SCIENTIFIC OPINION

Scientific Opinion on Flavouring Group Evaluation 49, Revision 1 (FGE.49Rev1): xanthine alkaloids from the priority list

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Abstract

Following a request from the European Commission, the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) was requested to deliver a scientific opinion on the safety assessment of the flavouring substances caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032] in the Flavouring Group Evaluation 49, Revision 1. Consequent to the 2015 scientific opinion from the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) on the safety of caffeine from all dietary sources, the CEF Panel considered it inappropriate to evaluate the two substances through the Procedure. For caffeine, the Panel based its assessment on the safety threshold of 5.7 mg/kg body weight (bw) per day for adults, except pregnant/lactating women, and 3 mg/kg bw per day for children, adolescents, pregnant and lactating women, as established by the NDA Panel. The safety evaluation of theobromine takes into account that approximately 11% of an oral dose of caffeine is metabolised to theobromine and that both substances have a similar pharmacological profile. For the exposure assessment, a brand loyalty model was chosen. In this model, it was assumed that a consumer is exposed on a long-term basis to a specific category of food (i.e. non-alcoholic beverages), containing caffeine or theobromine at their respective maximum use levels. For the rest of the categories, normal use levels applied. Daily dietary exposure to caffeine and theobromine (excluding systemic exposure) added as a chemically defined flavouring substance ranged 0–2.3 and 0–0.4 mg/kg bw, respectively, across all population groups. The Panel concluded that caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032] would not be expected to present safety concern based on their estimated levels of intake from their use as flavouring substances.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 2232/96 of the European Parliament and the Council[1] lays down a Procedure for the establishment of a list of flavouring substances, the use of which will be authorised to the exclusion of all other substances in the European Union (EU). In application of that Regulation, a Register of flavouring substances used in or on foodstuffs in the Member States was adopted by Commission Decision 1999/217/EC[2], as last amended by Commission Decision 2008/478/EC. Each flavouring substance is attributed a FLAVIS-number (FL-number) and all substances are divided into 34 chemical groups. Substances within a group should have some metabolic and biological behaviour in common.

Substances which are listed in the Register are to be evaluated according to the evaluation programme laid down in Commission Regulation (EC) No 1565/2000[3], which is broadly based on the opinion of the Scientific Committee on Food (SCF, 1999). For the submission of data by the manufacturer, deadlines have been established by Commission Regulation (EC) No 622/2002.

After the completion of the evaluation programme the positive list of flavouring substances for use in or on foods in the EU shall be adopted (Article 5 (1) of Regulation (EC) No 2232/96).

By Commission Decision 1999/217/EC, certain flavouring substances received priority in the evaluation programme, since concerns about the safety of the health of consumers were expressed by some Member States. In the Register, these substances received the following remark: 3. 'Substance to be given priority evaluation'.

In the Commission Decision 1999/217/EC, Parts 1–3, 18 flavouring substances received this remark. In May 2000, a revised list containing 49 flavouring substances with this remark was adopted (Commission Decision 2000/489/EC amending Commission Decision 1999/217/EC). By the amendment from January 2002 (Commission Decision 2002/113/EC amending Commission Decision 1999/217/EC), the list contains 43 flavouring substances with this remark (see Table 1).

Table 1: Status of 43 Flavouring Substances Given Priority Evaluation (in Commission Decision 2002/113/EC amending Commission Decision 1999/217/EC)

FL-no	Name	Status in the FLAVIS database, May 2008
01.015	Vinylbenzene	FGE.29 – Priority substance
08.017	Malic acid	JECFA-no: 619
08.041	Octadeca-9,12-dienoic acid	JECFA-no: 332
13.018	Furfural	EFSA opinion adopted 2004. ADI of 0.5 mg/kg bw. FGE.19 – EFSA evaluation of alpha,beta-unsaturated aldehydes and ketones under evaluation
13.035	Menthofuran	FGE.57 – EFSA consideration of JECFA evaluated substances – under evaluation
13.126	Furfural diethyl acetal	EFSA opinion adopted 2004. ADI of 0.5 mg/kg bw. FGE.19 – EFSA evaluation of alpha,beta-unsaturated aldehydes and ketones under evaluation
14.011	Quinine hydrochloride	FGE.35 – JECFA evaluation 1993: No concern up to 100 mg/L in soft drink (Commission Directive 2002/67/EC)
14.152	Quinine sulfate	FGE.35 – JECFA evaluation 1993: No concern up to 100 mg/L in soft drink (Commission Directive 2002/67/EC)
14.155	Quinine monohydrochloride dihydrate	FGE.35 – JECFA evaluation 1993: No concern up to 100 mg/L in soft drink (Commission Directive 2002/67/EC)
16.002	Diammonium sulfide	Not allocated any evaluation – suggested for deletion by DG SANCO
16.012	Glycyrrhizic acid	FGE.36 – SCF opinion adopted 2003 (Commission Directive 2004/77/EC). JECFA evaluation 2004: Data were inadequate to derive an ADI
16.016	Caffeine	FGE.49 – SCF opinions adopted 1999, 2003 (Commission Directive 2002/67/EC)

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[1] Regulation (EC) No 2232/96 of the European Parliament and of the Council of 28 October 1996. Official Journal of the European Communities 23.11.1996, L 299, 1–4.

[2] Commission Decision 1999/217/EC of 23 February 1999 adopting a register of flavouring substances used in or on foodstuffs. Official Journal of the European Communities 27.3.1999, L 84, 1–137.

[3] Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96. Official Journal of the European Communities 19.7.2000, L 180, 8–16.

FL-no	Name	Status in the FLAVIS database, May 2008
16.027	Thiamine hydrochloride	FGE.76 – Adopted EFSA consideration of JECFA evaluated substances
16.032	Theobromine	FGE.49 – SCF opinions adopted 1999, 2003 on caffeine
16.056	Taurine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
16.059	Ammonium hydrogen sulfide	FGE.46 – EFSA evaluation of ammonium and ammonium salts under evaluation
16.060	Glycyrrhizic acid, ammoniated	FGE.36 – SCF opinion adopted 2003 (Commission Directive 2004/77/EC). JECFA evaluation 2004: Data were inadequate to derive an ADI
17.001	β-Alanine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.002	l-Alanine	FGE.26Rev1 – Adopted EFSA evaluation of amino acids
17.003	Arginine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.005	Aspartic acid	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.006	Cystine	FGE.26 – Adopted EFSA evaluation of amino acids
17.007	Glutamine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.008	Histidine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.010	Isoleucine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.012	Leucine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.013	Lysine	FGE.26 – Adopted EFSA evaluation of amino acids
17.014	Methionine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.017	Phenylalanine (D,L)	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.018	Phenylalanine (L)	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.019	Proline	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.020	Serine	FGE.26 – Adopted EFSA evaluation of amino acids
17.021	Threonine	FGE.26 – Adopted EFSA evaluation of amino acids
17.022	Tyrosine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.023	Valine (D,L)	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.024	Alanine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.026	Lysine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.027	Methionine	FGE.26Rev1 – Adopted EFSA evaluation of amino acids
17.028	Valine (L)	FGE.26Rev1 – Adopted EFSA evaluation of amino acids
17.031	Lysine monochlorhydrate	FGE.26 – Adopted EFSA evaluation of amino acids
17.032	Cysteine hydrochloride	FGE.26Rev1 – Adopted EFSA evaluation of amino acids
17.033	Cysteine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances
17.034	Glycine	FGE.79 – Adopted EFSA consideration of JECFA evaluated substances

FL-no: FLAVIS number; FLAVIS: Flavour Information System; FGE: Flavouring Group Evaluation; JECFA: The Joint FAO/WHO Expert Committee on Food Additives; ADI: acceptable daily intake; bw: body weight; SCF: Scientific Committee on Food.

Of the 43 substances in Table 1, one is suggested for deletion from the Register, 12 have been evaluated in other Flavouring Group Evaluations (FGEs), and 22 have been evaluated by The Joint FAO/WHO Expert Committee on Food Additives (JECFA) (20 of these JECFA evaluated substances are also considered by EFSA).

The remaining eight substances, vinylbenzene [FL-no: 01.015], quinine hydrochloride [FL-no: 14.011], quinine sulfate [FL-no: 14.152], quinine monohydrochloride dihydrate [FL-no: 14.155], glycyrrhizic acid [FL-no: 16.012], glycyrrhizic acid, ammoniated [FL-no: 16.060], caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032] are considered in the following Flavouring Group Evaluations:

FGE.29: Aromatic hydrocarbon: vinylbenzene [FL-no: 01.015];

FGE.35: Quinoline alkaloids: quinine hydrochloride [FL-no: 14.011], quinine sulfate [FL-no: 14.152], quinine monohydrochloride dihydrate [FL-no: 14.155];

FGE.36: Triterpene glycosides: glycyrrhizic acid [FL-no: 16.012], glycyrrhizic acid, ammoniated [FL-no: 16.060];

FGE.49: Xanthine alkaloids: caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032].

Terms of Reference as provided by the European Commission

The European Food Safety Authority (EFSA) is requested to carry out a risk assessment on flavouring substances prior to their authorisation and inclusion in a positive list according to Commission Regulation (EC) No 1565/2000.

1.2. Interpretation of the Terms of Reference

The safety of the xanthine alkaloids caffeine and theobromine was considered in a previous version of this FGE (EFSA, 2009); however, the assessment could not be finalised. The current revision includes newly submitted information as well as the results of an extensive safety assessment of caffeine undertaken by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel), published in 2015 (EFSA NDA Panel, 2015).

2. Assessment

2.1. History of the evaluation of the substances in the present FGE (Table 2)

The Flavouring Group Evaluation 49, FGE.49 concerns the two xanthine alkaloids from the EU chemical group 30, Annex I of Commission Regulation (EC) No 1565/2000[3]: caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032].

Typically, in line with Regulation (EC) No 1565/2000, for the initial evaluation of flavouring substances the Panel applies as a standard the Maximised Survey-derived Daily Intake (MSDI) approach to assess exposure. This involves the acquisition of data on the amounts of the substances used in food as flavourings (SCF, 1999) which are derived from surveys on annual production volumes in Europe, conducted by the International Organization of the Flavour Industry (IOFI, 1995).

In 2008, as information on production volumes allowing for the derivation of then MSDI was not available (EFSA, 2009), the Panel concluded that the two flavouring substances could not be evaluated using the Procedure described in Regulation (EC) No 1565/2000 (hereafter 'the Procedure').

Table 2: History of safety evaluations concerning FGE.49

FGE	Opinion adopted by EFSA	Link	No. of candidate substances
FGE.49	22 May 2008	http://www.efsa.europa.eu/en/efsajournal/doc/741.pdf	2
FGE.49Rev1	31 January 2017	http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4729/full	2

FGE: Flavouring Group Evaluation.

In 2010, the flavour industry submitted the requested information on production volumes and data on normal and maximum use levels for the two substances caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032] (Flavour Industry, 2010), allowing for the evaluation of the two flavouring substances according to the Procedure (see Appendix A). However, in the light of the scientific opinion on the safety of caffeine issued by the NDA Panel (EFSA NDA Panel, 2015), the CEF Panel decided not to follow the Procedure for the safety evaluation of the two flavouring substances (see Section 2.2).

2.2. Evaluation approach

The safety of caffeine from all sources was previously evaluated by the SCF in 1999 and 2003 (see Appendix H). More recently, an extensive evaluation of caffeine from all major sources was undertaken by the NDA Panel (EFSA NDA Panel, 2015). Therefore, the CEF Panel considered it inappropriate to evaluate caffeine through the Procedure for the evaluation of chemically defined flavouring substances (see Appendix A) and instead chose to build on the NDA opinion for the revised evaluation of caffeine.

Like for caffeine, the Panel decided not to evaluate theobromine through the Procedure, but to base its assessment on the fact that theobromine is a major metabolite of caffeine. Thus, the information available on the safety of caffeine in the NDA opinion could also be used for the safety assessment of this substance, for which only limited toxicity data in humans are available. The scientific opinion from the EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) (EFSA, 2008) on the presence of theobromine as undesirable substance in animal feed was also not

used as a basis for the safety evaluation of theobromine in the present opinion, since it does not provide a point of departure for quantitative risk assessment on the safety of theobromine in human food.

Consequently, the Panel decided to structure this opinion in a different way than the one typically used for other Flavouring Group Evaluations, in which the Procedure for the safety evaluation of flavouring substances is applied (described in Appendix A).

2.3. Identification of the flavouring substances

The two flavouring substances under consideration, as well as their chemical Register names, FLAVIS- (FL-), Chemical Abstract Service- (CAS-), Council of Europe- (CoE-) and Flavor and Extract Manufacturers Association- (FEMA-) numbers and structure are listed in Table 3. Specifications, including purity criteria for the two substances are also provided (Flavour Industry, 2010).

Judged against the requirements in Annex II of Commission Regulation (EC) No 1565/2000, the information is adequate for the two candidate substances (Table 3).

2.4. Exposure assessment

2.4.1. Introduction

To assess exposure to caffeine and theobromine as chemically defined flavouring substances in food, the CEF Panel decided to consider the information available in the NDA opinion on the safety of caffeine (EFSA NDA Panel, 2015) for the following reasons:

- To take advantage of the extensive evaluation carried out by the NDA Panel and to be consistent with its output.
- To investigate the contribution of the intake from flavouring use to the exposure from all dietary sources.
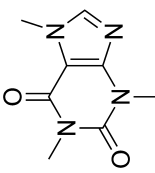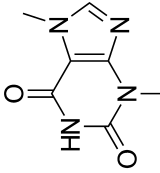
For the purposes of this assessment, the Panel derived exposure estimates for (i) each of the chemically defined flavouring substances caffeine and theobromine when directly added to food and (ii) total exposure to each of these substances from all sources, taking into account natural occurrence and intentional use. The combined exposure to theobromine from intake of theobromine as such and from intake of caffeine was also assessed. In this assessment, systemic exposure to theobromine as metabolite of caffeine was added to the intake of theobromine as such, to facilitate comparison of the total exposure with a reference value derived for theobromine.

2.4.2. Methodology

Dietary exposure to caffeine and theobromine from their use as chemically defined flavouring substances was estimated by combining food consumption data available within the EFSA Comprehensive European Food Consumption Database (hereafter Comprehensive Database)[4] (EFSA, 2011a) with the maximum permitted levels and/or reported use levels submitted to EFSA by the flavour industry, as appropriate. In this assessment, a brand loyalty model was chosen. In this model, it is assumed that a consumer is exposed on a long-term basis to a specific category of food, containing the flavouring substance of interest at the maximum use/permitted level. For both caffeine and theobromine, it was decided that this category of food will be the one resulting in the highest potential dietary exposure.

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[4] http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

Table 3: Specification summary of the substances in the FGE.49Rev1

FL-no	EU register name	Structural formula	FEMA no CoE no CAS no	Phys. form Mol. formula Mol. weight	Solubility[a] Solubility in ethanol[b]	Boiling point, °C[c] Melting point, °C ID test Assay minimum	Refrac. index[d] Spec. gravity[e]	Specification comments
16.016	Caffeine 1H-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-		2224 11741 58-08-2	Solid $C_8H_{10}N_4O_2$ 194.19	Soluble Soluble	235–238 IR 98%	n.a. n.a.	
16.032	Theobromine 1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-		3591 83-67-0	Solid $C_7H_8N_4O_2$ 180.17	Slightly soluble Soluble	357 IR 98%	n.a. n.a.	Sublimes at 290–295°C

FL-no: FLAVIS number; FEMA: Flavor and Extract Manufacturers Association; CoE: Council of Europe; CAS: Chemical Abstract Service; ID: identity; IR: infrared spectroscopy.

(a): Solubility in water, if not otherwise stated.
(b): Solubility in 95% ethanol, if not otherwise stated.
(c): At 1,013.25 hPa (1 atm), if not otherwise stated.
(d): At 20°C, if not otherwise stated.
(e): At 25°C, if not otherwise stated.

For the remaining categories, normal use levels were applied. This is in line with the added portions exposure technique (APET) calculations as developed in the guidelines for flavourings (EFSA CEF Panel, 2010).

Dietary exposure to caffeine from all non-flavouring sources (i.e. natural sources, stimulant use) was estimated by combining food consumption data available within the Comprehensive Database (see Section 2.4.3) with occurrence data from the literature, as used by the NDA Panel in their assessment (EFSA NDA Panel, 2015). For theobromine, data reported in the literature was used (Appendix C, Table C.4). For the systemic exposure to theobromine resulting from caffeine intake, a factor of 0.11 (see Section 2.4.4.2.c) was applied, based on the metabolic conversion of caffeine into theobromine.

Caffeine and theobromine exposure estimates were calculated for each individual in the Comprehensive Database. Only surveys with collected data for at least 2 days were used. For each individual, exposure from all identified food groups was summed up over the entire survey period and subsequently divided by the number of survey days to derive average daily intakes. Finally, the so derived estimates were normalised for individual body weight (bw), resulting in an individual average daily exposure per kg bw for the survey period (absolute intake values in mg of flavouring substance per day are also provided in Appendix D, Tables D.1 and D.2). High-level exposure was calculated for only those population groups where the sample size was sufficiently large to allow calculation of the 95th percentile (EFSA, 2011b).

Uncertainties on the exposure assessment were identified and discussed in each relevant section.

2.4.3. EFSA Comprehensive European food consumption database[4]

Since 2010, the Comprehensive Database has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment') (EFSA, 2011a). New consumption surveys[5] recently added in the Comprehensive database were also taken into account in this assessment (see Appendix B, Table B.1).

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database represents the best available source of food consumption data across Europe at present.

Food consumption data from the following population groups: toddlers, children, adolescents, adults and the elderly were used for the exposure assessment. For the present assessment, food consumption data were available from 41 different dietary surveys carried out in 23 European countries (Table 4).

Table 4: Population groups considered for the exposure estimates of caffeine and theobromine

Population	Age range	Countries with food consumption surveys covering more than 1 day
Toddlers	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children[(a)]	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
Elderly	From 65 years up to 74 years of age	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Romania, Sweden, UK
Very elderly	From 75 years of age and above	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Romania, Sweden, UK

(a): The terms 'children' corresponds, to 'other children' in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011b).

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[5] Available online: http://www.efsa.europa.eu/en/press/news/150428.htm

Consumption records were coded according to the FoodEx classification system (EFSA, 2011b). For the purposes of the present assessment, nomenclature from the FoodEx classification system was linked to the Food Categorisation System (FCS) as presented in Annex III of Reg. (EC) 1565/2000 (see Appendix C, Table C.3).

