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REVIEW

Caffeinated energy drinks in the Canadian context: health risk assessment with a focus on cardiovascular effects

Sébastien La Vieille, Zoe Gillespie, Yvette Bonvalot, Karima Benkhedda, Nancy Grinberg, Joel Rotstein, Jennifer Barber, and Andrew D. Krahn

Abstract: In Canada, caffeinated energy drinks (CEDs) currently sold under Temporary Marketing Authorizations must meet strict eligibility criteria. These criteria, which include compositional and labelling requirements, were developed based on the outcome of a health risk assessment conducted by Health Canada (HC) in 2013. HC updated its assessment by reviewing new information with the focus on potential cardiovascular effects associated with the consumption of CEDs available for sale in Canada. Due to limited data on CED consumption among Canadians to derive accurate exposure information, the composition of a typical CED was characterized to assess the potential effects of single ingredients and synergistic interactions between ingredients on the cardiovascular system. Surveillance data on potential adverse effects related to CED consumption was also analyzed. After extensive review, HC's updated assessment confirms the current risk management approach for CEDs is health protective for Canadian consumers, including the potential for cardiovascular effects. The available evidence supports that moderate consumption (up to 500 mL per day) of a typical CED authorized for sale in Canada is safe for the general population of healthy adults and adolescents. It also re-confirms that vulnerable sub-populations (i.e., children, pregnant and/or breastfeeding women, and caffeine-sensitive individuals) should not consume CEDs.

Novelty:

- Consumption up to 500 mL per day of a typical CED is not associated with an increased risk of cardiovascular effects.
- Children, pregnant and/or breastfeeding women, and caffeine-sensitive individuals should not consume CEDs.

Key words: energy drinks, caffeine, taurine, cardiovascular system, risk assessment, food safety.

Résumé : Au Canada, les boissons énergisantes contenant de la caféine (« CED ») actuellement vendues en vertu d'autorisations de mise en marché temporaires doivent répondre à des critères d'admissibilité stricts. Ces critères, qui comprennent des exigences en matière de composition et d'étiquetage, sont élaborés en fonction des résultats d'une évaluation des risques pour la santé menée par Santé Canada en 2013. Santé Canada a mis à jour son évaluation par l'examen de nouvelles informations en mettant l'accent sur les effets cardiovasculaires potentiels associés à la consommation de CED en vente au Canada. En raison du peu de données sur la consommation de CED chez les Canadiens pour obtenir des informations précises sur l'exposition, la composition d'une CED typique est caractérisée pour évaluer les effets potentiels d'ingrédients uniques et les interactions synergiques entre les ingrédients sur le système cardiovasculaire. Les données de monitorage des effets indésirables potentiels liés à la consommation de CED sont aussi analysées. Après un examen approfondi, l'évaluation mise à jour par Santé Canada confirme que l'approche actuelle de gestion des risques pour les CED protège la santé des consommateurs canadiens, y compris les effets cardiovasculaires potentiels. Les données probantes disponibles soutiennent qu'une consommation modérée (jusqu'à 500 mL par jour) d'une CED typique autorisée pour la vente au Canada est sans danger pour la population générale d'adultes et d'adolescents en bonne santé. Ces mêmes données confirment également à nouveau que les sous-populations vulnérables (c.-à-d. les enfants, les femmes enceintes et/ou allaitantes et les personnes sensibles à la caféine) ne devraient pas consommer de CED. [Traduit par la Rédaction]

Les nouveautés :

- La consommation jusqu'à 500 mL par jour d'une CED typique n'est pas associée à un risque accru d'effets cardiovasculaires.
- Les enfants, les femmes enceintes et/ou allaitantes et les personnes sensibles à la caféine ne devraient pas consommer de CED.

Mots-clés : boissons énergisantes, caféine, taurine, système cardiovasculaire, évaluation des risques, sécurité alimentaire.

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S. La Vieille, Z. Gillespie, and J. Rotstein. Bureau of Chemical Safety, Food Directorate, Health Canada, Ottawa, ON, Canada.
Y. Bonvalot. Biostatistics and Modelling Division, Bureau of Food Surveillance and Science Integration, Food Directorate, Health Canada, Ottawa, ON, Canada.
K. Benkhedda, N. Grinberg, and J. Barber. Bureau of Nutritional Sciences, Food Directorate, Health Canada, Ottawa, ON, Canada.
A.D. Krahn. Center for Cardiovascular Innovation, Division of Cardiology, The University of British Columbia, Vancouver, BC, Canada.
Corresponding author: Sébastien La Vieille (email: sebastien.lavieille@canada.ca).

