Saudi Food and Drug Authority

Drug Sector

Review of Energy Drinks

Prepared By:

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June 2014

1. REQUEST:

[redacted] was requested by the [redacted] to prepare a concise review for Energy Drinks (EDs). The [redacted], thus, aimed to focus on three core objectives for this review, as follows:

- To provide an introduction and define products known as EDs.
- To provide a regulatory background of EDs.
- To discuss the potential health risk associated with common ingredients found in EDs.

2. RESPONSE:

Executive Summary:

Energy drinks (EDs) promote mental and physical stimulation for a short period of time. The three most common ingredients are caffeine, taurine, and glucuronolactone. When too many are consumed or when they are mixed with alcohol, problems can occur. Though individuals may drink EDs to remain energetic during periods of intense physical activity or to quench their thirst, these drinks may actually lead to dehydration. The regulatory status of EDs is still unclear; in many jurisdictions, the products are regulated as food products, though claims of their physiological benefits, such as mental stimulation, would indicate that they be regulated as drugs. Some of the constituents of these products, such as caffeine, have no recommended daily dietary allowances. It is impossible to analyze these products using a risk versus benefit assessment because they do not fulfill any therapeutic or dietary requirements. Likewise, an assessment of the long-term effects of EDs is impossible because testing the safety and efficacy of these products for any length of time is not feasible.

Introduction:

Components (i.e. Ingredients) of Energy Drinks:

Generally, EDs include methylxanthines (such as caffeine), B vitamins, and herbs. Other common ingredients are guarana, which has a high caffeine content, taurine, various forms of ginseng, maltodextrin, carbonated water, inositol, carnitine, creatine, glucuronolactone, and Ginkgo biloba. Some contain high levels of sugar, and many brands offer artificially sweetened diet versions. The central ingredient in most energy drinks is caffeine, the same stimulant found in coffee and tea, often in the form of guarana or yerba mate.

Table 1 illustrates the information based on the GCC standardization organization (GSO), number 1926/2009 for requirements of the most commonly EDs available in Saudi Market, such as: POWER HORSE, RED BULL, BISON ENERGY DRINK.

Ingredients	Maximum permitted per 100ml
Caffien الكافيين	32 mg
inositol انيستول	20 mg
Glucuronolactone جلوكورونلاكتون	240 mg
Taurine تاورين	400 mg

Table 2 & 3 demonstrate the content of caffeine in kola-type beverage as well as Coffee and Tea Beverages

Table 2: Comparison of the caffeine content in Kola-type beverages

Kola-type beverages	Caffeine content (mg/100ml)
Coke Zero%	9.5
Coca Cola#	9.0
Mountain Dew(NZ)^	13.5
Mountain Dew(Aus)^	15.0
Pepsi%^	10.7
Pepsi Max%^	12.0

Table 3: Comparison of the caffeine content in coffee and tea beverages

Coffee and Tea Beverages	Caffeine content (mg/100ml)
Tea, black, brewed#	22.5
Tea, green, brewed#	12.1
Coffee, cappuccino, double shot, 285ml takeaway cup, café variety#	101.9
Coffee, flat white, double shot, 285ml takeaway cup, café variety#	86.9
Coffee, longblack, double shot, 285ml takeaway cup, café variety#	74.7
Coffee, mocchaccino, double shot, 300ml takeaway cup, café variety#	97.4
Coffee, from ground coffee beans, espresso style@	194.0

Source: Table 2 & 3 adapted from Food regulation policy options paper. The regulation of caffeine in foods, Augest 2013 available at:
https://www.health.gov.au/internet/main/publishing.nsf/Content/A294B740C7928C3CCA257BF0001CFFF4/$File/The%20Regulation%20of%20Caffeine%20in%20Foods.docx- accessed on 02-06-14.

Potential for Interaction between ingredients of Energy Drinks:

There are extensive data on the toxicokinetics of caffeine and taurine but less information on glucuronolactone. Consideration of the chemical nature of the three parent compounds and their metabolites, and the fact that differing processes are involved in their absorption, distribution, metabolism and excretion did not, in the experts view, raise any a priori reasons to expect any toxicokinetic interactions, even at high intakes of any one constituent. The physiological handling and lack of toxicological effects of glucuronolactone did not, in the experts view, raise any a priori reasons to expect toxicodynamic interactions from this constituent. Caffeine and taurine, on the other hand, each affect the functioning of the central nervous system, kidneys and heart, thus there is a need to consider the potential for toxicodynamic interactions between these two constituents.

Caffeine is a central nervous system stimulant whereas taurine generally act as an inhibitory neuromodulator. Caffeine exerts stimulatory effects by blocking the inhibitory action of adenosine at its binding sites, with subsequent increases in the levels in some brain regions of several neurotransmitters, including adrenaline, noradrenaline, tryptophan and dopamine. It also modulates the effects of GABA and serotonin.