2.4.4. Food categories and concentration data considered for the exposure assessment

2.4.4.1. Caffeine

a) Levels of caffeine when used as chemically defined flavouring substance

Use and use levels were provided to EFSA by the flavour industry (Flavour Industry, 2010) and are detailed below (see Table 5 and Appendix C, Table C.2).

Table 5: Caffeine use and use levels reported by the flavour industry, maximum permitted levels (MPLs) and levels used in the exposure assessment (mg/kg or mg/L)

Food category[a]	MPL[b]	Use levels provided by the Flavour Industry		Level used in the exposure assessment[c]	Notes
		Normal	Maximum		
		(mg/kg or mg/L)			
1. Dairy products	70	20	70	20	Only 'flavoured milk products' were considered
3. Edible ices	70	20	70	20	Only 'milk and non-milk based ice-creams' were considered
5. Confectionary	100	25	100	25	Since cocoa is a natural source of caffeine, only the category of non-chocolate confectionery was considered.
14.1 Non-alcoholic beverages	150	100	175	150	Only 'caffeinated cola drinks' were considered
14.2 Alcoholic beverages	–	25	100	–	Unauthorised use[2] and not taken into account

(a): According to Annex III of Reg. (EC) 1565/2000[3].
(b): Set by Reg. (EC) 1334/2008[6].
(c): Assumption that the consumer is loyal to non-alcoholic beverages.

Use and use levels were provided for five categories; however, only four food categories were included in the exposure assessment. The use of caffeine in the food category alcoholic beverages is not authorised and was therefore not taken into account in the present assessment. This may result in an underestimation of the exposure.

The matching food categories were selected from the EFSA Comprehensive Database, at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b) (see Appendix C, Table C.3).

In order to take brand loyalty into account, it was assumed that a consumer is exposed, on a long-term basis, to caffeine present at the maximum reported use level in the food category resulting in the highest potential dietary exposure (i.e. cola beverages) and exposed at normal reported use levels for the remaining food categories. However, the maximum reported use level for caffeine in cola beverages exceeded the maximum permitted level (MPL), which constitutes a non-compliance, and therefore, in this case, the MPL was used instead. This may result in an underestimation of the exposure.

b) Natural and non-flavouring caffeine concentrations in food and beverages

For the purposes of assessing intake from all sources, additional data on non-flavour use (e.g. stimulant use) and natural occurrence of caffeine was used. For caffeine, this data – taken from the

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[6] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC. OJ L 354, 31.12.2008, p. 34–50.

literature – is the same as used by the NDA Panel in their assessment of caffeine (EFSA NDA Panel, 2015) (see Table 6).

Table 6: Natural and non-flavour caffeine concentrations (mg/kg or mg/L) in food and beverages, considered in the assessment of caffeine from all sources

Food groups	Subgroups	Used in the intake assessment (mg/kg or mg/L)[a]
Chocolate	Chocolate bar	111
	Milk chocolate	168
	Chocolate snacks	
	Cocoa beverage-based on cocoa powder	
	Cocoa beverage-based on cocoa-beverage preparation powder	42
	Dark chocolate	525
Coffee	Coffee drink	445
	Cappuccino	273
	Espresso coffee	1,340
	Decaffeinated and imitates	21
	Instant coffee, ready to drink	445
Tea	Black tea	220
	Green tea	151
	Tea (unspecified)	165
	Tea, decaffeinated	25
Beverages	'Energy drinks'	320

(a): See opinion of the NDA Panel for full details and considerations (EFSA NDA Panel, 2015).

The concentration data reported by the NDA Panel for the above four food groups was used to derive exposure estimates from natural and non-flavouring sources. The use of caffeine in energy drinks, in excess of MPLs for flavouring use[6], is permitted for purposes other than imparting flavour. For these high use levels, specific labelling requirements are included in the legislation.[7] Therefore, caffeine from energy drinks was included in the exposure assessment from all sources, which was reported in excess of the applicable MPL for flavouring use, in this assessment scenario, but it was not included in the exposure assessment for use as a flavouring substance.

The matching food categories were selected from the EFSA Comprehensive Database, at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b) (see Appendix C, Table C.3).

2.4.4.2. Theobromine

a) Levels of theobromine when used as chemically defined flavouring substance

Use and use levels were provided to EFSA by the flavour industry (Flavour Industry, 2010) and are detailed below.

According to the flavour industry, theobromine is added for flavouring purposes in non-alcoholic beverages and dairy products (Flavour Industry, 2010) (see Table 7 and Appendix C, Table C.2).

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[7] Regulation (EU) No 1169/2011 of the European Parliament and of the Council on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004.

Table 7: Theobromine use and use levels reported by industry, maximum permitted levels (MPLs) and levels used in the exposure assessment

Food category[a]	MPL[b]	Use levels provided by the Flavour Industry		Level used in the exposure assessment[c]	Notes
		Normal	Maximum		
		(mg/kg or mg/L)			
1. Dairy products	70	20	70	20	Only 'flavoured milk products' were considered
14.1 Non-alcoholic beverages	100	75	100	100	Only 'soft drinks with bitter principle' and 'soft drinks mixed flavours' were considered

(a): According to Annex III of Reg. (EC) 1565/2000[3].
(b): Set by Reg. (EC) 1334/2008[6].
(c): Assumption that the consumer is loyal to non-alcoholic beverages.

As for caffeine, a brand loyal exposure assessment method (see Section 2.4.4.1.a) was followed, whereby it was assumed that a consumer is exposed long term to theobromine present at the maximum reported use in the food category resulting in the highest potential dietary exposure at the individual level (i.e. non-alcoholic beverages) and exposed at reported normal use levels for the remaining food category.

The matching food categories were selected from the EFSA Comprehensive Database, at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b) (see Appendix C, Table C.3).

b) Natural and non-flavouring theobromine concentrations in food and beverages

For the purposes of assessing exposure from all sources, additional data on non-flavour use (e.g. stimulant use) and natural occurrence of theobromine was used. These data was derived from the literature (see Appendix C, Table C.4 for further details). The average across all reported values was typically used (see Table 8); however, the Panel noted that the range of theobromine concentrations in the various food matrices was highly variable and therefore the magnitude and direction of the uncertainty associated with the estimate could not be determined in this case. Therefore, this assessment only presents a snapshot of exposure.

Table 8: Natural and non-flavouring theobromine concentrations (mg/kg or mg/L) in food and beverages, considered in the assessment of theobromine from all sources

Food groups	Subgroups	Used in the intake assessment (mg/kg or mg/L)
Cocoa powder		22,000
Chocolate	Chocolate bar	1,400
	Milk chocolate	
	Chocolate snacks	
	Cocoa beverage-based on cocoa powder	370
	Cocoa beverage-based on cocoa-beverage preparation powder	93
	Dark chocolate	5,500
Tea	Black tea	26
	Green tea	45
	Tea (unspecified)	40
Beverages	'Energy drinks'	100

No specific occurrence levels for theobromine in energy drinks were reported by industry. However, to stay in line with the approach followed for the assessment of caffeine from all sources, theobromine from energy drinks was included in this scenario to cover uses other than for flavouring purposes. Therefore, in line with the approach followed for caffeine, theobromine from energy drinks was not included in the exposure assessment for use as a flavouring substance (e.g. stimulant use as a flavouring substance).

c) Systemic sources of theobromine

An additional source of exposure to theobromine is consumption of caffeine, as approximately 11% of a dose of caffeine is converted to theobromine after ingestion (see Section 2.5). Therefore, to account for this systemic exposure to theobromine, caffeine values (see Sections 2.4.4.1.a and b) were converted into theobromine via application of a conversion factor of 0.11 and included in the assessment to theobromine, to cover combined exposure.

2.4.5. Exposure estimates

2.4.5.1. Caffeine

a) From dietary sources where caffeine is added as a chemically defined flavouring substance

Daily exposure to caffeine added as a chemically defined flavouring substance in food ranged from 0 to 2.3 mg/kg bw per day across all population groups (see Table 9 and Appendix D, Table D.1).

Table 9: Summary of dietary exposure to caffeine from its use as chemically defined flavouring substance, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Exposure from flavouring use (mg/kg bw per day)[(a)]					
	Toddlers	**Children**	**Adolescents**	**Adults**	**The elderly**	**Very elderly**
	(12–35 months)	**(3–9 years)**	**(10–17 years)**	**(18–64 years)**	**(65–74 years)**	**(> 75 years)**
Mean	0–1.0	0–0.5	0–0.6	0–0.4	0–0.1	0
95th percentile	–[(b)]	0–2.2	0–2.3	0–1.7	0–0.4	0–0.3

bw: body weight.
(a): Based on the data described in Section 2.4.4.1.a.
(b): The data were insufficient to reliably calculate this figure.

Cola beverages were found to be by far the main contributor to the exposure to caffeine used as a chemically defined flavouring substance (see Appendix D, Table D.1 and Appendix E, Table E.1).

b) From all dietary sources

Daily exposure to caffeine from all sources in food ranged from 0 to 10 mg/kg bw across all population groups (see Table 10, Appendix D, Tables D.1 and D.3).

Table 10: Summary of dietary exposure to caffeine from all sources, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Exposure from all dietary sources (mg/kg bw per day)[(a)]					
	Toddlers	**Children**	**Adolescents**	**Adults**	**The elderly**	**Very elderly**
	(12–35 months)	**(3–9 years)**	**(10–17 years)**	**(18–64 years)**	**(65–74 years)**	**(> 75 years)**
Mean	0–1.5	0.2–2.0	0.5–1.4	0.5–4.3	0.3–4.9	0.3–6.0
95th percentile	0.1–3.5	1.5–4.5	1.5–4.3	1.6–10	1.5–10	2.3–6.3

bw: body weight.
(a): Based on the data described in Sections 2.4.4.1.a and b.

Table E.1, Appendix E provides an overview of the food sources contributing to daily caffeine exposure for each survey and age group.

The CEF Panel noted that the outcome of the exposure estimate of caffeine from all dietary sources (including sources where caffeine is added as a flavouring substance) is in line with the one estimated by the NDA Panel where only the major dietary sources of caffeine were taken into consideration.

2.4.5.2. Theobromine

a) From dietary sources where theobromine is added as a chemically defined flavouring substance

Daily exposure to theobromine added as a chemically defined flavouring substance in food, excluding systemic exposure from caffeine, ranged from 0 to 0.4 mg/kg bw, across all population groups (see Table 11 and Appendix D, Table D.2). When including systemic exposure to theobromine from internal conversion of caffeine into theobromine, exposure ranged from 0 to 0.5 mg/kg bw per day across all population groups (see Table 11).

Table 11: Summary of dietary exposure to theobromine from use as chemically defined flavouring substance, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Toddlers	Children	Adolescents	Adults	The elderly	Very elderly
	(12–35 months)	(3–9 years)	(10–17 years)	(18–64 years)	(65–74 years)	(> 75 years)
Exposure from flavouring use (excluding systemic exposure from caffeine) (mg/kg bw per day)[a]						
Mean	0–0.1	0–0.1	0–0	0–0	0–0	0–0
95th percentile	0–0.3	0–0.4	0–0.1	0–0.1	0–0.1	0–0.1
Exposure from flavouring use (including systemic exposure from caffeine) (mg/kg bw per day)[b]						
Mean	0–0.2	0–0.1	0–0.1	0–0.1	0–0	0–0
95th percentile	–	0–0.5	0–0.2	0–0.2	0–0.1	0–0.1

bw: body weight.
(a): Based on the data described in Section 2.4.4.2.a.
(b): Based on the data described in Sections 2.4.4.2.a and c.

b) From all dietary sources

Daily exposure to theobromine from all sources in food, excluding systemic exposure from caffeine, ranged from 0.1 to 7.1 mg/kg bw across all population groups (see Table 12, Appendix D, Tables D.2 and D.4). When including systemic exposure to theobromine from internal conversion of caffeine into theobromine, exposure ranged from 0.1 to 7.4 mg/kg bw across all population groups (see Table 12).

Table 12: Summary of dietary exposure to theobromine from all sources, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Toddlers	Children	Adolescents	Adults	The elderly	Very elderly
	(12–35 months)	(3–9 years)	(10–17 years)	(18–64 years)	(65–74 years)	(> 75 years)
Exposure from all sources (excluding systemic exposure from caffeine) (mg/kg bw per day)[a]						
Mean	0.1–2.9	0.5–2.3	0.3–1.5	0.2–0.7	0.1–0.5	0.1–0.6
95th percentile	0.3–4.9	2–7.1	1.4–6.5	0.8–2.6	0.4–1.4	0.6–1.6
Exposure from all sources (including systemic exposure from caffeine) (mg/kg bw per day)[b]						
Mean	0.1–3.1	0.6–2.4	0.4–1.6	0.3–1.1	0.1–0.9	0.2–1.2
95th percentile	0.3–5.1	2.1–7.4	1.5–6.9	1.1–2.9	0.6–2.1	–1.9

bw: body weight.
(a): Based on the data described in Section 2.4.4.2.a and b.
(b): Based on the data described in Section 2.4.4.2.a, b and c.

Table E.2, Appendix E provides an overview of the food sources contributing to daily caffeine intake for each survey and age group.

2.5. Absorption, distribution, metabolism and elimination (Appendix F)

In humans, caffeine is rapidly and completely absorbed after oral intake. It is metabolised by the liver to a complex set of metabolites, including theobromine and theophylline, by cytochromes (CYP) 1A2 and 3A4, as well as xanthine oxidase and *N*-acetyltransferase (Lelo et al., 1986a,b). Approximately 11% of a dose of caffeine is converted to theobromine according to pharmacokinetic studies in six human volunteers who were dosed with equimolar doses of caffeine (270 mg), as well as its mono-demethylated

metabolites theobromine, theophylline and paraxanthine (250 mg). For each of these compounds and each volunteer, the pharmacokinetics based on their plasma levels were determined. The mean fractional conversion of caffeine to paraxanthine, theobromine and theophylline was 80 ± 21%, 10.8 ± 2.4% and 3.7 ± 1.3%, respectively. This is supported by a pharmacokinetically less extensive study in 10 volunteers (Rodopoulos and Norman, 1996).

Caffeine has a short plasma half-life of 4 h (range 3–10 h). The metabolites are readily excreted by the kidney and are not chemically reactive.

For theobromine, the human data are more limited. Also, in this case, uptake is virtually complete, and its metabolism results mainly in the same metabolites as caffeine, which are excreted in urine. The plasma half-life of elimination is somewhat longer and ranges from 7 to 12 h. Also, for theobromine the metabolites are not chemically reactive. A more detailed description of the metabolism is given in Appendix F.

2.6. Genotoxicity data

2.6.1. Caffeine

A large number of studies is published on caffeine and its potential genotoxic (mutagenic and clastogenic) effects alone or in combination with physical and chemical genotoxic agents.

Genotoxicity of caffeine has been evaluated by different international expert groups and Regulatory Agencies such as IARC (1991), OECD (2002) and by FDA (2011). A comprehensive review is also available (D'Ambrosio, 1994).

IARC (1991) reported that caffeine affects photoreactivation, excision repair and post-replication repair (IARC, 1991). The antagonistic effect of caffeine on mutations induced by UV light has been explained on the basis of inhibition of an error-prone, post-replicative and recombination repair process. Caffeine can modulate the effects of various xenobiotics by acting on: (i) cytochrome P450; (ii) cAMP metabolism: (iii) DNA metabolism and repair, chromatin structure and function, (iv) nucleotide pools, (v) cell cycle checkpoints. These observations were confirmed and extended by additional studies (Sarkaria et al., 1999; Asaad et al., 2000; Jirmanova et al., 2005; Bode and Dong, 2007; Gabrielli et al., 2007; Tichý et al., 2011; Hatzi et al., 2015).

In the evaluation by IARC (1991), it was concluded that 'although it has been suggested that caffeine may induce gene mutations in mammals and man, direct evidence *in vivo* is limited and the indirect evidence is largely based on extrapolation from results in lower organisms in which there is no doubt about the mutagenic action of caffeine, and from cultured mammalian cells, in which caffeine is clastogenic at high concentrations'. In the comprehensive review by D'Ambrosio (1994), it was concluded that 'It is difficult to implicate caffeine, even at the highest levels of dietary consumption, as a genotoxin to humans'. In the evaluation of OECD (2002), it is reported that, generally gene mutation assays in bacteria and mammalian cells were negative and that chromosomal aberrations *in vitro* were observed only at high concentrations above the recommended levels (> 10 mM). Most of the *in vivo* studies resulted negative for gene mutation and chromosomal damage except for a few positive results obtained for induction of sister chromatid exchanges (SCE's) whose toxicological relevance was considered questionable. In this report, it is concluded that, 'under exposure relevant conditions there are no indications of genotoxicity of caffeine' (OECD, 2002).

In the present evaluation, only well-documented studies, relevant for risk assessment (from 1965 up to December 2016) have been evaluated, even though not all of them are in compliance with Good Laboratory Practice (GLP) and OECD guidelines.

Caffeine has been shown to be consistently negative for the induction of gene mutation in adequately conducted *Salmonella typhimurium* his⁻ reversion mutation assays (McCann et al., 1975; Dunkel et al., 1985; Mortelmans et al., 1986; Prival et al., 1991) and in mammalian cells *in vitro* (Amacher and Zelljadt, 1984; Clive et al., 1990; Ogawa et al., 2009). Positive results observed in the mouse lymphoma tk$^{-/-}$ mutation assay turned out to be the result of clastogenic events (Clive et al., 1990; Ogawa et al., 2009). Caffeine did not show reactivity with DNA in Syrian hamster embryo cells *in vitro*, as evidenced by the absence of DNA strand breakage and unscheduled DNA synthesis (Casto et al., 1976).

