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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Scoping paper on the potential risks from energy drinks in the diet of children and adolescents.

Introduction

1. Energy drinks (EDs) are defined by the presence of compounds, mainly caffeine, that are intended to enhance the consumer's physical performance and cognitive state, as opposed to "sports" drinks, which are formulated to replace water and electrolytes lost during exercise.

2. In 2016, more than 20 brands of ED were on sale in the UK.[1] A recorded 3.74 million people drank Red Bull in the UK that year, making it the most popular ED brand by its number of users. This was followed closely by Lucozade Energy with 3.7 million consumers. Sales of EDs constituted 13.4% of the soft drinks market in the same year [2]

3. The global market research company Mintel produced a report in 2017 on sports and EDs. EDs are reported to have had 19% volume growth since 2012 to 669 million litres in 2017, with low- or zero-sugar varieties proving popular. The company forecast a further 10% volume growth for the energy drinks market over 2017-22 to 739 million litres, and to 25% growth by 2022, passing the £2 billion litre mark. https://store.mintel.com/uk-sports-and-energy-drinks-market-report

4. EDs vary in price but can be cheap, costing £0.25 per can (bought as a pack of 6 costing £1.50) (Tesco Blue Spark).

5. The EU has had legislation in place since 2011 that requires all drinks (excluding tea and coffee) containing over 150mg of added caffeine per litre, with the statement as "High caffeine content. Not recommended for children or pregnant or breast-feeding women". In addition, the amount of caffeine in mg per 100 ml of drink must appear after this statement.

[1] https://www.statista.com/statistics/308493/leading-brands-of-energy-drinks-excluding-colas-or-mixers-for-alcoholic-drinks-in-the-uk/

[2] https://www.statista.com/statistics/422739/soft-drink-market-share-by-category-in-the-united-kingdom/

6. Some countries, such as Australia and Canada also require a maximum daily consumption limit to be stated on packaging (500 ml or 160 mg caffeine in Australia: Peacock *et al* (2016))

7. The British Soft Drink Association, the trade body for soft drink manufacturers, produced a Code of Practice in 2015, laying down rules for the labelling and the responsible marketing for EDs to the effect that consumers are aware of the potential risk of drinking these products and the exposure of school-age children to related advertising is kept to a minimum.

8. EFSA (Zucconi *et al* , 2013) published a report on the gathering of consumption data on specific consumer groups of EDs. A total of 31,070 validated questionnaires were collected from adolescents in schools across Europe. Of the respondents, 68% had drunk at least 1 ED in the previous year and 28% had drunk one in the previous 3 days. Seventy-five percent of the 15-18 age group and 55% of the 10 – 14 age group were consumers, comprising 74% of males and 63% of females. Thirty-six percent of the total sample had consumed EDs with alcohol in the previous year.

9. The Mintel report states that a ban the sale of energy drinks to under- 16s was recommended by the Food Research Collaboration, part of the Centre for Food Policy of City University London in July 2016. This was itself part of a report suggesting that these drinks are associated with a range of health complaints and risky behaviours, although gaps in the available evidence were acknowledged.

10. The Chef Jamie Oliver's company has made a public statement (Matthews, 2018), saying that there should be a ban on the sale of so-called EDs to consumers under the age of 16 years.

11. The supermarket Waitrose was the first UK retailer to restrict the sale of EDs to people over 16 years of age (Gillingham, 2018). Waitrose were followed in this by all of the major food retailers in the UK and most recently by Boots.

12. HM Government has recently (from 1 April 2018) enacted legislation to tax industries producing or importing soft drinks with an added sugar content of greater than 5g/ 100ml. The provisions of this Soft Drinks Industry Levy are provided in Guidance on the Gov.UK website. The intention of this measure is to encourage industry to reformulate their products into healthier versions in the light of increasing rates of type 2 diabetes, tooth decay and childhood obesity and obesity related diseases. Companies thus have the choice of reformulating their products or paying the duty and thence possibly passing on the cost to the consumer or absorbing it

Sugar content of EDs

13. An internet search reveals that the sugar content of EDs varies depending upon brand and type, i. e. "diet", "light" or "regular". Diet varieties contain no sugar but contain artificial sweeteners, light varieties contain from 1 to 6 g of sugar per 8 fl.oz serving (237 ml), in addition to artificial sweeteners, and the regular varieties

contain from 13 to 33 g of sugar per 8 fl.oz serving, some of which also contain artificial sweeteners. http://www.sugarydrinkfacts.org/resources/nutrition/Energy-Drink-Tables.pdf

14. The regular drinks above would all exceed the 5 g/100 ml legal limit described in paragraph 9 and thus would be subject to the new tax or have to be reformulated.

15. Hashem *et al* (2017) reported cross-sectional surveys of the amount of sugar, energy and caffeine in EDs in the UK and changes that had taken place between 2015 and 2017 before the new tax came into effect. Very small changes in sugar content were noted over the reporting period (10.6% in 2015 to 9.5% in 2017) but caffeine content and serving sizes remained high (31% and up to 500 ml),

16. Non-sugar components of EDs

Caffeine

17. Caffeine (1,3,7-trimethylxanthine) is a secondary metabolite of a number of plant species that has been taken as a stimulant in beverages made from these plants for thousands of years. Caffeine is widely present in tea, coffee and chocolate at differing concentrations.

