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**Opinion  
of the French Agency for Food, Environmental  
and Occupational Health & Safety**

**on the assessment of risks concerning the  
consumption of so-called “energy drinks”**

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*ANSES undertakes independent and pluralistic scientific expert assessments.*

*ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.*

*It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.*

*It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).*

*Its opinions are made public.*

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On 21 August 2012, the French Agency for Food, Environmental and Occupational Health & Safety issued an internal request for an assessment of the risks related to the consumption of so-called energy drinks (scEDs).

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## **1. BACKGROUND AND PURPOSE OF THE REQUEST**

"Energy drink" is a commercial designation and is not defined by any specific regulations. Manufacturers of these beverages present them as having stimulant properties that enhance physical and intellectual performance. These so-called energy drinks contain a mixture of different compounds, most often caffeine, taurine, glucuronolactone and B vitamins, and sugars or sweeteners. They may also contain plant extracts, such as guarana and ginseng. ANSES has examined the safety of scED consumption several times as have food safety agencies in several other countries. These beverages should not be confused with those known as "sports drinks". The nutritional composition of sports drinks is designed for consumption in conjunction with physical exercise and there are specific regulations regarding these beverages<sup>1</sup>.

Here, so-called "energy drinks" will be designated by their abbreviation, scED.

### **1.1. Previous assessments carried out in France**

In 1996, the French High Council for Public Health (CSHPF) issued an unfavourable opinion regarding the marketing of scEDs. Since then, AFSSA assessed studies, provided by applicants, on the safety of taurine and glucuronolactone in scEDs. Because these studies did not demonstrate the safety of these substances for consumption, AFSSA indicated that additional studies were needed to confirm or refute the suspicions of renal failure for glucuronolactone and of undesirable neurobehavioural effects for taurine. Moreover, AFSSA highlighted the fact that the levels of taurine and glucuronolactone contained in scEDs were much higher than those consumed as part of normal dietary intake. AFSSA also asserted that some uses of scEDs, such as during physical activity or when consumed together with alcohol, posed cardiovascular risks during intense exercise and reduced the perception of the effects of alcohol (Afssa, 2001; Afssa, 2003; Afssa, 2006a; Afssa, 2006b).

### **1.2. European and international assessments**

Many expert assessments have been carried out on the international level regarding the safety of scEDs.

#### **1.2.1. Assessments by the European food safety agency (formerly SCF, now EFSA)**

In accordance with the conclusions that AFSSA drew in its opinions on scEDs, the Scientific Committee on Food (SCF) concluded twice (in 1999 and in 2003) that it was impossible to determine whether the levels of taurine and glucuronolactone in scEDs presented any health risks and recommended additional studies to determine the upper safe levels for daily intake of these substances (SCF 1999; SCF 2003).

However, based on the toxicological data provided to the European Food Safety Authority (EFSA) by the applicant, EFSA issued an opinion on 15 January 2009 concluding that the "exposure to taurine and D-glucurono- $\gamma$ -lactone at the levels presently used in "energy drinks" [...] is not of safety concern" (EFSA, 2009).

#### **1.2.2. Other international assessments**

ANSES contacted European and international food safety agencies to identify any expert assessments or early warning signs in various countries regarding scEDs. In its 2010 expert assessment, the National Public Health Institute of Quebec (INSPQ) concluded that the risks posed by scEDs are mainly due to their caffeine content and that excessive consumption and consumption together with alcohol or other drugs may lead to harmful health effects. The INSPQ also drew attention to the risks for sensitive populations, particularly children and adolescents, and raised concern as to the impact of the marketing strategies used to sell these beverages, stressing the need for a stricter regulatory framework for scEDs (INSPQ, 2010). Similarly, in 2008, the German food safety agency (BfR) noted that scEDs were not recommended for children, pregnant and nursing women and people sensitive to the effects of caffeine (including people who suffer from cardiovascular or psychiatric disorders) (BfR, 2008). Several risks related to the co-consumption of

<sup>1</sup> Ministerial order of 20 July 1977 in application of the decree of 24 July 1975 on dietetic and weight-loss products.

caffeine and alcohol were identified by the Italian food safety agency (CNSA) in an opinion issued in 2012, including a masking of the depressive effects of alcohol, alcohol dependence, risk of dehydration, alteration of cardiac rhythm and disturbance of kidney function (CNSA, 2012). In open letters addressed to several beverage manufacturers who market alcoholic beverages with added caffeine, the American Food and Drug Administration (FDA) deemed that the "generally recognised as safe" (GRAS) status of caffeine did not apply when it is added to alcoholic beverages. In 2009, the BfR issued an opinion specifically on energy "shots". It deemed that consumers were not likely to follow the manufacturer's recommendations of only one shot per day and that consumption of large quantities of shots posed risks. Existing labelling was judged insufficient to guard against such behaviour (BfR, 2009). Lastly, in 2013, Lithuania notified the European Commission that it was introducing legislation to define scEDs and banning the sale of scEDs to people under the age of 18, particularly with regard to the increased risk of addiction in this population.

### **1.3. Regulations**

Following the unfavourable opinion issued by the CSHPF in 1996, the marketing of scEDs was prohibited in France. In 2006, the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) requested AFSSA to determine if there were any established health risks that would argue against placing scEDs on the French market. In the absence of any formal demonstration of proven risk, and despite the suspicions raised in AFSSA's opinion of 9 November 2006 (AFSSA, 2006), the marketing of scEDs was authorised in France in 2008 in accordance with the principle of free movement of goods legally manufactured and marketed on the European market.

At the request of the French Ministry of Health, the French Institute for Public Health Surveillance (InVS) set up a monitoring system in 2008 to identify any reports of adverse effects from scEDs. Through its Nutritional Vigilance scheme, launched in 2009, AFSSA (now ANSES) took over this monitoring programme as stipulated in the French Act on Regional Health Governance (Act no. 2009-879) of 21 July 2009.

### **1.4. Purpose of the internal request**

As part of the Nutritional Vigilance scheme, ANSES has compiled the reports of undesirable effects suspected to be related to scED consumption. These products are covered by the Nutritional Vigilance scheme as food having added substances with nutritional or physiological effects as defined by Regulation (EC) no. 1925/2006<sup>2</sup> (commonly designated as "fortified foods"). Several cases were recently reported to ANSES and were included with those already reported as part of the InVS-led monitoring programme of adverse effects potentially related to scEDs (2008), reported through the network of toxicant and poison control centres (CAPTVs).

The purpose of this opinion is to assess the risks related to the consumption of scEDs. The specific goals were to:

- Analyse the reported incidents of adverse effects related to ED consumption according to the method for determining causality developed by ANSES (ANSES, 2011)
- Compare these cases with a literature review of the data on the dangers and risks related to ED consumption;
- Utilise data on consumption;
- Utilise information on the conditions of consumption; and
- Identify vulnerable populations.

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<sup>2</sup> Regulation (EC) no 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods

## **2. ORGANISATION OF THE EXPERT ASSESSMENT**

The expert assessment was carried out according to the French standard NF X 50-110 "Quality criteria for expert assessments – General requirements for undertaking an assessment" (May 2003).

The assessment was carried out by the "Nutritional Vigilance" Working Group (WG) working together with the Expert Committee (CES) on Human nutrition. ANSES assigned 15 rapporteurs to the task. The work was presented to the Nutritional Vigilance WG for discussion of both the methodological and scientific aspects during meetings held between November 2012 and June 2013. They were adopted by the Human Nutrition CES, which met on 30 May and on 28 June 2013.

The analysis of the causality of the cases reported was carried out using a method developed by ANSES (2011) as part of the Nutrition Vigilance scheme. In all, 257 were brought to the attention of ANSES, of which 21 had been directly reported to ANSES and 236 had been reported to CAPTVs and subsequently sent to ANSES. However, these two schemes have different rationales for collecting cases of adverse effects and employ different methods. The toxicant monitoring coordinating committee (CCTV) was thus invited to present the conclusions of its analysis report on the cases recorded by CAPTVs between 2009 and 2012 to the Nutritional Vigilance WG (CCTV, 2013). The report indicated that cases of medium or high severity were consistent with a massive overdose of caffeine (tachycardia, heart rhythm disorders, hypertension, hypokalaemia, convulsions). As for the most severe cases (including cerebral haemorrhage or even death), it did not rule out the possibility that they may have resulted from sudden hypertension, paroxysmal arrhythmia or convulsions, although there was no strong evidence in support of a direct causal link with scED consumption. The report also stressed that there was insufficient proof that caffeine intoxication causes serious complications, particularly due to the lack of information on exposure and because caffeine levels in the plasma were generally not measured during the reported incidents.

Regarding the literature review, the PubMed and Scopus databases were searched using keywords related to energy drinks, the substances that they contain and occasionally specific populations (pregnant women, athletes). Approximately 1500 articles were extracted with this first approach, and about 300 of these were selected for their pertinence to the overall study. This documentation was provided to the experts so that they could carry out a literature analysis and was complemented with other references that the experts had found during their specific searches relative to their research topics.

The review and assessment of consumption and exposure data was based on a survey of scED consumption in France carried out by ANSES's Food Consumption Observatory Unit (UOCA), and data on scED composition and that of common foods were compiled by ANSES's Food Quality Observatory Unit (UOQNA). The results on scED consumption and exposure to the main substances found in scEDs are detailed in the report found in Annex 5.

The purpose of the survey of scED consumption was to characterise the consumers of these beverages, and to determine the quantity consumed and the conditions of consumption. The survey was carried out in 2011 in households that do or do not purchase scEDs<sup>3</sup>. An on-line, self-administered questionnaire was filled out by 1055 individuals of 14 years of age and older. The sample of respondents to this survey was adjusted so as to be representative of the general population<sup>4</sup>. These data will be used in various parts of this opinion to describe the percentages and profiles of scED consumers, as well as the conditions under which these beverages are consumed. The complete report (available in Annex 5) also presents data on the sale and purchase of scEDs,

<sup>3</sup> Neilsen Homescan Consumer Panel

<sup>4</sup> Sample of households adjusted according to socioprofessional category, region, number of members in household, income, age of head of household, and data on individuals adjusted according to age, sex, whether they were a member of an ED purchasing household or not.

which are not given in this opinion (percentage of purchasing households, quantity bought during each purchase, profile of purchasing households according to socioprofessional category, etc.).

European food safety agencies were also contacted to provide insight gained from their surveys and assessments on the safety of scEDs (see §1.2 European and international assessments).

Finally, ANSES consulted several stakeholders as part of this internal request:

- the consumer association CLCV (*Consommation, logement et cadre de vie*);
- the French Society of Sports Nutrition (SFNS);
- representatives of scED manufacturers: the National Refreshment Beverages Association (SNBR) and the Red Bull company;
- the National Public Health Institute of Quebec (INSPQ) which produced a substantial assessment report on scEDs in 2010.

These organisations were invited to answer questions posed by ANSES and divulge any information that would be useful for the risk assessment of scED consumption. The minutes from these consultations are given in Annex 1. They provide the information imparted during these interviews as well as the viewpoints of the stakeholders.

The CLCV consumer association in particular expressed its concern over the new packaging formats of scEDs. Large capacity cans (500 mL compared to the normal 250 mL cans) have appeared on the market and may encourage increased consumption. So-called EDs in “shot” (small-volume) format have also appeared on the market. Compared to classic packaging, “energy shots” have high concentrations of caffeine and facilitate the consumption of multiple units in a single drinking session, thereby leading to high caffeine intake. They also facilitate co-consumption with alcohol, which is a cause for concern at CLCV with regard to some recent publications that highlight the risks of co-consumption.

The CLCV also expressed its concern with respect to the potential toxicity of caffeine, particularly in certain sensitive individuals, in light of diets in which there are many sources of caffeine.

The CLCV also called attention to the fact that scEDs are unsuitable, or even pose potential risks, for use during physical exercise. Furthermore, the CLCV noted that, in their marketing communication efforts, manufacturers increasingly associate scED consumption with physical exercise.

The French Society for Sports Nutrition (SFNS) also raised the issue of scED consumption as a sports drink. As part of its conclusions in regard to the results of a survey of various populations (athletes and non-athletes), the SFNS reported to the Agency that the studied population frequently confounds scEDs with sports drinks. Among the reasons listed for consumption, 58% of the respondents declared that they consume scEDs for their taste and 35% to satisfy their curiosity. Prolonged alertness, excitement or an increase in performance were the reasons that motivated 26%, 22% and 10% of the respondents respectively. Roughly one-third of the respondents felt that scEDs were appropriate for physical exercise and 18% felt that they increased performance.

During its interview, the National Refreshment Beverages Union (SNBR) presented its code of good practices in regard to the recommendations of consumption and recommended labelling for scEDs. In particular, scED labels should include the following information:

- “Consume with moderation.”
- “Not recommended for children and pregnant or nursing women.”

The following communication principles should also be followed:

- No communication or advertising directed to children under 12.
- No distribution of scED samples near primary or early secondary schools (French *collèges*).
- No advertising to promote consumption of these beverages along with alcohol.
- No claims — such as those carried by sports drinks — that scEDs rehydrate the body.

This code was first developed with the Union of European Soft Drinks Associations (validated in 2010), then adopted by the SNBR in France

ANSES was surprised as to the discrepancy between the marketing communication of certain manufacturers, which emphasizes the association with sporting activities, and the principles listed in

this code of good practice. Questioned on this point, the Red Bull company stressed that it did not promote its beverage as a rehydrating beverage for physical exercise.

During the interview with the INSPQ, the conclusions of the 2010 INSPQ report were discussed. The purpose of this report was to provide an overview of the available information on scEDs and the substances they contain. Beyond these aspects, the conclusions of the INSPQ also mention

- the need to monitor scED consumption and its trends;
- the need to better inform healthcare professionals and the general population;
- the need for a stricter regulatory framework for scEDs, particularly with regard to their caffeine content;
- the need for better labelling.

### 3. ANALYSIS AND CONCLUSIONS OF THE NUTRITIONAL VIGILANCE WORKING GROUP

#### 3.1. Composition of scEDs

##### 3.1.1. Identification of scEDs on the French market

Identification of the scEDs on the French market was carried out by the Observatory for the nutritional quality of foods Unit. The data used were taken from the Oqali<sup>5</sup> database (2009-2010 data), and the Global New Products Database (GNPD<sup>6</sup>) on product innovations in France (1997-2012 data) and included information from Kantar Worldpanel on sales volumes by product reference (2009-2010 data). Additional data were collected through eight product sheets provided by manufacturers as part of the National Nutritional Vigilance Scheme.

In the absence of a regulatory definition, the presence of one of the following substances of interest was used to define scEDs: caffeine, taurine, glucuronolactone, guarana extract and ginseng extract. In this way, 120 scEDs available on the French market were identified. These ingredients were chosen to characterise scEDs on the French market either because they are often found in products marketed as energy drinks, or because they are marketed as having energy-enhancing properties, i.e. ginseng or guarana extract.

Vitamins, particularly those in group B, are also often included in scEDs but were not retained to characterise scEDs on the market because their presence is not specific to this type of product. scEDs also contain sugar or sweeteners. Finally, other substances are less systematically found in scEDs, such as maltodextrins, carnitine, creatine or *Ginkgo biloba* extracts.

Of the 120 scEDs identified, only the 103 products that displayed a list of ingredients were taken into account to characterise the composition of scEDs on the market in France. Nutritional composition data were obtained from information indicated on the packaging (Oqali and GNPD data), and from information provided in the eight product sheets forwarded by manufacturers as part of the formal request.

##### 3.1.2. Substances contained in scEDs

###### a. Frequency of substances

Caffeine is the substance that is most frequently found in scEDs. Its presence is indicated in 91 beverages, i.e. 88% of products. Among these, 54 also indicated guarana content. Eight beverages that do not indicate caffeine in their composition contain nonetheless guarana extracts, i.e. 8% of products. Only four products out of 103 do not contain caffeine, on the basis of an absence of caffeine and guarana in the list of ingredients<sup>7</sup>. Overall, 96% of the drinks identified on the French market (99/103) contain caffeine, either synthetic caffeine or guarana.

Taurine and glucuronolactone are found in 52% (n=54) and 33% (n=34) of the identified beverages, respectively.

Vitamins are found in 67% of the identified products, i.e. 69 beverages. Vitamin content is specified for 51 drinks, including 44 that contain group B vitamins, 11 that contain vitamin C, and 2 that contain vitamin E.

Ginseng extracts are found in 20% of the beverages.

<sup>5</sup> French Observatory of Food Quality, Oqali nutrition department responsible for food supply and food characteristics <http://www.oqali.fr/oqali/>

<sup>6</sup> GNPD Global New Products Database [http://www.gnpd.com/sinatra/gnpd/frontpage/?\\_\\_cc=1](http://www.gnpd.com/sinatra/gnpd/frontpage/?__cc=1)

<sup>7</sup> Following investigation, it appears that these four beverages concern brands that have a small market share or are no longer marketed in France.

**b. Co-occurrence of the main substances<sup>8</sup>**

Co-occurrence of caffeine, taurine and glucuronolactone in the 103 scEDs under study was examined and the results are shown in the diagram below (Figure 1).

Of the 103 beverages identified as scEDs that provide a list of ingredients:

- 32% (n=33) contain caffeine, glucuronolactone and taurine;
- 50% (n=52) contain both caffeine and taurine;
- 33% (n=34) contain both taurine and glucuronolactone.

In the studied beverages, glucuronolactone is never present alone but systematically with taurine (n=34/34 beverages containing glucuronolactone) and almost systematically with caffeine (n=33/34). Caffeine is almost systematically included with taurine (n=52/54 beverages containing taurine). Only one beverage contains taurine alone, without caffeine or glucuronolactone.

Finally, caffeine is mainly present in combination with glucuronolactone and/or taurine (n=52/91 beverages containing caffeine), but 39 beverages out of the 91 containing caffeine contain neither taurine nor glucuronolactone.

**3.1.3. Amounts of caffeine, taurine and glucuronolactone in scEDs**

For the 103 scEDs providing a list of ingredients, the specific amounts are not systematically indicated.

- The amount of caffeine is not indicated by 68% of the scEDs containing this substance (n=91);
- The amount of taurine is not indicated by 48% of the scEDs containing this substance (n=54);
- The amount of glucuronolactone is not indicated by 59% of the scEDs containing this substance (n=34).

When data on quantities are available, the minimum, maximum, mean and median contents are as follows (Table 1):

**Table 1: Caffeine, taurine and glucuronolactone content in scEDs when quantities of these substances are indicated**

Substances (mg/100 ml)	Weighted mean based on market share	Minimum content	Maximum content
Caffeine	30	12	32
Taurine	380	250	410
Glucuronolactone	170	24	240

When indicated on the label, caffeine and taurine show small variations in content among the studied scEDs, while glucuronolactone content may vary by a factor of 10, depending on the specific beverages.

For the 54 scEDs containing both guarana extract and added caffeine, several types of wording can be found:

- (1) specific indication of the respective caffeine and guarana extract contents;
- (2) indication of the caffeine content, specifying "including guarana caffeine";
- (3) indication of the caffeine content without specifying the guarana content.

<sup>8</sup> The study of co-occurrences of the main substances in EDs and the presentation of the main constituents (metabolism, pharmacokinetics, effects) concerned caffeine, taurine and glucuronolactone, which are the most frequently found, most specific and best identified substances in EDs. Plant extracts added to EDs, such as guarana and ginseng extracts, contain a large number of other substances that are in no way as clearly identified.

The absence of clear information on whether or not the caffeine content mentioned includes caffeine in guarana form hinders assessment of the caffeine content in scEDs. Only indicated caffeine content was considered, including guarana caffeine, depending on the case (case (2)).

About one hundred scEDs were identified on the market in France. Caffeine was the most frequently found ingredient in scEDs, and was often combined with taurine or glucuronolactone, but not systematically. Caffeine content varies from 12 to 32 mg/100 ml.

### 3.2. Main constituents of scEDs: Description, pharmacology, metabolism and effects<sup>9</sup>

#### 3.2.1. Caffeine

Caffeine (Figure 1) belongs to the methylxanthine family.

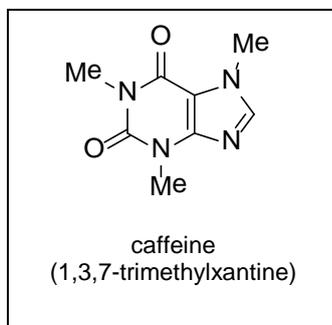


Figure 1 : Chemical structure of caffeine –CAS [58-08-2] *M*: 194.1906 g.mol<sup>-1</sup>

The substance is present naturally in more than 60 plants, including coffee, tea, kola nuts, guarana and yerba mate, among which coffee and tea are the main dietary sources of caffeine. Caffeine can also be produced by chemical synthesis. Once ingested, caffeine is rapidly and completely absorbed in the gastro-intestinal tract. The peak plasma concentration can be reached within 15 minutes to 2 hours after ingestion. Caffeine is rapidly distributed throughout the body, including to the extravascular space. It crosses the blood-brain barrier, the placenta and is excreted in breast milk. In the brain, caffeine mainly acts as a competitive antagonist of adenosine A<sub>1</sub> and A<sub>2A</sub> receptors. Caffeine can thus counteract the sedative effect induced by activation of these receptors by adenosine (Arnaud, 1993; Heckman *et al.*, 2010).

The pharmacokinetics of caffeine is independent of its route of administration, as shown by its high bioavailability following oral intake. The plasma concentration vs time curves following oral and parenteral administration can be superimposed, indicating the absence of a first pass liver effect (Blanchard et Sawers, 1983).

Caffeine (1,3,7-trimethylxanthine) is metabolised in the liver primarily by the cytochrome P450 enzyme system. The 1A2 isoenzyme of cytochrome p450, encoded by the *CYP1A2* gene, is directly involved in demethylation of caffeine to paraxanthine (1,7-dimethylxanthine, 84% of the parent compound), theobromine (3,7-dimethylxanthine, 12%) and theophylline (1,3-dimethylxanthine, 4%). Each of these three metabolites is then in turn metabolised, and excreted in urine (Miners et Birkett, 1996; Heckman *et al.*, 2010).

#### 3.2.2. Taurine

Taurine is an amino acid that is abundant in the body, but it is not used in protein synthesis. In adults, it is synthesized from cysteine particularly in the liver, and is also supplied in the diet through products of animal origin. An increase in the taurine plasma concentration is observed about 90 minutes after consumption of a meal rich in taurine, while the plasma concentration returns to initial values within 3 to 5 hours (Efsa, 2009). Taurine is found in many organs and systems, including the heart, muscle, and central nervous system. It is involved in many physiological functions,

<sup>9</sup> The study of co-occurrences of the main substances in EDs and the presentation of the main constituents (metabolism, pharmacokinetics, effects) concerned caffeine, taurine and glucuronolactone, which are the most frequently found, most specific and best identified substances in EDs. Plant extracts added to EDs, such as guarana and ginseng extracts, contain a large number of other substances that are in no way as clearly identified.

specifically the formation of bile salts required for lipid digestion, the stabilisation of cell membranes, and the regulation of the osmotic cell balance (Stapleton *et al.*, 1997; Lourenco et Camilo, 2002).

### **3.2.3. Glucuronolactone**

D-glucurono- $\gamma$ -lactone is a derivative of glucose metabolism in the liver. At physiological pH, it is in balance with its immediate precursor, glucuronic acid. When ingested by humans, D-glucurono- $\gamma$ -lactone is rapidly absorbed, metabolised and excreted as glucaric acid, xylitol and L-xylulose (Efsa, 2009).

### 3.3. Analysis of adverse events reported as part of the National Nutritional Vigilance Scheme and characterisation of the hazards associated with consumption of scEDs

#### 3.3.1. Overall analysis of the causality of cases according to the nutritional vigilance method

Between the implementation of the National Nutritional Vigilance Scheme in 2009 and June 2012, ANSES received six reports of adverse effects associated with consumption of scEDs. These reports, along with the 24 cases identified in the report of the Toxicant monitoring coordination committee regarding prospective follow-up of adverse effects related to consumption of scEDs, published in May 2009, prompted ANSES to issue a press release on 6 June 2012, inviting healthcare professionals to report cases of intoxication that they may have observed.

Further to this release, 15 new case reports were submitted to ANSES.

In addition to these 21 cases reported directly to ANSES, 236 cases had been collected by poison control centres. These cases were forwarded by the French Institute for Public Health Surveillance (InVS) at the end of July 2012, further to a request from ANSES, to be examined by the nutritional vigilance causality method. In parallel to the analysis by nutritional vigilance, cases collected by the poison control centres between 1 January 2009 and 30 November 2012 were assessed in a report by the Toxicant monitoring coordination committee, which identified among the symptomatic cases associated solely with consumption of scEDs, 54 cases of unlikely causality (I1), 25 cases of possible causality (I2) and 9 cases of probable causality (I3) as per the toxicant monitoring method (CCTV, 2013).

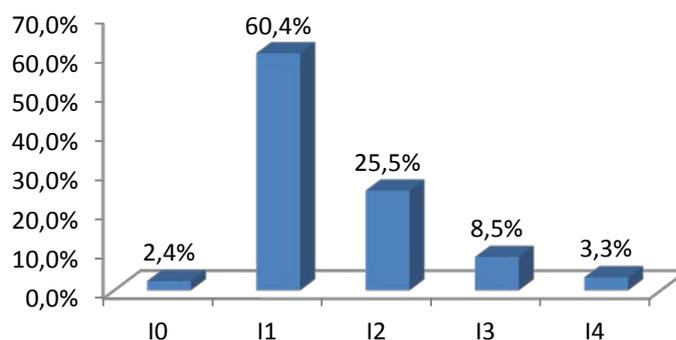
In all, ANSES collected 257 cases for analysis using the method defined in the ANSES opinion of 11 May 2011 regarding development of a causality methodology for adverse effect reports in nutritional vigilance (Anses, 2011). The causality scores were determined on the basis of the conclusions of two rapporteurs and group discussions within the Nutritional vigilance working group. The intrinsic causality score, determined for each case, incorporates a chronological and a semiological score. The chronological score includes information concerning the time of onset, the course of the adverse effect, and re-occurrence if the product was reintroduced. This score is higher if the time of onset is compatible, the course suggestive of an effect, and reintroduction positive. The semiological score is determined after other possible causes for the observed effect have been considered, irrespective of any bibliographic data on the product's effects or those of its ingredients. This score is higher when another cause is unlikely. The qualifiers associated with the scores used in the causality method (I4: very likely; I3: likely; I2: possible; I1: unlikely, I0: ruled out) can only be interpreted in the framework of this method.

Of these cases, 45 were not retained because of the lack of clarity concerning the beverage that was consumed, consumption of products that were found not to be scEDs, consumption of scEDs that had a potential quality flaw (e.g. expiry date exceeded), the absence of an adverse effect, absence of information on the patient (gender, age), a context of intake of multiple substances masking the effects potentially related to the scED (e.g. massive alcohol intake, suicide attempts, etc.) or a context of malicious intent (addition of GHB<sup>10</sup> in a scED).

Of the remaining 212 cases, causality was ruled out in 5 cases (I0: 2.4%), 128 cases were considered to have unlikely causality (I1: 60.4%), 54 possible causality (I2: 25.5%), 18 likely causality (I3: 8.5%) and 7 very likely causality (I4: 3.3%) as per the nutritional vigilance method (Figure 2).

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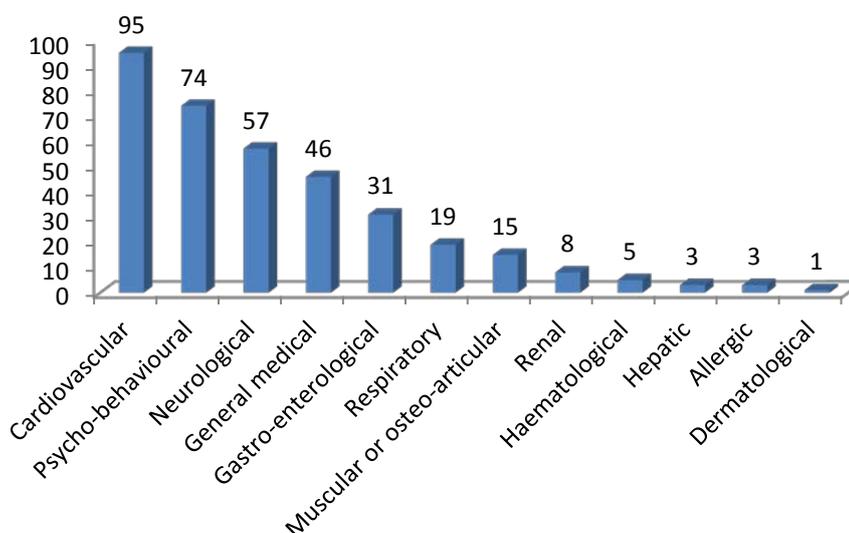
<sup>10</sup> Gamma hydroxybutyric acid



**Figure 2: Distribution of intrinsic causality scores**

I4: very likely causality; I3: likely causality; I2: possible causality;  
I1: unlikely causality; I0: causality ruled out

Most of the reported effects were cardiovascular (95 cases), followed by effects that were psycho-behavioural (74 cases), neurological (57 cases), general medical<sup>11</sup> (46 cases), digestive (31 gastro-intestinal and 3 hepatic cases), respiratory (19 cases), and muscular or osteo-articular (15 cases). Allergic, haematological and renal manifestations were also reported but with lower incidence (< 10 cases). Figure 3 shows the distribution of cases by type of adverse effect. The sum of the indicated cases exceeds the number of retained cases because of the combination of various effects in certain reports (e.g. a case reporting both hypertension and sleeping disorders).



**Figure 3: Distribution of cases by type of adverse effect**

Analysis of causality by type of effect indicates that high-level causality cases (I3 and I4) concern cardiovascular, gastro-enterological, neurological, psycho-behavioural and muscular or osteo-articular effects (Table 2).

<sup>11</sup> Principal symptoms of general medicine observed: headaches, asthenia, shaking, trembling, malaises (without further description), etc.

**Table 2: Analysis of causality by type of adverse effect (in number of cases)**

	Cardiovascular	Psycho-behavioural	Neurological	General medical	Gastro-enterological	Respiratory	Muscular or osteo-articular	Renal	Haematological	Hepatic	Allergic	Dermatological
I0	1	0	3	4	0	1	0	0	0	0	0	0
I1	55	46	34	23	19	13	9	7	0	2	1	1
I2	25	19	13	16	7	4	3	1	2	1	1	0
I3	9	7	7	3	4	1	3	0	3	0	1	0
I4	5	2	0	0	1	0	0	0	0	0	0	0
Total	95	74	57	46	31	19	15	8	5	3	3	1

I4: very likely causality; I3: likely causality; I2: possible causality; I1: unlikely causality; I0: causality ruled out

The proportions of different causality levels for the main types of adverse effects (n > 10) are presented in Table 3.