In the *in vitro* chromosomal aberration assay, caffeine proved to be a clastogenic compound although at concentrations close or exceeding 1 mM equal to 195 μg/mL (Kuhlmann et al., 1968; Ishidate et al., 1984; Wakata and Sasaki, 1987). Induction of chromosomal damage (mainly chromatid breaks) appears to be generated during S phase only, as reported by Kuhlmann et al. (1968). The S-dependent

mechanism of induction of chromosomal aberrations has been proved also in different studies performed at 37°C, the physiological temperature of mammalian cell growth (Kihlman, 1955, 1961; Scott and Evans, 1964; Kihlman and Odmark, 1965). When the temperature was lowered, the S-dependent mechanism of chromosomal aberration formation decreased and, at temperatures between 30°C and 15°C, it was replaced by an S-independent mechanism as that observed in plants (Kihlman et al., 1971a, b). These observations indicate that under physiological conditions caffeine may interfere with replicative DNA synthesis in mammalian cells determining marked increases of replication units through activation of new origins of replication (Lehmann, 1972; Tatsumi and Strauss, 1979; Painter, 1980; Schnös and Inman, 1982; Barone and Grice, 1990) and that the observed effects on the origin of DNA replication (replicons) are responsible for the S-dependent production of chromosomal aberrations at concentrations close to or exceeding 1 mM.

In a large number of *in vivo* genotoxicity tests (micronuclei, SCE's, chromosome aberrations aneuploidy, dominant lethal), both at somatic and germ cell levels, caffeine gave negative results, although few positive results were observed in some studies (see also references in D'Ambrosio (1994), IARC (1991), OECD (2002) and by FDA (2011)). Significant induction of SCE's, chromosome aberrations and micronuclei were observed following *in vivo* treatment of Chinese hamsters and mice (Basler et al., 1979; Aeschbacher et al., 1986; Haynes et al., 1996; Choudhury and Palo, 2004). However, these increases were observed only at the highest dose levels and were generally small in quantitative terms. Furthermore, in the study by Choudhury and Palo (2004) where micronuclei and chromosome aberrations were evaluated in bone marrow cells following the same treatment regime, only chromosome aberrations turned out to be significantly increased. Inconsistency between cytogenetic endpoints was also noted. Under these conditions, inhibition of cell cycle checkpoints and DNA repair mechanisms which induce both decrease of DNA repair capacities and apoptosis could explain the clastogenic effect of caffeine observed at high concentrations *in vitro* and *in vivo* by indirect mechanisms with possible threshold.

On this basis, the Panel considered that caffeine is rapidly metabolised in most mammals including human and that only very high doses of 100 mg/kg bw or higher in animal studies (equivalent to about 6,000 mg/person per day) resulted in chromosomal damage. This finding was consistent with negative results (no increase in the frequency of chromosomal damage) observed by Weinstein et al. (1972) in lymphocytes of human volunteers exposed *in vivo* for 4 weeks to 800 mg of caffeine per day (equal to about 13 mg/kg bw); the highest concentrations of caffeine in plasma was 30 μg/mL.

Overall, the Panel considered caffeine not to be of concern for genotoxicity when used as flavouring substance.

2.6.2. Theobromine

Since theobromine is one of the metabolites of caffeine, the Panel considered that the conclusion on caffeine is valid also for theobromine.

2.7. Toxicity data

2.7.1. Caffeine

For the safety assessment of caffeine a very broad human database is available, which eliminates the need for animal data. The (clinical) pharmacology of caffeine has been extensively studied. Its favourable central nervous system (CNS) effects (see e.g. (Fredholm et al., 1999; Fredholm, 2011; Winston et al., 2005) for reviews) are the reason for its wide consumption in e.g. coffee and 'energy drinks'. Major effects are CNS stimulation, diuresis, stimulation of cardiac muscle and relaxation of smooth muscle. Caffeine is registered as a medicine for various indications, including treatment of apnoea in prematurely born babies (EMEA, 2009; EMA 2015).

The main mechanism of action of caffeine is antagonism of the adenosine A_1 and A_2 receptors; at increased dose levels it inhibits phosphodiesterases. Side effects in humans, occurring at higher doses per day (50–250 mg), are mostly related to the pharmacological actions of caffeine. Beaudoin and Graham (2011) discussed the epidemiological evidence of effects of caffeine and coffee on several human health parameters. These authors claim that caffeine intakes are several orders of magnitude above the proposed levels of its intake as a food additive and therefore the use of caffeine for the latter specific purpose does not raise safety concerns (Beaudoin and Graham, 2011).

The safety of caffeine from various dietary sources has been evaluated by the SCF in 1999 and 2003 (see Appendix H) which established a safety threshold of up to 300 mg/day for healthy adults.

The SCF further concluded that: 'For children who do not normally consume much tea or coffee, and who might substitute 'energy' drinks for cola or other soft drinks, consumption of 'energy' drinks might represent an increase in daily caffeine exposure compared with their previous intake. The Committee considered that this could result in transient behavioural changes, such as increased arousal, irritability, nervousness or anxiety. Risk assessment of caffeine in relation to pregnancy is more difficult. While intakes up to 300 mg/day appear to be safe, the question of possible effects on pregnancy and the offspring at regular intakes above 300 mg/day remains open. This suggests that moderation of caffeine intake, from whatever source, is advisable during pregnancy' (SCF, 2003).

The SCF evaluation was supported by the critical assessment of Nawrot et al. (2003), who concluded that below 400 mg/day there are no adverse effects to be expected in the general healthy population; for pregnancy a threshold of 300 mg/person per day was recommended at that time, and for children an exposure less than 2.5 mg/kg per day was advised. A recent review of Heckman et al. (2010) supports this analysis. Schaefer, who also evaluated the use of caffeine and coffee during pregnancy, concluded that no problem is raised for consumption of 'normal amounts of caffeine and theobromine in pregnancy, which correspond to three cups of normal strength coffee with 50–100 mg of caffeine, or equivalent amounts of other caffeine-containing drinks' (Schaefer, 2001).

The EFSA NDA Panel has recently evaluated the safety of caffeine from all dietary sources and came to the following conclusions (EFSA NDA Panel, 2015):

- Caffeine intake from all sources up to 400 mg/day (about 5.7 mg/kg bw per day) does not raise safety concerns for adults in the general population, except pregnant women.
- Caffeine intake from all sources up to 200 mg/day (about 3 mg/kg bw per day) by pregnant or lactating women in the general population does not raise safety concerns for the fetus or breast-fed baby, respectively
- The NDA Panel considered that caffeine intake 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.

In line with the outcome of the NDA Panel, establishing a no concern level for caffeine of 5.7 mg/bw per day for adults except pregnant/lactating women and 3 mg/kg bw per day for children, adolescents, pregnant and lactating women, the CEF Panel decided to apply these caffeine no concern levels as reference levels for the safety evaluation of caffeine when used as a flavouring substance.

2.7.2. Theobromine

The pharmacology of theobromine has been reviewed by Smit (Smit, 2011). Its major pharmacological effects in humans include diuresis, relaxation of the smooth muscle, myocardial stimulation and vasodilatation. Unlike caffeine, theobromine is a very mild stimulant of the CNS, showing a much lower affinity for most adenosine receptors than caffeine (Baggott et al., 2013; Judelson et al., 2013). This might explain why theobromine is often regarded as an inert molecule with respect to its effects on the CNS. Theobromine has been reported to be 2–3 times less active than caffeine as adenosine A_1 receptor antagonist, and at least 10 times less active than caffeine as A_2 receptor antagonist. Overall, the pharmacological effects of caffeine and theobromine overlap, but these substances show differences in relative potency with respect to their effects on e.g. the CNS, the kidneys or the heart (Tarka, 1982).

The safety of theobromine as undesirable substance in animal feed was evaluated by the EFSA CONTAM Panel (EFSA, 2008). The Panel concluded that, although theobromine can affect the health of domestic animals above certain exposures, it is not expected to affect humans who consume the animal products thereof (see Appendix H).

The CONTAM Panel concluded that target organs of theobromine toxicity in rodents are the testes (Sertoli cells) and the thymus. Tarka et al. (1979) conducted a 28-day study on the effects of theobromine incorporated to food in rats, mice and hamsters. Total body and organ weights, as well as limited organ histopathology, were assessed. Rats treated with the lowest dose of theobromine (94 mg/kg bw per day for males and 110 mg/kg bw per day for females), (0.2% in the diet) already showed a lower thymus weight than controls (40% in females and 48% in males). No histopathological changes were observed at that level. At threefold higher exposures (0.6% in the diet), microscopy showed pronounced histopathological changes. This atrophic effect on the thymus appears similar to that observed with caffeine: at 185 mg caffeine/kg bw per day by gavage for 14 days in adult rats a decrease of about 60% in thymus weight resulted. No information on

histopathology is available from that study (Peters and Boyd, 1967). Mice and hamsters were more resistant to theobromine. In mice, testicular toxicity appeared at doses of 1,800 mg/kg bw per day of theobromine (1.2% in the diet) and was accompanied by histopathological changes and high mortality. In the hamster, no such toxicity was observed even at the highest dose, 1,027 mg/kg bw per day (1.0% in the diet). In rats fed theobromine in the diet for 49 days, the no observed adverse effect level (NOAEL) for testicular toxicity was identified at 88 mg/kg bw per day (Tarka et al., 1981). One testis was surgically removed after those 49 days (unilateral orchiectomy), and subsequently, the rats had a recovery period of 49 days (without theobromine in the food). At the 88 mg/kg bw per day initial dose (during the first 49 days), again no damage was observed when the remaining testis was analysed after that recovery period. However, at the two higher initial exposure levels (244 and 334 mg/kg bw per day), pronounced and irreversible toxicity was observed. In rats and rabbits, the NOAEL for delay in skeletal development of the off-spring was 48 and 21 mg/kg bw per day, respectively (Tarka et al., 1986a,b).

The studies on reproduction and developmental toxicity in various animal species have been extensively reviewed by Tarka (2010). Based on an in-depth safety assessment of all available data on cocoa powder and theobromine, Tarka (2010) concluded that the data support a NOAEL for theobromine of about 50 mg/kg bw per day in animals. Similar developmental effects have been described in rodents for caffeine after gavage of caffeine, with a developmental NOAEL of approximately 30 mg/kg per day and a teratological NOAEL of 40–100 mg/kg per day (see Nehlig and Debry, 1994; OECD, 2002; and Brent et al., 2011, for reviews). The CEF Panel noted that the issue of developmental toxicity of caffeine in animals was considered by the NDA Panel (p. 14 of the NDA report). However, the NDA Panel derived the level that does not raise a safety concern for pregnant women (i.e. 200 mg/day) from the available information from epidemiological studies (p. 63–67 and p. 70 of the NDA report). Thus, when setting a reference level for theobromine based on the no concern level derived for caffeine (see below), the CEF Panel implicitly took into account any possible developmental effects of caffeine and theobromine.

Unlike for caffeine, no specific toxicological information on the safety of long-term exposure to theobromine in humans is available.

In a randomised, double-blind, placebo-controlled human intervention study with a within-subjects Williams design, the effects of single oral doses of theobromine (250, 500 and 1,000 mg) on mood, cognitive performance, blood pressure and heart rate were assessed in 84 healthy volunteers using caffeine (200 mg) as positive control and placebo as neutral control (Baggott et al., 2013). The most commonly reported adverse effect was headache, which occurred 13 times, nine of which with the 1,000 mg theobromine dose. The second most commonly reported adverse effect was nausea, which occurred eight times, six of which with the 1,000 mg theobromine dose and two with caffeine. Heart rate decreased after ingestion of placebo or theobromine but the decrease was slightly less in the 500 and 1,000 mg theobromine groups than in the placebo group. The difference with the decrease in the placebo group was small (3.5 or 4.9 beats per minute, respectively). No statistically significant difference was observed in heart rate between placebo and the 250 mg theobromine group. Theobromine had no influence on blood pressure at any of the dose levels studied. For a single oral dose, the level of 250 mg/person could be considered as a NOAEL for theobromine in this study.

Only two human studies were identified in which theobromine was consumed daily for longer periods of time.

In a double-blind, placebo-controlled, cross-over intervention study in healthy volunteers (n = 42), each subject consumed a flavanol-rich cocoa drink naturally containing 106 mg of theobromine, a theobromine-enriched cocoa drink containing 979 mg theobromine and placebo for 3 weeks each, separated by a 2-week wash-out period (Van den Bogaard et al., 2010). The daily single dose was administered on an empty stomach in the morning, 1 h before breakfast. Haemodynamic measurements were taken after an overnight fast at the beginning of each intervention period and after consuming the last test drink at the end of each intervention period. The 106 mg theobromine dose had no effects on blood pressure. The 979 mg dose increased 24-h ambulatory systolic blood pressure (3.2 ± 1.1 mm Hg; mean ± SE; compared to placebo) while lowering central systolic blood pressure (4.3 ± 1.4 mm Hg, also compared to placebo), whereas peripheral systolic blood pressure was unaffected. A significant increase in 24-h ambulatory systolic blood pressure was only observed within the 2 h following the consumption of the test drink. A frequent side effect was laxation, which occurred in 10 out of 42 volunteers at the 979 mg theobromine dose. Two volunteers withdrew at that dose because of nausea (n = 1) and headache (n = 1), which rapidly disappeared upon withdrawal. This study shows that most healthy volunteers can tolerate daily oral doses of theobromine as high as

979 mg (14.0 mg/kg bw) for 3 weeks, although such doses of theobromine have side effects. Daily doses of 106 mg/day (approx. 1.5 mg/kg bw per day) had no such side effects and were well tolerated. The Panel notes, however, that this study does not provide information about the long-term health effects of chronic exposure to theobromine.

Another clinical trial was reported by Neufingerl et al. (2013). In this double-blind, randomised, placebo-controlled, full factorial parallel study, volunteers were assigned, after a 2-week run-in period, to one of four groups (all groups n = 38, 50% females) each consuming daily, for 4 weeks, a 200 mL chocolate-flavoured acidified milk drink containing one of the following: (1) cocoa naturally providing 150 mg theobromine (2.1 mg/kg bw); (2) 850 mg of pure theobromine (12.1 mg/kg bw); (3) cocoa plus added theobromine, with a total theobromine content of 1,000 mg (14.2 mg/kg bw); (4) placebo, containing no cocoa powder or added theobromine. The test drink was consumed in the morning, 1 h before breakfast. Blood lipids, apolipoproteins, blood pressure and heart rate were measured at baseline and at the end of the study. Adverse events were monitored throughout the study period, i.e. were spontaneously reported by the subjects or noted by the investigator during one of the visits in the study centre. Theobromine increased HDL-cholesterol and apolipoprotein A-I, while decreasing apolipoprotein B and LDL-cholesterol. Theobromine had no effect on systolic or diastolic blood pressure or 24-h heart rate, An acute transient increase in heart rate during the first few hours after consumption of the high (added) theobromine doses (groups 2 and 3) was observed. A total of 18, 43, 57, and 10 adverse effects were reported in groups 1, 2, 3 and 4, respectively. The most commonly reported adverse effects were nausea, vomiting, headache, and diarrhoea, and all except one were of mild to moderate intensity and resolved before the end of the study. Adverse events lead to the premature withdrawal of eight subjects, of which six were in group 3, one in group 2 and one in group 4. One volunteer from group 1 left the study because of 'personal reasons'. The Panel notes that doses of 150 mg theobromine/day in cocoa were well tolerated in this study, whereas the number adverse events increased with (added) theobromine at doses of 850 mg/day and were highest with the highest total dose of theobromine (1,000 mg/day from cocoa plus added theobromine). The Panel also notes that, in this study, the intervention lasted 4 weeks only.

In these two clinical trials (Van den Bogaard et al., 2010; Neufingerl et al., 2013), doses of 1.5 and 2.1 mg/kg bw of theobromine were well tolerated when consumed daily in a single dose and in fasting conditions for 3–4 weeks. However, the Panel decided to use these studies as supportive evidence rather than to derive a reference dose for the safety assessment of theobromine because the studies were not designed to assess safety (but rather focus on effects that might reduce the risk of cardiovascular disease), were of short duration, and do not reflect the conditions in which theobromine is likely to be consumed (spread out throughout the day).

Therefore, for the evaluation of the safety of theobromine as a flavouring substance in food, the Panel chose to base its assessment on the data on caffeine. To derive a reference dose for theobromine from the caffeine data, the Panel used the results of pharmacokinetic studies on caffeine and its metabolites (Lelo et al., 1986a,b). In these studies, six human volunteers were dosed with equimolar doses of caffeine (270 mg), as well as its mono-demethylated metabolites theobromine, theophylline and paraxanthine (250 mg). For each of these compounds and each volunteer, the pharmacokinetics based on their plasma levels were determined. The mean fractional conversion of caffeine to paraxanthine, theobromine and theophylline was $80 \pm 21\%$, $10.8 \pm 2.4\%$ and $3.7 \pm 1.3\%$, respectively. This is supported by a pharmacokinetically less extensive study in 10 volunteers (Rodopoulos and Norman, 1996). Consequential to these studies, the Panel decided to use this information for the safety assessment of theobromine (i.e. 11% of the oral intake of caffeine is converted to theobromine within the body) (see Appendix F and Lelo et al., 1986a,b). Caffeine intakes of no safety concern of 5.7 mg/bw per day for adults except pregnant/lactating women and of 3 mg/kg bw per day for children, adolescents, pregnant and lactating women (EFSA NDA Panel, 2015) would hence translate into theobromine exposures of 0.6 mg/kg bw for adults and 0.3 mg/kg bw per day for children and adolescents, respectively, which in fact represent a systemic exposure to theobromine. The Panel considered that these exposure levels of theobromine do not raise a safety concern. Thus, the Panel decided to use them in the current revision of FGE.49.

The Panel considered the following:

- The reference value which is used for the current assessment of theobromine as a chemically defined flavouring substance is based on the systemic exposure to theobromine after caffeine intake. However, it does not take into account the food matrix effects, which may decrease the extent of absorption (see Appendix F).

- In the clinical studies of 3–4-week duration, no adverse effects were reported at the dose of 1.5–2.1 mg/kg bw per day.
- The use of values of 0.6 and 0.3 mg theobromine/kg bw per day implies that all effects which led to the derivation of reference levels of 5.7 and 3 mg/kg bw per day for caffeine, are exclusively due to theobromine, a worst-case assumption for theobromine. However, this is unlikely because caffeine is pharmacologically more active than theobromine, as indicated by differences in receptor affinities.

Based on these considerations, the Panel recognised that the values of 0.6 and 0.3 mg/kg bw per day for theobromine are conservative reference values. While in the clinical studies of 3–4-week duration no adverse effects were reported at dose levels of 1.5–2.1 mg/kg bw per day, the actual 'no adverse effect level' of theobromine for humans is not known, but it is probably higher. Therefore, the values of 0.6 and 0.3 mg/kg bw per day could be used as conservative reference points for the safety evaluation of theobromine when used as flavouring substance. Firm conclusions concerning potential health risks from total dietary exposure to theobromine can therefore not be drawn, however, exceedance of the reference value does not necessarily represent a safety concern.

