Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the risks related to the consumption of energy drinks

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Abstract

The consumption of energy drinks has increased substantially over the past decades, reaching 2 % of all soft drinks in Spain. In addition to caffeine, energy drinks generally contain other ingredients such as taurine, L-carnitine, glucuronolactone, guarana, ginseng and B vitamins, among others. They may also provide up to 11 g of sugar per 100 ml, although "sugar free" options are also available.

After a risk assessment of the Spanish population's dietary exposure to the active components generally present in energy drinks, the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) has concluded that energy drinks are not recommended for children and pregnant or lactating women. It also recommends collaborating with the drinks industry to improve the consumer information provided in energy drink labels, promoting not only the enumeration of all active ingredients in the list of ingredients but also their content.

With regard to caffeine content in energy drinks, consuming energy drinks with low levels of caffeine is more advisable in order to prevent and reduce the probability of disruptions to the sleep

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cycle and other adverse health effects, depending on different population groups. Future actions should include an assessment of the consumption, exposure, and risks related to other "caffeine consumption models" such as caffeine shots.

With regard to D-glucuronolactone, the daily energy drink intake of 250 ml in consumers weighing 60 and 70 kg of body weigth has a margin of safety greater than or equal to 100.

The consumption of energy drinks entails a high risk of hypervitaminosis for Vitamin B3 (nicotinic acid or niacin), medium risk for vitamins B3 (nicotinamide) and B6, and low risk of hypervitaminosis for vitamins B2, pantothenic acid, and B12.

With reference to the presence of plant-based ingredients, the biological activity of the different active ingredients and their drug interaction potential must not be underestimated. The consumer must be informed not only of the included contents but also of the possibility/risk of drug interaction, as well as those situations where their intake is contraindicated. Thus, energy drinks that contain ginseng must be avoided not only in pregnancy, when breastfeeding, and in children, but also in adolescents below the age of 18, given the absence of an assessment of the effects of ginseng on these population groups. Energy drinks containing ginkgo must also be avoided during pregnancy and when breastfeeding.

With regard to sugar intake from the consumption of energy drinks that contain sugar, it is estimated that an intake of 250 ml may represent 10 % of the energy in 2200-2400 kcal diets, which would make it very easy to exceed the recommended daily intake of simple sugars.

The growing preoccupation with assessing the health risks of energy drinks is accompanied by an interest in improving consumer knowledge, promoting moderate consumption and avoiding unsafe behaviours, especially in combination with alcoholic drinks. Spain must join European efforts to compile data on energy drink consumption and consumption trends by means of annual actions to monitor and raise awareness within the community. This would enable an assessment of the contribution of these energy drinks to the dietary exposure to caffeine and other active ingredients in specific consumer groups; make a risk assessment; and design action plans differentiating the population groups at greatest risk (children and adolescents).

In addition, a greater control of advertising is suggested, especially that directed to the young population.

It is recommended to promote compliance with the industry commitment in the commercialization of small packages (not exceeding 250 ml) that contribute to moderate exposure to the different active components, some of them psychoactive, and to study the possibility of suspending the commercialization of 500 ml packages.

Key words

Energy drinks, caffeine, taurine, L-carnitine, glucuronolactone, guarana, ginseng, B vitamins.

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1. Introduction

The large number of non-alcoholic drinks available in the market include soft drinks, sports drinks and energy drinks, all of which have a high sugar content, with the exception of their "sugar-free" versions. According to the centre for information on soft drinks of the Spanish Soft Drinks Association (ANFABRA, 2019), currently there are more than 2000 soft drinks available in the Spanish market, and 150 new drinks are launched on average each year. The consumption of energy drinks has spiked in the last decades, constituting 2 % of all soft drinks in Spain.

The international report on energy drinks published by Zenith International (2009) already pointed out that the total global consumption of these drinks reached 3.9 billion litres in 2008, passing from a global per capita consumption of 0.4 litres in 2003 to 0.8 litres in 2008. North America accounted for 37 % of the total global consumption in 2008, the Asia-Pacific, another 30 %, and Western Europe 15 %. According to estimates by Euromonitor International, the global expansion of the energy drinks market has continued at an accelerated pace over the last years as well, with a growth of 45 % between 2006 and 2011. In the United States, the sale of energy drinks in 2018 increased by 4.1 % when compared with the same period in 2017 (Harfmann, 2018).

Apart from caffeine, energy drinks usually contain other novel and increasingly popular ingredients such as taurine, L-carnitine, glucuronolactone, guarana, ginseng and Group B vitamins, among others. Their sugar content is generally up to 11 g per 100 ml although there are "sugar-free" versions. The caffeine content of these drinks is usually 80 mg/250 ml, that is to say, 32 mg/100 ml although the concentration may range between 15 and 55 mg/100 ml. Additionally, a typical energy drink formula (250 ml) generally contains 1000 mg of taurine (4000 mg/l), 600 mg of glucuronolactone (2400 mg/l), 18 mg of niacin (72 mg/l), 2 mg of Vitamin B6 (8 mg/l), 0.001 mg of Vitamin B12 (0.004 mg/l), 6 mg of pantothenic acid (24 mg/l), 2 mg of thiamine (8 mg/l), 1.65 mg of riboflavin (5.40 mg/l) and 50 mg of inositol (200 mg/l) (EFSA, 2009) (VKM, 2019). Regarding plant-based ingredients such as ginseng, guarana and ginkgo, there is little information available on their content.

However, it must be considered that the volume of the packages sold may vary, reaching up to 500 ml in some cases. The members of Energy Drinks Europe (EDE), an association that represents the interests of European manufacturers of energy drinks, has undertaken, in its Code of Practices for the Marketing and Labelling of Energy Drinks, to make packages with a net content of 250 ml their main selling proposition for consumption (EDE, 2014). It is also worth mentioning that there are other models of consumption, of which "caffeine/energy shots", i.e., small-volume caffeine/energy drinks that can provide concentrated amounts of caffeine between 200 and 420 mg in less than 60 ml, are especially noteworthy (Heckman et al., 2010a).

Against this background and faced with the growing international evidence on the increased consumption and possible impact on and risk to consumer health, the Spanish Agency for Food Safety and Nutrition (AESAN) has requested the Scientific Committee to make a risk assessment of the Spanish population's dietary exposure to the active ingredients generally present in energy drinks. This report is divided into sections that review the legal framework for energy drinks in Europe and Spain, the problems regarding its consumption and sale, current knowledge of its main active components (caffeine, taurine, D-glucuronolactone, L-carnitine, sugars, vitamins and active

ingredients such as ginseng, guarana and ginkgo); and which calculate and assess the intake of each ingredient for different scenarios in order to make certain recommendations for their safe consumption.

2. Legal framework and sale

Non-alcoholic drinks include fruit and vegetable juices and products thereof, soft drinks and "horchata". They all fall under specific European and Spanish regulations (MAPA, 2017). Nevertheless, there is no specific classification, denomination or regulation of energy drinks. They may be considered a type of soft drink within the category "Other soft drinks" which may contain caffeine, among other raw materials, with the only restriction that they cannot contain alcohol in quantities greater than 0.5 % of the volume (BOE, 2003, 2011).

Undoubtedly, the absence of specific regulation for these drinks is a matter of concern for public administrations and the scientific community, as in addition to the lack of a definition that narrows them down, there are also no specific indications regarding the ingredients they may contain, nor their maximum concentration or combinations. Some European countries, however, such as Germany and Denmark (2011), have established regulations for the standardisation of energy drinks which limit their caffeine content to 32 mg/100 ml. Germany has also established regulatory limits on taurine (4000 mg/l), inositol (200 mg/l) and glucuronolactone (2400 mg/l) (Bundesgesetzblatt, 2012).

The term "energy drink" continues to be a vague term that is not defined or included in legislation, albeit an opinion published by the European Commission's Scientific Committee on Food (SCF) in 1999 (SCF, 1999) and revised in 2003 (SCF, 2003), states that "*It should be noted however that the term "energy" drink is a commercial designation. It is neither an agreed legal term for a category of foods in the EU, nor does the Committee offer any view in this opinion as to whether claims that these drinks provide energy, in the conventional nutritional sense, are scientifically justified".*

The FoodEx2 classification developed by the European Food Safety Authority (EFSA, 2015a) describes the energy drinks group in an explanatory note on the scope of the term as "*The group includes any type of Energy drinks, non-alcoholic functional beverages usually containing caffeine and other ingredients such as vitamins and taurine. The part consumed/analysed is by default the whole marketed unit or a homogeneous representative portion".* Without being a definition as such, this explanatory note is the description used when classifying food consumption in surveys.

With regard to labelling, Regulation (EU) No. 1169/2011 of the European Parliament and of the Council on the provision of food information to consumers (EU, 2011) includes the labelling requirements for drinks with a high caffeine content. Thus, if the caffeine content is higher than 150 mg caffeine/l, it must display "High caffeine content. Not recommended for children or pregnant or breast-feeding women" along with the mention of the caffeine content expressed in mg per 100 ml. Beyond legal stipulations, the European soft drinks industry has voluntarily adopted a code for the labelling, advertising and marketing of energy drinks. Thus, for example, some brands include the advisory *"Consume moderately"* on their drinks labels (EDE, 2014). Nevertheless, it is worth highlighting the heterogeneity of the information on composition in the labelling of energy drinks.

3. Problems and estimates of energy drink consumption

While the popularity of these drinks as anti-fatigue products has increased among adolescents and other vulnerable groups, there is growing concern regarding evidence of their adverse effects on health and their consumption in inadvisable circumstances (Nowak and Jasionowski, 2015) (De Sanctis et al., 2017) (Cruz Muñoz et al., 2020) (Oliver Anglès et al., 2020).

Apart from stimulating the Central Nervous System (CNS) and the cardiovascular system and its links to excess weight and obesity, the regular intake of energy drinks has been linked to caffeine overdose, hypertension, loss of bone density and osteoporosis and other cardiovascular diseases (Nowak and Jasionowski, 2015). Some notable side-effects of the regular consumption of energy drinks include palpitations, insomnia, nausea, vomiting and frequent urination. It has also been argued that the excessive consumption of energy drinks may serve as an indicator of other substance abuse and risky behaviours such as mixing them with alcoholic drinks (Flotta et al., 2014) (De Sanctis et al., 2017). For these reasons, some researchers already emphasise this increased consumption of energy drinks as justification for prevention and safety measures, and that it deserves a more detailed analysis (Majori et al., 2018) as the pattern of consumption may vary depending on socio-demographic characteristics, highlighting the role of gender and risky behaviours (Oliver Anglès et al., 2020). With regard to their consumption and the interactions between their ingredients, some authors consider that their levels are too low to provoke adverse reactions or beneficial effects (Ishak et al., 2012).

In 2003, the SCF estimated consumption levels in Europe at 0.5 cans of 250 ml/day (125 ml/day) for the average consumer, 1.4 cans of 250 ml/day (350 ml/day) for the high consumer and 3 cans of 250 ml/day (750 ml/day) for the acute consumer (SCF, 2003).

Subsequently, based on the study commissioned by the EFSA in 2011 to compile data on the prevalence of energy drink consumption in children, adolescents and adults in 16 Member States, including Spain, Zucconi et al. (2013) estimated the consumption of energy drinks in European adults (18-65 years) at 2 l/month. Approximately 12 % of all adult consumers said they were habitual consumers with high consumption levels distributed over various intake occasions, that is to say, they consumed energy drinks 4-5 times a week or more (13.3 % in "young adult" consumers), consuming an average volume of 4-5 l/month. Excessive consumers, with an elevated intake on a single occasion (they consumed at least 1 l/occasion) accounted for 11 % of all adult consumers of energy drinks, mainly in "young adults" (13.4 %). These authors estimated the average consumption of energy drinks in European adolescents (10-18 years), at 2 l/month. Around 12 % of adolescent consumers identified themselves as "chronic high" consumers, that is to say, they consumed energy drinks 4-5 times a week or more, with an average energy drink volume of 7 l/month. Another section of the 12 % of adolescent consumers turned out to be "very acute" consumers or those who consumed at least 1 l of energy drinks on each occasion. The consumption of these energy drinks in European children (3-10 years) is surprising, given that the average consumed volume was 0.5 l/week. Approximately 16 % of the surveyed children were "chronic high" consumers, that is to say, they consumed energy drinks 4-5 times a week or more, with an average volume of nearly 1 l/week (Zucconi et al., 2013).

If we focus on the results of the study on the Spanish population, the prevalence of energy drink consumption in Spanish adults (18-65 years) is 31 % (30 % in Europe), of which 16 % correspond to chronic consumers. Among Spanish adolescents (10-18 years), prevalence is 62 % (68 % in Europe) with 10 % classified as chronic consumers. We once again note the elevated consumption of this type of drink among children (3-10 years) given that, if the prevalence for the entire European Union is 18 % then our country reaches 26 %, even though the study does not mention chronic consumption for this age group. Currently the food consumption data at the European level, including energy drinks, is compiled by the EFSA in the Comprehensive European Food Consumption Database (FCDB). However, the data on energy drinks consumption in Spain is not available in the FCDB. The national surveys ENALIA 1 and 2 collected consumption data for our country between 2012-2015 (ENALIA, 2015, 2017). Additionally, the ESTUDES survey (Survey on the Use of Drugs in Secondary Schools), of the Spanish Observatory on Drugs and Addictions (OEDA), affiliated to the Government Delegation for the National Plan on Drugs (DGPNSD) of the Ministry of Health, estimates the prevalence of energy drink consumption among Spanish students who are 14 to 18 years old to be 49.7 % in boys and 31.1 % in girls. According to Oliver Anglès et al. (2020), in the province of Barcelona, the prevalence of energy drink consumption in fourth-year secondary school students (16-17 years) was estimated to be 30.9 % (according to consumption data in the last week), being higher in male students, first-generation migrants and children of parents without formal education.

This problem of energy drink consumption in the adolescent population has been reflected in different studies internationally. Within Europe, the prevalence of energy drink consumption in adolescents in Italy was around 57 % with 9 % high chronic consumption, 31 % mean chronic consumption, and 8 % acute high consumption. Additionally, while in Calabria, 55 % adolescents between the ages of 15 to 19 stated they had consumed energy drinks in the past 30 days (Flotta et al., 2014), energy drink consumption decreases to 38.6 % among Italian university students (Majori et al., 2018).

Meanwhile, in Germany 21.4 % of adolescents have consumed energy drinks in the last 30 days, (Galimov et al., 2019), in Poland, 16 % of adolescents are frequent consumers (Nowak and Jasionowski, 2015) and in Norway, 3.5 % of adolescents are high consumers (male children: 36.3 ml/day; female children: 18.5 ml/day) (Degirmenci et al., 2018).

In the United States, between 2003 and 2016, the prevalence of energy drink consumption spiked significantly in adolescents (from 0.2 to 1.4 %), young adults (from 0.5 to 5.5 %) and middle-aged adults (0.0 to 1.2 %) (Vercammen et al., 2019).

In Australia, the energy drink consumption patterns in adolescents between the ages of 12 to 18 revealed that 36 % had exceeded the recommended two energy drinks/day and 56 % of consumers had experienced adverse physiological effects on health after consumption (Costa et al., 2016).

4. Consumer knowledge/acceptance/perception of energy drinks

Energy drinks have gained widespread acceptance among young people and the perception of risks associated with their consumption tends to be low. A recent study on adolescents in New Caledonia linked the health impact of energy drinks to positive or neutral perceptions (Frayon et

al., 2019). Regarding consumer knowledge on these drinks, a study on Italian adolescents showed that only 13 % were aware that drinking energy drinks was the same as drinking coffee, while a considerable percentage thought that drinking energy drinks was the same as drinking carbonated drinks, or rehydrating themselves with sports drinks (Flotta et al., 2014). In Poland, nevertheless, most consumers tend to be aware of the ingredients in energy drinks (Nowak and Jasionowski, 2015). According to this study, when selecting an energy drink, young people judge the taste, cost, and effect. Nevertheless, being male is significantly associated with greater consumption of these drinks (Nowak y Jasionowski, 2015) (Stacey et al., 2017) (Degirmenci et al., 2018) (Cofini et al., 2019) (Frayon et al., 2019) (Galimov et al., 2019). Daily and elevated consumption has also been independently associated with physical inactivity, more leisure screen time, low socio-economic status, rural residence (Degirmenci et al., 2018), substance abuse, poor dietary habits, greater body mass index, search for sensations, poor school performance and more frequent exposure to advertising (Galimov et al., 2019). In the review by Alhyas et al. (2015) on awareness regarding the composition of energy drinks and associated side-effects, approximately 70 % of the participants were unaware of them. What was more concerning was that some considered them to be soft drinks.