**Table 3: Percentages of different levels of causality for the main types of adverse effects**

	Cardiovascular	Psycho-behavioural	Neurological	Gastro-enterological	Respiratory	Muscular or osteo-articular	Overall
I0	1.1%	0%	5.3%	0%	0%	0%	2.4%
I1	57.9%	62.2%	59.6%	61.3%	68.4%	60%	60.4%
I2	26.3%	25.7%	22.8%	22.6%	21.1%	20%	25.5%
I3	9.5%	9.5%	12.3%	12.9%	5.3%	20%	8.5%
I4	5.2%	2.7%	0%	3.2%	0%	0%	3.3%

I4: very likely causality; I3: likely causality; I2: possible causality; I1: unlikely causality; I0: causality ruled out

### 3.3.2. Analysis of cases in view of bibliographic data and mechanisms likely to explain the observed adverse effects

#### a. Cardiovascular effects

Cardiovascular manifestations were reported in 95 cases examined by the Agency. Analysis of causality provided the following results:

- very likely for 5 cases;
- likely for 9 cases;
- possible for 25 cases;
- unlikely for 55 cases;
- ruled out for 1 case.

Further analysis involved distinguishing between the various types of cardiac effects observed.

#### i. Cardiac arrest

Eight cases of cardiac arrest were reported to the Agency in relation to consumption of scEDs. Two cases were considered inadmissible due to the lack of information provided. Since the cases were fatal, they were nonetheless evaluated by a cardiologist but were not analysed in terms of causality and no causality score was therefore attributed. For the six other cases, causality related to

consumption of scEDs was considered unlikely in 3 cases, possible for 2 cases, and very likely for the last case (Table 4).

**Table 4: Cases of cardiac arrest with very likely causality (I4) or possible causality (I2)**

Reference	Quantity consumed	Subject	Effects	Identified concomitant intake	Context	I (overall)
2012-021	?	F, 16 years 50 kg	Death	Alcohol	Dance	I4
361678 (= 2012-019)	1 glass of mixed scED and vodka	M, 19 years 70 kg	Death	Alcohol	Dance	I2
2012-211	2-6 cans/day	M, 16 years 75 kg	Cardiac arrest followed by recovery	-	Sport	I2

I4: very likely causality; I3: likely causality; I2: possible causality

NB: the quantity is sometimes indicated in number of cans but it is not possible to expand on this information since the volume of the cans is not given in the report. For information, according to a survey monitoring consumption of scEDs carried out by ANSES (see Annex 5), in 2011, 82% of consumers only drank cans containing 250 ml and 3% only cans containing 500 ml (15% therefore consumed both formats); in addition, 50% of all products (by volume) were sold in the 250 ml containers.

The report for which the causality was considered very likely (2012-021) involved a case of sudden death in a young woman of 16 years of age, occurring immediately after the subject stopped dancing in a night club. Her companions reported consumption of alcohol and scED, but no intake of other substances. The toxicological analysis revealed caffeine (2.4 mg/l) and alcohol (0.86 g/l) in the blood. The autopsy report indicated heart rhythm dysfunction. It also mentioned the presence of amiodarone in the blood (anti-arrhythmic agent probably administered during the attempted resuscitation procedure<sup>12</sup>).

### ***Bibliographic data and possible mechanisms***

- Overview of cardiac function

Cardiac contractions are produced through propagation of action potentials in the membranes of cardiac muscle cells. Muscle cells have a refractory period during which cell membranes cannot undergo repeat depolarisation, ensuring that contraction of cardiac muscle cells is perfectly synchronised, in turn providing appropriate cardiac output.

The action potential (AP) begins with membrane depolarisation resulting from a rapid influx of sodium into the cell (phase 0 of AP). Transient efflux of potassium repolarises the membrane around 0 mV (phase 1 of AP). Calcium influx via the voltage-dependant calcium channels then maintains the plateau of the action potential (phase 2). During phase 2, excitement/contraction coupling occurs, with release of large quantities of intracellular calcium. Repolarising potassium efflux enables the membrane potential to return to values around -80 mV (phase 3 then 4 of AP).

This cascade of events leads to the characteristic form of the cellular action potential whose duration is between 200 and 300 ms. The action potential profile differs depending on the type of cardiac tissue. Ventricular summation of all action potentials can be estimated by measuring the QT<sup>13</sup> interval on the electrocardiogram; this value is usually lower than 450 ms when it is corrected by the duration of the cardiac cycle<sup>14</sup>.

<sup>12</sup> Therapeutic indication for Cordarone (amiodarone) in intravenous administration in the Vidal Drug Compendium 2012: "Cardio-pulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shocks".

<sup>13</sup> Duration measured between the start of the Q-wave and the end of the T-wave on the electrocardiogram

<sup>14</sup> According to Bazett's formula

- Mechanisms underlying arrhythmias

Arrhythmias develop when two anomalies occur in conjunction: abnormal depolarising currents and heterogeneous refractory periods. Heterogeneity of refractory periods of the different types of cells that make up the myocardium tends to maintain and propagate an arrhythmic process once it begins.

*Heterogeneity of refractory periods*

Heterogeneity of refractory periods can be assessed by studying the dispersion of the QT interval on the electrocardiogram (ECG). Prolongation of the interval is caused by prolongation of certain action potentials, reflecting uneven refractory periods between the different cell types (the refractory period corresponds to certain phases of the action potential).

The outward potassium current of phase 3,  $I_{K_s}$ , is made up of two distinct currents:  $I_{K_s}$  and  $I_{K_r}$ . Inhibition of  $I_{K_r}$  current is a major factor in prolongation of the action potential. A number of drugs inhibit  $I_{K_r}$  current.

*Abnormal depolarising currents*

There are two types of anomalies that may occur during repolarisation: EADs (early after-depolarisations) and DADs (delayed after-depolarisations). These after-depolarisations result from inappropriate re-entry of  $Ca^{2+}$  ions in particular, likely to induce a new action potential. They appear to provide the conditions for polymorphic ventricular arrhythmias. If the action potential is prolonged, this can reactivate the inward channels that are likely to result in EADs. During the action potential plateau, significant calcium release occurs within the cell through stimulation of RYR2 ryanodine receptors in the sarcoplasmic reticulum (calcium channels). One of the agonists of these receptors is caffeine, which causes potent stimulation of calcium release, which in turn may induce DADs.

- Risk factors for arrhythmias

Adrenergic stimulation, in relation for example to physical effort (sport, dancing), maintained or prolonged by caffeine, may precipitate the development of rhythm disorders when the QT interval is prolonged. Experimentally, alpha1 adrenergic stimulation, when applied with drugs that prolong the QT interval, precipitates the occurrence of torsades de pointes. Alpha1 adrenergic blocking prevents this from occurring. This is the basis of animal models of torsades de pointes in which the sensitivity of the model to the occurrence of arrhythmia is exacerbated by the addition of the adrenergic agonist methoxamine (Carlsson *et al.*, 1990). In addition, the influence of the sympathetic nervous system is demonstrated by the remarkable efficacy of beta-blockers in protecting against sudden death in patients with congenital long QT syndrome.

Moreover, exercise increases the heterogeneity of refractory periods and can increase the number of early or delayed after-depolarisations.

As mentioned above, caffeine can have a strong stimulatory effect on calcium release from the sarcoplasmic reticulum, which ensures storage of cell calcium. This effect may induce DADs. Caffeine can also attenuate the  $I_{K_r}$  potassium current.

Individuals with asymptomatic channelopathies, which result from genetic mutations affecting the channels involved in depolarisation and repolarisation, may be a particularly high risk population for torsades de pointes and other polymorphic ventricular arrhythmias.

With no other associated risk factor, residual functioning of the channels may remain normal and successive cardiac depolarisation/repolarisation may only be slightly affected. In favourable circumstances that reduce the "repolarisation reserve", such as hypokalaemia or bradycardia, or in the event of major stimulation of the sympathetic nervous system (or even massive absorption of caffeine), it is possible that serious ventricular arrhythmias may develop in these subjects, although they would not occur in the general population.

Therefore, in individuals with long QT electrophysiological sequelae, EADs or DADs may result in ventricular arrhythmia possibly leading to sudden death. This is what occurs in a third of patients with type 1 long QT, whose ECG is normal and in whom arrhythmias are induced by effort.

The prevalence of channelopathies has been estimated in certain studies. According to these evaluations, the prevalence of Brugada syndrome appears to be 1:1000 worldwide (Fowler et Priori, 2009), congenital long QT 1:2000 (Schwartz *et al.*, 2009)<sup>15</sup>, and catecholaminergic polymorphic ventricular tachycardia (CPVT)<sup>16</sup> 1:10,000 (Orphanet, 2011)<sup>17</sup>. The prevalence of hypertrophic cardiomyopathies, which are sometimes caused by a channelopathy, is estimated to be 1:500 worldwide (Nistri *et al.*, 2009).

The repolarisation reserve can be diminished in different ways depending on the presence of one or several risk factors that may be cumulative (bradycardia, female gender, medication that blocks the channels such as antihistamines, hypokalaemia, etc.). The individual role of any one of these factors is therefore difficult to establish.

- scEDs and arrhythmias

Several recent articles have reported the facilitating role of scEDs in the occurrence of arrhythmias in patients with long QT syndrome (Dufendach *et al.*, 2012; Rottlaender *et al.*, 2012). The first case concerns a young woman suffering sudden cardiac death in a nightclub due to torsades de pointes degenerating to ventricular fibrillation, after consumption of 6 cans of scED over the preceding four hours, with subsequent resuscitation. Corrected QT interval was 492 ms and returned to normal subsequently. The patient's genotype revealed a mutation in the gene coding for a potassium channel, inducing a repolarising potassium current, *KCNQ1*. The patient therefore had Type 1 congenital long QT syndrome. The second case report concerned a young girl of 13 years of age who complained of palpitations, dizziness and precordial pain after consuming at least 33 cl of anscED. ECG revealed corrected QT of 622 ms (normal value = < 470 ms). The next day, the QT interval had returned to 453 ms, then to 428 ms two days later. This patient also harboured a mutation in *KCNQ1* (LQT1) with a normal electrocardiogram at baseline.

The prolonged QT interval observed in these two cases following intake of an scED makes this cause particularly plausible for the occurrence of arrhythmia. Some authors have even suggested that scEDs may reproduce the effects of stress tests or adrenaline provocation tests used to screen for long QT syndromes or other genetic disorders of cardiac rhythm (Dufendach *et al.*, 2012; Gray *et al.*, 2012; Rutledge *et al.*, 2012).

These increases in the QT interval are not reported in the nutritional vigilance cases analysed by ANSES presented above<sup>18</sup>, since the ECG tracings are only rarely available, except in the single case where the patient was admitted to intensive care.

Some studies have investigated the effects of consumption of scEDs on heart rate in healthy subjects. Although a prospective epidemiological study did not find a link between consumption of caffeine and occurrence of supra-ventricular tachycardia (Frost et Vestergaard, 2005), other findings suggest the contrary. One article describes two cases of atrial fibrillation in two adolescents aged 14 and 16 years (Di Rocco *et al.*, 2011). The first case occurred two hours after intensive running, with the patient reporting palpitations identical to those experienced 5 days earlier following intake of a can of an scED. The day before the running event, the patient had consumed an unknown amount of scED. The second case involved consumption of an scED with alcohol in an asthmatic patient. In both cases, the author points to the highly plausible role of caffeine in the onset of these rhythm disorders. Other authors have suggested the possible role of taurine in the development of rhythm disorders (Berger et Alford, 2009).

Steinke *et al.* (2009) studied the cardiac effects of consumption of two cans of scEDs (500 ml) before and after one week of consumption. Measurements of cardiac and haemodynamic function were taken over 4 hours following consumption. The QT interval did not increase the 1st day and an increase of 5% at the limit of statistical significance ( $p = 0.052$ ) was observed after one week of consumption.

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<sup>15</sup> Data from a study in the Italian population

<sup>16</sup> Severe genetic arrhythmogenic disease in which ventricular tachycardia develops during physical activity and during activation of the adrenergic system

<sup>17</sup> Reference portal on rare diseases - Orphanet is led by a consortium of around 40 countries, coordinated by a French INSERM team

<sup>18</sup> With the exception of one case for which causality to an ED was considered unlikely

Finally, the results of a recent meta-analysis on the effects of scEDs on the QT interval were presented at the “Epidemiology & Prevention (EPI) and Nutrition, Physical Activity & Metabolism (NPAM)” meeting of the American Heart Association in March 2013. Seven studies were retained for the analysis, which included 93 subjects. The authors indicated that consumption of an scED increased QT/corrected QT by 10.0 ms<sup>19</sup> [CI<sub>95%</sub> = 0.41-19.67; Cochrane Q *p*=0.505]<sup>20</sup>.

**Cardiac arrest**

- There are genetic predispositions to serious ventricular arrhythmias that can result in sudden or unexplained death, particularly congenital anomalies of certain ion channels, primarily sodium, potassium, and calcium channels involved in myocardial repolarisation.
  - A number of factors may underlie heart rhythm disorders, specifically:
    - electrolyte disorders (hypokalaemia, etc.);
    - changes in heart rate: bradycardia or tachycardia, promoting after-depolarisations;
    - certain substances that block ion channels (such as quinine, certain antihistamines, antipsychotics, etc.);
    - calcium channel receptor agonists: adrenergic agonists including caffeine and its metabolites.
- The risk of arrhythmia is also higher in women than in men.
- Therefore, cases of cardiac arrest reported under the Nutritional Vigilance Scheme and cases reported in the literature appear to occur in all likelihood in genetically predisposed subjects and seem to be related to rhythm disorders resulting from a combination of one or several of the risk factors mentioned above, in combination with the consumption of scEDs.

**ii. Other rhythm disorders, angina pectoris, hypertension**

Other types of cardiovascular disorders have been reported to the Agency. Among those for which causality to an scED was considered very likely or likely (Table 5), episodes of tachycardia (confirmed clinically or described as such) were reported in 7 cases for consumption of between 3 and 20 cans. A case of bradycardia is reported with likely causality, and an intake volume of 15 cans of scED. One patient presented salvos of ventricular extrasystoles (resolving with flecainide), two hours after consumption of a large can of scED. Signs of angina pectoris or chest tightness were reported in 3 cases, and arterial hypertension in 1 case.

**Table 5: Cases with very likely causality (I4) and likely causality (I3) in which cardiovascular effects such as tachycardia/angina pectoris/hypertension/bradycardia were reported**

Ref	Amount consumed	Subject	Effects	Alcohol	Sport/Exercise	I (overall)
100229354	500 ml	M, 13 years 38 kg	Precordial pain	-	-	I4
2012-047	7 cans	M, 28 years 75 kg	Tachycardia/Hyperactivity/Night awakenings/Visual hallucinations	Alcohol	-	I4
2012-050	5-6 cans	M, 24 years 78 kg	Tachycardia	Alcohol	-	I4
2012-054	1 can	M, 32 years 80 kg	Rhythm disorder – salvos of ventricular extrasystoles	-	-	I4
306636	20 cans	F 48 years 32 kg	Tachycardia/Hallucinations/Mydriasis	Zyprexa, Lexomil, librax, klipal codeine, havlane, corticosteroids	-	I3
361716	15 cans	M, 17 years	Bradycardia	Alcohol	-	I3

<sup>19</sup> An increase in the duration of QT of 30 ms is generally considered cause for concern in the medical community, according to the author.

<sup>20</sup> Shah, A.S.; Lacey, C.S.; Riddock, I.C.; Lee, M.; Dargush, A.E. Impact of Energy Drinks on Electrocardiographic and Blood Pressure Parameters: A Meta-Analysis of Clinical Studies. *Circulation*. 2013; 127: AP324

Ref	Amount consumed	Subject	Effects	Alcohol	Sport/Exercise	I (overall)
384948	?	M, 12 years	Tachycardia/Hypersudation	-	-	I3
322460	4 cans	F, 16 years 48 kg	Nausea / Agitation / Excitement / Hypertension / Tachycardia / Vomiting	-	-	I3
363871	?	M, 20 years	Chest tightness / Paraesthesia of the extremities / Rhabdomyolysis / CPK elevation	Alcohol	-	I3
369130	3 cans	M, 8 years	Chest pain	-	-	I3
369428	1.2 l	M, 30 years	Tachycardia / CPK elevation	-	-	I3
271628	1 can	F, 21 years	Palpitations / Panic attack / Headache	-	-	I3
2012-053	3 cans	M, 20 years	Tachycardia / Sleep disorders	-	-	I3

I4: very likely causality; I3: likely causality

NB: the quantity is sometimes indicated in number of cans but it is not possible to expand on this information since the volume of the cans is not given in the report. For information, according to a survey monitoring consumption of scEDs carried out by ANSES (see Annex 5), in 2011, 82% of consumers only drank cans containing 250 ml and 3% only cans containing 500 ml (15% consumed both containers); in addition, 50% of all products were sold in the 250 ml containers.

### ***Bibliographic data and possible mechanisms***

#### *Tachycardia, hypertension and reflex bradycardia*

Tachycardia is one of the classic symptoms of caffeine intoxication. Consumption of caffeine leads to an increase in blood pressure (Mosqueda-Garcia *et al.*, 1990; Sung *et al.*, 1990; Cohen et Townsend, 2006; Arciero et Ormsbee, 2009). These effects appear to be more marked when large amounts are consumed and when the consumer is caffeine-naive, i.e. not used to caffeine consumption, which is often the case in the adolescent population.

The effects of taurine alone on blood pressure are not well documented. In a literature review of the potential protective effect of taurine on cardiovascular disease, the authors highlight data indicative of a positive effect of taurine in animals, but at doses and in models that cannot be transposed. In humans, several transverse studies indicate an inverse relationship between taurine urine concentrations and blood pressure (Wojcik *et al.*, 2010).

Consumption of scEDs or the combination of taurine and caffeine increase blood pressure (Bichler *et al.*, 2006; Steinke *et al.*, 2009; Worthley *et al.*, 2010), with some evidence suggesting that this effect might be greater than caffeine alone (Franks *et al.*, 2012).

Furthermore, the increase in blood pressure induced by caffeine or scEDs can be accompanied by reflex bradycardia, as described in certain cases from nutritional vigilance (361716). Nonetheless, the effects of the taurine-caffeine combination or consumption of an scED on the heart rate are not clear given the discrepancies in results between the various studies (Geiß *et al.*, 1994; Baum et Weiß, 2001; Bichler *et al.*, 2006; Steinke *et al.*, 2009; Ragsdale *et al.*, 2010; Worthley *et al.*, 2010).

An effect of taurine on increased systolic ejection volume is possible. This effect has been observed following consumption of an scED, but not after consumption of an analogue of this drink free from taurine, in the recovery period after exercise (Baum et Weiß, 2001).

#### *Angina pectoris, chest pain and myocardial infarction*

Attacks of angina pectoris may result from spasms in the coronary arteries, which may lead to coronary circulatory arrest and infarctions, as shown in cases in the literature. These spasms may result in more minor disorders: cardiac pain, like in the cases reported as part of the Agency's Nutritional Vigilance Scheme. Tachycardia may also promote the occurrence of angina pectoris if there is underlying stenosis, or simply through increased oxygen consumption by the myocardium.

Berger and Alford (2009) suggest that taurine and caffeine may induce these coronary vasospasms since experimental *in vitro* studies show that caffeine and taurine play a positive inotropic role

(increased myocardial contractility) and that taurine accentuates the effects of caffeine in this context. Both substances induce an increase in intracellular calcium concentrations in smooth muscle fibres, and it is possible that they may cause vasospasms.

The case of resuscitated sudden death in a motorcyclist of 28 years of age after consumption of 8 cans of an scED (infarction with "normal coronaries") and the case of acute infarction with intracoronary clot but no associated coronary lesion, reported after consumption of these drinks, are suggestive of vasospasm promoted by caffeine and/or taurine, as indicated by the authors (Berger et Alford, 2009; Scott *et al.*, 2011).

*Other rhythm disorders, angina pectoris, hypertension*

- The reported events reflect the expected adverse effects following ingestion of caffeine in high quantities.
- Effects have been reported starting at consumption of 500 ml (i.e. two standard cans of scED).
- Consumption of scEDs may present a risk in patients with severe or poorly controlled hypertension.
- Caffeine, and possibly also taurine, play a positive inotropic role; taurine may accentuate the effects of caffeine, causing coronary vasospasm.
- The effects of scEDs on blood pressure may be explained not only by the action of caffeine, but also by taurine; the caffeine-taurine combination may therefore constitute a specific risk related to the consumption of scEDs.

**iii. Stroke**

Six cases of stroke observed following consumption of scEDs were reported to the Agency (in one of the cases, the diagnosis of stroke is not certain but the symptoms are highly suggestive). A causal relationship with scEDs was considered unlikely in 4 cases, and possible in 2 cases occurring in men aged 18 and 26 years, particularly in the absence of another clear cause. However, 30% of strokes in young subjects have no determined etiological factors, even when a complete work-up was performed. The extent of investigations is unknown for one of the cases.

***Bibliographic data and possible mechanisms***

A case of stroke associated with an attack of epilepsy was reported in a 37-year-old male patient following consumption of 3 cans of scED with vodka (Dikici *et al.*, 2013). The authors note that caffeine may result in coronary vasospasm and that scEDs in combination with alcohol may contribute to the risk of stroke by increasing blood pressure and heart rate.

**Cardiovascular effects of scEDs**

*Cardiac arrest*

- There are genetic predispositions to serious ventricular arrhythmias in individuals with channelopathies, which are often not diagnosed, some forms of which could concern as many as 1 person in 1000.
- In these subjects, adrenergic stimulation related for instance to physical exercise (sport, dancing), could be maintained and prolonged by the caffeine contained in scEDs, and thus precipitate the development of rhythm disorders.
- The risk of ventricular arrhythmia can also be enhanced by various factors (tachycardia, bradycardia, hypokalaemia, intake of certain medications, etc.). The risk is also higher in women than in men.
- Therefore, cases of cardiac arrest reported under the Nutritional Vigilance Scheme and cases reported in the literature appear to occur in all likelihood in genetically predisposed subjects and seem to be related to rhythm disorders resulting from a combination of one or several of the risk factors mentioned above, in combination with the consumption of scEDs.

*Other rhythm disorders, angina pectoris, hypertension, stroke*

- The cardiovascular effects reported after consumption of scEDs, such as tachycardia, tightness of the chest or chest pain (angina pectoris), hypertension and reflex bradycardia reflect the expected adverse effects following intake of caffeine in large quantities.
- The increase in blood pressure and coronary vasospasm (that could respectively lead to hypertension and attacks of angina pectoris), may not be related only to caffeine. It is possible that taurine adds to the effect.
- Consumption of scEDs may present a risk in patients with severe or poorly controlled hypertension.
- Elevated blood pressure and vasospasms promoted by scEDs could increase the risk of stroke.

**b. Neurological and psycho-behavioural effects**

**i. Psycho-behavioural effects**

Psycho-behavioural disorders were reported in 72 cases analysed by the Agency. These include anxiety, distress, panic attacks/tetany, excitement, agitation, nervousness, aggressiveness, delusion, hallucination, obnubilation, mental confusion, spatio-temporal disorientation, and other behavioural disorders.

The conclusions of the causality analysis for these cases are as follows:

- Very likely causality (I4): 2 cases
- Likely causality (I3): 6 cases
- Possible causality (I2): 18 cases
- Unlikely causality (I1): 46 cases

The eight cases for which a causal relationship to consumption of an scED was considered very likely (I4) or likely (I3) are presented in Table 6 below:

**Table 6: Cases with very likely (I4) and likely causality (I3) involving psycho-behavioural effects**

Reference	Quantity consumed	Subject	Effects	Identified concomitant intake	I (overall)
100210265	4 cans	M 4 years	Agitation/Excitement	-	I4
2012-047	7 cans	M 28 years 75 kg	Hyperactivity/Night awakenings/Visual hallucinations/Tachycardia	Alcohol	I4
271628	1 can	F 21 years	Panic attacks/Headache/Palpitations	-	I3
306636	20 cans	F 48 years 32 kg	Hallucinations/Mydriasis/Tachycardia	Zyprexa, Lexomil, librax, klipal codeine, havlane, corticosteroids	I3
322460	4 cans	F 16 years 48 kg	Agitation/Excitement/Nausea/Vomiting/Hypertension/Tachycardia	Ventolin	I3
369274	?	M 29 years	Distress/Anxiety/Consciousness disorders/Asthenia	Alcohol + tablet containing ketone, caffeine, glucose	I3
2009-056	3 glasses	F 23 years	Spatio-temporal disorientation/Malaise/Amnesia/Vomiting	Alcohol	I3
2012-017	500 ml	M 43 years 90 kg	Behavioural disorders/Aggressiveness	Alcohol	I3

I4: very likely causality; I3: likely causality

NB: the quantity is sometimes indicated in number of cans but it is not possible to expand on this information since the volume of the cans is not given in the report. For information, according to a survey monitoring consumption of scEDs carried out by ANSES (see Annex 5) in 2011, 82% of consumers only drank cans containing 250 ml and 3% only cans containing 500 ml (15% consumed containers of both volumes); in addition, 50% of all products were sold in the 250 ml containers.

Several cases of distress/anxiety and agitation/excitement sometimes related to partial or total caffeine intoxication syndromes (with co-occurrence of tachycardia in particular) have been observed at quantities varying from 1 to 7 cans of scED, with or without consumption of alcohol. A case that included a panic attack was observed with consumption of 1 can. Cases in children and adolescents aged 4 and 16 years have been reported with high intake volumes, approximately 1 litre.

### ***Bibliographic data and possible mechanisms***

#### *Cases reported in the literature*

There have been reports of occurrence of manic episodes after consumption of scEDs. The constituent that appears to play the greatest role is caffeine, a substance known to induce this type of episode at high doses, even in patients without a psychiatric history (Ogawa et Ueki, 2003; Hedges *et al.*, 2009).

The development of manic episodes in well-controlled bipolar patients has been attributed to consumption of scEDs (Machado-Vieira *et al.*, 2001; Sharma, 2010; Proudfoot *et al.*, 2011). Likewise, exacerbation of psychosis has been reported after consumption of scEDs in patients whose disorders were previously well controlled by drug therapy, with a return to the former state on discontinuation of the product (Chelben *et al.*, 2008; Cerimele *et al.*, 2010).

#### *Effects of caffeine*

Caffeine has a large number of biochemical targets in the central nervous system (CNS), such as GABA receptors and A<sub>1</sub> and A<sub>2A</sub> adenosine receptors. It modulates the activity of protein kinases and phosphodiesterases. The psycho-active properties of caffeine have been associated with blockade of striatal A<sub>2A</sub> adenosine receptors, with genetic polymorphism of the receptor contributing to consumption and to the effects of caffeine.

Intake of caffeine can induce psycho-behavioural disturbance, including nervousness, irritability and anxiety, or even panic attacks or psychotic manifestations, particularly hallucinations. Single intakes of 300 or 400 mg of caffeine may induce mental tension and anxiety, particularly if the patient is in a stressful context (Smith, 2002; Childs et de Wit, 2008). It appears that psychiatric complications are mainly observed in patients with a past history of psychiatric disease, particularly generalised chronic anxiety disorders and panic states (Bruce *et al.*, 1992; Nardi *et al.*, 2007), or that they could unmask these disorders. In these subjects, nervousness, anxiety disorders or even distress, nausea, palpitations and tremor can be observed after acute intake of caffeine. These effects can last for several hours (Nardi *et al.*, 2007). Onset or increased frequency of manic episodes in patients with bipolar disorder or psychosis have also been reported (Ogawa et Ueki, 2003; Hedges *et al.*, 2009; Rizkallah *et al.*, 2011). Aside from the direct dopaminergic effect of caffeine, some authors have pointed to reduced efficacy of the patients' usual maintenance drug therapy, through competitive inhibition of the activity of cytochrome P450 (Carrillo et Benitez, 2000; Cauli et Morelli, 2005).

Chronic use of high doses of caffeine (i.e. greater than 300 mg/day) could increase the risk of hallucination, particularly in stressful conditions, as suggested by a study carried out in students (Jones et Fernyhough, 2008).

Paradoxically, it has been demonstrated that intake of 300 mg/day of caffeine, in combination with administration of a selective serotonin reuptake inhibitor, may improve symptoms in patients with obsessive compulsive disorders (Koran *et al.*, 2009).

#### *Effects of taurine*

The possibility of a taurine-induced acute central nervous effect was mentioned by AFSSA in its opinion of 5 May 2003 (Afssa, 2003), following evaluation of an initial toxicity study carried out in the rat, submitted by an applicant as part of an assessment of the use of taurine, D-glucuronolactone, various vitamins and caffeine in scEDs. In this 13-week investigation, rats were given taurine at doses of 0, 300, 600, and 1000 mg/kg/day. The study showed increased activity in the animals one hour after ingestion of taurine, with paw biting, and a possible decrease in motor performance, starting from the lowest doses in female rats (300 mg/kg/day), suggesting a possible acute central nervous effect.

In a subsequent evaluation in 2009, EFSA analysed the results of a publication on the absorption, distribution, metabolism and elimination (ADME) of taurine administered orally to rats following three protocols (Sved *et al.*, 2007). In the 1<sup>st</sup> protocol, 30 or 300 mg/kg bw of radio-labelled taurine was administered to rats, and distribution to tissue, blood, urine and faeces was measured for seven days following administration.

In the 2<sup>nd</sup> protocol, the rats were given 30 or 300 mg of taurine/kg bw/day for 14 days, then radio-labelled taurine on the last day. For the last dose, the fate of the compound was monitored for the first few hours, then for the following four weeks.

In the 3<sup>rd</sup> protocol, total taurine in different organs was measured two hours following administration, after 1 day, 7 days and 14 days.

On the basis of these data, EFSA concluded that ingestion of taurine did not lead to increased taurine levels in the brain, ruling out the possibility of a stimulant effect on the central nervous system.

Furthermore, a second 13-week neurotoxicity study conducted in the rat, and in compliance with GLP<sup>21</sup> recommendations, was submitted to EFSA in 2009. The taurine doses tested were 600 and 1000 mg/kg bw/day in two groups of rats force-fed taurine, and target doses were 1000 and 1500 mg/kg bw/day in two groups of rats given taurine by drinking water consumed *ad libitum*. EFSA considered that a NOAEL<sup>22</sup> of 1000 mg/kg bw/day for pathological changes, and of 1500 mg/kg bw/day for behavioural effects could be retained, given the absence of effects observed at these doses (equivalent to the highest administered doses) (EFSA, 2009).

The results of the second toxicity study provide reassuring findings concerning suspected neurotoxicity of taurine suggested in the first study. Although these data mitigate the worrying results of the first toxicity study, they do not completely invalidate them either. Concerning the ADME study (Sved *et al.*, 2007), it is unfortunate that brain taurine concentrations were not measured for two hours following oral administration, since the acute effects reported in the first study occurred during this period of time. On the whole, the findings of this study do not make it possible to rule out that ingestion of taurine may result in increased taurine concentrations in some parts of the brain, which could lead to neuro-behavioural effects.

**Psycho-behavioural disorders**

- The psycho-behavioural effects reported in the analysed cases, such as irritability, nervousness, anxiety, or even panic attacks, are common symptoms of caffeine intoxication.
- A panic attack was mentioned in one case report following consumption of a single can of scED.
- Episodes of anxiety and panic attacks appear to occur primarily in patients with known psychiatric conditions, or could unmask these types of conditions.