2.7.3. Carcinogenicity studies

IARC evaluated the carcinogenic properties of caffeine and theobromine in 1991. For caffeine, five studies in rats were available of which two were negative and the other three were found to be inadequate for evaluation; the mouse studies were also inadequate. The available epidemiological data did not show correlation with any tumour. IARC therefore classified caffeine in Group 3: 'not classifiable as to its carcinogenicity to humans' (IARC, 1991).

Many epidemiological investigations on associations between coffee and various cancer sites since then have been published; a meta-analysis from 2011 of these data concludes that there is no association; if anything, the analysis suggests that coffee may reduce the *total* cancer incidence (Yu et al., 2011). The latter is also mechanistically discussed by Beaudoin and Graham (2011). Earlier, IARC had classified 'coffee' as 2B (IARC, 1991), based on a signal for bladder cancer, while caffeine as pure compound was in group 3. The majority of high-quality studies that have subsequently been published, however, do not show consistent evidence that coffee consumption is associated with bladder cancer. Very recently, IARC re-evaluated 'drinking coffee' as to its carcinogenicity. They concluded that 'overall coffee drinking was evaluated as inclassifiable (group 3) as to its carcinogenicity to humans' based on the extensive epidemiological database available as well as on animal studies (IARC, 2016).

IARC classified theobromine in Group 3: 'not classifiable as to its carcinogenicity to humans' because of lack of data (IARC, 1991). The structurally related theophylline was evaluated in an NTP toxicology and carcinogenesis study (NTP, 1998). The complete 2 year carcinogenesis studies in rats and mice at maximum dose levels of 75 mg/kg bw by gavage showed no carcinogenicity of theophylline.

2.8. Safety assessment of caffeine and theobromine added as chemically defined flavouring substances to food

2.8.1. Caffeine [FL-no: 16.016]

For the evaluation of the present FGE, the most recent assessment on caffeine published by the NDA Panel was used. According to the NDA opinion, which refers to the major sources of caffeine, an intake of up to 400 mg/person per day is safe for healthy adults except pregnant and lactating women. For pregnant and lactating women, an intake of 200 mg/day does not raise safety concerns for the fetus and breastfed infant. The NDA Panel concluded that an (acute) intake of 3 mg/kg bw per day may serve as a basis to derive daily caffeine intakes of no concern for children and adolescents (EFSA NDA Panel, 2015).

Based on the maximum permitted use level[6] of 150 mg/kg in non-alcoholic beverages, and normal use levels of 20 mg/kg in dairy products, 20 mg/kg in edible ices and 25 mg/kg in confectionary, exposure could be calculated for various age groups for a large number of food surveys covering various European countries. The mean dietary intakes (ranging from 0 to 1 mg/kg bw per day) and the 95th percentile exposure estimates (ranging from 0 to 2.3 mg/kg bw per day) to caffeine as a chemically defined flavouring substance were below the 3.0 mg/kg bw per day level of no concern applicable to the population aged up to 18 years and the level of 5.7 mg/kg bw per day applicable to the population above 18 years of age (see Table 9).

The CEF Panel therefore concluded that caffeine would not be expected to present a safety concern from its use as flavouring substance at the use levels specified in Table 5 (see 'Level used in the exposure assessment'), as provided by the flavour industry.

The Panel noted that the outcome of the exposure estimate to caffeine from all dietary sources (including sources where caffeine is added as a chemically defined flavouring substance) is in line with the one estimated by the NDA Panel where only the major dietary sources of caffeine were taken into consideration. Cola beverages were found to be by far the main contributor to the exposure to caffeine used as a chemically defined flavouring substance (Flavour Industry, 2010).

2.8.2. Theobromine [FL-no: 16.032]

Like for caffeine, the Panel decided to not evaluate theobromine through the Procedure but to base its assessment on the fact that theobromine is a major metabolite of caffeine. Thus, the information available on the safety of caffeine in the NDA opinion could also be used for the safety assessment of theobromine. Unlike caffeine, having a broad human database of toxicity studies, no specific toxicological information on the safety of long-term theobromine exposure in humans is available. For the evaluation of theobromine, the Panel decided not to focus on the outcome of the animal studies available for this substance, but to base its assessment on the human data on caffeine.

To derive a reference value for the safety assessment of theobromine, the Panel used the results of pharmacokinetic studies on caffeine and its metabolites as described by Lelo et al. (1986a,b), that indicate that approximately 11% of the oral intake of caffeine is converted to theobromine (see Appendix F). Since caffeine intake levels of 5.7 mg/kg bw per day for adults except pregnant/lactating women and 3 mg/kg bw per day for children, adolescents, pregnant and lactating women, respectively, are not expected to be of safety concern (EFSA NDA Panel, 2015); consequently, for theobromine intake levels (in fact: systemic exposure levels) of at least 0.6 mg/kg bw for adults except pregnant/lactating women and 0.3 mg/kg bw per day for children, adolescents, pregnant and lactating women is also not anticipated to be of safety concern. The Panel noted that caffeine and theobromine interact with the same receptors and that, therefore, caffeine might modify the toxicity of theobromine. However, the available data suggest that the 0.6 and 0.3 mg/kg bw per day levels derived for theobromine from caffeine intake are conservative as outlined in Section 2.7.2.

Exposure of volunteers to theobromine for a duration of 3–4 weeks in valid clinical studies also indicate that the above reference values are conservative showing no adverse effects at an oral intake of 1–2 mg/kg bw per day, whereas at the higher dose of 12–15 mg/kg bw per day given as a single dose on an empty stomach, the side effects were mild. Nevertheless, these are short-term reports, mostly related to the beneficial effects of the substance rather than to its safety.

Therefore, the levels of 0.6 mg/kg bw per day for adults except pregnant/lactating women and 0.3 mg/kg bw per day for children, adolescents, pregnant and lactating women were used as reference values for the safety assessment of the flavouring substance theobromine.

Based on the maximum permitted use level[6]/maximum use level notified by industry of 100 mg/kg for non-alcoholic beverages and normal use level of 20 mg/kg for dairy products (see Table 7), the exposure to theobromine could be calculated for various age groups for a large number of food surveys in various European countries. The mean dietary intakes of theobromine as a chemically defined flavouring substance (ranging from 0 to 0.1 mg/kg bw per day) were below the 0.3 mg/kg bw per day level in all age groups and food surveys (see Table 11). The 95th percentile exposure estimates to theobromine as a chemically defined flavouring substance (ranging from 0 to 0.4 mg/kg bw per day) was below the 0.3 mg/kg bw per day level for all age groups except for children from 3 to 10 years old where the 95th percentile exposure estimate rose up to 0.4 mg/kg bw per day.

Also taking into account systemic exposure to theobromine as metabolite of caffeine, mean exposure across all population groups ranged from 0 to 0.2 mg/kg bw per day and 95th percentile exposure estimates ranged from 0 to 0.5 mg/kg bw per day (see Table 11). With the exception of children 3–10 years old (P95 exposure of 0.5 mg/kg bw per day), all exposure levels, resulting from use of caffeine and theobromine as flavouring substance, were below the extrapolated no concern level of 0.3 mg/kg bw per day.

The contribution of exposure to theobromine as chemically defined flavouring substance to the overall exposure to theobromine is negligible.

Considering the conservative nature of the derived reference values for theobromine (0.6 and 0.3 mg/kg bw per day for adults except pregnant/lactating women and children, adolescents pregnant and lactating women, respectively), the 95th percentile exposure estimates in all age groups and

dietary surveys are not considered to be of safety concern. The CEF Panel therefore concluded that theobromine would not be expected to present a safety concern from its use as a chemically defined flavouring substance at the use levels specified in Table 7 (see 'Level used in the exposure assessment'), as provided by the flavour industry.

The results of the evaluation of caffeine and theobromine are summarised in Appendix G, Table G.1.

3.   Conclusions

Following a request from the European Commission, the CEF Panel was asked to deliver scientific advice to the Commission on the implications for human health of chemically defined flavouring substances used in or on foodstuffs in the Member States. In particular, the Panel was requested to evaluate two flavouring substances in the FGE.49Rev1, using the Procedure as referred to in the Commission Regulation (EC) No 1565/2000. These two flavouring substances belong to chemical group 30, Annex I of the Commission Regulation (EC) No 1565/2000 and are both xanthine alkaloids from the priority list: caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032].

For the evaluation of the present FGE, information from the most recent assessment of caffeine, published by the NDA Panel is used. Based on this extensive evaluation, and the fact that theobromine is a metabolite of caffeine, the CEF Panel considered it inappropriate to evaluate caffeine and theobromine through the Procedure and decided to investigate the safety of both substances based on their common metabolic pathways and on the safety threshold values for caffeine (5.7 and 3 mg/kg bw per day for adults except pregnant/lactating women and children/adolescents/pregnant and lactating women, respectively), derived by the EFSA NDA Panel.

Specifications

Specifications including complete purity criteria and identity for the materials of commerce have been provided and considered adequate.

Use and exposure

The two candidate flavouring substances have been reported to occur naturally in foods such as coffee, chocolate, tea and cocoa beans as well as in some other plants such as guarana seeds, mate leaves and yoco bark.

Dietary exposure to caffeine and theobromine from their use as chemically defined flavouring substances was estimated by combining food consumption data available within the EFSA Comprehensive European Food Consumption Database[4] with the MPLs and/or reported use levels submitted to EFSA by the flavour industry.

In this assessment, a brand loyalty model was chosen. In this model, it was assumed that a consumer is exposed on a long-term basis to a specific category of food, containing the flavouring substance of interest at the maximum use/permitted level. For both caffeine and theobromine, it was decided that this category of food will be the one resulting in the highest potential dietary exposure. For the rest of the categories, normal use levels were applied.

Absorption, distribution, metabolism and elimination

In humans, caffeine is rapidly and completely absorbed after oral intake. It is metabolised by the liver to a complex set of metabolites, including theobromine (which comprises 11% of a caffeine dose) and theophylline, by CYP 1A2 and 3A4, as well as xanthine oxidase and N-acetyltransferase. It has a short plasma half-life of 4 h (range 3–10 h). The metabolites are readily excreted by the kidney and are not chemically reactive.

For theobromine, the human data are more limited. Also, in this case, uptake is virtually complete, while its metabolism results mainly in the same metabolites as caffeine, which are excreted in urine. The plasma half-life of elimination is somewhat longer and ranges from 7 to 12 h. Also for theobromine, the metabolites are not chemically reactive.

Genotoxicity

Based on the data available on the genotoxic potential of caffeine [FL-no: 16.016] and considering that theobromine [FL-no: 16.032] is a major metabolite of caffeine, it is concluded that there is no concern for genotoxicity for both candidate substances.

Toxicological basis of safety assessment

Caffeine and theobromine have similar pharmacological profiles. In 2015, the NDA Panel has evaluated the safety of caffeine from all dietary sources and came to the following conclusions (EFSA NDA Panel, 2015):

- Caffeine intake from all sources up to 400 mg/day (5.7 mg/kg bw per day) does not raise safety concerns for adults in the general population, except pregnant and lactating women.
- Caffeine intake from all sources up to 200 mg/day (about 3 mg/kg bw per day) by pregnant or lactating women in the general population does not raise safety concerns for the fetus or breast-fed baby, respectively.
- The NDA Panel concluded that a caffeine intake of no concern derived for acute consumption in adults (3 mg/kg bw per day) may serve as a basis to derive a daily caffeine intake of no concern for children and adolescents.

In line with the outcome of the NDA Panel, the CEF Panel decided to apply these levels of no safety concern, for the evaluation of caffeine when used as a chemically defined flavouring substance.

Unlike caffeine, having a broad database of human toxicity studies, no specific toxicological information on the safety of long-term exposure to theobromine in humans is available. For the evaluation of theobromine, the Panel decided not to focus on the outcome of the animal studies available for this substance, but to base its assessment on the human data on caffeine. To derive a reference dose for theobromine from the caffeine data, the Panel used the results of pharmacokinetic studies on caffeine and its metabolites indicating that approximately 11% of the oral intake of caffeine is converted to theobromine. Based on the no safety concern level of 5.7 mg/kg bw per day for adults except pregnant/lactating women and 3 mg/kg bw per day for children, adolescents, pregnant and lactating women derived by the NDA Panel (EFSA NDA Panel, 2015), a level (in fact: a systemic exposure level) of 0.6 mg/kg bw for adults except pregnant/lactating women and 0.3 mg/kg bw per day for children, adolescents, pregnant and lactating women could be anticipated to be of no safety concern for theobromine.

The Panel considered the following:

- The reference value which was used for the current assessment of theobromine as a chemically defined flavouring substance is based on the systemic exposure to theobromine after caffeine intake. However, it does not take into account the food matrix effects, which may decrease the extent of absorption.
- In the clinical studies of 3–4-week duration, no adverse effects were reported at the dose of 1.5–2.1 mg theobromine/kg bw per day.
- The use of values of 0.6 and 0.3 mg theobromine/kg bw per day implies that all effects which led to the derivation of reference levels of 5.7 and 3 mg/kg bw per day for caffeine, are exclusively due to theobromine, a worst-case assumption for theobromine. However, this is unlikely because caffeine is pharmacologically more active than theobromine, as indicated by differences in receptor affinities.

Based on these considerations, the Panel recognises that the values of 0.6 and 0.3 mg/kg bw per day for theobromine are conservative reference values. While in the clinical studies of 3–4-week duration, no adverse effects were reported at the dose levels of 1.5–2.1 mg/kg bw per day, the 'no adverse effect level' of theobromine for humans is not known but it is probably higher. The Panel noted that the most commonly reported adverse effects were nausea, vomiting, headache, and diarrhoea in doses higher than 500 mg theobromine consumed. Therefore, the values of 0.6 and 0.3 mg/kg bw per day could be used as conservative values for the safety evaluation of theobromine when used as flavouring substance. Firm conclusions concerning potential health risks from total dietary theobromine cannot be made and exceedance of the reference value does not necessarily represent a safety concern.

Safety assessment of caffeine and theobromine when used as chemically defined flavouring substances

Dietary exposure to caffeine could be calculated for various age groups for a large number of food surveys covering various European countries, based on the maximum permitted[6] use level available for the food category resulting in the highest potential dietary exposure (i.e. non-alcoholic beverages) and normal use levels for the rest of the categories (dairy products, edible ices and confectionary). The mean and 95th percentile exposure estimates to caffeine as a chemically defined flavouring substance

were below the 3.0 mg/kg bw per day level of no concern applicable to the population aged up to 18 years and the level of 5.7 mg/kg bw per day applicable to the population above 18 years of age.

The CEF Panel therefore concluded that caffeine would not be expected to present a safety concern from its use as flavouring substance at the use levels specified in Table 5 (see 'Level used in the exposure assessment'), as provided by the flavour industry.[8]

The Panel noted that the outcome of the exposure estimate of caffeine from all dietary sources (including sources where caffeine is added as a flavouring substance) is in line with the one estimated by the NDA Panel where only the major dietary sources of caffeine were taken into consideration. Cola beverages were found to be by far the main contributor to the exposure to caffeine used as a chemically defined flavouring substance.

Dietary exposure to theobromine was calculated for various age groups for a large number of food surveys covering various European countries, based on the maximum permitted[6] use level available for the food category resulting in the highest potential dietary exposure (i.e. non-alcoholic beverages) and normal use levels for the rest of the categories (dairy products). The so obtained mean and 95th percentile exposure estimates were below 0.3 mg/kg bw per day level in all age groups and food surveys except for children from 3 to 10 years old where the 95th percentile intake level was found to be 0.4 mg/kg bw per day.

The combined exposure to theobromine from intake of theobromine as such and from intake of caffeine was also assessed. In this assessment, systemic exposure to theobromine as metabolite of caffeine was added to the intake of theobromine as such to facilitate comparison of the total exposure with a reference value derived for theobromine.

The so obtained mean and 95th percentile exposure estimates were below 0.3 mg/kg bw per day in all age groups and food surveys except for children from 3 to 10 years old where the 95th percentile intake level rose up to 0.5 mg/kg bw per day.

The contribution of theobromine as chemically defined flavouring substance to the overall exposure to theobromine was found to be negligible.

Considering the conservative nature of the derived reference values for theobromine (0.6 and 0.3 mg/kg bw per day for adults and children/adolescents/pregnant and lactating women, respectively), the 95th percentile exposure estimates in all age groups and dietary surveys are not expected to be of safety concern for its use as flavouring. The CEF Panel therefore concluded that theobromine would not be expected to present a safety concern from its use as a chemically defined flavouring substance at the use levels specified in Table 7 (see 'Level used in the exposure assessment'), as provided by the flavour industry.

Conclusion

The Panel concluded that caffeine [FL-no: 16.016] and theobromine [FL-no: 16.032] do not present a safety concern from their use as chemically defined flavouring substances in food, on the basis of levels of intake as estimated from the use levels considered in the exposure assessment.

Documentation provided to EFSA

1) EFFA (European Flavour and Fragrance Association), 2002. Letter from EFFA to Dr. Joern Gry, Danish Veterinary and Food Administration. Dated 31 October 2002. Re.: Second group of questions. FLAVIS/8.26.

2) EFFA (European Flavour and Fragrance Association), 2004. Intake - Collection and collation of usage data for flavouring substances. Letter from Dan Dils, EFFA to Torben Hallas-Møller, EFSA. May 31, 2004.

3) EFFA (European Flavour and Fragrance Association), 2007. E-mail from EFFA to FLAVIS Secretariat, National Food Institute, Technical University of Denmark. Dated 8 February 2007. RE: FLAVIS submissions - use levels for Category 14.2 - Alcoholic beverages. FLAVIS/8.70.

4) Flavour Industry, 2010. Unpublished information submitted by Flavour Industry to EFSA and forwarded to FLAVIS Secretariat. A-49Rev1 [FL-no: 16.016 and 16.032].

5) IOFI (International Organization of the Flavor Industry), 1995. European inquiry on volume of use.

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[8] The maximum use level provided by industry for 14.1 non-alcoholic beverages was 175 mg/kg, which exceeds the MPL of 150 mg/kg; however, assuming that official control would remove non-compliant products from the market, the assessment was based on the MPL and might therefore lead to an underestimate of exposure.