18. The stimulatory effects of caffeine on the central nervous system are mediated by binding to adenosine A1 and A2a receptors. Antagonism of the A1 receptor leads to the effects of caffeine on sleep and arousal whereas antagonism of A2a potentiates dopaminergic neurotransmission, leading to a “reward” -type stimulus. (review by Temple 2009) Other effects of caffeine such as cyclic AMP phosphodiesterase inhibition and effects on calcium levels only begin to be seen at doses where toxicity becomes evident.

19. Single doses of caffeine of no concern derived for adults (3 mg/kg bw per day for a 70-kg adult) may also apply to children, considering that caffeine clearance in children and adolescents is at least that of adults, and that the limited studies available on the acute effects of caffeine on anxiety and behaviour in children and adolescents support this level of no concern. As for adults, caffeine doses of about 1.4 mg/kg bw may increase sleep latency and reduce sleep duration in some children and adolescents, particularly when consumed close to bedtime. (EFSA 2015)

20. Caffeine is known to promote diuresis and natriuresis by antagonising adenosine A1 receptors in the proximal tubule of the nephron. (Review by Osswald and Schnermann (2011)). Reisenhuber e*t al* (2006) found that with an ED containing 80 mg caffeine and 1g of taurine per 250 ml, the taurine, either alone or in combination with caffeine had no effect on urinary output, natriuresis nor urine osmolarity.

21. Caffeine intoxication is characterised by nervousness, irritability, anxiety, insomnia, tremor, tachycardia, palpitations and gastrointestinal upset. Other reported adverse effects include vomiting and abdominal pain, hypokalaemia, hallucinations, increased intracranial pressure, cerebral oedema, stroke, paralysis, rhabdomyolysis, altered consciousness, rigidity, seizures, arrhythmias, and death. (Reviewed by Seifert *et al* (2013))

22. Temple *et al* (2010) studied the effect of acute administration of caffeine at doses of 50, 100 and 200 mg to 28 male and 26 female adolescents aged 12 to 17 years from schools in Buffalo, Michigan, USA. The subjects were dosed orally in a double-blind, placebo-controlled manner with caffeine in a de-carbonated soft drink to reduce expectations of consuming caffeine and to mask its taste. Heart rate and blood pressure were measured, food preferences, reasons for ED consumption and behavioural effects were polled. Caffeine appeared to cause a dose-dependent fall in heart rate ($p = 0.001$) and increase in diastolic blood pressure ($p = 0.0001$). habitually high-caffeine consuming subjects (> 50 mg/day) were more disposed to eat high fat, high sugar or high-fat-and-sugar foods compared with low (< 50 mg/day) caffeine consumers. Boys gave greater importance to the feelings of increased overall energy, the immediate boost or “rush” and increase in physical performance after ED consumption than did girls.

23. Individuals differ in their response to caffeine by virtue of intrinsic rates of metabolism, and acquired tolerance due to frequency of exposure. Caffeine is metabolised in the liver, largely by CYP1A2, producing the partially demethylated products paraxanthene, theophylline and theobromine. Some individuals with poor expression of CYP 1A2 or the genetic variant PDSS2 metabolise caffeine slowly, thus prolonging its pharmacological and toxicological effects (Pirastu *et al* (2016))

24. Robertson *et al* (1981) performed a wash-out experiment on adults who had not consumed caffeine for 21 days prior to the experiment. Test subjects were initially dosed with a placebo of isotonic salts, then a dose of 250 mg/kg bw caffeine over 7 days, followed by placebo again for 4 days. Controls received placebo throughout. The caffeine raised systolic and diastolic pressure significantly relative to a placebo on the first day of dosing within 2 hours of ingestion, but, by day 7 of dosing, pressures were no longer affected. The same was true of plasma and urinary adrenaline, noradrenaline and plasma renin levels. There was no significant effect of the caffeine on heart rate in this study.

25. Chronic consumption of caffeine leads to withdrawal symptoms when it is interrupted. The major symptoms are headache and fatigue, but also may include depression, decreased cognitive performance, irritability, nausea and muscle aches (reviewed by Reissig *et al* 2009). The same review points out the possibility of caffeine dependence in some individuals.

26. Temple (2009) reviewed the effects of caffeine on children and covered effects on addiction, cross-sensitisation with other substances, brain development, sleep, behaviour, diet and obesity, and risk-taking behaviour. The conclusion was that at that time, caffeine consumption, including EDs, was increasing, with unknown consequences for health and development.

27. Caffeine contributes a bitter flavour to the taste of EDs in a dose-related manner and detracts slightly from their sweetness. (Tamamato *et al* (2010)). Some of the students in the attitude surveys (see below) felt that the difference in taste from other soft drinks made EDs attractive and "grown up" things to consume.

28. Boyle *et al* (2018) reviewed the evidence for interactions between the caffeine and the sugar in EDs. Caffeine in combination with glucose has been found to improve cognitive performance and subjective mood but there have been no dose-response studies or studies that take into account the different rates of absorption of the two compounds. Only 7 studies have looked at both components separately and in combination. There are potential mechanisms on central nervous system neurotransmitters that could account for possible interactions but further work would be needed to investigate these.

29. Mosca *et al* (2016) point out that energy drinks, like other sugary soft drinks may have a role in the currently increasing rates of childhood and adolescent obesity, which is related to type-2 diabetes, metabolic syndrome and non-alcoholic fatty liver disease.
https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/statistics-on-obesity-physical-activity-and-diet-england-2018

30. Miles-Chan *et al* (2015) compared the effects of caffeine alone with sugar-free and regular Red Bull on young male adults and found that all three treatments increased blood pressure. The Red Bull containing sugar increased heart rate, stroke volume, cardiac output and diastolic pressure, but decreased total peripheral resistance. Sugar-free Red Bull and caffeine alone, in contrast, increased total peripheral resistance. Since the SCF (2003) considered that taurine was not found to affect any of the measured parameters, the authors concluded that interactions between the sugar and the caffeine or the sugar and other components of the ED were responsible for this differential effect.