**ii. Sleep disorders**

Sleep disorders were reported in 8 cases analysed by the Agency in which a causal relationship to consumption of an scED was considered very likely (I4) in one case, likely (I3) in one case, possible (I2) in two cases, and unlikely (I1) in four cases. Table 7 below shows the cases for which the causal relationship to consumption of an scED was considered very likely or likely.

**Table 7: Cases with very likely (I4) and likely causality (I3) involving sleep disorders**

Reference	Quantity consumed	Subject	Effects	Identified concomitant intake	I (overall)
2012-047	7 cans	M 28 years 75 kg	Night awakenings/Hyperactivity/Visual hallucinations/Tachycardia	Alcohol	I4
2013-053	3 cans	M 20 years	Sleep disorders/Tachycardia	-	I3

I4: very likely causality; I3: likely causality

<sup>21</sup> Good laboratory practice

<sup>22</sup> No observed adverse effect level

NB: the quantity is sometimes indicated in number of cans but it is not possible to expand on this information since the volume of the cans is not given in the report. For information, according to a survey monitoring consumption of scEDs carried out by ANSES (see Annex 5) in 2011, 82% of consumers only drank cans containing 250 ml and 3% only cans containing 500 ml (15% consumed containers of both volumes); in addition, 50% of all products were sold in the 250 ml containers.

### ***Bibliographic data***

The effects of caffeine on sleep are well known. Individuals who consume excessive amounts of caffeine suffer from sleep disorders (sleep-onset insomnia), with negative implications for cognition in general, and attention and memory in particular (Mednick *et al.*, 2008). Consumption of caffeine is associated with lower sleep quality in subjects who are subjectively sensitive to caffeine (Retey *et al.*, 2007).

During acute consumption of high doses of scEDs, transient insomnia has been reported, particularly in adolescents not accustomed to these substances (Clauson *et al.*, 2008; Pennington *et al.*, 2010), and sometimes in a context of more complete caffeine intoxication syndrome. Regular consumers of scEDs more often report reduced sleep, particularly in the morning, and daytime drowsiness, effects that may result in increased consumption (Anderson et Horne, 2006; Jay *et al.*, 2006; Calamaro *et al.*, 2009; Ludden et Wolfson, 2010).

### **Sleep disorders**

- Sleep disorders associated with consumption of scEDs may be explained by the caffeine content.
- The consequences of reduced duration of sleep, which include daytime drowsiness, may result in increased consumption of scEDs.

### **iii. Epileptic seizures**

Sixteen cases of seizures were reported and analysed by the Agency. For these cases, the conclusions of the causality analysis in terms of consumption of scEDs are as follows:

- Very likely causality (I4): 0 cases;
- Likely causality (I3): 1 case;
- Possible causality (I2): 5 cases;
- Unlikely causality (I1): 9 cases;
- Causality ruled out (I0): 1 case.

The case for which causality was considered likely (case 371663) involved an adolescent of 14 years of age who consumed an unknown quantity of scED. He developed tonic-clonic seizures 45 minutes after intake while playing football. The patient had no history of epileptic seizures.

### ***Bibliographic data and possible mechanisms***

#### *Cases reported in the literature*

Onset of seizures following consumption of scEDs has been reported in several review articles (Cleary *et al.*, 2012; Gunja et Brown, 2012; Ishak *et al.*, 2012; Wolk *et al.*, 2012). Table 8 below summarises the cases reported in the literature.

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**Table 8: Cases of epilepsy following consumption of scEDs reported in the literature**

Ref	Adverse effect	Subject	Consumption of scEDs	Concomitant intake	Remarks	Course
(Trabulo <i>et al.</i> , 2011)	Episodes of epilepsy	M 28 years	6 cans of an scEdl	Coffee	No reported cofactors (sleep deficit, drugs or alcohol, fever or infection) Past history: previous consumption of drugs, hepatitis C, mitral insufficiency and post-infectious endocarditis No history of seizures	No further seizures during the following three months, during which time the patient abstained from scEDs
<b>(Iyadurai et Chung, 2007)</b>						
Case 1	2 episodes of epilepsy 4 months apart	M 25 years	High level of consumption of scEDs on an empty stomach for the first episode 1.5 l of an scED on an empty stomach 30 to 60 min before the second episode Routine consumption of 500 ml/day of an scED	None	No reported cofactors (sleep deficit, consumption of drugs or alcohol, fever, infection, or headache) No personal or familial history of seizures, no head trauma	No seizures in the 6 months following discontinuation of scEDs
Case 2	3 episodes of epilepsy in 2 years	M 19 years	Several 750 ml cans of scED for each episode	None	Context of stress No reported cofactors (sleep deficit, consumption of drugs or alcohol, fever or infection) History of migraines	No further seizures in the 6 months following discontinuation of scEDs and FSs
Case 3	2 episodes of epilepsy 6 months apart	F 28 years	Consumption of 1.5 l of scED on a regular basis	Food supplement (FS) containing caffeine	Context of stress Episodes occurring during combination of scED + FS History of migraines	No further seizures in the 4 months following discontinuation of scEDs and FSs
Case 4	4 episodes of epilepsy in 2 years	M 26 years	Regular consumption of scED	None	Cofactors not indicated Seizures on consumption > 2 cans of 750 ml	No further seizures during the following 2 months
(Babu <i>et al.</i> , 2011)	1 episode of epilepsy	M 15 years	2 cans of "5-hour energy" scED (form = shots)	1 cup of coffee	No reported cofactors (consumption of drugs) No personal or familial history of seizures, no head injury	No further seizures in the 2 months following discontinuation of products containing caffeine
(Calabrò <i>et al.</i> , 2012)	1 episode of epilepsy	M 20 years	Consumption of 4 to 6 cans of an scEd per day for 5 months	None	No reported cofactors (sleep deficit, consumption of drugs, fever, infection) No personal or familial history of seizures	No further seizures in the following 2 years

In most cases, seizures occurred in subjects who had not experienced epileptic fits in the past, who had not drunk alcohol and who were not sleep deprived (known risk factors), thus leading to a suspected causal relationship to consumption of scEDs (Iyadurai et Chung, 2007; Babu *et al.*, 2011; Trabulo *et al.*, 2011; Calabrò *et al.*, 2012). The quantity of scED consumed was generally high (more than 1 litre) and follow-up revealed no recurrence of seizures in the subjects who abstained from further consumption of scEDs, suggesting that consumption of high quantities may induce seizures in susceptible individuals.

#### **Effects of caffeine**

Certain studies have indicated that caffeine may, at high doses, lower the seizure threshold and diminish the efficacy of antiepileptic treatments even at fairly low doses (Boison, 2011; Chroscinska-Krawczyk *et al.*, 2011). The seizure-inducing effects of methylxanthines such as caffeine may be explained by their antagonist action *versus* adenosine, which exerts an anticonvulsant effect on the brain. Treatments that aim to increase adenosine concentrations in the brain are effective in reducing the occurrence of epileptic episodes, while adenosine receptor antagonists, such as methylxanthines, generally increase this risk (Boison, 2011).

However, the relationship between consumption of caffeine and *de novo* onset of epilepsy has not been clearly established (Dworetzky *et al.*, 2010). Therefore, it appears at this time that high consumption levels of caffeine increase the risk of seizures primarily in known epileptic patients or in predisposed individuals (Kaufman et Sachdeo, 2003; Bonilha et Li, 2004).

#### **Effects of taurine**

The possibility of taurine being implemented in the onset of epileptic seizures is discussed in two case studies. Calabro *et al.* (2012) suggest that convulsive episodes could result from neuronal hyperexcitability caused by high chronic intake of taurine. According to Iyadurai *et al.* (2007), studies on animal models suggest that taurine could be an anticonvulsant while also being epileptogenic

Taurine has GABAergic effects and plays an inhibiting role in the central nervous system. It acts preferentially on the receptors of the sub-type GABA<sub>A</sub>, of which it is a direct agonist. Although chronic administration certainly seems to increase expression of glutamic acid decarboxylase (GAD) and, consecutively, that of GABA, it reduces expression of the sub-units  $\beta 2$  and  $\beta 3$  of the GABA<sub>A</sub> receptor (L'Amoreaux *et al.*, 2010).

It has been suggested that a taurine deficit in the brain could play a role in the onset of convulsions, although this factor is neither necessary nor sufficient (Oja et Saransaari, 2013).

Conversely, it has also been suggested that the effects of chronic taurine intake on reduced expression of the  $\beta$  sub-units of the GABA<sub>A</sub> receptor could be the result of desensitisation reducing the efficacy of the inhibitory synapses in the post-synaptic membrane. A reduction in motor learning following chronic administration of taurine has been observed in rats, which was attributed to neuronal hyperexcitability resulting from this desensitisation (L'Amoreaux *et al.*, 2010; Santora *et al.*, 2013). It is difficult to draw conclusions regarding this hypothesis in the current state of knowledge, as the  $\beta 2$  and  $\beta 3$  sub-units have only rarely been described as being specifically and irreplaceably implemented in any particular function of the GABA<sub>A</sub> receptor.

#### **Epilepsy**

- Consumption of scEDs appears to increase the risk of onset of seizures in known epileptic patients and in predisposed individuals.
- These effects may be mediated by caffeine, which may lower the seizure threshold.

**Psycho-behavioural and neurological effects of scEDs**

- Consumption of scEDs may induce neurological and psycho-behavioural adverse effects, even in individuals with no specific past history.
- The risk of psychiatric events following consumption of scEDs appears to be higher in subjects with chronic psychiatric disorders, particularly psychosis, bipolar disorder and anxiety disorders. However, analysis of the cases recorded by the Agency's Nutritional Vigilance Scheme did not show this relationship.
- Consumption of scEDs appears to increase the risk of onset of seizures in known epileptic patients and in predisposed individuals.

**c. Gastro-intestinal effects**

**i. Cases reported under the Nutritional Vigilance Scheme**

Gastro-intestinal symptoms were reported in 31 cases analysed by the Agency as part of this expert assessment. The analysis of causality provided the following results:

- Very likely (I4) in one case;
- Likely (I3) in 4 cases;
- Possible (I2) in 7 cases;
- Unlikely (I1) in 19 cases.

Table 9 below presents the cases for which causality was considered very likely or likely.

**Table 9: Cases with very likely (I4) and likely causality (I3) in which gastro-intestinal effects were reported**

Ref	Quantity consumed	Age	Effects	Identified concomitant intake	I (overall)
336929	1 can	M, 12 years	Lower abdominal pain (lower epigastric)	-	I4
404128	11 l	M, 19 years 80 kg	Epigastric pain/Intestinal haemorrhage/Melaena/Diarrhoea/Digestive pain (poorly localised)	-	I3
480008	2 l	M, 19 years	Lower abdominal pain (lower epigastric) / Dizziness/Headache	-	I3
322460	4 cans	F, 16 years 48 kg	Nausea/Vomiting/Agitation/Excitement/Hypertension/Tachycardia	-	I3
2012-056	3 glasses	F, 23 years	Vomiting/Malaise/Amnesia/Spatio-temporal disorientation	Alcohol	I3

I4: very likely causality; I3: likely causality

NB: the quantity is sometimes indicated in number of cans but it is not possible to expand on this information since the volume of the cans is not given in the report. For information, according to a survey monitoring consumption of scEDs carried out by ANSES (see Annex 5) in 2011, 82% of consumers only drank cans containing 250 ml and 3% only cans containing 500 ml (15% consumed containers of both volumes); in addition, 50% of all products were sold in the 250 ml containers.

**ii. Bibliographic data and possible mechanisms**

The hyperosmolarity of scEDs may promote accelerated intestinal transit, diarrhoea and/or abdominal pain.

Caffeine, which decreases pressure in the lower sphincter of the oesophagus, may promote gastro-oesophageal reflux or even vomiting.

The reported case of melaena may have been caused by upper gastro-intestinal tract haemorrhage (stomach or gastroesophageal junction) related to acute ulceration, or more likely acute tearing of the junction between the oesophagus and the stomach (Mallory-Weiss syndrome), which results in sometimes abundant bleeding with rapid healing. This type of bleeding is usually associated with retching but another cause could be significant reflux induced by the high quantities of scED consumed. However, the symptoms described in the case of melaena included neither vomiting nor reflux, making it impossible to interpret the case further.

**Gastro-intestinal effects of scEDs**

- The hyperosmolarity of scEDs may promote accelerated intestinal transit and promote the occurrence of gastro-intestinal disorders.
- The caffeine content in scEDs may promote gastro-oesophageal reflux.

**d. Respiratory effects**

**i. Cases reported under the Nutritional Vigilance Scheme**

Nineteen cases of respiratory adverse effects were reported to the Agency. Analysis of causality provided the following results:

- Likely (I3) in 1 case;
- Possible (I2) in 4 cases;
- Unlikely (I1) in 13 cases;
- Ruled out (I0) in 1 case.

In the cases with likely or possible causality, the symptoms described included respiratory pain or discomfort with or without chest tightness or chest pain.

**ii. Bibliographic data and possible mechanisms**

A literature search provided no results for possible respiratory adverse effects directly related to scEDs. Some indirect data are however available.

**Case report**

(Trabulo *et al.*, 2011) reported the case of a 28-year-old patient with a past history of drug abuse, mitral valve disease and stroke, hospitalised for coma following generalised epileptic seizures occurring within 4 hours of consuming about 6 cans of scED, together with coffee. The hypoxemia observed in this patient seemed to be related to alveolar hypoventilation secondary to the potential effects of the substances ingested, including caffeine and taurine, on the central nervous system.

**Observational study**

One study reports a frequency of 4.9% for respiratory discomfort (without further information) among reported cases associated with consumption of scEDs, with or without concomitant alcohol intake. This symptom was the least frequent of the reported effects, which included mainly palpitations, agitation, tremor and gastro-intestinal disorders. These data were recorded at the largest Australian poison control centre and were obtained between 2004 and 2010 (Gunja *et al.*, 2012).

**Study of the respiratory effects of the main constituents of scEDs (caffeine and taurine)**

**Caffeine**

Caffeine has not been reported to have respiratory adverse effects, whether in healthy subjects or in patients. It is however known to have bronchodilator effects. Since caffeine increases the breathing rate, it is used effectively to stimulate ventilation in premature infants in order to reduce recurrent apnoea (Henderson-Smart *et al.*, 2010). The exact mechanism underlying this stimulant effect may be related to increased sensitivity of the respiratory centres to carbon dioxide (Chou, 1992). Along with its mild bronchodilator effects, caffeine is also known to reduce fatigue in respiratory muscles (Woodcock *et al.*, 1981; Bukowskyj *et al.*, 1987; Welsh *et al.*, 2010). Caffeine is a phosphodiesterase inhibitor and competitive antagonist of adenosine receptors, and it is these properties that probably underlie its relaxant effect on bronchial muscles.

*Taurine*

Adverse effects on the respiratory system have not been described with taurine, whether in healthy subjects or in patients. A recent *in vitro* study demonstrated the relaxant effects of taurine on bronchial smooth muscle cells. This effect is induced by the agonist activity of taurine on the  $\alpha 4$  subunit of GABA<sub>A</sub> receptors in bronchial smooth muscle cells in guinea pigs and humans (Gallos *et al.*, 2012).

**Respiratory effects of scEDs**

- A bibliographic search showed no results for possible direct respiratory adverse effects related to consumption of scEDs.
- There are currently no data that could explain the mechanism underlying respiratory discomfort.
- There is no evidence in support of a link between respiratory effects and consumption of scEDs.

**e. Muscular and osteo-articular effects (rheumatological effects)**

**i. Cases reported under the Nutritional Vigilance Scheme**

Fifteen cases submitted to the Agency described muscular or osteo-articular effects following consumption of scEDs. The effects included primarily muscle pain, joint pain, rhabdomyolysis, and elevated creatine phosphokinase (CPK). Analysis of causality provided the following conclusions:

- Likely (I3) in 3 cases;
- Possible (I2) in 3 cases;
- Unlikely (I1) in 9 cases.

The three cases with a likely causal relationship to scEDs are presented in Table 10 below:

**Table 10: Cases with likely causality (I3) in which muscular or osteo-articular effects were reported**

Ref	Quantity consumed	Age	Effects	Identified concomitant intake	Sport/Exercise	I (overall)
363871	2 glasses scED/vodka	M, 20 years	Rhabdomyolysis/Respiratory pain/Chest tightness/Paraesthesia/Elevated CPK	Alcohol	-	I3
397575	200 ml	F, 27 years	Tremor in the extremities/Increased osteo-tendinous reflexes/Muscle pain	-	-	I3
369428	1.2 l	M, 30 years	Tachycardia/Elevated CPK	-	-	I3

I3: likely causality

**ii. Bibliographic data and possible mechanisms**

Rhabdomyolysis can have different origins, among which are the consumption of drugs and alcohol, muscular ischemia, and intense physical exercise. Rhabdomyolyses have been described following the consumption of very large quantities of caffeine. Medical incidents of this nature have been observed for daily intake greater than 900 mg/d, or for massive doses (greater than 1000 mg) in a single ingestion (Phillips *et al.*, 2012) (for review). Regular consumption of caffeine, mostly via food supplements, in association with other psycho-stimulants such as ephedrine, could be a facilitating factor (Young *et al.*, 1998; Mansi et Huang, 2004).

No clear explanatory mechanism has been proposed. The role played by caffeine in calcium flows via ryanodine receptors (RyR1) has been mentioned, as causing an increase in intracellular concentrations of calcium which could prolong the potential for action and the duration of contractions, liable to cause muscle damage. Caffeine in very high doses (greater than 1000-2000 mg) could explain the activation of calcium-dependant proteases, and clinical episodes of rhabdomyolysis. At repeated, but lower, doses, caffeine could potentiate the effects of psycho-stimulants such as ephedrine and its derivatives, on the triggering of rhabdomyolysis.

**Muscular effects of scEDs:**

- The case of rhabdomyolysis reported under the Nutritional Vigilance scheme was observed in association with alcohol. Cases of rhabdomyolysis have been reported in the literature following consumption of very high doses of caffeine (> 1000 mg), far above the doses observed in the Nutritional Vigilance cases.

**f. Renal effects**

**i. Cases reported under the Nutritional Vigilance Scheme**

Eight cases of renal adverse effects were reported and analysed as part of this expert appraisal. Analysis of causality provided the following results:

- Possible (I2) in 1 case;
- Unlikely (I1) in 7 cases.

The causal relationship to consumption of an scED was considered possible in 1 case involving dark urine associated with mild low back pain in a 23-year-old male patient, following consumption of scED in combination with alcohol the previous evening, and in the evening of the day before that. The colouration of urine could be related to concentration caused by dehydration following consumption, if the patient's fluid intake was insufficient.

**ii. Bibliographic data and possible mechanisms**

*Cases reported in the literature*

Two cases of acute renal failure related to consumption of scEDs were reported in the literature (Lehtihet *et al.*, 2006; Schöffl *et al.*, 2011) (Table 11).

**Table 11: Cases of renal insufficiency reported in the literature related to consumption of scEDs**

Reference	Subject	Adverse effect	Consumption of scED	Concomitant intake	Other causes investigated	Course
Lehtihet <i>et al.</i> , 2006	M 31 years	Acute renal failure and rhabdomyolysis one week after a 3 km run  Creatinine reaching 835 µmol/l	750 ml	-	-	Normalisation of renal function
Schöffl <i>et al.</i> , 2011	M 17 years	Acute renal failure 24 hours after admission for vomiting and confusion following 2 x 100 m runs at school	3 litres of scED the previous evening	1 litre of vodka	Investigation of autoimmune disease negative + negative viral serology tests (hepatitis A, B, C, HIV, hantavirus)	Normalisation of renal function

In the first case (Lehtihet *et al.*, 2006), acute renal failure was secondary to rhabdomyolysis. Although rhabdomyolysis has been observed following consumption of high quantities of caffeine (Wrenn et Oschner, 1989; Chakraborty et Rajeswaran, 2007), with no clear causative mechanism

as mentioned above, it appears unlikely that the rhabdomyolysis observed in this case could be attributed to intake of scEDs in the reported quantities.

In the second case (Schöffl *et al.*, 2011), the role of concomitant intake of scED and alcohol in the onset of renal insufficiency appears likely. The authors point out that the scEDs consumed by the adolescent were in 1 litre bottles, and they considered that this pack size could encourage consumers to drink high quantities.

*Study of the renal effects of the main constituents of scEDs (caffeine, taurine, glucuronolactone)*

*Caffeine*

Caffeine has a diuretic effect (Nawrot *et al.*, 2003) (for review). Consumption of caffeine increases urinary excretion of calcium, magnesium, potassium, sodium and chloride. The diuretic effect is lower in regular consumers of coffee (Maughan et Griffin, 2003).

Since adenosine has a protective effect on the kidneys (Nagase *et al.*, 1984), caffeine-induced antagonism of adenosine appears to indicate renal toxicity of caffeine (Tofovic *et al.*, 2002). An *in vivo* study in obese diabetic rats demonstrated an increase in proteinuria, intra-renal resistance, and accelerated deterioration of renal function on intake of caffeine (Tofovic *et al.*, 1999).

A case of hypokalaemia in a 50-year-old woman revealed by muscle fatigue led to a diagnosis of caffeine intoxication related to daily intake of more than 1200 mg (Tajima, 2010). Several mechanisms for the development of hypokalaemia have been proposed, such as release of catecholamines, inhibition of phosphodiesterase, or a direct tubular action.

*Taurine*

Experimental data from *in vitro* or animal models have not provided evidence of possible adverse effects of taurine on renal function. In contrast, administration of taurine was associated with positive effects in these studies (Hu *et al.*, 2009; Ikubo *et al.*, 2011; Das et Sil, 2012; Rovetta *et al.*, 2012).

Furthermore, taurine has a diuretic effect by inhibiting antidiuretic hormone (ADH) release and vasopressin release in the central nervous system, resulting in salt and water losses (Gentile *et al.*, 1994). However, the diuretic effect of scEDs appears to be primarily related to caffeine with no taurine-caffeine synergistic effect (Riesenhuber *et al.*, 2006).

*Glucuronolactone*

Two 13-week toxicology studies in CrI:CD(SD) rats were carried out with D-glucuronolactone administered orally at doses of 0, 300, 600 and 1000 mg/kg bw/day. The studies were performed by an applicant manufacturing scEDs to evaluate the safety of glucuronolactone in these drinks. In its 2009 opinion, EFSA reported the results of these two studies (EFSA, 2009).

The first study demonstrated cytoplasmic vacuolisation in 6/20 male rats in the control group and in 4/20 male rats receiving a dose of 1000 mg/kg bw/day. In female rats, vacuolisation was observed in 11/20 cases in the control group, 9/20 in the group receiving 300 mg/kg bw/day, 11/20 in those receiving 600 mg/kg bw/day, and in 11/20 receiving the dose of 1000 mg/kg bw/day. Incidence did not increase with treatment. However, lesions were described as mild (level 2) rather than minor (level 1) in 1/20, 1/20, 5/20 and 8/20 female animals respectively in the control group and the groups receiving 300 mg/kg bw/day, 600 mg/kg bw/day or 1000 mg/kg bw/day respectively, indicating a dose-dependent increase in lesion severity in female rats.

In the second study, histopathological findings revealed renal inflammation in a few male and female animals in the test and control groups. The applicant pointed out that these lesions were observed only in a few animals, at all doses, that they are unilateral and not related to treatment, and that they were typical of the strain of rat in the study. EFSA noted the absence of cytoplasmic vacuolisation in the various groups. On the basis of these data, EFSA granted the NOAEL of 1000 mg/kg bw/day proposed by the applicant, equivalent to the highest administered dose.

Furthermore, no clinical case report of nephrotoxicity directly implicating glucuronolactone was identified as part of this expertise.

#### *Renal effects of hyperosmolarity*

Another important characteristic of scEDs is their high sugar content. With an osmolarity of about 630 mOsm/l, most of these drinks<sup>23</sup>, like many sodas, are hyperosmolar (iso-osmolarity: between 270 and 330 mOsm/l). This hyperosmolarity may worsen dehydration.

#### **Renal effects of scEDs**

- scEDs have a diuretic effect attributable to caffeine and may therefore enhance water/electrolyte losses.
- The hyperosmolarity of some of these drinks is an exacerbating factor for dehydration.
- Consumption of scEDs increases the risk of dehydration. scEDs may further impair renal function in patients with pre-existing renal insufficiency or presenting risk factors (particularly diabetes and obesity).
- Concomitant consumption of alcohol is an additional factor for dehydration.

#### **g. Haematological effects**

##### **i. Cases reported under the Nutritional Vigilance Scheme**

Five cases of haematological effects were reported to the Agency. A causal relationship with consumption of scEDs was considered possible in two cases, one of eosinophilia and one of thrombocytopenia. Analysis of causality concluded that the relationship was unlikely in three cases, including two of thrombocytopenia (one with another cause considered very probable, primary immune post-vaccination thrombocytopenia).

##### **ii. Bibliographic data and possible mechanisms**

#### ***Cases reported in the literature***

Few data are available in the literature on the haematological effects of scED intake. A study of 50 young adults showed increased platelet aggregation one hour after consumption of 250 ml of scED (Worthley *et al.*, 2010). Another study reported major operative bleeding in two male patients whose daily consumption was estimated to be between 0.5 and 1.5 litres of scED. However, other possible causes of bleeding are not documented in the study (Foran *et al.*, 2012). No cases of thrombocytopenia were identified.

#### ***Study of the haematological effects of the main constituent of scEDs***

##### *Caffeine*

Several studies in animals and humans failed to demonstrate evidence of caffeine-related effects on platelet aggregation and function (Natella *et al.*, 2008; Toda *et al.*, 2010). However, it has been found that chronic consumption of caffeine resulted in increased expression of A<sub>2A</sub> adenosine receptors in platelets, along with an increased anti-aggregant effect of their agonist (Varani *et al.*, 1999; Varani *et al.*, 2000). Caffeine may improve endothelial function in humans (Umemura *et al.*, 2006).

<sup>23</sup> In 2011, scEDs containing sugar accounted for more than 94% of scED sales in supermarkets (>400m<sup>2</sup>) according to a monitoring survey on energy drinks in France (see. Annex 5)

*Taurine*

Taurine is a component of platelets. A study has shown reduced platelet aggregation following three months of taurine supplementation in subjects with type 2 diabetes (with decreased intra-platelet taurine concentrations), while no such change was found in healthy subjects receiving taurine supplementation (Franconi *et al.*, 1995). In contrast, a double-blind randomised study did not show evidence of an effect following taurine supplementation with 1.5 g/day for 8 weeks in 20 male subjects at risk for type 2 diabetes (Spohr *et al.*, 2005). Another study demonstrated decreased platelet aggregation induced by taurine supplementation at doses between 400 and 1600 mg/day in healthy subjects (Hayes *et al.*, 1989).

*In vitro* and animal studies have shown that taurine results in decreased platelet aggregation (Miglis *et al.*, 2002; Park *et al.*, 2007; Anand *et al.*, 2010).

A decrease in lymphocytes and an increase in neutrophils starting at 50 mg/kg bw/day of taurine administered for 60 days was also demonstrated in the rat (Anand *et al.*, 2010).

**Haematological effects of scEDs**

- The cases reported under the Nutritional Vigilance Scheme involved thrombocytopenia, but no explanation for their occurrence is currently available.
- The constituents of scEDs do not appear likely to cause increased platelet aggregation.

**h. Hepatic effects**

**i. Cases reported under the Nutritional Vigilance Scheme**

Clinical signs of suspected hepatic dysfunction have been observed in relation to consumption of scEDs in 3 cases reported to the Agency. The causal relationship to consumption of scEDs was considered possible in 1 case (changes in urine colouration associated with lumbar-pelvic pain) and unlikely in 2 cases (a case of subicterus associated with urticaria and a case of hepatitis and pancreatitis).

**ii. Bibliographic data and possible mechanisms**

**Cases reported in the literature**

Two published case reports (Apestegui *et al.*, 2011; Vivekanandarajah *et al.*, 2011) concern hepatic toxicity with a suspected causal relationship to scEDs (Table 12):

**Table 12: Cases of hepatic toxicity reported in relation to consumption of scEDs**

Reference	Adverse effect	Subject	Consumption of scED	Concomitant intake	Other investigated causes	Course
Vivekanandarajah <i>et al.</i> , 2011	Acute cytolytic hepatitis with secondary jaundice	F 22 years	10 cans/day over the preceding 2 weeks	None	Contrast-enhanced abdominal CT scan normal. Viral serology negative (hepatitis A, B, C and E) and toxicology negative (paracetamol). Auto-immune hepatitis not investigated.	Spontaneously favourable course. 1-month hepatic follow-up normal.
Apestegui <i>et al.</i> , 2011	2 episodes of hepatitis, without then with jaundice	M 16 years with liver transplant 4 years earlier, then 1 year before the 1 <sup>st</sup> episode	- 15 cans in 3 days, 2 weeks before the 1 <sup>st</sup> episode - 3 cans in 4 hours 2 days before the 2 <sup>nd</sup> episode	2 <sup>nd</sup> episode: 800 mg ibuprofen Chronic intake of immunosuppressant (tacrolimus)	Viral, auto-immune causes, vascular and biliary abnormalities ruled out	Not mentioned

In both these cases, the authors suspected the role of niacin (vitamin B3), a substance known to be potentially hepatotoxic at high doses. The scED consumed in the 1<sup>st</sup> case contained 30 mg of niacin per can (150% of the daily recommended allowance in the United States), equivalent to an intake of 300 mg/day via the drink for 2 weeks. The report did not indicate the type of niacin content (nicotinic acid or nicotinamide). The drink consumed in the 2<sup>nd</sup> case contained 20 mg of niacin/can.

Niacin is found as nicotinic acid or nicotinamide. The hepatic toxic effects of nicotinic acid have been observed frequently at a dose of 3 g/day<sup>24</sup> (EFSA, 2006). A case of acute hepatic insufficiency has been reported in a patient receiving treatment consisting of 500 mg/day nicotinic acid. EFSA therefore concluded that the severe adverse effects of nicotinic acid, particularly hepatotoxic effects, are mainly observed at doses higher than 500 mg/day<sup>25</sup>.

Concerning nicotinamide, few data are available but it is commonly thought that the risk of adverse effects is low at doses below 3g/day (EFSA 2006; FSA 2003). The maximum tolerable intake level for nicotinamide was established as 900 mg/day in adults, on the basis of the NOAEL determined in these studies, with a safety factor of 2.

#### **Hepatic effects of scEDs**

- No hepatic adverse effect reported under the Nutritional Vigilance Scheme was considered to have a likely causal relationship to consumption of scEDs.
- Two cases of hepatitis have been reported in the literature at high intake levels.

#### **3.3.3. Conclusions concerning the analysis of adverse effects reported under the Nutritional Vigilance Scheme and the characterisation of the hazards associated with consumption of scEDs**

Of the 212 cases that were analysed, a causal relationship to consumption of energy drinks was considered likely (13) or very likely (14) in 12% of cases, and possible (12) in 26% of cases. In view of the bibliographic data and the possible mechanisms analysed, the main symptoms observed were cardiovascular, neurological, and psycho-behavioural, and to a lesser extent gastro-intestinal. Given the current status of knowledge, the adverse effects described in relation to scEDs could be attributable to caffeine, in combination with predisposing factors or specific consumption patterns. There is however some evidence that other constituents of scEDs, such as taurine, may contribute to the effects and this aspect needs to be better documented.