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Abbreviations

7-MX	7-methylxanthine
ADI	acceptable daily intake
AFMU	5-acetylamino-6-formylamino-3-methyluracil
APET	added portions exposure technique
BW	body weight
cAMP	cyclic adenosine monophosphate

CAS	Chemical Abstract Service
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CNS	central nervous system
CoE	Council of Europe
CONTAM	EFSA Panel on Contaminants in the Food Chain
CYP	cytochrome
EFFA	European Flavour and Fragrance Association
FAO	Food and Agriculture Organization of the United Nations
FCS	Food Categorisation System
FEMA	Flavor and Extract Manufacturers Association
FGE	Flavouring Group Evaluation
FLAVIS (FL)	Flavour Information System (database)
GLP	Good Laboratory Practice
HDL	high-density lipoprotein
IARC	International Agency for Research on Cancer
ID	identity
IOFI	International Organization of the Flavour Industry
IR	infrared spectroscopy
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
LDL	low-density lipoprotein
MPL	maximum permitted level
MSDI	Maximised Survey-derived Daily Intake
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NOAEL	no observed adverse effect level
OECD	Organization for Economic Co-operation and Development
SCE	sister chromatid exchange
SCF	Scientific Committee on Food
WHO	World Health Organization

Appendix A – Procedure for the safety evaluation

Although for the evaluation of caffeine and theobromine the conventional Procedure as described in this Appendix has not been used, in various places in the opinion, reference to this Procedure is made. For sake of clarity, this appendix, in which the Procedure is outlined, has been maintained.

The approach for a safety evaluation of chemically defined flavouring substances as referred to in Commission Regulation (EC) No 1565/2000, named the 'Procedure', is shown in schematic form in Figure A.1. The Procedure is based on the Opinion of the Scientific Committee on Food expressed on 2 December 1999 (SCF, 1999), which is derived from the evaluation Procedure developed by the Joint FAO/WHO Expert Committee on Food Additives at its 44th, 46th and 49th meetings (JECFA, 1995, 1996, 1997, 1999).

The Procedure is a stepwise approach that integrates information on intake from current uses, structure–activity relationships, metabolism and, when needed, toxicity. One of the key elements in the Procedure is the subdivision of flavourings into three structural classes (I, II and III) for which thresholds of concern (human exposure thresholds) have been specified. Exposures below these thresholds are not considered to present a safety concern.

Class I contains flavourings that have simple chemical structures and efficient modes of metabolism, which would suggest a low order of oral toxicity. Class II contains flavourings that have structural features that are less innocuous, but are not suggestive of toxicity. Class III comprises flavourings that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity (Cramer et al., 1978). The thresholds of concern for these structural classes of 1,800, 540 or 90 μg/person per day, respectively, are derived from a large database containing data on subchronic and chronic animal studies (JECFA, 1996).

In Step 1 of the Procedure, the flavourings are assigned to one of the structural classes. The further steps address the following questions:

- Can the flavourings be predicted to be metabolised to innocuous products[9] (Step 2)?
- Do their exposures exceed the threshold of concern for the structural class (Steps A3 and B3)?
- Are the flavourings or their metabolites endogenous[10] (Step A4)?
- Does a NOAEL exist on the flavourings or on structurally related substances (Steps A5 and B4)?

In addition to the data provided for the flavouring substances to be evaluated (candidate substances), toxicological background information available for compounds structurally related to the candidate substances is considered (supporting substances), in order to assure that these data are consistent with the results obtained after application of the Procedure.

The Procedure is not to be applied to flavourings with existing unresolved problems of toxicity. Therefore, the right is reserved to use alternative approaches if data on specific flavourings warranted such actions.

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[9] 'Innocuous metabolic products': Products that are known or readily predicted to be harmless to humans at the estimated intakes of the flavouring agent' (JECFA, 1997).

[10] 'Endogenous substances': Intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included (JECFA, 1997).

Step 1.

Decision tree structural class

Step 2.

Can the substance be predicted to be metabolised to innocuous products?

Step A3.

Do the conditions of use result in an intake greater than the threshold of concern for the structural class?

Step A4.

Is the substance or are its metabolites endogenous?

Step A5.

Does a NOAEL exist for the substance which provides an adequate margin of safety under conditions of intended use, or does a NOAEL exist for structurally related substances which is high enough to accommodate any perceived difference in toxicity between the substance and the related substances?

Step B3.

Do the conditions of use result in an intake greater than the threshold of concern for the structural class?

Step B4.

Does a NOAEL exist for the substance which provides an adequate margin of safety under conditions of intended use, or does a NOAEL exist for structurally related substances which is high enough to accommodate any perceived difference in toxicity between the substance and the related substances?

Data must be available on the substance or closely related substances to perform a safety evaluation

Substance would not be expected to be of safety concern

Additional data required

Figure A.1: Procedure for the safety evaluation of chemically defined flavouring substances

Appendix B – Dietary surveys used for the assessment of the intake of caffeine and theobromine

Table B.1: Dietary surveys used for the assessment of the intake of caffeine and theobromine

Country	Survey acronym	Survey period	Survey duration (no of days per subject)	No of subjects						
				Toddlers	Other children	Adolescents (mean age)	Adults	Elderly	Very elderly
Austria	ASNS_Children[b]	2010	3	–	128	237 (15a)	–	–	–
Austria	ASNS_Adults[b]	2010	2	–	–	–	308	67	25
Belgium	Regional Flanders[a]	2002	3	36	625	–	–	–	–
Belgium	Diet National 2004[a]	2004	2	–	–	576 (16a)	1,292	511	704
Bulgaria	NSFIN[a]	2004	1	–	–	162	691	151	200
Bulgaria	NUTRICHILD[a]	2007	2	428	433	–	–	–	–
Cyprus	Childhealth[a]	2003	3	–	–	303 (13a)	–	–	–
Czech Republic	SISP04[a]	2003–2004	2	–	389	298 (13a)	1,666	–	–
Denmark	DANSDA 2005-08[b]	2005–2008	7	–	298	377 (13a)	1,739	274	12
Denmark	IAT 2006 07[b]	2006–2007	7	917	–	–	–	–	–
Estonia	NDS 1997[a]	1997	1	–	–	–	1,866	–	–
Finland	DIPP 2001 2009[b]	2001–2009	3	500	750	–	–	–	–
Finland	NWSSP07 08[b]	2007–2008	4	–	–	306 (13a)	–	–	–
Finland	FINDIET2012[b]	2012	2	–	–	–	1,295	413	–
France	INCA2[a]	2007	7	–	482	973 (14a)	2,276	264	84
Germany	VELS[b]	2001–2002	6	348	293	–	–	–	–
Germany	EsKiMo[b]	2006	3	–	835	393 (11a)	–	–	–
Germany	National Nutrition Survey II[a]	2007	2	–	–	1,011 (16a)	10,419	2006	490
Greece	Regional Crete[a]	2004–2005	3		838	–	–	–	–
Greece	DIET LACTATION GR	2005–2007	3	–	–	–	65	–	–
Hungary	National Repr Surv[a]	2003	3	–	–	–	1,074	206	80

Country	Survey acronym	Survey period	Survey duration (no of days per subject)	Toddlers	Other children	Adolescents (mean age)	Adults	Elderly	Very elderly
Ireland	NANS 2012[b]	2008–2010	4	–	–	–	1,274	149	77
Italy	INRAN SCAI 2005 06[a]	2005–2006	3	36	193	247 (14a)	2,313	290	228
Latvia	EFSA TEST[a]	2008	2		187	453 (14a)	1,271	–	–
Latvia	FC PREGNANTWOMEN 2011[b]	2011	2	–	–		1,002	–	–
Netherlands	VCP kids[a]	2006–2007	3	322	957	–		–	–
Netherlands	VCPBasis AVL2007 2010[b]	2007–2010	2	–	447	1,142 (14a)	2,057	173	
Netherlands	VCP-Elderly[b]	2010–2012	2	–	–	–		289	450
Poland	IZZ FAO 2000[a]	2000	1	79	409	666 (14a)	2,527	329	124
Romania	Dieta Pilot Children[b]	2012	1	–	205	567 (14a)		–	–
Romania	Dieta Pilot Adults[b]	2012	7	–	–	–	1,254	83	45
Slovakia	SK MON 2008[a]	2008	1	–	–	–	2,761	–	–
Slovenia	CRP 2008[a]	2007–2008	1	–	–	–	407	–	–
Spain	enKid[a]	1998–2000	2	17	156	209 (12a)		–	–
Spain	AESAN[a]	1999–2001	3	–	–	–	410	–	–
Spain	NUT INK05[a]	2004–2005	2		399	651 (14a)		–	–
Spain	AESAN FIAB[a]	2009	3			86 (17a)	981	–	–
Sweden	NFA[a]	2003	4		1,473	1018 (12a)		–	–
Sweden	Riksmaten 2010[b]	2010–2011	4				1,430	295	72
United Kingdom	NDNS-Rolling ProgrammeYears1-3[b]	2008–2011	4	185	651	666 (14a)	1,266	166	139
United Kingdom	DNSIYC 2011[b]	2011	4	1,314	–	–	–	–	–

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

Appendix C – Dietary sources and occurrence data

Normal and maximum use levels of the flavouring substances

The flavour industry reports a 'normal use level' and a 'maximum use level' for each one of the food categories in which the candidate substances are used (Table C.2). These food categories are part of the 18 food categories reported in Annex III of Regulation (EC) No 1565/2000 (Table C.1).

According to the flavour industry, the 'normal use' is defined as the average of reported usages and 'maximum use' is defined as the 95th percentile of reported usages (EFFA, 2002). The normal and maximum use levels in different food categories have been extrapolated from figures derived from 12 model flavouring substances (EFFA, 2004).

Table C.1: Food categories according to Commission Regulation (EC) No 1565/2000

Food category	Description
01.0	Dairy products, excluding products of category 02.0
02.0	Fats and oils, and fat emulsions (type water-in-oil)
03.0	Edible ices, including sherbet and sorbet
04.1	Processed fruit
04.2	Processed vegetables (including mushrooms & fungi, roots & tubers, pulses and legumes), and nuts & seeds
05.0	Confectionery
06.0	Cereals and cereal products, including flours & starches from roots & tubers, pulses & legumes, excluding bakery
07.0	Bakery wares
08.0	Meat and meat products, including poultry and game
09.0	Fish and fish products, including molluscs, crustaceans and echinoderms
10.0	Eggs and egg products
11.0	Sweeteners, including honey
12.0	Salts, spices, soups, sauces, salads, protein products, etc.
13.0	Foodstuffs intended for particular nutritional uses
14.1	Non-alcoholic ('soft') beverages, excluding dairy products
14.2	Alcoholic beverages, including alcohol-free and low-alcoholic counterparts
15.0	Ready-to-eat savouries
16.0	Composite foods (e.g. casseroles, meat pies, mincemeat) – foods that could not be placed in categories 01.0–15.0

Table C.2: Normal and maximum use levels (mg/kg) for caffeine and theobromine when added as flavouring substances (Flavour Industry, 2010)

FL-no		Food categories																
	01.0	02.0	03.0	04.1	04.2	05.0	06.0	07.0	08.0	09.0	10.0	11.0	12.0	13.0	14.1	14.2	15.0	16.0
	Normal use levels (mg/kg)																	
16.016	20	–	20	–	–	25	–	–	–	–	–	–	–	–	100	25[a]	–	–
16.032	20	–	–	–	–	–	–	–	–	–	–	–	–	–	75	–	–	–
	Maximum use levels (mg/kg)																	
16.016	70	–	70	–	–	100	–	–	–	–	–	–	–	–	175	100[a]	–	–
16.032	70	–	–	–	–	–	–	–	–	–	–	–	–	–	100	–	–	–

FL-no: FLAVIS number.
(a): EFFA, 2007.

Table C.3: Food categories used in the assessment of caffeine and theobromine when directly added as chemically defined flavouring substances

Food category in Annex III of Reg. (EC) 1565/2000	FoodEx food category	FoodEx refined level	Caffeine	Theobromine
1. Dairy products	Flavoured milk	L3	x	x
3. Edible ices	Ice cream, milk-based	L3	x	
	Ice cream, non-milk-based		x	
5. Confectionary	Non-Chocolate	L3	x	
	Flavoured sugar		x	
14.1 Non-alcoholic Beverages	Cola, caffeinic	L3	x	
	Cola, caffeinic, low calories		x	
	Cola mix		x	
	Cola, decaffeinated		x	
	Cola, decaffeinated, low calories		x	
	Soft drink with bitter principle	L4		x
	Soft drink, mixed flavours			x
14.2 Alcoholic Beverages[a]	Alcoholic	L2	x	
	Mixed drinks		x	

(a): The addition of caffeine in alcoholic beverages consists of unauthorised use and was not taken into account in the estimation of the exposure.

Table C.4: Natural and non-flavour theobromine concentrations (mg/kg or mg/L) in food and beverages, considered in the assessment of theobromine from all sources

Groups	Subgroups	Used in the intake assessment	Kobori et al. (2013)	Risner (2008)	Srdjenovic et al. (2008)	Kaspar (2006)	Lin et al. (1998)	Craig and Nguyen (1984)	De Vries et al. (1981)	Zoumas et al. (1980)	Englis and Miles (1954)
Cocoa powder		22,000[a]	29,210	(18,640–26,321)	–	–	–	20,300	(21,900–28,400)	(14,600–26,600)	(21,500–25,000)
Chocolate	Chocolate bar	1,400[a]	–	–	–	–	–	1,360	–	–	–
	Milk chocolate		–	–	1,004	–	–	1,880	–	(1,350–1,860)	–
	Chocolate snacks		–	–	–	–	–	(700–2,280)	–	–	–
	Cocoa beverage based on cocoa powder[b]	370	–	–	–	–	–	–	–	–	–
	Cocoa beverage based on cocoa–beverage preparation powder	93[c]	–	–	–	–	–	–	–	–	–
	Dark chocolate	5,500[a]	–	–	–	(4,000–7,555)	–	4,410	–	(3,590–6,280)	–
Tea	Black tea	26[d]	–	–	–	–	2,600[e]	–	–	–	–
	Green tea	45[d]	–	–	–	–	4,500[e]	–	–	–	–
	Tea (unspecified)	40[d]	–	–	–	–	4,000[e] (2,800–6,000)	–	–	–	–
Energy drinks		100[f]	–	–	–	–	–	–	–	–	–

(a): Mean value from all available references.
(b): Cocoa beverage products have been prepared or recorded differently in the different dietary surveys. When needed, a correction factor equal to 60 has been applied to transform 'cocoa powder' and 'cocoa mass' into cocoa beverage (assuming that 60 g of cocoa beverage contain 1 g of cocoa powder).
(c): 'Cocoa-beverage preparation powder' was assumed to contain only 25% of the cocoa and, consequently, 25% of theobromine.
(d): Derived from Lin et al. (1998). A correction factor equal to 100 has been applied to transform 'tea leaves' into tea beverage (assuming that 100 g of tea beverage contain 1 g of tea leave).
(e): Concentration in the leave. Green tea: mean value from 28 samples from China and Japan; Black tea: mean value from 37 samples from China and Japan; Tea (unspecified): mean value from China and Japan.
(f): Maximum permitted limit set by Reg. (EC) No 1334/2008. The same occurrence is used for energy drinks. No analytical data on the content of theobromine in energy drinks were identified. Some nutritional facts are available on the labelling of commercially available products but are limited and therefore not representative.
–: No value provided in the respective references.

Appendix D – Daily caffeine and theobromine intake from all dietary sources and by country survey and age class

Table D.1: Daily caffeine intake for all subjects by age class and food group across different dietary surveys from added flavourings and other sources

Age class	Food groups	Mean caffeine intake				95th percentile caffeine intake[a]			
		mg per day		mg/kg bw per day		mg per day		mg/kg bw per day	
		Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Toddlers (12 to < 36 months; 10 surveys)	Cola beverages	0.0	12	0.0	0.8	0.0	0.0	0.0	0.0
	Other flavouring sources	0.0	1.4	0.0	0.1	0.3	4.6	0.0	0.3
	All flavouring sources	**0.0**	**13**	**0.0**	**1.0**	**0.3**	**6.6**	**0.0**	**0.4**
	Chocolate	0.3	18	0.0	1.2	0.5	24	0.1	1.8
	Coffee	0.0	1.9	0.0	0.2	0.0	0.0	0.0	0.0
	Tea	0.0	6.6	0.0	0.5	0.0	43	0.0	3.2
	Total intakes[c]	**0.4**	**20**	**0.0**	**1.5**	**0.9**	**49**	**0.1**	**3.5**
Other children (3 to < 10 years; 18 surveys)	Cola beverages	0.0	8.7	0.0	0.4	0.0	38	0.0	2.1
	Other flavouring sources	0.1	1.7	0.0	0.1	1.0	6.9	0.0	0.4
	All flavouring sources	**0.1**	**9.8**	**0.0**	**0.5**	**1.0**	**40**	**0.0**	**2.2**
	Chocolate	2.1	22	0.1	0.9	6.5	57	0.4	2.7
	Coffee	0.0	10	0.0	0.4	0.0	45	0.0	1.6
	Tea	0.0	32	0.0	1.3	0.0	70	0.0	2.8
	'Energy drinks'	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0
	Total intakes	**3.9**	**47**	**0.2**	**2.0**	**22**	**104**	**1.5**	**4.5**
Adolescents (10 to < 18 years; 17 surveys)	Cola beverages	0.0	37	0.0	0.6	0.0	149	0.0	2.3
	Other flavouring sources	0.1	1.4	0.0	0.0	0.6	5.7	0.0	0.1
	All flavouring sources	**0.1**	**37**	**0.0**	**0.6**	**0.6**	**149**	**0.0**	**2.3**
	Chocolate	2.8	32	0.1	0.6	9.8	130	0.2	2.9
	Coffee	0.5	22	0.0	0.4	0.0	134	0.0	2.1
	Tea	0.0	36	0.0	0.8	0.0	122	0.0	2.4
	'Energy drinks'[d]	0.0	5.7	0.0	0.1	0.0	40	0.0	0.8
	Total intakes	**22**	**79**	**0.5**	**1.4**	**63**	**226**	**1.5**	**4.3**
Adults (18 to < 65 years; 18 surveys)	Cola beverages	0.0	25	0.0	0.4	0.0	112	0.0	1.7
	Other flavouring sources	0.1	0.8	0.0	0.0	0.5	4.0	0.0	0.1
	All flavouring sources	**0.1**	**25**	**0.0**	**0.4**	**0.7**	**112**	**0.0**	**1.7**
	Chocolate	1.9	9.5	0.0	0.1	8.4	50	0.1	0.8
	Coffee	22	281	0.3	3.7	80	737	1.1	9.7
	Tea	0.5	89	0.0	1.2	0.0	247	0.0	3.4
	'Energy drinks'[e]	0.0	4.4	0.0	0.1	0.0	34	0.0	0.4
	Total intakes	**37**	**323**	**0.5**	**4.3**	**110**	**745**	**1.6**	**10**
Elderly (65 to < 75 years; 14 surveys)	Cola beverages	0.0	4.8	0.0	0.1	0.0	32	0.0	0.4
	Other flavouring sources	0.0	1.1	0.0	0.0	0.3	6.0	0.0	0.1
	All flavouring sources	**0.0**	**5.1**	**0.0**	**0.1**	**0.3**	**32**	**0.0**	**0.4**
	Chocolate	1.0	5.0	0.0	0.1	4.2	30	0.1	0.4
	Coffee	19	331	0.3	4.4	94	712	1.4	10
	Tea	1.4	124	0.0	1.7	15	297	0.2	4.0
	'Energy drinks'	0.0	0.7	0.0	0.0	0.0	0.0	0.0	0.0
	Total intakes	**23**	**363**	**0.3**	**4.9**	**96**	**716**	**1.5**	**10**

Age class	Food groups	Mean caffeine intake				95th percentile caffeine intake[a]			
		mg per day		mg/kg bw per day		mg per day		mg/kg bw per day	
		Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Very elderly (≥ 75 years; 12 surveys)	Cola beverages	0.0	2.6	0.0	0.0	0.0	19	0.0	0.3
	Other flavouring sources	0.0	1.0	0.0	0.0	0.3	5.7	0.0	0.1
	All flavouring sources	**0.1**	**2.7**	**0.0**	**0.0**	**0.5**	**19**	**0.0**	**0.3**
	Chocolate	1.5	9.3	0.0	0.1	4.4	37	0.1	0.6
	Coffee	17	383	0.2	5.5	134	417	1.8	5.9
	Tea	0.8	126	0.0	1.8	48	283	0.7	4.2
	'Energy drinks'	0.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total intakes	**22**	**417**	**0.3**	**6.0**	**174**	**456**	**2.3**	**6.3**

bw: body weight.

