects refrained from caffeine 24 hours prior to the tests. A
 1353 minimum clinically relevant difference in hyperaemic MBF of 20 % between baseline and caffeine
 1354 was considered for power calculations. Resting MBF was not significantly affected by caffeine in
 1355 either group. Exercise-induced hyperaemic MBF and MFR significantly decreased 50 min after
 1356 caffeine ingestion as compared to baseline measurements without caffeine. MFR significantly
 1357 decreased in healthy subjects by 14 % (p < 0.05) and in CAD patients by 18 % (p < 0.05) in remote
 1358 segments and by 25 % (p < 0.01) in stenotic segments. The Panel notes that the decrease in MFR in
 1359 healthy subjects following consumption of 200 mg of caffeine was not considered clinically relevant
 1360 by the authors for that population group under normal environmental conditions.

1361 The Panel notes that the order in which resting and exercise-induced MBF were measured in relation
 1362 to caffeine consumption was not randomised in these studies, so that caffeine measurements were
 1363 always performed following an exercise test whereas non-caffeine measurements were not, and thus
 1364 the physiological condition of the subjects in relation to the outcome variables tested may not have
 1365 been comparable.

1366 ¹⁵O-labeled H₂O and PET were also used to assess the effects of caffeine on resting and regadenoson-
 1367 induced hyperaemic MBF, and the resulting MFR, in a double-blind, randomized, placebo-controlled
 1368 cross-over study (Gaemperli et al., 2008). A total of 41 healthy volunteers (15 female) aged ≥ 18
 1369 years, nonsmokers, and regular coffee drinkers received in a blinded fashion either a 200 mg caffeine
 1370 capsule on day 1 and placebo on day 2 (2-14 days washout) or the inverse after refraining from
 1371 methylxanthine-containing products for at least 24 h. MBF was measured each day 2 hours after
 1372 capsule ingestion at rest and after and intravenous administration of regadenoson. The MBF (mean ±
 1373 SEM) was not significantly different between caffeine and placebo at rest (1.13 ± 0.04 mL/min per g
 1374 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
 1375 not MFR (2.75 ± 0.16 vs. 2.97 ± 0.16). The data show with 1-sided 95 % confidence that any MFR

1376 reduction associated with caffeine intake was < 20 %. However, a similar study using regadenoson-
 1377 stress SPECT MPI in patients with CAD showed that doses of caffeine of 200 mg and 400 mg
 1378 significantly decreased the number of cardiac segments with reversible vascularisation defects,
 1379 suggesting that caffeine at doses of 200 mg or above could significantly counteract the vasodilator
 1380 effect regadenoson in the coronary arteries in these patients (Tejani et al., 2014).

1381
 1382 The Panel notes that caffeine antagonises the vasodilator effect of adenosine and other A_{2A} receptor
 1383 agonists in the coronary arteries in a dose-dependent manner and this effect leads to a reduction of
 1384 MBF and MFR during intense physical exercise primarily in subjects with CAD, but also in healthy
 1385 subjects to some degree. However, on the basis of the data available, the Panel considers that caffeine
 1386 at doses of 200 mg consumed 1-2 hours prior to exercise does not induce clinically relevant reductions
 1387 of the coronary flow reserve in healthy adult subjects under normal environmental conditions. The
 1388 Panel notes that the effect of higher doses of caffeine has not been tested.

1389 4.4.1.3. Cardiovascular disease risk

1390 There is marked diurnal variation in the onset time of cardiovascular events, with a peak in early
 1391 morning, which parallels the significant diurnal variation in BP observed in hypertensive subjects,
 1392 with a decrease during sleep and a surge in the morning (Kario, 2010). It has been hypothesised that
 1393 the morning surge in BP could trigger cardiovascular events in subjects with underlying
 1394 atherosclerosis. Similarly, it has been hypothesised that the transient increase in BP induced by acute
 1395 caffeine intake could increase the risk of cardiovascular events in the first hour after consumption,
 1396 when BP reaches its peak.

1397 The effect of transient exposure to coffee on the risk of onset of acute cardiovascular events, including
 1398 sudden cardiac death (SCD), myocardial infarction (MI), and ischemic stroke, has been investigated
 1399 using case-crossover study designs. Control information for each case is based on his/her past
 1400 exposure experience, and a self-matched analysis was conducted (Maclure, 1991).

1401 One study (Selb Semerl and Selb, 2004) was conducted in Slovenia among the 309 out-of-hospital
 1402 SCD victims who died in the period from January 2000 to March 2001 in that country (253 men and
 1403 56 women, median age at death of 57.1 and 57.7 years, respectively). Information on exposure to
 1404 coffee and alcohol, as well as on lifestyle, health, and several socio-demographic variables were
 1405 obtained by mailing one questionnaire to the family members of the deceased and one to the attending
 1406 physician. Cases were those who died of SCD within 1 hour after coffee consumption or within 2
 1407 hours after ingesting alcohol; controls were those who died in the hours when they were not exposed
 1408 to coffee or alcohol. The relative risk of dying within exposed hours in comparison to non-exposed
 1409 hours was the parameter estimated for each risk factor. On average, each subject had 2.8 risk factors
 1410 for ischemic heart disease. The estimated RR of dying during 1 hour after coffee consumption was
 1411 1.73 (95 % CI=1.13-2.65), and 3.00 (95 % CI=1.61-5.68) within 2 hours after alcohol consumption.
 1412 Alcohol drinking did not appear to influence the risk in coffee drinkers.

1413 In another study (Baylin et al., 2006), 503 first incident cases of nonfatal MI between 1994 and 1998
 1414 were recruited in Costa Rica. Information on habitual coffee intake was retrieved by a FFQ, which
 1415 showed high correlation with seven 24-hour recalls for caffeine intake (0.83) and took into account
 1416 serving size and type of coffee as well as nine frequencies of consumption. Intake of coffee during the
 1417 time prior to the MI was collected by asking “when was the last time you had coffee before your heart
 1418 attack?” The number of cups consumed was also recorded. The median time between hospital
 1419 discharge and data collection was 11 days with most people (82 %) completing the interview within
 1420 two weeks after discharge. Out of the 530 incident cases of nonfatal MI recruited, complete and
 1421 consistent information was available for 503 cases regarding intake of coffee during the 24 hours and
 1422 days before the event and regarding habitual intake of coffee. Most patients reported drinking 2–3
 1423 cups of coffee per day and only 37 (7 %) reported no intake of coffee. All coffee consumed was
 1424 caffeinated coffee; 93 % of respondents reported drinking filtered coffee.

1425 A hazard period of one hour was selected based on the absorption and bioavailability of caffeine in
 1426 blood. Of the 503 patients, 80 had at least 1 cup of coffee in the hour before the onset of MI (69 had 1
 1427 cup of coffee, nine had 2 cups, and one had 3 cups). The RR for MI in the hour after taking coffee was
 1428 1.49 (95 % CI = 1.17–1.89). The RR after coffee intake was not significantly increased when two or
 1429 three hours were selected as hazard period, suggesting that the risk dropped to basal conditions
 1430 between one and two hours after drinking coffee. When stratifying by usual intake of coffee, patients
 1431 with light/occasional intake of coffee (up to 1 cup per day; n = 66) had a RR of MI in the hour after
 1432 taking coffee of 4.14 (95 % CI = 2.03–8.42), those with moderate consumption of coffee (2–3 cups per
 1433 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
 1434 a RR of 1.06 (0.69–1.63; p = 0.006, test for interaction). This was the only variable significantly
 1435 modifying the risk, whereas age, sex or physical activity, history of diabetes, hypercholesterolemia,
 1436 hypertension, smoking status, or having at least three (n = 101) or less than three of these risk factors
 1437 for disease did not.

1438 In the Stroke Onset Study, the relationship between coffee and alcohol consumption and the onset of
 1439 ischemic stroke was reported in two publications (Mostofsky et al., 2010a; Mostofsky et al., 2010b).
 1440 Between January 2001 and November 2006, 390 subjects (209 men, 181 women) were interviewed a
 1441 median of three days (range 0-14) after acute ischemic stroke. Subjects were asked about caffeinated
 1442 coffee and alcohol intake the year prior to the stroke, and consumers were asked about the frequency
 1443 of consumption and the last time they consumed coffee or alcohol before the event. The same
 1444 questions were asked for caffeinated tea and cola. Each subject's coffee consumption in the hour
 1445 before stroke symptoms was compared with his or her usual frequency of consumption in the prior
 1446 year. Of the 390 subjects, 304 (78 %) drank coffee in the prior year, 232 within 24 hours and 35 within
 1447 one hour of stroke onset; of the 248 subjects who drank alcohol in the previous year, 169 subjects
 1448 reported alcohol exposure during the week before stroke, 104 subjects drank alcohol within 24 hours
 1449 and 14 within one hour of stroke onset. Of the 35 people exposed to coffee in the hour prior to stroke
 1450 onset, three were also exposed to vigorous physical activity, one experienced feelings of anger, one
 1451 smoked a cigarette, and one drank an alcoholic beverage. Of the 14 people exposed to alcohol in the
 1452 hour before stroke onset, four were also exposed to vigorous physical activity and one drank coffee.

1453 The relative risk (RR) of stroke in the hour after consuming coffee was 2.0 (95 % CI, 1.4 to 2.8;
 1454 p < 0.001). There was no apparent increase in risk in the hour following consumption of caffeinated
 1455 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
 1456 because of the lower caffeine content of these beverages or their lower consumption. The association
 1457 between ischemic stroke in the hour after coffee consumption was only apparent among those
 1458 consuming ≤ 1 cup per day but not for patients who consumed coffee more regularly (p for
 1459 trend = 0.002). Relative risks were similar when the sample was restricted to those who were not
 1460 simultaneously exposed to other potential triggers (such as vigorous physical activity, feelings of
 1461 anger, smoking of a cigarette, drinking an alcoholic beverage) and the results remained significant
 1462 after stratifying by time of day. The risk of stroke onset was 2.3-fold higher (95 % CI, 1.4 to 4.0;
 1463 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
 1464 compared with periods of non use. The RR and returned to baseline thereafter. Results remained
 1465 similar when analyses were limited to subjects with no prior MI (n = 283) or were conducted
 1466 excluding the 75 people exposed to any potential stroke trigger in the hour preceding stroke onset.

1467 The Panel notes that these three case-crossover studies suggest an increased risk of acute
 1468 cardiovascular events in the hour following consumption of caffeinated coffee, particularly in subjects
 1469 with low habitual coffee intake. Although not formally tested, co-consumption of caffeine and alcohol
 1470 does not appear to modify the risk. The Panel also notes that these studies conducted in subjects with
 1471 an established (fatal or non fatal) cardiovascular event included few cases, which may limit the value
 1472 of the sensitivity and sub-group analyses conducted to explore modifying factors (e.g., influence of
 1473 other risk factors for the event, like disease conditions or physical activity prior to the event), and do

1474 not provide information about the risk of acute cardiovascular events following caffeine consumption
 1475 in the general population, or on the dose of caffeine which could trigger such events.

1476 4.4.1.4. Conclusions on the cardiovascular system

1477 A single dose of 200 mg of caffeine consumed 1-2 hours pre-exercise significantly increases BP
 1478 during resistance training in caffeine-naïve subjects as well as in habitual coffee consumers upon 24-
 1479 48 h of caffeine withdrawal. A single dose of 200 mg of caffeine also decreases myocardial blood flow
 1480 if consumed approximately one hour prior to endurance exercise (i.e. when the BP-raising effect of
 1481 caffeine reaches its peak). Whereas such changes could increase the risk of acute cardiovascular events
 1482 in subjects with an increased risk for CVD (e.g. with underlying hypertension and/or advanced
 1483 atherosclerosis), the Panel considers them to be of low clinical relevance for healthy individuals in the
 1484 general population under normal environmental conditions. Although not formally tested, the Panel
 1485 considers that changes in BP and MBF induced by repeated intakes of caffeine at doses and time
 1486 intervals which would not exceed the maximum plasma concentrations achieved with a single dose of
 1487 200 mg of caffeine would also be of low clinical relevance for healthy individuals in the general
 1488 population under normal environmental conditions. Consumption of alcohol in combination with
 1489 caffeine does not appear to modify the CVD risk. The studies available do not provide sufficient
 1490 information to conclude on whether co-consumption of synephrine or of substances commonly found
 1491 in “energy drinks” other than caffeine may affect the risk associated with caffeine consumption alone.

1492 **4.4.2. Hydration status and body temperature**

1493 *Caffeine*

1494 It is well established that caffeine has a diuretic effect (SCF, 1983; EFSA, 2009). However, any
 1495 diuretic effects resulting from chronic caffeine consumption are unlikely to have adverse health
 1496 consequences for the healthy general population. In addition, doses of caffeine up to 6 mg/kg bw per
 1497 day consumed for four days by habitual caffeine consumers (one week run-in with doses of 3 mg/kg
 1498 bw) did not lead to significant changes in body mass, urine osmolality, urine specific gravity, urine
 1499 color, 24-h urine volume, 24-h Na⁺ and K⁺ excretion, 24-h creatinine, blood urea nitrogen, serum Na⁺
 1500 and K⁺, serum osmolality, hematocrit, or total plasma protein compared to placebo (Armstrong et al.,
 1501 2005).

1502 It has been suggested, however, that acute consumption of caffeine prior to exercise, and particularly
 1503 at high temperatures, could increase body temperature and sweating as well as diuresis, leading to
 1504 water-electrolyte imbalances which may pose a risk to health. Acute caffeine intake at doses of about
 1505 100-600 mg prior to exercise did, however, not lead to a significant increase in urinary volume,
 1506 significantly different water retention during dehydration, or induce adverse water-electrolyte
 1507 imbalances compared to water or placebo, particularly in habitual caffeine consumers (Armstrong,
 1508 2002).

1509 A number of studies have investigated the acute effects of caffeine at doses of 3-9 mg/kg bw on
 1510 hydration status and/or body temperature before and during endurance exercise under different
 1511 conditions of temperature and humidity.

1512 In a double-blind-randomized cross-over study (Kim et al., 2011), 13 male student, non-habitual
 1513 caffeine consumers, who followed daily aerobic training, completed two experimental trials (i.e.,
 1514 running for 30 min at 60 % of VO₂max) in thermo-neutral conditions (24 °C, 40 % relative humidity)
 1515 one week apart, in which they received caffeine (3 mg/kg bw and 200 mL of water) or water only
 1516 (200 mL) 40 min before the test. Core (tympanic) and skin temperature were measured after caffeine
 1517 consumption at rest, pre-exercise (40 min after caffeine/placebo consumption) and post-exercise (after
 1518 30 min of running at 60 % VO₂max). Mean body temperature (calculated from tympanic and skin
 1519 temperatures) was significantly higher in pre (by 0.08 °C) and post-exercise (by 0.14 °C) following

1520 caffeine consumption compared to water, whereas tympanic body temperature only increased
1521 significantly pre-exercise (by 0.12 °C). After caffeine consumption, sweating rate was significantly
1522 higher and the onset of sweating significantly delayed during exercise.

1523 In another double-blind, randomized cross-over study (Del Coso et al., 2008), seven endurance-trained
1524 cyclists pedalled for 120 min at 63 % of VO_{2max} in a hot-dry environment (36 °C; 29 % humidity)
1525 under six different testing conditions: no fluid, water (WAT) to replace 97 % fluid losses, the same
1526 volume of a 6 % carbohydrate-electrolyte solution (CES), or each of these treatments along with
1527 caffeine at 6 mg/kg bw. Caffeine or placebo capsules were ingested about 50 min prior to the trial.
1528 Core (rectal) temperature and serum osmolality as an indicator of fluid balance were measured
1529 throughout the six trials. Rehydration with WAT or CES, with or without caffeine, prevented the
1530 significant losses of body fluid, the increase in serum osmolality and the significant raise in core
1531 temperature observed with no fluid replacement, with or without caffeine. No significant differences
1532 in fluid losses, serum osmolality, or core temperature were observed between the WAT and CES
1533 groups with caffeine and those without caffeine. This is consistent with the results from a more recent
1534 study (Ping et al., 2010) conducted in nine male recreational runners (normally non-caffeine users)
1535 who consumed caffeine (5 mg/kg bw) one hour prior to a running exercise (at 70 per cent of VO_{2max})
1536 in a hot environment (31 °C, 70 % relative humidity) but received regular hydration (3 mL of cool
1537 water/kg bw every 20 min) during the trial. No significant differences in core temperature were
1538 observed between the caffeine and placebo conditions.

1539 The same dose of caffeine (6 mg/kg bw) was tested by Roelands et al. (2011) in a double-blind-
1540 randomized cross-over study, in which eight healthy trained male cyclists who were habitual “mild”
1541 caffeine consumers completed two experimental trials (at 30 °C). Subjects ingested either placebo or
1542 caffeine 1 h prior to exercise, which consisted of cycling for 60 min at 55 % of W_{max} , immediately
1543 before a time trial to measure performance. Compared to placebo, caffeine significantly increased core
1544 (rectal) temperature during exercise up to about 0.5 °C, whereas it had no significant effect on skin
1545 temperature, heart rate, loss of body mass or sweat rate.

1546 Compared to placebo, acute doses of 9 mg/kg bw caffeine consumed after 4 days of caffeine
1547 abstinence also showed to increase core (rectal) body temperature (by 0.20-0.30 °C), but not skin
1548 temperature, in 10 healthy men performing 30-min of cycle ergometry at 50 % VO_2 peak followed by
1549 a 15-min performance time trial at 40 °C and 20-30 % relative humidity (Cheuvront et al., 2009).
1550 “Caffeine sensitive” and heavy caffeine drinkers (> 400 mg per day) were excluded from this study.
1551 Conversely, mean body temperature was significantly higher (by 0.27 °C) one hour after caffeine
1552 consumption compared to placebo only at the beginning of the exercise (cycling for 30 min at 50 % of
1553 VO_2 peak in a 40 °C, 25 % relative humidity environment) in another study using the same caffeine
1554 dose, whereas no differences between caffeine and placebo were observed with respect to core, skin or
1555 mean temperature during exercise (Ely et al., 2011).