5. Link to other risky behaviours. Community interventions

It has been argued that an excessive consumption of energy drinks may serve as an indicator of substance abuse and other risky behaviours (Flotta et al., 2014) such as alcohol and tobacco consumption and illegal drug use (De Sanctis et al., 2017) (Ruiz and Scherr, 2018). A significant point of information is that more than half (53 %) of the children and adolescents surveyed by Zucconi et al. (2013) had occasionally consumed energy drinks mixed with alcohol. The consumption of alcohol mixed with energy drinks leads to altered states of awareness including diminished perception of alcohol intoxication, increased stimulation and greater desire to drink (De Sanctis et al., 2017). Regular smoking in Italian adolescents is linked to the use of energy drinks, and approximately half of all energy drink consumers used them in conjunction with alcohol (Cofini et al., 2019). Surprisingly, in the United Kingdom, alcohol consumption in adolescents was significantly lower on the occasions when they consumed the alcoholic drink along with an energy drink, in comparison with occasions when they only consumed the alcoholic drink (Johnson et al., 2016).

An epidemiological study (Gunja and Brown, 2012) pointed out that energy drinks with caffeine accounted for the majority of the calls (297) made to the Poisons Information Centre of a children's hospital in Sydney, Australia (January 2004 - December 2010). The most common type of exposure was recreational (217), accidental paediatric (62), deliberate self-poisoning as part of a polypharmacy overdose (16), allergic reaction (1) and paediatric lactational exposure (1). The variety of symptoms reported were in line with caffeine overdose and potential stimulant abuse. Although limited to a minority of subjects, serious toxicity leading to cardiac complications (cardiac ischaemia, arrhythmia) and neurological complications (hallucinations, psychosis, convulsions) were a serious cause for concern.

With regard to the worrying results on health, lifestyle and risky behaviours, back in 2016, Costa et

al. (2016) emphasised the urgent need for the regulation of energy drinks, limiting their consumption in children and adolescents, and greater visibility of the recommendations on consumption. Among the different strategies proposed to limit consumption and to minimise health risks to adolescents from these drinks, we may point to the design and implementation of educational programmes on the potential health effects and the risks of combining alcoholic drinks-energy drinks (Flotta et al., 2014) (Jackson and Leal, 2018) (Frayon et al., 2019), increased awareness and risk perception not only among adolescent consumers but also among parents and teachers (Jackson and Leal, 2018), adopting policies to regulate and limit direct marketing to minors (De Sanctis et al., 2017) (Galimov et al., 2019), educational and sensitisation programmes tailored according to gender and age (Lebacq et al., 2020), and promoting the active monitoring of adolescents (Jackson and Leal, 2018).

Against this background and faced with the elevated prevalence of consumption, and the growing international evidence on the increased consumption of energy drinks and their impacts and possible risks to consumer health, the Scientific Committee undertakes the commission from the AESAN Board to perform this risk assessment of the Spanish population's dietary exposure to the most common active ingredients present in energy drinks.

6. Caffeine

6.1 Caffeine: general characteristics, dietary sources, kinetics and mechanism of action

Caffeine (1,3,7-trimethylxanthine) belongs to the chemical group of xanthines or dioxypurines, which are substances with alkaloid characteristics, that also include theophylline or theobromine, all of which proceed from different plant species. It is naturally present in more than 60 plants, such as coffee (*Coffea arabica*), tea (*Camellia sinensis*) and cocoa (*Theobroma cacao*), kola nuts (*Cola nitida*), guarana (*Paullinia cupana*) and mate tea (*Ilex paraguariensis*), however it is synthetically produced for use in the pharmaceutical and food industry (Ashihara and Crozier, 2001) (Svorc et al., 2012) (Zucconi et al., 2013). It belongs to the pharmacotherapeutic group of psychostimulants derived from xanthine.

Dietary sources of caffeine are diverse and some of its most notable sources are cola drinks, tea-based soft drinks, coffee, chocolate products and energy drinks. Caffeine contents vary in each of these sources. Caffeine levels are estimated at 90 mg in a 200 ml cup of filtered coffee, 80 mg in a 60 ml espresso, 50 mg in a 220 ml cup of black tea, 40 mg in a standard 355 ml can of cola, 25 mg in a 50 g slice of bread with chocolate spread, and 10 mg in a 50 g bar of milk chocolate (EFSA, 2015b). Energy drinks usually contain 15, 32, 40 or even 55 mg of caffeine/100 ml (VKM, 2019).

According to the EFSA (2015b), coffee was the main dietary source of caffeine for European adults, contributing 40-94 % of the total caffeine intake. In Ireland and the United Kingdom nevertheless, tea was the main source of caffeine, contributing 59 and 57 % of the total caffeine intake, respectively. In the case of European adolescents, there are significant differences between countries with regard to the contribution of different sources to the total caffeine intake. In most countries, chocolate (which also includes chocolate drinks) was the main source of caffeine for children between the ages of 3 to 10, followed by tea, and cola drinks. The Norwegian Ungkost 3

Study (VKM, 2019) estimated that energy drinks provide up to 76 % of the total dietary caffeine, the quantity of this substance from these drinks standing at 36.8 mg/day (the total daily consumption of caffeine is estimated at 48.4 mg/day, as it considers other sources of caffeine such as chocolate milk products, coffee, tea, sweets and chocolates/confectionary).

Caffeine is absorbed through oral and parenteral routes. The bioavailability of caffeine administered orally is practically total, being absorbed within 30 to 60 minutes and achieving peak plasma concentration in 30 minutes to 2 hours (Magkos and Kavouras, 2005). Its half-life in adults in 3 to 7 hours (it displays marked inter- and intraindividual variation). In habitual doses, peak plasma concentration is achieved in 15-45 minutes. In high doses, the maximum effects may be delayed up to 3 hours, although symptoms may be observed within 30 to 60 minutes after consumption, and there are cases where maximum effects have been observed in only 10 minutes (ANSES, 2013) (EFSA, 2015b) (VKM, 2019).

Caffeine is distributed in all compartments of the organism, it rapidly crosses the blood-brain barrier and the placental barrier, and it also passes into milk. Its plasma protein binding is 25-36 %.

The demethylation and oxidation of caffeine occurs partially in the liver, and it is eliminated through the kidneys as methyluric acid or as monomethylxanthines in 86 %. It is barely eliminated through the urinary tract (1.1 %) and only 5-10 % of what is recovered in urine is unmetabolized caffeine. It barely appears in breast milk, and a daily quantity of around 500 mg is considered safe when lactating.

Caffeine results in numerous metabolites: paraxanthine (1,7-dimethylxanthine, 84 % of the original compound), theobromine (3,7-dimethylxanthine, 12 %), theophylline (1,3-dimethylxanthine, 4 %), 1-methylxanthine, 3-methylxanthine, 1,3,7-trimethyluric acid, 1,7-dimethyluric acid, 1,3-dimethyluric acid, and 1-methyluric acid. The isoenzyme 1A2 of cytochrome P450, coded by the gene CYP1A2, is directly involved in the demethylation of caffeine into paraxanthine. CYP1A2 activity is responsible for 95 % of caffeine clearance. The polymorphism of this isoform is probably responsible for variations in caffeine metabolism among human beings (Miners and Birkett, 1996) (Heckman et al., 2010a). Caffeine metabolism is sped up in adult smokers (by hepatic microsomal enzyme induction produced by the polycyclic hydrocarbons of tobacco smoke) and after exercising. In contrast, metabolization is slow in liver cirrhosis patients, in pregnancy and in new-borns. The level of plasmatic caffeine increases in pregnant women, which entails lower metabolization during gestation. This is because CYP1A2 activity is reduced in pregnancy increasing the half-life of caffeine. It has been proved that in the end-stage of pregnancy, the half-life of caffeine is three to four times longer.

Caffeine blocks adenosine receptors subtypes A1, A2A, A2B, generating a mild nervous excitement, as the absorption of adenosine by the cells of the nervous system is one of the mechanisms that trigger sleep and sedation. Additionally, it is a non-specific inhibitor of phosphodiesterase and increases AMPc levels which appears to be related to the relaxation of the smooth muscle and reduced histamine release by mast cells. The release of catecholamines and renin also appears to be increased, at least in overdoses, releasing norepinephrine, dopamine and serotonin in the brain area. Intracellular calcium is also mobilised, increasing its free concentration, and there is also research on possible caffeine binding to benzodiazepine receptors. The interaction with the

adenosine A1 receptor, which inhibits the renal reabsorption of water and increases diuresis and natriuresis, may explain the diuretic activity of caffeine (EFSA, 2015b). Additionally, caffeine has a positive chronotropic and inotropic effect on the heart, that is to say, it stimulates the cardiac rhythm and increases cardiac output.

6.2 Caffeine: effects and uses

In recent years, the effects of regularly consuming caffeine and coffee in the development of chronic ailments such as cancer and cardiovascular diseases have been studied in detail. This evidence, which arises mainly from population-based studies with large groups of people and long-term monitoring, suggests that the regular consumption of coffee may reduce the risk of melanoma, breast cancer, prostate cancer, endometrial cancer and liver cancer. The regular consumption of coffee has also been strongly linked to lower risk of Type 2 diabetes, Parkinson's disease, acute myocardial infarction, strokes, coronary disease and death from cardiovascular disease (Van Dam et al., 2020). Nevertheless, it is important to highlight that these beneficial effects may not be due solely to caffeine but to other active biological ingredients that are found in coffee, including polyphenols, alkaloids, magnesium, potassium and Vitamin E. For this reason, these beneficial effects cannot be extrapolated to other dietary sources of caffeine.

The therapeutic role of caffeine has been known throughout history. Currently, caffeine is an ingredient in 34 pharmaceutical specialities authorised in Spain (AEMPS-CIMA, 2021). As an active ingredient, it is included as caffeine, caffeine citrate or caffeine anhydrous, and is usually accompanied by a wide variety of active ingredients among which are paracetamol, acetylsalicylic acid, ibuprofen, dimenhydrinate, ascorbic acid, chlorphenamine maleate, propyphenazone, codeine phosphate hemihydrate, pyridoxine hydrochloride, thiamine hydrochloride, ergotamine tartrate, dextromethorphan hydrobromide, phenylephrine hydrochloride, brompheniramine maleate, salicylamide, nitroglycerine and propyphenazone. Most of these pharmaceutical specialities do not require a medical prescription and are available as over-the-counter products to consumers.

It is worth mentioning that as the only active ingredient it can reach formulations of up to 300 mg and its therapeutic indication is the symptomatic and occasional alleviation of occasional states of asthenia in patients older than 12 years. The maximum recommended dose is 1000 mg/day (3 capsules daily), divided into several doses and the last dose should not be taken within 6 hours before going to bed, in order to avoid possible insomnia. Additionally, the summary of product characteristics approved by the Spanish Agency of Medicines and Medical Devices (AEMPS) mention within their special warnings and precautions for use that it should not be administered to children less than 12 years old. Pharmaceutical specialities that contain caffeine additionally include the list of adverse effects associated with this molecule in their package leaflets and summary of product characteristics. The most common adverse effects (in 1 out of 10 patients) of caffeine are insomnia, restlessness and excitement; the common adverse effects (in less than 1 out of 10 but in more than 1 of every 100 patients) are nausea, vomiting, diarrhoea, abdominal cramps, headache, buzzing in ears, disorientation, cardiac arrhythmia, irritability, hot flushes, rapid breathing, increased urinary elimination. High doses of caffeine may provoke anxiety and distress.

While further studies are needed in order to acquire greater knowledge of the possible negative results of energy drinks on consumer health (De Sanctis et al., 2017), many of the health effects observed in consumers may be predicted from current knowledge of the multi-organ functions of caffeine, which are summarised below.

6.2.1 Effects on the Central Nervous System (CNS)

Apart from possessing different biochemical targets (GABA receptors, adenosine A1 and A2A receptors), caffeine modulates the activity of kinase proteins and phosphodiesterases. Thus, blocking striatal adenosine A2A receptors has been linked to the psychoactive properties of caffeine which include the sustained increase of intellectual capacity, motor skills, state of alertness and rapid and clear thinking, and reduced sensation of mental fatigue, which improves interpersonal relationships. Nevertheless, caffeine consumption is associated with lower sleep quality in subjects with subjective sensitivity to caffeine (Retey et al., 2007) and the consumption of excessive quantities leads to sleep disorders (sleep onset insomnia), negative implications for cognition in general, and especially for attention and memory (Mednick et al., 2008). Additionally, caffeine intake may lead to psycho-behavioural disorders, which include nervousness, irritability and anxiety, or even panic attacks or psychotic episodes, especially hallucinations. The chronic consumption of high doses of caffeine (addiction to coffee), estimated at doses higher than 300 mg/day, may be manifested in five general psychiatric syndromes: anxiety syndrome, hypochondriac syndrome, syndrome characterised by insomnia and headaches, depression, and withdrawal. According to Jones and Fernyhough (2008) caffeine addiction may increase the risk of hallucinations, especially in stressful conditions. The sole intake of 300 or 400 mg of caffeine may provoke mental tension and anxiety, if the patient is in a stressful situation (Smith, 2002) (Childs and de Wit, 2008). At high doses, it may reduce the convulsion threshold.

6.2.2 Effects on the cardiovascular system

The cardiovascular system is a target organ for the acute effects of caffeine (EFSA, 2015b). Among its effects may be observed: catecholamine release, increased cardiac rhythm and arrhythmia, decreased cardiac preload (due to peripheral vasodilation); increased contractility, tachycardia (classic symptom of caffeine intoxication); increased blood pressure (Cohen and Townsend, 2006) (Arciero and Ormsbee, 2009); chest angina (Berger and Alford, 2009) (Scott et al., 2011) peripheral vasodilation due to the smooth muscle relaxation of the vascular tunic and cerebral vasoconstriction (thus its use in migraines).

Possible cardiovascular risks associated with the consumption of energy drinks in Europe have been widely reviewed (Ehlers et al., 2019). Thus, the moderate consumption of energy drinks (excessive intake of caffeine up to 200 mg) does not lead to clinically relevant cardiovascular changes in healthy young adults. Nevertheless, the high intake of energy drinks (approximately 1 l) is associated with moderate to serious adverse effects (for example, prolonged QTc interval, palpitations) (Ehlers et al., 2019).

For this reason, the population groups that may be more susceptible to the adverse effects

of energy drinks and caffeine include persons who are at risk for certain cardiac ailments and conditions such as congenital prolonged QTc syndrome.

6.2.3 Effects on the respiratory system

No adverse effects of caffeine on the respiratory system have been detected. As a matter of fact, given its bronchodilating effects, it is especially recommended for apnea of prematurity (Henderson-Smart and De Paoli, 2010). Its mechanism of action is centred on the direct stimulation of the respiratory centre, increased respiratory rate per minute, increased hypercapnic response (Chou, 1992), increased skeletal muscle tone, as well as reduced diaphragmatic fatigue. Additionally, caffeine reduces fatigue in respiratory muscles (Welsh et al., 2010). The relaxing effect on bronchial muscles may be attributed to its capacity to inhibit phosphodiesterases and antagonise adenosine receptors.

6.2.4 Effects on the osteomuscular system

Caffeine is a smooth muscle relaxant, which is responsible for its bronchodilating effect and in striated muscle tissue, it increases muscle endurance through greater contractility and decreased fatigue. This is due, in large part, to the release of calcium. In massive doses, however, it may provoke cell lysis. Rhabdomyolysis has been reported after the consumption of daily intakes exceeding 900 mg/day and of massive doses (higher than 1000 mg) in a single intake (Phillips et al., 2012). This may be explained by the activation of calcium-dependent proteases. In repeated but lower doses, caffeine may boost the effects of psychostimulants such as ephedrine and its derivatives for triggering rhabdomyolysis. Additionally, in post-menopausal women, it leads to increased bone density loss (Wikoff et al., 2017).