(a): The 95th percentile estimates obtained from dietary surveys and age classes with less than 60 subjects may not be statistically robust (EFSA, 2011b) and were consequently not considered in this table. As a result of this, for some of the age groups, the intake at the 95th percentile level may be lower than the mean intake (e.g. 'toddlers, all flavourings sources').

(b): Ranges of minimum and maximum of mean and 95th percentiles values across the number of individual surveys indicated for each age class.

(c): 'Total intakes' reflect the minimum and maximum intakes calculated across the individual surveys for all food categories. N.B. Total intakes are not derived by summing the values in each column for each age group.

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

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

Table D.2: Daily theobromine intake for all subjects by age class and food group across different dietary surveys from added flavourings and other sources

Age class	Food groups	Mean theobromine intake				95th percentile theobromine intake[a]			
		mg per day		mg/kg bw per day		mg per day		mg/kg bw per day	
		Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Toddlers (12 to < 36 months; 10 surveys)	**Flavouring sources**	**0.0**	**1.3**	**0.0**	**0.1**	**0.0**	**4.6**	**0.0**	**0.3**
	Chocolate	0.9	43	0.1	2.9	3.3	59	0.3	4.9
	Tea	0.0	1.6	0.0	0.1	0.0	11	0.0	0.8
	'Energy drinks'	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total intakes[c]	**0.9**	**43**	**0.1**	**2.9**	**3.3**	**60**	**0.3**	**4.9**
Other children (3 to < 10 years; 18 surveys)	**Flavouring sources**	**0.0**	**1.6**	**0.0**	**0.1**	**0.0**	**6.7**	**0.0**	**0.4**
	Chocolate	11	57	0.5	2.3	43	177	1.9	7.1
	Tea	0.0	7.7	0.0	0.3	0.0	15	0.0	0.7
	'Energy drinks'	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0
	Total intakes	**11**	**58**	**0.5**	**2.3**	**43**	**182**	**2.0**	**7.1**
Adolescents (10 to < 18 years; 17 surveys)	**Flavouring sources**	**0.0**	**1.3**	**0.0**	**0.0**	**0.0**	**5.7**	**0.0**	**0.1**
	Chocolate	15	77	0.3	1.5	62	294	1.3	6.5
	Tea	0.0	7.9	0.0	0.2	0.0	24	0.0	0.4
	'Energy drinks'[d]	0.0	1.8	0.0	0.0	0.0	13	0.0	0.3
	Total intakes	**19**	**78**	**0.3**	**1.5**	**65**	**294**	**1.4**	**6.5**
Adults (18 to < 65 years; 18 surveys)	**Flavouring sources**	**0.0**	**0.9**	**0.0**	**0.0**	**0.0**	**4.0**	**0.0**	**0.1**
	Chocolate	9.1	41	0.1	0.6	46	165	0.6	2.5
	Tea	0.1	11	0.0	0.1	0.0	34	0.0	0.5
	'Energy drinks'[e]	0.0	1.4	0.0	0.0	0.0	11	0.0	0.1
	Total intakes	**10**	**47**	**0.2**	**0.7**	**57**	**174**	**0.8**	**2.6**

Age class	Food groups	Mean theobromine intake				95th percentile theobromine intake[a]			
		mg per day		mg/kg bw per day		mg per day		mg/kg bw per day	
		Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]	Min[b]	Max[b]
Elderly (65 to < 75 years; 14 surveys)	**Flavourings sources**	**0.0**	**1.4**	**0.0**	**0.0**	**0.0**	**6.0**	**0.0**	**0.1**
	Chocolate	3.6	26	0.1	0.4	26	102	0.3	1.4
	Tea	0.4	15	0.0	0.2	4.3	37	0.0	0.5
	'Energy drinks'	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0
	Total intakes	**4.6**	**33**	**0.1**	**0.5**	**28**	**102**	**0.4**	**1.4**
Very elderly (≥ 75 years; 12 surveys)	**Flavourings sources**	**0.0**	**1.1**	**0.0**	**0.0**	**0.0**	**6.0**	**0.0**	**0.1**
	Chocolate	4.4	38	0.1	0.5	28	87	0.4	1.4
	Tea	0.2	15	0.0	0.2	6.5	34	0.1	0.5
	'Energy drinks'	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0
	Total intakes	**5.8**	**44**	**0.1**	**0.6**	**36**	**103**	**0.6**	**1.6**

bw: body weight.
(a): The 95th percentile estimates obtained from dietary surveys and age classes with less than 60 subjects may not be statistically robust (EFSA, 2011b) and were consequently not considered in this table.
(b): Ranges of minimum and maximum of mean and 95th percentiles values across the number of individual surveys indicated for each age class.
(c): 'Total intakes' reflect the minimum and maximum intakes calculated across the individual surveys for all food categories. N.B. Total intakes are not derived by summing the values in each column for each age group.
(d): Only one study (the Netherlands) with a sufficient number (≥ 60) of subjects who had consumed 'energy drinks' was available to estimate a statistically robust 95th percentile.
(e): Only two studies (the Netherlands and Ireland) with a sufficient number (≥ 60) of subjects who had consumed 'energy drinks', were available to estimate statistically robust 95th percentiles.

Table D.3: Daily caffeine intake from all dietary sources by country survey and age class

Age class	Country	Survey	Number of subjects	Caffeine intake			
				mg per day		mg/kg bw per day	
				Mean	P95[a]	Mean	P95[a]
Toddlers (12 to < 36 months) 10 surveys	Belgium	Regional Flanders	36	20	–	1.5	–
	Bulgaria	NUTRICHILD	428	3.0	17	0.3	1.4
	Denmark	IAT 2006-2007	917	3.7	12	0.3	0.9
	Finland	DIPP 2001-2009	500	0.4	0.9	0.0	0.1
	Germany	VELS	348	6.2	27	0.5	2.2
	Italy	INRAN SCAI 2005-2006	36	3.8	–	0.3	–
	Netherlands	VCP kids	322	10	49	0.7	3.5
	Spain	enKid	17	18	–	1.2	–
	United Kingdom	NDNS-Rolling Programme Years 1-3	185	5.1	31	0.4	2.2
		DNSIYC 2011	1,314	2.1	7.8	0.2	0.7
Other children (3 to < 10 years) 17 surveys	Austria	ASNS_Children	128	19	60	0.6	2.0
	Belgium	Regional Flanders	625	14	50	0.8	3.0
	Bulgaria	NUTRICHILD	433	3.9	22	0.2	1.5
	Czech Republic	SISP04	389	47	94	2.0	4.0
	Denmark	DANSDA 2005-2008	298	19	47	0.7	1.9
	Finland	DIPP 2001-2009	750	11	39	0.6	2.0
	France	INCA2	482	22	66	1.0	3.0
	Germany	EsKiMo	835	18	59	0.7	2.2
		VELS	293	14	47	0.8	2.7

Age class	Country	Survey	Number of subjects	Caffeine intake			
				mg per day		mg/kg bw per day	
				Mean	P95[a]	Mean	P95[a]
	Greece	Regional Crete	838	10	35	0.5	1.7
	Italy	INRAN SCAI 2005-2006	193	27	83	1.1	4.5
	Latvia	EFSA TEST	187	45	98	1.5	3.9
	Netherlands	VCP kids	957	17	62	0.8	3.2
		VCPBasis AVL2007-2010	447	29	104	1.0	3.9
	Spain	enKid	156	23	60	0.9	2.7
		NUT INK05	399	20	54	0.8	2.0
	Sweden	NFA	1,473	13	46	0.5	1.8
	United Kingdom	NDNS-Rolling Programme Years 1-3	651	11	51	0.5	1.9
Adolescents (10 to < 18 years) 16 surveys	Austria	ASNS_Children	237	24	99	0.5	2.2
	Belgium	Diet National 2004	576	79	212	1.3	3.5
	Cyprus	Childhealth	303	38	134	0.7	2.4
	Czech Republic	SISP04	298	50	120	1.1	2.5
	Denmark	DANSDA 2005-2008	377	36	99	0.7	1.8
	Finland	NWSSP07-08	306	55	179	1.0	3.5
	France	INCA2	973	33	104	0.7	2.0
	Germany	National Nutrition Survey II	1,011	63	222	1.0	3.6
		EsKiMo	393	24	73	0.6	2.0
	Italy	INRAN SCAI 2005-2006	247	46	144	0.9	2.5
	Latvia	EFSA TEST	453	69	158	1.4	3.1
	Netherlands	VCP Basis AVL2007-2010	1,142	77	226	1.4	4.3
	Spain	AESAN FIAB	86	43	120	0.7	2.5
		enKid	209	25	63	0.5	1.5
		NUT INK05	651	40	96	0.7	1.8
	Sweden	NFA	1,018	22	72	0.5	1.8
	United Kingdom	NDNS-Rolling Programme Years 1-3	666	42	138	0.8	2.4
Adults (18 to < 65 years) 16 surveys	Austria	ASNS_Adults	308	128	302	1.8	4.5
	Belgium	Diet National 2004	1,292	201	553	2.8	7.6
	Czech Republic	SISP04	1,666	125	270	1.7	3.8
	Denmark	DANSDA 2005-2008	1,739	323	745	4.3	10
	Finland	FINDIET2012	1,295	237	540	3.1	6.9
	France	INCA2	2,276	156	416	2.3	6.4
	Germany	National Nutrition Survey II	10,419	236	538	3.1	7.2
	Hungary	National Repr Surv	1,074	106	268	1.5	3.9
	Ireland	NANS 2012	1,274	151	346	2.0	4.7
	Italy	INRAN SCAI 2005-2006	2,313	140	324	2.1	4.8
	Latvia	EFSA TEST	1,271	150	310	2.0	4.4
	Netherlands	VCP Basis AVL2007-2010	2,057	265	596	3.4	7.8
	Romania	Dieta Pilot Adults	1,254	37	110	0.5	1.6
	Spain	AESAN	410	57	167	0.8	2.6
	Spain	AESAN FIAB	981	69	162	1.1	2.7
	Sweden	Riksmaten 2010	1,430	187	405	2.5	5.7
	United Kingdom	NDNS-Rolling Programme Years 1-3	1,266	142	323	1.9	4.5

Age class	Country	Survey	Number of subjects	Caffeine intake			
				mg per day		mg/kg bw per day	
				Mean	P95[a]	Mean	P95[a]
Elderly (65 to < 75 years) 13 surveys	Austria	ASNS_Adults	67	125	242	1.6	3.5
	Belgium	Diet National 2004	511	217	467	3.0	6.4
	Denmark	DANSDA 2005-2008	274	363	716	4.9	10
	Finland	FINDIET2012	413	215	416	2.8	5.9
	France	INCA2	264	131	309	1.9	4.4
	Germany	National Nutrition Survey II	2,006	233	472	3.0	6.1
	Hungary	National Repr Surv	206	77	179	1.0	2.3
	Ireland	NANS 2012	149	168	349	2.3	5.1
	Italy	INRAN SCAI 2005-2006	290	123	322	1.7	4.6
	Netherlands	VCPBasis AVL2007-2010	173	282	548	3.7	7.6
	Netherlands	VCP-Elderly	289	267	470	3.5	6.1
	Romania	Dieta Pilot Adults	83	23	96	0.3	1.5
	Sweden	Riksmaten 2010	295	206	389	2.8	5.1
	United Kingdom	NDNS-Rolling Programme Years 1-3	166	166	378	2.2	5.3
Very elderly (≥ 75 years) 11 surveys	Austria	ASNS_Adults	25	146	–	2.0	–
	Belgium	Diet National 2004	704	197	423	2.8	6.3
	Denmark	DANSDA 2005-08	12	417	–	6.0	–
	France	INCA2	84	108	272	1.6	3.8
	Germany	National Nutrition Survey II	490	197	373	2.7	5.2
	Hungary	National Repr Surv	80	70	174	1.0	2.3
	Ireland	NANS 2012	77	160	292	2.4	5.9
	Italy	INRAN SCAI 2005-2006	228	102	263	1.5	4.2
	Netherlands	VCP-Elderly	450	240	456	3.2	5.9
	Romania	Dieta Pilot Adults	45	22	–	0.3	–
	Sweden	Riksmaten 2010	72	172	268	2.4	4.0
	United Kingdom	NDNS-Rolling Programme Years 1-3	139	152	305	2.2	4.7

bw: body weight.
(a): 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 ('–').

Table D.4: Daily theobromine intake from all dietary sources by country survey and age class

| Age class | Country | Survey | Number of subjects | Theobromine intake | | | |
| | | | | mg per day | | mg/kg bw per day | |
				Mean	P95[a]	Mean	P95[a]
Toddlers (12 to < 36 months) 10 surveys	Belgium	Regional Flanders	36	26	–	1.9	–
	Bulgaria	NUTRICHILD	428	5.3	28	0.4	2.5
	Denmark	IAT 2006-2007	917	16	52	1.2	4.0
	Finland	DIPP 2001-2009	500	0.9	3.3	0.1	0.3
	Germany	VELS	348	18	59	1.4	4.9
	Italy	INRAN SCAI 2005-2006	36	5.7	–	0.5	–
	Netherlands	VCP kids	322	17	60	1.2	4.2
	Spain	enKid	17	43	–	2.9	–
	United Kingdom	NDNS-Rolling Programme Years 1-3	185	5.4	20	0.4	1.6
		DNSIYC 2011	1,314	4.6	17	0.4	1.6
Other children (3 to < 10 years) 17 surveys	Austria	ASNS_Children	128	34	102	1.1	3.5
	Belgium	Regional Flanders	625	20	57	1.1	3.4
	Bulgaria	NUTRICHILD	433	11	60	0.7	3.6
	Czech Republic	SISP04	389	46	122	1.9	5.5
	Denmark	DANSDA 2005-2008	298	47	116	1.8	4.5
	Finland	DIPP 2001-2009	750	23	81	1.2	4.2
	France	INCA2	482	41	121	1.9	5.6
	Germany	EsKiMo	835	44	119	1.6	4.4
		VELS	293	37	110	2.2	6.2
	Greece	Regional Crete	838	20	68	0.9	3.4
	Italy	INRAN SCAI 2005-2006	193	28	112	1.2	5.0
	Latvia	EFSA TEST	187	58	182	2.0	7.0
	Netherlands	VCP kids	957	24	68	1.3	3.5
		VCPBasis AVL2007-2010	447	35	95	1.2	3.5
	Spain	enKid	156	57	165	2.3	7.1
		NUT INK05	399	48	117	1.8	4.5
	Sweden	NFA	1,473	13	55	0.5	2.1
	United Kingdom	NDNS-Rolling Programme Years 1-3	651	12	43	0.5	2.0
Adolescents (10 to < 18 years) 16 surveys	Austria	ASNS_Children	237	20	68	0.5	1.7
	Belgium	Diet National 2004	576	53	174	0.9	2.8
	Cyprus	Childhealth	303	41	127	0.9	2.8
	Czech Republic	SISP04	298	39	119	0.9	3.3
	Denmark	DANSDA 2005-2008	377	58	180	1.2	3.5
	Finland	NWSSP07-08	306	78	294	1.5	6.5
	France	INCA2	973	40	126	0.8	2.7
	Germany	National Nutrition Survey II	1,011	35	143	0.6	2.5
		EsKiMo	393	45	117	1.2	3.2
	Italy	INRAN SCAI 2005-2006	247	29	119	0.6	2.3
	Latvia	EFSA TEST	453	64	264	1.3	5.1
	Netherlands	VCP Basis AVL2007-2010	1,142	45	133	0.9	2.8
	Spain	AESAN FIAB	86	48	146	0.8	2.6
		enKid	209	54	164	1.1	3.1
		NUT INK05	651	53	139	1.1	3.2