1556 *Caffeine in combination with taurine*

1557 The acute diuretic effects of caffeine do not appear to be modified by the concomitant ingestion of
1558 taurine or by any other component of “energy drinks” (EFSA, 2009).

1559 In a human intervention study (Riesenhuber et al., 2006), 12 participants received, in a random order,
1560 each of four different test drinks at weekly intervals in a blinded fashion (each 750 mL of fluid)
1561 containing: a) 80 mg caffeine and 1 g taurine per 250 mL; b) 80 mg caffeine per 250 mL, c) 1 g
1562 taurine per 250 mL, and d) neither caffeine nor taurine. Caffeine significantly increased urinary output
1563 and natriuresis, whereas taurine had no effect on either outcome and did not appear to modify the
1564 diuretic effects of caffeine when administered simultaneously.

1565 4.4.2.1. Conclusions on hydration status and body temperature

1566 The Panel notes that caffeine at doses of 3 mg/kg bw (equivalent to 210 mg for a 70-kg adult) ingested
 1567 about one hour prior to endurance exercise appear to induce only a modest increase in body
 1568 temperature compared to placebo. The Panel also notes that higher doses of caffeine (6 mg/kg bw
 1569 equivalent to 420 mg for a 70-kg adult) ingested about one hour prior to prolonged endurance exercise
 1570 in a hot environment do not affect body temperature or hydration status beyond what could be
 1571 expected from the testing conditions, and that changes in body temperature and hydration status under
 1572 these conditions are of no health concern if fluid losses can be timely replaced.

1573 **4.4.3. Central nervous system**

1574 4.4.3.1. Sleep, anxiety and behavioural changes

1575 *Adults*

1576 In adults, single doses of caffeine of about 100 mg (1.5 mg/kg bw per day in a 70 kg adult) have been
 1577 shown to increase sleep latency and reduce sleep duration when consumed close to bedtime (Landolt
 1578 et al., 1995), whereas doses < 100 mg do not appear to have such an effect on sleep (Dorfman and
 1579 Jarvik, 1970).

1580 Higher doses (\geq 400-500 mg) consumed either in a single occasion or within short periods of time
 1581 have been reported to increase anxiety upon oral consumption mostly in patients with psychiatric
 1582 anxiety disorders, but also in healthy adults, particularly if non-habitual caffeine consumers (FSANZ,
 1583 2000; Nawrot et al., 2003; Childs and de Wit, 2006; NNT, 2008; SHC, 2012). Polymorphisms of the
 1584 adenosine receptor gene ADORA_{2A} have been suggested to account for part of the inter-individual
 1585 variability observed in the anxiogenic response to caffeine (Childs et al., 2008; Rogers et al., 2010).

1586 *Children and adolescents*

1587 A number of human intervention studies (Elkins et al., 1981; Rapoport et al., 1981b; (Rapoport et al.,
 1588 1984); Leviton, 1992; Baer, 1987; Bernstein et al., 1994; (Rapoport et al., 1981b; Hale et al., 1995;
 1589 Davis and Osorio, 1998) and a systematic review and meta-analysis of human studies (Stein et al.,
 1590 1996) which investigated the effects of caffeine on behaviour in children and adolescents have been
 1591 already considered by other assessment bodies. No new studies have become available since then in this
 1592 population sub-group.

1593 Stein et al. (1996) searched for human studies reporting the effects of caffeine on cognitive,
 1594 behavioral, sleep, or psychological effects which included a caffeine comparison (either placebo,
 1595 alternate drug treatment, baseline, or matched control group). Nine studies were indentified, of which
 1596 five were in children with attention-deficit hyperactivity disorders (ADHD) and four in healthy
 1597 children. The Panel considers that results obtained in children with ADHD cannot be extrapolated to
 1598 children in the general population and will not be further considered in this opinion (e.g. Leviton,
 1599 1992).

1600 Of the studies mentioned above, only two (three publications) have assessed the effects of single doses
 1601 of caffeine in healthy children (Elkins et al., 1981; Rapoport et al., 1981b; Bernstein et al., 1994). Both
 1602 studies investigated two caffeine doses using randomised, placebo-controlled, cross-over designs.

1603 The behavioural and cognitive effects of single doses of caffeine (3 and 10 mg/kg bw) were
 1604 investigated in 19 prepubertal boys (mean age 10.6 ± 2.5 years) and 20 young men (mean age $21.7 \pm$
 1605 3.4 years) (Elkins et al., 1981; Rapoport et al., 1981b). Children were not recruited on the basis of their
 1606 habitual caffeine consumption, which was on average 125 ± 160 mg per day. Subjects were asked to
 1607 complete the anxiety scale “What I think I feel” and an 11-item caffeine side-effect questionnaire
 1608 (headache, stomachache, nausea, chest pain, heart pounding, feeling flush, feeling faint, feeling

1609 nervous/jittery, increased diuresis, difficulty sleeping) one hour after caffeine administration. Items
 1610 were rated on a 3-point scale. Nine items of behaviour (fidgety, distractible, tense, hypoactive,
 1611 pressured speech, physical complaints, euphoria-elation, and nervous habits and mannerisms) from a
 1612 Psychiatric Rating Scale were rated on a 7-point scale by a research assistant. No significant
 1613 differences in self-reported side effects were observed in children for any caffeine dose compared to
 1614 placebo, with the exception of feeling “nervous/jittery”. Scores for this side effect were significantly
 1615 higher for the 3 mg/kg bw dose than for placebo, and for the 10 mg/kg bw dose compared to the 3
 1616 mg/kg bw. No significant differences in self-rated anxiety or investigator-rated items of behaviour
 1617 were found between placebo and caffeine at any dose.

1618 The study by Berstein et al. 1994 investigated the effects of two single doses of caffeine (2.5 and
 1619 5 mg/kg body weight) on self-reported anxiety in 21 children (mean age 10.6 ± 1.3) after 12-15 hours
 1620 of abstinence from caffeine. Self-reported anxiety was evaluated using the Visual Analogue Scale for
 1621 Anxiety Revised (VAA-R), which assessed how anxious was the child at the time of testing (anxiety
 1622 state) and most of the time (anxiety trait), the State-Trait Anxiety Inventory for Children (STAIC),
 1623 which assessed anxiety trait and anxiety state, and the Revised Children’s manifest Anxiety Scale
 1624 (RCMAS). Caffeine intake was not significantly associated with any of these measures of self-
 1625 reported anxiety, whereas a significant linear association was reported between caffeine concentrations
 1626 in saliva and the anxiety state item in the VAA-R scale only. The Panel notes that caffeine intakes
 1627 were not significantly associated with anxiety, and that caffeine concentrations in saliva were
 1628 generally not associated with self-reported measures of anxiety in this study. The Panel also notes that
 1629 the above-mentioned tools to assess self-reported anxiety have been developed to discriminate
 1630 between children with high and low anxiety levels, rather than to assess changes in anxiety.

1631 The Panel notes that these studies do not show an effect of single doses of caffeine ranging from 2.5 to
 1632 10 mg/kg bw on most self-reported measures of anxiety in children. The Panel also notes that single
 1633 doses of caffeine of 3 and 10 mg/kg bw (Rapoport et al., 1981b) had no effect on nine investigator-
 1634 rated items of behaviour, and that a dose-response relationship was observed only for one out of the 11
 1635 self-reported side effects tested (“feeling nervous/jittery”).

1636 4.4.3.2. Perceived exertion during exercise

1637 In 2011, health claims on caffeine and endurance capacity, endurance performance and reduction in
 1638 the rated perceived exertion/effort during exercise were evaluated by the NDA Panel with a positive
 1639 outcome. The conditions of use for these claims were that caffeine should be consumed one hour prior
 1640 to exercise at doses of 3 mg/kg bw for claims on endurance capacity and performance, and of 4 mg/kg
 1641 bw for claims on reduction in the rated perceived exertion/effort during exercise (EFSA NDA Panel,
 1642 2011).

1643 The scientific substantiation of the claim on the reduction in the rated perceived exertion/effort during
 1644 exercise was based on a meta-analysis of 22 laboratory-based, double-blind, fully randomised (and
 1645 mostly cross-over), placebo-controlled intervention studies which examined the effects of caffeine
 1646 ingestion on ratings of perceived exertion (RPE) during exercise (Doherty and Smith, 2005).
 1647 Compared to placebo, caffeine significantly reduced RPE during exercise (in 20 out of the 22 studies)
 1648 by 5.6 % (95 % CI -4.5 to -6.7). RPE could account for 29 % of the variance in the improved exercise
 1649 performance (based on 16 studies where changes in exercise performance were tested). This analysis
 1650 comprised studies from 1975 to 2004 representing over 200 subjects (74 % men) who were 20 to 35
 1651 years of age, ranging from physically active individuals to extremely well trained elite athletes, and
 1652 included both habitual caffeine users and non-users (half of the studies did not provide information on
 1653 coffee use). The protocols varied, including work intensities from 50 % to 125 % (mean = 80 %) of
 1654 VO_{2max} . The caffeine doses ranged from 4 mg/kg bw to 10 mg per kg bw (median 6 mg/kg bw) and
 1655 were typically given one hour before the start of the exercise test after a period of caffeine withdrawal.
 1656 The caffeine abstinence of the subjects varied from 12 to 240 hours (median = 24 hours). Since only
 1657 the effect-size difference between caffeine and placebo was calculated in the meta-analysis, it was

1658 unclear whether the between-group difference observed was owing to an increased perception of
 1659 fatigue due to caffeine deprivation, to a decreased perception of fatigue due to caffeine consumption,
 1660 or both. The effect of a single dose of caffeine on fatigue perception in either caffeine abstainers or in
 1661 caffeine consumers which are not caffeine-deprived was not investigated.

1662 These conclusions were supported by the results of a double-blind, cross-over, placebo-controlled
 1663 intervention study published after the meta-analysis by Doherty and Smith (2005), where nine
 1664 competitive male rugby players ingested either caffeine (6 mg/kg bw) or placebo (dextrose) 70 min
 1665 before performing a rugby test consisting of seven circuits in each of two 40-min halves with a 10-min
 1666 half-time rest (Stuart et al., 2005). The development of fatigue during the test was significantly
 1667 reduced after caffeine consumption compared to placebo.

1668 In the health claim opinion (EFSA, 2011c), a reduction in the rated perceived exertion/effort during
 1669 exercise was considered by the Panel as a plausible mechanism by which single doses of caffeine
 1670 administered after at least 12-24 hours of caffeine deprivation could increase endurance capacity and
 1671 performance. In this context, the Panel considered this to be a beneficial physiological effect for adults
 1672 performing endurance exercise willing to obtain such effect.

1673 In the context of this opinion, however, a reduction in the perceived exertion/effort during exercise can
 1674 be considered a potential adverse health effect under the assumption that the perception of fatigue is a
 1675 physiological mechanism leading to the spontaneous ending of physical activities that, due to their
 1676 high intensity, extended duration, or both, may compromise the cardiovascular and/or the
 1677 musculoskeletal systems. The Panel notes that single doses of caffeine which have been observed to
 1678 reduce the rated perceived exertion/effort during exercise (≥ 4 mg/kg bw) are equivalent to 280 mg of
 1679 caffeine for a 70 kg adult.

1680 4.4.3.3. Subjective perception of alcohol intoxication

1681 It has been suggested that consumption of caffeinated beverages (including “energy drinks”) together
 1682 with alcohol may ‘mask’ or alter the subjective perception of alcohol intoxication, which could
 1683 increase the likelihood of engaging in potentially dangerous activities while intoxicated (i.e. risk-
 1684 taking behaviour).

1685 In addition to the review of the literature considered by the UK COT (Verster et al., 2012), a recent
 1686 systematic review and meta-analysis of RCTs, which includes all the studies identified by Verster et
 1687 al. (2012), has addressed this question (Benson et al., 2014). Studies were included if they had
 1688 assessed the effects of alcohol with and without any type of caffeinated beverages (including, but not
 1689 limited to, “energy drinks”) on a direct measure of subjective intoxication and provided enough data to
 1690 be included in a meta-analysis. Of the 16 publications identified by the literature search, nine meet
 1691 these criteria (Fillmore and Vogel-Sprott, 1999; Fillmore et al., 2002; Marczinski and Fillmore, 2006;
 1692 Howland et al., 2011; Marczinski et al., 2011; Marczinski et al., 2012; Heinz et al., 2013; Marczinski
 1693 et al., 2013; Peacock et al., 2013). Alcohol doses were typically 0.65 g/kg bw (in six studies) and
 1694 ranged from 0.29 to 1.068 g/kg bw, producing peak blood alcohol concentrations (BAC) ranging from
 1695 0.032 to 0.12 %. Caffeine doses ranged from 0.6 to 5.5 mg/kg bw. Four studies used “energy drinks”
 1696 as source of caffeine. Three had a cross-over and six a parallel design. Sample size (per arm) varied
 1697 between 7 and 74 subjects. Subjective intoxication was measured using the Beverage Rating Scale
 1698 (BRS) in six studies, a self-estimate BAC in one study, a Subjective Intoxication Scale (SIS) in one
 1699 study, and a ‘feel any effects’ visual analogue scale (VAS) in one study. A meta-analysis of all studies
 1700 combined showed no masking effect of caffeine when combined with alcohol relative to alcohol alone
 1701 on direct measures of subjective intoxication. The only individual study reporting a significant
 1702 masking effect of caffeine was Heinz et al. (2013), which had the biggest sample size (BAC 0.088 %,
 1703 caffeine 5.0 mg/kg bw for females and 5.5 mg/kg bw for males). Marczinski and Fillmore (2006)
 1704 reported a masking effect of caffeine at the highest caffeine dose tested (4 mg/kg bw), whereas
 1705 Howland et al. (2011), who tested the highest dose of alcohol (target BAC 0.12 %) and caffeine (5.0

1706 mg/kg bw) in heavy alcohol drinkers and used the second biggest sample (n = 35 alcohol plus caffeine,
1707 n = 28 caffeine) showed no significant masking effect of caffeine.

1708 Seven studies addressing the research question were excluded from the meta-analysis because they did
1709 not address subjective intoxication directly (Liguori and Robinson, 2001; Ferreira et al., 2006; Alford
1710 et al., 2012) or the publication did not contain sufficient detail to calculate the effect size for pooling in
1711 a meta-analysis (Rush et al., 1989; Azcona et al., 1995; Marczinski and Fillmore, 2003; Attwood et al.,
1712 2012). Doses of alcohol targeted BAC between 0.03 and 0.10 % and caffeine doses were between 1.14
1713 and 7 mg/kg bw (80-500 mg). Two studies used “energy drinks” as source of caffeine. No significant
1714 differences between the alcohol and the alcohol plus caffeine groups were reported in these studies in
1715 relation to direct or indirect measures of subjective intoxication.

1716 Another systematic review (Peacock et al., 2013) had restricted the question to the consumption of
1717 alcohol together with “energy drinks” (rather than with caffeine from any source) and addressed a
1718 wide variety of (physiological and psychological) outcomes, mostly using cross-sectional studies. All
1719 the RCTs on the combination of “energy drinks” with caffeine reviewed in this publication were
1720 already considered in the systematic review by Benson et al. (2014).

1721 The Panel considers that caffeine consumed at doses up to 3 mg/kg bw (corresponding to 210 mg in a
1722 70-kg adult) from all sources, including “energy drinks”, is unlikely to mask the subjective perception
1723 of alcohol intoxication which could lead to an increased risk-taking behaviour when alcohol is
1724 consumed at doses of about 0.65 g/kg bw. Higher doses of alcohol have not been systematically
1725 investigated.

1726 4.4.3.4. Conclusions on the central nervous system

1727 Single doses of caffeine up to about 200 mg per day (3 mg/kg/bw for a 70-kg adult) do not appear to
1728 induce anxiety in unselected adult subjects from the general population, to reduce the perceived
1729 exertion/effort during exercise when consumed one hour prior to exercise after 12-24 hours of caffeine
1730 withdrawal, or to alter the subjective perception of alcohol intoxication when alcohol is consumed at
1731 doses of about 0.65 g/kg bw. In children, similar single doses of caffeine on a weight basis (3 mg/kg
1732 bw) do not appear to induce anxiety or behavioural changes, although inter-individual variability in
1733 relation to habitual caffeine intakes has not been studied. The Panel notes that 100 mg of caffeine
1734 (about 1.5 mg/kg bw) may increase sleep latency and reduce sleep duration in some individuals,
1735 particularly when consumed close to bedtime.

1736 4.5. Adverse effects of longer-term and habitual caffeine consumption

1737 Adverse effects of daily caffeine consumption over longer periods of time (> 7 days) on the CNS and
1738 the cardiovascular system have been reported in human intervention studies. These concern sustained
1739 changes in BP and children’s behaviour.

1740 Data on the relationship between habitual consumption of caffeine in foods and beverages and risk of
1741 chronic diseases (e.g., CVD, cancer, diabetes mellitus type II, Parkinson disease, Alzheimer disease,
1742 bone fractures), adverse pregnancy outcomes, male fertility, and birth defects (neural tube defects, oral
1743 clefts), mostly comes from human observational studies. With the exception of CVD risk and adverse
1744 pregnancy outcomes, the scientific publications identified almost exclusively reported no relationship
1745 or an inverse relationship between caffeine intake and adverse health effects in relation to these
1746 outcomes. Therefore, the Panel will focus on CVD risk and on adverse pregnancy outcomes (e.g. pre-
1747 term delivery, fetal growth retardation or small for gestational age, miscarriage or spontaneous
1748 abortion, stillbirth) to assess the safety of habitual caffeine consumption in adults.

1749 **4.5.1. Central nervous system**

1750 In adults, tolerance to the anxiogenic effect of caffeine develops with frequent consumption, even in
1751 genetically susceptible individuals (Rogers et al., 2010).

1752 In children, four studies have investigated the effects of caffeine consumed for longer periods of time
1753 (up to two weeks) using randomised, placebo-controlled, parallel or cross-over designs (Rapoport et
1754 al., 1981a; Rapoport et al., 1984; Baer, 1987; Halle et al., 1995).