6.2.5 Effects on the urinary system

Caffeine has a diuretic effect (Nawrot et al., 2003). Caffeine consumption increases urine volume, the excretion of electrolytes (Ca, Mg, K, Na and Chloride) and also inhibits Na reabsorption. The diuretic effect is reduced in regular coffee drinkers (Maughan and Griffin, 2003).

6.2.6 Effects on the digestive system

Caffeine increases acid secretion (although it does not appear to be a risk factor for ulcers), gastrin and pepsin. The increased secretion of gastric acid may be the cause of acid reflux symptoms but it has been attributed to other components of coffee. Nevertheless, the reduced pressure in the interior sphincter of the oesophagus may provoke gastroesophageal reflux disease or even vomiting. It also promotes secretagogue action (histamines, cholinergic and pentagastrin) at the level of the small intestine which, in some cases, may provoke diarrhoea (Boekema et al., 1999).

6.2.7 Effects on the endocrine system

It has been confirmed that caffeine increases the basal metabolic index by up to 10 %, promotes catecholamine release, and increases plasma renin and PTH. Increased insulin secretion (glucose-

stimulated) is mediated by a hyperglycaemic effect induced by sympathetic stimulation. This is demonstrated in increased glucogenolysis, lipolysis and gluconeogenesis (Dewar and Heuberger, 2017).

6.3 Caffeine: recommendations and intake limits

Several health agencies have established maximum threshold values for caffeine intake. The proposed doses vary greatly as some represent doses where adverse effects have already been observed and others are doses without observed adverse effects. Additionally, they are based on limited scientific evidence (sometimes only one study) which vary in their nature according to the values considered (epidemiological data, experimental studies, etc.).

The EFSA (2015b) associates the intake of 3 mg caffeine/kg b.w./day as the consumption responsible for general adverse effects for health (cardiovascular and haematological, neurological and psycho-behavioural effects) and the intake of 1.4 mg caffeine/kg b.w./day as the consumption associated with sleep disorders (sleep onset latency and reduced sleep duration). Nevertheless, the Norwegian Scientific Committee for Food Safety (VKM, 2019) recently concluded that the point of reference of 3 mg/kg b.w./day established by the EFSA did not necessarily protect people at risk for certain cardiac ailments.

According to the EFSA (2015b), the total caffeine intake by sub-groups that would not raise safety concerns regarding adverse effects to the health of the healthy population would be:

- Healthy adults (70 kg), not including pregnant and lactating women:
  - Single doses of up to 200 mg (approximately 3 mg/kg b.w.).
  - Doses of up to 200 mg when consumed within less than 2 hours prior to intensive physical exercise under normal environmental conditions.
  - Single doses of 100 mg (approximately 1.4 mg/kg b.w.) may increase sleep onset latency and reduce sleep duration in some individuals, especially when ingested around sleeping time.
  - Doses of up to 400 mg/day (approximately 5.7 mg/kg b.w.) do not pose a risk for healthy adults, except in the case of pregnant women (EFSA, 2015b). The evidence generally supports the absence of any link between these doses in healthy adults and observable adverse cardiovascular effects or behavioural, reproductive or developmental effects, or acute effects or bone density effects (Wikoff et al., 2017).
- Children and adolescents:
  - 3 mg/kg b.w./day is the proposed theoretical daily intake limit of caffeine, as there are no studies on caffeine consumption for this age group.
  - Doses of 1.4 mg/kg b.w./day may increase sleep onset latency and reduce sleep duration in some children and adolescents, especially when ingested around sleeping time.

Health Canada (2011) recommends that the maximum daily caffeine intake for children below the age of 12 should not exceed 2.5 mg/kg b.w. Adolescents should follow the precautionary recommendation of 2.5 mg/kg b.w./day and older and heavier adolescents may consume up to the adult limit of 400 mg/day. Wikoff et al. (2017) argues that the available evidence suggests that 2.5 mg of caffeine/kg b.w./day is still an appropriate recommendation. Likewise, Health Canada

(2011) supports the establishment of the maximum caffeine limit that does not exceed 180 mg per packaging that is presented as an individual container.

With regard to healthy pregnant women, the evidence upholds the opinion that an intake of up to 300 mg of caffeine/day is generally not associated with adverse effects for reproduction and development (Wikoff et al., 2017). Nevertheless, with regard to energy drinks, Regulation (EU) No. 1169/2011 of the European Parliament and of the Council on the provision of food information to consumers (EU, 2011) mentions that if the caffeine content exceeds 150 mg/l, it must display the statement "High caffeine content. Not recommended for children or pregnant or breast-feeding women" along with the mention of the caffeine content expressed in mg per 100 ml.

6.4 Caffeine: dependency, withdrawal and overdose

Caffeine may generate moderate physical dependency and tolerance. Its strengthening effect has been demonstrated (dependency sets in at 100 mg/day). Caffeine addiction, the name given to caffeine dependency, is usually characterised by a state of nervousness, agitation, anxiety and insomnia. Occasionally there might be gastrointestinal, cardiac and CNS disorders with intakes higher than 250 mg/day.

When consumption is halted in addicted patients, it produces a characteristic withdrawal syndrome in 12 to 24 hours of the last consumption, peaking between 24 and 48 hours and which appears to be due to the blocking of adenosine receptors (especially A1 type) and the deregulation of beta-adrenergic receptors. The signs and symptoms of withdrawal are characterised by headache (the most characteristic symptom), facial redness, fatigue, anxiety, psychomotor disorders, lethargy, depression, some loss of cognitive function, caffeine craving and psychomotor disorders with attention deficit in children. It generally disappears with caffeine intake.

Most cases of caffeine intoxication usually have few serious symptoms. The first signs of an orally ingested overdose are usually gastrointestinal: nausea, vomiting or pyrosis and epigastric pain. They are followed by nervous symptoms marked by disquiet, anxiety, irritability, tremors, together with tachycardia, occasionally arrhythmia, hypo- or hypertension and metabolic acidosis. At the cardiovascular level, palpitations, extreme flushing, arrhythmia, tachycardia, increased QRS duration and systolic pressure have been noted on occasions.

Doses of 1 g may cause serious symptoms, although the lethal dose would be around 150-200 mg/kg b.w., which is equivalent to a range of 7.5 to 15 g for an adult. These toxic doses are, however, highly difficult to establish, owing to differences between individuals, caffeine tolerance, or the presence of concomitant diseases.

6.5 Caffeine: estimate and assessment of dietary exposure due to the consumption of energy drinks

In 2013, Zucconi et al. estimated the average caffeine exposure from energy drinks at 22.4 mg/day (0.32 mg/kg b.w./day) for adult European consumers (18-65 years) and the contribution of energy drinks to total caffeine exposure at 8 %. Caffeine exposure increased to 48.3 mg/day (0.7 mg/kg b.w./day) in chronic high consumers, with a relative energy drink contribution of approximately 13 %. In

European adolescents (10-18 years) the average caffeine exposure from energy drinks was 23.5 mg/day (0.38 mg/kg b.w./day); with an average energy drink contribution of 13 % to total caffeine exposure. Caffeine exposure from energy drinks increased to 75.08 mg/day (1.18 mg/kg b.w./day) in chronic high adolescent consumers, which contributed 16 % of the total caffeine exposure. The average caffeine exposure from energy drinks in European children between the ages of 3 to 10 years was 21.97 mg/day (1 mg/kg b.w./day), with a relative energy drink contribution of 43 % to the total caffeine exposure. Caffeine exposure from energy drinks increased to 42.9 mg/day (1.98 mg/kg b.w./day) in chronic high consumers, with a relative energy drink contribution of approximately 48 % (Zucconi et al., 2013).

In 2015, the average daily intakes of caffeine were re-estimated, having observed a wide variability between Member States of the European Union. According to EFSA (2015b) estimates, they ranged between 22-417 mg for the very elderly (75 years and above), 23-362 mg for the elderly (65-75 years), 37-319 mg for adults (18-65 years), 0.2-2.0 mg/kg b.w. for children (3-10 years) and 0-2.1 mg/kg b.w. for toddlers (12-36 months).

A substantial proportion of children and adolescents (12 % in 16 Member States of the European Union) consume energy drinks in large quantities (≥1 l) and these may pose a risk to the health of this group (Ehlers et al., 2019). For this reason, the recommendations on consumption with maximum intake limits for different types of beverages (based on their caffeine content) may be highly useful for the management and communication of the risks associated with this substance.

The literature review by Verster and Koenig (2018) of 18 reports on representative studies on caffeine consumption at the national level revealed that the total average daily intake of caffeine in children, adolescents and adults are below caffeine intake recommendations such as those established in 2015 by the EFSA (3 mg/kg b.w./day for children and adolescents, and 400 mg/day for adults) and in 2011 by Health Canada (2.5 mg/kg b.w./day for children and adolescents, and 400 mg/day for adults). The total daily caffeine intake has stayed stable in the last 10 to 15 years, and coffee, tea and soft drinks have been the most significant sources of caffeine. In all age groups, energy groups contribute little to the total caffeine intake (Verster and Koenig, 2018).

Other authors however consider caffeine consumption from energy drinks to have increased in recent years (Ruiz and Scherr, 2018). In the United States, the consumers of energy drinks had a total caffeine intake that was significantly above the total caffeine intake of those who do not consume energy drinks, at 227.0 mg compared to 52.1 mg in adolescents, 278.7 mg compared to 135.3 mg in young adults and 348.8 mg compared to 219.0 mg in middle-aged adults (Vercammen et al., 2019).

With the knowledge that energy drink packages marketed in Spain usually have volumes of 250 ml and 500 ml, different scenarios of consumption may be proposed: 250 ml/day, 500 ml/day (1 package of 500 ml or 2 packages of 250 ml) and 1000 ml (4 packages of 250 ml or 2 packages of 500 ml).

To calculate caffeine intake derived from the consumption of these volumes of energy drinks (Table 1), apart from body weight, we shall consider the normal caffeine concentrations in the different commercial presentations: 15, 32, 40 and 55 mg caffeine/100 ml. Although it is known from the ENALIA (2017) survey that the average body weight of the Spanish adult, adolescent and children's population is: 81.4 kg for all adult males, 66.9 kg for adult women, 68.7 kg for young adults

between the ages of 18 and 30, 76.4 kg for adults between the ages of 31 to 50, 74.8 kg for adults between the ages of 51 and 70, 73.2 kg for adults beyond the age of 70, 59.4 kg for adolescents aged 14 to 17, 46.6 kg for adolescents between the ages of 11 and 13, 36.9 kg for children aged 9 and 10 years; it was decided to use the approximate body weights of 50, 60 and 70 kg for this assessment.

Table 1. Estimate and evaluation of caffeine ingestion based on consumption of 250, 500, 1000 ml of energy drink with caffeine content 15, 32, 40 and 55 mg/100 ml

caffeine/ 100 ml		Volume of energy drink ingested (ml)		
		250 ml	500 ml	1000 ml
		Caffeine intake (mg total and mg/kg b.w.)		
15 mg	**mg total**	**37.5 mg**	**75 mg**	**150 mg**
	if 50 kg b.w.	0.75 mg/kg b.w.	1.5 mg/kg b.w.	3 mg/kg b.w.
	if 60 kg b.w.	0.62 mg/kg b.w.	1.25 mg/kg b.w.	2.5 mg/kg b.w.
	if 70 kg b.w.	0.53 mg/kg b.w.	1.07 mg/kg b.w.	2.14 mg/kg b.w.
32 mg	**mg total**	**80 mg**	**160 mg**	**320 mg**
	if 50 kg b.w.	1.6 mg/kg b.w.	3.2 mg/kg b.w.	6.4 mg/kg b.w.
	if 60 kg b.w.	1.3 mg/kg b.w.	2.6 mg/kg b.w.	5.3 mg/kg b.w.
	if 70 kg b.w.	1.14 mg/kg b.w.	2.28 mg/kg b.w.	4.57 mg/kg b.w.
40 mg	**mg total**	**100 mg**	**200 mg**	**400 mg**
	if 50 kg b.w.	2 mg/kg b.w.	4 mg/kg b.w.	8 mg/kg b.w.
	if 60 kg b.w.	1.66 mg/kg b.w.	3.33 mg/kg b.w.	6.6 mg/kg b.w.
	if 70 kg b.w.	1.43 mg/kg b.w.	2.86 mg/kg b.w.	5.71 mg/kg b.w.
55 mg	**mg total**	**137.5 mg**	**275 mg**	**550 mg**
	if 50 kg b.w.	2.75 mg/kg b.w.	5.5 mg/kg b.w.	11 mg/kg b.w.
	if 60 kg b.w.	2.3 mg/kg b.w.	4.6 mg/kg b.w.	9.2 mg/kg b.w.
	if 70 kg b.w.	1.96 mg/kg b.w.	3.93 mg/kg b.w.	7.86 mg/kg b.w.

Intakes <1.4 mg caffeine/kg b.w./day: no risks.

Intakes >1.4 mg caffeine/kg b.w./day: associated with sleep disorders (sleep onset latency and reduced sleep duration) (EFSA, 2015b).

Intakes >3 mg caffeine/kg b.w./day: responsible for general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) (EFSA, 2015b).

The evaluation of these consumption habits (250, 500 and 1000 ml/day) based on the limits recommended by the EFSA (2015b) of 1.4 mg/kg b.w./day and 3 mg/kg b.w./day as daily doses associated with sleep disorders (sleep onset latency and reduced sleep duration) and general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) respectively, suggest that:

- For any consumer with body weight between 50 and 70 kg, consuming 1 can of 250 ml of energy drink of 15, 32, 40 and 55 mg caffeine/100 ml is not associated with general adverse effects on

health (cardiovascular and haematological, neurological and psycho-behavioural effects) as the caffeine intake is <3 mg/kg b.w./day.

- For consumers with body weight of 50 kg:
  - Consuming 1000 ml of any energy drink (15, 32, 40 and 55 mg caffeine/100 ml) or consuming 500 ml of energy drink with 32, 40 and 55 mg caffeine/100 ml is associated with sleep disorders (sleep onset latency and reduced sleep duration) and general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) as the caffeine intake exceeds the dose of 1.4 and 3 mg/kg b.w./day associated with them.
  - Consuming 500 ml of energy drink of 15 mg caffeine/100 ml is not associated with general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) as the caffeine intake is <3 mg/kg b.w./day, but it is associated with sleep disorders as the maximum caffeine ingested is 75 mg/day, which for 50 kg b.w. entails a maximum of 1.5 mg/kg b.w./day > 1.4 mg/kg b.w./day recommended by the EFSA (2015b).
  - Consuming any marketed package (250 or 500 ml) of drinks of 32, 40 or 55 mg caffeine/100 ml is associated with sleep disorders as it exceeds the 1.4 mg/kg b.w./day recommended by the EFSA (2015b).

    It is recommended to avoid these drinks of 32, 40 and 55 mg/100 ml in order to prevent sleep disorders in persons with a body weight of 50 kg.
- For consumers with body weight of 60 kg:
  - Consuming up to 500 ml/day of energy drink with 15 mg caffeine/100 ml is not associated with sleep disorders as the maximum content of caffeine ingested is 75 mg/day which for 60 kg b.w. entails a maximum of 1.25 mg/kg b.w./day < 1.4 mg/kg b.w./day mentioned by the EFSA.

    It is recommended to not exceed 500 ml of drinks with caffeine content 15 mg/100 ml in order to prevent sleep disorders.
  - Consuming up to 250 ml/day of energy drink with 32 mg caffeine/100 ml is not associated with sleep disorders as the maximum content of caffeine ingested is 80 mg/day which for 60 kg b.w. entails a maximum of 1.33 mg/kg b.w./day < 1.4 mg/kg b.w./day.

    Consuming 500 ml of a drink of 32 mg/100 ml exposes the consumer to sleep disorders as it exceeds the recommended dose of 1.4 mg/kg b.w./day.

    It is recommended to limit consumption to one package of 250 ml of drinks with caffeine content 32 mg/100 ml in order to prevent sleep disorders.
  - Consuming 500 ml of energy drinks of 15 and 32 mg caffeine/100 ml is not associated with general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) as the caffeine intake is <3 mg/kg b.w./day.
  - Consuming any marketed package (250 or 500 ml) of drinks of 40 or 55 mg caffeine/100 ml is associated with sleep disorders as it exceeds the recommended 1.4 mg/kg b.w./day.