Taurine, on the other hand, depresses the activity of excitable membranes in the brain. Centrally, taurine acts as an agonist of the more sedating glycine receptors and inhibits the more excitatory actions of NMDA receptors and glycine neurotransmitter function. It therefore could modulate the excitatory actions of some other amino acids. While these data may appear to indicate that if there were any interactions, taurine might reduce caffeine-mediated excitation. Taurine is found naturally in meat, fish and breast milk, and it's commonly available as a dietary supplement. It is promoted to enhance athletic and mental performance.

Both caffeine and taurine can have short-term diuretic actions, causing loss of body water and sodium. Taurine acts via inhibition of central release of the anti-diuretic hormone, vasopressin. Caffeine does not inhibit vasopressin release but has a direct action on kidney tubule functions, such as ionic reabsorption and renal perfusion, probably via adenosine receptor blockade.

A high dose of taurine in the drinking water, equivalent to about 1500 mg/kg body weight, was required to elicit diuresis and natriuresis in rats, whereas 1g or more intravenously over 15 minutes (about 15 mg/kg body weight) was sufficient in sensitive humans with liver cirrhosis and ascites. Bearing in mind that taurine is rapidly absorbed across the gut via an active transport mechanism, the diuretic effects in normal subjects with an acute consumption of 750 ml of energy drink containing 3g of taurine are difficult to predict.

Caffeine can increase heart rate, force of contraction of heart muscle and blood pressure. Taurine, on the other hand, depresses the activity of excitable membranes in the heart. Caffeine enhances catecholamine synthesis and release from adrenal cells in vitro, probably related to its effects on intracellular calcium. Numerous in vivo studies have shown oral caffeine at doses of 6 mg/kg body weight or more increases plasma catecholamine concentrations, especially adrenaline, in a dose-related manner during exercise, though one study giving 8.8 mg/kg in an energy drink found no increase. The acute consumption estimate for energy drinks of 750 ml is equivalent to a caffeine intake of 4 mg/kg body weight for a 60 kg adult.

There is no evidence that taurine increases catecholamine release; if anything it has an inhibitory effect on excessive sympathetic activity in rat models of hypertension, with reduction of plasma catecholamines . Neither does taurine given alone have any effect on heart rate or blood pressure in rats or humans. Both taurine and caffeine influence the activity of angiotensin II, an endogenously formed substance that raises arterial blood pressure and reduces the excretion of sodium and water by the kidney, but their action on angiotensin II is in opposite directions. In vivo caffeine augments the action of angiotensin II on the kidney and may raise plasma renin levels, whereas taurine attenuates the effects of circulating angiotensin II.

Human metabolic considerations indicate the body is likely to handle small quantities of glucuronolactone without any problems. However, the intake of glucuronolactone from consumption of some energy drinks is possibly as much as two orders of magnitude greater than that from the rest of the diet. There is very little information available for risk assessment of glucuronolactone at such intakes. While there is no indication from the available data that there is any risk to health from consumption of high amounts of glucuronolactone, there is a lack of scientific evidence to support the safety of glucuronolactone present in beverages at concentrations that may result in intakes as much as two orders of magnitude greater than that obtained from the rest of the diet. [1,2,3]

International regulatory status of EDs: [4,5,6]

US-FDA

The US Food and Drug Administration (FDA; 2003) code of federal regulations, number 21CFR182.1180, describes caffeine as being generally recognized as safe (GRAS) when used in cola drinks at 0.02%, or 71 mg for a 12 oz soft drink. However, this regulation does not apply to EDs. In the US, the amount of caffeine ED companies can include in their beverages is unlimited because the FDA has set no restrictions regarding this.

Health Canada

Health Canada recognizes EDs as food but has set safety requirements regarding their composition and labeling:

- *Composition Requirements*

Specific requirements will be established to better control the types and levels of ingredients added to EDs. These requirements include, for example, setting minimum and maximum limits for caffeine from all sources (natural and synthetic sources), vitamins and minerals as well as other ingredients e.g. herbal extracts.

Specific to caffeine, Health Canada's scientific assessment supports the establishment of an initial maximum limit for total caffeine of **400 mg per liter** with a maximum amount of caffeine not to exceed **180 mg per container presented as a single-serve container**. Health Canada has determined that any Energy Drink container that cannot be resealed will be treated as a single-serve container. Health Canada has determined that re-sealable containers equal to or less than 591 mL will be treated as single-serve containers.