1755 In the study by Halle et al. (1995), 18 adolescents (11-15 years) underwent six independent
1756 randomised, double-blind, placebo-controlled, trials. On each trial, participants were given a
1757 noncaffeinated and a caffeinated soft drink (providing 33 mg of caffeine) in a 2-day cross-over,
1758 followed by two days in which subjects were given concurrent access to the two drinks, which were
1759 consumed *ad libitum*. No behavioural symptoms were reported by any participant. Average caffeine
1760 intake among the four subjects who tended to select caffeinated soft drinks repeatedly was 167 mg per
1761 day (about 3.3 mg/kg bw per day).

1762 In the placebo-controlled, cross-over study by Baer et al. (1987), six 5-year old children were
1763 administered daily a caffeine-free or a caffeinated soft drink (providing 1.6-2.5 mg/kg bw of caffeine
1764 per day) for two weeks, at the end of which the drink conditions were reversed. No consistent effects
1765 on behavioural outcomes such as off-task behaviour or motor activity were noted. Anxiety was not
1766 assessed.

1767 Two studies by the same authors have investigated daily caffeine consumption (10 mg/kg bw per day)
1768 for two weeks in relation to self-reported anxiety, parents/teachers ratings of childrens behaviour and
1769 side effects in prepubertal children (mean age about 10 years, age range 6-13 years). These studies
1770 were either planned (Rapoport et al., 1984) or analysed considering habitual caffeine intakes and used
1771 a randomised, double-blind, placebo controlled, cross-over design. In the first study, (Rapoport et al.,
1772 1981a), data from 19 children were analysed depending on whether they were “low” (< 50 mg per
1773 day) or “high” (> 300 mg per day) caffeine consumers. In the second study, 19 “high” habitual caffeine
1774 consumers (> 500 mg per day) and 19 “low” habitual caffeine consumers (< 50 mg per day) matched
1775 by age, gender and teacher were recruited and separately randomised. Collectively, these two studies
1776 provide evidence that “high” habitual caffeine consumers (and their parents) tend to report more side
1777 effects during the caffeine withdrawal period, whereas the reverse is observed in “low” caffeine
1778 consumers, suggesting the development of tolerance and withdrawal symptoms in “high” habitual
1779 consumers.

1780 The Panel notes that regular consumption of caffeine up to about 3 mg/kg bw per day does not appear
1781 to induce behavioural changes in children and adolescents, whereas higher intakes (10 mg/kg bw per
1782 day) may increase anxiety and adversely affect behaviour and sleep in habitual low caffeine
1783 consumers. Children appear to develop tolerance to the central effects of caffeine at high habitual
1784 intakes (> 300 mg per day) and show withdrawal symptoms. The Panel also notes that the studies
1785 available at doses of ≤ 3 mg/kg bw are small and heterogeneous in design, and that doses between 3
1786 mg/kg bw per day and 10 mg/kg bw per day have not been investigated.

1787 **4.5.2. Cardiovascular system**

1788 4.5.2.1. Methodological considerations

1789 There is a wealth of human prospective cohort studies which have investigated the relationship
1790 between caffeine-containing foods and beverages (e.g., coffee, tea, soft drinks, chocolate) and risk of a
1791 number of CVD-related outcomes, including incident hypertension, (fatal, non-fatal, total) CHD,
1792 (total, non-fatal) MI, (total, fatal and non-fatal) stroke (all types, haemorrhagic, ischemic), arrhythmias

1793 (mostly atrial fibrillation), and total CVD risk. There is also a wealth of meta-analyses published in
 1794 relation to these outcomes which will be used to summarise the evidence available.

1795 Case-control and cross-sectional studies will not be considered specifically in this section. Previous
 1796 meta-analyses of case-control and prospective cohort studies have consistently reported positive
 1797 associations between habitual consumption of caffeine-containing foods and beverages (mostly coffee)
 1798 and risk of CVD from case-control studies, but not from prospective cohort studies (Greenland, 1993;
 1799 Kawachi et al., 1994; Sofi et al., 2007). Possible explanations for this discrepancy include recall bias
 1800 for exposure in cases (over-reporting), low caffeine consumption in controls recruited from inpatients
 1801 with chronic conditions, differences in outcome measures (case-control studies usually report on non-
 1802 fatal events only) and lack or inappropriate control for confounding variables in case-control studies
 1803 (Wilhelmsen et al., 1977; Kawachi et al., 1994; Sofi et al., 2007).

1804 The prospective cohort studies available are heterogeneous with respect to the exposure used as
 1805 independent variable. Coffee (unspecified), caffeinated coffee, decaffeinated coffee, tea (unspecified),
 1806 green tea, oolong tea, black tea, (sugar-containing and sugar-free) caffeinated soft drinks, and
 1807 chocolate, as well as caffeine from all sources, have been investigated in relation CVD-related
 1808 outcomes in one or more of these studies. In some, tea has been assessed but only used as confounding
 1809 variable to adjust models on coffee.

1810 **Appendix I** provides an overview of the prospective cohort studies considered in the most recently
 1811 published systematic reviews and meta-analyses which have investigated the association between
 1812 habitual consumption of coffee or caffeine from all sources and CVD-related outcomes. Meta-analyses
 1813 of prospective cohort studies investigating only tea in relation to CVD-related outcomes are not tabled,
 1814 but will be discussed in the sections below where appropriate. Individual prospective cohort studies
 1815 investigating only tea in relation to CVD-related outcomes will not be considered specifically because
 1816 tea contains lower amounts of caffeine than coffee, coffee is the major source of caffeine for adults in
 1817 the majority of European countries, and caffeine intakes in countries where tea is the major source of
 1818 caffeine are generally lower than caffeine intakes in “coffee-drinking” countries (see section 3 on
 1819 dietary intake).

1820 Although some of the meta-analyses in **Appendix I** occasionally include one or more prospective
 1821 cohort studies where the study population has been selected on the basis of a disease condition or a
 1822 risk factor for disease (hypertension, previous MI, type 2 diabetes mellitus), the vast majority of the
 1823 studies included were conducted in unselected samples from the general population. Individual studies
 1824 (Martin et al., 1988; Hakim et al., 1998; Bidel et al., 2006; Palatini, 2007; Silletta et al., 2007;
 1825 Mukamal et al., 2009; Zhang W et al., 2009; Zhang WL et al., 2009b) and meta-analyses (Mesas et al.,
 1826 2011) focusing on particular population subgroups with a disease condition or a risk factor for disease
 1827 will not be considered specifically.

1828 4.5.2.2. Blood pressure

1829 *Caffeine*

1830 *Prospective cohort studies*

1831 A systematic review (Zhang et al., 2011) identified four prospective cohort studies which had
 1832 investigated the association between coffee drinking and long-term changes in BP measured in fasting
 1833 conditions. Two were conducted in the Netherlands (Uiterwaal et al., 2007; Driessen et al., 2009), one
 1834 in the US (Klag et al., 2002), and one in Australia (Jenner et al., 1988). Sample size varied from 340 to
 1835 5 189 subjects and follow-up between six and 33 years. Data from these studies could not be pooled in
 1836 a meta-analysis because different BP variables were used as outcomes (e.g., residuals of BP, mean
 1837 arterial BP, SBP and DBP) and the results were mixed: whereas the Australian study found a negative
 1838 association between coffee drinking and long-term changes in BP, the Dutch studies found no

1839 association and the US study a positive association. An additional prospective cohort study published
 1840 thereafter (Giggey et al., 2011), investigated the relationship between habitual caffeinated coffee
 1841 consumption and long-term changes in resting BP and pulse pressure in 2 442 participants (865
 1842 women and 1 577 men) from the Baltimore Longitudinal Study of Aging. In men, significant quadratic
 1843 (non-linear) interactions were observed between coffee consumption, age, and time since baseline on
 1844 SBP and pulse pressure, but not in women. The models predicted an increase in SBP and pulse
 1845 pressure with age which, beyond 70 years, would be potentiated by the intake of ≥ 6 cups of coffee per
 1846 day. The Panel notes that the results from prospective cohort studies on the association between
 1847 habitual caffeine consumption and long-term changes in BP are mixed.

1848 *Randomised controlled trials lasting ≥ 7 days*

1849 Three meta-analyses of RCTs (Jee et al., 1999; Noordzij et al., 2005; Steffen et al., 2012) have
 1850 investigated the effects of caffeine or coffee consumption during ≥ 7 days (after habituation to caffeine
 1851 takes place) on fasting BP in unselected populations. The characteristics of the studies included in
 1852 each meta-analysis are summarised in **Appendix H**.

1853 Noordzij et al. (2005) selected RCTs in humans that had investigated the effects of caffeinated coffee
 1854 or caffeine consumption for ≥ 7 days on fasting BP and heart rate (HR). Studies using co-interventions
 1855 (e.g. caffeine plus epinephrine) which did not allow conclusions on caffeine or coffee were excluded.
 1856 The meta-analysis included 11 trials on coffee (18 strata) and five trials on caffeine (7 strata)
 1857 published between 1984 and 2000 which varied in sample size from 10 to 123 participants (median:
 1858 45), for a total of 1 010 subjects, of which ≥ 50 % were men in 17 strata. All trials were in adults (23
 1859 to 77 years) and lasted 7 to 84 days (median: 42 days). Six strata (24 %) included study populations
 1860 with high normal BP or hypertension, with two strata having subjects on antihypertensive treatment.
 1861 The coffee trials were conducted using instant coffee ($n = 8$), filtered coffee ($n = 7$), boiled coffee ($n =$
 1862 2) or coffee that was boiled and subsequently filtered ($n = 1$). Daily coffee dose in active treatment
 1863 groups varied from 450 mL to 1 235 mL, which corresponds to a caffeine dose of 225-798 mg per day
 1864 (one cup of coffee was assumed to contain 150 mL and 90 mg of caffeine when not reported in the
 1865 original publication). In caffeine trials, caffeine was administered in tablets at doses ranging from 295
 1866 to 750 mg per day. In coffee and caffeine trials combined, the median caffeine dose was 410 mg per
 1867 day. The control groups of coffee trials either received no coffee (11 strata) or decaffeinated coffee
 1868 (seven strata). In the caffeine trials all control groups received placebo tablets.

1869 Average pre-treatment BP ranged from 109 to 143 mm Hg for systolic BP (median 122 mm Hg) and
 1870 from 65 to 94 mm Hg for diastolic BP (median 74 mm Hg). Mean pre-treatment HR ranged from 61 to
 1871 78 bpm (median 71 bpm). Net BP changes in coffee and caffeine trials ranged from -1.6 to 12.0 mm
 1872 Hg for systolic BP and from -2.4 to 5.0 mm Hg for diastolic BP. Combining all caffeine and coffee
 1873 studies, SBP significantly increased by 2.04 mm Hg (95 % CI, 1.10– 2.99) for systolic and DBP
 1874 0.73 mm Hg (95 % CI, 0.14–1.31). After excluding nine coffee trials with an open design, changes in
 1875 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
 1876 significantly. In stratified analyses adjusted for type of intervention (coffee or caffeine), age (< 40 or \geq
 1877 40 years), sex (proportion of males < 50 % or ≥ 50 %), baseline BP ($< 130/85$ or $\geq 130/85$ mm Hg),
 1878 baseline caffeine intake (< 400 or ≥ 400 mg per day), and caffeine dose ($<$ or \geq the median intake of
 1879 410 mg per day in all the coffee and caffeine studies combined), except when used as stratification
 1880 factor, the type of intervention, sex, and caffeine dose significantly affected changes in BP, whereas
 1881 age, baseline BP, baseline caffeine intake and study duration (< 6 weeks or ≥ 6 weeks) did not.
 1882 Changes (mean and 95 % CI) in SPB and DBP for coffee (18 strata) were and 1.22 mm Hg (0.52,
 1883 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
 1884 2.41 mm Hg (0.98, 3.84). Caffeine from any source at doses ≥ 410 mg per day significantly increased
 1885 SPB (mean 2.98; 95 % CI, 2.15, 3.80) and DBP (mean 1.96; 95 % CI, 1.19, 2.73), whereas caffeine
 1886 doses < 410 mg per day did not (change in SBP = mean 0.72, 95 % CI = - 0.35, 1.78; change in DBP =
 1887 mean - 0.52, 95 % CI = - 1.62, 0.57). Caffeine significantly increases SBP and DBP in studies with a

1888 majority of women (n = 8), but not in those with a majority of men (n = 17). The Panel notes that this
 1889 meta-analysis shows a sustained BP-raising effect of continuous (≥ 7 days) caffeine consumption at
 1890 doses of about 400 mg per day, but not at lower doses.

1891 The meta-analysis by Steffen et al. (2012) aimed to assess the effects of daily coffee consumption (> 7
 1892 days) on fasting BP. The effects of caffeine *per se*, or the effects of caffeine in coffee, were not
 1893 assessed. The search targeted RCTs which included an intervention group that consumed coffee and a
 1894 control group that consumed either no coffee or less coffee, which lasted > 7 days to eliminate any
 1895 acute pressor effect of coffee. Studies (or intervention arms within a study) which used decaffeinated
 1896 coffee as control were excluded. Of the 10 RCTs included (**Appendix H**), six had been considered in
 1897 the meta-analysis by Noordzij et al. (2005). Five studies had a parallel design and five had a cross-
 1898 over design, and duration of the intervention was between 2 and 11 weeks. Seven trials included two
 1899 strata and six used the same control group to compare the two interventions. Of these, only one
 1900 intervention group with coffee was selected for inclusion in the meta-analysis, giving preference to the
 1901 most common types of coffee consumed (caffeinated, filtered), so that only the effects of caffeinated
 1902 coffee as compared to no coffee were explored in the meta-analysis. Most of the study populations
 1903 were healthy, normotensive individuals. Coffee consumption varied between trials and ranged from
 1904 three to over six cups daily. Only four trials used a standard amount of coffee in the intervention,
 1905 whereas the other trials defined a minimum amount of consumption, but no maximum. The pooled
 1906 weighted difference in mean change of SBP was -0.55 mm Hg (95 % CI -2.46 to 1.36) and of DBP
 1907 was -0.45 mm Hg (95 % CI -1.52 to 0.61). Heterogeneity in the pooled SBP ($I_2=72$ %) and DBP
 1908 ($I_2=41$ %) analysis was explored by considering type of coffee, sex, and pre-study BP in subgroup
 1909 analyses, but no significant interactions were found. The Panel notes that this meta-analysis does not
 1910 show a significant increase in fasting BP following consumption of caffeinated coffee for > 7 days at
 1911 doses of about three to six cups per day.

1912 A previous meta-analysis of RCTs on the effects of caffeinated coffee on fasting BP (Jee et al., 1999)
 1913 included nine studies with duration of the intervention ranging between 2 and 11 weeks. Eight had
 1914 been considered by Noordzij et al. (2005) and four by Steffen et al. (2012). The overall pooled
 1915 estimates of treatment effect associated with coffee drinking were 2.4 mm Hg (95 % CI, 1.0 to 3.7) for
 1916 SBP and 1.2 mm Hg for DBP (95 % CI, 0.4 to 2.1). Duration of run-in and coffee dose significantly
 1917 modified the effect of coffee on BP. Studies with the shorter run-in and the highest doses of coffee
 1918 showed the biggest effect on BP. A significant effect of caffeinated coffee on BP was only observed
 1919 by pooling studies using ≥ 5 cups of coffee, but not in studies using ≤ 4.5 cups.

1920 One study not included in the meta-analyses above (Hodgson et al., 1999) assessed the effects of
 1921 consuming 250 mg of caffeine in hot water, black tea or green tea (five cups per day) for seven days
 1922 on 24-h ambulatory SBP and DBP in 13 subjects with high-normal systolic and diastolic BP in a
 1923 cross-over design. Changes in 24-h ambulatory BP did not differ significantly among interventions of
 1924 with respect to baseline. Consistent with the finding by Noordzij et al. (2005), this study suggests that
 1925 caffeine intake for one week at doses of 250 mg per day (< 400 mg per day) does not increase fasting
 1926 BP significantly, regardless of the caffeine source.

1927 *Caffeine and synephrine*

1928 The majority of human intervention studies available which have investigated the health effects of
 1929 daily consumption (> 7 days) of synephrine in food supplements containing *C. aurantium* extracts
 1930 have addressed energy metabolism, body weight and body composition as measures of efficacy
 1931 (reviewed in Stohs et al. (2012)). Cardiovascular outcomes (SBP, DBP, HR) have only been evaluated
 1932 in one study using 98 mg per day of synephrine (in two doses of 49 mg each) for 60 days (Kaats et al.,
 1933 2013) and in one study using a combination of synephrine (10 mg per day) and caffeine (400 mg per
 1934 day) for 14 days (Kalman et al., 2002). None of these studies found a significant effect of the
 1935 intervention on BP compared to placebo. The Panel notes that these studies provide no information on

1936 whether the co-consumption of synephrine may modify the effects of daily caffeine consumption on
 1937 fasting BP.

1938 The Panel notes that caffeine intakes at doses of about 400 mg per day did not raise fasting BP
 1939 significantly after caffeine habituation in human intervention studies. The studies available do not
 1940 provide sufficient information to conclude on whether consumption of synephrine modifies the effects
 1941 of daily caffeine consumption on fasting BP.

1942 4.5.2.3. Hypertension

1943 Two systematic reviews and meta-analyses of prospective cohort studies have addressed the
 1944 association between coffee consumption and risk of incident hypertension (Zhang et al., 2011; Steffen
 1945 et al., 2012). They considered the same six cohort studies reported in five publications (**Appendix I**),
 1946 which included a total of 172 567 participants and 37 135 incident cases of hypertension. Mean
 1947 follow-up ranged from 6.4 to 33 years. Three studies reported in two publications were conducted in
 1948 the US (Klag et al., 2002; Winkelmayr et al., 2005) and three were conducted in Europe: one in
 1949 Finland (Hu et al., 2007), one in Italy (Palatini et al., 2007), and one in the Netherlands (Uiterwaal et
 1950 al., 2007).