    It is recommended to avoid drinks with 40 and 55 mg caffeine/100 ml in order to prevent sleep disorders.
  - Consuming 1000 ml of any energy drink (15, 32, 40 and 55 mg caffeine/100 ml) or consuming 500 ml of energy drink with 40 and 55 mg caffeine/100 ml is associated not only with sleep

disorders (sleep onset latency and reduced sleep duration) but also with general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) as the caffeine intake exceeds the dose of 1.4 and 3 mg/kg b.w./day associated with them.

It is recommended to avoid consumptions of 1000 ml of any energy drink.

- For consumers with body weight of 70 kg:
  - Consuming up to 500 ml/day of energy drink with 15 mg caffeine/100 ml, or up to 250 ml of energy drink with 32 mg/100 ml is not associated with sleep disorders as the maximum content of caffeine ingested is <1.4 mg/kg b.w./day.
  - Consuming 1000 ml/day of energy drinks of 15 mg/day; 500 ml of drinks of 32 mg caffeine/100 ml; 250 and 500 ml/day of drinks of 40 mg caffeine/100 ml or 250 ml of drinks of 55 mg caffeine/100 ml exposes the consumer to 70 kg at caffeine intakes >1.4 mg caffeine/kg b.w./day which would lead to sleep disorders (sleep onset latency and reduced sleep duration).
  - Consuming 1000 ml of energy drinks of 32 and 40 mg caffeine/100 ml or more than 500 ml of drinks of 55 mg caffeine/100 ml is associated with general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) as the caffeine intake is >3 mg/kg b.w./day.

The following Table describes and presents a colour-coded view of the probability of sleep disorders (orange) and/or general adverse effects on health (red) depending on body weight and the volume of each drink type (15, 32, 40 and 55 mg caffeine/100 ml) consumed (Table 2).

Table 2. Risk of sleep disorders and general effects on health according to V consumed (250, 500, 1000 ml) and C caffeine content of the energy drink (15, 32, 40 and 55 mg caffeine/100 ml) for each consumer type grouped by weight (50, 60, 70 kg b.w.)

Caffeine/ 100 ml	Volume of energy drink consumed								
	250 ml			500 ml			1000 ml		
	50 kg	60 kg	70 kg	50 kg	60 kg	70 kg	50 kg	60 kg	70 kg
15 mg	No sleep disorder	No sleep disorder	No sleep disorder	Sleep disorder	No sleep disorder	No sleep disorders	Sleep disorder	Sleep disorder	Sleep disorder
	No general effects on health	No general effects on health	No sleep disorder	No general effects on health	No general effects on health	No general effects on health	General effects on health	No general effects on health	No general effects on health

Table 2. Risk of sleep disorders and general effects on health according to V consumed (250, 500, 1000 ml) and C caffeine content of the energy drink (15, 32, 40 and 55 mg caffeine/100 ml) for each consumer type grouped by weight (50, 60, 70 kg b.w.)

Caffeine/ 100 ml	Volume of energy drink consumed								
	250 ml			500 ml			1000 ml		
	50 kg	60 kg	70 kg	50 kg	60 kg	70 kg	50 kg	60 kg	70 kg
32 mg	Sleep disorder	No sleep disorder	No sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder
	No general effects on health	No general effects on health	No general effects on health	No general effects on health	No general effects on health	No general effects on health	General effects on health	General effects on health	General effects on health
40 mg	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder
	No general effects on health	No general effects on health	No general effects on health	General effects on health	General effects on health	No general effects on health	General effects on health	General effects on health	General effects on health
55 mg	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder
	No general effects on health	No general effects on health	No general effects on health	General effects on health	General effects on health	General effects on health	General effects on health	General effects on health	General effects on health

1.4 mg/kg b.w./day: dosage associated with sleep disorders (sleep onset latency and reduced sleep duration) (EFSA, 2015b).

3 mg/kg b.w./day: daily dosage responsible for general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) (EFSA, 2015b).

Considering the age groups and body weights described in the ENALIA 2 survey (2015) for the Spanish population, the energy drink quantities (ml/day) that may be consumed, assuming that there is no other dietary source of caffeine, without exceeding the two points of reference by age group and caffeine concentrations (15, 32, 40 and 55 mg/100 ml of energy drink), are listed in the following Table 3.

Table 3. Maximum quantities to be consumed (ml) by age group and body weight of each energy drink in order to prevent risk of sleep disorders and/or general effects on health

Caffeine/ 100 ml	Age (years) (ENALIA, 2015)					
	11-13	14-17	18-30	11-13	14-17	18-30
	Body weight (kg) (ENALIA, 2015)					
	46.6	59.4	68.7	46.6	59.4	68.7
	Maximum quantity (ml) of energy drink to be consumed to maintain intake <1.4 mg of caffeine/kg b.w./day and prevent sleep disorders (EFSA, 2015b)			Maximum quantity (ml) of energy drink to be consumed to maintain intake <3 mg of caffeine/kg b.w./day and prevent general adverse effects on health (EFSA, 2015b)		
15 mg	434.9	554.4	641	932	1188	1374
32 mg	203.9	259.9	300.6	436.9	556.9	644.1
40 mg	163.1	207.9	240.4	349.5	445	515.2
55 mg	118.6	151.2	174.9	254.2	324	374.7

If we consider drinks with 32 mg of caffeine/100 ml as the most common ones then, to prevent sleep disorders, consumption must be limited to 200 ml (80 % of the 250 ml package) in adolescents between the ages of 11 and 13 years, to 250 ml in adolescents between the ages of 14 and 17, and to 300 ml in young adults aged 18 to 30.

To prevent general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects), the consumption of drinks containing 32 mg caffeine/100 ml should not exceed 436.8, 556.9, and 644 ml in adolescents between the ages of 11-13, 14-17, and adults aged 18-30, respectively.

7. Taurine

7.1 Taurine: general characteristics

Taurine (2-aminoethanesulfonic acid, CAS No.: 107-35-7) is a non-essential amino sulfonic acid that occurs naturally in foods. The main dietary sources of taurine are meat products, fish and seafood, but it is also present in dairy products, eggs, nuts and legumes (Brosnan and Brosnan, 2006). It is estimated that the daily intake of taurine in human beings is between 10 and 400 mg/day (Shao and Hathcock, 2008), although other authors have placed it at 20-200 mg/day (Babu et al., 2011). As a reference value, it is estimated that average dietary exposure from an omnivorous diet is 58 mg taurine/day, it may be practically non-existent in strict vegetarian diets (EFSA, 2009). Taurine dietary exposure in people may also result from food supplements where it is used as an ingredient.

Taurine is rapidly absorbed by organisms, reaching peak plasmatic concentration between 60 and 90 minutes, and returning to base levels after 3 to 5 hours (SCF, 2003) (EFSA, 2009). Taurine excretion is highly efficient in organisms. Taurine is mainly excreted in urine as taurine, but also as its derivative, sulfate. Taurine may be synthesised in the liver at levels between 50 and 125 mg/day from cysteine and methionine by means of L-cysteine sulfinate decarboxylase, which requires the oxidation of hypotaurine to taurine at the final stage, although it can also be biosynthesised from other sulphur compounds (Stipanuk, 2004).

Taurine has a highly diverse biological role as it participates in several physiological processes within a very wide spectrum. Taurine is mainly involved in the stabilisation of bile salts that participate in lipid digestion, but it is also involved in osmoregulation and cell membrane stability, as well as calcium metabolism, correct neural activity and skeletal muscle functions (Brosnan and Brosnan, 2006). Taurine is one of the more abundant free amino acids in the human body, it is present in relatively high concentrations in the cardiac muscle and the central nervous system (Stapleton et al., 1997) (Lourenco and Camilo, 2002) (Schaffer et al., 2010).

The alteration of taurine homeostasis has been linked to cardiovascular incidents and neural disorders, including autism and epilepsy (Junyent et al., 2009) (Kuwabara et al., 2013). Taurine deficiency is associated with myocardiopathies, renal dysfunction, developmental anomalies and severe damage to retinal neurones. Other frequently-reported adverse effects were moderate fatigue, drowsiness, cognitive changes (attention deficit) and ataxia (Pearl et al., 2014).

7.2 Taurine: presence in energy drinks

Taurine is regularly found in energy drinks. Although there are certain types of energy drinks with a highly heterogenous composition in the international market, most of them share the same ingredient profile, being blends that usually contain caffeine, taurine and glucuronolactone in varying proportions. The most common format of distribution of these products is usually the 250 ml can, but "shots" are also widespread, involving concentrated amounts of approximately 60 ml and powdered versions (Heckman et al., 2010b).

A standard energy drink formula of 250 ml contains 80 mg caffeine (320 mg/l), 1000 mg taurine (4000 mg/l), 600 mg glucuronolactone (2400 mg/l), 18 mg of niacin (72 mg/l), 2 mg of Vitamin B6 (8 mg/l), 0.001 mg of Vitamin B12 (0.004 mg/l), 6 mg of pantothenic acid (24 mg/l), 2 mg of thiamine (8 mg/l), 1.65 mg riboflavin (5.40 mg/l) and 50 mg of inositol (200 mg/l) (EFSA, 2009) (VKM, 2019). In some countries such as Germany, regulatory limits of 4000 mg/l on taurine have been established (AendVO2_FruchtsaftVO, 2012). Given that shellfish; beef and poultry meat contain significant quantities of taurine; the consumption of 1 or 2 energy drinks could lead to the daily individual intake exceeding accepted limits (Brown et al., 2020).

In the assessment performed in 2013 by the *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travai* (ANSES) 126 energy drinks marketed in France were studied, of which only 103 of the products displayed a complete ingredients list and of these, 52 % (n= 54) contained taurine (ANSES, 2013). The presence of taurine in the drink formula was accompanied in 98 % of cases by caffeine and glucuronolactone. The study undertaken by EFSA (2013) focused on 53 energy drinks in the European market, of which 49 contained taurine in their formula, and additionally, it appears jointly with caffeine and glucuronolactone.

Currently, the average taurine content in energy drinks is relatively stable, although it has increased progressively since the first marketed formulas (Sha and Hathcock, 2008). The study of Triebel et al. (2007) on 80 energy drink samples shows an average concentration of taurine at 3180 mg/l. The ANSES study (2013) describes an average content of 3800 mg/l of taurine, and the EFSA study (2013) describes a mean content of 3412 mg/l and median content of 4000 mg/l of taurine in

energy drinks. Average taurine content in energy drinks marketed in Canada is 4000 mg/l, although there are also products with taurine content ranging from 40 mg/l to 8000 mg/l (Rotstein et al., 2013). Consequently, a realistic reference would be an average content of 4000 mg taurine/l in energy drink formulae for exposure and risk assessment studies.

7.3 Taurine: dietary exposure from the consumption of energy drinks

The EFSA estimated chronic exposure to taurine from energy drink consumption in different age groups (adults, adolescents and children) for 16 Member States, including Spain (EFSA, 2013). European exposure to taurine from energy drink consumption by the adult population is at 271.9 mg/day (3.82 mg/kg b.w./day), reaching 585.8 mg/day (8.49 mg/kg b.w./day) in chronic adult consumers. For adolescents, taurine exposure is at 283.9 mg/day, and at 924.3 mg/day in chronic adolescent consumers. In the case of children, exposure is at 278.4 mg/day, increasing to 543.6 mg/day in the case of chronic consumers. On the other hand, acute exposure to taurine in the European adult population is at 1851 mg/day and at 1809 mg/day for the European adolescent population. It is important to note that more than half (53 %) of the children and adolescents surveyed in the EFSA study had occasionally consumed energy drinks along with alcohol.

In the case of Spain, it may be extrapolated from the results of the global study that taurine exposure in adults from energy drink consumption is at 290 mg/day and 149 mg/day in the adolescent population. Results could not be accessed for the Spanish children's population that consumed energy drinks as this information was not available in the report (EFSA, 2013).

The EFSA study estimated an average taurine exposure in energy drink consumers in the European Union of 3.82, 4.6, and 12.83 mg/kg b.w./day for adults, adolescents and children, respectively. The results of average taurine exposure from energy drinks for the Spanish people who are chronic consumers of these drinks are 4.08 and 3.89 mg/kg b.w./day in adults and adolescents, respectively (EFSA, 2013).

The ANSES study (2013), based on a weighted taurine content of 3800 mg/l from the analysis of energy drinks available in the French market, estimated an average daily taurine intake of 181 mg/day (3.02 mg/kg b.w./day; b.w.= 60 kg) for all consumers of energy drinks, with levels of 429 mg/day (7.5 mg/kg b.w./day; b.w.= 60 kg) in regular consumers, and 714 mg/day (53.57 mg/kg b.w./day; b.w.= 60 kg) for chronic consumers (P90).

7.4 Taurine: Risks and effects associated with dietary exposure

The toxicity studies conducted until now refer to the taurine molecule in single administration in rats. Toxicological studies do not indicate a genotoxic, teratogenic or carcinogenic potential for taurine (SCD, 1999). Additionally, studies on the biological effects of taurine show no differences between the natural form and the synthetic form (Heckman et al., 2010b). Taurine may be chemically synthesised from monoethanolamine and sulphuric acid or ethylene oxide and sodium bisulfite as starting materials, achieving at least 98.5 % of output (EFSA, 2009).

Taurine activity in organisms has been associated with the normal development, activity and cytoprotection of the nervous system. Taurine interacts with multiple neurotransmitters and cerebral

regions, the hypothalamus being one of the areas most sensitive to taurine administration (Hruska et al., 1975). Taurine favours the proliferation of neural stem cells and synapsis in the cerebral structures necessary for long-term memory. Taurine is found in high levels in the hypothalamus, hippocampus and the adult cerebellum (Shivaraj et al., 2012). Taurine's mechanism of action in the nervous system is highly diverse, but basically, taurine has been described as being able to alter neural signals through multiple pathways such as GABA shunts, serotonin, dopamine and norepinephrine (Aldegunde et al., 1983) (Hashimoto-Kitsukawa et al., 1988) (Huxtable, 1989) (Sava et al., 2014). In contrast to caffeine, taurine generally acts as an inhibitory neuromodulator, for example, it acts as a glycine receptor agonist and inhibits the more excitatory actions of NMDA receptors (Font et al., 2001).

Taurine levels in the brain decrease significantly with age, therefore, along with the antioxidant and anti-inflammatory properties of taurine, some studies have suggested the possible neuroprotective effect of taurine supplements on an aged brain (Zhang et al., 2017). The mechanism for action appears to be restoring the normal level of glutathione in accordance with the antioxidant properties of taurine. Taurine doses of 100 or 200 mg/kg/day in drinking water reduced lipid oxidation and restored acetylcholinesterase activity in male Wistar rats, apart from restoring the activity of the antioxidant enzymes superoxide dismutase and catalase (Adedara et al., 2017). However, and given that taurine levels are higher in adolescence and adulthood, it is less likely that taurine supplements are required for a healthy person, and excessive taurine would have a negative and persistent effect on the cognitive function and behaviour of adolescents and young adults (Brown et al., 2020).

There are studies that point to the direct beneficial effects of taurine supplements during episodes of toxicity in the nervous system (Chen et al., 2019). Taurine prevents or reverses the damage caused by exposure to manganese in rats (Ommati et al., 2019), it improved learning and motor function in a rat model of Angelman Syndrome (Guzzetti et al., 2018), reduced beta-amyloid levels in a rat model with Alzheimer's disease (Zhu et al., 2019), inhibited microglia-mediated neuroinflammation in rat models that simulated Parkinson's disease (Hou et al., 2018). Nevertheless, the mode of action for the adverse effects of taurine have not been described in detail (EFSA, 2009, 2013).