<sup>24</sup> Dose administered in most clinical trials for the treatment of high cholesterol

<sup>25</sup> The maximum tolerable intake level for nicotinic acid was established as 10 mg/day in adults because it can cause skin redness, occurring at doses about 10 times below the initial doses at which hepatotoxicity has been observed

### 3.4. Study of the specific composition of scEDs

The nutritional vigilance working group studied the possibility that some of the risks associated with consumption of scEDs may be linked to the specific composition of these drinks, making them different to other drinks containing caffeine, particularly coffee and tea. The caffeine content in scEDs was compared with the caffeine content in other drinks containing this substance. The possibility of different caffeine bioavailability depending on the source of the caffeine was also investigated. The hypothesis was that caffeine contained in scEDs may have higher bioavailability compared to caffeine found in tea or coffee, which have natural bonds, specifically phenol ligands.

#### 3.4.1. Caffeine content in various drinks

A comparison of the caffeine content in various caffeine-containing drinks, including scEDs, is given in Table 13. The data on scED caffeine content are based on the indicated values for the 32% of these drinks on the French market that provide this information (see Section 3.1). Data on the caffeine content in the other drinks are based on the results of a bibliographic survey performed by the Observatory for the nutritional quality of foods Unit.

Table 13: Caffeine content in various drinks

Drink	Caffeine content in mg/100 g			Caffeine levels for standard containers	Source of data
	Minimum content	Maximum content	Mean content		
scED	12	32	30 <sup>26</sup>	72.5 (250 ml can)	See Section 3.1
<i>Other drinks</i>					
Espresso coffee	25	214	71.3	35.7 (50 ml)	(Desbrow <i>et al.</i> , 2007; Rudolph <i>et al.</i> , 2012)
Filter coffee or long espresso/espresso Americano coffee in pods	17,5	124,4	51,3	51.3 (100 ml)	(Camargo <i>et al.</i> , 1999; McCusker <i>et al.</i> , 2003; Olmos <i>et al.</i> , 2009; Yamada <i>et al.</i> , 2010; Jarosz <i>et al.</i> , 2012; Rudolph <i>et al.</i> , 2012)
Black generic "ready-to-drink" coffee*	19.7	214	55.1		(de Aragao <i>et al.</i> , 2005; Desbrow <i>et al.</i> , 2007; Olmos <i>et al.</i> , 2009; Yamada <i>et al.</i> , 2010; Jarosz <i>et al.</i> , 2012; Rudolph <i>et al.</i> , 2012; Fitt <i>et al.</i> , 2013)
Instant reconstituted coffee	20.1	85.6	48.4	48.4 (100 ml)	(de Aragao <i>et al.</i> , 2005; Olmos <i>et al.</i> , 2009; Jarosz <i>et al.</i> , 2012; Rudolph <i>et al.</i> , 2012)
Decaffeinated coffee	1.5	12	2.1	2.1 (100 ml)	(McCusker <i>et al.</i> , 2006a; Yamada <i>et al.</i> , 2010)
Brewed tea	9	50	27.2	54.2 (200 ml)	(de Aragao <i>et al.</i> , 2005; Olmos <i>et al.</i> , 2009; Yamada <i>et al.</i> , 2010; Jarosz <i>et al.</i> , 2012; Rudolph <i>et al.</i> , 2012; Fitt <i>et al.</i> , 2013)
Soda containing cola	4.1	13.2	9.7	32 (330 ml can)	(McCusker <i>et al.</i> , 2006b; Chou et Bell, 2007; Yamada <i>et al.</i> , 2010; Rudolph <i>et al.</i> , 2012) + French manufacturer data (2006)

\*This group combines different types of coffee, with or without details concerning the way it is consumed.

Certain scEDs sold in very small volumes (shots) can have much higher concentrations of caffeine.

<sup>26</sup> Weighted mean by market share

### 3.4.2. Description of phenol composition in coffee and tea

Polyphenols in tea and the factors affecting polyphenol content are well known and have been investigated in many studies (Astill *et al.*, 2001; Lin *et al.*, 2003; Wang *et al.*, 2009). Catechins are the most abundant phenols in green tea. Eight main catechins can be identified, whether esterified or not by gallic acid. Catechin content is much lower in black tea which does however contain theaflavins and thearubigins, formed from catechins. Consumption of one or two cups of tea provides about 30 mg of caffeine and 200 to 300 mg of phenols and polyphenols (i.e. a ratio of about 1 to 10).

Green tea contains about 5% phenol acids, including quinic acid, chlorogenic acid and caffeic acid (Viani, 1993; Bruneton, 2009; Wang *et al.*, 2009). Roasting leads to Maillard reactions which can reduce the caffeine content.

### 3.4.3. Study of complexations between caffeine and phenol molecules

Catechin-caffeine complexes with catechins in green tea (Hayashi *et al.*, 2004) and theaflavin-caffeine complexes with theaflavin in black tea (Charlton *et al.*, 2000) have been identified. These complexes have low binding energy and affinity.

Data available on coffee phenols are far less recent. Historically, chlorogenic acid was isolated for the first time in 1907 in the form of a complex with caffeine (Gorter, 1907; Gorter, 1908). A crystallographic study has been performed with potassium chlorogenate to investigate the structure of this complex. It showed the importance of hydrogen bonds, hydrophobic interactions, and potassium cation coordination in stabilisation of the complex (Martin *et al.*, 1986a; Martin *et al.*, 1986b).

In conclusion, caffeine forms a complex with phenol molecules in tea and coffee. However, the interactions are weak and can therefore easily be broken.

### 3.4.4. Study of the physiological implications of caffeine complexation by phenol compounds on caffeine availability profiles

The caffeine availability profiles were compared for various types of drinks. The saliva concentration was used as a marker of plasma concentrations and no differences were found for the caffeine saliva peaks ( $C_{max}$ ) following intake of a cola-type drink, coffee, or coffee capsules containing 400 mg of caffeine. The absorption rate was however higher when caffeine was consumed in the two drinks compared to caffeine intake in capsule form. The study showed no differences in pharmacokinetics between caffeine intake through coffee or a caffeine-containing soda, whether in terms of quantity absorbed or absorption rate (Liguori *et al.*, 1997). These results are consistent with findings in another investigation (van der Merwe *et al.*, 1988). However, an older study carried out in a very small number of subjects showed that caffeine absorption via a soda appeared to be delayed and protracted in time *versus* caffeine intake via coffee (Marks *et al.*, 1973). Moreover, a study appears to indicate that the half-life of caffeine is shorter after consumption in the form of a soda than as coffee. The study however had a small sample size, the data are presented in a fragmented way, and the caffeine intake differs depending on the form (Bonati *et al.*, 1982).

The different absorption rates sometimes observed between sodas and coffee could be explained by other properties of these drinks. The temperature of the drink affects the rate of gastric emptying and its availability in the large intestine, as well as its composition, density in caffeine and above all its carbohydrate content, osmolarity, and its energy load; all significantly slow gastric emptying (Brouns, 1998).

As a result of this mechanism, it is possible that absorption of caffeine may be slowed and the caffeine plasma peak delayed for hyperosmolar drinks like scEDs. However, there are no experimental data directly concerning scEDs confirming this hypothesis.

The pharmacokinetics of caffeine has also been evaluated for other intake forms. It has been shown that a 200 mg dose of caffeine was more rapidly absorbed when consumed as chewing gum *versus* caffeine consumed in capsule form ( $t_{max} = 55$  min for chewing gum vs 120 min for capsules), probably as a result of sublingual absorption in the case of chewing gum. Nonetheless, differences

between the intake form were found neither for the peak concentration nor the area under the curve (Kamimori *et al.*, 2002). This lack of difference could be related to significant inter-individual variability.

In addition to the analytical bioavailability studies on caffeine, the physiological effects of various intake forms on the level of physical performance have been measured. In well-trained athletes who received 4.45 mg/kg of caffeine in various forms, an improvement in endurance of nearly 31% (maximum time of continued running equivalent to 85% VO<sub>2</sub>max) was observed 1 hour after intake of caffeine capsules, compared to all other situations: caffeine equivalent in coffee, decaffeinated coffee, decaffeinated coffee + added caffeine, placebo capsule (Graham *et al.*, 1998). These results demonstrate a difference in the physiological effects of caffeine consumed either in capsule form, or in coffee. No difference in caffeine and paraxanthine plasma concentration levels was observed between the groups receiving caffeine, while adrenaline concentration before the run, one hour after intake, was higher in the group receiving caffeine in capsule form. It has therefore been suggested that there may be components in coffee that lessen the expected effects of caffeine. Compounds resulting from roasting of coffee beans may indeed alter the effects of caffeine, specifically by reducing its adenosine inhibitor effects (de Paulis *et al.*, 2002).

Phenols and polyphenols in coffee and tea may form complexes with caffeine but it appears that, in solution, this complexation is unlikely to cause appreciable changes in caffeine availability. Therefore, currently available data do not support the hypothesis that certain adverse effects observed after consumption of scEDs may be related to higher caffeine bioavailability in scEDs compared to coffee or tea. There is however little direct data to compare the bioavailability of caffeine depending on the form, whether an scED, coffee, or tea.

### 3.5. At-risk populations

#### 3.5.1. Characterisation of scED consumers

##### a. Characterisation of scED consumers in the Nutritional Vigilance cases

About 80% of the 212 eligible cases concerned males. The mean age of consumers was about 23 years, with a range of a few months to 66 years. Children and adolescents account for 65 cases. One case was reported in a pregnant woman<sup>27</sup>.

##### b. scED consumer prevalence and profiles according to the ANSES monitoring survey of scED consumption in France

According to the monitoring survey of scED consumption in France (ANSES, 2011) (see Annex 5 and Section 2. Organisation of the expert appraisal), 17% of individuals over 14 years of age<sup>28</sup> consumed scEDs in 2011. Extrapolation to the entire French population would indicate that there are about 9 million consumers in France aged over 14 years. Among these consumers, a quarter are below 25 years of age and 60% are male (Figure 4).

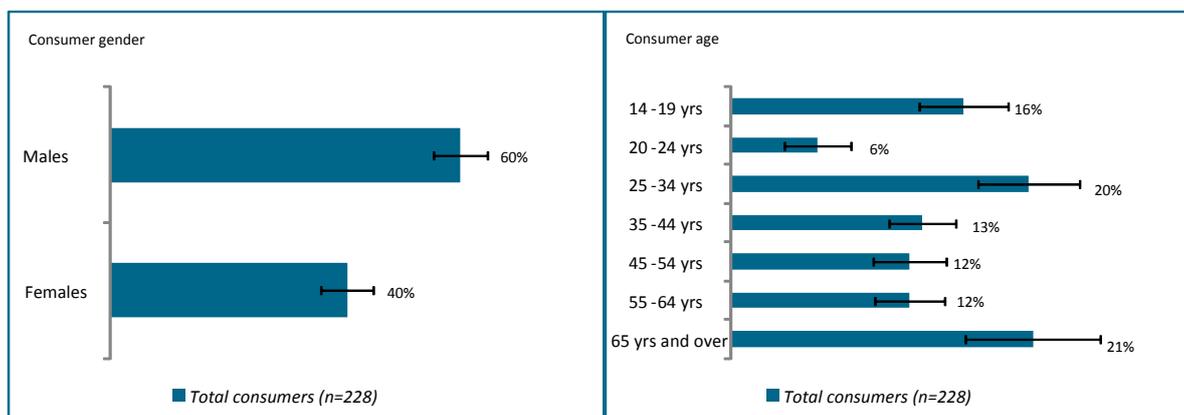


Figure 4 : Age and gender of scEDs consumers

##### c. Prevalence of consumption according to the EFSA consumer study (Zucconi *et al.*, 2013)

A survey concerning scED consumption was carried out at the request of EFSA (Zucconi *et al.*, 2013). It covered 16 European countries and included adults, adolescents and children.

About 30% of adults reported scED consumption at least once in the preceding year, with prevalence varying from 14 to 50% depending on the country, and with a higher prevalence in young adults. Approximately 12% of adult consumers were identified as "chronic heavy users", i.e. individuals who consume scEDs more than 4 or 5 times/week. "Acute heavy users", i.e. at least 1 litre per scED intake, accounted for 11% of adult consumers.

Consumption patterns in children and adolescents were also characterised as part of the European survey. 68% of adolescents (10-18 years of age) reported consuming scEDs at least once in the previous year. The prevalence of chronic and acute heavy users was of the same order of magnitude as that found in adults, i.e. about 12%. Approximately 18% of children (3-10 years of age) reported consumption of scEDs at least once in the previous year, with prevalence varying from 6 to 40% depending on the country. 16% of child consumers were considered to be chronic heavy users.

<sup>27</sup> Causality considered unlikely

<sup>28</sup> Age limit for the study population

### 3.5.2. Individual variability in responses to caffeine

Significant inter-individual differences in the responses to intake of a given amount of caffeine can be observed, concerning for example the anxiogenic effects (Silverman et Griffiths, 1992), the ability of the substance to delay sleep onset and affect sleep quality (Bchir *et al.*, 2006) and its expected effects on physical performance (Doherty, 1998; Meyers et Cafarelli, 2005). This inter-individual variability makes it difficult to determine the daily doses of caffeine that should not be exceeded to avoid effects on health. The level of tolerance can vary considerably depending on genetic factors (genetic variants coding for the proteins involved in the metabolism and/or action of caffeine) and non-genetic factors (physiological state, health status, and various co-exposures such as tobacco or alcohol).

#### a. Genetic factors modulating acute response to caffeine

##### i. Genetic modulation of caffeine consumption

Genetic factors have an age-dependent impact on spontaneous consumption of caffeine (irrespective of the source; coffee, tea, etc.), with the role of genetic factors increasing in adolescence and stabilising in adulthood (Kendler *et al.*, 2008). The genetic determinants of spontaneous consumption of caffeine are specific to this type of substance and are not associated with increased consumption of other substances, such as alcohol or nicotine (Hettema *et al.*, 1999; Kendler et Prescott, 1999). Likewise, the genetic markers of coffee dependence, and the extent of clinical signs of withdrawal, are not associated with dependence on other substances (Kendler *et al.*, 2007). In short, there is a genetic component to spontaneous consumption of caffeine that appears to be highly specific to this type of substance (Yang *et al.*, 2010). This component plays a greater role in heavy consumers (Kendler et Prescott, 1999). The role played by some genotypes of cytochrome P450 isoenzyme 1A2, or of adenosine receptors have been studied. The hypothesis was that these genetic variants, which accentuate the effects of caffeine, may reduce spontaneous consumption of caffeine. The findings showed that polymorphism of the gene for the A<sub>2A</sub> adenosine receptor is associated with spontaneous intake of caffeine, and the genotype associated with the most pronounced individual effects of caffeine is found primarily in subjects who consume low quantities (Cornelis *et al.*, 2007). Polymorphism of the *AHR* gene (gene coding for the aromatic hydrocarbon receptor), which regulates the activity of 1A2 isoenzyme, also plays a role (Cornelis *et al.*, 2011; Josse *et al.*, 2012). A relationship between polymorphism of the 1A2 isoenzyme (presented in the next paragraph) and spontaneous caffeine consumption has not been demonstrated (Cornelis *et al.*, 2007), although it remains a plausible determinant for consumption of caffeine (Cornelis *et al.*, 2011).

##### ii. Genetic variations in caffeine metabolism

The activity of the cytochrome P450 isoenzyme 1A2 accounts for 95% of caffeine metabolism. The activity of isoenzyme 1A2 is highly variable and constitutes a major source of variability in caffeine pharmacokinetics and inter-individual variability of the effects of caffeine. Studies in twin pairs have shown that the metabolism kinetics of caffeine is always more consistent in homozygous twins than in heterozygous pairs, confirming the heritability of cytochrome P450 isoenzyme 1A2 activity (Rasmussen *et al.*, 2002).

More than 150 different forms of the DNA coding sequence for the isoenzyme 1A2 differing by a single nucleotide (single-nucleotide polymorphism or SNP) have been described (Gunes et Dahl, 2008). SNP involving the presence of adenine or cytosine on intron 1 of the isoenzyme 1A2 gene has a strong influence on enzyme activity, with "variant C" being associated with slower caffeine metabolism (Sachse *et al.*, 1999). Conversely, carriers of the homozygous A/A genotype eliminate caffeine rapidly. The A allele appears to be recessive, with higher metabolic activity of isoenzyme 1A2 found in subjects with an A/A genotype compared to those with the C allele, who metabolise caffeine more slowly. In the initial description of this polymorphism, the distribution of genotypes C/C, A/C and A/A in a population of 236 subjects was 10, 44 and 46%, respectively (Sachse *et al.*, 1999). The proportion of individuals with the C allele (genotypes A/C and C/C), who metabolise

caffeine more slowly, was also 54% in another study with a larger sample size in a different population (Cornelis *et al.*, 2006).

Moreover, occurrence of adverse effects following intake of caffeine has been associated with isoenzyme 1A2 activity levels (Carrillo et Benitez, 1996). Some findings suggest, in addition, that genetic polymorphism for isoenzyme 1A2 may modify the observed association between consumption of caffeine and the risk of certain diseases, such as the risk of myocardial infarction (Cornelis *et al.*, 2006), hypertension (Palatini *et al.*, 2009; Guessous *et al.*, 2012), miscarriage (Signorello *et al.*, 2001), ovarian cancer (in A/A genotypes) (Goodman *et al.*, 2003), or reduced bone mineral density (Hallstrom *et al.*, 2010).

N-acetyltransferase 2 (NAT2) is also a key enzyme involved in caffeine metabolism. The NAT2 genotype also influences the 17U (1,7-dimethyluric acid) + 17X (1,7-dimethylxanthine)/137X (caffeine) ratio, which reflects caffeine metabolism (Welfare *et al.*, 2000). Common polymorphisms of the NAT2 gene determine the haplotypes (group of alleles of different genes located on the same chromosome and usually transmitted together) that are “slow” or “rapid” acetylators.

### **iii. Genetic variations in adenosine receptors**

Recent studies have shown polymorphism of the A<sub>1</sub> and A<sub>2A</sub> adenosine receptors. Polymorphism of the A<sub>2A</sub> receptors may underlie the different sensitivity levels to the effects of caffeine. Its effects on sleep are modulated by polymorphism of the gene coding for the A<sub>2A</sub> receptor (Rezey *et al.*, 2007; Byrne *et al.*, 2012; Landolt, 2012). Other genotypes and specific polymorphisms of this receptor are associated with another important adverse effect of caffeine, i.e. anxiety. This association was demonstrated for caffeine doses of about 150 mg (Alsene *et al.*, 2003; Childs *et al.*, 2008). Certain forms of A<sub>2A</sub> receptor polymorphism also appear to explain panic states or major anxiety reported after administration of psychotropics; these subjects are therefore particularly sensitive to anxiety induced by caffeine (Nardi *et al.*, 2009).

### **iv. Genetic variations in dopaminergic receptors**

Dopamine is one of the substances that mediates the stimulant effects of caffeine on motor activity (Zahniser *et al.*, 2000). Co-localisation of A<sub>2A</sub> adenosine receptors and D<sub>2</sub> dopamine receptors underlies functional interaction between these two neuromediators. Caffeine intake potentiates the excitomotor effects of cocaine and amphetamines, and this effect is enhanced by repeated intake of caffeine, suggesting modulation of D<sub>2</sub> receptors by caffeine via adenosine receptors (Cauli et Morelli, 2005). A relationship has been reported between polymorphism of the D<sub>2</sub> dopamine receptor and anxiety states induced by caffeine (Childs *et al.*, 2008), but the complex interactions between A<sub>2A</sub> and D<sub>2</sub> receptors, and responses to caffeine intake remain to be clarified.

### **v. Other genetic polymorphisms**

Less systematic associations between certain polymorphisms for other genes and response to caffeine have been found:

- In carriers of the neuropeptide S receptor genotype associated with anxiety and panic disorders, caffeine caused an increase in the jumpiness/startle response (Domschke *et al.*, 2012).
- Polymorphism of the *PRIMA1* proline-rich membrane anchor 1 gene may influence caffeine-induced insomnia (Byrne *et al.*, 2012).
- Catechol-O-methyl transferase (COMT) is an enzyme that degrades catecholamines such as dopamine, adrenaline and noradrenaline. Polymorphism of the gene coding for this protein is associated with the effect of caffeine on the self-reported increase in heart rate. Carriers of the Met/Met genotype, which results in slow COMT activity, self-report an increased heart rate *versus* Val/Val genotype carriers. These findings suggest that caffeine may increase the heart rate in a genetic subgroup of the population that has an altered ability to breakdown catecholamines such as adrenaline and noradrenaline (Brathwaite *et al.*, 2011).
- The effect of caffeine on bone loss is associated with the vitamin D receptor (VDR) genotype. Women with the *tt* genotype have levels of bone loss that are significantly higher

in the vertebral column than women with the TT genotype, when their consumption of caffeine is higher than 300 mg/day (Rapuri *et al.*, 2001).

## **b. Physiological factors**

### **i. Age**

#### *Childhood and adolescence*

Children and adolescents may have higher sensitivity to the effects of caffeine. In children, the effects of caffeine on anxiety have been observed from 2.5 mg/kg bw/day (Bernstein *et al.*, 1994). Other adverse effects such as nervousness, agitation, hyperactivity or sleep disorders have been observed at doses between 3 and 10 mg/kg bw/day (Nawrot *et al.*, 2003) (for review). On the basis of these findings, Health Canada considers that the caffeine intake in children should not exceed 2.5 mg/kg bw/day, equivalent to a mean of 45 mg for children aged 4 to 6 years, 62.5 mg/day for children aged 7 to 9, and 85 mg/day for those aged 10 to 12 years.

#### *Adults and the elderly*

Consumption of caffeine may increase urine excretion of calcium and other minerals, and decrease the efficacy of calcium absorption (Massey et Berg, 1985; Massey et Opryszek, 1990; Massey et Wise, 1992; Barger-Lux et Heaney, 1995). High intake of coffee has been associated with significantly reduced bone mineral density in middle-aged and older women (> 40 years), although this is not always observed (Nawrot *et al.*, 2003; Hallström *et al.*, 2012). Elevated caffeine intake in the absence of adequate calcium may therefore constitute a specific risk for adult and elderly women, a population that is at risk of osteoporosis.

### **ii. Gender**

Some of the effects of caffeine have been found to differ between men and women. It has been observed for example that women are more susceptible than men to sleep disorders related to caffeine consumption (Luciano *et al.*, 2007), even though the pharmacokinetics of the compound is not markedly affected by gender (McLean et Graham, 2002). There does not appear to be a gender difference concerning increased blood pressure after intake of coffee (Farag *et al.*, 2010).

### **iii. Pregnancy**

Caffeine crosses the placental barrier and is excreted in breast milk. Its half-life is increased during pregnancy, and an association has been found between duration of pregnancy and caffeine half-life (Ortweiler *et al.*, 1985; Nawrot *et al.*, 2003).

Several large-scale reviews have documented the risks of caffeine during pregnancy, specifically the risk of miscarriage, premature labour, intra-uterine growth retardation, and the risk of congenital malformations. Health Canada (Nawrot *et al.*, 2003) concluded that pregnant women represent a risk group requiring specific control of caffeine intake, which should be limited to 300 mg/day. The most recent evaluation was performed in 2008 by the British Food Standards Agency (FSA). It concluded that caffeine intake during pregnancy was associated with intra-uterine growth retardation. It was not possible to confirm with certainty that there was a causal relationship or whether it was related to residual confounding bias. Nonetheless, as a precaution the hypothesis of a causal relationship was retained. It was not possible to determine a minimum level below which no increase in risk was observed, but it appeared probable that the risk of intra-uterine growth retardation was higher for daily intakes of 200 mg, or even less. However, even if there is a causal relationship, it appears likely that the increased incidence of foetal growth delay at intakes below 200 mg/day is less than 2%. A literature review suggested a positive association between caffeine intake levels and the risk of miscarriage. Uncertainties concerning the link could not be clarified due to recall bias (on retrospective evaluation of caffeine consumption) and because of difficulties in taking all possible confounding factors into consideration. Data on other types of risks, such as prematurity or malformations, were insufficient to conclude on the effects of caffeine consumption. In view of these findings, the FSA recommended that pregnant women limit their consumption to less than 200 mg per day, thus lowering their former recommendation of 300 mg/day (FSA, 2008).

These data suggest that women should limit their consumption of caffeine during pregnancy and breast-feeding.

**iv. Ethnic origin**

People of African and Asian descent metabolise caffeine more slowly than Caucasians as a result of interethnic differences in the genetic distribution of the isoenzyme 1A2 of the cytochrome P450 (Gunes et Dahl, 2008).

**c. Specific effects of caffeine in certain diseases**

**i. Hypertension**

Caffeine is known to increase blood pressure, which constitutes a cardiovascular risk factor. Unlike the other consequences of caffeine intake, regular consumption does not completely abolish the hypertensive response (James, 1996). A family history of hypertension may also enhance the hypertensive response to consumption of caffeine (Greenstadt *et al.*, 1988).

**ii. Mental disorders**

Caffeine intake may increase anxiety states and this effect may be enhanced in individuals with higher baseline levels of anxiety, or with panic disorders (Lee *et al.*, 1985; Beck et Berisford, 1992; Totten et France, 1995; Keogh et Chaloner, 2002).

**iii. Liver disease**

Caffeine is more slowly metabolised in patients with severe liver disease, with the delay depending on disease severity (Statland *et al.*, 1976; Baker *et al.*, 1995; Bechtel *et al.*, 2000).

**iv. Urinary or faecal incontinence**

Due to its diuretic effect, high intake levels of caffeine may be detrimental in subjects with chronic urinary incontinence. Studies have shown that caffeine consumption is associated with an increased risk of urinary incontinence (Jura *et al.*, 2011; Gleason *et al.*, 2013).

For individuals with faecal incontinence, it is generally inadvisable to consume caffeine-containing drinks that may stimulate intestinal motility and relax the internal anal sphincter (Crowell *et al.*, 2010).

**v. Gastro-intestinal disorders**

Patients are generally advised to limit their consumption of caffeine if they have oesophagitis or gastro-oesophageal reflux.

**d. Effects of regular consumption of caffeine**

It was demonstrated early on that subjects develop tolerance to the effects of caffeine (Robertson *et al.*, 1981; Evans et Griffiths, 1992). A questionnaire administered to more than 200 young housewives showed that the subjective effects of caffeine depend on previous consumption (Goldstein et Kaizer, 1969; Goldstein *et al.*, 1969). Furthermore, heavy consumers of coffee have fewer sleep disruptions and fewer obvious signs of nervousness after coffee taken in the morning compared to non-consumers (Bolton et Null, 1981). The increase in sleep onset time is less pronounced in heavy consumers of caffeine after intake of 150 to 200 mg of caffeine before going to bed (Goldstein *et al.*, 1965b). Nonetheless, habituation to caffeine consumption does not prevent increased heart rate at rest in response to a combination of caffeine and stress (Lane *et al.*, 1990).

Regular consumption of caffeine affects the activity of cytochrome P450 isoenzyme 1A2, and thereby caffeine metabolism. As a result, caffeine plasma concentrations following coffee intake decrease more rapidly in subjects who are less sensitive to the effects of the substance on sleep, i.e. those who consume the highest quantities (Bchir *et al.*, 2006). Repeated intake of large quantities of caffeine (more than 3 cups of coffee per day) increases expression of adenosine A<sub>1</sub> receptors in the central nervous system (Marangos *et al.*, 1984), and results in increased isoenzyme 1A2 activity, in turn reducing the stimulant effects of caffeine (Djordjevic *et al.*, 2008). In addition, this significant effect of high levels of coffee intake on caffeine metabolism is enhanced by certain genotypes of the gene coding for the isoenzyme 1A2 of cytochrome P450 (Djordjevic *et al.*, 2010).

Regular consumption of caffeine should therefore be taken into account when studying the expected effects of intake of coffee at determined doses.

#### **e. Implications of co-exposures on the effects of caffeine**

##### **i. Smoking**

Consumption of tobacco interferes with caffeine metabolism and the effects of tobacco depend on polymorphism of isoenzyme 1A2. For certain genotypes, consumption of tobacco increases enzyme activity and accelerates caffeine metabolism (Gunes *et al.*, 2009), while for others, tobacco slows caffeine metabolism and enhances its stimulant effects (Nakajima *et al.*, 1999). An acceleration of caffeine metabolism by tobacco is observed in subjects with short caffeine half-lives (A/A genotype), whereas tobacco slows metabolism of caffeine in carriers of the C allele in whom caffeine is slowly eliminated (C/C and A/C genotypes) (Sachse *et al.*, 1999; Cornelis *et al.*, 2006).

Moreover, combined consumption of caffeine and tobacco has a detrimental synergistic effect on aortic stiffness (Vlachopoulos *et al.*, 2004).

##### **ii. Alcohol consumption**

Alcohol may inhibit caffeine metabolism as a result of metabolic competition for P450 cytochromes. An increased half-life and decreased caffeine clearance have been demonstrated in humans following single intake of 0.8 mg/kg of alcohol (Mitchell *et al.*, 1983), and after intake of 50 g of alcohol/day for one week (George *et al.*, 1986).

The effect of alcohol consumption on caffeine activity will be discussed in detail in Section 3.6.2 concerning the study of the specific risks related to combination of scEDs and alcohol.

##### **iii. Drug therapy**

Caffeine may interact with certain medicines and potentially alter their effects. This is particularly the case for psychotropic drugs (Berkowitz *et al.*, 1971; Pakes, 1979; Bolton *et al.*, 1981). Oral contraceptives also affect caffeine metabolism by reducing clearance of the compound (Fantoli, 1981; Abernethy *et al.*, 1985; Balogh *et al.*, 1995). Although caffeine reduces melatonin levels in women in the luteal phase, it has little effect on melatonin levels in users of oral contraceptives (Wright *et al.*, 2000).

- The high variability observed in the excitatory and psychostimulant effects of caffeine can be explained by the inter-individual variability both in the metabolism of caffeine, and its biological effects on the central nervous system.
- This variability is related in particular to the genotype, the physiological state, caffeine consumption habits, and co-exposure such as tobacco or medicinal products.
- Caffeine metabolism may be slowed in patients with certain disorders (liver disease) and its adverse effects enhanced (hypertension, mental disorders, urinary and faecal incontinence, ulcer, oesophagitis, gastroesophageal reflux).

- Polymorphism of the gene for isoenzyme 1A2 of cytochrome P450 involved in the hepatic metabolism of caffeine is a major factor underlying variations in the pharmacokinetics of caffeine and the inter-individual variability of its effects. Studies in various populations have estimated the prevalence of slow metabolisers to be about 55% of the population.
- Polymorphism of the A<sub>2A</sub> adenosine receptors of the central nervous system may also explain differences in susceptibility to the effects of caffeine on sleep and anxiety.
- These variability factors for the biological effects of caffeine make it difficult to determine the dose associated with adverse effects and complicate analysis of the risks related to certain intake levels. Interactions between these different factors can be complex, such that it is difficult to isolate the effect of a given factor.