1951 Two studies used drug-treated hypertension as the outcome: one recruited only untreated
 1952 hypertensives at baseline (Palatini, 2007) and the second recruited both normotensives and untreated
 1953 hypertensives (Hu et al., 2007). The remaining studies were conducted in normotensive individuals at
 1954 baseline and used either diagnosis of hypertension or drug treatment for hypertension at follow-up as
 1955 the outcome (Klag et al., 2002; Winkelmayr et al., 2005; Uiterwaal et al., 2007). Two studies only
 1956 assessed intake of caffeinated coffee (Klag et al., 2002; Palatini et al., 2007); the Finnish study did not
 1957 discriminate between caffeinated and decaffeinated coffee, but the use of the latter was very low
 1958 (about 0.8 %) in Finland at the time (Hu et al., 2007); one study assessed both caffeinated and
 1959 decaffeinated coffee (Uiterwaal et al., 2007), and two studies reported in one publication
 1960 (Winkelmayr et al., 2005) assessed caffeine intake from all sources, including caffeinated and
 1961 decaffeinated coffee. Both meta-analyses assessed the relationship between habitual consumption of
 1962 (any) coffee and incident hypertension, and stratified analyses by type of coffee were not possible with
 1963 the data available.

1964 In both the meta-analyses data from original studies were categorised into four categories of coffee
 1965 consumption: reference (< 1 cup per day), low (1–3 cups per day), moderate (3–5 or 3–6 cups per day),
 1966 and high (> 5 or > 6 cups per day). In the meta-analysis by Zhang et al. (2011), the group consuming
 1967 > 0-3 cups per day was used as reference category for the study by (Uiterwaal et al., 2007) instead of
 1968 coffee abstainers due to the low number of the latter, and the group consuming 3-6 cups per day as the
 1969 second category. For the study by Palatini et al. (2007), the group consuming > 3 cups per day
 1970 (highest category) was taken as the high category and the group of 1-3 cups per day as the low
 1971 category. Compared with the reference category, the pooled RRs (95 % CI) for hypertension were 1.09
 1972 (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
 1973 cups per day), and 1.08 (0.96, 1.21) for the highest category. In a dose-response meta-analysis, the
 1974 best-fitting model showed an inverse “J-shaped” curve (p for quadratic term < 0.001), with the risk of
 1975 hypertension increasing up to 3 cups per day (RR for the comparison of 3 with 0 cups per day: 1.07;
 1976 95 % CI: 0.97, 1.20) and decreasing with higher intake (RR for the comparison of 6 with 0 cups per
 1977 day: 0.99; 95 % CI: 0.89, 1.10). The Panel notes that the risk of hypertension did not increase
 1978 significantly at any dose of coffee consumption in this dose-response analysis. In the meta-analysis by
 1979 Steffen et al. (2012), the study by Uiterwaal et al. (2007) was excluded from the combined analysis
 1980 because it used > 0-3 cups of coffee per day as the reference category. Coffee drinking was not
 1981 significantly associated with an increased risk of hypertension at any category of coffee intake
 1982 compared to the reference category.

1983 Among the individual studies considered, the study by Palatini et al. (2007) reported an increased risk
 1984 of developing sustained hypertension associated with caffeinated coffee consumption as compared to
 1985 no consumption, with no significant difference in risk among categories of coffee intake (0, 1-3, and
 1986 > 3 cups per day). A subsequent study by the same authors (Palatini et al., 2009) reported an increased
 1987 risk of developing sustained hypertension requiring pharmacological treatment with increasing
 1988 caffeinated coffee consumption in carriers of the slow C/C or C/A allele (59 %) of the CYP1A2 gene,
 1989 but not in carriers of the fast A/A allele, suggesting that the risk of developing hypertension associated
 1990 with caffeine consumption may depend on the genetic background. However, these two studies
 1991 enrolled exclusively subjects with never treated stage 1 hypertension at baseline (incidence of
 1992 hypertension requiring medication of 50.7 % in the 6-year follow-up) and do not provide information
 1993 about the general (unselected) adult population. Caffeinated coffee drinking was also positively
 1994 associated with initiation of antihypertensive treatment (p for trend = 0.024 across categories of coffee
 1995 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)
 1996 in the study by Hu et al. (2007) which enrolled never-treated hypertensive and normotensive subjects,
 1997 but the association was no longer significant when baseline BP was considered in the analysis. No
 1998 association between caffeinated coffee consumption and risk of incident hypertension was observed
 1999 after adjusting for confounding variables in the study by Klag et al. (2002) in normotensive young
 2000 males. In the study by Uiterwaal et al. (2007), where the category of > 0-3 cups per day was taken as
 2001 reference, higher coffee intake was not associated with an increased risk of hypertension, whereas
 2002 coffee abstainers showed a decreased risk compared to the reference category. The Panel notes the low
 2003 number of coffee abstainers included in the study and the low number of incident cases of
 2004 hypertension in this group. The Panel also notes that the interaction between coffee intake and sex on
 2005 the incidence of hypertension was not statistically significant, and thus subgroup analyses by sex were
 2006 not statistically justified.

2007 In the Nurses' Health Studies (NHSs) I and II of 155 594 US women free from physician-diagnosed
 2008 hypertension were followed up over 12 years (Winkelmayer et al., 2005). Food frequency
 2009 questionnaires were used to measure dietary intake and were completed in 1990, 1994, and 1998 for
 2010 NHS I (30 to 55 years of age at recruitment) and 1991, 1995, and 1999 for NHS II (25 to 42 years) and
 2011 referred to the previous year. Relevant beverages included on the questionnaire were low-calorie and
 2012 regular cola drinks, and caffeinated and decaffeinated tea and coffee. Caffeine content was assumed to
 2013 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
 2014 per serving of chocolate candy. A total of 19 541 (32 %) incident cases of physician-diagnosed
 2015 hypertension were reported in NHS I and 13 536 (14.3 %) in NHS II. In both cohorts, no linear
 2016 association between caffeine consumption and risk of incident hypertension was observed after
 2017 multivariate adjustment. Using categorical analysis, an inverse U-shaped association between caffeine
 2018 consumption and incident hypertension was found. Compared with participants in the lowest quintile
 2019 of caffeine consumption (mean intakes 14.8 and 19.6 mg per day), those in the third quintile (209.3
 2020 mg per day and 174.7 mg per day) had a significant 14 % and 15 % increased risk of hypertension in
 2021 NHS I and NHS II, respectively, whereas no increased risk was observed in the highest quartile (608.1
 2022 mg per day and 597.4 mg per day). In multivariate models including beverage type, rather than actual
 2023 caffeine intake, significant inverse associations between intake of caffeinated coffee (p for trend =
 2024 0.02 and 0.03 in NHS I and NHS II, respectively), but not of decaffeinated coffee (p for trend = 0.08
 2025 and 0.67 in NHS I and NHS II, respectively), and risk of hypertension was observed in both cohorts. A
 2026 significant association between caffeinated tea intake and incident hypertension was found in the
 2027 cohort of younger women in NHS II (p for trend=0.01), but not in NHS I (p for trend=0.79). A
 2028 significant inverse association between the intake of sugar-containing (p for trend = 0.03 and < 0.001
 2029 in NHS I and NHS II, respectively) and sugar-free (p for trend = 0.03 and < 0.001 in NHS I and NHS
 2030 II, respectively) caffeinated cola drinks and incident hypertension was observed in both cohorts. The
 2031 Panel notes that this study shows an inverse U-shape relationship between total caffeine intake
 2032 calculated from dietary sources and incident hypertension. An increased risk of hypertension was
 2033 reported for women with mean caffeine intake of about 200 mg per day compared to women with very
 2034 low (about 15-20 mg per day) or high (about 600 mg per day) intake. The Panel also notes that

2035 different types of caffeinated beverages were differently associated with the risk of incident
 2036 hypertension. Whereas caffeinated (but not decaffeinated) coffee was inversely associated with the
 2037 risk of hypertension, caffeinated tea (in one cohort) and cola beverages (in both cohorts) were directly
 2038 associated with that risk.

2039 The Panel notes that BP values are used for CVD risk stratification and as a therapeutic target in
 2040 prevention studies, and that hypertension is an independent risk factor for CVD, including CHD and
 2041 stroke, so that studies on the relationship between caffeine intake and risk of CVD may help to define
 2042 habitual caffeine intakes which pose no concern in relation to the CVS. The Panel also notes that data
 2043 from prospective cohort studies on the relationship between habitual caffeine intake and risk of
 2044 incident hypertension is conflicting. An increased risk for any level of intake, an inverse U-shape
 2045 relationship and no relationship have been reported in the individual studies, whereas the meta-
 2046 analyses which combined data from all the studies available do not find an increased risk of
 2047 hypertension at any level of caffeine intake. Although it has been suggested that polymorphisms of
 2048 the CYP1A2 gene may affect the risk of hypertension associated with caffeine consumption and
 2049 explain in part the different findings among studies, this hypothesis has not been tested prospectively
 2050 in unselected populations.

2051 4.5.2.4. Coronary heart disease

2052 The dose-response meta-analysis by Ding et al. (2014) assessed prospective cohort studies on the
 2053 relationship between coffee consumption and CVD risk (i.e. CHD, stroke, heart failure, CVD
 2054 mortality). The 36 studies included (**Appendix I**) comprised $\approx 1\,283\,685$ study participants and 47
 2055 779 CVD cases, including 28 347 CHD cases, 12 030 stroke cases, and 7402 other CVD cases.
 2056 Duration of follow-up for incident CVD ranged from 6 to 44 years, with a median follow-up of 10
 2057 years. Twenty-one studies were conducted in Europe, 12 in the United States, and three in Japan. Nine
 2058 studies assessed the association of caffeinated coffee consumption with CVD risk, and four studies
 2059 assessed the association of decaffeinated coffee consumption with CVD risk. The outcome in 17
 2060 studies was risk of stroke, whereas the outcome in 22 studies was risk of CHD.

2061 Compared with the lowest category of coffee consumption (median, 0 cups per day), the RRs of CHD
 2062 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–
 2063 0.97) for the second category (median, 3.5 cups per day), and 0.93 (95 % CI, 0.84–1.02) for the third
 2064 category of coffee consumption (median, 5 cups per day). A significant heterogeneity between studies
 2065 was found for the second and third categories. In the dose-response analysis, a nonlinear ($p < 0.001$)
 2066 association between coffee consumption and CHD risk with significant trend ($p < 0.001$) and
 2067 significant heterogeneity ($p = 0.001$) was reported. Coffee consumption was inversely associated with
 2068 the risk of CVD up to 8 cups per day. No association was observed between coffee consumption and
 2069 CHD risk at higher intake. Caffeinated and decaffeinated coffee were not analysed separately for this
 2070 outcome.

2071 Two meta-analyses of prospective cohort studies have specifically addressed the association between
 2072 coffee consumption and CHD risk (Sofi et al., 2007; Wu et al., 2009).

2073 Sofi et al. (2007) searched for articles published between 1966 and April 2006 and included 10
 2074 independent prospective cohort studies (nine publications) with a total of 403 631 participants that
 2075 were followed for between 3 and 44 years. Studies were excluded if they included a category other
 2076 than that of very low consumption as a reference, if subjects were selected on the basis of a disease
 2077 condition (hypertension), if categories of coffee consumption were not reported, or if only
 2078 decaffeinated coffee was studied. The cumulative RR for all cohort studies was 1.04 (95 % CI 0.90-
 2079 1.19) for the first category of coffee consumption (1-2 cups per day), 1.05 (95 % CI 0.90-1.22) for the
 2080 second category (3-4 cups per day), and 1.16 (95 % CI 0.95-1.41) for the third category (> 4 cups per
 2081 day), as compared to the reference category (none or < 1 cup per day). Sensitivity analyses removing
 2082 for each category the studies contributing more for heterogeneity gave similar results. Stratified

2083 analyses by region (US and Europe), publication year (before or after the median, 1995), fatal vs non-
 2084 fatal events, and number of years if follow-up (more or less than the median of 15 years) showed that
 2085 only the publication year had an influence on the outcome (i.e. coffee consumption was associated
 2086 with an increased risk of CHD in studies published before or in 1995 but not in studies published after
 2087 1995).

2088 In the meta-analysis by Wu et al. (2009), the literature search was limited to articles in English
 2089 published between 1966 and 2008. Studies were excluded if they only had two categories of coffee
 2090 consumption, if subjects had type 2 diabetes or CVD at baseline, or if only caffeine intake (and not
 2091 coffee) were reported. A total of 21 independent prospective cohort studies (20 publications) were
 2092 included in the analysis, eight of which had already been considered by Sofi et al. (2007). The 21
 2093 studies included 433 054 participants and 17 149 cases. Categories of coffee consumption were
 2094 defined as follows: light (reference), US studies, ≤ 1 cup per day; European studies, ≤ 2 cups per day;
 2095 moderate: US studies, 1–3 cups per day, European studies, 3–4 cups per day; heavy: US studies 4–5
 2096 cups per day, European studies, 5–6 cups per day; and very heavy level: US studies, ≥ 6 cups per day;
 2097 European study, ≥ 7 cups per day. The pooled RRs of CHD for all studies combined were 0.96 (95 %
 2098 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,
 2099 1.32) for the very heavy categories of coffee consumption, respectively. Stratified analyses by sex,
 2100 region, study quality, duration of follow up and adjustment for confounding variables did not affect
 2101 the results significantly.

2102 Among the 56 prospective cohort studies included in the meta-analyses above, eight studies, seven of
 2103 which were published on or before 1995, reported a positive association between coffee consumption
 2104 and risk of CHD, including fatal and non-fatal coronary artery disease, fatal ischemic heart disease,
 2105 and fatal and non-fatal MI. The risk increased significantly at 1-4 cups per day (Murray et al., 1981),
 2106 ≥ 3 cups per day (Lindsted et al., 1992), 3-4 cups per day (Klag et al., 1994); 4-6 cups per day
 2107 (Klatsky et al., 1990); for non-fatal MI, but not for other coronary cases), 5-6 cups per day (Stensvold
 2108 and Tverdal, 1995), ≥ 6 cups per day (LeGrady et al., 1987). In the study by Tverdal et al. (1990), only
 2109 ≥ 9 cups per day were compared to < 1 cup. In the study by Happonen et al. (2004), the reference
 2110 category was 376 to 813 mL per day of coffee, and thus does not allow concluding on the amount of
 2111 coffee associated with an increased risk compared to no coffee consumption. Two studies (Murray et
 2112 al., 1981; Stensvold and Tverdal, 1995) were not adjusted for any confounding variable. All these
 2113 studies investigated coffee except Klatsky et al. (1990), which also investigated tea and found no
 2114 increased risk of CHD in relation to tea consumption.

2115 Four studies investigated the relationship between total caffeine intake (from various sources) and risk
 2116 of CHD.

2117 Grobbee et al. (1990) assessed caffeine intake from coffee, brownies, candies, chocolate and chocolate
 2118 cookies, cocoa, cola beverages and tea in 45 589 men participating in the US Health Professionals
 2119 Follow-up Study. Mean caffeine intakes were 236.7 mg per day in the sample, 52.6 mg per day in non-
 2120 coffee consumers, 268.6 mg per day in consumers of any coffee, 312.3 mg per day in caffeinated
 2121 coffee consumers and 211.1 mg per day in decaffeinated coffee users. The risk of CHD (total, non-
 2122 fatal MI and fatal CHD), coronary-artery bypass grafting (CABG) and percutaneous transluminal
 2123 coronary angioplasty (PTCA), stroke or total CVD did not increase significantly across categories of
 2124 caffeinated or decaffeinated coffee consumption (≤ 1 cup, 2-3 cups and ≥ 4 cups per day compared to
 2125 none) or of total caffeine intake (quintiles: 0-74 mg per day, 74-148 mg per day, 149-285 mg per day,
 2126 286-491 mg per day, 492-1 796 mg per day), except for a significant P per tend (0.04) for an increased
 2127 risk of CABG and PTCA in the highest category of decaffeinated coffee consumption.

2128 The publication by Lopez-Garcia et al. (2006) reports on two independent cohorts: the Health
 2129 Professionals Follow-up Study (44 005 men) and the Nurses' Health Study (84 488 women).
 2130 Documented events were 2 173 incident cases of CHD (1 449 nonfatal MI and 724 fatal cases of

2131 CHD) among men and 2 254 cases (1 561 nonfatal MI and 693 fatal cases of CHD) among women.
 2132 Total caffeine intake was estimated from caffeinated beverages (coffee, tea, soft drinks) and chocolate
 2133 candies. Total caffeine intake from all sources across categories of coffee consumption (<1/mo, 1/mo–
 2134 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
 2135 per day in men and 118, 134, 218, 418, 751, and 881 mg per day in women, respectively. After
 2136 adjustment for confounders, neither coffee nor total caffeine intake were significantly associated with
 2137 the risk of CHD in either men or women. The results did not change when only the most recent
 2138 information on coffee consumption before the event was considered in the analyses to assess short-
 2139 term effects. Stratification by smoking status, alcohol consumption, history of type 2 diabetes mellitus,
 2140 and body mass index gave similar results.

2141 Using data from 6 594 men and women participating in the first National Health and Nutrition
 2142 Examination Survey (NHANES I) Epidemiologic Follow-Up Study (NHEFS), Greenberg et al. (2008)
 2143 studied the relationship between caffeine intake from caffeinated beverages (ground and instant
 2144 caffeinated coffee, tea, cola drinks) and chocolate snacks, consumption of all caffeinated beverages
 2145 combined, and risk of CHD, stroke, and total CVD. Analyses were given for subjects < 65 years and
 2146 ≥ 65 years of age separately, and were also stratified by history of hypertension. The risk of CHD,
 2147 stroke, and total CVD did not increase significantly across categories of total caffeine intake (> 30,
 2148 30–100, 100–350, and ≥ 350 mg per day) or of caffeinated beverages consumed (< 0.5, 0.5 to <2, 2 to
 2149 < 4, and ≥ 4 servings per day). The risk of CVD and CHD mortality significantly decreased across
 2150 categories of caffeine and caffeinated beverages consumption in subjects ≥ 65 years of age, in
 2151 normotensives and in subjects with untreated (stage 1) hypertension, whereas consumption of
 2152 decaffeinated beverages did not affect the risk.