Curran and Marczinski (2017) identified the main limitations of the studies conducted until now on taurine in laboratory animals, which are: i) exclusive use of male animals, ii) incomplete information on age, iii) inconsistency in the route of administration, iv) lack of data on the dose-response relationship, v) herd effects not assessed, vi) inadequate sample size for behavioural studies, and vii) nonspecific assessment criteria. Still, the authors conclude that given the wide variety of lifestyles and the possible confounders in studies on human beings, rodent animal models are of great value in detecting differential effects associated with the consumption of taurine, and in combination with caffeine and alcohol. Other authors reviewed the evidence on the cognitive and physiological effects of trials on human beings and concluded that many of them had been conducted incorrectly. The combined proof of human and animal studies was unable to support the marketing claim that taurine improved physical or mental performance (McLellan and Lieberman, 2012).

The EFSA concluded that taurine intake did not lead to increased taurine levels in the brain, discarding the possibility of a stimulant effect on the CNS (EFSA, 2009). However, the importance of

taurine for normal brain development cannot be ignored, and the human brain continues to develop in adolescence and early adulthood (Gogtay et al., 2004). With regard to the activity of taurine intake on cognitive and behavioural development, it appears to vary according to sex, dosage and duration of treatment in rat models (Brown et al., 2020). Further research is required to precisely determine the cognitive and behavioural endpoints of taurine in energy drinks.

The effects of taurine on cardiovascular risk and blood pressure are not well-documented in isolation. Cardiac effects are exacerbated when taurine and caffeine are ingested together, which may be a factor for concern that should be better assessed (Curran and Marzinski, 2017). Taurine acts as an antagonist to caffeine in the cardiovascular system. Taurine attenuates the actions of circulating angiotensin II (Schaffer et al., 2000). A possible protective effect of taurine on cardiovascular diseases has been described, based on animal models but in doses and models that cannot be transposed to humans. In human beings, several crossover studies indicate an inverse relationship between taurine concentrations in urine and blood pressure (Wojcik et al., 2010).

Since 2003, ANSES (formerly, AFSSA: *Agence française de sécurité sanitaire des aliments*) has performed a series of studies on the safety of the marketing of the mentioned energy drinks (AFSSA, 2003, 2006a, b). These studies concluded that there was insufficient evidence to confirm or reject the suspected neurological adverse effects of taurine consumption, although they pointed out that taurine concentrations in energy drinks were significantly higher to that provided by a normal diet.

Based on toxicological information compiled until now, the EFSA concluded in 2009 that regular exposure to taurine at levels used in energy drinks (4000 mg taurine/l) does not pose a risk to consumer health (EFSA, 2009). The No Observed Adverse Effect Level (NOAEL) of 1000 mg/kg b.w./day for pathological effects is approximately 120 times higher than the average taurine exposure in an adult (b.w.= 60 kg) through energy drink intake. In this risk assessment, the EFSA highlighted that taurine is a natural component of organisms, it is naturally present in foods and it has a highly effective renal clearance rate. Therefore, it is considered that taurine consumption up to 1000 mg/kg b.w./day is not linked to adverse effects even when the intake in the 95th percentile of chronic consumers reaches 350 ml/day. The EFSA considers that there is sufficient safety margin for medium to high-level regular consumers of energy drinks, who drink on average 125 ml (0.5 can) and 350 ml (1.4 can) per person per day, respectively.

This was reiterated by Zucconi et al. (2013) indicating that an unambiguous relationship could not be established with health risk from taurine consumption in energy drinks, although further studies are recommended. The EFSA concluded that daily taurine intakes of up to 1400 mg/day (23.3 mg/kg b.w./day; b.w.= 60 kg) did not pose a risk to consumer health (EFSA, 2009). The exposures used in this opinion are based on the chronic consumption of a daily average of 0.5 cans per person and a high chronic exposure in the 95th percentile of 1.4 cans per regular consumer. The NOAEL of 1000 mg/kg b.w./day for pathological changes is 120 times higher than the estimated average and 43 times higher than the estimated exposure of the 95th percentile to taurine exclusively from "energy" drinks, when calculated for a person with body weight 60 kg.

The health risk assessment conducted by Health Canada concluded that an adult could safely consume 2 units (250 ml) of an energy drink every day, without consequences to their health

(Health Canada, 2011). The conclusion was based on the safety of the non-caffeine ingredients present in a standard energy drink (4000 ml taurine/l) and the level of consumption, and the fact that caffeine from other dietary sources does not pose a risk to the adult population. However, Health Canada states that the consumption of energy drinks should be limited, in children, adolescents and pregnant women, to the maximum caffeine intake values recommended for this subset of the population (Rotstein et al., 2013). The same report describes that the acute oral toxicity of taurine is deemed relatively low and no adverse effects have been observed in a single administration in rats up to 7000 mg/kg b.w., or up to 150 mg/kg b.w. in human beings (10 500 mg; b.w.= 70 kg).

The toxicological studies on taurine intake conducted in laboratory animals until now have established an NOAEL of 1000 mg/kg b.w./day for toxicological effects, including the histopathological assessment of taurine, and of 1500 mg/kg b.w./day for effects on behaviour (neurobehavioural effects or psycho-behavioural toxicity). The values refer to the highest doses tested during the 90 days of the study. However, further studies are required in order to understand how taurine affects females, as most animal studies were focused exclusively on male subjects (Curran and Marczinski, 2017).

In 2015, the VKM performed a risk assessment of taurine intake from energy drinks and food supplements (VKM, 2015). The limited studies available on taurine exposure in human beings show signs of cardiovascular and neurological effects (Sirdah et al., 2002) (Brons et al., 2004) (Spohr et al., 2005). The VKM draws attention to the fact that the available studies on human beings are not of sufficient quality (owing to the low number of participants, unhealthy populations and short duration) to establish a precise risk characterisation. For risk characterisation, the VKM applies the Margin of Exposure (MOE) focus that establishes the relationship between the NOAEL and taurine exposure. An acceptable MOE value for an NOAEL-based taurine evaluation extrapolated from a study in animals is ≥100, which includes a factor 10 for extrapolation from animals to humans and a factor 10 for inter-individual human variation. The VKM concludes that an intake of up to 21 mg/kg b.w./day (1500 mg/day; b.w.= 70 kg) does not pose a health risk and the probability of causing adverse effects in adults is low (VKM, 2015). In the chronic intake model of energy drinks for all age groups studied (children, adolescents, and adults), the estimated values of the MOE exceed the value of 100, and the estimated intakes were all below the reference value of 21 mg/kg b.w./day which is deemed low probability of adverse effects on health according to studies on human beings of all age groups. Therefore, the VKM does not consider it very probable that the average chronic intake of taurine may lead to adverse effects on health for any age group. However, the VKM considers that a high chronic intake of taurine from the consumption of energy drinks may pose a risk to the health of small children (3 to <10 years), but it does not pose a risk for children (10 to 14 years), adolescents (14 to <18 years) and adults (>18 years).

The uncertainty factors associated with the toxicological and neurobehavioural effects of taurine intake have been described as most studies do not draw a distinction between the joint effects of taurine with other substances also present in energy drinks such as caffeine, apart from the confounders generated by the consumption of these drinks along with alcohol. Another aspect of uncertainty is the non-existence of studies on long-term chronic intakes over periods higher than 12 months that may unequivocally link taurine intake to adverse effects on health.

7.5 Taurine: assessment of exposure from energy drinks

Table 4 describes taurine exposure in three consumption scenarios, considering an average volume of 250 ml/can and with an average taurine content of 4000 mg/l. Scenario A refers to a consumption of 250 ml/day, Scenario B to a consumption of 500 ml/day and Scenario C to a consumption of 1000 ml/day.

If we assume that there is no other dietary source of taurine intake, the calculated exposure varies between 14.3 mg/kg b.w./day in adults (70 kg) for Scenario A, until maximum levels of 80.0 mg/kg b.w./day in adolescents (60 kg) in Scenario C. The margin of safety of taurine exposure in each scenario calculated from the NOAEL of toxicological risk (1000 mg taurine/kg b.w./day) ranges between 70 in adults in a scenario of consumption A and 13 in adolescents in a scenario of acute consumption of 4 daily cans (Scenario C). The margin of safety of taurine exposure ranges between 105 in adults (b.w.= 70 kg) in Scenario A, and 19 in young adolescents (b.w.= 50 kg) in Scenario C.

Scenario B of consumption, two cans of energy drink of 250 ml containing an average concentration of 4000 mg taurine/ml exceeds the intake recommendation under 1400 mg taurine/day (EFSA, 2009). If we jointly consider the reference value of 21 mg/kg b.w./day and the margin of safety value of 100 for the risk assessment of dietary exposure to taurine through the consumption of energy drinks, the low probability of adverse effects on health shall only be considered in the Scenario A of consumption (intake of 1000 mg taurine/day, 1 can/day) for consumers with weights of 50, 60 and 70 kg.

On the other hand, the uncertainty associated with the potential effects of the joint consumption of taurine and caffeine still remains to be clarified and may influence the risk assessment.

Table 4. Estimated exposure to taurine and margin of safety from the consumption of energy drinks with an average content of 4000 mg taurine/l in three consumption scenarios (A: 250 ml; B: 500 ml; C: 1000 ml) and depending on body weight (50, 60 and 70 kg). Pathological NOAEL (1000 mg/kg b.w./day), psycho-behavioural NOAEL (1500 mg/kg b.w./day)

Consumption Scenario			
	A	**B**	**C**
Drink units (can)	1	2	4
Drink volume (ml)	250	500	1000
Intake (mg/day)	1000	2000	4000
Body weight (b.w.)	**Estimated exposure (mg/kg b.w./day)**		
50 kg	20.0	40.0	80.0
60 kg	16.7	33.3	66.7
70 kg	14.3	28.6	57.1
Body weight (b.w.)	**Margin of safety**		
NOAEL (toxicological)			
50 kg	50	25	13
60 kg	60	30	15
70 kg	70	35	18

Table 4. Estimated exposure to taurine and margin of safety from the consumption of energy drinks with an average content of 4000 mg taurine/l in three consumption scenarios (A: 250 ml; B: 500 ml; C: 1000 ml) and depending on body weight (50, 60 and 70 kg). Pathological NOAEL (1000 mg/kg b.w./day), psycho-behavioural NOAEL (1500 mg/kg b.w./day)

NOAEL (psycho-behavioural)			
50 kg	75	38	19
60 kg	90	45	23
70 kg	105	53	26

8. D-glucuronolactone

8.1 D-glucuronolactone: general characteristics

D-glucuronolactone (CAS No.: 32449-92-6) is a natural metabolite of glucose that originates in the liver. At physiological pH, it is in equilibrium with glucuronic acid, its immediate precursor. D-glucuronolactone and its hydrolysed product glucuronic acid, are endogenous metabolites in human beings and other mammals, and are found in various natural dietary sources, they are metabolised as harmless products and excreted. Glucuronic acid is an important component of fibrous and connective tissue. It is also found in plants, especially in gum plants, linked to other oses forming part of heterogenous polysaccharides. The regular dietary intake of D-glucuronolactone is between 1 and 2 mg/day, and the dietary contribution of an energy drink unit (600 mg/250 ml) is much higher.

D-glucuronolactone is rapidly absorbed, metabolised and excreted in urine as glucaric acid, xylitol and L-xylulose. There are no toxicological studies on its genotoxic, teratogenic or carcinogenic potential, although a neoplastic effect is less probable, given that D-glucuronolactone is a regular metabolite in organisms.

D-glucuronolactone is a common ingredient in energy drinks. In the ANSES study (2013), 33 % of energy drinks in the French market contained D-glucuronolactone and always in conjunction with taurine and caffeine. 59 % of the energy drink packages that contained D-glucuronolactone did not mention the quantity in the labelling. The average content of D-glucuronolactone, weighted by the presence of the commercial brand in the market, was 1700 mg/l. However, the minimum and maximum content values ranged between 240 and 2400 mg/l. It is important to highlight the disparity with regard to D-glucuronolactone content in energy drinks compared to the variability in caffeine and taurine. A similar situation was observed in the study conducted by Health Canada where D-glucuronolactone content varied between 2400 mg/l and 4800 mg/l (Rotstein et al., 2013).

In 2003, the SCF expressed concern regarding the safety of its inclusion in energy drinks, based on the finding of unspecified renal lesions (renal papillary inflammation) after 13 weeks of supplementation in rats (SCF, 2003). The NOAEL for these effects was 300 mg/kg b.w./day, which is around 20 times higher than the estimated chronic intake of D-glucuronolactone of 14 mg/kg b.w./day for an adult of 60 kg. Nevertheless, rats differ from human beings in how they metabolise D-glucuronolactone. Contrary to human beings, rodents have an additional metabolic pathway that

allows them to use glucuronic acid to synthesise Vitamin C. Mice and rats can also use exogenous D-glucuronolactone to produce glucuronic acid and generate Vitamin C. This additional pathway was the reason for some uncertainty regarding the suitability of the rodent models, but after assessment, they were not deemed relevant (SCF, 2003). In a second study with a larger number of individuals, the histopathological findings revealed renal inflammation in some male and female animals in test and control groups. These lesions were only observed in a few animals, for all applied doses (300, 600 and 1000 mg/kg b.w.), unilaterally and unrelated to the treatment. Additionally, they were typical of the rat strain used in the study. Based on these toxicity results, the EFSA granted the NOAEL of 1000 mg/kg b.w./day, equivalent to the highest administered dose (EFSA, 2009). Additionally, there was no evidence of any effect on gonads in these studies, which might point to the need for studies on reproductive toxicity.

In the absence of new data on chronic and acute exposure, D-glucuronolactone exposure is based on data from the SCF in 2003, considering an average chronic daily consumption of 0.5 cans (250 ml/can) per person and a chronic high exposure in the 95th percentile of 1.4 cans for a regular consumer (SCF, 2003). Assuming a can contains 250 ml and 2400 mg/l of D-glucuronolactone, the SCF calculated that these values resulted in an average daily exposure of 300 mg of D-glucuronolactone (5.0 mg/kg b.w./day for a person weighing 60 kg). The 95th percentile of exposure of regular consumers would ascend to 840 mg of D-glucuronolactone/day (14 mg/kg b.w./day for a person weighing 60 kg).

The SCF's reservations were expressed in the context of an estimated chronic daily high intake of D-glucuronolactone of 840 mg/day and an acute intake of up to 1800 mg/day from energy drink consumption, in comparison to an estimated intake of D-glucuronolactone/day from natural dietary sources of 1-2 mg/day. Although this quantity is still much higher than normal exposure from omnivorous diets, it is still considerably below the level that would trigger food safety problems.

Based on the NOAEL (1000 mg/kg b.w./day) established for toxicological effects of D-glucuronolactone which is 200 times higher than the estimated average exposure and 71 times higher than the estimated exposure of the 95th percentile of D-glucuronolactone in energy drinks for a person weighing 60 kg, the EFSA concluded that exposure to D-glucuronolactone at the concentrations used in energy drinks does not represent a safety problem. Additionally, it is less probable that D-glucuronolactone has any interaction with caffeine, taurine, alcohol or the effects of exercise. It is necessary to compile further data on real exposure from the consumption of energy drinks, especially for adolescents and young adults (EFSA, 2009).

Zucconi et al. (2013), calculated European exposure to D-glucuronolactone from energy drinks, showing higher levels of exposure in children (5.13 mg/kg b.w./day), in comparison with adolescents (1.65 mg/kg b.w./day) and adults (1.78 mg/kg b.w./day), increasing for high chronic consumers (10, 4.9 and 3.9 mg/kg b.w./day, respectively). The consumption of energy drinks exposes European adults to an average D-glucuronolactone of 125.95 mg/day (1.78 mg/kg b.w./day) increasing to 268.84 mg/day (3.91 mg/kg b.w./day) in high chronic consumers. The energy drink contribution to the total D-glucuronolactone exposure in adults was 98.8 % (99.4 % in high chronic consumers). The data of the Nomisma European survey (Zucconi et al., 2013) estimated that adult Spanish consumers

of energy drinks were exposed to 906.32 mg/day (12.87 mg/kg b.w./day) in acute consumption and 143 mg/day (2.02 mg/kg b.w./day) in chronic consumption. For European adolescents, the average D-glucuronolactone exposure from energy drinks estimated by Zucconi et al. (2013) was 100.14 mg/day (1.65 mg/kg b.w./day), increasing to 311.6 mg/day (4.9 mg/kg b.w./day) in high chronic consumers. In Spanish adolescents who are chronic and acute consumers of energy drinks, the intake of D-glucuronolactone from energy drinks was estimated at 74.50 mg/day (1.27 mg/kg b.w./day) and 551.49 mg/day (9.56 mg/kg b.w./day), respectively. In European children, the average D-glucuronolactone exposure from energy drinks was 111.35 mg/day (5.13 mg/kg b.w./day), increasing to 217.43 mg/day (10 mg/kg b.w./day) for high chronic consumers.