### 3.5.3. Study of the specific risks for children and adolescents

Energy drinks constitute a new source of caffeine intake in children and adolescents. So-called EDs account for up to 15% of the total caffeine intake in French children according to the consumption data collected by EFSA (Zucconi *et al.*, 2013).

#### a. Presentation of paediatric cases reported under the Nutritional Vigilance Scheme

For the 65 eligible paediatric cases, analysis of the causal relationship to scEDs provided the following results:

- Very likely (I4) in 4 cases;
- Likely (I3) in 6 cases;
- Possible (I2) in 20 cases;
- Unlikely (I1) in 32 cases;
- Ruled out in 3 cases.

Cases with very likely, likely or possible causality<sup>29</sup> are presented in Table 14 below.

**Table 14: Paediatric cases under the Nutritional Vigilance Scheme with very likely (I4), likely (I3) and possible (I2) causality (listed by age)**

Ref	Quantity consumed	Subjects	Effects	Identified concomitant intake	Exercise	Causality
353321	3 sips	M, 1 year 8 m 11 kg	Agitation/Excitement	-		I2
465939	0.5 can	M, 3½ years	Drowsiness/Obnubilation	-		I2
100210265	4 cans	M, 4 years	Agitation/Excitement	-		I4
369130	3 cans	M, 8 years	Chest pain	-		I3
370105	4 cans	M, 10 years 30 kg	Distress/Anxiety/Generalised tremor/Shivering	-	-	I2
318723	500 ml	M, 11 years	Agitation/Excitement	-	-	I2
353426	1.75 l	F, 12 years	Tachycardia	-	-	I2
336929	1 can	M, 12 years	Lower abdominal pain (sub-epigastric)	-	-	I4
384948	?	M, 12 years	Tachycardia/Hyperhidrosis	-	-	I3
369450	50 ml	M, 12 years 30 kg	Tremor/Memory disorders	-	-	I3
100229354	500 ml	M, 13 years 38 kg	Precordial pain	-	-	I4
363136	500 ml	M, 13 years	Tachycardia/Respiratory pain/Chest tightness	-	-	I2

<sup>29</sup> The cases in children and adolescents with possible causality are presented in addition to likely and very likely cases for information purposes, in view of the specific attention paid to this population group.

Ref	Quantity consumed	Subjects	Effects	Identified concomitant intake	Exercise	Causality
353336	1 l	F, 13 years 85 kg	Nausea/Generalised tremor/Shivering/Tachycardia/Agitation/ Excitement	-	-	I2
100209869	2.5 l	M, 13 years 90 kg	Digestive pain (poorly localised)	-	-	I2
371663	?	M, 14 years	Tonic-clonic seizures with loss of consciousness and head trauma (left and frontal temporal haematomas due to fall)	-	Exercise	I3
225480	250 ml	M, 14 years	Generalised tremor/Shivering/Agitation/ Excitement	-	-	I2
340244	1 can	F, 14 years 53 kg	Delusions/Hallucinations/Sleep disorders/Tachycardia	-	-	I2
385526	125 ml	F, 15 years 50 kg	Hypotonia	-	-	I2
437574	1.5 l	F, 15 years 55 kg	Agitation/Excitement/Generalised tremor/Shivering/Tachycardia/Character and behavioural disorders (aggressiveness/negativity/irritability)/ Malaise (state of)	-	-	I2
19019	750 ml	M, 15 years	Agitation/Excitement/Malaise (State of)	-	-	I2
396954	5 cans	M, 16 years	Tachycardia/Digestive pain (poorly localised)/Nausea	-	-	I2
2012-211	2-6 cans/day	M, 16 years 75 kg	Resuscitated heart attack	-	Exercise	I2
2012-021	?	F, 16 years 50 kg	Death (cardiac arrest)	-	-	I4
322460	4 cans	F, 16 years 48 kg	Nausea/Agitation/Excitement/Hypertension/ Tachycardia/Vomiting	-	-	I3
361716	15 cans	M, 17 years	Bradycardia	-	-	I3
355270	750 ml	M, 17 years	Tachycardia/Hypertension	-	-	I2
403847	6-7 cans	M, 17 years	Hyper eosinophilia (blood)	-	-	I2
528529	500 ml/day	F, 17 years 70 kg	Attention disorder/Joint pain/Headache	-	-	I2
346557	1 can	M, 17 years	Dyspnoea/Tachypnoea/Polypnoea/ Hyperpnoea/Urticaria/Tachycardia	-	Exercise	I2
369589	30 cans	M, 17 years	Tachycardia/Joint pain/Distress/Anxiety	-	-	I2

I4: very likely causality; I3: likely causality; I2: possible causality

NB: the quantity is sometimes indicated in number of cans but it is not possible to expand on this information since the volume of the cans is not given in the report. For information, according to a survey monitoring consumption of scEDs carried out by ANSES (see Annex 5), in 2011, 82% of consumers only drank cans containing 250 ml and 3% only cans containing 500 ml (15% consumed containers of both volumes); in addition, 50% of all products were sold in 250 ml containers.

In these cases in children and adolescents, the most commonly reported symptoms, such as agitation and excitement, anxiety, tachycardia, or chest pain, were cardiovascular and psycho-behavioural, reflecting symptoms that are likely to be observed after intake of high quantities of caffeine.

Of the three cases of cardiac arrest with causality considered at least possible (see Table 4), two were in adolescents of 16 years of age.

The sample includes cases of young children (below 10 years of age) consuming large quantities of scED (3 to 4 cans).

#### **b. Bibliographic data**

Several recent review articles have focused on the specific effects of scED intake, specifically caffeine, in children and adolescents (Temple, 2009; Bigard, 2010; Pennington *et al.*, 2010; Seifert

*et al.*, 2011). These studies underscore the fact that childhood and adolescence are risk periods during which caffeine may have specific dangers for the developing body.

**i. Risk of exceeding upper limit values**

The first important point is that at the same level of intake, the ingested dose in children and adolescents in relation to body weight is higher than in adults. This involves a greater risk in children and adolescents of reaching limit values at which adverse effects are described. As such, intake of one can of scED containing 80 mg of caffeine results in a dose of 2.7 mg/kg bw in a 10-year-old child weighing 30 kg, and in a dose of 3.2 mg/kg bw in an 8-year-old child weighing 25 kg. These levels exceed the dose of 2.5 mg/kg bw of caffeine considered by many agencies as the upper limit value for daily consumption in children (see Section 3.7.1.b).

**ii. Sleep and caffeine in children and adolescents**

Sleep parameters such as duration, and time of awakening and falling asleep, change with age. Marked changes occur during puberty: decreased duration of sleep, change in sleep times (delay in phases and sleep onset), changes in the durations of the various phases (slow-wave sleep and REM sleep). These changes are related to circadian and homeostatic modifications associated with puberty, but also to changes in environmental and psychosocial factors in adolescence.

Adolescents tend to go to sleep late and their bedtime may be delayed by consumption of psychostimulant substances such as caffeine. Their commitments, particularly at school, mean that they get up early, resulting commonly in sleep deficits in this population.

*Harmful effects of insufficient sleep*

Insufficient duration of sleep has multiple consequences.

Sleep deficits may lead to daytime drowsiness. A recent meta-analysis showed that in children, the duration of sleep is correlated with cognitive efficiency, particularly executive functions, performing complex tasks that require several cognitive functions, and school performance. Unlike in the adult population, it is not correlated to attention and memory (methodological differences and immaturity of the brain in children have been suggested as explanations for these differences). A short duration of sleep is also associated with greater behavioural problems (Astill *et al.*, 2012).

Sleep disorders are also linked to increased risk of somatic diseases (hypertension, cardiovascular diseases, diabetes, obesity, etc.) or psychiatric disorders (anxiety, depression, etc.) (Bonnet *et al.*, 2010; Lund *et al.*, 2010; Hargens *et al.*, 2013), although the nature of these relationships needs to be clarified.

Poor sleep quality may also be a factor that increases the risk of addictive behaviour, particularly in children and adolescents in whom the brain is not yet mature. Sleep disorders are common in individuals with excessive consumption of alcohol (Perney *et al.*, 2012; Spiegelhalter *et al.*, 2013). They are also associated with a risk of relapse in alcohol-dependent individuals who have become abstinent (Brower *et al.*, 2010). The association appears to involve a relationship between consumption of alcohol and circadian rhythm and sleep genes. In this way, a variant of the *Per2* gene involved in the functioning of the suprachiasmatic circadian oscillator (regulator of circadian rhythms) and in sleep quality, also appears to be associated with increased alcohol consumption (Wulff *et al.*, 2010). A correlation has been demonstrated between occurrence of sleep disorders at 3 to 8 years of age and early onset of psychoactive substance use (only in boys) (Wong *et al.*, 2009).

Recent progress in neurobiology provides some insight into the relationship between sleep and behaviour. A<sub>2A</sub> adenosine receptors which play a role in alertness and locomotor activity are highly expressed in the dorsal striatum but also in the ventral striatum (nucleus accumbens) where they regulate glutamatergic transmission. It is perhaps significant that the nucleus accumbens (one of

the structures in the pleasure and reward circuit) is a brain region highly involved in the development of addictive behaviours (Ferre *et al.*, 2007; Lazarus *et al.*, 2011).

As a result, there is a functional relationship between sleep regulation and motivated behaviours. Sleep deficit may disrupt this relationship, resulting in deregulation of these behaviours, related to increased reactivity of the neurocircuits that act in pleasure and reward, and that may in this way underlie addictive behaviour.

#### *Effects of caffeine on sleep*

Caffeine has well-known effects on sleep: delay of sleep onset, reduced sleep duration, and poor sleep quality. These effects vary from person to person particularly because of genetic polymorphism of adenosine receptors.

Consumption of caffeine in adolescents is therefore likely to exacerbate the sleep disorders observed in this population, as well as their negative consequences. In a study enrolling American high-school students between 12 and 18 years of age, 33% of participants reported falling asleep in class and caffeine consumption was 76% higher in these subjects (Calamaro *et al.*, 2009). A more recent study carried out by the same team showed that children (6-10 years) who consumed caffeine-containing drinks slept 15 minutes less per night than non-consumers (Calamaro *et al.*, 2012). Furthermore, Giannotti *et al.*, (2002) compared "evening-type" adolescents (14-18 years) to "morning-type" adolescents. Evening-types slept less, complained more of daytime drowsiness, and had more attention disorders. They also consumed greater volumes of caffeine-containing drinks but also sleep-inducing substances.

### **iii. Caffeine and the risk of developing addictive behaviour**

Although the risk of developing caffeine dependence remains controversial, studies have shown that about 20% of adolescents who consume caffeine could be considered dependent based on generally accepted criteria (Temple, 2009).

It is possible that early consumption of caffeine, for example in the form of scEDs, may contribute to the development of addictive behaviours either to caffeine, which nevertheless has a low addiction potential, or to other substances. Early consumption of other psychoactive substances such as alcohol, tobacco, and cannabis is considered to be a risk factor for the subsequent development of addiction (Hingson *et al.*, 2006; Schneider, 2008; Chen *et al.*, 2009; Picherot *et al.*, 2010; Kendler *et al.*, 2013). This may be explained by neocortical immaturity in children and young adolescents, which could compromise rhinencephalon control involved in emotion. Children and young adolescents may therefore be more likely to feel the emotions and effects related to certain substances and situations. Delaying the age of initial consumption is one of the strategies used to prevent the development of addictive behaviour.

#### *Study of the specific risks in children and adolescents*

- In the cases reported under the Nutritional Vigilance Scheme in children and adolescents, the most commonly described symptoms, such as agitation and excitement, anxiety, tachycardia, or chest pain, reflect effects that are likely to be observed following consumption of caffeine in high quantities. It is cause for concern that high quantities of scED (3 to 4 cans) can be consumed by young children (< 10 years of age).
- Given their lower body weight, children and adolescents have a higher risk of adverse effects due to caffeine compared to adults for the same amount of caffeine. These effects include neurological, psycho-behavioural and cardiovascular disorders.
- Consumption of caffeine in children and adolescents may cause sleep disorders and disrupt changes in sleep described in adolescents.
- The resulting sleep disorders lead to tiredness and daytime drowsiness. This may lead to development of a vicious circle with intake of caffeine to counteract drowsiness.
- Poor sleep quality affects cognitive abilities and academic performance.
- Chronic sleep deficit may promote somatic disorders (hypertension, cardiovascular diseases, diabetes, obesity), and psychiatric disorders (anxiety, depression, etc.).

- Finally, sleep disorders may disrupt the relationship between sleep and motivated behaviours due to increased reactivity of the neurocircuits implicated in pleasure and reward. Such deregulation may be a risk factor for the occurrence of addictive behaviour, particularly in children and adolescents who have not reached full brain development.
- Early consumption of psychoactive substances like caffeine is a risk factor for progression to addictive behaviour.
- As a result, caffeine and caffeine-containing drinks should be avoided in children and adolescents.

***Conclusions concerning inter-individual variability in responses to caffeine and risk populations***

- Sensitivity to scEDs varies from person to person, particularly as a result of inter-individual variability to the effects of caffeine.
- This increased sensitivity in some consumers may explain why cases are reported at very different doses, from a single can in certain reports.
- Inter-individual differences in sensitivity to caffeine's effects are related to genotype, particularly polymorphism of the genes for cytochrome P450 and adenosine receptors, to physiological or health status, to caffeine consumption habits, and to co-exposures such as tobacco or intake of medicinal products.
- Interactions between genotype, physiological or pathological conditions, and co-exposures may potentiate the effects of caffeine.
- Children, adolescents and pregnant women are at-risk populations with increased sensitivity to the effects of caffeine and in which scEDs should be avoided.
- In patients with certain disorders, caffeine metabolism is slowed (liver disease) and its adverse effects enhanced (hypertension, arrhythmia, psychiatric disorders, urinary and faecal incontinence, renal insufficiency, ulcer, oesophagitis, gastroesophageal reflux).

### 3.6. At-risk situations

#### 3.6.1. Patterns of scED consumption

##### a. Patterns observed from the Nutrition Vigilance scheme

Of the 212 cases ultimately included in the study, the quantity of scEDs consumed varied greatly, ranging from a few sips to 40 cans<sup>30</sup>.

Co-consumption of alcohol and scED occurred in 27% of the studied cases. Furthermore, 4% of the reported cases were observed in people who consumed scEDs in a context of physical exercise.

##### b. Patterns of consumption observed in a survey of scED use in France (ANSES survey, 2011)

###### i. Frequency of consumption

According to the survey of scED consumption in France carried out by ANSES in 2011 (see Annex 5), 32% of scED users indicated that they drank scEDs at least once a week (Figure 5). An equal percentage (33%) consumed scED less than once a month.

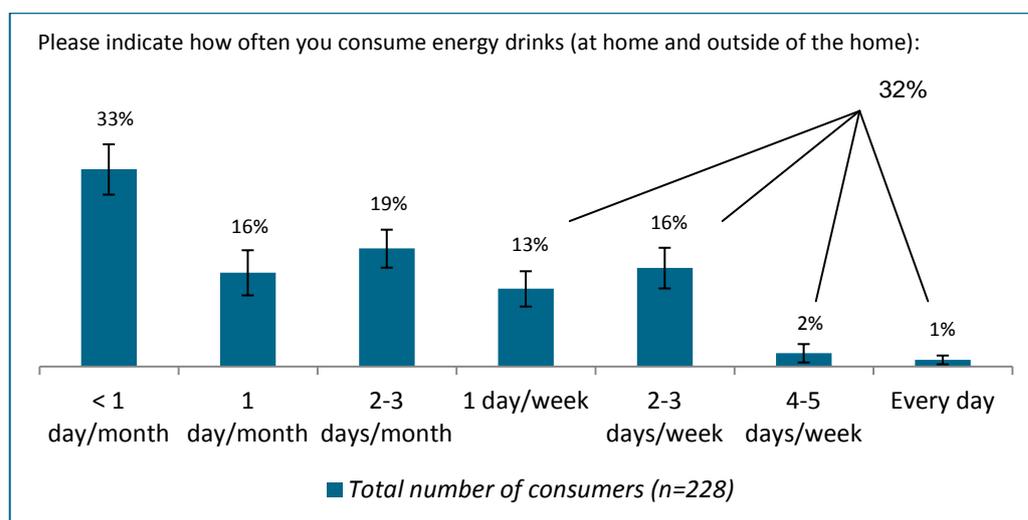


Figure 5: Frequency of scED consumption

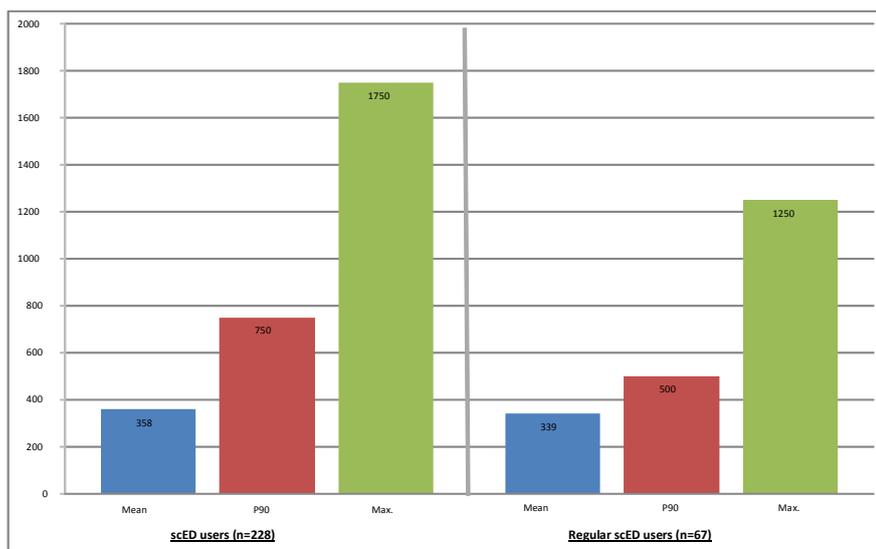
This survey showed that there are daily or near-daily consumers, although the percentage of these consumers could not be precisely estimated given the small sample size (n = 228).

###### ii. Quantities consumed

Figure 6 gives the average quantities consumed, as well as the 90<sup>th</sup> percentile and the maximum amount consumed, in one drinking day. The average consumption in one drinking day is 358 mL in all scED consumers and is fairly similar in regular consumers, defined as those who consume scEDs at least once a week (339 mL). One-quarter consume more than 500 mL during one scED drinking day. The highest observed amount consumed was 1.75 L in one day.

Additional analyses show that the quantity consumed in one day is not significantly associated with the age of the consumer.

<sup>30</sup> These quantities may have been consumed over periods of very different duration, as this is not always indicated in the reports.



**Figure 6: Quantity of scED consumed (mL) during one drinking day**

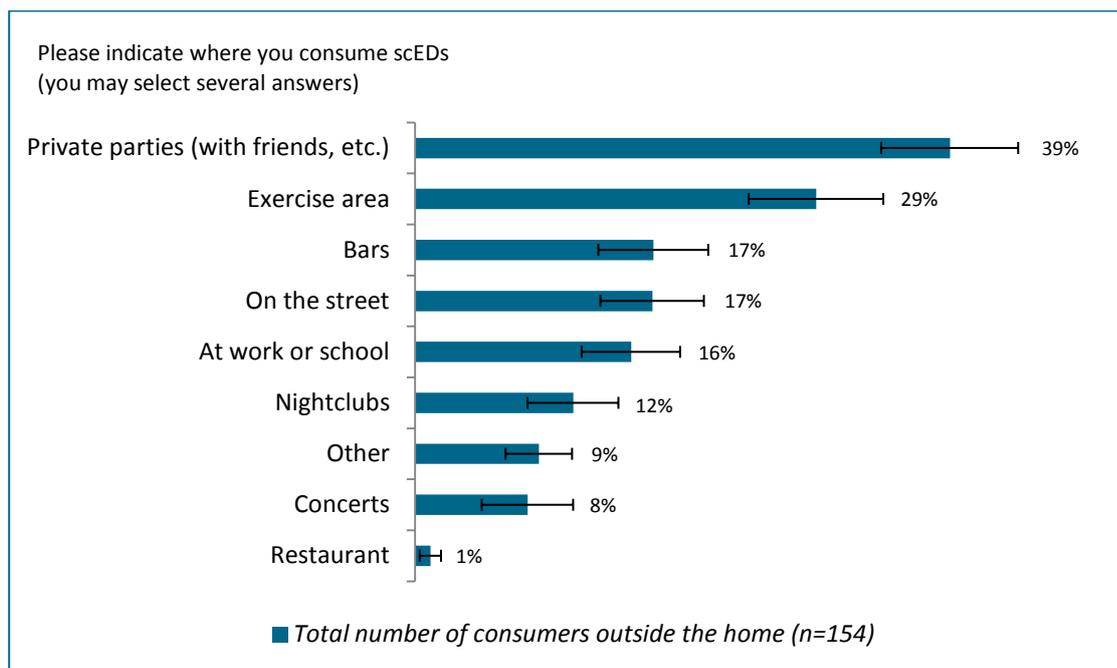
Multiplying the frequency of consumption with the number of cans ingested in one drinking day provides the average daily consumption of scEDs. Thus, average daily consumption is 46 mL (median = 21 mL; 90<sup>th</sup> percentile = 89 mL), or about the equivalent of one-fifth of a 250 mL can. In regular users, average daily consumption is twice as high (108 mL) due to the increased frequency of use.

According to the ANSES survey, 82% of consumers only drink 250 mL cans and 3% only drink 500 mL cans (15% consume both formats) (note: in 2011, 50% by volume of all scEDs were sold in the 250 mL format). On one drinking day, 76% consume only one 250 mL can, 18% consume two cans and 6% consume more than two cans. The majority of 500 mL can users only consume one can in one drinking day.

### iii. Places of consumption

Those who consume scEDs outside the home were questioned on where they consume scEDs. scED consumption is a relatively festive activity because 39% of consumers declared that they consume scEDs during parties, 18% in bars or restaurants, 12% in night clubs and 18% during concerts (Figure 7).

For 29% of consumers, consumption took place during a sporting activity. Finally, slightly more than 5% of the population consume scEDs in a car, on motorways or during travel (accounting for 63% of the "Other" places of consumption).



**Figure 7: Places of scED consumption**

**c. Study of high scED consumers by the German food safety agency (BfR)**

The German food safety agency (BfR) carried out a study to characterise the patterns of high scED consumption. These results were presented at a round table held on 19 November 2012 at the BfR. The purpose of the BfR study was to study consumption in high consumers of scEDs. High consumers were defined as those who had consumed at least 500 mL of scEDs – or 60 ml in shot format – in the previous 24 h. They were recruited in various settings where consumption can be high, such as at parties or in night clubs (Group 1), during music festivals (Group 2), sports events (Group 3) or during weekends of on-line gaming (Group 4). Of the 6765 consumers contacted, 508 interviews were completed (8% of the contacted subjects), of which 489 provided useful information and fitted with the criteria of high consumers.

This population of high consumers was made up of more males than females (from 67 to 87% men, depending on the group) and the average age was between 21 and 25 years.

Half of the respondents consumed scEDs at least once a week and the main reasons for consumption included enhanced physical performance, the stimulating and invigorating effects of scEDs and their taste. The average volumes of scEDs consumed pure (without being mixed with another beverage) during the 24 h preceding the interview was between 680 mL and 1545 mL depending on the group, whereas consumption at the 95<sup>th</sup> percentile was between 1500 mL and 3849 mL. The highest consumed amount was 6.5 L. The average quantities consumed together with alcohol were higher. Moreover, more than two-thirds of the population had consumed other beverages containing caffeine the day of the study (in particular coffee and cola drinks).

**3.6.2. Analysis of the risks related to the consumption of scEDs together with alcohol**

According to the French survey of scED consumption, 16% of scED consumers mix scEDs with alcoholic beverages at least occasionally (rarely, often, or always), of which 33% mix them often or always (i.e. 5% of all consumers). Young people mix scEDs with other beverages the most often: 22% mix alcohol and scEDs at least occasionally in the 35 years and younger group, whereas only 13% of the 35-54 age group and 10% in the 55 and older group do so. However, 35-54 year olds show the highest frequency of mixing scEDs with other beverages (often or always).

In the EFSA survey of European consumption (Zucconi *et al.*, 2013), 56% of adults and 53% of adolescents who consume scEDs in Europe indicated that they had consumed scEDs with alcohol at least once in the past year.

In addition, many cross-sectional studies, most of which concern university students 18 years and older, reveal frequent co-consumption (see Annex 2). The percentages of consumers mixing scEDs with other beverages are nonetheless difficult to compare among the different studies, particularly because consumption is evaluated over very different time periods: in a lifetime, the past year, the past month, past few weeks, etc.

This specific co-consumption was thus the subject of a separate risk analysis.

#### **a. Observation studies on scED consumption together with alcohol**

The majority of available studies concern university students. Alcohol consumption and scED consumption as well as behaviour associated with consumption of either beverage have almost always been assessed using questionnaires. These studies are thus based on declarative data, meaning that bias cannot be ruled out. Blood alcohol level was measured only in a few rare studies, as indicated below.

##### *scED consumption, alcohol consumption and risk-taking behaviour*

Several studies have compared alcohol consumption in scED users with that of non-users, or according to the frequency of scED consumption. Higher alcohol consumption has been observed in scED users compared to non-users (Arria *et al.*, 2010). Likewise, higher frequency of scED consumption has been associated with higher frequency of alcohol consumption and with higher quantities of alcohol consumed (Miller, 2008; Arria *et al.*, 2011; Velazquez *et al.*, 2012).

These studies also report more frequent risk-taking behaviour associated with scED consumption (Miller, 2008) as well as higher drug use (Miller, 2008; Arria *et al.*, 2011).

##### *Co-consumption of scEDs with alcohol and consumption of alcohol*

Furthermore, many cross-sectional studies have analysed the behaviour associated with co-consumption of scEDs and alcohol, by comparing it with behaviour observed during consumption of alcohol only.

In people who mix scEDs with alcohol, alcohol consumption is generally higher in terms of the quantities consumed, frequency of consumption, and the number of bouts of intoxication (O'Brien *et al.*, 2008; Thombs *et al.*, 2010; Brache et Stockwell, 2011). In the Thombs *et al.* (2010) study, the risk of having a high blood alcohol level is multiplied by a factor of three in people who combine alcohol and scEDs.

It has been suggested that the differences observed in those who mix scEDs and alcohol and those who consume alcohol only may be related to differences in personality (e.g. excitement-seeking, risk-taking, etc., which may be found more frequently in both those who drink scEDs and in those who drink alcohol). Thus in an attempt to separate the confounding factors that differ depending on whether the study population involves scED-users or non-users, de Haan *et al.* (2012) analysed the interaction between alcohol consumption and scED consumption using an intra-subject design on 6002 Dutch students. The study compared the quantity of alcohol consumed when drunk alone or when combined with an scED in the 1239 students who occasionally combine alcohol and scEDs. The data show that when scEDs are consumed together with alcohol, alcohol consumption and excessive alcohol intake are decreased. Woolsey *et al.* (2010) also noted this result in university athletes, although with more risk-taking behaviour and more negative consequences. In contrast, in a methodologically analogous study on 403 Australian students, Peacock *et al.* (2012) reported higher alcohol consumption when consumed together with scEDs. Price *et al.* (2010) also analysed alcohol consumption in 72 scED users who indicated that they consume more alcohol when combined with scEDs (8.6 drinks compared with 4.7 drinks).

*Co-consumption of scEDs and alcohol and risk-taking behaviour*

The effects of co-consumption of scEDs and alcohol on risk-taking behaviour were also documented in the above-mentioned studies.

In people who mix scEDs with alcohol, there are more negative alcohol-related consequences than those who drink alcohol only. O'Brien *et al.* (2008) observed a higher prevalence of taking the following risks in co-consumers, even after correcting for the amount of alcohol consumed: riding in a car with an intoxicated driver, having non-consensual sexual intercourse, being involved in fighting, or requiring medical treatment. According to Thombs *et al.* (2010), co-consumption of scED with alcohol involves a four-fold increased risk of intending to drive a motor vehicle upon leaving a bar compared to alcohol consumed alone (despite higher blood alcohol levels). In the Brache and Stockwell (2011) study, the frequency of scED consumption in association with alcohol is associated with a higher occurrence of risk-taking behaviour (driving after drinking alcohol, fighting), even after correcting for risk-taking tendencies. The frequency of co-consumption of scED and alcohol is also associated with a higher risk of casual sexual intercourse or intercourse under the influence of alcohol, but not unprotected sex (Miller, 2012). A different study shows that consumers mixing scEDs with alcohol have a higher risk of having unprotected sex (Berger *et al.*, 2013).

Of the studies with a within-subject design, de Haan *et al.* (2012) report that respondents indicated that there is less undesirable alcohol-related behaviour when scEDs are consumed with alcohol than when alcohol is consumed alone. However, in this study, less alcohol was consumed in co-consumption and the relationship with undesirable behaviour was not corrected for the amount of alcohol consumed. Furthermore, in the Peacock *et al.* (2012) study, in situations where scEDs are consumed with alcohol, individuals indicated that they take fewer risks, have less uninhibited behaviour and experience less physical and psychological sedation, even though alcohol consumption was higher in such situations of co-consumption.

In conclusion, these cross-sectional studies show a positive correlation between scED and alcohol co-consumption and the amount of alcohol consumed. However, it is not possible to establish any causal relationships.

The study of the effects of co-consumption of scEDs and alcohol leads to consideration of the following issues:

- acute pharmacodynamic interactions between alcohol and certain ingredients found in scEDs;
- chronic effects of co-consumption, i.e. whether when consumed frequently, particularly in young people, scEDs induce or facilitate the development of addictive behaviour, either in terms of scEDs or of other substances such as alcohol or other drugs.

**b. Acute pharmacodynamic interactions between alcohol and certain scED ingredients**

These interactions are mainly cardiovascular or neuropsychiatric in nature.

**i. Neuropsychiatric interactions**

The stimulating effects of caffeine are well-known: insomnia, anxiety, restlessness, shaking, etc. However, the effects of alcohol are biphasic: alcohol is a stimulant at low doses, but a sedative at high doses, and can ultimately lead to a coma.

Some consumers may therefore believe that the effects of the caffeine in scEDs and alcohol, consumed in large amounts, cancel each other out, with caffeine lessening the sedative effects of acute alcohol abuse. This belief may lead the consumer to underestimate his/her level of intoxication and thus drink more, experiencing the positive effects (excitement due to alcohol intake) and fewer adverse effects (i.e. the sedative effect of alcohol), even though there is nevertheless real cognitive and psychomotor impairment due to alcohol abuse, thereby creating a particularly dangerous situation.

This is the hypothesis that is being tested in several studies, such as in the one conducted by Marczyński *et al.* (2011) in which the participating students clearly indicate this reason for consuming scEDs together with alcohol. The interaction between scEDs and alcohol has been researched with experiments in animals and in humans in an attempt to test this hypothesis.