2153 One prospective study not included in the meta-analyses above (Bertoia et al., 2013) used data from
 2154 93 676 postmenopausal women who participated in the Women’s Health Initiative Observational
 2155 Study to assess the association between habitual alcohol and caffeine consumption and risk of sudden
 2156 cardiac death (SCD). FFQs were completed at baseline and at 3 years. A total of 239 women
 2157 experienced SCD after an average of 11 years of follow-up. Compared with very light alcohol intake
 2158 (0.1–5 g per day), no alcohol intake, moderate alcohol intake (15–30 g per day), and heavy alcohol
 2159 intake (> 30 g/d) were not associated with risk of SCD, whereas light alcohol intake (one drink or 5.1–
 2160 15 g per day) was associated with a reduced risk of SCD only when recent alcohol exposure was used
 2161 in the model. No association between total caffeine, caffeinated (regular) coffee, decaffeinated coffee,
 2162 or caffeinated tea and risk of SCD was found. Caffeine analyses were not adjusted for alcohol and
 2163 vice-versa and alcohol-caffeine interactions were not addressed because no correlation between
 2164 alcohol intake and caffeine intake ($r = 0.08$) was found in this population.

2165 One case-control study aimed to determine whether polymorphisms of the CYP1A2 gene (Cornelis et
 2166 al., 2006) and polymorphisms of the adenosine receptor gene ADORA2A, the serotonin receptor gene
 2167 HTR2A, and the dopamine receptor gene DRD2 (DaCosta, 2011) may modify the association between
 2168 coffee consumption and risk of acute non-fatal MI. Cases ($n = 2,014$) and population-based controls (n
 2169 $= 2 014$) living in Costa Rica matched for age, sex, and area of residence, were genotyped (CYP1A2
 2170 gene) and answered a FFQ to assess coffee intake. Fifty-five percent of cases ($n = 1 114$) and 54 % of
 2171 controls ($n = 1 082$) were carriers of the slow *1F allele, for which the multivariate-adjusted odds
 2172 ratios (ORs) and 95 % CIs for nonfatal MI associated with the consumption of < 1, 1, 2 - 3, and ≥ 4
 2173 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),
 2174 respectively. Corresponding ORs (95 % CIs) for individuals with the rapid *1A/*1A genotype were
 2175 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).
 2176 In sensitivity analysis stratified by age and smoking status, a significant gene x coffee interaction
 2177 ($p=0.003$) was observed only among the younger participants (< 59 years, the median age of the
 2178 sample). An increased risk of non-fatal MI with increasing coffee consumption in carriers of the slow
 2179 *1F allele was also observed among non-smokers, although the gene x coffee interaction did not reach
 2180 significance in either smokers or non-smokers. The DRD2 genotype was associated with caffeine

2181 consumption among non-smokers and the slow *1F allele carriers of the CYP1A2 gene. HTR2A
 2182 genotype was associated with caffeine consumption among non-smokers and subjects with the
 2183 ADORA2A TT genotype. Neither polymorphism modified the association between coffee
 2184 consumption and risk of MI, although a significant coffee x HTR2A interaction was seen among
 2185 subjects with the slow *1F allele. The Panel notes that, although this case-control study suggests that
 2186 polymorphisms of the CYP1A2 gene may affect the risk of MI in relation to caffeine consumption,
 2187 which may be further affected by polymorphisms of the serotonin receptor gene HTR2A, the results
 2188 have not yet been replicated or the hypothesis tested in prospective cohort studies.

2189 The Panel notes that three meta-analyses and the vast majority of the 56 prospective cohort studies
 2190 included in these review publications reported no increased risk of CHD associated with habitual
 2191 coffee consumption at any level of intake. The Panel also notes that almost no study reported an
 2192 increased risk of CHD associated with habitual coffee consumption of ≤ 4 cups per day, corresponding
 2193 to about 400 mg per day of caffeine, which may be an underestimation of total caffeine intake
 2194 considering that other sources of caffeine were not taken into account in the majority of the studies
 2195 (e.g., mean caffeine intake from all sources in the category of subjects drinking 4-5 cups of coffee per
 2196 day were 751 mg per day in the study by Lopez-Garcia et al. (2006), and 286-491 mg per day in
 2197 subjects drinking 3-4 cups of coffee per day in the study by Grobbee et al. (1990)).

2198 4.5.2.5. Atrial fibrillation

2199 Two systematic reviews and meta-analyses of prospective cohort studies have specifically addressed
 2200 the association between habitual caffeine consumption and risk of atrial fibrillation (AF) (Caldeira et
 2201 al., 2013; Cheng et al., 2014). Both considered the same six prospective cohorts (**Appendix I**), which
 2202 included a total of 228 465 adult participants (mean age 51-62 years) and 4 261 cases of AF during a
 2203 mean follow-up between 4 and 25.2 years. The meta-analysis by Caldeira et al. (2013) used, in
 2204 addition, data from one case-control study (Mattioli et al., 2005).

2205 Three prospective cohort studies (two in the US and one in Denmark) assessed caffeine from all
 2206 sources (i.e. coffee, tea, soft drinks, chocolate) and three assessed coffee as source of caffeine. To
 2207 calculate caffeine intake in the coffee studies, it was assumed in both meta-analyses that a cup of
 2208 coffee contained 140 mg of caffeine in Sweden (two studies) and 85 mg in the US (one study).
 2209 Caldeira et al. (2013) assumed 50 mg of caffeine per cup of coffee in the Italian case-control study
 2210 (Mattioli et al., 2005). There was no significant association between caffeine exposure and AF risk in
 2211 primary or subgroup analyses, considering age, sex, race, study quality, caffeine from coffee vs
 2212 caffeine from all sources, caffeine dose, or duration of follow-up. An inverse relationship was found
 2213 between habitual caffeine intake and risk of AF in a dose-response analysis (Cheng et al., 2014).
 2214 Incidence of AF decreased by 6 % (RR, 0.94; 95 % CI, 0.90-0.99) for every 300 mg per day increment
 2215 in habitual caffeine intake up to about 1 000 mg per day. No single prospective cohort study reported
 2216 an increased risk of AF associated with habitual caffeine or coffee consumption.

2217 The Panel notes that habitual caffeine consumption from all sources up to about 1 000 mg per day was
 2218 not significantly associated with an increased risk of stroke in these two meta-analyses. The Panel also
 2219 notes that no single prospective cohort study reported an increased risk of AF associated with habitual
 2220 caffeine consumption.

2221 4.5.2.6. Heart failure

2222 A systematic review and a dose-response meta-analysis of prospective studies assessed the
 2223 relationship between habitual caffeinated coffee consumption and the risk of heart failure (Mostofsky
 2224 et al., 2012). The meta-analysis selected five independent prospective studies published between 2001
 2225 and 2011, which included, combined, 6 522 heart failure events among 140 220 participants. Four
 2226 studies were conducted in Sweden (Wilhelmsen et al., 2001b; Ahmed et al., 2009; Mukamal et al.,
 2227 2009; Levitan et al., 2011), where a standard cup of coffee is 150 mL, and one was conducted in

2228 Finland (Wang et al., 2011), where a serving was defined as 100 mL. Three of the studies consisted of
 2229 participants with no history of MI, one was in patients with MI and one included separate analyses for
 2230 people with and without a history of diabetes or MI. Two studies were in men, one in women, and two
 2231 included both sexes. A nonlinear association between coffee consumption and heart failure risk (p for
 2232 nonlinearity = 0.02; p for overall significance of curve = 0.02). Compared with no coffee
 2233 consumption, the pooled RR (95 % CI) for heart failure was 0.96 (0.90 to 0.99) for 1 to 2 servings per
 2234 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
 2235 (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
 2236 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
 2237 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
 2238 servings per day, and 1.03 (0.89 to 1.19) for 11 servings per day. With the exception of the study by
 2239 Mukamal et al. (2009), which was conducted in subjects with history of MI, the only source of
 2240 caffeine studied was coffee.

2241 The Panel notes that coffee intake up to 11 cups per day, corresponding to about 1 100 mg of caffeine,
 2242 were not significantly associated with an increased risk of heart failure in this meta-analysis. The
 2243 Panel also notes that no single prospective cohort study reported an increased risk of heart failure
 2244 associated with habitual coffee consumption.

2245 4.5.2.7. Stroke

2246 In dose-response meta-analysis by Ding et al. (2014), the risk of stroke was assessed in 17 studies.
 2247 Compared with the lowest category of coffee consumption, the RRs of stroke were 0.89 (95 % CI,
 2248 0.84–0.94) for the first category, 0.80 (95 % CI, 0.75–0.86) for the second category, and 0.95 (95 %
 2249 CI, 0.84–1.07) for the highest category of coffee consumption. No significant heterogeneity between
 2250 studies was found for any category of coffee consumption. In the dose-response analysis, a nonlinear
 2251 ($p < 0.001$) association between coffee consumption and CHD risk with significant trend ($p < 0.001$)
 2252 and non-significant heterogeneity ($p = 0.07$) was reported. Coffee consumption was inversely
 2253 associated with the risk of stroke up to about 4 cups per day. No association was observed between
 2254 coffee consumption and risk of stroke higher intake. Caffeinated and decaffeinated coffee were not
 2255 analysed separately for this outcome.

2256 Two meta-analyses of prospective cohort studies have specifically addressed the association between
 2257 coffee consumption and risk of stroke (Larsson and Orsini, 2011; Kim et al., 2012).

2258 The meta-analysis by Larsson and Orsini (2011) searched for prospective cohort studies published
 2259 between 1966 and 2011 which reported the risk of stroke for three or more categories of coffee
 2260 consumption. The meta-analysis included 11 prospective studies, with 479 689 participants and 10,003
 2261 cases of stroke. A nonlinear inverse association between coffee consumption and stroke risk was
 2262 observed (p for nonlinearity = 0.005). Compared with no coffee consumption, the pooled relative risks
 2263 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)
 2264 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
 2265 cups per day, and 0.93 (95 % CI: 0.79, 1.08) for 8 cups per day. When the RRs for comparable
 2266 categories of coffee consumption were pooled, the RRs of stroke were 0.88 (95 % CI: 0.86, 0.90) for
 2267 < 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 –
 2268 < 7 cups per day, and 0.93 (95 % CI: 0.76, 1.12) for ≥ 7 cups per day. In stratified analyses by sex
 2269 (men, 5 studies; women, 5 studies; both sexes, 4 studies), geographical region (Europe, 7 studies; US,
 2270 2 studies; Japan, 2 studies), duration of follow-up (≤ 10 years, 4 studies; > 10 years, 7 studies), or
 2271 stroke type (ischemic, 4 studies; haemorrhagic, 4 studies), coffee consumption was not associated with
 2272 an increased risk of stroke in any strata. Similar results were obtained in the meta-analysis by Kim et
 2273 al. (2012), in which the literature search was limited to articles in English published between 2001 and
 2274 July 2011. The meta-analysis included nine prospective cohort studies, six of which had also been
 2275 considered by Larsson and Orsini (2011). One meta-analysis (Arab et al., 2009) of prospective cohort
 2276 studies which assessed the relationship between green and black tea consumption and risk of stroke

2277 and included data from nine individual studies involving 4 378 strokes among 194 965 individuals in
 2278 total found similar results. The risk of stroke was assessed for 3 cups per day compared to low intake
 2279 or no tea.

2280
 2281 Among the prospective cohort studies included in the meta-analyses above, none reported a positive
 2282 association (increased risk) between coffee consumption and the risk of stroke of any type. The only
 2283 exception was the study by Hakim et al. (1998), which was conducted in a population of middle age
 2284 (45-68 years) men with hypertension at baseline and it is not considered by the Panel as pertinent to
 2285 this evaluation.

2286 Four studies investigated the relationship between total caffeine intake (from various sources) and risk
 2287 of stroke.

2288 In addition to the studies by Grobbee et al. (1990) and Greenberg et al. (2007) described above in
 2289 relation to CHD risk, two studies investigated the relationship between total caffeine intake from
 2290 coffee and tea (Larsson et al., 2008), or from coffee, tea, caffeinated soft drinks and chocolate candy
 2291 (Lopez-Garcia et al., 2009), and the risk of stroke. In the study by Larsson et al. (2008), a caffeine
 2292 content of 80 mg per 100 mL of coffee and of 26 mg per 100 mL of tea was assumed to calculate total
 2293 caffeine intake. Median caffeine intake was 186 mg per day. Consumption of caffeinated coffee,
 2294 caffeinated tea or total caffeine (from coffee and tea) was not associated with an increased risk of
 2295 ischemic or haemorrhagic stroke. In the study by Lopez-Garcia et al. (2009), consumption of
 2296 caffeinated beverages (cups) of < 1/month, 1/month–4/week, 5–7/week, 2–3 per day, and ≥ 4 per day
 2297 corresponded to median total caffeine intakes of 71, 191, 318, 423, and 687 mg per day. Total caffeine
 2298 intake, consumption of caffeinated beverages (tea, caffeinated soft drink, and caffeinated coffee), and
 2299 consumption of decaffeinated coffee were not significantly associated with an increased risk of stroke.

2300
 2301 The Panel notes that coffee intake up to 8-11 cups per day, corresponding to about 800-1 100 mg of
 2302 caffeine per day, were not significantly associated with an increased risk of stroke in the meta-analyses
 2303 considered. The Panel also notes that no single prospective cohort study reported an increased risk of
 2304 stroke associated with habitual coffee or tea consumption in the general adult population.

2305 4.5.2.8. Cardiovascular disease risk (all outcomes combined)

2306 In the dose-response meta-analysis by Ding et al. (2014), compared with the lowest category of coffee
 2307 consumption (median, 0 cups per day), the relative risk (mean, 95 % CI) of CVD (all outcomes
 2308 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
 2309 the second category (median, 3.5 cups per day), and 0.95 (0.87–1.03) for the third (highest) category
 2310 (median, 5 cups per day) category. No significant interactions were found between coffee intake and
 2311 baseline hypertension or MI of the study population, smoking status, publication year, study quality
 2312 score, dietary assessment method (24-hour diet recall/diet record/food frequency questionnaire versus
 2313 other methods), stroke versus CHD as the outcome, country (US, Europe, Japan), sex, and type of
 2314 coffee (caffeinated coffee or decaffeinated coffee) when the analyses were stratified for these
 2315 variables. Compared with the lowest category of coffee consumption, the RRs (mean, 95 % CI) for
 2316 caffeinated (11 comparisons) and decaffeinated (five comparisons) coffee consumption were 0.89
 2317 (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
 2318 second category, and 0.91 (0.81, 1.03) and 1.00 (0.88, 1.14) and third category, respectively. In the
 2319 dose-response analysis, coffee consumption was inversely associated with the risk of CVD up to 6
 2320 cups per day. No association was observed between coffee consumption and CVD risk at higher
 2321 intake.

2322 An additional prospective cohort study published thereafter (Loomba et al., 2014) using data from the
 2323 US National Health Examination Survey III (NHAES III) reported no association between coffee
 2324 consumption and CVD mortality (including stroke, congestive heart failure and ischemia-related

2325 mortality) in multivariate analysis adjusted for confounding variables at any level of intake among
 2326 8 608 subjects >45 years of age.

2327 4.5.2.9. Conclusions on the cardiovascular system

2328 Data from RCTs suggests that caffeine intake (from coffee or supplements) at doses \leq 400 mg per day
 2329 does not raise fasting BP significantly after caffeine habituation takes place. Prospective cohort studies
 2330 on the relationship between habitual caffeine intake and long-term changes in BP and on the risk of
 2331 incident hypertension are conflicting and difficult to interpret. Equal number of studies reporting
 2332 positive, negative and no association between habitual caffeinated coffee consumption and long-term
 2333 changes in BP are available. Whereas meta-analyses combining data from all the prospective studies
 2334 available do not find an increased risk of hypertension at any level of caffeine intake, an increased risk
 2335 for any level of intake, an inverse U-shape relationship and no relationship have been reported in the
 2336 individual studies.

2337 Hypertension is an established risk factor for CVD, and in particular for stroke, CHD and heart failure.
 2338 A wealth of prospective cohort studies investigating the relationship between caffeinated coffee
 2339 consumption (the type of coffee mostly consumed and the main source of caffeine intake in most
 2340 European populations) and the risk of total CVD and CVD subtypes (fatal and non-fatal CHD
 2341 including MI and SCD, stroke and stroke subtypes, arrhythmias-mostly AF), as well as systematic
 2342 reviews and dose-response meta-analyses summarising their results, are available. Habitual caffeinated
 2343 coffee consumption has not been associated with an increased risk of total CVD or CVD subtypes in
 2344 the general adult population at any level of intake in any summary publication. Among the individual
 2345 studies, a positive association between habitual caffeinated coffee consumption and CVD risk has only
 2346 been reported for CHD (but not for stroke, AF, or heart failure) in 8 out of the 56 studies reviewed,
 2347 only six of which had any type of adjustment for confounding variables. Of these, only two reported
 2348 an increased risk of CHD associated with habitual coffee consumption of \leq 4 cups per day (one for \geq 3
 2349 cups per day, one for \geq 3-4 cups per day), corresponding to about 400 mg per day of caffeine, which
 2350 may be an underestimation of total caffeine intake considering that other sources of caffeine were not
 2351 taken into account in these studies.