Other Components

31. In addition to sugar and caffeine, EDs vary in their lesser components. For instance, the most popular brand, Red Bull also contains the compound taurine and B-group vitamins. Red Bull no longer lists D-glucurono-γ-lactone in its ingredients but other brands contain this compound as well as guarana (a tropical shrub, the berries of which contain caffeine, theophylline and theobromine), ginseng, gingko biloba, L-carnosine, inositol, or a mixture of these and other minor components, but all at levels too low to be of toxicological concern in most individuals. (Higgins *et al* (2010).

Taurine

32. Taurine (2-aminoethanesulfonic acid**)**, is widely distributed in animal tissues and a constituent of bile. It is sometimes described as an amino acid.

33. Taurine is involved in the conjugation of bile acids, antioxidation, osmoregulation, membrane stabilization, phase 2 drug metabolism and modulation of calcium signalling. It is essential for cardiovascular function, and development and function of skeletal muscle, the retina, and the central nervous system (Higgins *et al* (2010). Taurine acts as a neurotransmitter in the central nervous system (Wu and Prentice, 2009) and appears to protect neurones against glutamate-induced excitotoxicity.

34. Miles-Chan *et al* (2015) compared the effects of sugar-free Red Bull with those of caffeine and water on the resting energy expenditure and respiratory quotient of 8 healthy young male volunteers. The ED enhanced thermogenesis and shifted the RQ in favour of carbohydrate metabolism, and this was mimicked by the caffeine solution. The authors concluded that the other components of the ED played no part in its stimulatory effects.

35. Peacock *et al* (2013) found that the presence of taurine in a caffeine-containing drink to some extent ameliorated the stimulatory effects of the caffeine. On its own, caffeine maintained levels of wakefulness and attention for a longer time than a placebo. In the presence of taurine, these attributes degraded over time similarly to the placebo. This would be in line with the known pharmacological attenuation effects of taurine receptor activation although rat studies suggest that ingested taurine has little effect on the levels in the brain (Sved *et al*, 2007).

36. Taurine does not appear to contribute to the taste of EDs at up to approximately 4200 mg/l (Tamamato *et al* (2010)).

D-glucurono-γ-lactone

37. D-glucurono-γ-lactone is naturally present in the human body as a metabolite of glucose and may be involved in the phase 2 metabolism of drugs as a source of glucuronic acid. It appears to have few if any pharmacological or toxicological properties. In other animals, including some mammals, this compound is known to be a substrate for ascorbic acid biosynthesis. Since this pathway does not occur in primates and guinea pigs, rodents may not be ideal as toxicological models for humans. EFSA (2009)

Reasons for, and patterns of, ED consumption

38. Several papers report polling young people for their reasons for consuming EDs and their choice of product. Some papers quantified the responses and these have been tabulated below (Table 1). The column titles are not exactly as stated in all of the papers tabulated but amount to the same response: for example a response like “Help me stay awake” and another like “Give me energy” have been combined in the column “Energy boost”. “Other” are minor miscellaneous responses that do not have equivalents in all of the papers.

39. In Italy, Gallimberti *et al* (2013) used a 63-question questionnaire to poll ED use among 916 young adolescents, aged 11 – 13 years. In this study the age-and-sex group in the highest “at least one ED a week” category was 11-year-old girls,

with a score of 90.3%. Seventy-five percent of boys of the same age group were in that category. Weekly consumption of EDs decreased with age, although infrequent but continuing consumption increased to 50.4% in boys and 35.6% in girls by the age of 13. Consumption of EDs was also significantly associated with smoking (p = 0.015) and drinking alcohol (p =0.009)

40. Costa *et al* (2014) interviewed 40 Australian adolescents aged 12 – 15 years regarding their use of EDs. The interviews consisted of 7 specific questions that covered knowledge, frequency, reasons for drinking, influences, psychological and physiological effects. Most participants knew what EDs were although there was some confusion with sports drinks and other beverages such as Coca Cola. EDs were easily accessible, sometimes from parents, consumed for sport or to increase wakefulness. Taste was a positive factor, as was peer pressure and advertising. Adverse effects were also recognised and put some students off continued consumption.

41. Turton *et al (*2016) explored adolescent attitudes and beliefs on caffeine and caffeinated beverages in two schools in different areas of London, Ontario, Canada. Participants seemed well aware of the levels of caffeine in beverages and of its potential to cause adverse effects. Taste was a major deciding factor, as was availability. Some older adolescents felt that drinking caffeinated beverages made them feel more mature and believed that younger siblings should not drink them. The media and advertising were strong positive influences, as well as parental role modelling, although parents also exerted a controlling influence on consumption. Finally, adhering to what was perceived to be the social norm influenced some pupils.

42. Temple *et al* (2016) performed a study on a small group (36) of adolescents and adults 15 to < 30 years old. relating to the influence of price and labelling on ED purchase. “Consumers” (>= 2 EDs per week) were more affected in their willingness to purchase EDs by changes in the price of the product than were “non-consumers” (< 1 ED/ month) (p<0.001 v p,0.01 respectively), Adolescents, but not adults were persuaded to reduce their consumption of EDs by labelling giving the caffeine content or a warning (p = 0.007).