### **Studies in animals**

The effects of different doses of scEDs with or without alcohol on the locomotor activity in mice have been studied (Ferreira *et al.*, 2004). So-called EDs consumed alone increase locomotor activity in mice compared to the control. Low quantities of alcohol alone or mixed with scEDs have no effect on this activity. However, the decrease in locomotor activity observed with high doses of alcohol is counteracted by scEDs.

### **Studies in humans**

Studies in humans make it possible to evaluate the effects of scED or caffeine consumption on cognitive performance (objective measures) and on subjective perceptions of alcohol intoxication after drinking alcoholic beverages. The methodology employed varies according to the study. The studies differ not only with regard to the doses of caffeine and alcohol consumed, but also in how the effects of alcohol are measured. The objective measures of cognitive functioning address reaction times, motor coordination, or behaviour. Subjective measures address the perception of the level of alcohol intoxication, mood, sedation or stimulation. Effects were sometimes tested with an scED, sometimes with caffeine. The alcohol doses used in the experiments are less than the high doses of alcohol that are sometimes consumed during parties or social events.

Regarding cognitive functioning, studies report the absence of any effect of caffeine or scED consumption. For instance, in a study on 26 volunteers who had consumed vodka (0.6 g/kg or 1 g/kg body weight (bw)), scEDs (3.57 mL/kg bw) – equal to 1 can for a person weighing 70 kg) did not significantly reduce the objective deficits caused by alcohol on motor coordination and visual reaction time and there were no differences in the breath alcohol concentration (Ferreira *et al.*, 2006). In a study of 18 volunteers, alcohol (0.65 g/kg bw) slowed performance in tests of information processing and impaired (simple and complex) motor coordination. The co-administration of scEDs (3.57 mL/kg bw, or 1.2 mg/mg bw of caffeine) did not affect the changes induced by alcohol on these objective measures of performance (Marczinski *et al.*, 2012). The authors report results obtained previously (Marczinski et Fillmore, 2006) showing that caffeine doses of 2 mg/kg and 4 mg/kg counteracted the effects of alcohol on reaction times in a cognitive test (dual-task interference); the authors suggest that a caffeine dose of 2 mg/kg may be the threshold beyond which caffeine can noticeably counteract the effects of alcohol. Nevertheless, caffeine did not have any effect on the number of errors caused by alcohol consumption. In a study on 127 students, Howland *et al.* (2011) did not demonstrate any effect of caffeine ingested at a dose greater than 300 mg on attention and reaction time in a test administered after alcohol intake.

In other studies, only some cognitive impairments related to alcohol consumption are reduced by caffeine or scEDs. For example, in a study in 28 participants, there were no differences between drinking sessions with alcohol alone and alcohol together with caffeine (0.6 mg/kg of alcohol and 2 mg/kg of caffeine) on objective measures of behavioural control and reaction time, except for performance on a cognitive test (stop-signal test), which was improved after caffeine consumption (Attwood *et al.*, 2012). In another study, drinking scEDs containing 80 mg caffeine after consuming alcohol (blood alcohol level, 0.87 g/L) led to an improvement in performance for only one cognitive test (Stroop test), whereas no other differences were observed for the other cognitive tests (Alford *et al.*, 2012). In two other studies (Marczinski et Fillmore, 2003; Marczinski *et al.*, 2011), the effects of scEDs or caffeine (caffeine doses of between 1 and 4 mg/kg) on objective measures of behavioural control were lessened, scEDs and caffeine only counteracting the effects of alcohol on the “activational mechanisms” and not on the “inhibitory mechanisms” of behavioural control. In a study by Liguori and Robinson (2001) on 15 participants receiving 200 or 400 mg of caffeine, both doses of caffeine partially counteracted the effects of alcohol intake (0.6 g/kg bw) on brake latency but not on reaction time in a choice reaction time test or in body sway. Brake latency after alcohol and caffeine intake remained higher than the time observed with a placebo.

Depending on the study, cognitive impairment due to alcohol as measured objectively is not reduced by scEDs or caffeine or is only reduced for some types of temporary cognitive impairment. Some results suggest that the level of cognitive performance, even when improved by scED or caffeine consumption, remains altered compared to when there is no alcohol intake.

Regarding subjective measures of performance, the results are not clear cut, but often show that scED or caffeine modify the subjective effects of alcohol. Thus, in a study of 26 volunteers, the

consumption of a mixture of scEDs (3.57 mL/kg bw, equivalent to 1 can for a 70 kg person) and vodka (0.6 g/kg or 1 g/kg bw) significantly reduced the volunteer's perception of different signs related to alcohol intake alone: headaches, weakness, dry mouth, perception of impaired motor coordination (Ferreira *et al.*, 2006). In a study of 18 volunteers, co-consumption of scEDs and alcohol (0.65 g/kg alcohol and 3.57 mL/kg scED) altered subjective perceptions of intoxication compared to alcohol alone, with a reduction in the perception of mental fatigue and enhanced feelings of stimulation (Marczinski *et al.*, 2012).

In a study of 28 participants, Attwood *et al.* (2012) did not demonstrate any effect of caffeine (2 mg/kg) on subjective measures of perception of alcohol intoxication, anxiety and alcohol craving, but there was an interaction between the effects of time and those of the type of beverage on the level of stimulation: stimulation decreased over time in groups consuming the placebo or alcohol and increased over time in the group consuming alcohol and caffeine. The authors deemed that caffeine may have changed the nature of intoxication, with an enhanced feeling of stimulation. This is compatible with the idea that caffeine allows an individual to drink longer, thereby increasing the risk of alcoholic intoxication.

Alford *et al.* (2012) compared the subjective effects experienced by two groups of 10 individuals drinking either an scED (containing 80 mg caffeine) with alcohol (leading to a blood alcohol level of 0.87 g/L), or alcohol only. There were no differences in the scores measuring clearheadedness, coordination, sleepiness, energy, or mental slowness in the two groups.

With the exception of this last study, studies on subjective perception suggest that consuming scED/caffeine may alter the perception of alcoholic intoxication and induce a feeling of reduced fatigue or enhanced stimulation.

#### **Expected effects**

Some behaviour and effects observed after consuming scEDs with or without alcohol may arise from expectations. Simply believing that these beverages and their ingredients can induce certain effects may lead to feeling the expected effects. These expected effects occur due to the substances found in scEDs, particularly caffeine which is known for its stimulating effect, but also to the alcohol that may be mixed with scEDs. They may also result partly from the promotional advertising for scEDs, presented as beverages that give an energy boost and are (psychologically) stimulating and thus considered likely to enhance performance.

- The consumption of scEDs or caffeine only partially counters cognitive impairment due to alcohol consumption; it can however reduce the perception of alcohol intoxication, with a reduced sensation of fatigue or an enhanced feeling of stimulation.
- Drinking scEDs or caffeine with alcohol can thus lead to potentially risky situations due to poor judgment of one's actual capacities, which can thus lead to longer alcohol consumption.

#### **ii. Cardiovascular interactions**

Caffeine can cause high blood pressure, tachycardia and supra-ventricular rhythm disorders. These effects vary among individuals.

Heart rhythm disorders after an episode of acute ingestion of large quantities of alcohol ("binge drinking") has also been reported (Nissen *et al.*, 1984). Such heavy drinking can increase the duration of the QT interval (Uyarel *et al.*, 2005). Chronic heavy drinking is also a risk factor for atrial fibrillation (Djousse *et al.*, 2004).

The association of alcohol and caffeine can thus potentiate arrhythmias in predisposed patients.

Moreover, Wiklund *et al.* (2009) have shown that associating scEDs (approximately 3 cans) and alcohol (0.4 g/kg bw) before exercise leads to a slower return to a normal heart rate after exercise in healthy individuals and thus to a reduction in heart rhythm variability (impaired adaptive response).

#### **c. Chronic effects of mixing scEDs with alcohol and addictive behaviour tendencies**

In young adults, scED consumption with or without alcohol in a quest for enhanced performance or stimulation (and scED marketing promotion strategies may participate in creating this motivation) could facilitate addictive tendencies.

Several studies demonstrate an association between scED consumption and the use of psychoactive drugs. In a Taiwanese study of a cohort of 13,501 males and 8584 females, 9.4% of men and 0.8% of women abused alcohol, whereas in regular consumers of scEDs mixed with alcohol (6% of men and 0.7% women), alcohol abuse was 38.7% and 23.3%, respectively (Cheng *et al.*, 2012). Arria *et al.* (2010 and 2011) show a similar pattern. As indicated above, the work published in 2010 on 1097 American students followed for 3 years shows that scED users consume more alcohol and are more likely to have used other drugs than non-scED users (Arria *et al.*, 2010). The second paper of this study demonstrates that regular scED users had a higher risk of alcohol dependence than non-scED users and occasional users (Arria *et al.*, 2011). One explanation is that scED consumption increases alcohol and other psychoactive drug use.

The increase in alcohol consumption observed in regular scED users, reported in the large majority of observational studies, could be attributed to an increase in alcohol priming (increased desire to drink more alcohol). In a study of 80 participants, scEDs mixed with alcohol increase the desire for more alcohol, more than alcohol alone, even though both types of beverages were equally attractive (Marczinski *et al.*, 2013). Thus, scEDs mixed with alcohol may increase the motivation to drink alcohol. Moreover, scED/alcohol mixes have a better taste than some alcoholic beverages alone, making them likely to favour alcohol consumption (Bigard, 2010). The effect of scEDs on alcohol use is worth exploring in other experimental studies.

Early use of an addictive substance is one of the most clearly established risk factors for addictive behaviour later in life. Early consumption of scED/alcohol mixes may make children and adolescents more prone to developing addictive behaviour in the future, to caffeine or to other products, by virtue of the fact of having experienced psychotropic effects at an early age and by inciting them to seek stimulation and enhanced performance in various domains.

***Conclusions on the analysis of the risks related to the consumption of scEDs in conjunction with alcohol***

- Alcohol can potentiate arrhythmia induced by caffeine in predisposed people.
- The subjective perceptions of alcohol intoxication seem often to be minimised by scED consumption, although cognitive and psychomotor impairment due to alcohol (motor coordination, reaction times, etc.) are not or are only partially reduced by scED or caffeine consumption.
- The consumer may thus underestimate his/her state of alcoholic intoxication and be incited to drink more, feeling the stimulating effects of alcohol rather than its sedative effects.
- The association of diverse psychoactive substances for the purpose of cumulating their effects, may be actively sought out by users of scEDs, alcohol, or other drugs. In this case, not only is the risk of acute consequences increased, but the risk of developing addictive behaviour is also higher.

**3.6.3. Effects on cognitive and sporting performance that motivate scED consumption and its risk assessment**

**a. Effects on cognitive performance that motivate scED use**

One of the alleged effects of scED – as promoted by scED manufacturers – is the improvement in cognitive performance, particularly in maintaining alertness.

***Effects of scEDs***

Speed of attention and secondary memory are improved 30 min after consuming an scED (Scholey *et al.* Kennedy, 2004b). Other experiments confirm this increase in vigilance, characterised by a

decrease in reaction time to an external stimulus, better concentration, and a decrease in subjective measures of mental fatigue (Alford *et al.*, 2001; Howard et Marczinski, 2010).

### **Caffeine**

Caffeine has long been known and consumed for its effects on vigilance and alertness. It is likely that caffeine is the main ingredient responsible for the effects of scEDs on cognitive functioning (Smit *et al.*, 2004), although the carbohydrates present in these beverages act in synergy with caffeine (Scholey et Kennedy, 2004a). These properties have been particularly well studied in soldiers who experience sleep debt and need to stay alert. In these experimental conditions, and using double-blind and placebo-controlled protocols, doses of 600-800 mg of caffeine, administered in the form of chewing gum, have demonstrated their effectiveness on maintaining vigilance (McLellan *et al.*, 2005a; McLellan *et al.*, 2005b; McLellan *et al.*, 2007). Various cognitive properties that exemplify vigilance have been assessed, such as reaction time, working memory or motor learning. All tests exploring vigilance are improved by caffeine intake, even for caffeine doses of 200 mg which seems to be – for the study population – the minimal dose having favourable effects (Lieberman *et al.*, 2002). In these specific situations of physical exertion and mental and physical stress, slow-release caffeine has proved to be of interest, particularly for high sleep deprivation of up to 96 h (Beaumont *et al.*, 2001).

In the work environment, cognitive functioning of stationed workers is recovered by caffeine intake even though these individuals are tired due to a mental workload or due to a full night of intellectual work (Johnson *et al.*, 1990; Walsh *et al.*, 1990; Zwyghuizen-Doorenbos *et al.*, 1990; Brice et Smith, 2001).

Taken together, these studies on the effect of caffeine on cognitive functions show that the consequences on sleep, as shown for the duration of effects on cognitive performance, vary greatly among individuals. For the most part, individual age, sex and consumption habits explain this variability. In regular caffeine consumers for example, caffeine has a shorter-term effect on maintaining vigilance compared to non-consumers (Goldstein *et al.*, 1965a; Alford *et al.*, 1996). Caffeine thus generally seems to help maintain alertness and vigilance in sleep-deprived individuals. The duration of these effects depends greatly on caffeine consumption habits.

### **Other ingredients often found in scEDs**

Regarding the effects of scED ingredients other than caffeine, there is only limited evidence for the additional effect of taurine on cognitive functioning, and results are contradictory (McLellan and Lieberman, 2012).

The role played by carbohydrates in the improvement of cognitive functioning has also been evaluated. Various experiments have shown the influence of the carbohydrates contained in scEDs on the cognitive effects of caffeine. For instance, Horne and Anderson (2005) found that a mixture of caffeine and glucose maintains vigilance better after sleep deprivation than caffeinated beverages. The importance of the association of caffeine with glucose in improved cognitive performance (long-term memory, attention) has been confirmed, with each ingredient taken alone having a lesser effect (Scholey et Kennedy, 2004a). Glucose enhances the specific effects of caffeine on maintaining vigilance in sleep-deprived individuals.

Thus, in sleep-deprived individuals, the effect of scEDs on alertness and vigilance can easily be attributed to caffeine and glucose, and is observed for moderate doses of caffeine. These effects are not specific to scEDs.

### **b. Expected effects of scEDs and their ingredients on performance during extended aerobic exercise**

According to the French survey of scED users, 41% of scED consumers consume these beverages in conjunction with a sporting activity, either before (17%), during (17%) or after (12%) the activity. The EFSA European survey shows that 52% of adult respondents and 41% of adolescent respondents who consume scEDs use this beverage before, during or after a session of physical exercise (Zucconi *et al.*, 2013).

Given this setting of consumption, several questions were considered in this expert assessment: 1) Do scEDs have any proven effects on the physical performance of athletes? 2) If so, which

ingredients are responsible for this effect? 3) Does consuming scEDs when practicing sport pose any health risks? 4) Given their nutritional composition, are scEDs indicated for physical exercise?

Sporting performance can be measured as part of aerobic exercise (physical activities of extended duration that mobilise aerobic metabolism to synthesise more ATP), anaerobic exercise (physical activities of short duration that mobilise anaerobic metabolism to synthesise more ATP), or in sports disciplines that essentially require muscle power.

#### **i. Effects of scEDs**

From the start, studies soon focused on the effects of scEDs on aerobic exercise, practised for an extended time and requiring endurance. One of the first studies of this type showed that consuming 500 mL of scEDs with 160 mg caffeine and 2 g taurine 30 min after beginning exercise on an ergocycle improves performance in an endurance test that ends with an intense exercise, compared to the consumption of the same volume of a) an isocaloric beverage without taurine or glucuronolactone or b) of an isocaloric beverage without taurine, glucuronolactone or caffeine (Geiß *et al.*, 1994). Since this first study to report improvement in performance after consuming an scED, this result has been confirmed, with scEDs improving the time period over which extended exercise at constant intensity can be maintained, after consuming 30 to 60 min before exercise (Alford *et al.*, 2001; Ivy *et al.*, 2009; Rahnama *et al.*, 2010). All of these studies suggest improvement in endurance, without elucidating the respective roles of taurine, caffeine or, in some cases, sugars.

Finally, some authors report that scED consumption has a favourable effect on postponing the advent of fatigue, mainly in terms of attention, during prolonged, low-intensity physical exercise (Horne et Reyner, 2001). This effect on the central nervous system must not be neglected in the explanation of improved endurance.

Hypocaloric scEDs are sometimes proposed as part of physical training. The effects of a beverage providing 200 mg of caffeine has been assessed when one can (250 mL) is drunk 15 min before each training session (Lockwood *et al.*, 2010). Individuals who regularly consume these beverages during physical training note that their endurance improves, along with more marked lipolysis and improvements in body composition than when the exercise programme does not include scED consumption (Lockwood *et al.*, 2010). Caffeine can influence the stimulation of lipolysis by activating beta-adrenergic pathways, which induce the activation of adenylate cyclase and hormone-sensitive lipase (Powers et Dodd, 1985); this effect may explain the decrease in fat mass. Another explanation may lie in a slight increase in the oxidation of fatty acids during the recovery period of these exercise sessions.

The few studies available that assess the effects of scEDs on endurance performance therefore seem to show that endurance is enhanced.

#### **ii. Effects due to caffeine alone**

There are many experimental studies that address the effects of caffeine on endurance performance (Goldstein *et al.*, 2010). These effects have been attributed to an increase in lipolysis observed during exercise, but generally without any clear increase in fatty acid oxidation or the expected muscle glycogen stores. More recently, attention has turned to the potential effects of caffeine on fatty acid oxidation during recovery and maximal intestinal absorption of exogenous glucose ingested during exercise (Van Nieuwenhoven *et al.*, 2000; Yeo *et al.*, 2005). There is as yet no consensus regarding these hypotheses, however.

Recent extensive reviews have led to the conclusion that caffeine consumed at 3 to 6 mg/kg bw can improve endurance at maximal aerobic capacity (Graham et Spriet, 1995; Goldstein *et al.*, 2010). However, the physiological effects of caffeine depend on many factors, including the conditions of caffeine intake, the dose consumed and individual response to caffeine.

(a) The form in which caffeine is ingested can influence the patterns of observed performance; thus, caffeine administered in capsule form<sup>31</sup> results in a clear improvement in endurance (31% compared to the placebo control), whereas drinking coffee (decaffeinated or caffeinated) does not influence performance (Graham *et al.*, 1998).

<sup>31</sup> There is no information on the chemical form of caffeine administered, although caffeine capsules on the market usually contain the anhydrous form of caffeine.

The effects of caffeine consumed as coffee or in tablet form are now relatively well known, although its effects are not as well reported when ingested via other drinks. There is only one study showing that caffeine intake via a beverage consumed 30 min before exercising can improve endurance at maximal aerobic capacity (Hoffman *et al.*, 2007).

(b) The issue of a dose-effect relationship of caffeine has been addressed in several experiments. Testing increasing quantities of caffeine taken in the form of capsules in well-trained athletes, the observed improvement in endurance was similar whatever the dose (Pasman *et al.*, 1995). The plateauing effects of caffeine on performance has been confirmed with another experiment during which performance improves at a dose of 200 mg without any additional benefits with higher doses (Lieberman *et al.*, 2002). In addition, the secondary effects that penalise improvement in endurance generally appear at doses higher than 9 mg/kg bw (Graham and Spriet, 1995).

(c) Given the high variability of observed effects, taking inter-individual variability into account in the response to caffeine is crucial, including in its ergogenic effects, although many published studies fail to do so. Most results are presented as means for a group of volunteers (Doherty et Smith, 2004; Skinner *et al.*, 2010). This individual response is modulated by many factors, including the level of physical training, coffee drinking habits or time since last meal, etc. It has been shown that caffeine consumption immediately after a meal considerably attenuates its effects on performance (Skinner *et al.*, 2010). Of the endogenous factors that can explain inter-individual variability of response to caffeine intake (see Chapter 3.5.2), a clear improvement in endurance capacity is observed in athletes who are homozygous for the A allele of the *CYP1A2* gene that encodes isoenzyme 1A2 of cytochrome p450 (Womack *et al.*, 2012). Rapid metabolism of caffeine thus seems to be a factor that favours improvement in endurance capacity.

Research attempting to identify the ergogenic effects of caffeine on endurance performance has shown that caffeine taken in capsule form has more pronounced effects than when caffeine is taken as coffee, and that the expected effects are obtained for individual doses of 3 to 6 mg/kg bw.

### **iii. Effects due to taurine alone**

To date, there are few data demonstrating any effect of taurine on physical performance. Thus, supplementation with 5 g/day of taurine does not change its concentration in muscles and does not affect muscle metabolism (Galloway *et al.*, 2008). Consuming a hypocaloric beverage containing 1.66 g of taurine 1 h before an exercise test does not improve endurance performance compared to two other isocaloric beverages without taurine (Rutherford *et al.*, 2010).

In addition to studies on humans, some studies have assessed the effects of taurine on the physical performance of animal models. After two weeks of supplementation with taurine (15 mg/kg bw), the endurance performance of rodents improved (Imagawa *et al.*, 2009). However, it is difficult to extrapolate these results to humans and the results of this lone study, carried out on an animal model, must be confirmed by other studies.

In conclusion, there are only few compelling experimental data reported in methodologically robust studies that seem to indicate that taurine in a caffeinated beverage may have an additional effect on endurance performance.

### **iv. Effects specific to other ingredients: glucuronolactone, carbohydrates, etc.**

To date, there is no experimental proof that glucuronolactone has any ergogenic effect likely to affect endurance performance (McLellan et Lieberman, 2012).

As for carbohydrates, they have well-known effects on endurance performance but their concentrations in scEDs vary greatly. Iso-osmolar beverages containing 6 to 8% of carbohydrates have a favourable effect on endurance performances of over 90 min. However, most scEDs have much higher carbohydrate content and are hyperosmolar, making them incompatible with improved performance.

Moreover, there are no convincing studies that suggest that caffeine and carbohydrates have additive effects on endurance performance (Hulston et Jeukendrup, 2008; Ganio *et al.*, 2010). Adding caffeine to a carbohydrate drink (containing from 6 to 8% carbohydrates) only slightly improves endurance performance (Conger *et al.*, 2011). The respective effects of carbohydrates and potentially caffeine are therefore not additive.

- The results of the studies included here, all carried out using suitable experimental conditions (although not always with appropriate controls), point to the conclusion that scEDs improve endurance performance. Obvious flaws in the existing literature nevertheless suggest that caution should be taken as to the conclusions that can be drawn from the current state of knowledge, because:
  - the studied scEDs are not always the same, and they can vary greatly in caffeine content;
  - in many studies, coffee consumption habits are not considered and in most studies no measures have been taken to evaluate individual sensitivity to caffeine (endo- and exogenous factors or environmental factors);
  - the experimental protocols are not always appropriate for the study's goals.
- When scEDs improve endurance performance, it seems mainly due to caffeine. These effects are more pronounced when caffeine is administered in capsule form. There is high variability in the response to scED consumption due to high inter-individual variability in sensitivity to caffeine.

### **c. Effects of scEDs and their ingredients on performance during predominantly anaerobic activities that require muscle strength and power**

#### **i. Effects of scEDs**

Although the composition of scEDs differs widely, the results obtained from studies using robust experimental protocols do not provide any grounds for attributing any favourable effects to scEDs on performance during intense, short-term – and sometimes repeated – physical exercise. For example, consuming a can of scED 1 h before three series of eight timed sprints does not improve performance compared to drinking an isocaloric beverage that does not contain any other ingredients (Astorino *et al.*, 2012). Likewise, in athletes who practise weight lifting but do not regularly drink coffee, the consumption of an scED calculated to provide 2 mg/kg of caffeine 60 min before exercise did not improve performance in muscle power (Forbes *et al.*, 2007). However, several experiments suggest that scED consumption providing 2 to 3 mg/kg bw caffeine may have a positive effect on power performance in some weight-lifting tests (Campbell *et al.*, 2010a; Campbell *et al.*, 2010b). None of these experiments demonstrate any ergogenic effect of scEDs on peak (anaerobic) power measured using the Wingate test (Hoffman *et al.*, 2009; Campbell *et al.*, 2010b). The effects of scEDs do not seem to be easy to reproduce, and vary according to the tests used to assess performance, beverage composition, quantity of active ingredients and individual response. Some experiments however show some positive effects of these beverages on muscle power or the number of repetitions of weight-lifting sets.

Similarly, the potential interest of hypocaloric scEDs (45 kcal, 200 mg of taurine, 120 mg of caffeine in a beverage of 250 mL) has been assessed. For example, in repeated sprint tests in American football players, there is no effect on performance compared to an isocaloric placebo beverage (Gwacham et Wagner, 2012). Similarly, there are no positive effects observed after consumption of a hypocaloric scED providing 2 mg/kg bw caffeine on performance of prolonged high-intensity exercise (Candow *et al.*, 2009).

In conclusion, scEDs do not have any reproducible effects on power or improvement of resistance to muscle fatigue. There are no reports of any clear and reproducible improvement in peak anaerobic power.

#### **ii. Effects due to caffeine alone**

Although caffeine should hypothetically influence muscle function and affect its energy metabolism, experimental results show many disparities (Astorino et Roberson, 2010). One study has shown the absence of improvement in performance of a test assessing peak anaerobic power after ingestion of a high-caffeine beverage (450 mg vs. a caffeine-free beverage) 30 min before the beginning of the exercise test (Hoffman *et al.*, 2009). In addition, caffeine intake at 6 mg/kg bw was shown to improve performance of repeated sprint sessions (Stuart *et al.*, 2005; Glaister *et al.*, 2008). Likewise, compared to a decaffeinated beverage, a beverage providing 3 mg/kg bw of caffeine can improve muscle power by 3% during maximal jump tests, the peak speed during repeated sprint tests and various measures of performance during a simulated soccer game (Del Coso *et al.*, 2012). Disparities between obtained results may be related in part to the different quantities of

caffeine administered and, of course, to inter-individual variability, neither factor being sufficiently taken into account in any of these studies.

**iii. Effects due to taurine alone**

The very few studies of the effects of taurine alone on muscle performance involve mainly animal models. The available results are very controversial. It has been suggested that taurine can increase calcium reserves in the sarcoplasmic reticulum and help amplify muscle force responses (Bakker et Berg, 2002). However, these results were obtained on animal models and cannot easily be extrapolated to humans. It seems that although taurine has positive effects on muscle contraction, these effects are only observed for high quantities of taurine, from 2 to 6 g (Baum et Weiß, 2001; Zhang *et al.*, 2004). Although a deficiency in taurine affects muscle force response (Hamilton *et al.*, 2006), excess taurine is not associated with an improvement in muscle performance.

**iv. Effects due to other compounds: glucuronolactone, carbohydrates, etc.**

To date, there are no robust experiments that demonstrate that other common scED ingredients have any ergogenic properties with regard to aerobic exercise and/or activities that require muscle power (McLellan et Lieberman, 2012).

**d. Nutritional composition of scEDs and study of the nutritional advantages for athletes**

To be able to make specific claims promoting consumption during physical exercise, sports drinks must have a certain number of qualities.

- Used in the indicated amounts, in preparation for a sports event or during an intense training session, sports drinks must be iso-osmolar, providing 20 to 40 g/L of carbohydrates with a low glycaemic index, consumed in quantities of 100 to 200 mL every 15 to 20 min depending on environmental conditions (Bigard et Guezennec, 2007). The hyperosmolar nature of scEDs, which are high in carbohydrate content and high in calories, clearly does not at all meet the expected characteristics of a sports drink. Moreover, the diuretic nature of caffeine (Spriet, 1995; Grandjean *et al.*, 2000) negates the nutritional goal of a sports drink, which is to replenish fluids and restore water-electrolyte balance during exercise.

- Used during exercise, sports drinks must have certain qualities, which are now well established. To correct quickly any water-electrolyte imbalance due to transpiration, they must promote gastric emptying and be rapidly absorbed in the small intestine. To fulfil this goal, sports drinks must be iso- or hypo-osmolar and provide 60 to 80 g/L of glucose polymers (with or without fructose) and 0.6 to 1 g/L of sodium chloride (Bigard et Guezennec, 2007). Consumed during physical exercise, hyper-osmolar beverages stagnate in the stomach (Vist et Maughan, 1995) and are not rapidly available for the intestine to compensate hydric or electrolyte imbalance due to transpiration and are the cause of highly negative consequences of gastric distress. Moreover, caffeine consumed during exercise will augment water loss due to its diuretic effect. Therefore, scEDs offer none of the qualities required of a sports drink and cannot be indicated for preventing and replenishing water or electrolyte losses due to transpiration.

**e. Health risks and safety of use of scEDs in sports activities and in physical recreational activities**

In regard to use by amateur or highly trained sportspeople, the potential risks posed by mixing scEDs with alcohol will not be addressed here. So-called EDs contain in particular carbohydrates and caffeine. Using scEDs to improve physical performance can only be considered for preparation of a competitive sports event, at most 1 h before the event.

In these conditions, the carbohydrate content – usually with a high glycaemic index and rapid absorption, in quantities varying from 20 to 50 g – may impair glycaemic control and cause a large insulin response, two occurrences that are not compatible with participation in a sports event. This risk is even higher in diabetics.

The caffeine content in scEDs is likely to affect the health of an athlete. The same well-known secondary effects described in sedentary subjects are also observed in athletes (whatever their

level of training) who use scEDs, including central nervous system (CNS) effects (insomnia, nervousness, anxiety, etc.), cardiac effects (tachycardia, etc.), digestive effects, etc. Similarly, athletes also show inter-individual variability in the expression of these secondary effects.

One of the potential hazards of scEDs, due to the presence of caffeine, involves temperature regulation during exercise in hot environments. Consuming 6 mg/kg of caffeine 1 h before prolonged exercise on an ergocycle at a room temperature of 30°C causes a significant increase in body temperature, compared to a placebo control (Roelands *et al.*, 2011). Caffeine intake leads to an increase in body temperature very early on in the test and reaches 0.7°C by the end of the test. These results confirm those that were recently published (Del Coso *et al.*, 2008; Chevront *et al.*, 2009). Caffeine is known to block adenosine receptors in the CNS and adenosine is known to act on dopamine release. Therefore, the heat storage observed during exercise in hot environments is probably due to an increase in cerebral dopamine and activation of dopaminergic signalling. Dopamine probably increases thermogenesis, although this possibility is still under debate (Roelands et Meeusen, 2012). These indirect effects of caffeine must be clarified in the near future because therein may lie situations of risk for an accident in hot environments, particularly heatstroke that can occur during exercise, for which medical prognosis is always uncertain. It is also important to remember that caffeine has pronounced diuretic effects and consuming caffeine in hot environments, particularly when exercising, is bound to aggravate water-electrolyte loss and disrupt thermolysis. Increase in thermogenesis and disruption of thermolysis lead to an increased risk of heatstroke.

In the few experimental studies on exercising in hot environments, caffeine never improves performance. Given the absence of the expected effects of caffeine on exercise performance in hot environments, and its dramatic effect on thermal regulation, scEDs must not be consumed when exercising in hot environments.