- *Labeling Requirements*

- The amount of caffeine from all sources in mg per container or serving size.
- A statement on the label identifying the product as a "high source of caffeine" given that a ED will be required to contain a minimum amount of caffeine that is deemed to be sufficiently high.
- A statement indicating that the product is "Not recommended for children, pregnant or breastfeeding women, and individuals sensitive to caffeine"
- The statement "Do not mix with alcohol"

European Union

In the European Union the use of caffeine as flavoring in foods has to be clearly indicated on the label. Commission Directive 2002/67/EC provides for consumers to be given clear and precise information on the presence of caffeine in a foodstuff. Caffeine must be mentioned by name in the list of ingredients immediately after the term "flavoring".
Beverages that contain a proportion of more than 150 mg of caffeine per liter must be labeled „High caffeine content", followed by the quantity of caffeine expressed in milligrams per 100mL. This wording must appear in the same field of vision as the name of the drink. These labeling requirements do not apply to products sold as "tea" and "coffee".

In the European Union, there is a requirement to label EDs on the basis of informing consumers about high levels of caffeine present in foods and soft drinks that would not normally contain caffeine. A beverage that contains caffeine in excess of 150 mg/L must place the following message on its label directly under where the product name is stated: "High caffeine content". This message must then be followed in brackets by the caffeine content expressed in mg/100 ml.

The caffeine level of 150 mg/L is used in the EU as the regulatory differentiator between energy drinks and other beverages. For other beverages caffeine is permitted as a flavoring agent up to 150 mg/L. When used in this way, caffeine must be mentioned by name in the list of ingredients immediately after the word "flavoring". There is, however, no requirement for quantification of the caffeine present in the foodstuff.

Energy shots are addressed separately in the EU through Commission Directive 2002/46/EC, which governs food supplements. Under this Directive, food supplements may contain a wide range of nutrients and other ingredients including vitamins, minerals, various plants and herbal extracts. Whilst caffeine cannot be added in its chemical form, guarana and other herbal sources of caffeine could be included. There are specific labeling requirements, including the names and quantities of substances (including quantity per portion), which characterize: the product; daily recommended doses and warnings against exceeding that dose; and that the products should be stored out of the reach of children. This Directive notes that specific rules regarding other substances with nutritional or physiological effects should be laid down at a later stage.

Meanwhile, EU member states can institute their own national legislation where they consider it is in the public health and safety interests of their population. With regard to energy drinks this has been exemplified by the setting of upper caffeine levels (e.g. Denmark and France), reported „banning" of energy drinks, or additional labeling requirements (e.g. Finland).

In February 2013, the European Commission made a request to conduct a scientific opinion on the safety of caffeine. Concern was raised by several Member States that consumption of caffeine may be encouraged following the favorable evaluation of caffeine-related health claims on sports performance. The European Commission has therefore asked EFSA to review the available data with a view to determining intake levels which would pose no safety concern for the main population sub-groups". The work requested is an extensive literature search and review as part of a safety assessment for caffeine. It is proposed that this work will commence in March 2013 and take a period of six months. The deadline for completion of the scientific opinion has not yet been determined (European Food Safety Authority, 2013).

Ireland

A review of the health effects of stimulating drinks was undertaken by safe-food, a British-Irish food safety agency. The subsequent report made a number of recommendations regarding labeling, marketing and promotion, further research needs, and advice for

pregnant women, cautioning consumption by children less than 16 years of age and during sports or exercise.

Other Bodies

Regulations for EDs in other countries are quite varied and include:

- Limits on claims that can be made on the label (e.g. Japan, which limits claims if energy drinks are marketed as foods but not if they have been assessed and categorised as Foods for Specified Health Uses);
- labeling requirements that specify the quantity of caffeine per serving size and per 100 mL (e.g. South Africa); and
- Health warning labels or advisory warning statements regarding the unsuitability of the product for particular population groups (e.g. South Africa, United Arab Emirates, and India).

Safety of EDs:

This section will highlight the most commonly reported adverse events in the medical literature associated with consumption with EDs.

Cardiovascular adverse events:

A recent systematic review by Goldfarb, et al, included 17 published cases of adverse cardiovascular events following ingestion of energy drinks. The following table (Table 4) presents a summary of cases included in the review.