2352 It has been suggested that certain substances in coffee (and tea) other than caffeine may decrease the
 2353 risk of CVD and thus counteract any adverse effects of caffeine in the CVS which may become
 2354 evident if the same amounts of caffeine are consumed from other sources (e.g., supplements,
 2355 caffeinated soft drinks, “energy drinks”). However, total caffeine intake was not associated with an
 2356 increased CVD risk in any of the studies which have investigated all sources of caffeine. In addition,
 2357 the individual studies and meta-analysis available which have investigated the relationship between
 2358 the consumption of caffeinated and decaffeinated beverages and CVD risk separately have reported
 2359 either no association for any type of beverage (caffeinated or decaffeinated) or a J-shaped relationship
 2360 (decreased risk for up to 3-5 cups per day and no increased risk thereafter compared to low or no
 2361 consumption) for caffeinated beverages (mostly coffee, but also tea), which was not observed for
 2362 decaffeinated beverages (mostly coffee, no change in risk across levels of intake). Although no firm
 2363 conclusions can be drawn from these observations due to the low intake and/or low percentage of
 2364 consumers of decaffeinated beverages, and of caffeinated beverages other than coffee (except in the
 2365 US) in these studies, the Panel considers that, on the basis of the data available, habitual caffeine
 2366 intake up to about 400 mg per day from all sources does not increase the risk of CVD in the general
 2367 adult population.

2368 Some case control and one prospective cohort study in hypertensive subjects suggest that
 2369 polymorphisms of genes involved in caffeine metabolism could affect the relationship between
 2370 caffeine intakes and CVD-related outcomes. The Panel notes that prospective cohort or human
 2371 intervention studies investigating this hypothesis are currently not available for any subgroup of the
 2372 general population. The Panel also notes that, considering that the distribution of “fast” and “slow”

2373 caffeine metabolisers in the general population is roughly 50:50, both phenotypes may have been
2374 equally represented in the human studies considered.

2375 The vast majority of prospective cohort studies assessed habitual alcohol intake (alcohol consumers
2376 were not excluded) and used this variable to adjust multivariate models, rather than to explore
2377 interactions between alcohol and coffee or caffeine intake on CHD risk. In addition, the intervention
2378 study which assessed the effect of coffee on longer-term BP in habitual alcohol drinkers did not
2379 control for (or report on) caffeine intake. Despite the scarcity of data available on the combined effects
2380 of habitual caffeine and alcohol consumption on CVD risk, the Panel considers that habitual caffeine
2381 intake up to about 400 mg per day from all sources does not increase the risk of CVD in habitual
2382 alcohol drinkers from the general adult population.

2383 4.5.3. Pregnancy outcomes

2384 Different mechanisms have been proposed by which caffeine consumption during pregnancy could
2385 adversely affect fetal development. Caffeine is rapidly absorbed, passes freely across the placenta, and
2386 it is poorly metabolised by the fetus (Aldridge et al., 1979; Aldridge et al., 1981). By increasing the
2387 levels of circulating catecholamines, caffeine could induce uteroplacental vasoconstriction and fetal
2388 hypoxia (Kirkinen et al., 1983), as well as impair normal cell development by increasing cellular
2389 cyclic adenosine monophosphate (Weathersbee and Lodge, 1977).

2390 Pregnancy outcomes that have been investigated in relation to the potential adverse health effects of
2391 caffeine consumption during pregnancy include length of gestation and related outcomes (e.g., pre-
2392 term delivery), birth weight and related outcomes (e.g. FGR, small for gestational age), fetal death-
2393 related outcomes (miscarriage or spontaneous abortion, stillbirth), and infant death. Pre-term delivery,
2394 FGR and small for gestational age (SGA) are associated with increased risk of perinatal morbidity and
2395 mortality. FGR correlated with increased risk of metabolic diseases later in life.

2396 4.5.3.1. Human intervention studies

2397 Two Cochrane systematic reviews, addressing the effects of maternal caffeine consumption during
2398 pregnancy on fetal, neonatal and/or pregnancy outcomes and conducted four years apart (Jahanfar and
2399 Sharifah, 2009; Jahanfar and Jaafar, 2013), identified only one human intervention study which
2400 addressed this question (Bech et al., 2007). No other human intervention studies have been identified
2401 by the Panel.

2402 In a double-blind RCT, 1 207 Danish women who were less than 20 weeks pregnant were recruited
2403 from either those booked for delivery at a Aarhus University Hospital or from a national birth cohort
2404 (Bech et al., 2007). Data on inclusion and exclusion criteria (pre-enrolment) were retrieved through a
2405 mailed questionnaire at 16 weeks of pregnancy and by a telephone interview at about 12 weeks of
2406 pregnancy, respectively. Eligibility criteria included regular consumption of at least three cups of
2407 coffee per day and no history of a low birthweight baby (< 2 500 g), preterm delivery, kidney diseases,
2408 epilepsy, diabetes, or metabolic disorders. Eligible women were randomised to receive caffeinated
2409 instant coffee (n = 568) or decaffeinated instant coffee (n = 629) in identical boxes provided by the
2410 same manufacturer and were asked to replace their regular coffee with that provided, but were not
2411 advised on how much to drink or asked to avoid regular coffee offered by others or intake of other
2412 caffeinated beverages such as tea, cocoa, or cola. Women were interviewed about daily consumption
2413 of the study coffee, of other caffeinated beverages (coffee, tea, cola, or cocoa), and smoking status at
2414 weeks 20, 25, and 34 of gestation and at week 4 after the expected date of delivery. Caffeine intake
2415 from all sources during the study in both groups were calculated from data collected during the
2416 interviews, assuming a caffeine content per cup of 65 mg and 0 mg for caffeinated and decaffeinated
2417 study coffees (according to manufacturer), 100 mg for other caffeinated coffees, 50 mg for tea, and of
2418 5 mg and 20 mg per glass (2 dL) of drinking chocolate and cola drinks, respectively. Assuming a

2419 standard deviation of birth weight of 500 g, a sample size of 800 women was calculated to detect a
 2420 difference in birth weight of at least 100 g with 80 % power at a 5 % two sided significance.

2421 Total median daily caffeine intake (IQR) was 317 mg (229-461 mg) mg and 117 mg (56-228 mg) in
 2422 the caffeinated and decaffeinated coffee groups, respectively. Data on birth weight and length of
 2423 gestation were obtained for 1 150 and 1 153 live-born singletons, respectively. The adjusted difference
 2424 in length of gestation between the decaffeinated and caffeinated coffee groups was -1.31 days (-2.87 to
 2425 0.25). After adjustment for length of gestation, parity, pre-pregnancy BMI and smoking at baseline,
 2426 the mean birth weight of babies born to women in the decaffeinated coffee group was 16 g (95 % CI, -
 2427 40 to 73) higher than those born to women in the caffeinated group. The Panel notes that this study did
 2428 not report an effect of decreasing caffeine consumption from about 300 mg per day to about 100 mg
 2429 per day in the last four months of pregnancy on length of gestation or birthweight.

2430 4.5.3.2. Prospective cohort studies

2431 Five prospective cohort studies have investigated the relationship between maternal intake of caffeine
 2432 from caffeinated beverages and pregnancy (fetal and neonatal) outcomes, including length of gestation
 2433 and related outcomes (e.g., pre-term delivery), birth weight and related outcomes (e.g. FGR, SGA),
 2434 fetal death-related outcomes (miscarriage or spontaneous abortion, stillbirth), and infant death. In
 2435 these studies, statistical analyses have been adjusted for a number of potentially confounding
 2436 variables, including alcohol drinking and smoking during pregnancy, parity and socio-economic
 2437 status. Maternal age, height and weight, maternal education, the baby's sex, length of gestation,
 2438 outcome of previous pregnancies and occasionally pregnancy-related symptoms (e.g. nausea,
 2439 vomiting) were also generally considered for birth weight and related outcomes.

2440 The Care Study Group examined the relationship between maternal caffeine intake and birth weight,
 2441 FGR (primary outcome, defined as birth weight < 10th centile on a customised centile chart), late
 2442 miscarriage (spontaneous pregnancy loss between 12 and 24 weeks), pre-term delivery (delivery at <
 2443 37 completed weeks), and stillbirth (CARE Study Group, 2008; Greenwood et al., 2010). A total of
 2444 2 635 low risk pregnant women (out of the 13 071 invited; 20 %) 18-45 years old living in the UK
 2445 were recruited between 8 and 12 weeks of pregnancy. Caffeine intakes were estimated using a
 2446 validated questionnaire designed to record habitual caffeine intake before and during pregnancy from
 2447 all sources, including over the counter medications. The questionnaire was administered three times:
 2448 the first at recruitment, when women were asked to recall caffeine intake from 4 weeks before
 2449 pregnancy to 8-12 weeks of pregnancy, the second covered the period 13-28 weeks of pregnancy and
 2450 the third covered the period 29-40 weeks of pregnancy. The prevalence of FGR in the cohort was
 2451 343/2635 (13 %). The women's mean caffeine intake during pregnancy was 159 mg per day, which
 2452 decreased from 238 mg per day before pregnancy to 139 mg per day between weeks 5 and 12 of
 2453 pregnancy, remained almost unchanged during the second trimester, and gradually increased to 153
 2454 mg per day in the third trimester. The main sources of caffeine were tea (62 %), coffee (14 %), cola
 2455 drinks (12 %), chocolate (8 %), and soft drinks (2 %). Hot chocolate, "energy drinks", and alcoholic
 2456 drinks contributed 2 %, 1 %, and < 1 % to caffeine intake, respectively.

2457 After adjustment for confounding variables, the relation between total caffeine intake in pregnancy
 2458 and FGR showed a significant trend with increasing caffeine intake (p for trend = 0.02). Compared
 2459 with caffeine intake of < 100 mg/ day, the odds ratio of having a baby with FGR were 1.2 (95 % CI,
 2460 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
 2461 1.4 (1.0 to 2.0) for intakes of ≥ 300 mg per day. Caffeine consumption of > 200 mg per day during
 2462 pregnancy was associated with a reduction in birth weight of about 60-70 g, with a significant trend
 2463 for greater reduction in birth weight with higher caffeine intake (p = 0.004). These relations were
 2464 consistent across all three trimesters. When caffeine intake was analysed as a continuous variable, the
 2465 risk of FGR increased exponentially up to 30 mg per day and linearly thereafter, and no threshold was
 2466 identified (CARE Study Group, 2008). The association between caffeine intake and FGR did not
 2467 appear to be mediated by nausea and vomiting during pregnancy (Boylan et al., 2013). Caffeine intake

2468 was also associated with an increased risk of late miscarriage or stillbirth (Greenwood et al., 2010).
 2469 Compared to women consuming <100 mg per day of caffeine, ORs were 2.2 (95 % CI: 0.7–7.1) for
 2470 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
 2471 (p per trend = 0.004).

2472 The Panel notes that this study shows a dose-dependent positive association between caffeine intake
 2473 during pregnancy and adverse birthweight- and fetal death-related outcomes, and that the risk becomes
 2474 significant at caffeine doses ≥ 200 mg per day for FGR and at ≥ 300 mg per day for late miscarriage or
 2475 stillbirth.

2476 The association between maternal caffeine intake from different sources (coffee, black tea, cola,
 2477 “energy drinks”, chocolate milk) and gestational length, the risk for spontaneous preterm delivery
 2478 (PTD), birth weight and the risk of a baby being SGA was investigated in 59,123 Norwegian women
 2479 with uncomplicated pregnancies giving birth to a live singleton (Sengpiel et al., 2013). SGA was
 2480 diagnosed using three different growth curves and definitions. Caffeine intake in the first 4-5 months
 2481 of pregnancy was assessed using a semi-quantitative FFQ at week 22 of pregnancy, which was
 2482 validated using 4-day weighed food dairies. The way in which coffee was prepared was considered in
 2483 calculating caffeine intake from this source. At weeks 15-17 and 30 of pregnancy, women also
 2484 reported their current and pre-pregnancy consumption of coffee, tea and caffeinated soft drinks in cups
 2485 or glasses per day. Coffee (56 %), black tea (22 %), sugar-containing soft drinks including “energy
 2486 drinks” (7 %), sugar-free soft drinks (7 %) and chocolate (7 %) accounted for > 98 % of caffeine
 2487 intake, although predominant sources of caffeine varied across quartiles of caffeine intake (chocolate
 2488 in the first, black tea in the second and third, and coffee in the fourth quartile). Self-reported pre-
 2489 pregnancy median intake of caffeine from coffee, black tea and soft drinks was 126 mg per day (IQR
 2490 40 to 254 mg per day) for all 59 123 women, including 7 406 (12.5 %) women who did not consume
 2491 any caffeine at all. At gestational week 17, the number of non-consumers was almost doubled (14 012
 2492 women, 24 %) and the median caffeine intake had decreased to 44 mg per day (13 to 104 mg per day).
 2493 At gestational week 30, the median caffeine intake had increased again to 62 mg per day (21 to
 2494 130 mg per day) and 9 792 (16.5 %) women remained non-consumers.

2495 When caffeine intake and intake of caffeinated beverages were analysed as a continuous variables, and
 2496 after adjusting for confounding variables, total caffeine and coffee caffeine were significantly
 2497 associated with increased gestational length. Conversely, total caffeine and soft drink caffeine were
 2498 significantly associated with decreased gestational length in non-coffee drinkers, whereas no
 2499 association was found with black tea or chocolate caffeine. Total caffeine and caffeine intake from the
 2500 individual sources were significantly associated with lower birthweight. An additional 100 mg total
 2501 caffeine per day was associated with a 21 to 28 g birthweight decrease, depending on the growth
 2502 curve. There were 1 451 cases of spontaneous PTD (240 early spontaneous PTDs, between weeks 22
 2503 and 33 + 6 days, and 1 211 late spontaneous PTDs, between weeks 34 and 36 + 6 days). There was no
 2504 significant association between total or coffee caffeine intake and the odds for overall, early or late
 2505 spontaneous PTD, whereas black tea caffeine was associated with increased risk of early spontaneous
 2506 PTD (OR 1.61, 95 % CI 1.10 to 2.35, p = 0.01). Total and coffee caffeine intake was significantly
 2507 associated with higher odds for SGA in all three SGA models, and with soft drink and black tea
 2508 caffeine in two SGA models. All these associations remained when only non-smokers were considered
 2509 (n=54 136) in the analyses. The analysis were also conducted with caffeine intake as a categorical
 2510 variable (six categories) to test threshold effects (0 to 14.6, reference; 14.6 to 32.1; 32.1 to 57.3; 57.3
 2511 to 96.0; 96.0 to 163.8; > 163.8 mg per day). The odds ratios for SGA consistently increased in the
 2512 three models of SGA from the third sextile upwards compared with the reference category.
 2513 Categorising caffeine intake according to current Nordic (up to 200 mg per day) and WHO
 2514 recommendations (up to 300 mg per day), women with a daily caffeine intake of 51 to 200 mg per day
 2515 (43.5 %), of 200 to 300 mg (7.7 %) and of > 300 mg (3.3 %) had significantly higher odds for SGA
 2516 (1.09 to 1.18, 1.27 to 1.62, and 1.62 to 1.66, respectively, depending on the SGA definition) compared
 2517 to the lowest (0 to 50 mg per day) reference category. The Panel notes that this study shows a dose-

2518 dependent positive association between caffeine intake during pregnancy and adverse birthweight-
 2519 related outcomes. The risk becomes statistically significant at caffeine doses > 50 mg per day but
 2520 increases notably at > 200 mg per day. The Panel also notes that the relationship between caffeine
 2521 intake and outcomes related to the length of gestation is inconsistent.

2522 The relationship between coffee and fetal death was investigated in a cohort of 88 482 Danish
 2523 pregnant women who agreed to have a telephone interview at 16 weeks of gestation (Bech et al.,
 2524 2005). Women were asked about the number of cups of coffee, tea or cola they had per day, and about
 2525 potential confounding variables that could affect the outcome of interest. Fetal death was defined as
 2526 defined as either miscarriage (gestational age < 196 days) or stillbirth (gestational age ≥ 196 days) and
 2527 did not include intra-partum death. Coffee intake was considered as a categorical variable (0, 0.5–3, 4–
 2528 7, and > 8 cups per day) and as a continuous variable (number of cups per day) in a test for trend.
 2529 Although almost all caffeine intake came from coffee, data were also analysed according to caffeine
 2530 intake by using average levels of 100 mg of caffeine for a cup of coffee and 50 mg for a cup of tea.

2531 There were 1 102 fetal deaths. A total of 49 042 (55.4 %) women did not report drinking coffee during
 2532 pregnancy; 27 803 women (31.4 %) drank ½–3 cups per day, 8 619 women (9.7 %) drank 4–7 cups
 2533 per day, and 3 018 women (3.4 %) drank > 8 cups per day. The adjusted hazard ratios for fetal death
 2534 associated with coffee consumption of 0.5-3, 4-7, and ≥ 8 cups of coffee per day were 1.03 (95 % CI:
 2535 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
 2536 coffee consumption. The risk increased with increasing coffee intake (p for trend = 0.001), with no
 2537 statistically significant departure from linearity. No statistically significant interaction between coffee
 2538 consumption and fetal death during specific periods of gestation was found. The increased risk of fetal
 2539 death for coffee intakes ≥ 4 cups per day (about 400 mg caffeine) was similar in smokers and non-
 2540 smokers, and in alcohol drinkers and non-alcohol drinkers, and the association did not change when
 2541 caffeine intake from tea and coffee were considered. The risk of stillbirth due to placental dysfunction
 2542 was increased among consumers of ≥ 4 cups of coffee per day (hazard ratio = 2.27, 95 % CI: 1.21,
 2543 4.28), but not the risk of stillbirth for other causes. The Panel notes that this study shows a dose-
 2544 dependent positive association between caffeine intake at week 16 of pregnancy and fetal death-related
 2545 outcomes (miscarriage and stillbirth), that the risk becomes significant at caffeine intakes of about ≥
 2546 400 mg per day, and that stillbirth associated to higher caffeine intake was mostly due to placental
 2547 dysfunction.