The VKM (2015) estimated an average D-glucuronolactone intake from energy drinks of 58, 65, 64 and 71 ml/day for small children (between 3 and <10 years), older children (between 10 and <14 years), adolescents (between 14 and 18 years) and adults, respectively. However, the highest chronic intake profile displayed a consumption of 163, 180, 211 and 320 ml/day for small children (between 3 and <10 years), older children (between 10 and <14 years), adolescents (between 14 and 18 years) and adults, respectively. In this study, the VKM considered an average D-glucuronolactone content of 240 mg/l, lower than the established reference content in energy drinks. The VKM concluded that it was improbable that a chronic intake of D-glucuronolactone in energy drinks would cause adverse effects in children, adolescents or adults. When an average content of 24 000 mg/l is considered, the intake would be 768 mg/day in the worst consumption scenario (320 ml/day), which represents an exposure of 10.97 mg/kg b.w./day (b.w.= 70 kg).

Considering an average D-glucuronolactone content of 2400 mg/l in energy drinks, the exposure and margin of safety for this substance in the three proposed consumption scenarios (250 ml, 500 ml and 1000 ml) are estimated (Table 5). The estimated D-glucuronolactone exposure ranges between 8.6 and 48.0 mg/kg between the three scenarios. Only the daily consumption scenario of one energy drink can (250 ml) with an average content of 2400 mg/l for consumers weighing 60 and 70 kg has a margin of safety equal to or greater than 100. This result is in line with the EFSA conclusion that finds no health risk in a high chronic consumption scenario (P95) of up to 840 mg/day (corresponding to 350 ml/day) (EFSA, 2009). Nevertheless, the consumption of three cans of energy drinks significantly reduces the margin of safety for D-glucuronolactone, placing it between 21 mg/kg b.w./day for a person weighing 50 kg and 29 mg/kg b.w./day for a person weighing 70 kg.

Table 5. D-glucuronolactone intake and margin of safety based on consumption of 250, 500 and 1000 ml of energy drink with D-glucuronolactone content of 2400 mg/l for different body weights. NOAEL of 1000 mg/kg b.w./day for adverse toxicological effects

Consumption Scenario			
	A	**B**	**C**
Drink units (can)	1	2	4
Drink volume (ml)	250	500	1000
Intake (mg/day)	600	1200	2400

Table 5. D-glucuronolactone intake and margin of safety based on consumption of 250, 500 and 1000 ml of energy drink with D-glucuronolactone content of 2400 mg/l for different body weights. NOAEL of 1000 mg/kg b.w./day for adverse toxicological effects

Body weight (b.w.)	**Estimated exposure (mg/kg b.w./day)**		
50 kg	12.0	24.0	48.0
60 kg	10.0	20.0	40.0
70 kg	8.6	17.1	34.3
Body weight (b.w.)	**Margin of safety**		
NOAEL (toxicological)			
50 kg	83	42	21
60 kg	100	50	25
70 kg	117	58	29

9. L-carnitine

9.1 L-carnitine: general characteristics, bioavailability, pharmacokinetics and metabolism

L-carnitine or 3-hydroxy-4-(trimethylazaniumyl)butanoate (also known as levocarnitine, as in its natural state it exists as an L-stereoisomer) is a quaternary ammonium compound derived from the amino acids L-lysine and L-methionine.

Widely distributed in all mammalian tissue and highly abundant in muscle tissue, L-carnitine is endogenously synthesised in the liver, kidneys and brain from the essential amino acids lysine and methionine (Bremer et al., 1983) and/or through the intake of foods of animal origin. Its synthesis is catalysed by four enzymatic reactions that have been reviewed in detail by Vaz and Wanders (2002), and requires Vitamin C, Vitamin B6, niacin and reduced iron as cofactors. Carnitine is responsible for transporting fatty acids into the inner mitochondria, cell organelles tasked with energy production. At the tissue level, an estimated 95 % of L-carnitine is stored in the heart and skeletal muscles, with much lower concentrations found in the liver, kidneys and plasma (Brass et al., 1995). The muscle content is some 70 times greater than the blood plasma content.

It is estimated that 75 % of the body's carnitine reserve in human beings is derived from dietary intake, however, this intake is highly variable. Its main source is red meat, which provides up to 140-190 mg of L-carnitine per 100 g of uncooked meat (for example, beef). Milk and fish also constitute an important source, conversely plant-based foods contain insignificant amounts of L-carnitine. Consequently, vegetarians obtain very little L-carnitine from dietary sources. Nevertheless, the benefits of L-carnitine supplements for this population continue to be a topic of debate, as it appears that the bioavailability of L-carnitine in this group is comparable to that of the general population (Flanagan et al., 2010).

The average L-carnitine intake of the population with a varied diet is 100-300 mg/day (Feller and Rudman, 1988) (Rebouche, 2004). In the year 2012, AESAN, in its "*Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the conditions of use of certain substances other than vitamins, minerals and plants to be used in food supplements*" proposed a

maximum daily quantity of L-carnitine of 2 g from L-carnitine, L-carnitine hydrochloride as sources, and 3 g in the case of L-carnitine L-tartrate (AESAN, 2012). This proposal was based on the SCF's (2003) opinion and on the Danish authorisation of food supplements for L-carnitine and L-carnitine L-tartrate (Denmark, 2011).

The administration of L-carnitine as a food supplement may take place in three different ways: L-carnitine, propionyl-L-carnitine and acetyl-L-carnitine. Although acetyl-L-carnitine is usually employed in its hydrochloride form or by forming a salt with tartaric acid (L-carnitine L-tartrate) (AESAN, 2012).

In 2011, the EFSA published a scientific opinion on the verification of L-carnitine health claims: i) faster recovery from muscle fatigue after exercise, ii) repairing skeletal muscle after exercise, iii) increase in endurance capacity, iv) maintenance of normal blood LDL-cholesterol concentrations, v) contribution to normal spermatogenesis, and vi) increasing L-carnitine concentrations and/or decreasing free fatty acids in blood during pregnancy Based on the submitted information, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) could not establish any cause and effect relationship for any of the above.

Subsequently, due to an application submitted by Lonza Ltd. for authorising a health claim pursuant to Article 13 (5) of Regulation (EC) No. 1924/2006 via the Competent Authority of Germany, the EFSA NDA Panel was requested to provide its opinion on the scientific substantiation of a health claim related to L-carnitine and normal lipid metabolism. In accordance with the tests submitted, it arrived at the conclusion that a cause-and-effect relationship had not been established between L-carnitine consumption and its contribution to normal lipid metabolism in the general population (EFSA, 2018).

In mammals, the carnitine pool consists of nonesterified L-carnitine and many acylcarnitine esters. Of these esters, acetyl-L-carnitine is quantitatively and functionally the most significant. Carnitine homeostasis is maintained by dietary absorption, a modest synthesis rate and an efficient renal reabsorption. Dietary L-carnitine is absorbed by active and passive transfer across enterocyte membranes. The bioavailability of dietary L-carnitine is 54-87 % and is dependent on the amount of L-carnitine in the meal. The absorption of L-carnitine dietary supplements (0.5-6 g) is primarily passive; bioavailability is 14-18 % of the dose. Unabsorbed L-carnitine is mostly degraded by gut bacteria in the large intestine (Allard et al., 2006) (Jameson et al., 2016). Circulating L-carnitine is distributed to two kinetically defined compartments: one large and slow-turnover (presumably muscle), and another relatively small and rapid-turnover (presumably liver, kidney, and other tissues).

At normal dietary L-carnitine intake, whole-body turnover time in humans is 38 to 119 hours. *In vitro* experiments suggest that acetyl-L-carnitine is partially hydrolysed in enterocytes during absorption. *In vivo*, circulating acetyl-L-carnitine concentration is increased by 43 % after oral acetyl-L-carnitine supplements (2 g/day), indicating that acetyl-L-carnitine is absorbed at least partially without hydrolysis. After single-dose intravenous administration (0.5 g), acetyl-L-carnitine is rapidly, but not completely hydrolysed, and acetyl-L-carnitine and L-carnitine concentrations return to baseline within 12 hours. At normal circulating l-carnitine concentrations, its renal

reabsorption is highly efficient (90-99 % of filtered load) but displays saturation kinetics. Thus, as circulating L-carnitine concentration increases (for example, after high-dose intravenous or oral administration of L-carnitine), the efficiency of reabsorption decreases and clearance increases, resulting in the rapid decline of circulating L-carnitine concentration to the baseline (Rebouche, 2004). The elimination kinetics for acetyl-L-carnitine are similar to those for L-carnitine.

There are a series of factors that may affect L-carnitine synthesis, such as L-carnitine content in the diet and certain pathological states (renal insufficiency, diabetes, alcoholism and cancer). Among the known causes of L-carnitine deficiency, deficiency of precursor amino acids (lysine or methionine), iron deficiencies, vitamins C, B3 or B (other precursor factors), intestinal malabsorption, and especially hereditary or acquired defects in the mechanisms of synthesis or transport, are considered the main cause of L-carnitine deficiency, which is responsible for pathologies such as cardiomyopathy and skeletal muscle myopathy (Flanagan et al., 2010).

9.2 L-carnitine: effects, consumption and dietary exposure from energy drinks

L-carnitine plays an important role in energy metabolism, as it facilitates the entry of long-chain fatty acids into the mitochondrial matrix where they are oxidised. It also helps to transfer short-chain fatty acids from the mitochondria to the cytosol, decreases lactate production and improves cell membrane stability.

Very little scientific data is available on the specific quantity and frequency of consumption of L-carnitine as an ingredient in energy drinks. Within the composition of these drinks, L-carnitine is generally included as a nonspecific component of the formula without including concrete information on its quantity in these drinks. It is possibly one of the components of these drinks on which the least data has been published regarding its exposure from consumption, neither by age groups nor by consumer types. No well-designed and controlled studies that verify the possible beneficial or adverse effects of L-carnitine from energy drink consumption have been reported.

The available data indicates that L-carnitine is commonly added to energy drinks to help boost muscle function and physical performance, owing to its effect in mobilising fatty acids in adipose tissue and thus using them as an energy source. However, the scientific data that lets us assess its effects are from studies that are directly approach L-carnitine as a food supplement.

The link between L-carnitine supplement levels, especially in plasma and muscle, and the increased capacity for exercise has been reported in many *in vitro* studies with animals and in clinical trials (for a recent review, see (Fielding et al., 2018)). This detailed review examines available studies with carnitine doses between 2 and 4 g/day from supplements administered in a single dose or various times during the day and by durations that vary from weeks to months. In studies on human beings conducted on healthy and active subjects, endurance athletes, and young untrained men and women, the effect of the nutritional supplement on physical performance, oxygen capacity, and muscle strength were examined. The intake facilitates the recovery process after exercise. The scientific data indicates that athletes may benefit from L-carnitine intake as it reduces the side-effects of high-intensity training by reducing the magnitude of hypoxia caused by exercise

and muscle damage (Fielding et al., 2018). Studies on animals provided proof of multifaceted mechanisms; L-carnitine exerts a beneficial effect by increasing protein synthesis and reducing muscle atrophy.

The review by Wassef et al. (2017) on the cardiovascular effects of energy drinks, concludes that there is an overwhelming lack of evidence to justify that L-carnitine, when added to these products, contributes to improved physical or cognitive performance.

With regard to research on tolerance in human beings, amounts of up to 15 g of L-carnitine per day are generally well-tolerated, although they cause gastrointestinal discomfort and diarrhoea in some persons (Lurz and Fischer, 1998). In the case of L-carnitine L-tartrate, there is a randomised, double-blind, crossover study with a 1-week wash, where the administration of 3 mg/day of L-carnitine L-tartrate for 3 weeks does not affect biochemical, haematological parameters, hepatic and renal functions (Rubin et al., 2001). Nevertheless, this same work points out that doses of 4-6 g/day may produce gastrointestinal discomfort and diarrhoea. Besides, it has been associated with convulsions in patients with a seizure disorder (Seifert et al., 2011). Finally, it must be remembered that acetyl-L-carnitine may interfere with the thyroid metabolism (Hendler and Rorvik, 2001) (Zdanowicz, 2001), therefore the consumption of L-carnitine supplements in any form of acetyl-L-carnitine is not recommended for persons under medication for thyroid pathologies or who suffer from any thyroid disorder.

10. Sugars and sweeteners

10.1 Sugars and sweeteners: general characteristics and intake recommendations

One of the ingredients present in energy drinks is sugars. They are nutrients whose dietary amounts must be monitored. The World Health Organisation (WHO) has established a strict recommendation that added simple sugars must account for less than 10 % of the total energy content of our diet. This recommendation is based on scientific evidence that links sugar intake to body weight and dental cavities. It also establishes a more restrictive recommendation based on lower-grade scientific evidence. Thus, the recommendation is for added simple sugars to not exceed 5 % of the total energy of the diet and is based on the evidence provided by ecological studies where a positive dose-response relationship is observed between sugar intake and dental cavities (WHO, 2015).

With regard to body weight, WHO experts conducted a systematic review that included 30 random clinical trials and 38 cohort studies to establish the recommendation (Te Morenga et al., 2013). The meta-analysis of the 5 clinical trials conducted on adults, on whom no dietary restrictions were imposed, showed that the decreased intake of added simple sugars was linked to decreased body weight. The meta-analysis of 10 clinical trials where the intake of these sugars increased (mainly due to sugary drinks) in the participants, showed an increase in body weight. Finally, the meta-analysis of 11 clinical trials that examined the effects of replacing other carbohydrates with added simple sugars under isocaloric conditions, showed no changes in body weight.

The review also included 5 clinical trials on children, where the intervention consisted of establishing recommendations to reduce added sugar intake in foods and drinks. These trials did

not reveal changes to the children's body weight, but it is believed that this result was due to low compliance with these recommendations. Nevertheless, the meta-analysis of 5 prospective cohort studies, over at least 1 year, revealed that children with higher intakes of sugary drinks showed greater possibility of developing excess weight and obesity than children with lower intakes.

From these studies it may be deduced that the increased or decreased intake of added sugars is associated with parallel changes of increased or decreased body weight, regardless of the level of sugar intake, and the weight gain associated with the excessive intake of sugars is due to the associated excessive energy intake. Taking into consideration the quality of the studies, both for adults and children, included in the WHO's systematic review (2015), experts considered their recommendation to be based on moderately scientific evidence.

The consumption of added simple sugars may also be linked to the development of other pathologies such as diabetes and dyslipidemia. Similarly, a meta-analysis of 11 prospective cohort studies, 3 of which were focused on the metabolic system and 8 on Type 2 diabetes mellitus, showed that the intake of sugary drinks was linked to the development of Type 2 diabetes. The authors indicate that while is true that part of the effect on diabetes is mediated by the increase in energy intake and body weight that usually results from the intake of this type of drink, there is also a negative effect that is independent of these factors (Malik et al., 2010).

With regard to the dyslipidaemias, Te Morenga et al. published a meta-analysis which included 39 random clinical trials, of which 38 contained results referring to plasma triglycerides, 36 to total cholesterol, 22 to LDL-cholesterol and 28 to HDL-cholesterol. The meta-analysis shows that high intakes of added simple sugars are associated with elevated plasma concentrations of triglycerides, total cholesterol and LDL-cholesterol. It is important to highlight that, in the case of triglycerides and LDL-cholesterol, the associations were produced mainly in those studies where differences in simple sugar intake were produced in isocaloric conditions with regard to the group that had the lowest intake, and in studies where no significant differences in body weight were detected between the different experimental groups (Te Morenga et al., 2014).