43. A qualitative study was performed by Visram *et al* (2017) on the perceptions of EDs in focus groups of young people in England (aged 10 – 11 years, n = 20 and 13 – 14 years, n = 17). Reasons given by the participants for consuming EDs covered taste of the product, pricing relative to other soft drinks, and ready availability and promotion. Consumption took place in public places, in relation to social and sporting activities and computer gaming (especially amongst boys). Even though the policy of a school was not to allow EDs, some children drank them on the way to and from school and clubbed together with friends to buy them. Parents and other adults had a role in facilitating or limiting consumption but some of the children themselves thought some age restrictions should be necessary. No single dominant factor was recognised to address the consumption of EDs by young teenagers.

44. Reid *et al* (2017) polled young Canadians aged 12 – 17 years on their use of EDs. A total of 1103 adolescents took part in the study. 57% of th 12 – 14 year-olds

and 69% of 15 – 17 year-olds had ever consumed an ED . The main locations for consumption were at home (48 and 43%) and at school (35 and 42%). Major reasons for consumption were curiosity/novelty (33 and 42%), taste (26 and 26%) and because friends drank them (23 and 28%). 3% and 16% respectively drank EDs in conjunction with alcohol use

45. Ha *et al* (2017) found that among 833 adolescent Korean ED consumers, aged 16 - 17 years, 95% were aware of the high levels of caffeine in EDs and 35% consumed them habitually. Twenty-eight percent of users felt that the drinks posed a severe health threat, while 54% did not ($p < 0.05$). Thirty-six percent reported being exposed to ED advertising while 33% did not.

46. Kumar *et al* (2015) polled 779 adolescents, aged 12 to 17 years, on their perceptions and use of EDs. Of the sample, 9% drank EDs, At least once-weekly ED consumption was highest among 16 to 17-year olds who were physically active 3 or more times in the week. Nineteen percent of the sample thought that EDs were safe for teenagers, and 12.5% thought that EDs were a type of sports drink. These beliefs were positively correlated with ED consumption.

Table 1. Reasons for consuming EDs

		Reason for consumption %					
Country	Physical performance	Help with study	Energy boost	Taste	Peer pressure/ advertising/availability/ price	Other	reference
Trinidad & Tobago	8.5	19.7	47.0	23.1		1.7	Babwah *et al* (2014)
Poland	51	33	10	65		56	Górnicka *et al* (2014)
Canada	33.4	48.1	72.8	30.2	37.1	70.7	Wiggins *et* al (2017)
USA	35	12	67			57	Bashir *et al* (2016)
EU countries	7		38	40		15	Zucconi *et al* (2013)
USA	29	32	61	6	28	34	Nordt *et al* (2017)
Bahrain	6.1	4.4	43.3	40	1.7	4.5	Nassaif *et al* 2015
Poland	23.6			69.4	48	10.3	Nowak & Jasionowski 2015
Poland				47	33	22	Nowak & Jasionowski 2016

Effects on behaviour

47. Utter *et al* (2018) found that ED consumption in 8500 New Zealand adolescents (aged <= 13 to =17 years) correlated positively and in a dose-related manner (No ED < 1-3 ED < 4+ ED in the previous 7 days) with unsafe behaviours such as risky motor vehicle use, violence, unsafe sex, binge drinking, smoking and disordered eating. Measures of mental health were also negatively impacted (for example depressive symptoms, $p < 0.001$) but body-mass index was unaffected by increasing ED consumption ($p < 0.26$). Once again, this study, although reasonably large was cross sectional, self-reported and may have been influenced by the drop-out rate of 32%

Effects on sleep

48. Aepli *et al* (2015) found that adolescents and children (aged 10 to 16.9 years) consuming caffeine at a mean of 2.5 mg/kg bw/day showed a significant ($p<0.05$) reduction in electrical slow-wave brain activity in the first two hours of sleep, associated with deep NREM sleep, compared with controls (consuming caffeine at 0.1 mg/kg bw/day). This effect was not significant during the last two hours of sleep. This effect was associated with later bedtimes and poorer overall sleep quality.

49. Sampassa-Kanyinga *et al* (2018) found a significant reduction in sleep duration in ED-consuming students in middle-school (13 -15 years old), $p<0.016$, and high-school (16-18 years old), $p<0.001$. The effect was significant when the data were adjusted for age, sex, ethnic background, subjective socioeconomic group, substance use, physical activity and BMI z-score, but not when unadjusted. The authors recognised that the study had limitations in that it was cross sectional, which did not allow causal inferences to be drawn, self-reported and thus subject to personal bias, missed out the 8% of students in private or alternative schools and without parental supervision, leading to possible non-responders and confounding factors such as abuse of other substances.

50. Conversely, Patte *et al* (2018) found no longitudinal effect on sleep duration in grade 9 to 12 school students (aged 15 to 18) following an increase in caffeine intake by a change in consumption of EDs from < 3 days per week to 3+ days per week. Positive associations were found for cyber bullying, screen time and homework time. The effect of other substance use (alcohol, tobacco and cannabis) was inconsistent.

51. Galland *et al* (2017) surveyed the sleep hygiene practices and sleep quality of 692 New Zealand adolescents, aged 16 to 17 years, including their consumption of EDs and other caffeinated beverages. EDs were consumed in relatively small amounts after the evening meal compared with other beverages, especially tea, coffee and Coco Cola. In general, boys drank more EDs and girls drank more of the other beverages. Evening caffeine consumption from any source did not affect sleep quality but did lead to increased odds of poor daytime functioning, as evaluated by the Pittsburgh Sleep Quality Index.

52. Carskadon and Tarokh (2014) reviewed the current knowledge of the physiology of sleep regulation and the changes in sleeping patterns in adolescents.