Case	Year (Reference)	Presentation	Age (yrs)/Sex	ED and Co-Ingestions	Caffeine Consumed (mg)	Cardiac Investigations	Cardiac Abnormalities Identified*	Outcome
1	2011[6]	AF	16 M	Red Bull	Unknown	ECG TTE	None	Conversion to SR
2	2011[6]	AF	14 M	Red Bull; vodka	Unknown	ECG TTE	None	Conversion to SR
3	2012[7]	AF	13 M	—	85	ECG TTE	None	Conversion to SR
4	2007[8]	AF	58 M	—	575	ECG TTE Cath	EF 45% $\geq$ 65%	Conversion to SR
5	2008[9]	SVT	23 F	GNC Speed Shot	250	ECG	None	Conversion to SR
6	2012[10]	Prolonged QT	13 F	—	160	ECG EST Gen	LQTS1 (KCNQ1)	QT interval $\downarrow$
7	2012[11]	TdP	22 F	—	480	ECG TTE Cath Gen	LQTS1 (KCNQ1)	Aborted SD
8	2001[12]	VF	25 F	Race Energy Blast	570	ECG Autopsy	MVP	SD
9	2009[13]	VF	28 M	—	640	ECG TTE Cath	EF $\downarrow \geq$ nl	Aborted SD
10	2013 (case 1)	VF	19 M	Monster; marijuana	160	ECG TTE Cath EPS‡	None	Aborted SD
11	2012[14]	VF	24 M	Red Bull; vodka	80	ECG	Brugada type 1	Aborted SD
12	2013 (case 2)	Cardiac arrest†	57 M	NOS	1,300	ECG TTE Cath	LVH with RWMA	Aborted SD
13	2012[15]	VT/SVT	24 M	—	—	ECG TTE Cath MRI	EF $\downarrow \geq$ nl	Conversion to SR
14	2012[16]	ST elevation	17 M	Red Bull, Monster	560–800	ECG TTE Nuc	EF $\downarrow \geq$ nl	Resolution
15	2012[17]	ST elevation	24 M	XL; MDMA	1,600	ECG	None	SD
16	2011[18]	ST elevation	19 M	Red Bull	160–240	ECG TTE Cath	None	Resolution
17	2012[19]	ST elevation	24 M	—; vodka	—	ECG TTE Cath	Acute thrombosis	Emergent CABG

Dash indicates no information was available.

AF = atrial fibrillation; CABG = coronary artery bypass graft; Cath = cardiac catheterization with angiography; ECG = electrocardiogram; EF = ejection fraction; EPS = electrophysiologic study; EST = exercise stress test; F = female; Gen = genetic studies; LQTS1 = long QT syndrome type 1; LV = left ventricle; LVH = left ventricular hypertrophy; M = male; mg = milligrams; MDMA = 3,4-methylenedioxy-N-methamphetamine ("ecstasy"); MVP = mitral valve prolapse; nl = normal; Nuc = nuclear perfusion study; RWMA = regional wall motion abnormalities; SD = sudden death; SR = sinus rhythm; SVT = supraventricular tachycardia; TdP = torsades de pointes; TTE = transthoracic echocardiogram; VF = ventricular fibrillation; VT = ventricular tachycardia.

* Only abnormal results are listed; other available investigations were normal.

† Initial rhythm strip before defibrillation from emergency medical services was not documented.

‡ Provocative testing with procainamide and epinephrine was performed.

involved teenagers and young adults, the largest demographic of ED consumers. Results are

Table 4: adapted from Goldfarb, Tellier, et al. Review of Published Cases of Adverse Cardiovascular Events After Ingestion of Energy Drinks. American Journal of Cardiology 2014; 113:168-172.

in keeping with the recent US Substance Abuse Services and Mental Health Administration report that indicated this is the most common age group to present to the emergency department with symptoms attributed to ED consumption. On the basis of published case series, it cannot be concluded that any specific additive or brand appeared to be more frequently involved. However, it is found that heavy consumption of EDs was implicated in at least 7 cases, and 5 cases were associated with co-ingestion of alcohol or other drugs. Of note, in all 4 reported cases of ST-elevation, the presenting symptom was severe chest pain. It is also reported that 11 cases presented with serious adverse events, including cardiac arrest. Of these serious cases, the majority occurred either with acute heavy consumption of EDs or in combination with alcohol or other drugs.

However, there are several limitations to the review. First, the rates of co-ingestions with EDs may be underestimated because toxicology results were not always reported. Second, although heavy consumption of EDs were temporally associated with these events and in many cases no alternative etiology could be identified, it cannot be excluded that some of these cases are rare spontaneous CV events not directly related to ED consumption. However, it is important to note that these types of spontaneous events are normally exceedingly rare in youth and young adults, who make up a large part our case series.[7]

Energy drink consumption in association with athletic training:

A review article by Higgins, et al, concluded that consuming one can of energy drinks during a single athletic training session is safe for most healthy individuals. However, excess consumption and consumption with other caffeine-containing beverages or alcohol may lead to adverse effects and possibly death. In addition, the review article advised that patients with clinically relevant underlying medical conditions, including heart disease and hypertension, should consult with their physicians before drinking EDs.[8]

Energy drinks consumption plus alcohol:

A recent survey carried out on nearly 22,000 US secondary school students and published in Journal of Addiction Medicine, found that teens who consume EDs were more likely to use alcohol and drugs. [9]

On Nov. 17, 2010, the US FDA announced and warned that mixing or drinking EDs in which contain caffeine, with alcohol may lead to life-threatening behaviors, as caffeine can mask sensory cues. This means that individuals drinking these beverages may consume more alcohol—and become more intoxicated.

REFERENCES:

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