Nevertheless, it must be pointed out that most of the commercial brands have marketed "sugar-free" versions of their energy drinks in order to prevent this problem. Although it is true that the use of sweeteners is a solution that reduces sugar consumption, there are two aspects that must be taken into consideration. Being used to a high sweet taste detection threshold may lead us to consume other sweet foods where sugars have not been replaced with sweeteners and therefore result in an excessive sugar intake. Secondly, and this is a topic that requires further study, we must be aware of the effects of the regular intake of sweeteners upon gut bacteria as today it is known that the microbiota may influence the development of diseases such as obesity or diabetes.

10.2 Sugars and sweeteners: estimation and assessment of exposure from energy drinks, links to obesity and recommendations

Given that simple added sugars are ingredients found in energy drinks and considering the limitations on the consumption of these sugars established by the WHO, it is important to analyse the sugar content of energy drinks and their contribution to the total intake of added simple sugars in the diet.

The quantity of sugars in energy drinks ranges between 10 and 12 g per 100 ml, but the packages provide volumes that are much higher. Table 6 displays information on package sizes available in the market and the quantity of sugars in said packages for the most popular brands of energy drinks.

Table 6. Quantity of simple sugars in energy drinks and contributions (g) from regularly marketed packages

Sugars/100 ml	Sugars/250 ml	Sugars/500 ml
11 g	27.5 g	55 g
12 g	30 g	60 g

Given that nutritional information is usually expressed in 100 ml of the drink, initially it may seem that energy drinks do not contain high levels of simple sugars. Nevertheless, this is not the case, as we must consider that the packages usually contain 250 ml or 500 ml. This leads to intakes ranging between 27.5 and 60 g of sugar per package.

To place it in context, some additional data may be provided. For example, a teaspoon of sugar provides approximately 5 grams of sugar. Therefore, one can containing 250 ml of energy drink with 11 g of sugar/100 ml provides the equivalent of 5 teaspoons and a half of sugar, and a can of 500 ml, the equivalent of 11-12 teaspoons.

Since each gram of sugar contains 4 kcal, one 500 ml can therefore contains 220-240 kcal of sugars. This represents 10 % of the recommended calorie intake in a 2200-2400 kcal diet -the upper limit recommended by the WHO- implying that consumers of 500 ml of energy drinks per day are extremely likely to consume more sugars than recommended in their overall diet.

11. Vitamins in energy drinks

11.1 Vitamins in energy drinks: general characteristics

In addition to the aforementioned compounds, energy drinks also include vitamins and minerals in their composition. Generally, they are Group B water-soluble vitamins, and more concretely, Vitamin B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B5 and B12.

In accordance with Regulation (EC) No. 178/2002 (EU, 2002a), all foods must be safe and the operator responsible for their marketing must take all necessary measures in this regard, including warnings on labels or other measures. Regulation (EU) No. 1169/2011 (EU, 2011) establishes that the mandatory nutrition declaration may be supplemented voluntarily with the amounts of other nutrients such as: vitamins or minerals Annex VIII includes the concrete list of vitamins and minerals that may be declared and their Nutrient Reference Values (NRV), considering the general population as adult population without differentiating on the basis of age, sex or physiological status.

Table 7 lists the minimum and maximum contents displayed in the labelling of energy drinks marketed in Spain (data corresponding to 10 commercial brands in different presentations). It must be highlighted that in accordance with the regulations, the data displayed in the labelling is expressed in terms of 100 ml of the drink, however, these products are generally marketed in packages containing 250 and 500 ml, and even 1 l in some cases. With these considerations, the

Table shows the maximum and minimum percentages covered by the nutrient reference values (NRV) for each vitamin. It must be pointed out that in many cases, they are above 100 % of the NRV.

Regulation (EU) No. 1169/2011 also permits specific declarations such as "source of", "high in..." provided the food in question contains a significant amount of the highlighted substance, significant amount being content that exceeds 7.5 % of the nutrient reference values specified in Point 1, per 100 ml in the case of drinks. These values are widely exceeded in most drinks available in our markets.

Table 7. Group B vitamin content in energy drinks and their link to the Nutrient Reference Values (NRV)

Vitamin	Volume	Range in commercial samples		NRV	% NRV	
		Min.	Max.		Min.	Max.
Vitamin B2	100 ml	0.56	3.2	1.4 mg/day	40	228.6
	250 ml	1.12	6.4		80	457.1
	500 ml	2.24	12.8		**160**	914.3
	1000 ml	4.48	25.6		**320**	1828.6
Vitamin B3	100 ml	1.6	8	16 mg/day	10	50.0
	250 ml	3.2	16		20	**100.0**
	500 ml	6.4	32		40	200.0
	1000 ml	12.8	64		80	400.0
Vitamin B5	100 ml	1.2	2	6 mg/day	20	33.3
	250 ml	2.4	4		40	66.7
	500 ml	4.8	8		80	**133.3**
	1000 ml	9.6	16		**160**	266.7
Vitamin B6	100 ml	0.15	2	1.4 mg/day	10.7	**142.9**
	250 ml	0.3	4		21.4	285.7
	500 ml	0.6	8		42.9	571.4
	1000 ml	-	-		85.7	1142.9
Vitamin B12	100 ml	0.38	2.5	2.5 µg/day	15.2	**100.0**
	250 ml	0.76	5		30.4	200.0
	500 ml	1.52	10		60.8	400.0
	1000 ml	3.04	20		**121.6**	800.0

With regard to physiological functions, these Group B vitamins have different beneficial physiological effects that justify their consideration as nutrients. They also contribute to the normal energy yield and participate in functions such as carbohydrate and protein metabolism at the same time that they help to improve mental performance (pantothenic acid) and reduce tiredness and fatigue (niacin, pantothenic acid, B6 and B12). Currently, and in accordance with Regulation (EU) No. 1924/2006 (EU, 2006a), the EFSA has issued favourable declarations on the authorisation of the statement "contributes to maintaining a normal energy yield" (EC, 2021) for the following vitamins: B2, niacin, B6, B12, provided their food content is higher than 15 % in solid foods and 7.5 % in

drinks. This health claim is employed in some of the commercial brands available in our markets, for Vitamin B3 (niacin) and B6 content (EU, 2006a, b).

11.2 Vitamins: risks associated with intake from energy drinks. Possible hypervitaminosis

All Group B vitamins are water-soluble; thus, the excess does not accumulate in the body but is flushed out in urine. This process of elimination may be hampered in the case of people with kidney problems, and in cases of frequent intake, may cause physiological changes. It must be pointed out that for many vitamins, an intake of just 100 ml exceeds 200 % of the NRV for Vitamin B2, and 205 ml in the case of Vitamins B6 and B12. Other vitamins require higher intakes: 500 ml in the case of Vitamin B3 and 1000 ml in the case of Vitamin B5.

Following the stipulations of Article 5 of Directive 2002/46/EC, on food supplements (EU, 2002b), the *Direction Générale de la Concurrence, de la Consommation et de la Répression des Fraudes* (DGCCRF, 2019) has established three groups of nutrients according to their low/null, moderate or high levels of risk, linked to their tolerable upper intake levels versus their P95 intakes through diet. According to this classification, Vitamin B2, pantothenic acid and Vitamin B12 have a low level of risk; Vitamins B3 (nicotinamide) and B6 have a moderate risk; and Vitamin B3 (nicotinic acid) has a high risk. As a matter of fact, the tolerable upper intake level for niacin is set at 900 mg of nicotinamide, or 10 mg of nicotinic acid, and at 25 mg for Vitamin B6 by the SCF (2000). These levels are not reached by the energy drinks available in our markets therefore we do not expect to find cases of hypervitaminosis derived from their intake. In the event that hypervitaminosis was to occur, the resulting disorders would be nausea and hepatic alterations (Harb et al., 2016).

The samples available in Spanish markets do not exceed this Vitamin B3 content.

12. Ginseng, Guarana and Ginkgo

12.1 Ginseng, Guarana and Ginkgo: general characteristics

Energy drinks generally contain plant-based ingredients that supplement the stimulating power of caffeine and play an important role in their sensory characteristics as well as in enhancing their perception and acceptance by the consumer.

Some of the most common constituents are ginseng, guarana and ginkgo, used as water-soluble liquid extracts. Some preparations also include pollen or royal jelly (Suna et al., 2019).

12.2 Ginseng

Ginseng is widely used in traditional medicine in Korea, Japan and China for its adaptogenic effects or metabolic regulation; it is a stimulant included in energy drinks to boost energy and reduce stress. Ginseng content in energy drinks may range between 6 mg and 300 mg/355 ml (Mandel and Loeb, 2015). Additionally, its roots and rhizomes are used as a food item and as dietary supplements in several countries. While there are sweets and drinks in the United States that contain ginseng, soups and salads with ginseng are common in Korea, and ginseng extract is added to alcoholic drinks in China (Szczuka et al., 2019).

Its main active ingredients are ginsenosides (2-3 %), a complex series of mono and bidesmosidic tetracyclic triterpenoid saponins. It also contains heterogenous polysaccharides (panaxanes subtypes A-U), polyynes (panaxiol, panaxitriol), proteins, (panaxagin, quinqueginsin), steroids and phenolic compounds (Vanaclocha and Cañigueral, 2019).

Ginsenosides are divided into three groups depending on the aglycone structure:

- Protopanaxadiols: ginsenosides Ra1, Ra2, Ra3, Rb1, Rb2 and Rb3, notoginsenosides R4, Rs1, Rs2, Rs3 and Rs4, and malonyl-ginsenosides Rb1, Rc and Rd.
- Protopaxanatriols: Re, Rf, Rg1, and notoginsenoside R1.
- Oleanolic acids: ginsenoside Ro.

Ginsenosides may display different pharmacological effects and mechanisms of action as they have different chemical structures (Lü et al., 2009), for this reason, some ginseng-based preparations must be assessed.

According to the European Pharmacopoeia, the plant drug, Korean ginseng, consists of the roots of *Panax ginseng* C.A. Meyer (Araliaceae) either cut and dried (white ginseng) or treated with water vapour and dried (red ginseng), with a minimum content of 0.4 % of ginsenosides Rg1 and Rb1, in the dried drug. American ginseng refers to the roots of *P. quinquefolius.* It also includes the definition of Chinese ginseng obtained from the vapour-treated and dried primary root of *P. notoginseng* (Burkill) F.H. Chen or of *P. pseudoginseng* Wall, with a minimum content of 3.8 % of ginsenosides Rg1 and Rb1 in the dried drug.

Ginseng acts as a stimulant and is a general tonic that enhances the general feeling of wellbeing and the capacity to work, reduces physical fatigue and psychological stress, it has immunomodulatory (immunostimulant), anti-inflammatory, antineoplastic, cardiovascular, antioxidant, endocrine, ergogenic effects and especially affects the CNS. It stimulates/depresses the CNS, regulates blood pressure, and acts as a lipid-lowering agent, hypoglycaemic agent and anabolic agent (Lü et al., 2009) (Vanaclocha and Cañigueral, 2019). It has also been thought to protect against infections and toxins, and some of these effects have been proven in clinical trials.

A randomised, double blind, crossover and placebo-controlled trial on 32 healthy adults (Jackson et al., 2020) assessed the cognitive, mood-related, and cerebral circulation effects of three drinks containing beet extract (10 g, standardised for 1.5 % nitrate and 0.4 % betalains), ginseng extract (170 mg, 4.5 % ginsenosides) and sage extract (280 mg), in addition to one of the following three phenolic extracts: 1.1 g of coffee berry extract (440 mg of chlorogenic acid), or 275 mg of apple extract (234 mg flavanols expressed as epicatechin equivalents), or 2.49 g of blueberry extract (300 mg anthocyanins). It was observed that the coffee drink reduced mental fatigue, confusion/bewilderment and mood changes. This effect may be partially attributed to the 22 mg of the coffee extract, but a similar study with decaffeinated coffee berry extract also revealed diminishing perceptions of fatigue and decreased state of alert after performing tasks that were equally demanding cognitively, which suggests that other components of coffee contributed to these effects. Additionally, it has been stated that the combined consumption of low doses of caffeine enhances the bioavailability of phenolic compounds, exercising a synergistic effect.

The traditional use of ginseng and its products to treat asthenia, fatigue, and sensations of

weakness is approved by the European Medicines Agency (EMA, 2013a). Its consumption must be avoided in pregnancy, when breastfeeding, and in children and adolescents below the age of 18, given the absence of evaluations of the effects of ginseng in these population groups.

Often athletes and other individuals seek recourse to dietary measures that include plant-based products for improved endurance and strength performance, avoiding the consumption of synthetic drugs which consumers generally associate with greater health risk. Most of these plant-based products have a low to moderate effect on oxidative stress, resistance to fatigue and endurance capacity. Nevertheless, ginseng is recognised as an excellent performance booster in sports as it increases endurance capacity, heart and lung function, physical performance and muscle strength, and reduces endurance time and plasma lactate production (Sellami et al., 2018). Additionally, it appears to enhance alertness and reaction times.

Ginseng is present in energy drinks below the regular daily dosage. However, consumers must be aware that, similar to all active ingredients, ginseng may have side-effects such as skin hypersensitivity, insomnia, gastrointestinal disorders, nausea, vomiting, diarrhoea or constipation. In high doses, it may cause anxiety, irritability, nervousness, insomnia, hypertension, angina and oestrogenic effects, that disappear when the dose is reduced or the treatment is stopped. Likewise, ginseng may interact with other active ingredients, therefore the consumer must be aware of its presence in the energy drink and avoid these interactions that may be clinically significant depending on the amount of ginseng ingested, the doses and dosage schedules of the medicines taken concomitantly (De Sanctis et al., 2017). The capacity of ginseng to boost the effect of monoamine oxidase inhibitors is also known and it may cause hypertension, headaches, psychoses and manias (Vanaclocha and Cañigueral, 2019) and inhibit the anticoagulant effect of warfarin. Ginseng is also contraindicated in cases of arrhythmia, hypertension, anxiety and nervousness.

Ginseng undoubtedly has a high potential for positive health effects and therefore requires the formulation of precise nutritional recommendations and assessment of its suitability in preventing and treating certain disorders.

12.3 Guarana

Guarana contains approximately double the caffeine concentration found in coffee grounds (2-4 % caffeine in guarana seeds compared to 1-2 % in coffee grounds). It is added to energy drinks for its antioxidant properties and other physiological effects in amounts that range between 1.4 mg and 300/355 ml (Mandel and Loeb, 2015).

Guarana or guarana paste is obtained from the plant species *Paullinia cupana* Kunth. (synonym *Paullina sorbilis* Mart.) of the Sapindaceae family, from seeds that have been shelled, toasted and ground into powder, then mixed with water to form a paste that is moulded and dried. It is sold as a powder or as a brown cylinder, mostly to prepare energy drinks and stimulants.

Guarana contains xanthic bases, mostly caffeine (3.6-5.8 %) and less than 0.2 % of theobromine and theophylline. It has a high tannin content (5-16 %, mainly proanthocyanidins), fatty acids, flavonoids, resin, saponins, essential oil and mucilage. It improves fatigue resistance, muscle strength, endurance performance, immune response and levels of plasma catecholamine (Sellami

et al., 2018). It is used as a tonic for asthenia, physical exhaustion due to disease or sports, treatment of diarrhoea and as adjuvants to treat obesity. It has been used traditionally as a natural energiser and cognitive stimulant, as an aromatic agent in drinks and as a component in natural weight-loss products, however, clinical data does not support its use as a natural energiser or weight-loss aid. Limited clinical trials have been conducted with only guarana (doses of 75 mg to 1000 mg/day), with some proof of its usefulness in chemotherapy-related fatigue.

The administration of guarana has been associated with decreased total food intake, fat content and plasma lactate concentration in trained rats. Kennedy et al. (2004) observed the psychoactive properties of a single dose of guarana extract (75 mg) in healthy adults. They reported improvements in memory-related performance and response times. Using different doses of guarana extract (37.5, 75, 150 and 300 mg), Haskell et al. (2007) confirmed improved cognitive performance and notable changes in mood. Interestingly, they observed an increase in the "alert mood" self-assessment with the higher dose of guarana and an increased self-assessed "content mood" after all doses.

Some researchers suggest that the revitalising effects of guarana are partially due to its antioxidant activity. The possible effects of guarana in suppressing appetite and inducing energy are probably related to its caffeine content.