Introduction

In Canada, caffeinated energy drinks (CEDs) previously gained market access as natural health products (NHPs), since there were specific provisions in the *Food and Drug Regulations* limiting the addition of caffeine, vitamins, mineral nutrients and amino acids to foods outlined. In 2011, Health Canada (HC) announced its intent to transition CEDs from the NHP regulatory framework to the food regulatory framework, based on consumer perception of CEDs as food and history of use. Currently, CEDs must be approved by HC and issued a Temporary Marketing Authorization (TMA) before they can legally be sold as foods. HC issues TMAs for products that meet strict compositional requirements, including maximum limits on the amount of caffeine and other vitamins and minerals. The labels of CEDs sold in Canada must also carry a number of caution statements, including: "high in caffeine, should not be mixed with alcohol, and not recommended for children, pregnant and/or breastfeeding women and individuals sensitive to caffeine". These requirements were developed based on a risk assessment conducted by HC in 2013 (Rotstein et al. 2013). As a condition of the TMAs, companies are must also report consumption incidents reported by consumers, annual sales data, and research data on Canadians' consumption patterns of CEDs, understanding and use of label information on CEDs (Health Canada 2013).

The purpose of this article is to update the 2013 HC risk assessment with a focus on newly available information on potential cardiovascular effects related to CED consumption, and reassess if existing risk management measures for CEDs remain health protective.

Materials and methods

The composition of a typical CED was defined based on the formulations of products currently available on the Canadian market. An extensive literature review was conducted to identify relevant publications on potential cardiovascular effects associated with specific ingredients (e.g., caffeine, taurine) and potential interactions between them, as well as intervention and observational studies focused on cardiovascular effects associated with CED consumption. The major ingredients of CEDs are defined based on the composition of the most popular products sold in Canada. In addition, Canadian consumption patterns of CEDs are presented.

A literature search was conducted in the Scopus, MEDLINE and Embase databases with the following key words in the title/keywords/abstract: Search ("energy drink" OR "caffeinated energy drink") AND ("cardiovascular" OR "cardiac effect" OR "cardiac event" OR "blood pressure" OR "heart rate" OR "Arrhythmia") AND NOT ("performance" OR "cognitive") between January 2009 and March 2020. The literature review that supported HC's 2013 health risk assessment on CEDs included articles published before 2009. Studies were eligible for inclusion if they were intervention studies (randomized controlled studies) and observational studies (prospective cohort, case-control and cross-sectional studies). Case-reports were also reviewed.

An additional literature search in Scopus, MEDLINE and Embase databases was conducted for evidence of interactions between caffeine and other ingredients in CEDs, their potential for physiological synergy or the possibility of generating a health hazard to the cardiovascular system. Articles published between 2001 and 2020 were identified with the following key words at least once in the title/keywords/abstract: search ("ingredient X" AND "caffeine" AND ("cardiovascular" OR "cardiac effect" OR "cardiac event" OR "blood pressure" OR "heart rate" OR "arrhythmia") on one hand, and ("ingredient X" AND "caffeine" AND "interactions") on the other hand. We provided only a summary of results for cardiovascular effects of caffeine alone in this article because detailed information is found elsewhere.

Articles identified through the described keyword searches were screened to exclude duplicates and to determine inclusion based on title, abstract, and full-text review.

Results

Regarding the literature search focused on CEDs and cardiovascular effects, a total of 503 articles were identified. 289 articles were excluded because they were not available (n = 12), not available in English (n = 20), or were focused on animal models, on adverse effects of caffeine alone, CED consumption data only and not effects, or concomitant use of CED with alcohol/drugs, or CED with exercise (n = 257). Articles considered potentially eligible (n = 214) included case reports, research studies and reviews. Duplicate articles (n = 75) were excluded as well as some reviews with articles related to conference presentations (abstracts) that were subsequently published in peer-reviewed journals (n = 18). All remaining 121 articles identified in the search were screened using a 2-stage strategy, namely 1) title and abstract screen and 2) full-text review. Case-reports generally provide insufficient information and are not representative of the general population. Although reviewed, articles describing case-reports (n = 32) were not included in the assessment. The results obtained from databases, led to a total of 89 articles considered as eligible for inclusion on analysis of the cardiovascular effects related to the CED consumption. To identify other relevant articles, reference lists of primary studies were screened and additional articles were included as appropriate.