***Conclusions on the expected effects and the risks of consuming scEDs when practising a sport***

- scEDs are used by some to improve physical performance.
- scEDs do not appear to improve sporting performance during short and very intense exercise (i.e. those requiring high anaerobic power and muscle strength).
- Although scEDs can improve exercise endurance in some people, this result cannot be extrapolated to the general population because there is high variability in observed individual responses. It is probably caffeine that explains the effects on endurance performance and the variable individual sensitivity to caffeine explains the high inter-individual variability in the effects of scEDs.
- In contrast to sports drinks, whose nutritional composition is adapted to the needs of physical exercise, scEDs provide no nutritional benefits for exercising and do not restore the water and electrolyte balance.
- In contrast, due to its diuretic effects, the caffeine in scEDs can exacerbate water and electrolyte loss.
- The hyperosmolarity of some scEDs can aggravate dehydration.
- Moreover, caffeine alters body heat regulation during physical exercise in hot environments, causing heat storage due to a probable increase in endogenous heat production. This elevated body temperature increases the risk of heat stroke.
- Of the health risks due to the consumption of scEDs during physical activity, caffeine has well-known adverse effects.

### 3.7. Assessment of the risk of exceeding maximum threshold values for caffeine, taurine and glucuronolactone

#### 3.7.1. Assessment of the risk of exceeding the maximum threshold value for caffeine

##### a. Determining maximum threshold values for caffeine

Several health agencies have established maximum threshold values for caffeine.

##### **Health Canada (Nawrot *et al.*, 2003)**

In 2003, Health Canada carried out a large-scale literature review of the effects of caffeine on human health (Nawrot *et al.*, 2003). This is the most thorough analysis carried out on the issue to date and has been used by many countries and health agencies.

In this review, the authors indicate that the acute lethal dose is estimated to be 10 g. One fatal case was reported after ingestion of 6.5 g but another patient survived despite ingesting 24 g of caffeine. Concerning the general toxicity of caffeine, the authors mention symptoms of nervousness, irritability, insomnia, sensory dysfunction, diuresis, arrhythmia, tachycardia, accelerated respiration and gastrointestinal disorders. The authors consider that doses of 500 to 600 mg/d are excessive and involve substantial risk. Intake exceeding 400 mg/d can increase the risk of bladder instability in women, and intake between 200 and 400 mg/d can increase this risk in women already presenting bladder disorders.

On the basis of the literature review carried out, the authors also conclude that daily caffeine intake of up to 400 mg/d is not likely to have adverse effects on the healthy adult population, in terms of general toxicity, cardiovascular effects, effects on bone health and the calcium balance (as long as calcium consumption is higher than 800 mg/d), changes to behaviour, the incidence of cancer, and effects on male fertility.

The authors identified women who were either pregnant or intending to become pregnant as an at-risk population on account of the possible adverse effects of caffeine consumed in high doses on the risk of miscarriage or congenital malformations, and the effects on foetal growth, duration of pregnancy and postnatal development. Health Canada considered that caffeine intake of less than 300 mg/d was unlikely to be a risk factor for these populations.

The authors identified children as another at-risk population. Despite the limited data available concerning this population, changes to behaviour, including anxiety, were observed in children and pre-adolescents ( $\leq 12$  years) after ingestion of caffeine, down to the lowest dose tested which was 2.5 mg/kg bw/d. As a result, in the absence of more robust data, and bearing in mind the immaturity of the nervous system in children, Health Canada considered that a dose of 2.5 mg/kg bw/d could serve as a reference dose for assessment of the risks related to consumption of caffeine in children.

##### **Health Canada finally adopted the following maximum threshold values:**

- **for the healthy adult population: intake of less than 400 mg/d is unlikely to constitute a health risk**
- **for women who are pregnant or intend to become pregnant: intake should not exceed 300 mg/d**
- **for children: intake should not exceed 2.5 mg/kg bw/d**

##### **Food Standards Agency (FSA, 2008)**

In 2008, Britain's Food Standards Agency carried out an assessment of the potential adverse effects of caffeine during pregnancy (FSA, 2008). The assessment concluded that caffeine intake during pregnancy was associated with retarded foetal growth. It was not possible to state with certainty whether this implied a causal relationship or whether it was the result of residual confounding bias. As a precaution, it was nonetheless decided to consider that there is a causal relationship. It was not possible to determine a threshold beneath which there was no increase in risk, but it seemed probable that the risk of retarded foetal growth was increased at a daily intake of 200 mg, or even less. However, if there is a causal relationship, it appears likely that the increased incidence of intra-uterine growth retardation at doses lower than 200 mg/d is less than 2%. The

review of the literature also suggested a positive association between levels of caffeine intake and the risk of miscarriage. It was not possible to remove all uncertainties concerning this relationship, as a result of recall bias and other confounding factors.

The data concerning other types of risk such as premature birth and malformations were not sufficient to reach a conclusion on the effects of caffeine consumption.

***In view of these data, the Food Standards Agency recommended that pregnant women not exceed caffeine intake of 200 mg/d.***

***Nordic Working Group on Food Toxicology and Risk Evaluation (NNT) (Meltzer et al., 2008)***

The health agencies of the Nordic countries also carried out a risk assessment concerning the consumption of caffeine in children and adolescents (Meltzer et al., 2008). A literature review of epidemiological and clinical studies enabled them to adopt the following doses:

- ***For the development of tolerance to the effects of caffeine:***
  - NOEL<sup>32</sup> (no observed effect level) = 0.3 mg/kg bw
  - LOEL<sup>32</sup> (lowest observed effect level) = 1.0-1.3 mg/kg bw
- ***For the onset of symptoms of anxiety and nervousness:***
  - LOAEL (lowest observed adverse effect level) = 2.5 mg/kg bw
- ***For the onset of sleep disorders:*** although the effects of caffeine in sleep disorders in children are known, the authors found no studies evaluating this type of effect in children. Nevertheless, the authors adopted a value obtained from a study in adults:
  - LOAEL = 1.4 mg/kg bw

***New Zealand Food Safety Authority (NZFSA, 2010)***

In 2010, the New Zealand Food Safety Authority published a report assessing the risks related to the presence of caffeine in scEDs. Its assessment of the adverse effects of caffeine was based essentially on its prior expert appraisal of 2000 (Smith et al., 2000), on the conclusions of Health Canada (2003), and on the conclusions of an assessment of scEDs carried out by the Food Safety Authority of Ireland in 2002, to which it added certain more recent references from the literature.

In addition to the values given above as adopted by other health agencies, the NZFSA mentioned the following values:

- Cases of mortality related to caffeine intake in excess of 5 g, although certain subjects survived following ingestion of 30 g of caffeine.
- Heightened anxiety in adults at a dose of 3 mg/kg bw/d, which corresponded to a dose of 210 mg/d for an adult weighing 70 kg<sup>33</sup>.
- Difficulties in sleep onset for certain subjects at a dose of 100 mg of caffeine (1.4 mg/kg bw/d for adults weighing 70 kg).

On the basis of these findings, the New Zealand Food Safety Authority emphasised that there is currently no recognised reference value for an acceptable daily intake (ADI) for caffeine. **In the absence of any such value, and as a basis for risk assessment, the NZFSA adopted a protective limit value of 3 mg/kg/d for the entire population** (excluding pregnant women), which corresponds to the dose for which heightened anxiety has been observed in adults (Nickell et Uhde, 1994) as well as in children (value adjusted to 2.5 mg/kg/d). The value of 200 mg/d of caffeine adopted for pregnant women corresponds to the most recent and most protective value suggested by Britain's FSA in 2008 (FSA, 2008).

***Belgium's Supreme Council of Health (2012) (CSS, 2012)***

In 2012, Belgium's Supreme Council of Health reviewed the above assessments and adopted the following values:

- On the basis of the review by Health Canada, **a value of 5.7 mg/kg bw/d** (i.e. 400 mg/d for an adult weighing 70 kg) was adopted for the healthy adult population as having no observable adverse effects regarding general toxicity, cardiovascular effects, behavioural changes, greater incidence of cancer, or effects on male fertility;

<sup>32</sup> For these two doses, the effect was not described as adverse because the authors were unable to determine whether the development of tolerance to caffeine was an effect of an adverse nature.

<sup>33</sup> It should be noted that the study on which this is based was carried out by intravenous administration of caffeine (Nickell & Uhde, 1994). However, the pharmacokinetics of caffeine is independent of the administration route (see §3.2.1).

- **A value of 3 mg/kg bw/d** (i.e. 210 mg/d for an adult weighing 70 kg) was also adopted as a threshold above which heightened anxiety was observed;
- In children, **a value of 2.5 mg/kg bw/d was adopted** as a threshold above which behavioural changes may appear, including anxiety, as well as a possible effect on development of the nervous system. **The other values taken from the assessment by the Nordic agencies were also adopted: NOEL (no observed effect level) of 0.3 mg/kg bw/d and LOEL (lowest observed effect level) of 1.0 to 1.3 mg/kg bw/d for the development of tolerance to the effects of caffeine; LOAEL of 1.4 mg/kg bw/d for the onset of sleep disorders;**
- For women of childbearing age, **values of 300 mg/d from the Health Canada assessment and of 200 mg/d from the British assessment were mentioned.**

On the basis of this review of maximum recommended threshold values for caffeine, and in order to assess risks taking into account the population's level of exposure, several values were adopted for the purposes of this expert appraisal. They are listed in Table 15 below. However, several limitations applying to this study should be mentioned:

- The doses adopted are of very different types: some represent doses for which adverse effects have already been observed, others represent doses with no observed effects;
- They are based on limited scientific evidence (sometimes a single study), which differs in nature depending on the values considered (epidemiological data, experimental study, etc.)

Two values were adopted for adults related to different types of adverse effects: the upper value of 400 mg/d corresponds to a value below which the risk of long-term adverse effects is low. The value of 210 mg is a lower value above which symptoms of anxiety have been observed. These values are approximate benchmarks for the general population to avoid certain types of adverse effects. Bearing in mind the high inter-individual variability of responses to caffeine, adverse effects can occur at lower doses in certain individuals. Sleep disorders have been reported at intakes of as little as 100 mg/d (Smith *et al.*, 2000; Meltzer *et al.*, 2008).

Upper and lower values were also adopted for children: a value of 2.5 mg/kg bw/d corresponds to the value most frequently used in the literature as the dose not to be exceeded by children, above which symptoms of anxiety have been observed. A dose of 1.0 mg/kg bw/d corresponds to the dose above which the development of tolerance and withdrawal symptoms have been observed. It is preferable that the values taken from these expert assessments be calculated for bodyweight, making it possible to take account of the considerable variability in the child population.

**Table 15: Maximum threshold values adopted for risk assessment related to high caffeine intake in consumers of scEDs**

Population	Type of effect	Maximum threshold values adopted	Source
Adults	No general toxicity or adverse cardiovascular effects, effects on bone health or the calcium balance (for a calcium intake > 800 mg/d), changes in behaviour, greater incidence of cancer or effects on male fertility, for daily consumption of caffeine up to 400 mg/d	400 mg/d	Health Canada, 2003
	Heightened anxiety	210 mg/d	NZFSA, 2010 Smith 2000
Children and adolescents	Heightened anxiety	2.5 mg/kg bw/d (LOAEL)	Health Canada, 2003 NNT, 2008
	Development of tolerance and withdrawal symptoms	1.0 mg/kg bw/d (LOEL)	NNT, 2008

The risk of exceeding these threshold values is presented first for the general population, considering caffeine intake from a normal diet, and then for consumers of scEDs.

**b. Estimation of caffeine intake by the French population and the risks of exceeding maximum threshold values**

**Method**

The data used to estimate caffeine intake in the general population were taken from the INCA 2 individual and national food consumption survey (2006/2007). They take account of caffeine intake from normal foods containing caffeine (coffee, tea, soft drinks, chocolate and derived products, etc.); on the other hand, intake from scEDs is not taken into account as the sample for this study included only three consumers of scEDs. Potential intake from food supplements was not included either. Minimum, mean and maximum levels of caffeine were estimated from bibliographical data for foods such as coffee and tea; for composite foods including these ingredients, levels of caffeine were calculated on the basis of the recipes for these products.

Two approaches were used to calculate caffeine intake for the population: by considering either mean levels or maximum levels of caffeine in foods; the second approach offers the best protection for consumers.

**Caffeine intake in the general population**

In adults, mean daily caffeine intake was estimated at 168 mg/d with 438 mg/d at the 95<sup>th</sup> percentile, if mean levels of caffeine in food are considered. Mean intake and the 95<sup>th</sup> percentile are respectively 533 and 1580 mg/d if the maximum levels in the source foods are considered. Intake is lower in children and adolescents, irrespective of the levels considered: mean intake is between 14 and 34 mg/d depending on age range if mean levels of caffeine are considered, and between 20 and 75 mg/d if maximum levels are considered. Caffeine intake was also estimated for pregnant women, but based on a very small sample (n = 28). All results are given in Table 16 below.

**Table 16: Mean daily intake of caffeine (mg/d) in the general population**

Population	Number of individuals	With mean levels of caffeine			With maximum levels of caffeine		
		Mean	P95	Max.	Mean	P95	Max.
Children 3-10 yrs	n=574	14.0	36.3	473.4	19.8	45.4	802.7
Children 11-14 yrs	n=456	19.3	60.4	238.0	31.4	115.2	856.9
Children 15-17 yrs	n=425	33.5	120.4	353.4	75.0	342.7	970.9
Adults 18 yrs and >	n=2624	168.0	437.9	1526.5	533.4	1580.3	5920.6
Pregnant women	n=28	50.2	168.3	296.5	128.0	581.3	1029.7

In children, alcohol-free cold drinks contribute 28% of total caffeine intake, coffee contributes 12%, other hot drinks contribute 15% and chocolate 10%. Coffee becomes the primary contributor of caffeine among 15-17 year-olds, providing 39% of intake. In adults, it contributes 80% of total caffeine intake.

**Risks of exceeding maximum threshold values for caffeine in the general population**

The risks of exceeding identified maximum threshold values were calculated for these populations.

Between 2 and 5% of children and adolescents are likely to have caffeine intakes higher than the threshold value of 2.5 mg/kg bw/d, if mean levels of caffeine in the diet are considered. This proportion rises to between 4 and 12% if maximum levels of caffeine in the diet are considered.

About 7% of adults are at risk of exceeding the maximum threshold value of 400 mg/d if mean levels of caffeine are considered, with this proportion reaching 50% if maximum levels of caffeine

are considered. About 28% of adults exceed the 210 mg/d level, and up to 67% of them if maximum levels of caffeine in the diet are considered.

About 14% of pregnant women exceed the value of 200 mg/d if maximum levels of caffeine in the diet are considered, although the confidence interval related for this value [CI = 3.8% - 23.5%] is large considering the methodological limitations of the study for this population.

The results are given in Table 17 and Annex 3.

**Table 17: Prevalence of caffeine consumption exceeding threshold values in the general population**

% exceeding threshold values [CI 95%]	Children 3-10 years (n=573)	Adolescents 11-14 years (n=454)	Adolescents 15-17 years (n=423)	Adults 18 years and over (n=2624)	Pregnant women (n=28)
<b>Approach 1: Mean level of caffeine</b>					
1.0 mg/kg bw/d	11.1% [8.3%-13.8%]	7.2% [4.8%-9.5%]	13.1% [9.4%-16.8%]	na	na
2.5 mg/kg bw/d	1.9% [0.7%-3.1%]	1.5% [0.6%-2.4%]	4.6% [2.0%-7.2%]	na	na
200 mg/d	na	na	na	na	4.5% [0.0%-12.4%]
210 mg/d	na	na	na	28.2% [26.2%-30.3%]	na
400 mg/d	na	na	na	6.5% [5.4%-7.6%]	na
<b>Approach 2: Maximum level of caffeine</b>					
1.0 mg/kg bw/d	16.2% [13.0%-19.4%]	11.4% [8.4%-14.3%]	25.0% [19.5%-30.5%]	na	na
2.5 mg/kg bw/d	3.8% [2.2%-5.4%]	4.6% [2.6%-6.5%]	11.9% [8.5%-15.4%]	na	na
200 mg/d	na	na	na	na	13.6% [3.8%-23.5%]
210 mg/d	na	na	na	67.1% [65.0%-69.2%]	na
400 mg/d	na	na	na	50.1% [47.9%-52.4%]	na

There is therefore a risk to the general population of exceeding maximum threshold values for caffeine merely through a normal non-enriched diet, without considering dietary supplements; the risk can be high for certain populations if maximum caffeine levels are considered.

**c. Estimation of caffeine intake in consumers of scEDs and the risk of exceeding maximum threshold values**

**Method**

Caffeine intake in consumers of scEDs was calculated on the basis of ANSES's most recent scED consumer monitoring survey (Annex 5), carried out in 2011 and including 228 consumers of scEDs over the age of 14. This study enabled caffeine intake among consumers of scEDs to be calculated via scEDS, via coffee or via both. Total caffeine intake taking account of other drinks or foods that are sources of caffeine were not calculated for this population, as the study did not measure the consumption of these foods. Consumption of these foods calculated on the basis of a survey of the general population (INCA 2 data) was not used, as consumers of scEDs are likely to present different dietary behaviour (different consumption of soft drinks, for example). However, for information only, coffee is the principal vector of caffeine in adults in the general population, accounting for 80% of caffeine intake in the normal diet.

The data about the composition of scEDs were taken from the levels indicated directly, when these were available. However, as explained in Section 3.1.3, many scEDs do not indicate the quantities of caffeine they contain. To complete the missing values, the known levels for a product were

therefore assigned to products of the same brand and the same range for which levels were not known. This enabled mean levels to be obtained for the major brands. For other brands, a mean level was calculated based on the mean level of the major brands and occasionally based on other levels available for certain individual products from these other brands.

The scED consumption survey provided information about the frequency of consumption of scEDs and the quantities consumed on a day of consumption. From this, it was possible to estimate caffeine intake for two reference periods: intake for a day of consumption and mean daily intake, obtained by applying the declared frequency of consumption to the amount consumed in the course of a day of consumption. Mean daily intake is lower than intake on a day of consumption, bearing in mind the relatively low frequency of consumption of scEDs.

As for the general population, two approaches were used to estimate intake: either weighted mean levels based on market share, or maximum caffeine levels were considered, for intake via scEDs and intake via coffee<sup>34</sup>.

Intake was first calculated for all consumers of scEDs and then for regular consumers alone, with a distinction being made between those who did and did not consume coffee.

***Caffeine intake in consumers of scEDs estimated for a day of consumption***

If caffeine intake is considered for a day of consumption, taking mean levels of caffeine (Table 18), it is possible to calculate that mean caffeine intake via scEDs and coffee is 196 mg in all consumers of scEDs; 108 mg or 55% of this intake comes from scEDs. Total intake at the 90<sup>th</sup> percentile is 442 mg, while the maximum intake observed is 863 mg. Mean intake and intake at the 90<sup>th</sup> percentile are higher in coffee-drinkers than those who do not consume coffee ( $p < 0.0001$ ) (mean intake of 310 mg in coffee-drinkers compared with 119 mg in non-coffee-drinkers).

If maximum levels of caffeine are considered (Table 19), mean caffeine intake via scEDs and coffee is 420 mg (115 mg or 27% of which comes from scEDs) in all scED users. Overall intake at the 90<sup>th</sup> percentile is 1144 mg, with a maximum observed intake of 3140 mg.

Since there is little variation in caffeine levels between scEDs, the two approaches give very similar results regarding intake via scEDs, whereas the considerable variation in caffeine levels in coffee leads to different overall intake (from scEDs + coffee) in the two approaches.

In coffee-drinkers, total caffeine intake (scEDs + coffee) is higher than in non-coffee-drinkers (310.2 mg compared with 118.5 mg if mean caffeine levels are considered), with scEDs accounting for 30% of intake (and 12% if maximum caffeine levels in scEDs and coffee are considered).

**Table 18: Mean caffeine intake (mg) for a day of consumption in all consumers of scEDs (Approach 1: mean caffeine levels)**

	Caffeine intake (mg) for a day of consumption							
	"Total" (scEDs + coffee)				scEDs			
	Mean	P90	Max.	<i>p</i>	Mean	P90	Max.	<i>p</i>
<b>Non-coffee-drinkers (n=135)</b>	118.5	232.5	542.5	<i>&lt;0.0001</i>	118.5	232.5	542.5	<i>0.02</i>
<b>Coffee drinkers (n=93)</b>	310.2	517.2	862.9		93.0	155.0	310.0	
<b>All consumers (n=228)</b>	195.5	442.4	862.9		108.2	225.0	542.5	

<sup>34</sup> For the "mean levels" approach, each consumer of scEDs was randomly assigned a brand of scED, assignments being weighted according to market share; a mean caffeine level was also used for coffee. For the "maximum levels" approach, intake was calculated with maximum observed levels of caffeine in both scEDs and coffee.

**Table 19: Mean caffeine intake (mg) for a day of consumption in all consumers of scEDs (Approach 2: maximum caffeine levels)**

	Caffeine intake (mg) for a day of consumption							
	"Total" (scEDs + coffee)				scEDs			
	Mean	P90	Max.	<i>p</i>	Mean	P90	Max.	<i>p</i>
<b>Non-coffee-drinkers (n=135)</b>	125.2	240.0	560.0	<i>&lt;0.0001</i>	125.2	240.0	560.0	<i>0.03</i>
<b>Coffee drinkers (n=93)</b>	858.9	1674.3	3140.2		99.0	160.0	320.0	
<b>All consumers (n=228)</b>	420.2	1144.4	3140.2		114.7	240.0	560.0	

**Mean daily intake of caffeine in consumers of scEDs**

Mean daily intake was calculated by applying the declared frequency of consumption to the quantity consumed in a consumption episode, which gave intake values of caffeine lower than those calculated for a day of consumption, as the vast majority of consumers do not consume scEDs on a daily basis.

If mean levels of caffeine are considered (Table 20), mean caffeine intake from scEDs plus coffee is 101 mg/d, 14% of which comes from scEDs, with 321.8 mg/d at the 90<sup>th</sup> percentile.

If the maximum levels of caffeine for scEDs and coffee are considered (Table 21), mean daily caffeine intake from these drinks is more than three times higher than when mean caffeine levels are considered. This can be explained mainly by the high variability of caffeine levels in different coffees.

**Table 20: Mean daily caffeine intake (mg/d) in all consumers of scEDs (Approach 1: mean caffeine levels)**

	Mean caffeine intake (mg/d)							
	"Total" (scEDs + coffee)				scEDs			
	Mean	P90	Max.	<i>p</i>	Mean	P90	Max.	<i>p</i>
<b>Non-coffee-drinkers (n=135)</b>	16.6	50.0	249.1	<i>&lt;0.0001</i>	16.6	50.0	249.1	<i>0.02</i>
<b>Coffee drinkers (n=93)</b>	226.7	433.5	789.2		9.5	25.9	55.4	
<b>All consumers (n=228)</b>	101.1	321.8	789.2		13.8	27.7	249.1	

**Table 21: Mean daily caffeine intake (mg/d) in all consumers of scEDs (Approach 2: maximum caffeine levels)**

	Mean caffeine intake (mg/d)							
	"Total" (scEDs + coffee)				scEDs			
	Mean	P90	Max.	<i>p</i>	Mean	P90	Max.	<i>p</i>
<b>Non-coffee-drinkers (n=135)</b>	17.6	57.1	257.2	<i>&lt;0.0001</i>	17.6	57.1	257.2	<i>0.02</i>
<b>Coffee drinkers (n=93)</b>	770.0	1605.7	3061.5		10.1	28.6	57.1	
<b>All consumers (n=228)</b>	320.1	1055.2	3061.5		14.6	28.6	257.2	

**Risks of exceeding maximum threshold values in consumers of scEDs**

Most of the threshold values chosen for this expert appraisal were established on the basis of "chronic" effects, or were interpreted in this way by the health agencies. For this assessment, these values were thus compared with mean daily intake of caffeine (and not with the intake observed in a day of consumption).

When caffeine intake from scEDs plus coffee is considered, about 5% of consumers of scEDs exceed the value of 400 mg/d and 20% exceed the value of 210 mg/d if mean caffeine levels are considered. These percentages are closer to 30% if maximum caffeine levels are considered.

As many as 14% of adolescents consuming scEDs may exceed the threshold values of 1 mg/kg bw/d, rising to 2.5 mg/kg/d if maximum caffeine levels for both scEDs and coffee are considered (Table 22 and Annex 4).

**Table 22: Prevalence of exceeding threshold values for caffeine intake via scEDs and coffee in consumers of scEDs (n = 228)**

% exceeding threshold values [CI 95%]	Adolescents 14-17 years (n=28)	Adults 18 years and over (n=200)	All consumers (n=228)
<b>Approach 1: mean levels of caffeine</b>			
1.0 mg/kg bw/d	9.6% [0.0%-22.2%]	na	na
2.5 mg/kg bw/d	4.7% [0.0%-12.7%]	na	na
210 mg/d	na	22.3% [15.1%-29.5%]	20.2% [13.7%-26.6%]
400 mg/d	na	5.5% [2.0%-9.1%]	4.9% [1.8%-8.1%]
<b>Approach 2: maximum levels of caffeine</b>			
1.0 mg/kg bw/d	14.4% [0.0%-30.1%]	na	na
2.5 mg/kg bw/d	14.4% [0.0%-30.1%]	na	na
210 mg/d	na	35.1% [26.2%-44.0%]	31.7% [23.6%-39.8%]
400 mg/d	na	31.5% [22.8%-40.3%]	28.5% [20.6%-36.4%]

These figures for the prevalence of caffeine intake exceeding threshold values were calculated without taking account of caffeine intake from the rest of the diet and thus underestimate the risk of exceeding maximum threshold values in consumers of scEDs.

In coffee drinkers, the prevalence of caffeine intake exceeding threshold values is higher: if mean caffeine levels are considered, 12.2% exceed the threshold value of 400 mg/d and 49.5% exceed the value of 210 mg/d; if maximum caffeine levels are considered, 70.8% exceed the value of 400 mg/d and 78.1% exceed the value of 210 mg/d.

### 3.7.2. Taurine intake via consumption of scEDs and the safety factor<sup>35</sup>

If mean levels of taurine in scEDs are considered, mean daily intake of taurine from scEDs is 181 mg/d in all scED consumers (Table 14). In regular consumers, intake is 429 mg/d because of the higher frequency of consumption, and intake at the 90<sup>th</sup> percentile is 714 mg/d. Intake figures calculated on the basis of maximum taurine levels differ very little, as a result of the limited variability of taurine levels in scEDs.

**Table 23: Mean daily taurine intake via scEDs (mg/d)**

Intake (mg/d)	All consumers (n=228)			Regular consumers (n=67)		
	Mean	P90	Max.	Mean	P90	Max.
<i>Approach 1:</i> Mean level of taurine	180.5	357.2	3214.4	429.1	714.3	3214.4
<i>Approach 2:</i> Max. level of taurine	182.7	357.2	3214.4	433.6	714.3	3214.4

<sup>35</sup> Only mean daily intakes of taurine are given. They were calculated by applying the declared frequency of consumption of scEDs to the quantity consumed during a day of consumption. Taurine intake estimated for a day of consumption is presented in the report on the monitoring of scED consumption that can be found in Annex 5.

As a reminder and for comparative purposes, EFSA established an NOAEL of 1000 mg/kg bw/d in rats for pathological changes and an NOAEL of 1500 mg/kg/d for behavioural effects, on the basis of a new 13-week toxicity and neurotoxicity study, in the absence of any observed effects of taurine at these doses (EFSA, 2009).

If maximum taurine levels are considered, and for a body weight of 60 kg, the margin of safety between mean daily taurine intake and the NOAEL of 1000 mg/kg bw/d is 328, while the safety factor between daily intake at the 90<sup>th</sup> percentile and the NOAEL is 168. In regular consumers of scEDs, these safety margins are 138 and 84 respectively.

### 3.7.3. Glucuronolactone intake via the consumption of scEDs and the safety factor<sup>36</sup>

If mean levels of glucuronolactone in scEDs are considered, mean daily intake of glucuronolactone is 46 mg/d in all consumers and 115 mg/d in regular consumers (Table 15). Observed mean daily intake when maximum glucuronolactone levels in scEDs are more than twice as high, as a result of the considerable variability in glucuronolactone levels in scEDs.

**Table 24: Mean daily glucuronolactone intake via scEDs (mg/d)**

Intake (mg/d)	All consumers (n=228)			Regular consumers (n=67)		
	Mean	P90	Max.	Mean	P90	Max.
<i>Approach 1:</i> Mean level of glucuronolactone	46.3	114.3	1205.4	114.5	410.7	1205.4
<i>Approach 2:</i> Max.level of glucuronolactone	109.6	214.3	1928.6	260.1	428.6	1928.6

As a reminder and for comparative purposes, EFSA established an NOAEL of 1000 mg/kg bw/d in rats based on a 13-week toxicity study, with specific focus on the kidneys.

If maximum glucuronolactone levels in scEDs are considered, and for bodyweight of 60 kg, the safety margin between mean daily glucuronolactone intake and the NOAEL of 1000 mg/kg bw/d is 547, and the safety factor between daily intake at the 90<sup>th</sup> percentile and the NOAEL is 280. In regular consumers of scEDs, these safety margins are 230 and 140 respectively.

<sup>36</sup> Only mean daily intakes of glucuronolactone are given. They were calculated by applying the declared frequency of consumption of scEDs to the quantity consumed during a day of consumption. Glucuronolactone intake estimated for a day of consumption is presented in the report on the monitoring of scED consumption that can be found in Annex 5.

### **3.8. Summary and conclusions of the Nutritional Vigilance working group**

#### **3.8.1. Summary**

The Agency carried out several expert appraisals to assess the risks related to consumption of so-called energy drinks (scEDs) before they were marketed in France and these appraisals mentioned certain risks. So-called energy drinks contain a mix of different constituents, most commonly caffeine, taurine, glucuronolactone, B group vitamins, sugars or sweeteners.

#### **a. Results of the causality analysis for adverse effects reported to the Agency**

Since energy drinks were marketed in France in 2008, and as part of the Nutritional Vigilance Scheme, 257 cases of adverse effects have been reported to ANSES, including 212 for which causality was assessed. A causal relationship to consumption of scEDs for occurrence of these adverse effects was considered very likely or likely in 25 cases, i.e. 12% of reports, and possible in 54 cases, i.e. 25% of reports. The main symptoms observed in the 25 cases with likely or very likely causality were primarily cardiovascular (14 reports), psycho-behavioural (9 reports), neurological (7 reports), and gastro-intestinal (5 reports).

#### **b. Serious cardiovascular effects**

Among the serious cardiovascular effects, one case of cardiac arrest with a fatal outcome in a young woman of 16 years of age was considered to have very likely causality and two other cases of cardiac arrest (including one with recovery) in subjects aged 16 and 19 years were considered to have possible causality.

Patients with chanellopathies have a genetic predisposition to serious ventricular arrhythmias. These predispositions are rarely diagnosed but may have a prevalence ranging from 1/10,000 to 1/1000. In these subjects, adrenergic stimulation, related for example to physical exercise (sporting activities, dancing), can be favoured or prolonged by caffeine contained in scEDs, and thus promote the development of rhythm disorders. The risk of ventricular arrhythmia can also be enhanced in certain circumstances (tachycardia, bradycardia, hypokalaemia, intake of certain medications, etc.). This risk is also higher in women than in men. As a result, cases of cardiac arrest reported under the Nutritional Vigilance Scheme and those reported in the literature would most probably concern genetically predisposed individuals and would appear to be related to rhythm disorders caused by one or more of the risk factors mentioned above, in combination with consumption of scEDs.