Age class	Country	Survey	Number of subjects	Theobromine intake			
				mg per day		mg/kg bw per day	
				Mean	P95[a]	Mean	P95[a]
	Sweden	NFA	1,018	19	82	0.5	2.1
	United Kingdom	NDNS-Rolling Programme Years 1-3	666	18	65	0.3	1.4
Adults (18 to < 65 years) 16 surveys	Austria	ASNS_Adults	308	20	75	0.3	1.1
	Belgium	Diet National 2004	1,292	33	129	0.5	2.0
	Czech Republic	SISP04	1,666	18	74	0.3	1.0
	Denmark	DANSDA 2005-2008	1,739	47	141	0.7	2.0
	Finland	FINDIET2012	1,295	22	107	0.3	1.5
	France	INCA2	2,276	23	88	0.3	1.3
	Germany	National Nutrition Survey II	10,419	24	110	0.3	1.5
	Hungary	National Repr Surv	1,074	30	122	0.4	1.7
	Ireland	NANS 2012	1,274	24	71	0.3	1.0
	Italy	INRAN SCAI 2005-2006	2,313	10	57	0.2	0.8
	Latvia	EFSA TEST	1,271	36	174	0.5	2.6
	Netherlands	VCP Basis AVL2007-2010	2,057	33	108	0.4	1.5
	Romania	Dieta Pilot Adults	1,254	14	82	0.2	1.1
	Spain	AESAN	410	30	121	0.4	1.7
	Spain	AESAN FIAB	981	28	137	0.4	2.1
	Sweden	Riksmaten 2010	1,430	17	69	0.2	1.0
	United Kingdom	NDNS-Rolling Programme Years 1-3	1,266	21	64	0.3	0.9
Elderly (65 to < 75 years) 13 surveys	Austria	ASNS_Adults	67	16	70	0.2	0.9
	Belgium	Diet National 2004	511	23	102	0.3	1.4
	Denmark	DANSDA 2005-2008	274	33	100	0.5	1.3
	Finland	FINDIET2012	413	9.8	55	0.1	0.8
	France	INCA2	264	14	61	0.2	1.0
	Germany	National Nutrition Survey II	2,006	16	79	0.2	1.1
	Hungary	National Repr Surv	206	15	73	0.2	0.9
	Ireland	NANS 2012	149	24	73	0.3	1.0
	Italy	INRAN SCAI 2005-2006	290	4.6	28	0.1	0.4
	Netherlands	VCPBasis AVL2007-2010	173	21	73	0.3	1.0
	Netherlands	VCP-Elderly	289	26	79	0.3	1.2
	Romania	Dieta Pilot Adults	83	6.8	49	0.1	0.7
	Sweden	Riksmaten 2010	295	12	57	0.2	0.9
	United Kingdom	NDNS-Rolling Programme Years 1-3	166	24	72	0.3	1.0
Very elderly (≥ 75 years) 11 surveys	Austria	ASNS_Adults	25	23	–	0.3	–
	Belgium	Diet National 2004	704	17	86	0.2	1.2
	Denmark	DANSDA 2005-08	12	44	–	0.6	–
	France	INCA2	84	23	65	0.4	1.1
	Germany	National Nutrition Survey II	490	17	75	0.2	1.1
	Hungary	National Repr Surv	80	19	66	0.3	1.1
	Ireland	NANS 2012	77	22	55	0.3	0.8
	Italy	INRAN SCAI 2005-2006	228	5.8	36	0.1	0.6

Age class	Country	Survey	Number of subjects	Theobromine intake			
				mg per day		mg/kg bw per day	
				Mean	P95[a]	Mean	P95[a]
	Netherlands	VCP-Elderly	450	29	85	0.4	1.1
	Romania	Dieta Pilot Adults	45	11	–	0.1	–
	Sweden	Riksmaten 2010	72	13	67	0.2	0.8
	United Kingdom	NDNS-Rolling Programme Years 1-3	139	28	103	0.4	1.6

bw: body weight.

(a): 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 ('–').

Appendix E – Food sources contributing to daily caffeine and theobromine intake

Table E.1: Food sources contributing to daily caffeine intake

Population group	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Flavoured foods and beverages	Chocolate	Coffee	Energy Drinks[a]	Tea
Toddlers (12 to < 36 months)	Belgium	Regional Flanders	68	22	9.6	0.0	0.0
	Bulgaria	NUTRICHILD	3.1	49	0.0	0.0	48
	Denmark	IAT 2006 07	9.8	60	0.8	0.0	29
	Finland	DIPP 2001 2009	16	78	5.5	0.0	0.0
	Germany	VELS	7.4	80	0.3	0.0	12
	Italy	INRAN SCAI 2005 06	13	36	0.0	0.0	51
	Netherlands	VCP kids	13	19	2.4	0.0	66
	Spain	enKid	0.0	100	0.0	0.0	0.0
	United Kingdom	DNSIYC 2011	2.8	62	0.2	0.3	35
		NDNS-Rolling Programme Years 1-3	11	17	0.1	0.0	73
	Median		10	55	0.3	0.0	32
	Range		(0–68)	(17–100)	(0–10)	(0)	(0–73)
	Austria	ASNS_Children	6.0	44	3.0	1.1	46
Other children (3 to < 10 years)	Belgium	Regional Flanders	65	15	14	0.1	5.5
	Bulgaria	NUTRICHILD	25	69	0.0	0.0	6.1
	Czech Rep.	SISP04	0.6	27	5.3	0.0	67
	Denmark	DANSDA 2005-08	51	34	2.2	0.0	12
	Finland	DIPP 2001 2009	22	71	5.9	0.0	1.2
	France	INCA2	24	63	6.3	0.0	7.5
	Germany	EsKiMo	16	52	1.9	0.5	30
		VELS	7.1	81	0.2	0.0	12
	Greece	Regional Crete	17	78	1.7	0.0	3.4
	Italy	INRAN SCAI 2005 06	12	32	38	0.0	18
	Latvia	EFSA TEST	3.3	19	14	0.0	64
	Netherlands	VCPBasis AVL2007 2010	28	19	2.2	1.1	50
		VCP kids	25	16	2.1	0.0	57
	Spain	NUT INK05	16	82	2.6	0.0	0.3
		enKid	0.6	96	3.3	0.0	0.0
	Sweden	NFA	58	30	1.8	0.5	9.5
	United Kingdom	NDNS-Rolling Programme Years 1-3	36	19	2.0	2.4	41
	Median		19	39	2.4	0.0	12
	Range		(1–65)	(15–96)	(0–38)	(0–2)	(0–67)
	Austria	ASNS_Children	7.3	16	18	7.1	52
Adolescents (10 to < 18 years)	Belgium	Diet National 2004	47	13	21	4.6	15
	Cyprus	Childhealth	0.4	38	53	0.0	9.2
	Czech Rep.	SISP04	0.5	20	14	0.0	65
	Denmark	DANSDA 2005-08	43	21	15	0.0	21
	Finland	NWSSP07 08	19	58	19	3.4	2.0
	France	INCA2	29	35	21	0.0	15
	Germany	EsKiMo	27	39	2.4	0.8	31
		National Nutrition Survey II	23	15	31	0.0	31
	Italy	INRAN SCAI 2005 06	20	19	40	0.6	21

Population group	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Flavoured foods and beverages	Chocolate	Coffee	Energy Drinks[a]	Tea
	Latvia	EFSA TEST	3.6	11	32	0.3	53
	Netherlands	VCPBasis AVL2007 2010	30	11	13	7.4	39
	Spain	AESAN FIAB	21	39	38	0.0	1.0
		NUT INK05	29	49	21	0.0	1.9
		enKid	0.6	87	13	0.0	0.0
	Sweden	NFA	53	27	2.2	1.3	17
	United Kingdom	NDNS-Rolling Programme Years 1-3	41	6.6	9.0	9.2	35
	Median		23	20.8	19	0.3	21
	Range		(0–53)	(7–87)	(2–53)	(0–9)	(0–65)
Adults (18 to ≤ 65 years)	Austria	ASNS_Adults	1.9	1.6	80	0.8	16
	Belgium	Diet National 2004	13	2.7	79	0.7	5.5
	Czech Rep.	SISP04	0.1	2.6	72	0.0	26
	Denmark	DANSDA 2005-08	2.9	2.0	87	0.0	8.1
	Finland	FINDIET2012	1.5	2.0	93	0.6	2.5
	France	INCA2	4.1	3.0	80	0.0	13
	Germany	National Nutrition Survey II	4.4	1.9	83	0.0	11
	Hungary	National Repr Surv	7.2	8.3	56	0.0	29
	Ireland	NANS 2012	5.4	1.3	32	2.9	59
	Italy	INRAN SCAI 2005 06	2.2	1.9	91	0.1	5.0
	Latvia	EFSA TEST	0.9	2.2	75	0.1	22
	Netherlands	VCPBasis AVL2007 2010	8.5	1.7	68	1.3	20
	Romania	Dieta Pilot Adults	4.3	12	82	0.3	2.1
	Spain	AESAN	23	15	39	3.8	19
		AESAN FIAB	12	14	74	0.3	0.7
	Sweden	Riksmaten 2010	4.0	1.0	82	0.3	12
	United Kingdom	NDNS-Rolling Programme Years 1-3	9.2	1.4	33	1.1	55
	Median		4.3	2.0	79	0.3	13
	Range		(0–23)	(1–15)	(32–93)	(0–4)	(1–59)
	Austria	ASNS_Adults	0.1	1.3	77	0.5	21
Elderly (65 to < 75 years)	Belgium	Diet National 2004	1.6	1.6	92	0.2	4.1
	Denmark	DANSDA 2005-08	0.6	1.4	91	0.0	7.0
	Finland	FINDIET2012	0.2	1.0	97	0.0	1.7
	France	INCA2	0.7	1.5	79	0.0	19
	Germany	National Nutrition Survey II	0.7	0.9	86	0.0	13
	Hungary	National Repr Surv	2.8	5.2	57	0.0	35
	Ireland	NANS 2012	1.2	1.6	23	0.0	74
	Italy	INRAN SCAI 2005 06	0.4	0.8	92	0.0	6.6
	Netherlands	VCP-Elderly	1.1	1.1	73	0.0	25
		VCPBasis AVL2007 2010	1.8	0.6	79	0.0	19
	Romania	Dieta Pilot Adults	0.1	10	84	0.0	6.3
	Sweden	Riksmaten 2010	0.6	0.7	88	0.0	11
	United Kingdom	NDNS-Rolling Programme Years 1-3	1.2	1.2	33	0.4	65
	Median		0.7	1.3	81	0.0	16
	Range		(0–3)	(1–10)	(23–97)	(0–1)	(2–74)
	Austria	ASNS_Adults	0.7	1.0	72	0.0	26

Population group	Country	Survey	Food sources contributing to daily caffeine intake (%)				
			Flavoured foods and beverages	Chocolate	Coffee	Energy Drinks[a]	Tea
Very elderly (≥ 75 years)	Belgium	Diet National 2004	1.4	1.1	93	0.0	4.9
	Denmark	DANSDA 2005-08	0.2	2.2	92	0.0	5.9
	France	INCA2	0.6	7.1	81	0.0	11
	Germany	National Nutrition Survey II	0.2	1.3	84	0.0	15
	Hungary	National Repr Surv	1.7	7.2	41	0.0	50
	Ireland	NANS 2012	0.1	1.2	20	0.0	78
	Italy	INRAN SCAI 2005 06	0.4	1.5	88	1.0	9.0
	Netherlands	VCP-Elderly	0.8	1.5	66	0.1	32
	Romania	Dieta Pilot Adults	1.8	18	77	0.0	3.9
	Sweden	Riksmaten 2010	0.1	0.9	88	0.0	12
	United Kingdom	NDNS-RollingProgramme Years 1-3	0.8	3.3	28	0.2	68
	Median		0.6	1.5	79	0.0	13
	Range		(0–2)	(1–18)	(20–93)	(0–1)	(4–78)

(a): For dietary surveys included in the 2010 release, which was based on the FoodEx classification, products coded as 'carbohydrate-rich energy food products for sports people' or 'carbohydrate-electrolyte solutions for sports people' at the 3rd level of FoodEx, within the first level category of 'Products for special nutritional use', were used to calculate caffeine consumption from 'energy drinks' and their contribution to total caffeine intake.

Table E.2: Food sources contributing to daily theobromine intake

Population group	Country	Survey	Food sources contributing to daily theobromine intake (%)				
			Flavoured foods and beverages	Chocolate	Coffee	Energy Drinks[a]	Tea
Toddlers (12 to < 36 months)	Belgium	Regional Flanders	5.1	95	0.0	0.0	0.0
	Bulgaria	NUTRICHILD	0.0	93	0.0	0.0	6.7
	Denmark	IAT 2006 07	1.3	97	0.0	0.0	1.7
	Finland	DIPP 2001 2009	0.0	100	0.0	0.0	0.0
	Germany	VELS	1.2	96	0.0	0.0	2.8
	Italy	INRAN SCAI 2005 06	0.0	93	0.0	0.0	7.1
	Netherlands	VCP kids	3.6	87	0.0	0.0	9.6
	Spain	enKid	0.0	100	0.0	0.0	0.0
	United Kingdom	DNSIYC 2011	0.1	96	0.0	0.0	3.8
		NDNS-Rolling Programme Years 1-3	0.6	91	0.0	0.0	8.7
	Median		0.3	95	0.0	0.0	3.3
	Range		(0–5)	(87–100)	(0)	(0)	(0–10)
	Austria	ASNS_Children	3.8	90	0.0	0.2	6.1
Other children (3 to < 10 years)	Belgium	Regional Flanders	8.0	91	0.0	0.0	1.0
	Bulgaria	NUTRICHILD	0.2	99	0.0	0.0	0.6
	Czech Rep.	SISP04	0.3	83	0.0	0.0	17
	Denmark	DANSDA 2005-08	1.6	97	0.0	0.0	1.2
	Finland	DIPP 2001 2009	0.0	100	0.0	0.0	0.2
	France	INCA2	0.2	99	0.0	0.0	1.0
	Germany	EsKiMo	1.0	96	0.0	0.1	3.0
		VELS	1.4	97	0.0	0.0	1.6
	Greece	Regional Crete	1.3	98	0.0	0.0	0.4
	Italy	INRAN SCAI 2005 06	0.0	97	0.0	0.0	3.3

Population group	Country	Survey	Food sources contributing to daily theobromine intake (%)				
			Flavoured foods and beverages	Chocolate	Coffee	Energy Drinks[a]	Tea
	Latvia	EFSA TEST	0.0	89	0.0	0.0	11
	Netherlands	VCPBasis AVL2007 2010	2.4	90	0.0	0.3	7.8
		VCP kids	3.6	87	0.0	0.0	9.6
	Spain	NUT INK05	0.3	100	0.0	0.0	0.0
		enKid	0.0	100	0.0	0.0	0.0
	Sweden	NFA	6.4	91	0.0	0.2	2.4
	United Kingdom	NDNS-Rolling Programme Years 1-3	1.2	93	0.0	0.7	4.7
	Median		1	96	0	0	2
	Range		(0–8)	(83–100)	(0)	(0–1)	(0–17)
	Austria	ASNS_Children	6.4	77	0.0	2.6	15
Adolescents (10 to < 18 years)	Belgium	Diet National 2004	0.4	92	0.0	2.1	5.0
	Cyprus	Childhealth	0.1	98	0.0	0.0	2.1
	Czech Rep.	SISP04	0.2	79	0.0	0.0	21
	Denmark	DANSDA 2005-08	1.9	95	0.0	0.0	3.3
	Finland	NWSSP07 08	0.0	99	0.0	0.7	0.4
	France	INCA2	0.3	97	0.0	0.0	2.9
	Germany	EsKiMo	1.3	94	0.0	0.1	4.1
		National Nutrition Survey II	0.3	88	0.0	0.0	12
	Italy	INRAN SCAI 2005 06	0.0	94	0.0	0.3	6.1
	Latvia	EFSA TEST	0.1	88	0.0	0.1	12
	Netherlands	VCPBasis AVL2007 2010	1.7	82	0.0	3.9	12
	Spain	AESAN FIAB	0.0	100	0.0	0.0	0.2
		NUT INK05	0.4	99	0.0	0.0	0.3
		enKid	0.1	100	0.0	0.0	0.0
	Sweden	NFA	5.0	90	0.0	0.5	4.5
	United Kingdom	NDNS-Rolling Programme Years 1-3	2.2	81	0.0	6.7	9.8
	Median		0	94	0	0	5
	Range		(0–6)	(77–100)	(0)	(0–7)	(0–21)
	Austria	ASNS_Adults	3.7	71	0.0	1.7	23
Adults (18 to ≤ 65 years)	Belgium	Diet National 2004	2.0	90	0.0	1.3	7
	Czech Rep.	SISP04	0.1	57	0.0	0.0	43
	Denmark	DANSDA 2005-08	1.0	86	0.0	0.0	13
	Finland	FINDIET2012	0.0	90	0.0	1.9	7.9
	France	INCA2	0.4	77	0.0	0.0	22
	Germany	National Nutrition Survey II	0.4	81	0.0	0.0	19
	Hungary	National Repr Surv	2.9	84	0.0	0.0	13
	Ireland	NANS 2012	0.9	47	0.0	5.9	46
	Italy	INRAN SCAI 2005 06	0.0	89	0.0	0.6	10
	Latvia	EFSA TEST	0.0	80	0.0	0.2	20
	Netherlands	VCPBasis AVL2007 2010	2.7	68	0.0	3.2	26
	Romania	Dieta Pilot Adults	0.1	98	0.0	0.2	1.3
	Spain	AESAN	0.4	89	0.0	2.2	8.6
		AESAN FIAB	0.3	99	0.0	0.2	0
	Sweden	Riksmaten 2010	0.8	77	0.0	1.1	21

Population group	Country	Survey	Food sources contributing to daily theobromine intake (%)				
			Flavoured foods and beverages	Chocolate	Coffee	Energy Drinks[a]	Tea
	United Kingdom	NDNS-Rolling Programme Years 1-3	3.1	48	0.0	2.4	47
	Median		0	80	0	1	19
	Range		(0–4)	(47–99)	(0)	(0–6)	(0–47)
	Austria	ASNS_Adults	8.9	57	0.0	1.2	33
Elderly (65 to < 75 years)	Belgium	Diet National 2004	1.4	91	0.0	0.7	7.1
	Denmark	DANSDA 2005-08	1.0	80	0.0	0.0	19
	Finland	FINDIET2012	1.0	88	0.0	0.2	11
	France	INCA2	0.3	58	0.0	0.0	42
	Germany	National Nutrition Survey II	0.4	69	0.0	0.0	31
	Hungary	National Repr Surv	7.7	72	0.0	0.0	21
	Ireland	NANS 2012	0.8	38	0.0	0.0	62
	Italy	INRAN SCAI 2005 06	0.0	78	0.0	0.0	22
	Netherlands	VCP-Elderly	2.0	61	0.0	0.0	37
		VCPBasis AVL2007 2010	4.7	59	0.0	0.0	37
	Romania	Dieta Pilot Adults	0.0	95	0.0	0.0	5.4
	Sweden	Riksmaten 2010	0.2	73	0.0	0.0	27
	United Kingdom	NDNS-Rolling Programme Years 1-3	2.8	37	0.0	0.9	59
	Median		1	70	0	0	29
	Range		(0–9)	(37–95)	(0)	(0–1)	(5–62)
	Austria	ASNS_Adults	0.7	67	0.0	0.0	32
Very elderly (≥ 75 years)	Belgium	Diet National 2004	2.2	89	0.0	0.1	8.7
	Denmark	DANSDA 2005-08	0.2	86	0.0	0.0	13
	France	INCA2	0.1	87	0.0	0.0	13
	Germany	National Nutrition Survey II	2.4	70	0.0	0.0	27
	Hungary	National Repr Surv	5.8	72	0.0	0.0	23
	Ireland	NANS 2012	0.7	31	0.0	0.0	68
	Italy	INRAN SCAI 2005 06	0.0	75	0.0	5.3	20
	Netherlands	VCP-Elderly	2.4	62	0.0	0.3	36
	Romania	Dieta Pilot Adults	0.0	98	0.0	0.0	2.1
	Sweden	Riksmaten 2010	0.2	77	0.0	0.0	23
	United Kingdom	NDNS-RollingProgramme Years 1-3	2.6	51	0.0	0.3	46
	Median		1	73	0	0	23
	Range		(0–6)	(31–98)	(0)	(0–5)	(2–68)

(a): For dietary surveys included in the 2010 release, which was based on the FoodEx classification, products coded as 'carbohydrate-rich energy food products for sports people' or 'carbohydrate-electrolyte solutions for sports people' at the 3rd level of FoodEx, within the first level category of 'Products for special nutritional use', were used to calculate caffeine consumption from 'energy drinks' and their contribution to total caffeine intake.