Regarding the literature search focused on interactions between caffeine and other ingredients, a similar strategy was conducted with a total of 391 articles identified. 241 articles were excluded because they were not available in English or were focused on animal models, on adverse effects of caffeine alone, or were assessed in the context of concomitant use of alcohol/drugs/exercise, or focused on physiopathological mechanisms not relevant for this review. A total of 150 articles were considered as of interest including articles that were already identified in the search using keywords "CEDs and cardiovascular effects/events" and related searches (n = 119).

Defining the composition of a typical CED sold in Canada

Although Canada does not have a standard definition for CEDs, they typically refer to beverages containing caffeine in combination with other ingredients such as taurine and B vitamins. In Canada, a CED can only be sold under a TMA once they have been assessed and confirmed to meet compositional and labelling requirements for specific ingredients. CEDs available on the Canadian market are typically sold in 250 mL or 473 mL containers (Table 1). Products from 3 companies comprised 95.3% of the sales reported for 2019 (HC internal document, 2019). The composition of a typical CED serving in 2019 is based on the average amount of ingredient from the products with the most number of units sold per company. Some other ingredients possibly present in CEDs such as Guarana seed extracts or Panax ginseng have not been reviewed in this article; further research is needed to be able to assess their potential impact on cardiovascular diseases.

Some of these ingredients, notably caffeine, can modulate certain cardiovascular endpoints, particularly blood pressure (BP). It is also acknowledged that long-term daily consumption of sugar-sweetened beverages can lead to weight gain, increases in BP, and hypertension as reported in both a systematic review and meta-analyses (Jayalath et al. 2015; Malik et al. 2014). However, there is very limited evidence to substantiate potential interactions between caffeine and carbohydrates, as consumed in CEDs, with an impact on the cardiovascular system: 1 study (Rush et al. 2014) examined the effect of caffeine alone, sugar alone, and caffeine and sugar combined on physiological responses in 12 human volunteers, specifically analysing difference in heart rates (HR). However, the intra-individual variability was significant, such

Table 1. Average amounts of major ingredients* per serving of caffeinated energy drink (CED).

Ingredients	Range in CEDs† (per serving)	Typical CED in 2013 (per 250 mL serving)	Typical CED in 2019 (per 250 mL serving)	Typical CED in 2019 (per 473 mL serving‡,§)
Caffeine (mg)	40–180	80	80	160
Taurine (mg)	3–3000	1000	1000	2000
Glucuronolactone (mg)	5–1200	600	0	0
Inositol (mg)	5–200	50	0	0
Niacinamide (vitamin B3, mg)	3–100	18	20	36
Vitamin B6 (mg)	0.26–14	2	5	6
Vitamin B12 (μg)	0.48–25	1	5	12
Pantothenic acid (vitamin B5, mg)	1.13–100	6	5	13
Thiamine (vitamin B1, mg)	2.25	2	0	0
Riboflavin (vitamin B2, mg)	0.6–10.2	1.65	0	1.7
Sugar (g)	0 (sugar free)–93	0–93	0–27	0–55

*Some other ingredients such as Guarana seed extract, Panax ginseng etc. . . may be present in some CEDs. Further research needed to identify other potentially major ingredients.

†Serving size ranges from 250 to 710 mL.

‡Based on average amount of ingredient across the 3 dominant brands of a 473 mL CED.

§The maximum number of servings per day indicated on the product label is adjusted in accordance with the daily maximum levels established for ingredients.

that no consistent pattern could be observed. Another study that only included 8 individuals concluded that the sugar in the CED would act synergistically with the caffeine on BP; however, the study protocol did not include an appropriate sugar-only comparator (Miles-Chan et al. 2015). As the typical carbohydrate content of a sugar-sweetened CED compares to other sugar-sweetened beverages, any potential increased risk of cardiovascular effects associated with higher carbohydrate intake is not unique to CEDs, but would apply to the consumption of diets high in sugar. Based on this, potential health risks associated with a diet high in carbohydrate or sugars would be more appropriately addressed through general guidance about healthy dietary choices.