Intrinsic changes in sleeping patterns are at odds with the requirements of the school day, leading to shorter sleeping times and greater consumption of caffeinated beverages to stave off day-time sleep.

Adverse effects of EDs.

53. A number of reviews were picked up in the PubMed search that covered the health effects of EDs on children and adolescents: Seifert *et al* (2011), Owens *et al* (2014), Arria *et al* (2014), Alhyas *et al* (2015). Harris (2015), Visram *et al* (2015), Richards and Smith (2016a), Al-Shaar *et al* (2017), Temple *et al* (2017), De Sanctis *et al* (2017).

54. The general conclusions from all of these reviews are that the consumption of EDs by adolescents has been and is a growing problem on which little research had and has been performed to address. Most research that has been performed has taken the form of cross-sectional studies and self-completed questionnaires which leave the final analysis unable to ascribe causation and are subject to user bias.

55. The United States National Poisons Data System receives telephoned information from the public on cases of toxicity from ED consumption by children, adolescents and adults. In 2010 – 2011, the incidence of moderate – major adverse effects related to energy drinks was 15.2% of reports for EDs and 39.3% for alcoholic energy drinks. (Seifert *et al* (2013)). The total number of cases reported per month for EDs rose from just over 60 in October 2010 to around 170 in March 2011 and then fluctuated between 100 and 150 per month. Calls related to co-consumption with alcohol rose from <20 in October 2010 to Just >40 in November 2010, when a ban on the sale of pre-mixed alcoholic EDs came into force, and thereafter decline to 20/ month and fewer. Around half of the reported cases involved unintentional exposures by children < 6 years old.

56. Kristjansson *et al* (2014) found a dose-response relationship between ED consumption in Icelandic children aged 10 – 12 years for ED consumption (none – <1 per day – 1+ per day) and the prevalence of headaches, stomach aches, sleeping problems and low appetite. This study used a well-established protocol and questionnaire, with a 90% completion rate. However, it was cross-sectional, which did not allow cause and effect to be attributed, relied on two questions, without any biochemical tests, to verify caffeine intake and did not include measurements of the respondents' body mass index or sugar consumption, which could confound findings.

57. Schwartz *et al* (2015) found that ED consumption in middle school students was more prevalent in males than females and among black and Hispanic students than white. ED consumption was associated with a greater risk of hyperactivity / inattention at school ($p<0.004$). Sweetened beverage consumption in general, which included EDs, was also significantly associated with the end-point of the study ($p< 0.006$). This study provides data on young age ethnic and socioeconomic factors and type of beverage consumption but is cross-sectional, self-reported and gave no indication of the psychological drivers of consumption.

58. Park *et al* (2016) studied the effects of EDs on sleep, stress and suicidality in 68,043 Korean adolescents (aged 12 – 18 years). ED consumption was significantly positively associated in a dose related manner with sleep dissatisfaction, depressive mood, and with thinking of, planning and attempting suicide. Consumption of junk food (i. e. processed food high in sugar and/or fat) also correlated with ED drinking and appeared to exacerbate the adverse effects arising from it.

59. Richards and Smith (2016b) performed cross-sectional and longitudinal studies on the effects of caffeine consumption from EDs as well as other beverages on the health of English secondary school students (12 – 16 years old). Surveys were conducted at two time-points 6 months apart. Data on demographics, diet, emotional state and total caffeine consumption were collected. At both the earlier (T1) and later (T2) time points, adverse effects on health were seen in high level (>1000 mg/week) caffeine consumers until the data were controlled for dietary, demographic and lifestyle factors, when although the effects at T2 remained, those at T1 disappeared. The surveys used the term “general health” which may have been misinterpreted by some of the respondents, 6 months may not have been an adequate time-gap and the distribution of questionnaires at the two time-points may have been uneven. These factors may have confounded the results.

60. Kim *et al* (2017) also investigated relationships between stress, lack of sleep, low school performance and ED consumption with suicide attempts of over 120,000 Korean adolescents (aged 13 – 18 years) All of the above conditions were positively related to suicide attempts. Correcting for the stress, sleep and performance factors revealed frequent ED consumption to be positively associated with suicidality on its own. The authors suggested that consumption of EDs could exacerbate the other factors. Once more, causality could not be shown and the study, and the input relied on self-assessment.

61. Bashir *et al* (2016) reported on data from 612 questionnaires completed by adolescents aged 12 to 18 years regarding consumption of EDs and subsequent subjective experiences. Respondents recorded experiencing frequent headaches, feelings of anger, difficulty breathing, feeling weak, sleep disturbance and increased urination. This study was limited by the self-assessment nature of the data, the small size of the sample (that was also split between two locations) and being uncontrolled for the use of alcohol, tobacco and other caffeinated beverage consumption that may have modified the reported responses.

62. Hammond *et al* (2018) performed a survey of the adverse effects of caffeinated EDs on adolescents from 12 – 17 years and young adults from 18 – 24 years. Of 2058 respondents, 73.8% reported having consumed an ED, of whom 55.4% reported having had at least one adverse event (including fast heartbeat, difficulty sleeping and headache), 3.1% of ED consumers had sought or considered seeking medical assistance for the event. Of coffee drinkers, 36% had had an adverse event, of whom 1.4% had sought or considered seeking medical assistance for the event.