#### **c. Less serious adverse effects**

The other, less serious, cardiovascular adverse effects reported after consumption of scEDs, such as tachycardia, tightness of the chest and chest pain, hypertension, and reflex bradycardia reflect the adverse effects commonly observed after intake of large amounts of caffeine. Some data however suggest that taurine may have an additive effect on increased blood pressure and may promote the development of coronary vasospasm.

The neuro-psycho-behavioural adverse effects in the reported cases analysed, such as irritability, nervousness, anxiety, or even panic attacks, correspond to the frequently reported symptoms of caffeine intoxication. The risk of psychiatric events after consumption of scEDs would appear to be higher in subjects with chronic psychiatric disorders, specifically psychosis, bipolar disorder and anxiety disorders. Individuals with epilepsy appear to be at greater risk of seizures following intake of scEDs, with higher risks related to higher consumption levels.

Other adverse effects, reported less frequently, were also analysed. So-called EDs may cause gastro-intestinal disorders such as diarrhoea since they are hyperosmolar substances. Given their diuretic effects and hyperosmolar properties, scEDs also increase the risk of dehydration. In addition, scEDs may further impair renal function in patients with a pre-existing renal condition or with risk factors, in particular diabetes and obesity.

Given the current state of knowledge, the above-mentioned adverse effects related to scEDs could be attributable to caffeine, although no specificity has been found for caffeine contained in scEDs compared to caffeine found in other drinks like tea or coffee. There is however some evidence of possible additional adverse effects related to the other constituents of scEDs, such as taurine, which need to be better documented.

#### **d. Variable susceptibility to the effects of caffeine**

Adverse effects have been reported following consumption of highly variable amounts of energy drink, as little as a single can in some cases, suggesting greater susceptibility in some consumers. This difference between individuals is predominantly due to inter-individual variability in response to caffeine. Variability is related, in particular, to individual genotypes, physiological states or the presence of certain disorders, caffeine consumption habits, and co-exposures for example to tobacco, and intake of medicines.

##### *Genetic factors*

Polymorphism of the gene for cytochrome P450 isoenzyme 1A2 involved in hepatic caffeine metabolism is a significant source of variation in caffeine pharmacokinetics and can be used to distinguish between “rapid metabolisers” and “slow metabolisers”. There is a larger number of slow metabolisers in the population and they are more susceptible to the effects of caffeine. Another factor is polymorphism of A<sub>2A</sub> adenosine receptors in the central nervous system, which may also underlie differences in sensitivity to the effects of caffeine on sleep and anxiety.

#### **e. At-risk populations**

##### *Physiological state*

Energy drinks are a new source of caffeine intake in children and adolescents. They account for up to 15% of caffeine intake in French children, according to consumption data in a study published by EFSA in 2013. This population is however less exposed to caffeine than the adult population, and as such has higher susceptibility. Children and adolescents have a higher risk of developing adverse effects compared to adults, for the same amount of caffeine intake. Consumption of caffeine in children and adolescents may lead to sleep disorders and disrupt the normal changes in sleep patterns described in adolescents, resulting in fatigue and daytime drowsiness. This can lead to a vicious circle, in which caffeine is consumed to counter the drowsiness. Furthermore, poor sleep quality affects cognitive abilities and academic performance at school. Chronic sleep deficits have been associated with onset of somatic disorders (hypertension, cardiovascular disease, diabetes, and obesity) and psychiatric conditions (such as anxiety and depression). Sleep deficits and early consumption of psychoactive substances such as caffeine may contribute to the development of addictive behaviour. Caffeine and caffeine-containing drinks should be avoided in children and adolescents.

Pregnant or breast-feeding women are another risk population in which caffeine consumption should be limited. This recommendation stems primarily from the possible risk of intra-uterine growth retardation related to caffeine consumption during pregnancy.

##### *Presence of known disorders*

In patients with certain diseases, caffeine metabolism is slowed (liver disease) or its adverse effects enhanced (hypertension, arrhythmias, psychiatric disorders, urinary and faecal incontinence, renal insufficiency, oesophagitis, and gastro-oesophageal reflux).

Interactions between the genotype, and physiological and disease conditions of individuals, as well as co-exposures, may enhance the effects of caffeine.

#### **f. At-risk consumption patterns**

Although caffeine has been used worldwide for a very long time, caffeine in the form of scEDs has given rise to new consumption patterns involving specific risks.

Energy drinks are sometimes consumed in high quantities, as described in certain cases reported under the Nutritional Vigilance Scheme. Specific risks may be caused by certain scDE consumption habits.

#### *Concomitant consumption of scEDs and alcohol*

One of the specific consumption habits that is likely to involve risks is intake of scEDs in combination with alcohol, a practice described at least as occasional by 16% of scED consumers in France, 33% of whom report combining scEDs and alcohol often or systematically. Consumption of scEDs or caffeine does not correct or only partially corrects cognitive disruptions induced by alcohol; it may however mitigate the perception of alcohol intoxication by reducing fatigue or increasing excitement. Concomitant consumption of scED and alcohol carries a risk since the subjects may overestimate their abilities, which may lead them to continue consuming alcohol and increase risk-taking. Consumers of scEDs may attempt to consume several psychoactive substances simultaneously (particularly scEDs, alcohol and other drugs) with the aim of combining their effects. In such cases, there may be a greater risk not only of acute repercussions but also of addictive behaviour.

In addition, alcohol can potentiate caffeine-induced heart rhythm disorders in predisposed individuals.

Finally, concomitant consumption of scEDs and alcohol increases the risk of dehydration.

#### *Consumption of scEDs during physical exercise*

Some individuals use scEDs to improve their physical performance. In France, 41% of consumers of scEDs report intake before, during, and after physical activity. So-called energy drinks may improve long-duration performance in some subjects (but not generally) when consumed early enough before exercise. They have no nutritional value, however. Unlike sports drinks, which have a nutritional composition that is suitable for physical exercise, scEDs do not maintain the water-electrolyte balance. In fact, the caffeine content in scEDs has diuretic effects that accelerate water and electrolyte losses. The resulting dehydration is aggravated since these drinks are most often hyperosmolar. Moreover, caffeine alters thermoregulation processes when subjects exercise in warm conditions, resulting in increased body temperature and a higher risk of heatstroke.

Consumption of scEDs in a festive context may lead to accumulation of risk factors, in particular co-consumption with alcohol concomitant with physical exercise (dancing for example) and heat.

This expert appraisal evaluated only the risk of acute exposure, and did not assess the risks of chronic consumption of scEDs.

#### **g. Research recommendations**

- Inter-individual variability of the effects of caffeine should be better taken into account in studies.
- The dose-effect relationships of caffeine should be better documented.
- Studies should be conducted concerning the possible interactions between the constituents of energy drinks, particularly taurine and caffeine.

#### **3.8.2. Conclusions**

Consumption of scEDs in risk situations such as co-consumption with alcohol and physical exercise (especially in hot conditions) exposes the subject to a well-documented risk of serious, mainly cardiovascular, effects, especially in subjects with a predisposition.

Some forms of predisposition of genetic origin cannot be known in advance, making it necessary for consumers to remain particularly cautious, especially as scED consumption patterns promote accumulation of risk factors.

Consumption of scEDs should be avoided:

- in children and adolescents;
- in pregnant and breast-feeding women;
- in individuals who are sensitive to the effects of caffeine;
- in patients with specific disease states, in particular certain cardiovascular disorders (supra-ventricular tachycardia and certain specific ventricular rhythm disorders, high blood pressure, unstable angina), psychiatric and neurological disorders (including epilepsy), kidney failure, severe liver conditions.

Specific risks also appear in certain situations, in which the consumption of scEDs should also be avoided:

- risks related to the consumption of alcohol can be augmented by co-consumption of alcohol
- during physical activity, particularly in hot conditions, scEDs, which are not designed to meet the nutritional needs of exercise situations, can increase the risk of dehydration, thus exposing consumers to the risk of heatstroke.

The long-term risks in chronic consumers of scEDs should be studied clinically.

#### **4. THE AGENCY'S CONCLUSIONS AND RECOMMENDATIONS**

“Energy drink” is a marketing term unrelated to any specific regulatory framework concerning these products. So-called energy drinks (scEDs) are soft drinks fortified with various substances that are already found in food (caffeine, guarana, taurine, vitamins, ginseng, etc.) and required to meet the specifications of Regulation (EC) 1925/2006 governing “fortified foods”. ANSES has catalogued over 100 of these drinks marketed in France. Their composition is relatively heterogeneous except as regards caffeine, which is found almost systematically in these beverages. A standard 250 ml can of scED contains on average the same amount of caffeine as two espresso coffees (50 ml) or slightly more than two (2.3) cans of cola soda (330 ml).

Since so-called energy drinks first appeared on the market in France in 2008, 257 cases of adverse effects have been brought to the attention of ANSES, 212 of which were sufficiently well documented for causality to be analysed as part of the Nutritional Vigilance scheme. Causality of the consumption of so-called energy drinks in the occurrence of these adverse events was deemed very likely or likely for 25 cases, or 12% of those reported. The main symptoms observed in these cases were essentially cardiovascular (heart failure, feelings of tightness or pain in the chest, tachycardia, high blood pressure, etc.), psycho-behavioural or neurological (irritability, nervousness, anxiety and even panic attacks, hallucinations, epilepsy, etc.).

Regarding the cases of heart failure reported under the Nutritional Vigilance scheme and those reported in the literature, it seems very likely that these occur in subjects with a genetic predisposition (frequent canalopathies, which can affect as many as one individual in 1000 and which are generally undiagnosed) and may also be related to heart rhythm disorders resulting from the consumption of so-called energy drinks in association with certain supplementary risk factors such as physical exercise (sport, dancing, etc.), high alcohol consumption, hypokalemia, certain medicines or individual sensitivity to caffeine.

The other cardiovascular, psycho-behavioural or neurological effects reported correspond to adverse effects commonly observed after intake of large quantities of caffeine.

After analysis of the nutritional vigilance cases and the bibliographical data, the caffeine found in these drinks was considered as the key explanatory factor, although there is some incomplete data suggesting that taurine associated with caffeine in certain scEDs could have an additional effect on raising blood pressure and facilitate the onset of angina.

Caffeine is naturally present in more than 60 plants such as coffee, tea, cola, guarana and yerba mate, and can also be produced by chemical synthesis. The substance is well known both for its effects on vigilance, especially in situations of sleep debt, and for its several adverse effects: anxiety, tachycardia, sleep disorders and migraines. In the general population there is a wide variability of sensitivity to the effects of caffeine. This variability is related to different genetic profiles (50% of the population is considered to be made up of “poor metabolisers”, more sensitive to caffeine), physiological factors (age, pregnancy, etc.), caffeine consumption patterns, state of health or co-exposures such as with tobacco, alcohol and various medicines. This variability makes it complicated to assess the dose of caffeine associated with the adverse effects. On the basis of the various thresholds used as references internationally, it is nonetheless possible to observe that a non-negligible fraction of the French population exceeds the advised levels of caffeine intake (without taking into account the consumption of foods fortified with caffeine such as so-called energy drinks or certain food supplements):

- About 30% of the adult population and 1 to 2% of children and adolescents exceed the threshold established as causing anxiety (which for an adult corresponds to about six espresso coffees);
- 11% of 3 to 10-year-olds and 7% of 11 to 14-year-olds exceed the threshold for developing tolerance to caffeine and triggering withdrawal symptoms (which for a child weighing 35 kg corresponds to consumption of less than half of a standard can of so-called energy drink or one can of cola);
- and almost 7% of the adult population exceeds the threshold beyond which more general chronic toxicity is suspected (bone and cardiovascular health, cancer, male fertility, etc.).

Although caffeine has long been consumed throughout the world, its novel and increasingly popular presentation in the form of so-called energy drinks is changing consumption patterns. These new forms of consumption reported by the various surveys that have been carried out:

- affect consumers who until now had had little exposure to caffeine, including children and adolescents of whom, in Europe, 3% and 8% respectively consume scEDs more often than 4 to 5 times a week;
- sometimes involve very high quantities: 25% of French consumers of scEDs sometimes consume more than 500 ml in a single day;
- occur in new contexts of exposure: in France, about 32% of consumers of scEDs drink them during festive occasions (bars, discothèques, concerts, etc.), 41% in association with sporting activities, and 16% while also consuming alcohol.

ANSES considers that changes in practice concerning fortifying foods with caffeine, especially via so-called energy drinks, combined with the contemporary consumption patterns of these beverages, are likely to generate risk situations.

**The Agency considers that:**

- 1) Once EFSA's current work on the risks related to caffeine is complete, it would be advisable to study ways of improving legislation concerning fortifying foods with caffeine by listing this substance in the annexes to Regulation (EC) 1925/2006;
- 2) Work is needed to improve knowledge of the effects of taurine and the combined effects of caffeine and taurine.

**The Agency therefore recommends that consumers:**

**1) Moderate their consumption of caffeinated beverages.** Considering the levels of caffeine intake observed in the population, the Agency appeals especially to individuals subject to prolonged periods of anxiety and to sleep or cardiac rhythm disorders, to carefully review their caffeine consumption, if necessary with the help of a health professional.

The Agency also calls for vigilance concerning the potential development of the use of so-called energy drinks in the workplace supposedly to offset sleep debt (10% of consumers drink these beverages at their place of work or study).

**2) Be particularly vigilant concerning their caffeine intake**, especially the following groups:

- **pregnant women and nursing mothers**, particularly as caffeine can increase the risk of impaired foetal growth and also passes into breast milk;
- **children and adolescents**, a population particularly sensitive to caffeine, likely to suffer disturbed sleep patterns, daytime sleepiness and the risk of developing addictive behaviour in later life;
- **individuals sensitive to the effects of caffeine or presenting certain pathological conditions, especially:** certain cardiovascular or psychiatric and neurological disorders, kidney failure or serious liver diseases.

**3) Considering the frequency of genetic predisposition, which is often undiagnosed in the population, and the potential severity of cardiac effects, the Agency also recommends that consumers avoid:**

- **consuming so-called energy drinks in combination with alcohol, as:**
  - this is likely to potentiate cardiac rhythm disorders induced by caffeine in predisposed individuals;
  - caffeine can reduce the perception of alcoholic intoxication, thus favouring risk situations (the person may overestimate his or her aptitude, continue consuming alcohol and thus increase the likelihood of risk-taking).
- **consuming so-called energy drinks during physical exercise, as:**

- this constitutes a cardiac risk factor in predisposed individuals;
- this requires preserving the water-electrolyte balance, which is disturbed by the diuretic effects and the hyperosmolarity of so-called energy drinks;
- caffeine intake increases body temperature, thus increasing the risk of heat stroke.

**ANSES also draws attention to the emergence in other countries** (Canada, United States, Lithuania, etc.) **of government policies to regulate the market for scEDs**. Considering the divergence between the Agency's recommendations and current practice as reported in France, and also the lack of information among the public, ANSES calls for **measures to be taken** to inform vulnerable population groups and to regulate the advertising of scEDs to these groups and in contexts (festive, sporting, etc.) where consumption involves special risk.

**The Director General**

**KEY WORDS**

So called Energy drinks - scED – Nutritional Vigilance – Causality – Caffeine – Taurine – Glucuronolactone – Alcohol – Exercise

**ANNEXES**

**Annex 1: Proceedings of stakeholder hearings (refer to French version)**

**Proceedings of the hearing of the consumers association *Consommation, Logement et Cadre de Vie* (CLCV – Consumption, Housing and the Living Environment)**

**Proceedings of the hearing of the French association of cold drinks manufacturers  
(SNBR)**

**Proceedings of the hearing of the company Red Bull**

**Proceedings of the hearing of the *Institut National de Santé Publique du Québec* (INSPQ)**

**Proceedings of the hearing of the *Société Française de la Nutrition du Sport (SFNS)*  
(French Society for Sport Nutrition)**

**Synthèse du GT Nutrivigilance**  
**Saisine n° 2012-SA-0212**

**Annex 2: Observational studies on the consumption of scEDs and the contexts of consumption**

nr = Not reported

na = Not applicable

Reference	Country	Participants	Protocol	% of consumers of scEDs	% consuming scEDs in combination with alcohol	Related behaviour	Statistical analyses Adjustments or other characteristics of the model
Oteri 2007	Italy	450 medical students	Questionnaire sent to 500 students	56.9%	"Frequent" combination for 48.4% of consumers	nr	na
Malinauskas 2007	USA	496 students	Questionnaire sent to students recruited on the campus	51% more than one scED/month	54% of consumers of scEDs	na	na
Miller 2008	USA	602 students	Questionnaire	Nr	nr	Frequency of scED consumption combined with: use of cannabis, at-risk sexual conduct, fighting, not wearing safety belts, risk-taking + Among white students: smoking, alcohol consumption, alcohol-related problems, drug use	Logistic regression and multivariate linear regression  Gender, age, ethnic group, parental education, level of school achievement
O'Brien 2008	USA	4271 students, 2886 of whom had consumed alcohol in the previous 30 days	Online questionnaire sent to participants recruited at random in 10 universities	nr	24% of those who drink alcohol had consumed scEDs in combination with alcohol	Higher number of episodes of high alcohol consumption and of drunken episodes in consumers combining scED + alcohol than in other consumers of alcohol  Greater prevalence of risk behaviour: travelling in a car with a driver under the influence of alcohol, non-consensual sexual intercourse, fighting, need for medical attention.	Logistic regression  Gender, age, ethnic group, membership of student association, sporting activity
Arria 2010	USA	Cohort of 1097 students	Students recruited on admission to university, followed up over 3 years	26 and 33% in 2 <sup>nd</sup> and 3 <sup>rd</sup> year of	nr	Heavier consumption of alcohol, drugs and tobacco more frequent in consumers of scEDs, compared to non-consumers	Chi-square test

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Reference	Country	Participants	Protocol	% of consumers of scEDs	% consuming scEDs in combination with alcohol	Related behaviour	Statistical analyses  Adjustments or other characteristics of the model
			– Annual interview	university		Consumption of scEDs in 2 <sup>nd</sup> year associated with greater use of stimulants in 3 <sup>rd</sup> year + prescription of analgesics	Logistic regression  Age, gender, mother's education, sensation-seeking, caffeine consumption
Thombs 2010	USA	802 clients of a university bar	Interview of clients leaving university bars, chosen at random	na	na	Clients that had consumed scEDs in combination with alcohol were 3 times more likely to leave the bar with a high concentration of breath alcohol (> 0.08 g/210 l) and 4 times more likely to consider driving on leaving the bar compared to other clients	Logistic regression  Age, gender, ethnic group, day of the week, membership of student association, consumption of scEDs and alcohol not combined
Price 2010	Canada	72 consumers of scEDs	Interview	na	76%	Declare that they drink more alcohol when they combine scEDs with alcohol (8.6 drinks compared to 4.7 drinks)	Student's paired T-test
Berger 2011	USA	346 subjects > 18 years old	Telephone survey of participants chosen randomly from the telephone directory	31.4% (at some time in their lives)	21% of consumers of scEDs during the preceding year	When compared to those consuming only scEDs, consumers combining scEDs with alcohol are younger	Logistic regression  Gender, age, ethnic group, educational level, socio-economic status, etc.
Brache 2011	Canada	465 students	Questionnaires submitted to students recruited by email and by poster campaign	nr	13% of the total sample during the preceding month	Consumers of scEDs + alcohol consume more alcohol and more often than consumers of alcohol without scEDs Frequency of consumption of scEDs + alcohol associated with negative consequences such as injury, driving when intoxicated, etc.	Linear regression or logistic regression  Adjustment for age, gender and propensity to take risks.
Marczinski 2011	USA	706 students	Questionnaire submitted to students from the psychology department	81% > once in the past 36% > once in the previous two weeks	44% of the total sample > once in the past and 9% > once in the previous 15 days.	na	na
Thombs 2011	USA	328 clients of a university bar	Interview of clients leaving university bars, chosen at random	na	na	Breath alcohol higher for the caffeinated soda + alcohol group compared to the other 2 groups (scED + alcohol or only alcohol) No difference in breath alcohol concentrations between alcohol group and alcohol + scED group.	ANOVA

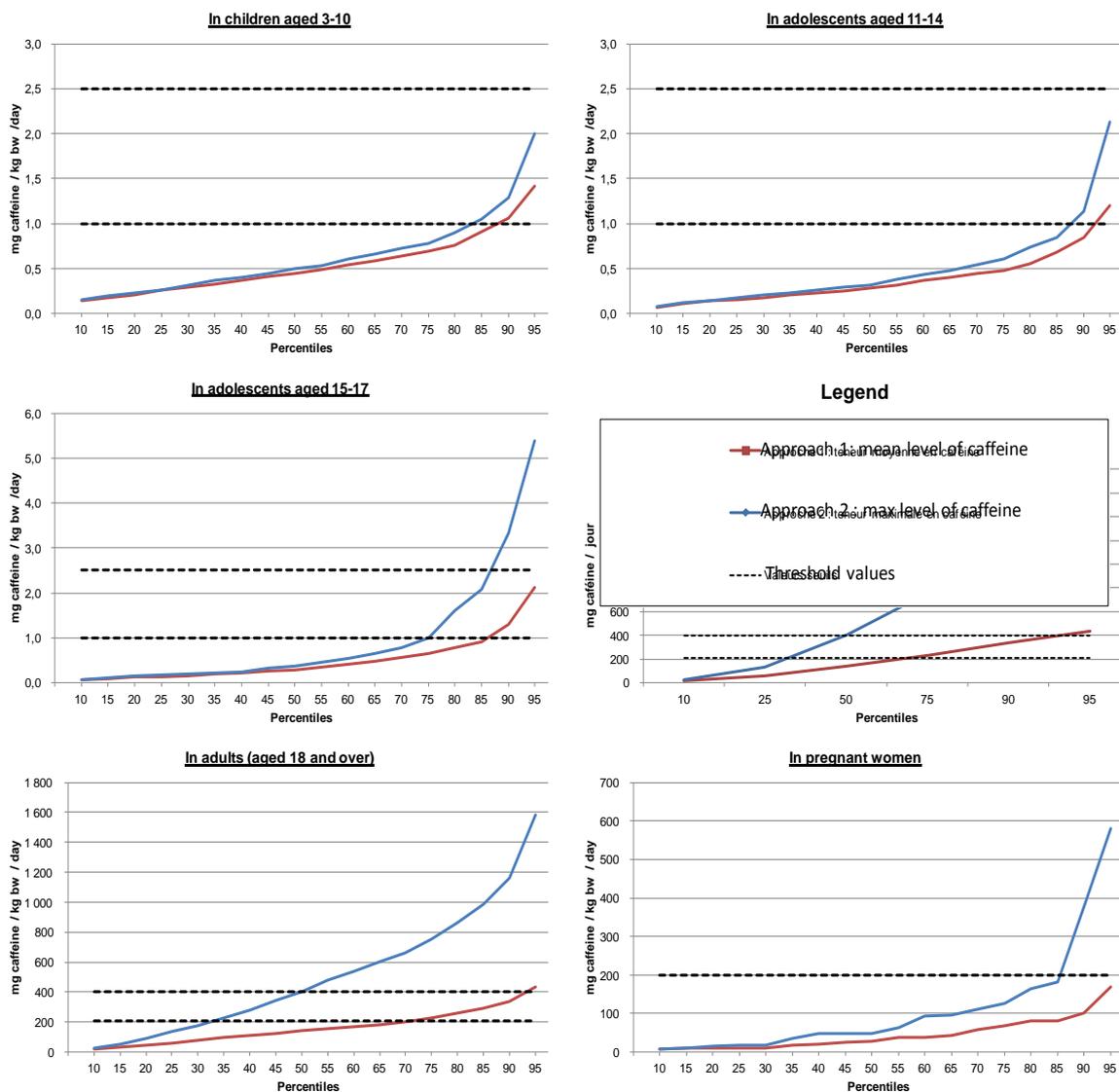
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Reference	Country	Participants	Protocol	% of consumers of scEDs	% consuming scEDs in combination with alcohol	Related behaviour	Statistical analyses Adjustments or other characteristics of the model
						Total number of caffeinated alcoholic drinks associated with breath alcohol concentration, which is not the case of non-caffeinated alcoholic mixtures	Multivariate linear regression Gender, night of the week, total number of alcoholic drinks consumed
Arria 2011	USA	1097 students	Interview of students Cohort recruited on entering university	10% consume > 52 days/year 51% consume < 52 days/year	nr	Regular consumers vs occasional consumers: drink alcohol more often and in greater quantities Greater risk of alcoholic dependency in regular consumers compared with non-consumers and occasional consumers No difference between occasional and non-consumers	- Chi-square test and logistical regression for dependence Age, gender, ethnic group, usual alcohol consumption, membership of student association, depression, parental history, use of drugs/alcohol, behavioural problems during childhood
Attila 2011	Turkey	439 students	Questionnaire administered to students in class	48% have already consumed 33% are current consumers	37% of current consumers	Consumption of scEDs combined with consumption of alcohol	? Logistic regression Age, subjects studied at university, socio-economic level
Miller 2012	USA	648 students	Questionnaire submitted to students recruited at university or by email	nr	29% of the total sample	Consumption of mixtures of alcohol + scEDs associated with a greater risk of casual, drunken or unprotected sexual intercourse.	Logistic regression Age, gender, frequency of alcohol consumption, risk taking
Peacock 2012	Australia	403 students	Questionnaire submitted to students recruited by posters, social networks, etc. Comparison between occasions when the subject consumed scED + alcohol and occasions when alcohol alone was consumed	nr	nr	Comparing mixture of alcohol + scEDs vs alcohol alone: Greater consumption of alcohol and higher risk of disorders related to excitement but less disinhibition and at-risk behaviour, with fewer subjects presenting sedative effects	nr

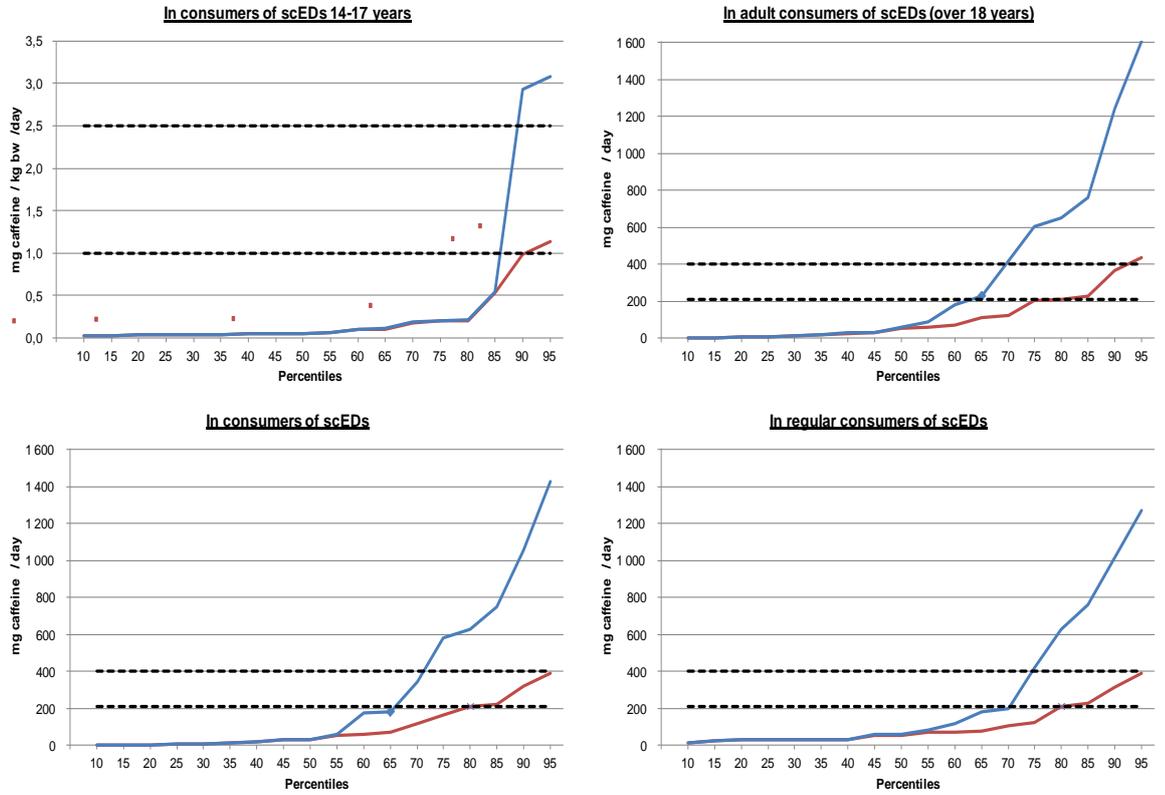
**ANSES Opinion  
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Reference	Country	Participants	Protocol	% of consumers of scEDs	% consuming scEDs in combination with alcohol	Related behaviour	Statistical analyses
							Adjustments or other characteristics of the model
Velasquez 2012	USA	585 students	Students asked to complete an online questionnaire	40% in the previous month, 17% in the previous week	15% of the total sample in the previous month	For each extra unit of scED consumed in the previous month: Probability of consuming alcohol ↑ by 80%, probability of heavy alcohol consumption ↑ by 80%, probability of mixing alcohol + scEDs ↑ 90%. Quantity of alcohol consumed associated with frequency of consuming scEDs	Logistic regression Age, gender, ethnic group
Arvers 2012	France	1000 students	3268 students chosen at random, asked to complete an online questionnaire	na	53.9% of the total sample	Percentages of consumers as a function of frequency	
de Haan 2012	Netherlands	6002 students: online questionnaire sent to 70,000 university students	Inter-individual comparisons: subjects consuming only alcohol and subjects sometimes combining alcohol with scEDs	na	1239, or 20% of the total sample occasionally combined scED + alcohol	Higher consumption and greater frequency of consumption and drunken episodes in consumers of mixtures compared with those consuming only alcohol	Student's T-test Chi-square test
			Intra-individual comparisons: subjects consuming only alcohol and the same subjects consuming alcohol and scEDs	nr		Number of drinks/consumption events, number of days of drunkenness, quantity consumed, and negative consequences related to alcohol lower when consuming mixtures of scED + alcohol versus alcohol alone.	Paired Student's T-test

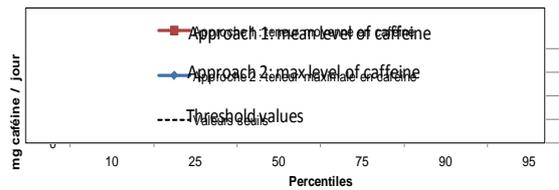
Annex 3: Mean daily caffeine intake in the general population and prevalence of consumption exceeding maximum threshold values



**Annex 4: Mean daily caffeine intake in consumers of scEDs (from scEDs and coffee) and prevalence of consumption exceeding maximum threshold values**



**Legend**



**Annex 5: So-called “energy drinks” in France – Composition, consumption and intake of caffeine, taurine and glucuronolactone – Study report (refer to French version)**

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