2548 Weng et al. (2008) conducted a population-based prospective cohort study in 1 063 pregnant women
 2549 living in the US in order to examine whether the risk of miscarriage was associated with caffeine
 2550 consumption during pregnancy after controlling for pregnancy-related symptoms. Information on
 2551 “caffeine” consumption during pregnancy was obtained during an in-person interview conducted soon
 2552 after a woman’s pregnancy was confirmed (the median gestational age at interview was 71 days).
 2553 Women were asked to report their intake of beverages since their last menstrual period and whether
 2554 patterns of consumption had changed since becoming pregnant. Sources of caffeine included
 2555 caffeinated or decaffeinated coffee and tea, caffeinated soft drinks, and hot chocolate. Conversion
 2556 factors to estimate the amount of caffeine intake were, for every 150 mL of a beverage, 100 mg for
 2557 caffeinated coffee, 2 mg for decaffeinated coffee, 39 mg for caffeinated tea, 15 mg for caffeinated
 2558 soda, and 2 mg for hot chocolate. Miscarriage was defined as spontaneous abortion at ≤ 20 weeks of
 2559 pregnancy. The 63 % of total caffeine consumed was from coffee. Coffee was the only source of
 2560 caffeine for 152 women (19 %), whereas 293 women (36.7 %) consumed caffeine only from sources
 2561 other than coffee and 351 women (43.9 %) from coffee and non coffee sources. Overall 172 of women
 2562 (16.18 %) miscarried. Whereas 264 women (25 %) reported no consumption of any caffeine-
 2563 containing beverages during pregnancy, 635 women (60 %) reported 0-200 mg of caffeine intake per
 2564 day, and 164 women (15 %) > 200 mg. After adjusting for potential confounders, the hazard ratio of
 2565 miscarriage was 1.42 (95 % CI, 0.93 to 2.15) and 2.23 (95 % CI, 1.34 to 3.69) for daily caffeine
 2566 consumption of 0-200 mg and > 200 mg, respectively (p for trend < 0.01), compared to the reference
 2567 category (no caffeine consumption). Stratified analyses by sources of caffeine did not change the

2568 association. The Panel notes that this study shows an increased risk of fetal death-related outcomes
 2569 (miscarriage) associated with caffeine intake at doses > 200 mg per day in early pregnancy, regardless
 2570 of the source.

2571 The relationship between caffeine intake before and during pregnancy and the risk of miscarriage
 2572 (≤ 20 weeks of pregnancy) and stillbirth (> 20 weeks of pregnancy) was also investigated in a
 2573 prospective cohort study (Fenster et al., 1997) of 5 144 pregnant women living in the US. Women
 2574 were asked to quantify (cups/cans per day) their daily consumption of decaffeinated coffee and
 2575 caffeinated beverages (coffee, tea, soft drinks) in the week before a computer-assisted telephone
 2576 interview, which took place between 4 and 13 weeks of pregnancy (mean 8 weeks), and during the
 2577 week around their last menstrual period. Caffeine consumption was calculated assuming a content of
 2578 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
 2579 drink.

2580 There were 499 cases of miscarriage and 32 stillbirths. About 74 % of women reported caffeine
 2581 consumption before pregnancy but only 50 % during pregnancy. About 13 % of women reported
 2582 caffeine consumption > 300 mg per day before pregnancy, but only 4 % during pregnancy. Caffeine
 2583 consumption and consumption of any type of caffeinated beverages, either before pregnancy or in the
 2584 first trimester of pregnancy, were not associated with an increased risk of miscarriage. The adjusted
 2585 OR for caffeine intake > 300 mg per day was 1.3 (95 % CI = 0.8, 2.1). Conversely, consumption of
 2586 > 3 cups of decaffeinated coffee per day in the third trimester of pregnancy was associated with an
 2587 increased risk of miscarriage (OR = 1.52, 95 % CI = 0.85, 2.72). Data on caffeine intake in relation to
 2588 the risk of stillbirth was not reported. The Panel notes that this study shows no association between
 2589 caffeine intake in early pregnancy and risk of fetal death-related outcomes (miscarriage).

2590 4.5.3.3. Case-control and cross-sectional studies

2591 The available case-control and cross-sectional studies on the relationship between caffeine
 2592 consumption and pregnancy-related outcomes published up to 2008 have been thoroughly reviewed in
 2593 previous assessments (COT, 2008). Overall, the results from these studies support a positive
 2594 association between caffeine intake and risk of adverse birth weight-related outcomes, whereas the
 2595 relationship between caffeine consumption during pregnancy and other pregnancy outcomes (e.g., in
 2596 relation to length of gestation or fetal death) is less consistent (COT, 2008), as observed in the
 2597 prospective cohort studies described above.

2598 Some of these studies have investigated whether the association between caffeine intake and adverse
 2599 pregnancy outcomes could be modulated by differences in the activity of enzymes involved in the
 2600 metabolism of caffeine, such as xanthine oxidase or N-acetyltransferase, or by genetic polymorphisms
 2601 of the CYP1A2, CYP1B1 and CYP2E1 genes (Fenster et al., 1998; Signorello et al., 2001; Karypidis
 2602 et al., 2006; Infante-Rivard, 2007). However, the results from these studies are not consistent and
 2603 whether genetic polymorphisms and/or phenotypic differences in the activity of enzymes involved in
 2604 caffeine metabolism modify the relationship between caffeine intakes and adverse pregnancy-related
 2605 outcomes has not been investigated in prospective studies.

2606 4.5.3.4. Conclusions on pregnancy outcomes

2607 The Panel notes that the prospective cohort studies available (CARE Study Group, 2008; Sengpiel et
 2608 al., 2013) show a dose-dependent positive association between caffeine intake during pregnancy and
 2609 risk of adverse birth weight-related outcomes (i.e, FGR, SGA). The relationship between caffeine
 2610 consumption during pregnancy and other pregnancy outcomes (e.g., in relation to length of gestation
 2611 or fetal death) is less consistent. The Panel also notes that the relationship between caffeine intakes
 2612 and adverse birthweight-related outcomes is observed at all levels of intake, with no threshold below
 2613 which the relationship is not observed. However, the Panel considers the risk to become clinically
 2614 relevant at daily doses of about 200 mg of caffeine from all sources. In addition, the Panel also notes

2615 that pregnant women tend to reduce (pre-pregnancy) consumption of caffeine, and that decreasing
 2616 caffeine intake from about 300 mg per day to about 100 mg per day in the third trimester of pregnancy
 2617 does not decrease the risk, as observed in one human intervention study (Bech et al., 2007). Major
 2618 sources of caffeine in the studies reviewed were coffee and tea, followed by soft drinks (including cola
 2619 drinks) and chocolate. “Energy drinks” contributed 2 % (alone) and 7 % (in combination with sugar-
 2620 containing soft drinks) to caffeine intake in the two studies reporting on this source (CARE Study
 2621 Group, 2008) and (Sengpiel et al., 2013), respectively.

2622
 2623 Genetic polymorphisms for genes involved in caffeine metabolism have been shown to explain only a
 2624 small proportion of the inter-individual variability in caffeine intake during and after pregnancy
 2625 (McMahon et al., 2014), and there is no evidence that such polymorphisms influence the risk of
 2626 adverse birth weight-related outcomes significantly, although prospective studies investigating this
 2627 question are lacking.

2628 **5. DOSE RESPONSE ASSESSMENT AND DERIVATION OF INTAKE LEVELS OF NO CONCERN**

2629 **5.1. Adults**

2630 Single doses of caffeine up to 200 mg, corresponding to about 3 mg/kg bw for a 70-kg adult, or the
 2631 same amount consumed within a short period of time, are unlikely to induce clinically relevant
 2632 changes in blood pressure, myocardial blood flow, hydration status or body temperature. This is the
 2633 case both at rest or when consumed less than two hours prior to intense physical exercise under normal
 2634 environmental conditions, and even in hot environments as long as body fluids are timely replaced.
 2635 This applies to non-habitual caffeine consumers, to caffeine-deprived subjects and to habitual caffeine
 2636 consumers. The Panel notes that this may not be the case when caffeine is consumed prior to physical
 2637 exercise under unusual environmental conditions (e.g. high altitude). The Panel also notes that no
 2638 studies are available in pregnant women or middle age/elderly subjects undertaking intense physical
 2639 exercise.

2640 Single doses of caffeine up to 200 mg (about 3 mg/kg bw) are unlikely to reduce the perceived
 2641 exertion/effort during exercise. Higher doses could lead to prolonged physical exercise that might
 2642 compromise the cardiovascular and/or the musculoskeletal systems.

2643 Single doses of caffeine up to 200 mg (about 3 mg/kg bw) are also unlikely to mask the subjective
 2644 perception of alcohol intoxication when alcohol is consumed at doses up to about 0.65 g/kg bw.

2645 The Panel notes that 100 mg (about 1.5 mg/kg bw) of caffeine may increase sleep latency and reduce
 2646 sleep duration in some adult individuals, particularly when consumed close to bedtime.

2647 The Panel considers that other common constituents of “energy drinks” (i.e. taurine, D-glucurono- γ -
 2648 lactone) or alcohol are unlikely to adversely interact with caffeine in relation to these outcomes at the
 2649 dose levels reported in the studies reviewed. The Panel also considers that the short-term effects of co-
 2650 consumption of caffeine and synephrine on the cardiovascular system have not been adequately
 2651 investigated in humans, particularly when consumed shortly before intense physical exercise.

2652 The Panel notes the absence of data for repeated caffeine doses in relation to the majority of health
 2653 outcomes discussed for single doses of caffeine. However, the Panel considers that repeated doses of
 2654 caffeine which do not raise safety concerns for adults in the general population should take into
 2655 account the half-life of caffeine (mean 4 hours, range 2-8 hours) so as not to exceed the maximum
 2656 plasma concentrations achieved with an acute 200 mg dose.

2657 Caffeine intakes from all sources up to 400 mg per day (corresponding to about 5.7 mg/kg bw for a
 2658 70 kg adult) do not raise safety concerns for adults in the general population, except pregnant women
 2659 (see section 5.2). No health concerns in relation to acute toxicity, bone status, cardiovascular health,

2660 cancer risk or male fertility have been raised by other bodies in previous assessments for this level of
2661 habitual caffeine consumption and no new data have become available on these or other clinical
2662 outcomes which could justify modifying these conclusions.

2663 The Panel notes that, in the prospective cohort studies considered in relation to CVD risk, the
2664 consumption of “energy drinks” was zero (i.e. studies which collected intake data before “energy
2665 drinks” appeared in the market) or unknown. However, the Panel considers that other common
2666 constituents of “energy drinks” (e.g. taurine, D-glucurono- γ -lactone) or alcohol are unlikely to
2667 adversely interact with caffeine in relation to these outcomes. The Panel also considers that the long-
2668 term effects of co-consumption of caffeine and synephrine on the cardiovascular system have not been
2669 adequately investigated in humans.

2670 **5.2. Pregnant women**

2671 Caffeine intakes from all sources up to 200 mg per day by pregnant women in the general population
2672 do not raise safety concerns for the fetus. This conclusion is based on two prospective cohort studies
2673 (CARE Study Group, 2008; Sengpiel et al., 2013) showing a dose-dependent positive association
2674 between caffeine intakes during pregnancy and risk of adverse birthweight-related outcomes (i.e.
2675 FGR, SGA). The association between caffeine intakes and other adverse pregnancy-related outcomes
2676 is less consistent.

2677 The Panel notes that prospective cohort studies cannot provide evidence for a causal association
2678 between caffeine and adverse birthweight-related outcomes. However, given the consistency of the
2679 association, the dose-response relationship observed in the studies available, and the plausibility of the
2680 proposed mode of action by which caffeine could affect fetal development, the Panel assumes that the
2681 relationship is causal in the context of this safety assessment. In the studies available, the contribution
2682 of “energy drinks” to total caffeine intake was low (about 2 % when considered alone, about 7 % in
2683 combination with sugar-containing soft drinks).

2684 **5.3. Lactating women**

2685 Single doses of caffeine up to 200 mg consumed by lactating women in the general population do not
2686 raise safety concerns for the breastfed infant. Daily caffeine intakes by the breastfed infant would not
2687 exceed 0.3 mg/kg bw (Hildebrandt and Gundert-Remy, 1983), which is tenfold below the lowest dose
2688 of 3 mg/kg bw tested in a dose finding study (Steer et al., 2003). For this dose, only one out of 42 pre-
2689 term infants showed tachycardia and jittering, and only tachycardia (with no jittering) was observed in
2690 eight out of 45 infants at doses 100 fold higher (30 mg/kg bw).

2691 Repeated doses of caffeine consumed by lactating women in the general population which do not raise
2692 safety concerns for the breastfed infant should take into account the half-life of caffeine (mean
2693 4 hours, range 2-8 hours) in women and the longer half-life in infants. In this context, doses of 400 mg
2694 per day (corresponding to 5.7 mg/kg bw per day) consumed by lactating women do not raise safety
2695 concerns for the breastfed infant.

2697 **5.4. Children and adolescents (1 year to < 18 years)**

2698 The Panel notes that the information available for this population subgroup on the relationship
2699 between caffeine intakes and health outcomes is insufficient to base a safe level of caffeine intake.

2700 The Panel considers that caffeine intakes of no concern derived for acute consumption in adults (3
2701 mg/kg bw per day) may serve as a basis to derive daily caffeine intakes of no concern for children and
2702 adolescents. The Panel notes that the caffeine clearance in children and adolescents is at least that of
2703 adults, if not faster, and that the limited studies available on the acute and longer-term effects of
2704 caffeine on anxiety and behaviour in children and adolescents support this level of no concern. The
2705 Panel also notes that, as in adults, caffeine doses of about 1.5 mg/kg bw may increase sleep latency

2706 and reduce sleep duration in some children and adolescents, particularly when consumed close to
2707 bedtime.

2708 **6. Characterisation of the risk**

2709 **6.1. Adults**

2710 **6.1.1. Single dose / single session**

2711 There are no data available to estimate single doses of caffeine intake. The EFSA energy drink report,
2712 however, provides information to estimate caffeine intakes from “energy drinks” at “single sessions”,
2713 defined as periods of time of a couple of hours, also in connexion with physical exercise.

2714 Considering the most common concentration of caffeine in “energy drinks” (320 mg/L) and the most
2715 common format (250 mL/can), it can be estimated that about 14 % of adult “energy drink” consumers
2716 and about 4 % of the total adult population may exceed caffeine intakes of 200 mg on a single sports
2717 session (Table 4).

2718 **6.1.2. Daily caffeine intakes**

2719 For seven out of 13 MSs, estimates of the 95th percentile of daily caffeine intake from all sources
2720 exceeded 400 mg. In these countries, the estimated proportion of the adult population exceeding daily
2721 intakes of 400 mg ranged from 5.8 % to almost one third (32.9 %) (Appendix B).

2722 **6.2. Pregnant women**

2723 The mean and the 95th percentile of the daily caffeine intakes from all sources in the only survey
2724 available were 109 mg and 206 mg per day, respectively. About 6.5 % of the women in that survey
2725 (n = 1 002) had daily caffeine intakes > 200 mg per day. The Panel notes the limited caffeine intake
2726 data available in this population subgroup (Appendix B).

2727 **6.3. Lactating women**

2728 The mean and the 95th percentile of the daily caffeine intakes from all sources in the only survey
2729 available were 31 mg and 97 mg per day, respectively, which are well below 200 mg. No women in
2730 that small survey (n = 65) consumed more than 400 mg of caffeine per day. The Panel notes the
2731 limited intake data available in this population subgroup (Appendix B).

2732 **6.4. Adolescents (10 to < 18 years)**

2733 **6.4.1. Single dose / single session**

2734 Like for adults, there are no data available to estimate single doses of caffeine by adolescents. The
2735 EFSA energy drink report can be used to estimate caffeine intakes from “energy drinks” at “single
2736 sessions”, also in connection with physical exercise, in absolute amounts, but not on a kg bw basis.

2737 Considering the most common concentration of caffeine in “energy drinks” (320 mg/L) and the most
2738 common format (250 mL/can), it can be estimated that about 11 % of adolescent “energy drink”
2739 consumers and about 8 % of all adolescents may exceed caffeine intakes of 200 mg on a single sport
2740 session (Table 4).

2741 **6.4.2. Daily caffeine intakes**

2742 For five out of 13 MSs, the 95th percentile of caffeine intake from all sources exceeded 3 mg/kg bw
2743 per day. In these countries, the estimated proportion of the adolescent population exceeding caffeine
2744 intakes of 3 mg/kg bw per day from all sources ranged from 5.2 % to 10 % (Appendix B). The mean
2745 age of the adolescents studied in the surveys of these five countries ranged from 13 years to 16 years.

2746 **6.5. Children (3 to < 10 years)**

2747 **6.5.1. Single dose / single session / single days**

2748 There are no data available to estimate caffeine intakes at single doses or at single sessions in children.
 2749 In the absence of such data, estimates on the proportion of single days in which caffeine intake
 2750 exceeds 3 mg/kg bw among all survey days may serve as a conservative approximation.

2751 For nine out of 16 MSs the estimated 95th percentile of caffeine intake from all sources on a single day
 2752 exceeded 3 mg/kg bw. The proportion of days on which daily intakes of caffeine from all sources
 2753 exceeds 3 mg/kg bw ranges from 6.2 % to 15.4 % (Appendix D).

2754 **6.5.2. Daily caffeine intakes**

2755 For six out of 14 Member States the estimates for the 95th percentile of mean daily caffeine intake
 2756 from all sources exceeds 3 mg/kg bw. The estimated proportion of children with intakes exceeding 3
 2757 mg/kg bw per day of caffeine from all sources range from 6.0 % to 12.6 % (Appendix B).

2758 **6.6. Toddlers (12 to < 36 months)**

2759 **6.6.1. Single dose / single session / single days**

2760 There are no data available to estimate single doses of caffeine or caffeine consumed at single sessions
 2761 for toddlers. In the absence of such data, estimates on the proportion of single days with caffeine
 2762 intakes exceeding 3 mg/kg bw among all survey days may serve as conservative approximation.

2763 For three out of ten MSs the estimated 95th percentile of caffeine intake from all sources on a single
 2764 day exceeded 3 mg/kg bw. The proportion of days in which daily intakes of caffeine from all sources
 2765 exceeds 3 mg/kg bw ranges from 7.3 % to 36.7 % (Appendix D).