63. Van Batenburg-Eddes *et al* (2014) observed a potentially adverse effect of EDs on executive functions – behavioural self-reflection and control - that develop

from the maturation of the prefrontal cortex of the brain, an area undergoing active development during adolescence. Self-estimation from psychological testing and parental estimation of behavioural problems were used in this study. Once again it was recognised that this study was limited by consumption being self-reported, small in group size (564 Dutch subjects aged 11 – 16 years, of whom 244 were females) and being cross-sectional in nature. It was recognised that pre-existing executive function deficiencies may have led to ED consumption and not vice versa.

64. Jain *et al* (2012) looked at the effect of a range of sports drinks and EDs on enamel dissolution. Samples of enamel taken from extracted teeth were weighed before being soaked in either a sport drink or ED for 15 minutes, followed by two hours of soaking in artificial saliva. This was repeated 4 times per day for 5 days and then the samples were dried and weighed again. Weight loss was significantly greater with EDs than with sports drinks. The titratable acidity of a drink was directly related to the weight loss in the samples: the higher the titratable acidity, the greater the weight loss. EDs had 3 – 4 times the level of titratable acidity than sports drinks, though all of the beverages had a pH low enough to lead to enamel demineralisation (< pH 5.5: pH of drinks was about 3).

65. In a letter to the editor of the Journal of Hepatology, Robin *et al* 2018) highlight the case of a 17-year old boy who admitted consuming up to six 500 ml cans of an ED per day and presented with non-alcoholic steatohepatitis (NASH). The authors referred to the work of Harb *et al* (2016) and Vivekanandarajah *et al* (2011) and postulated that, in addition to high levels of fructose (from the sucrose in the ED), the presence of high levels of niacin (vitamin B3, nicotinamide), could contribute to this toxic effect. When the boy lost weight, stopped consuming EDs, his blood ALT level fell from 274 U/l to 66 U/l seven months after his first referral.

Cardiovascular effects

66. A small number of recent case studies in adolescents have implied the involvement of ED consumption in their aetiology.

67. Usain and Jawaid (2012) described the case of a 16-year-old boy with a previously normal blood pressure presenting with readings of 140 – 160/ 80 – 100 mm Hg. He had drunk approximately 3 cans of the ED “Sting” per day for 2 weeks. He was advised to abstain from ED use and his symptoms resolved within 2 weeks.

68. Di Rocco *et al* (2013) described cases of atrial fibrillation in two boys aged 14 and 16 following ingestion of EDs. In the first case, the boy, aged 14, presented with an irregular heartbeat of around 130 beats per minute (bpm) two hours after a running race. He had consumed an unknown quantity of a highly caffeinated beverage the day before and a can of “Red Bull” five days earlier that had been accompanied by a “fluttering sensation” in his chest. A dose of 7.5 μg/kg bw of digoxin returned his heart to normal sinus rhythm and 70 – 80 bpm and one month later he had a normal ECG. The second patient had drunk an unknown quantity of “Red Bull” mixed with vodka and presented with a heart rate of 160 bpm and chaotic atrial tachycardia/ fibrillation. He was given 2 litres of normal saline and his heart rate

fell immediately and then reverted spontaneously to normal sinus rhythm 12 hours later.

69. Polat *et al* (2013) described the case of a 13-year-old boy who suffered acute onset "crushing" mid-sternal chest pain 8 hours after consuming an ED for the first time. Coronary angiography revealed extensive dissection of the left descending coronary artery, characterised by a separation of the layers of the artery wall, a rare condition carrying the risk of acute coronary syndrome and sudden cardiac death. The symptoms subsided after treatment with aspirin, enoxaparin (an anticoagulant), nitroglycerine, enalapril (an angiotensin converting enzyme inhibitor) and metoprolol (a β_1 noradrenaline receptor antagonist) and a month later, left ventricular function was normal.

70. Samanta (2015) reported a case of reversible cerebral vasoconstriction syndrome in a 16-year-old boy who had consumed 4 cans of an ED (total caffeine intake 320 mg) four hours earlier. MRI scans showed intermittent narrowing of the anterior, middle and posterior cerebral arteries, leading to the symptoms of thunderclap headache, vomiting, left leg numbness and gait difficulty. The patient was given analgesics and antiemetics followed by verapamil (an L-type calcium channel inhibitor) and was discharged with a warning to avoid EDs and caffeine. When scanned again 6 months later his cerebral arteries were normal.

Consumption of EDs relative to other substances

71. Several reports deal with co-consumption of EDs with other psychoactive substances, notably alcohol. Several reports consider the influence of this mixed consumption on "risky" behaviours such as drink driving and unsafe sex. Gallimberti *et al* (2015) suggest that energy drinks should be regulated in early adolescents since they provide a route into the taking of risks with other substances such as alcohol, tobacco and marijuana that act as gateways to the use of more damaging drugs.

72. Reid *et al* (2015) collected longitudinal data from a cohort of Ontario secondary school pupils aged 15 – 18 years relating to their ED consumption and their use of these products concurrently with alcoholic beverages. Overall, 17.5% of the sample (4016 respondents) reported using EDs with alcohol in the previous 12 months. 71.6% reported never doing this, 6.4% said they had not done this in the previous 12 months and 3.7% said that they did not know.

73. Miyake and Marmorstein (2015) found a positive relationship between high ED consumption by young New Jersey adolescents, 12 – 13 years old, (who consumed at least one ED per week) and alcohol consumption 16 months later, that was not seen with coffee or other soft drink consumption. The most probable cause for this finding was held to be lack of parental monitoring of the consumption of both types of beverage. Earlier alcohol use was not associated with later alcohol use.