While the dosage recommended by the European Scientific Cooperative on Phytotherapy (ESCOP, 2009) for adults is a daily dose of 1-3 g of powdered guarana or equivalent formulations, without exceeding 3 g/day, the EMA (2013b) recommended a traditional dose for adults of 450 mg of powdered guarana up to 5 times daily. There are no studies on pregnant or lactating women, therefore, its administration is not recommended. Its use is not recommended in children below the age of 12 as there is insufficient medical data to vouch for its safety.

The adverse effects of guarana are mild and temporary, although there have been reports of nervousness, insomnia, anxiety, hypertension, palpitations, upset stomach and other health risks in patients with caffeine sensitivity. Currently, it is believed that guarana has no adverse effects other than the potential toxicity of caffeine (De Sanctis et al., 2017). Most cases of toxicity in adults appear to be mild and clinically benign but accidental overdose in children may be more serious. As a precaution, it is recommended that patients with anxiety and hypertension, irritable bowels or palpitations avoid its consumption.

Similar to ginseng, guarana also displays significant interactions with other active ingredients such as monoamine oxidase inhibitors, sedatives or sympathomimetic drugs (EMA, 2013b). Additionally, given that its main component is caffeine, it can boost the effect of psychoanaleptics and other drinks containing caffeine (Drugs, 2020).

Guarana is not recommended for consumers with caffeine hypersensitivity, gastric and duodenal ulcers, cardiovascular diseases, hypertension and nervousness. It is also not recommended for pregnant and lactating women as its consumption has been linked to premature labour and low birth weight, and its safety has not been established for infants and children.

Guarana undoubtedly has potentially beneficial effects for health, but its toxicological assessment must be made and specific dietary recommendations drafted.

12.4 Ginkgo

Nootropic effects and cerebral and cardiovascular benefits have been attributed to ginkgo, owing to its antiplatelet action, improvements to blood flow and antioxidant potential, which is why it is used to improve cognitive performance. Ginkgo is marketed in various forms. A noteworthy form are infusions and currently energy drinks whose ginkgo content ranges between 15-20 mg/237 ml. These doses of ginkgo are far below those responsible for any cardiovascular or neurological benefit or hazard (Suna et al., 2019).

The dried, whole or fragmented leaf of *Ginkgo biloba* L. (Ginkgoaceae), constitutes the plant-based drug and must have a minimum 0.5 % of flavonoids expressed as flavonoid glycosides, in the dried drug, according to the European Pharmacopoeia. The main active ingredients are:

- Flavonoid compounds (0.5-1 %): flavonols (quercetin, kaempferol, isorhamnetin); p-hydroxycinnamates of quercetin and kaempferol glucorhamnosides; biflavones, (amentoflavone, bilobetin, 5'-methoxybilobetin, ginkgetin, isoginkgetin); oligomeric proanthocyanidins of delphinidin and cyanidin.
- Terpene lactones: hexacyclic diterpenes ginkgolides A, B, C, J and M (0.06-0.23 %); the sesquiterpene bilobalide (not less than 0.26 %).

It uses the powdered dry drug or dry refined and titrated ginkgo extract which contains 22-27 % of flavonoids calculated as flavonoid glycosides, 2.6-3.2 % of bilobalide, 2.8-3.4 % of ginkgolides A, B and C, and a maximum of 5 ppm of ginkgolic acids.

Ginkgo leaf has arterial vasodilator activity, it is venotonic, it increases capillary resistance and has antiplatelet activity (platelet-activating factor antagonist), it increases anoxia tolerance by increasing glucose and oxygen capture and reducing brain oxygen requirements. It is an antioxidant and neuroprotector (Vanaclocha and Cañigueral, 2019).

Ginkgo extract improves cerebral blood flow, microcirculation and tissue metabolism, it protects from hypoxia, inhibits platelet aggregation and reduces capillary permeability.

The EMA (2015) approved its use for mitigating cognitive deterioration associated with age and quality of life in mild dementia (240 mg/day of extract, 1 or 2 doses, for at least 8 weeks). Additionally, it approved its traditional use in alleviating heavy legs and minor circulatory problems (750 mg/day of powdered drug, in 2 or 3 doses).

The ESCOP (2003) and the European Commission (Blumenthal, 1998) have approved the therapeutic use of the refined and titrated dry extract within a range of 120-240 mg for 6-8 weeks, as applicable, to treat mild or moderate cerebrovascular insufficiency, intermittent claudication and other occlusive peripheral arterial diseases, vertigo and tinnitus of vascular and involutive origins.

While the rare side-effects of ginkgo include gastrointestinal discomfort (diarrhoea, nausea and vomiting) and headaches, when it interacts with other active ingredients, especially with anticoagulants and antiplatelet drugs, it has significant side-effects, therefore the concomitant use and consumption of ginkgo along with these treatments must be supervised by a medical practitioner. Although this recommendation is only applicable in cases of ginkgo hypersensitivity, the consumption of energy drinks with ginkgo must also be avoided by pregnant and lactating women.

Noteworthy precautions to be maintained when using ginkgo include the incidence of haemorrhage at doses higher than 240 mg/day, a dose that greatly exceeds that which is present in energy drinks albeit to ensure its safe use, specific dietary recommendations must be formulated.

12.5 Ginseng, guarana and ginkgo: dietary exposure from energy drinks

When the energy drink is formulated with other active ingredients in addition to caffeine, it is more likely to produce adverse effects on consumer health. The inclusion of these plant-based ingredients may not only increase caffeine content and the stimulating properties of these drinks further, but they may also generate uncertain interactions and exacerbate any risk (Visram et al., 2015).

In accordance with the document published by the EFSA Scientific Committee (2004 and 2009) on the quality and safety of plant-based products widely used as food supplements, ginkgo and ginseng are included as the most widely bought ingredients and whose drug interactions have been described. Nevertheless, the acute and long-term effects of the excessive and chronic consumption of these components either alone and/or in combination with caffeine are not fully known (De Sanctis et al., 2017).

It is known that guarana is an effective short-term stimulant with caffeine alone, and that low concentrations of glucose can improve the invigorating effects of guarana in the long term. This suggests that guarana, in combination with caffeine and glucose, provides a temporary stimulus at low concentrations (Moustakas et al., 2015). Nevertheless, a crossover, randomised, double blind and placebo-controlled trial with 34 young healthy volunteers of both sexes concluded that acute exposure to energy drinks with caffeine, regardless of whether they contain guarana and ginseng or not, significantly prolongs the QTc interval and blood pressure (Shah et al., 2019).

The consideration of these ingredients as plant-based supplements allows them to not be subject to the same information requirements as caffeine and sugars, and consequently, their concentration is generally not reported in the drinks labelling. Apart from consumer disinformation, this makes it impossible to conduct a risk assessment and intake estimate of each of these ingredients by the population, from these packages.

Nevertheless, using the range of contents mentioned by some authors (Mandel and Loeb, 2015) (Suna et al., 2019) and the three consumption scenarios considered in this evaluation for being the most common among the population (250, 500 and 1000 ml of energy drink), we may make an estimate of ginseng, guarana and ginkgo intake (Table 8).

Table 8. Ginseng, guarana and ginkgo content in energy drinks and exposure/intake estimate in three scenarios of energy drink consumption

Component	Content Min.-Max.	Volume of energy drink ingested		
		250 ml	500 ml	1000 ml
		Intake range (mg) (Min.-Max.)		
Ginseng	100-800 mg/l	25-200	50-400	100-800
Guarana	0.02-100 mg/l	0.005-25	0.01-50	0.02-100

Table 8. Ginseng, guarana and ginkgo content in energy drinks and exposure/intake estimate in three scenarios of energy drink consumption				
Ginkgo	63.3-84.4 mg/l (15-20 mg/237 ml)	16-21	31.6-42.2	63.3-84.4

As there are no intake recommendations or daily consumption limits for these three ingredients, a risk assessment cannot be performed.

In the case of ginseng however, its intake from energy drinks is considerably below the daily doses used traditionally for therapeutic purposes, for both white and red ginseng (Vanaclocha and Cañigueral, 2019).

Guarana intake from energy drinks in any of the three proposed scenarios would also be lower than the therapeutic doses of guarana used (1-3 g of powdered guarana or equivalent preparations) (ESCOP, 2009), without exceeding 3 g/day and 450 mg of powdered guarana up to 5 times daily (EMA 2013b).

Considering that the EMA (2015) approves the established use of ginkgo in doses of 240 mg/day of extract (1 or 2 doses) and the traditional use of 750 mg/day of powdered drug (2 or 3 doses), the intakes of this ingredient from energy drinks are very low in all three proposed consumption scenarios.

In this regard, some studies suggest that the caffeine content of guarana (40-80 mg/g of extract) should be included as additional to the caffeine content indicated in the list of ingredients (composition) in energy drinks, as the total content of the active ingredient caffeine may be higher than indicated in the list of ingredients. A retrospective observational study published by Gunja and Brown (2012) analysed the alerts linked to energy drink exposure recorded in the database of a Australian Poisons Information Centre for 7 years until 2010. Thus, the Food Regulations Code in some countries, including Australia, require labelling the total caffeine content from all sources (FSANZ, 2019). The clinical case of a 25-year-old Australian woman with pre-existing mitral valve prolapse, a condition that affects 2.4 % of the population, who developed untreatable ventricular fibrillation after consuming an energy drink with high caffeine content and guarana may have boosted the implementation of this measure, in order to manage and regulate the labelling of these drinks (Cannon et al., 2001) (Subaiea et al., 2019).

Conclusions and Recommendations of the Scientific Committee

The term "energy drink" continues to be an undefined term or one that is not covered in the legislation on the subject.

- More progress needs to be made on establishing its legal framework, including its definition, the ingredients it may contain, its maximum concentration and possible combinations.

There is a large variety of available energy drinks and their composition is highly diverse. The main ingredient, caffeine, is often accompanied by other active ingredients (taurine, L-carnitine, D-glucuronolactone, vitamins and even plant-based ingredients such as ginseng, guarana and

ginkgo, among others) which leads to wide heterogeneity in consumer information in the labelling.

- It is recommended to improve, in collaboration with the industry, consumer information provided in energy drink labelling, boosting not only the listing of all active ingredients, but also their quantity, in the list of ingredients.

With regard to **caffeine** in energy drinks, given that intakes higher than 1.4 mg caffeine/kg b.w./day are linked to sleep disorders (sleep onset latency and reduced sleep duration) and intakes higher than 3 mg caffeine/kg b.w./day are highlighted as responsible for general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects) (EFSA, 2015b), therefore:

- Generally, when consuming these drinks, it is recommended to select energy drinks low in caffeine in order to prevent and reduce the possibility of sleep disorders and other adverse effects on health.
- If we consider energy drinks with 32 mg of caffeine/100 ml as most frequently consumed:
  - To prevent sleep disorders, it is recommended to not exceed a consumption of 200 ml (in children between the ages of 11-13), 250 ml in children and adolescents (14-17 years), and 300 ml in young adults (18-30 years).

Higher consumption may lead to the appearance of general adverse effects on health (cardiovascular and haematological, neurological and psycho-behavioural effects).

- If we take a reference intake of 1.4 mg caffeine/kg b.w./day as responsible for this adverse effect of sleep disorder, and a reference intake of 3 mg caffeine/kg b.w./day as responsible for general adverse effects on health (cardiovascular, haematological, neurological and psycho-behavioural effects), then it is recommended that:
  - Consumers weighing 50 kg should avoid consuming energy drinks with more than 32 mg/100 ml in order to avoid sleep disorders.
  - Consumers weighing 60 kg should not consume 1000 ml of any energy drink (15-55 mg caffeine/100 ml) and in any case, they should not consume more than 500 ml of energy drinks with 40-55 mg caffeine/100 ml, as these consumptions are linked to both sleep disorders and general adverse effects on health. Consumers weighing 70 kg should not consume 1000 ml/day of energy drinks with 15 mg caffeine/day, 500 ml of drinks with 32 mg caffeine/100 ml, and 250 ml of drinks with 40-55 mg caffeine/100 ml as this would expose them to caffeine intakes higher than 1.4 mg caffeine/kg b.w./day, linked to sleep disorders.
  - Consumers weighing 70 kg should not consume 1000 ml of energy drinks with 32-40 mg caffeine/100 ml, or more than 500 ml of drinks with 55 mg caffeine/100 ml as the caffeine intake would be higher than 3 mg/kg b.w./day, linked to general adverse effects on health.
  - In any case, adults and older adolescents (70 kg) should not exceed the maximum intake of 400 mg caffeine/day recommended by the EFSA (2015b).
- It is recommended to verify that the labelling of energy drinks lists the total caffeine content from all the ingredients.

- It is worth considering, in line with some countries, regulating the maximum caffeine content of these drinks.

With regard to **D-glucuronolactone** in energy drinks and considering an average content of 2400 mg/l, the estimated exposure to D-glucuronolactone ranges between 8.6 and 48.0 mg/kg b.w./day upon consumption of 250 ml and 1000 ml of energy drinks, respectively. Only the daily consumption of a 250 ml energy drink by consumers weighing 60 and 70 kg has a margin of safety equal to or greater than 100. The consumption of three packages/day of energy drinks significantly reduces the margin of safety for D-glucuronolactone, placing it between 21 mg/kg b.w./day for a person weighing 50 kg and 29 mg/kg b.w./day for a person weighing 70 kg.

Regarding **L-carnitine**, very little scientific data is available on the quantity and frequency of consumption from energy drinks as L-carnitine is included in these drinks as a nonspecific component of the preparation without specific details regarding its quantity.

With regard to **sugar** intake from energy drinks that are not *sugar-free*, it is estimated that the consumption of 250 ml of energy drink provides between 27.5 and 30 g of sugar and the consumption of 500 ml of energy drink provides between 55 and 60 g of sugar. If we take the example of a 250 ml can, its sugar contribution is 220-240 kcal, which represents 10 % of the energy from diets containing 2200-2400 kcal, which would make it very difficult to not exceed our simple sugar intake limit.

Regarding **vitamin** composition, generally Group B water-soluble vitamins (B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6, B12), the consumption of energy drinks entails a low risk of hypervitaminosis for Vitamin B2, pantothenic acid and Vitamin B12; a moderate risk of hypervitaminosis for Vitamin B3 (nicotinamide) and B6; and high risk of hypervitaminosis for Vitamin B3 (nicotinic acid).

With regard to the content of **plant-based ingredients**, the biological activity of the different active ingredients and their potential for drug interaction should not be underestimated. The consumer should be informed, not only about the included contents but also the possibility/risk of interaction, as well as those situations where intake is not recommended. Thus, the consumption of energy drinks that contain ginseng must be avoided in pregnancy, when breastfeeding, and in children and adolescents below the age of 18, given the absence of evaluations of the effects of ginseng in these population groups. Energy drinks with ginkgo must also be avoided by pregnant and lactating mothers.

The growing concern with assessing the health risks of energy drinks is accompanied by an interest in enhancing consumer knowledge, promoting moderate consumption and avoiding risky behaviours, especially combining them with alcoholic drinks. Spain must join European efforts to compile data on energy drink consumption and its trends by means of annual monitoring and community awareness activities.

The annual monitoring of consumption trends will allow us to assess the contribution of these energy drinks to dietary exposure to caffeine and other active ingredients in specific consumer groups, to estimate their risks, and to draw up action plans to mitigate them.

Policies must be formulated, and communication and educational programmes implemented in order to increase people's awareness, improve risk perception, and minimise possible risks

associated with the excessive consumption of energy drinks with special consideration for population groups at greater risk (children and adolescents). Additionally, there should be greater control of advertising, especially that which targets the most sensitive section of the population (children and adolescents).

It is stressed that energy drinks are not recommended for children, pregnant or lactating women, and in accordance with Regulation (EU) No. 1169/2011, energy drinks that contain more than 150 mg/l of caffeine must display this advisory in their labelling.

It is recommended to promote compliance with the industry's commitment to marketing packages containing no more than 250 ml in order to minimise exposure to different active ingredients, some of which are psychoactive, and to study the possibility of preventing the marketing of 500 ml packages.

Among future actions to be taken, the consumption, exposure and risk of other "caffeine consumption models" such as "shots" or "caffeine/energy shots" must be assessed, which are products marketed in smaller sizes that provide, in less than 100 ml, elevated concentrations of caffeine much higher to those in energy drinks.

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