Appendix F − Absorption, distribution, metabolism and elimination

The pharmacokinetics and metabolism of caffeine and theobromine have been extensively reviewed by Arnaud (Arnaud, 2011).

Caffeine [FL-no: 16.016]

Absorption, distribution and elimination

Caffeine is rapidly and completely absorbed from the intestinal tract after oral intake, without appreciable first pass metabolism (Yesair et al., 1984; Arnaud, 2011). The pharmacokinetics of the substance in humans have been reviewed by Arnaud (Arnaud, 2011) and the following data were taken from that review and a few additional papers.

Peak plasma levels of 3 mg/L (range 2.0–4.0) occurred within 1 h after ingestion of 120 mg caffeine by 13 subjects (Routh et al., 1969); similar results were found by other authors (see Arnaud, 2011). As compared to capsule formulation of caffeine, the plasma peak concentration of caffeine in chocolate or cola showed a somewhat delayed absorption: the plasma peak occurred after 1.5–2 h instead of 30 min.

Caffeine is distributed across total body water and occurs in all body fluids. The unbound volume of distribution is 1.06 L/kg. Autoradiography of radiolabelled caffeine showed that there was no long-term accumulation in any tissue in the rat (Arnaud, 1976). Caffeine was shown to cross the blood–brain barrier in the rat and horse which, given the CNS effects of caffeine in humans, was to be expected. The substance also crosses the placenta to reach the foetus.

Caffeine is efficiently eliminated via the urine. The mean plasma terminal half-life is 4 h in adults (range 3–10 h) (Parsons and Neims, 1978; Lelo et al., 1986a). The mean systemic clearance in humans is of the order of 80 mL/min, mainly by metabolism in the liver. Most of the ingested amount is excreted as metabolites in the urine whereas less than 5% of the oral dose is eliminated unchanged (Callahan et al., 1982; Arnaud, 2011). The half-life of excretion of the metabolites may be more than twice the elimination half-life of caffeine from plasma (Callahan et al., 1982). At higher caffeine intake (70 mg or more), saturation of certain metabolic pathways may occur, leading to reduced clearance (Arnaud, 2011).

Metabolism

The metabolism of caffeine is rather complex and genetic polymorphisms within the human population lead to considerable variation in the metabolite pattern of the substance (Grant et al., 1983; Miners and Birkett, 1996; Arnaud, 2011). It has been extensively studied because of its use as a probe for several biotransformation pathways in humans: a massive body of information (see below) has been accumulated since the seventies of the last century.

Caffeine gives rise to at least 17 metabolites in urine (see Table F.1); (CYP-mediated) demethylation, hydroxylation and acetylation play a major role. It has been used as an *in vivo* probe for hepatic CYP1A2 for screening purposes: CYP1A2 catalyses the demethylation reactions and is responsible for some 90% of the caffeine clearance. In contrast, the C8-hydroxylation (*in vitro*) is almost entirely catalysed by CYP3A4. Also, xanthine oxidase plays a role in the oxidative reactions. The large interindividual variability of CYP1A2 activity in the human population influences the disposition of caffeine (Landi et al., 1999); these variations may be due to factors such as gender, race, genetic polymorphisms, and exposure to inducers (Rasmussen et al., 2002). The molar ratios of metabolites of caffeine used as an index of CYP1A2 activity in populations are distributed according to bimodal or trimodal distributions, and normal or unimodal distributions have also been suggested (Landi et al., 1999). At least two distinct liver CYP enzymes with different substrate affinities have the potential to catalyse caffeine N-demethylations and C8-hydroxylations *in vitro* but at the low concentrations routinely encountered *in vivo*, participation by the high-affinity site is expected to predominate.

Major human metabolites are 1-methylxanthine, 7-methylxanthine (7-MX), 1,7-dimethylxanthine (paraxanthine), 1,7-dimethyluric acid, 1-methyluric acid and 5-acetylamino-6-formylamino-3-methyluracil (AFMU) (see Table F.1). Part of caffeine is metabolised through theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine), which are further metabolised to the major caffeine metabolites.

The mean fractional conversion of caffeine to paraxanthine, theobromine and theophylline was $80 \pm 21\%$, $10.8 \pm 2.4\%$ and $3.7 \pm 1.3\%$, respectively (Lelo et al., 1986b). This was based on

extensive pharmacokinetic studies in six human volunteers. They were dosed sequentially with equimolar doses of caffeine (270 mg), as well as its mono-demethylated metabolites theobromine, theophylline and paraxanthine (250 mg). For each of these compounds and each volunteer, the pharmacokinetics based on their plasma levels were determined (Lelo et al., 1986a). Subsequently, during steady state oral administration of caffeine the partial clearances of each metabolic route in each volunteer were determined based again on plasma pharmacokinetic data. The fractional conversion data are therefore based on the initial demethylation step of caffeine metabolism, and are not influenced by the fact that some further metabolites may be derived from the same precursor (e.g. 7-MX may be derived from both theobromine and paraxanthine). Moreover, eventual deficits in urinary excretion of the metabolites do not play a role. Another study found that paraxanthine accounted for 63 ± 13% of the dimethylxanthines in plasma, theobromine 27 ± 15% and theophylline 10 ± 2.6% (Rodopoulos and Norman, 1996). In this single dose study, plasma concentration and excretion profiles of the major caffeine metabolites were determined and more assumptions were made which, according to the authors, resulted in an overestimation of the formation of theobromine. However, these results can be judged to be supportive of the results of Lelo et al. (1986b) above.

The formation of the acetylated metabolite 5-acetylamino-6-formylamino-3-methyluracil (AFMU) is subject to polymorphism of the *N*-acetyltransferase NAT2 phenotype. CYP 1A2 and 3A4 are also responsible for metabolic polymorphisms within populations (Miners and Birkett, 1996; Arnaud, 2011). This gives rise to a wide range of plasma elimination half-lives (3–10 h) for the metabolites of caffeine. Other factors that affect metabolism are age, gender and hormones, physical exercise, obesity, drugs, disease, smoking, diet and alcohol, as reviewed by Arnaud (2011).

None of the caffeine metabolites is chemically reactive and they are readily excreted in urine.

Table F.1: Urinary excretion of caffeine, theophylline and theobromine metabolites in humans (% of total urinary metabolites) (modified from Arnaud, 2011)

% Urinary metabolites	Substance orally consumed		
	Caffeine	**Theophylline**	**Theobromine**
Caffeine	1		
Theophylline	1	16	
Theobromine	2		20
Paraxanthine (1,7-dimethylxanthine)	6		
5-Acetylamino-6-formylamino-3-methyluracil (AFMU)	16		
1,7-Dimethyluric acid	6		
1,3-Dimethyluric acid	3	47	
3,7-Dimethyluric acid	1		1
1-Methylxanthine	19	1	
6-Amino-5-[*N*-formylmethylamino]-1-methyluracil	2		12
7-Methylxanthine	7		36
3-Methylxanthine	3	14	21
7-Methyluric acid			8
1-Methyluric acid	26	20	
Other (n = 4)	5		

Theobromine [FL-no: 16.032]

Absorption, distribution and elimination

The pharmacokinetics of absorption, metabolism and excretion of theobromine have been reviewed by Arnaud (2011), from which most of the data below are taken. Most of the theobromine dose administered orally to rats or humans is absorbed as indicated by the almost complete recovery in the form of metabolites in urine. Due to matrix interactions, the absorption of theobromine from chocolate is somewhat slower and less complete (80%). Autoradiography of radiolabelled theobromine in rats indicated that there was no accumulation in any organ. In man, theobromine is distributed throughout the total body water (Yesair et al., 1984). It has a volume of distribution comparable to total body water of approx. 0.8 L/kg bw. It crosses the blood–brain barrier, as well as the placenta; the available

data in rat suggest that the brain passage of theobromine is less complete than that of caffeine. Peak plasma concentration is reached after 2–3 h. Its plasma half-life ranges from 7 to 12 h (Arnaud, 2011), somewhat longer than that of caffeine or theophylline. Elimination from plasma was around 0.7–0.9 mL/min per kg bw in human volunteers (Miners et al., 1982; Arnaud, 2011). Some 90% of the dose of theobromine is excreted in urine as metabolites within 48 h.

Metabolism

Theobromine (3,7-dimethylxanthine) gives rise to a number of metabolites in humans, most of which are also found after ingestion of caffeine (see Table F.1) (Arnaud, 2011). Thus, Miners et al. recovered 91% of the 200 mg dose (4 volunteers) in urine, and identified 3-methylxanthine, 7-methylxanthine, 7-methyluric acid and 6-Amino-5-[N-formylmethylamino]-1-methyluracil as major metabolites (Miners et al., 1982). CYP1A2 plays a major role in theobromine metabolism. 3-N-Demethylation predominates (50–60% of metabolism), while 7-N-demethylation (20%) and C-8 oxidation (less than 15%) contribute as well. Polymorphism of CYP1A2 leads to variation in the elimination rate of theobromine metabolites. Much less is known about factors influencing metabolism of theobromine than is the case for caffeine (Arnaud, 2011).

None of the metabolites of theobromine is chemically reactive.

Theophylline

Theophylline is one of the metabolites of caffeine. It is registered as drug used in asthma and chronic obstructive pulmonary disease (COPD) at a dose level of 10–20 mg/kg bw (700,000–1,400,000 µg in a 70-kg person). Side effects at that dose level are gastrointestinal (e.g. nausea and vomiting), CNS (restlessness), cardiac (tachycardia, arrhythmia).

The major metabolites of the supporting substance theophylline are the same as major caffeine and theobromine metabolites: 3-methylxanthine, 1-methyluric acid and 1,3-dimethyluric acid; in addition, in neonates, 7-N-methylation to form caffeine occurs. Dose dependence of pharmacokinetics in male volunteers has been described (Dadashzadeh and Tajerzaden, 2001). The pharmacokinetics of theophylline have been reviewed by Arnaud (Arnaud, 2011).
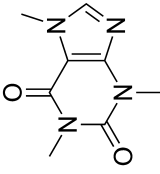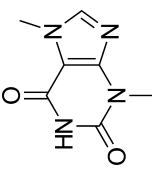
Summary and conclusions

The methylxanthines caffeine and theobromine are rapidly absorbed after oral intake, show little first pass metabolism in gut or liver (Yesair et al., 1984) and are almost completely excreted as such or as metabolites in urine. Their elimination half-life from plasma is of the order of 4–12 h. Both substances are distributed over total body water, cross placenta and blood–brain barrier. A very complex mixture of metabolites is generated in the liver by N-demethylation, 8-hydroxylation and N-acetylation.

Theobromine and theophylline are intermediary metabolites of caffeine, which are further metabolised. Cytochrome P450 1A2 plays a major role in the N-demethylation reactions, while 3A4 catalyses 8-hydroxylation. *N*-acetyltransferases catalyse the formation of acetylated metabolites. Xanthine oxidase also contributes to the formation of the oxidative metabolites of caffeine. Several of these enzymes show polymorphism in the human population, leading to variation in the elimination rate of the caffeine and theobromine and their metabolites. Interaction of methylxanthine metabolites with the food matrix as well as with drugs and other exogenous factors also results in variation in the rates of elimination of these substances.

Overall, it is anticipated that caffeine, theobromine and their identified metabolites are innocuous.

Appendix G – Summary of the safety evaluation

Table G.1: Summary of the safety evaluation for two substances in FGE.49 Revision 1

FL-no	EU register name	Structural formula	MSDI[a] (μg/capita per day)	Class[b] Evaluation procedure path[c]	Outcome on the named compound [d] or [e]	Outcome on the material of commerce [f],[g]or[h]	Evaluation remarks
16.016	Caffeine		380	Class III No evaluation through the Procedure	d	f	The safety evaluation of caffeine was based on the 2015 scientific opinion on the safety of caffeine from the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)
16.032	Theobromine		30	Class III No evaluation through the Procedure	d	f	The safety evaluation of theobromine was based on that of caffeine since it is a caffeine metabolite and has a similar pharmacological profile

FL-no: FLAVIS number; MSDI: Maximised Survey-derived Daily Intake.

(a): EU MSDI: Amount added to food as flavour in (kg/year) × 10E9/(0.1 × population in Europe (= 375 × 10E6) × 0.6 × 365) = μg/capita per day.

(b): Thresholds of concern: Class I = 1,800 μg/person per day, Class II = 540 μg/person per day, Class III = 90 μg/person per day.

(c): Procedure path A substances can be predicted to be metabolised to innocuous products. Procedure path B substances cannot be predicted to be metabolised to innocuous products.

(d): No safety concern based on their estimated levels of intake from their use as flavouring substances.

(e): Data must be available on the substance or closely related substances to perform a safety evaluation.

(f): No safety concern at the estimated level of intake of the material of commerce meeting the specification requirement.

(g): Tentatively regarded as presenting no safety concern (based on intake calculated by the MSDI approach) pending further information on the purity of the material of commerce and/or information on stereoisomerism.

(h): No conclusion can be drawn due to lack of information on the purity of the material of commerce.

Appendix H – Other evaluations/regulation status

SCF Opinion of the Scientific Committee on Food on additional information on 'energy' drinks (SCF, 2003)

The Committee was asked to review additional information submitted on energy drinks and indicate if the conclusions in its opinion of 21 January 1999 needed to be modified.

Conclusion

'Based on the submission of further data and developments in EU, the Committee's earlier Opinion on caffeine remains unchanged.'

In the SCF Opinion from 1999, it was concluded:

'For caffeine, it was concluded that the contribution of 'energy' drinks to overall caffeine intake was not a matter of concern for non-pregnant adults. For children who do not normally consume much tea or coffee, and who might substitute 'energy' drinks for cola or other soft drinks, consumption of 'energy' drinks might represent an increase in daily caffeine exposure compared with their previous intake. The Committee considered that this could result in transient behavioural changes, such as increased arousal, irritability, nervousness or anxiety. For pregnant adults, the Committee concluded that while intakes of caffeine up to 300 mg per day appeared to be safe, the question of possible effects on pregnancy and the offspring at regular intakes above 300 mg per day remained open. This suggested that moderation of caffeine intake, from whatever source, was advisable during pregnancy' (SCF, 2003).

EU Regulation No 1169/2011 of the European Parliament and of the Council on the provision of food information to consumers

Regulation (EU) No 1169/2011 requires that beverages containing more than 150 mg/L (other than those based on coffee or tea) are labelled as 'High caffeine content'. The following text has to be included: 'Not recommended for children or pregnant or breast feeding women'. Also, caffeine content expressed in mg per 100 mL must be declared.

A new requirement is that foods other than beverages where caffeine is added with a physiological purpose must be labelled as follows: 'Contains caffeine. Not recommended for children or pregnant women.' Caffeine content in mg per 100 g or mL must also be declared. In the case of food supplements, the caffeine content shall be expressed per portion as recommended for daily consumption on the labelling.

EFSA Scientific Opinion of the Panel on Contaminants in the Food Chain on 'Theobromine as undesirable substances in animal feed' (EFSA, 2008)

Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed established maximum levels for theobromine in complete feeding stuffs. The Scientific Committee on Animal Nutrition concluded that theobromine is a natural constituent of plants used for feed purposes. Above certain concentrations, they affect the health of domestic animals while they are without effects on the human consumer of products derived thereof. Any risk posed by feed ingredients containing these compounds is according to the Scientific Committee on Animal Nutrition managed by modern techniques of feed formulation. The Scientific Committee on Animal Nutrition therefore recommended that theobromine should be excluded from the list of undesirable substances in annex to Directive 2002/32/EC as it concerns a natural constituent of feed ingredients which is not relevant to the control of contamination.

Conclusion

The Panel on Contaminants in the Food Chain (CONTAM Panel) concluded that theobromine exposure from animal products such as meat, milk and eggs is expected to be negligible in comparison with direct consumption of cocoa products (EFSA, 2008).

EFSA Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies (NDA) on 'the safety of caffeine' (EFSA NDA Panel, 2015)

The safety of caffeine has been recently evaluated by the NDA Panel. According to this assessment referring to all dietary sources of caffeine and not only to its use as a flavouring substance, an intake up to 400 mg/person per day is safe for healthy adults. For pregnant and lactating women, an intake of 200 mg/day does not raise safety concerns for the fetus and breastfed infant, respectively. An (acute) intake of 3 mg/kg bw per day may serve as a basis to derive daily caffeine intakes of no concern for children and adolescents (EFSA NDA Panel, 2015).