74. Kponee *et al* (2014) found in a survey of adolescents from Boston, Mass. USA that those who consumed "caffeinate alcoholic drinks", either alcohol mixed with soft drinks, tea or coffee ("traditional CABs") or alcohol mixed with EDs , energy

shots or energy pills "(non-traditional CABs"), consumed more alcohol per month ($p<0.05$) and were more prone than non-consumers to engage in binge drinking ($p<0.05$).Consumers of "non-traditional CABs" were also more likely to engage in fighting and acquire alcohol-related injuries that required medical treatment. However, while the percentage of adolescents surveyed consuming any CAB was 52,4%, those using EDs, energy shots and caffeine pills totalled15.4%.

75. Scalese *et al* (2017) found that while mixing EDs with alcohol increased the probability of Italian adolescents to indulge in a wide range of risky behaviours such as binge drinking, cannabis and other drug use, unsafe sex, and fighting, the differences between the response to EDs alone and alcohol-plus-EDs were small. Perceived reduction in alcohol sedation was a motive for mixing it with EDs. The authors felt that education and changes in marketing were required to address the observed behavioural effects.

76. Vieno *et al* (2018) found that of 13.725 Italian adolescents, aged 15 – 19 years, 4495 reported gambling in the previous year, of whom 62.5% were male. Of the gamblers, 5.1% reported drinking alcohol-mixed EDs (AmEDs) 6 times or more that month. 43% of these were classified as at-risk and problem gamblers (ARPG), compared with 23.6% of 6-times or-more-alcohol-alone consumers. AmED consumers were 3 times more likely to be ARPG than non-consuming adolescents.

77. ED use has also been found to be associated with smoking and drug use (Mann *et al*, 2016, Terry-McElrath *et al* 2014, Polak *et al* 2016, Everen & Everen 2015.)

78. Williams *et all* (2017) found that recent (i.e. within the previous 7 days) consumers of energy drinks among 1570 teenagers were more likely to eat fried and high-sugar foods than those who had not consumed the drinks (foods such as cake, $p<0.011$; sugary cereal ($p<0.001$: or fried chicken, $p<0.001$).

Reported beneficial effects of EDs

79. Seidl *et al* 2000 found that consumption of Red Bull by graduate students maintained feelings of well-being, vitality and social extravertedness for longer than was seen with a placebo control. Since half of the subjects were non-caffeine-users, the observed effect was not attributed to recovery from caffeine withdrawal.

80. Alford *et al* (2001) also found beneficial effects relative to control drinks. Red Bull consumption increased significantly ($p < 0.05$) aerobic endurance and performance of subjects on cycle ergometers, as well as reaction time, concentration and memory.

81. Smit *et al* (2004) found that EDs maintained arousal compared with a sensory-matched placebo and that caffeine was mainly responsible for this effect, with a very minor contribution from the carbohydrate content of the drink. This effect was at least partially attributed to caffeine "withdrawal reversal". The effect of

carbonation on mood was variable but in some cases was consistent with reducing the uptake of caffeine and / or carbohydrates.

82. Abian-Vicen *et al* (2014) tested the effects of an ED on the physical performance of adolescent basketball players and found a small but significant ($p < 0.05$) increase in jump height 60 minutes after ingestion, but not in basketball shooting precision.

83. Prins *et al* (2014) found that ingesting Red Bull 60 minutes before completing a 5-km time trial on a treadmill led to a small but significant ($p = 0.016$) improvement in running performance in a group of 18 late teens and early adults. Subjects' rating of perceived exertion and mood were not altered by the ED.

84. Conversely, Jeffries *et al* (2017) found that ingestion of a gelatine capsule containing 80 mg caffeine and 1 g taurine, equivalent to many EDs, did not improve repeat-sprint cycling performance in a group of 11 male young adults. Greater fatigue appeared to be induced to ne induced within sprints and at the end of the trial, without affecting perceived exertion but with increased heart rate and blood lactate concentration.

Expert opinions

EFSA Caffeine

85. In 2015, EFSA stated that "Single doses of caffeine up to 200 mg (about 3 mg/kg bw for a 70-kg adult) do not give rise to safety concerns. The same amount does not give rise to safety concerns when consumed < 2 hours prior to intense physical exercise under normal environmental conditions... Habitual caffeine consumption up to 400 mg per day does not give rise to safety concerns for non-pregnant adults. Habitual caffeine consumption up to 200 mg per day by pregnant women does not give rise to safety concerns for the fetus. Single doses of caffeine and habitual caffeine intakes up to 200 mg consumed by lactating women do not give rise to safety concerns for breastfed infants. The Panel considers that caffeine intakes of no concern derived for acute caffeine consumption by adults (3 mg/kg bw per day) may serve as a basis to derive single doses of caffeine and daily caffeine intakes of no concern for these population subgroups."

86. In 1999 the SCF stated: "*For children who do not normally consume much tea or coffee and who might substitute "energy" drinks for cola or other soft drinks, consumption of "energy" drinks might represent an increase in daily caffeine exposure compared with their previous intake. …consumption of 160 mg caffeine/day from 0.5l of "energy drink would be equivalent to 5.3 mg/kg bw/day for a 10-year-old, 30 kg child. This could result in transient behavioural changes, such as increased arousal, irritability, nervousness or anxiety."*

87. EFSA (2011) collated the daily consumption of caffeine from EDs from different dietary surveys across the surveyed population in each study and across ED consumers in the same study. Across the whole sample, the group that

consumed the most caffeine from EDs was that of adolescents, aged from 10 to < 18 years (means from 0.0 to 5.7 mg/day and 95th percentile from 0.0 to 40.0 mg/day). Across ED consumers, The mean intake of caffeine by adolescents ranged from 29.0 – 90.1 mg/day and 95th percentile of 145.6 mg/day. 41% of adolescent ED consumers drank them in relation to sport.