2766 **6.6.2. Daily caffeine intakes**

2767 Only for one out of nine MS the 95th percentile of caffeine intake from all sources exceeds 3 mg/kg bw
 2768 per day. About 6 % of the toddlers had a daily consumption > 3 mg/kg bw in that country (Appendix
 2769 B).

2770 **CONCLUSIONS**

2771 **Adults**

2772 Single doses of caffeine up to 200 mg (about 3 mg/kg bw) from all sources do not raise safety
 2773 concerns for the general adult population. The same amount of caffeine does not raise safety concerns
 2774 when consumed less than two hours prior to intense physical exercise under normal environmental
 2775 conditions. No studies are available in pregnant women or middle age/elderly subjects undertaking
 2776 intense physical exercise. Single doses of 100 mg (about 1.5 mg/kg bw) of caffeine may increase sleep
 2777 latency and reduce sleep duration in some adult individuals, particularly when consumed close to
 2778 bedtime.

2779 Caffeine intakes from all sources up to 400 mg per day (about 5.7 mg/kg bw per day) do not raise
 2780 safety concerns for adults in the general population, except pregnant women (see below).

2781 Other common constituents of “energy drinks” (i.e. taurine, D-glucurono- γ -lactone) or alcohol are
 2782 unlikely to adversely interact with caffeine. The short- and long-term effects of co-consumption of
 2783 caffeine and synephrine on the cardiovascular system have not been adequately investigated in
 2784 humans.

2785 About 4 % of the adult population may exceed 200 mg of caffeine on a single session of “energy
2786 drink” consumption in connexion with physical exercise. This information is not available for other
2787 sources of caffeine.

2788 In seven out of 13 countries, the 95th percentile of daily caffeine intake from all sources exceeded 400
2789 mg. The estimated proportion of the adult population exceeding daily intakes of 400 mg in these
2790 countries ranged from 5.8 to almost one third (32.9 %).

2791 **Pregnant women**

2792 Caffeine intakes from all sources up to 200 mg per day by pregnant women in the general population
2793 do not raise safety concerns for the fetus. This is based on prospective cohort studies where the
2794 contribution of “energy drinks” to total caffeine intakes was low (about 2 %).

2795 Data on daily caffeine intake in this population subgroup is scarce.

2796 **Lactating women**

2797 Single doses of caffeine up to 200 mg and caffeine doses of 400 mg per day (about 5.7 mg/kg per day)
2798 consumed by lactating women in the general population do not raise safety concerns for the breastfed
2799 infant.

2800 Data on daily caffeine intake in this population subgroup is scarce.

2801 **Children and adolescents**

2802 Owing to the limited information available for this population subgroup, caffeine intakes of no
2803 concern derived for acute consumption in adults (3 mg/kg bw per day) may serve as a basis to derive
2804 daily caffeine intakes of no concern for children and adolescents. As in adults, caffeine doses of about
2805 1.5 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents,
2806 particularly when consumed close to bedtime.

2807 About 8 % of the adolescent population (10 to < 18 years) may consume more than 200 mg of caffeine
2808 from “energy drinks” on a single session in connexion with physical exercise. This information is not
2809 available for other sources of caffeine. In five out of 13 countries, the 95th percentile of caffeine intake
2810 from all sources exceeded 3 mg/kg bw per day, ranging from 5.2 to 10 % the percentage of
2811 adolescents exceeding that amount.

2812 In children (3 to < 10 years), the 95th percentile of caffeine intake from all sources on a single day
2813 exceeded 3 mg/kg bw in nine out of 16 countries (6.2 to 15.4 % of survey days). The proportion of
2814 children with daily caffeine intakes from all sources beyond 3 mg/kg bw ranged from 6.0 % to 12.6 %
2815 in the six out of 14 countries where the 95th percentile exceeded 3 mg/kg bw.

2816 For toddlers (12 to < 36 months), the estimated 95th percentile of caffeine intake from all sources on a
2817 single day exceeded 3 mg/kg bw in three out of 10 countries (7 to 37 % of survey days). Only in one
2818 out of nine countries the 95th percentile of daily caffeine intake from all sources exceeded 3 mg/kg bw
2819 (6 % of toddlers).

2820

2821

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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-Rolling Programme Years 1-3	2008-2011	4	185/737	651/2595	666/2653 (14a)	1266/5040	166/662	139/552
United Kingdom	DNSIYC 2011	2011	4	1314/5217	-	-	-	-	-

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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		> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
				Mean	P95 ⁽¹⁾	Mean	P95 ⁽¹⁾		

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		> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
				Mean	P95 ⁽¹⁾	Mean	P95 ⁽¹⁾		
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 Programme Years 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		> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
				Mean	P95 ⁽¹⁾	Mean	P95 ⁽¹⁾		
Adolescents (10 to < 18 yrs) 16 surveys	United Kingdom	NDNS-Rolling Programme Years 1-3	651	9.9	46.9	0.4	1.8	1.4	n.a.
	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)
		AESAN FIAB	86	40.3	114.3	0.7	2.3	2.3	0.0 (1.2)
	Spain	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		> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
				Mean	P95 ⁽¹⁾	Mean	P95 ⁽¹⁾		
Elderly (65 to < 75 yrs) 13 surveys	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)
	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		> 3 mg/kg bw	> 400 mg (> 5.7 mg/kg bw)
				Mean	P95 ⁽¹⁾	Mean	P95 ⁽¹⁾		
	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)

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- ⁽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

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

Age class	Food groups	95 th percentile caffeine intake ⁽¹⁾				95 th percentile caffeine intake ⁽¹⁾			
		(all days)				(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⁾
	Total intakes	0.0	82.5	0.0	7.1	(3)	(3)	(3)	(3)
Toddlers (12 to < 36 mon; 11 surveys)	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
	Total intakes	0.0	130.1	0.0	5.7	(3)	(3)	(3)	(3)
Other children (3 to < 10 yrs; 19 surveys)	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
	Total intakes	0.0	239.8	0.0	4.3	(3)	(3)	(3)	(3)
Adolescents (10 to < 18 yrs; 19 surveys)	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
	Total intakes	0.0	809.3	0.0	10.8	(3)	(3)	(3)	(3)
Adults (18 to < 65 yrs; 24 surveys)	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
	Total intakes	0.0	784.3	0.0	10.7	(3)	(3)	(3)	(3)
Elderly (65 to < 75 yrs; 15 surveys)	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
	Total intakes	0.0	801.0	0.0	13.1	(3)	(3)	(3)	(3)
Very elderly (≥ 75 yrs; 13 surveys)	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

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(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).

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

Age class	Country	Survey	Number of days	95 th 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
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.
		EsKiMo	2498	69.8	2.6	4.0	n.a.
	Germany	VELS	1610	51.7	3.0	5.0	n.a.
		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	95 th 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)
Adolescents (10 to < 18 yrs) 19 surveys	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.
	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	95 th 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)
		EFSA TEST	2655	338.2	4.8	n.a.	2.3 (2.2)
	Latvia	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.
	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	95 th 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)

- 3605 (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 (“-”).
- 3606 (2) n.a. = not applicable for the respective population group
- 3607 (3) % exceeding 200 mg/kg bw per day

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	
		EsKiMo	2.1	32.2	55.6	9.6	0.6	
	Germany	VELS	0.2	12.3	85.3	2.2	0.0	
		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	
		VCPBasis AVL2007 2010	2.5	55.7	21.3	19.2	1.3	
	Netherlands	VCP kids	2.4	64.9	18.3	14.4	0.0	
		NUT INK05	1.8	0.2	90.9	7.1	0.0	
	Spain	enKid	2.1	0.0	97.9	0.0	0.0	
		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
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	
		EsKiMo	2.6	34.0	42.7	19.7	0.9	
	Germany	National Nutrition Survey II	33.3	33.1	16.3	17.3	0.0	
		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
Adults (18 to ≤ 65 yrs)	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)
	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-Rolling Programme Years 1-3	27.9	68.1	3.3	0.5	0.2	
		Median		81	11	2	0	0
		Range		(28-93)	(4-79)	(1-18)	(0-1)	(0-1)

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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**

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Study	Design	Subjects, habitual daily consumption	Run-in ¹	n (I/C) ^c	Intervention	Caffeine (mg)	Control	Outcomes			
								Arterial stiffness	Endothelial function	BP	Other
Single doses of caffeine											
Vlachopoulos et al. (2003)	rdb-X	Healthy, >100 mg caffeine	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	-

Study	Design	Subjects, habitual daily consumption	Run-in ¹	n (I/C) ^c	Intervention	Caffeine (mg)	Control	Outcomes				
								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	-	

3613 AI = augmentation index; AP = augmented pressure; BP = blood pressure; DC = decaffeinated coffee; FCW= forward compression wave; FEW= forward expansion wave; HR= heart rate;
3614 MABP = mean arterial blood pressure; nr-P = non-randomised, parallel; NR = not reported; PWV= pulse wave velocity; rdb-X = randomised, double-blind, cross-over; rdb-P =
3615 randomised, double-blind, parallel; rsb-X = randomised, single-blind, cross-over; RPP = rate-pressure product; WR = wave reflections; WS = wave speed.
3616 ¹ Refers to the time of abstinence from caffeine before testing, unless otherwise noted
3617 ² Subjects consumed 0, 300 or 600 mg of caffeine (in three divided daily doses) per day for 5 days before testing
3618 ³ Subjects consumed 80 mg of caffeine three times per day for 6 days before testing
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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 et al. (2001)	rol-X	8h ³	13h	12	13.5	-	NS	NS
Min 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

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

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**

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	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

3636 a Included in Noordzij et al. (2005)

3637 b Included in Steffen et al. (2012)

3638 c Included in Jee et al. (1999)

3639 d Number of participants (intervention/control). Only one number is given for cross-over designs, where subjects were their own controls.

3640 e Duration of the intervention

3641 f Study not randomised. All subjects received no coffee/coffee in the same sequence

3642 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

3643 2 Estimated assuming that one cup of coffee corresponds to 150 ml.

3644 3 Estimated assuming that one cup of coffee corresponds to 90 mg of caffeine.

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

	Meta-analyses											
	Ding et al., 2014	Cheng et al., 2014	Caldeira et al., 2013 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) <i>Chicago Western Electric Company Study</i>	USA	M	f-CHD f-Stroke	X	-	-	-	-	-	-	X	-
Yano K et al. (1987)	USA	M	f-CHD nf-MI	-	-	-	-	-	-	-	X	-
Martin et al. (1988) <i>Hypertension Detection and Follow-up Program</i>	USA	M/F	f-CHD f-Stroke	X	-	-	-	-	-	-	X	-
Wilson et al., 1989	USA	M/F	CVD	-	-	-	-	-	-	-	X	-
Grobbbee et al. (1990) <i>Health Professionals Follow-up Study</i>	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) <i>Primary Prevention Study</i>	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 f-IHD	X	-	-	-	-	-	-	-	-	X	X
Klatsky et al. (1993)	USA	M/F	f-CHD	-	-	-	-	-	-	-	-	-	-	X
Klag et al. (1994)	USA	M	CHD MI	X	-	-	-	-	-	-	-	-	X	X
Gyntelberg et al. (1995) <i>Copenhagen Male Study</i>	DK	M	nf-IHD	X	-	-	-	-	-	-	-	-	X	X
Stensvold and Tverdal (1995)	NO	M/F	nf-MI	-	-	-	-	-	-	-	-	-	X	-
Hart and Smith (1997)	UK	M	f-CHD	X	-	-	-	-	-	-	-	-	X	X
Hakim et al. (1998) <i>Honolulu Heart Program</i>	USA	M	Stroke subtypes	X	-	-	-	-	-	-	-	-	-	-
Woodward and Tunstall-Pedoe (1999) <i>Scottish Heart Health Study</i>	UK	M/F	CHD	X	-	-	-	-	-	-	-	-	X	-
Kleemola et al. (2000)	FI	M/F	f-CHD nf-MI	X	-	-	-	-	-	-	-	-	X	-
Wilhelmsen et al. (2001b); Wilhelmsen et al. (2001a) <i>Multifactor Primary Prevention Study</i>	SE	M	HF, AF	-	X	X	X	-	-	-	-	-	-	-
Klag et al. (2002) <i>John Hopkins Precursors</i>	USA	M	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										
<i>Study</i>													
Jazbec et al. (2003)	HR	M/F	f-CVD	X	-	-	-	-	-	-	-	-	-
Happonen et al. (2004) <i>Kuopio Ischaemic Heart Disease Risk Factor Study</i>	FI	M	f-CHD nf-MI	X	-	-	-	-	-	-	-	X	-
Frost and Vestergaard (2005) <i>Danish Diet, Cancer, and Health Study</i>	DK	M/F	AF	-	X	X	-	-	-	-	-	-	-
Winkelmayer et al. (2005) <i>Nurses' Health Study I and II</i>	USA	F	HT	-	-	-	-	-	-	X	X	-	-
Bidel et al. (2006)	FI	M/F	f-CVD f-CHD f-Stroke	X	-	-	-	-	X	-	-	-	-
Andersen et al. (2006) <i>Iowa Women's Health Study</i>	USA	F	f-CVD	X	-	-	-	-	-	-	-	X	X
Lopez-Garcia et al. (2006) <i>Health Professionals Follow-up Study</i>	USA	M/F	CHD f-CHD nf-MI	X	-	-	-	-	-	-	-	X	X
Greenberg et al. (2007) <i>Nurses' Health Study NHANES I-NHEFS</i>	USA	M/F	f-CVD f-CHD f-Stroke	X	-	-	-	-	-	-	-	-	-
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										
<i>HARVEST study</i>													
Rosner et al. (2007)	SE	F	MI	-	-	-	-	-	-	-	-	X	-
<i>Swedish Mammography Cohort</i>													
Silletta et al. (2007) <i>GISSI-Prevention Trial</i>	IT	M/F	CV death nf-MI nf-stroke	X	-	-	-	X	X	-	-	-	-
Uiterwaal et al. (2007)	DK	M/F	HT	-	-	-	-	-	-	X	X	-	-
<i>Doetinchem Cohort Study</i>													
Greenberg et al., 2008	USA	M/F	CVD CHD Stroke	X	-	-	-	X	-	-	-	-	-
<i>Framingham Heart Study</i>													
Happonen et al. (2008)	FI	M/F	f-CVD	X	-	-	-	-	-	-	-	-	-
Larsson et al. (2008) <i>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study</i>	FI	M	Stroke	X	-	-	-	X	X	-	-	-	-
Ahmed et al. (2009) <i>Cohort of Swedish Men</i>	SE	M	HF	X	-	-	X	-	-	-	-	-	-
Lopez-Garcia et al. (2009)	USA	F	Stroke	X	-	-	-	X	X	-	-	-	-
<i>Nurses' Health Study</i>													
Mukamal et al. (2009)	SE	M/F	HF, AF, Stroke f-MI	X	X	X	X	X	X	-	-	-	-
<i>Stockholm Heart Epidemiology Program-</i>													
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) <i>Women' Health Study</i>	USA	F	AF		X	X	-	-	-	-	-	-	-
de Koning Gans et al. (2010) <i>EPIC-NL</i>	NL	M/F	CHD Stroke	X	-	-	-	X	X	-	-	-	-
Leurs et al. (2010)*** <i>the Netherlands Cohort Study</i>	NL	M/F	f-CHD f-Stroke	X	-	-	-	-	X	-	-	-	-
Shen et al. (2011) <i>Framingham Heart Study</i>	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 arrhythmias	-	X	X	-	-	-	-	-	-	-
Larsson et al. (2011) Levitan et al. (2011) <i>Swedish Mammography Cohort</i>	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) <i>FINRISK study</i>	FI	M/F	HF	-	-	-	X	-	-	-	-	-	-
Freedman et al. (2012) <i>National Institutes of</i>	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										
<i>Health-AARP Diet and Health Study</i>			Stroke										
Floegel et al. (2012)	DE	M/F	CVD MI Stroke	X	-	-	-	-	-	-	-	-	-
<i>EPIC-Germany</i>													
Rautiainen et al. (2012) <i>Swedish Mammography Cohort</i>	SE	F	MI	X	-	-	-	-	-	-	-	-	-
Kokubo et al. (2013)	JPN	M/F	CVD CHD Stroke	X	-	-	-	-	-	-	-	-	-

3648 * Prospective cohort and case-control study; ** nested case-control study; *** prospective case-control study

3649 ¹ Also includes a case-control study (Mattioli et al., 2005)

3650 AF = atrial fibrillation; CHD = coronary heart disease; CVD = cardiovascular disease; CSD= Caffeinated soft drinks; EPIC = European Prospective Investigation into Cancer and Nutrition;
 3651 f = fatal-; F = females; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; HF = heart failure; HT = hypertension; M = males; MI = myocardial
 3652 infarction; nf- = non-fatal; NHANES I- NHEFS = National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study; SHEEP = Stockholm Heart Epidemiology
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3657 **ABBREVIATIONS**

3658	ADHD	Attention-deficit hyperactivity disorder
3659	AF	Atrial fibrillation
3660	AHR	Aryl-hydrocarbon receptor
3661	ALSPAC	Avon Longitudinal Study of Parents and Children
3662	ANSES	French Agency for Food, Environmental and Occupational Health and Safety
3663	BMI	Body mass index
3664	BP	Blood pressure
3665	bw	Body weight
3666	CABG	Coronary-artery bypass grafting
3667	CAD	Coronary arterial disease
3668	CHD	Coronary heart disease
3669	CI	Confidence interval
3670	CVD	Cardiovascular disease
3671	CNS	Central nervous system
3672	CVS	Cardiovascular system
3673	DBP	Diastolic blood pressure
3674	FDA	US Food and Drug Administration
3675	FFQ	Food frequency questionnaire
3676	FGR	Fetal growth retardation
3677	FMD	Flow-mediated vasodilation
3678	FSANZ	Food Standards Australia and New Zealand
3679	HR	Heart rate
3680	IQR	Interquartile range
3681	MABP	Mean arterial blood pressure
3682	MBF	Myocardial blood flow
3683	MFR	Myocardial blood flow reserve
3684	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