88. The highest contribution to caffeine intake from EDs was from the UK (11%), followed by the Netherlands (8.1%) and Belgium (5.3%)

EFSA taurine and D-glucurono-γ-lactone

89. The SCF (1999) concluded that *"Toxicological studies did not reveal any indication for a genotoxic, carcinogenic or teratogenic potential of taurine. However, there is no adequate study on chronic toxicity/carcinogenicity. Investigation of subacute/subchronic toxicity has also been fragmentary. Overall, the available data are insufficient to establish an upper safe level for daily intake of taurine."* https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_scf_out22_en.pdf

90. In 2003 the SCF stated: "…*the potential for interactions between caffeine and taurine has not ruled out the possibility of stimulatory effects from both substances at the level of the central nervous system. At the cardiovascular level, if there are any interactions between caffeine and taurine, taurine might reduce the cardiovascular effects of caffeine. The main area for likely additive interactions is in the diuretic actions of caffeine and taurine, which could be further enhanced by ingestion of alcohol."*

91. The EFSA statement on the use of taurine and D-glucurono-γ-lactone as constituents of EDs (2009) concluded that since these compounds are both natural constituents of the human body and that the NOAEL for any adverse effects for both compounds is 2 orders of magnitude above their mean exposure in ED consumers, their presence in EDs would not be a concern for health.

92. EFSA (2015) stated Other constituents of "energy drinks" at typical concentrations in such beverages (about 300–320, 4 000 and 2 400 mg/L of caffeine, taurine and D-glucurono-γ-lactone, respectively), as well as alcohol at doses up to about 0.65 g/kg bw, would not affect the safety of single doses of caffeine up to 200 mg

93. Interactions of taurine with caffeine with regard to the diuretic effect of EDs were regarded as unlikely but other potential interactions between these compounds were not investigated.

94. It was held unlikely that D-glucurono-γ-lactone would interact with caffeine, taurine, alcohol or physical exercise.

COT

95. In their Statement on the interaction of caffeine with alcohol and their combined effects on health and behaviour (2012), the COT concluded that the available evidence did not show conclusively that the two drugs interact with one another in a toxicological or behavioural manner. Evidence that caffeine ameliorated the intoxicating effects of alcohol was found to be inconsistent, and it was uncertain whether reports of increased alcohol and caffeine consumption represented a psychological interaction or the fact that such co-consumers were predisposed to consume mixtures of psychoactive agents in general.

BfR

96. The BfR conducted a survey in Germany on the consumption of EDs by 7460 people, of which 8% or 508, fulfilled the consumption criteria and completed the interview. Forty five percent, 3063 people who were initially approached, had never had an ED. Several social scenarios were highlighted as situations for ED consumption and for 15 – 20-year-old subjects, music festivals and discos/dancing/parties were the main events. Taste and energy-boosting properties were given as the main incentives to drink EDs.

Conclusions

97. Energy drinks contain variable amounts of caffeine as their main active constituent; the pharmacological and toxicological effects of other non-caffeine constituents are unclear.

98. The effects of caffeine consumption appear to be modified by dose, genetics, tolerance, withdrawal symptoms, expectations and social situations.

99. Any beneficial effects of consuming energy drinks appear to be limited.

100. Children and adolescents have until recently had full access to energy drinks but new voluntary restrictions by food retailers should limit this. Taste of these products is a common driver for consumption but overall, drinking energy drinks is influenced by various, sometimes conflicting, factors including perceived stimulation, availability, warnings on packaging, advertising, peer pressure and parental influence. Most surveys suggest that boys consume a greater volume of energy drinks than do girls.

101. Use of energy drinks have been related to adverse effects including poor sleep, reduced school performance and acute physical effects probably related to excess caffeine consumption. Energy drinks are also consumed mixed with alcohol, which may lead to exacerbation of “risky” behaviours.

102. Most studies on the toxicological effects of energy drink consumption are cross sectional and involve self-reported questionnaires from which cause and effect cannot be determined and which are prone to subjective bias.

103. Some children and adolescents are aware that energy drinks can cause adverse health effects, whereas others are not.

104. Overall the consumption of energy drinks by children and adolescents is a complex social issue as well as a potential health issue and while the effects of acute consumption have been documented, chronic effects and any potential lasting effects from being consumed while brain development is still ongoing are still unknown.

105. This paper has concentrated on the effects of the use and abuse of energy drinks in adolescents, because this group has been the focus of recent interest in the media, although some overlap into mainly young adults has been unavoidable. If required, the scope could be widened to cover ED consumers of any age.

Questions for the Committee

1 Does the Committee agree with the summary of the available evidence drawn above?

2 Does the Committee consider that the studies outlined in this paper provide robust evidence that children and adolescents may be more susceptible to the combined effects sugar and caffeine from energy drinks than previously considered?

3 Does the Committee consider there are particular adverse physiological and behavioural effects from the consumption of energy drinks by children and adolescents?

4 Does the Committee consider that the safe level established by EFSA in its 2015 review remains valid for children and adolescents?

5 Do Members consider that the uncertainties in the evidence base are too great for robust conclusions and, if so, what suggestions would they make regarding research to reduce these uncertainties and what would be the priorities for future work?

6 What further considerations do the Committee have regarding the consumption of energy drinks by adolescents and children?

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Literature search terms

Energy drinks AND adolescents AND toxicity
health
consumption
components
alcohol
drugs
behaviour