Individual CED ingredients, cardiovascular effects and interactions with caffeine

Caffeine

In healthy adult populations, the effect of caffeine on arterial BP is well-documented. Single-occasion intakes of caffeine higher than 250 mg, up to 400 mg, have been shown to significantly raise systolic blood pressure (SBP) by 3–15 mm Hg and diastolic blood pressure (DBP) by 4–13 mm Hg as reported in several studies and meta-analysis (EFSA 2015; Mesas et al. 2011; Nawrot et al. 2003; Nurminen et al. 1999; VKM 2015*a*). Despite this well-described response to single-occasion intakes of coffee or caffeine, current evidence does not support an association between habitual coffee consumption (200–300 mg of caffeine) and increased BP or between habitual coffee or caffeine consumption and an increased risk of cardiovascular diseases in hypertensive subjects (Mesas et al. 2011).

It is generally recognized that modest changes in heart rate (HR) following moderate consumption of caffeine has no clinical relevance, except when caffeine exposure is above 400–450 mg/day which may result in tachycardia (Nawrot et al. 2003). Caffeine exposure above 400 mg/day also does not impact ECG parameters such as PR interval, QRS duration, corrected QT interval, RR interval, or corrected QT interval dispersion (Nurminen et al. 1999). In addition, caffeine alone is not responsible for arrhythmia except perhaps at extremely high doses (900–1000 mg caffeine per day) (Voskoboinik et al. 2018).

A dose–response meta-analysis (Ding et al. 2014) and a prospective cohort study (Loomba et al. 2016) found no association between coffee consumption (up to 5 cups per day, equivalent to 500 mg caffeine, per day) and cardiovascular disease-related mortality (i.e., stroke, congestive heart failure and ischemia-related mortality). Several recent publications (Doepker et al. 2018; McGuire 2014; Temple 2019) and reports from food safety authorities (EFSA 2015; VKM 2015*a*) corroborate HC's Recommended Maximum Daily Intakes (RMDIs) for caffeine of up to 400 mg/day for healthy adults, 300 mg/day for women who are planning to become pregnant, pregnant women and breast feeding mothers and 2.5 mg/kg bw/day for children (aged 4 to 13 years) (Nawrot et al. 2003). The most recent systematic review on the potential adverse effects of caffeine consumption in healthy populations, which took into consideration cardiovascular, behavioral, reproductive, developmental, calcium/bone and acute adverse effects, supports HC's RMDIs (Wikoff et al. 2017).

Taurine

Taurine naturally occurs in some food (notably meat and seafood), with mean dietary intakes estimated to vary between 40 and 400 mg/day (VKM 2015*b*). Human data on potential acute toxicity of taurine and long-term studies (>1 year) are not available. The available human studies related to taurine, while limited by the low number of participants, observations in non-healthy populations and short duration, did not report any significant adverse effects with a dose of taurine of 3 g per day for up to 7 weeks (Chauncey et al. 2003; Wojcik et al. 2010; Zhang et al. 2004), apart from gastrointestinal disturbances noted in 1 review (Wojcik et al. 2010). Clinical treatment with taurine at higher doses (10 g/day for 8.5 months) also showed no adverse effects (Pearl et al. 2014). In a more recent study (Schwarzer et al. 2018), no significant effects on systemic hemodynamics were reported in patients with portal hypertension treated for 4 weeks with a daily taurine regime of 6 g per day.

In a risk assessment article published in 2008, which considered the available published human clinical trials, Shao and Hathcock (2008), concluded that a dose of 3 g per day, is the most suitable endpoint for a reference dose for the safety of taurine. Taken together with a No-Observed-Adverse-Effect-Level (NOAEL) of 1000 mg/kg bw per day (equivalent to 70 g per day for an adult) based on animal studies (EFSA 2009), it is considered very unlikely that daily intakes of up to 3 g of taurine per day from CEDs (equivalent to 3 typical 250 mL cans, Table 1) would cause adverse health effects in healthy individuals. To be considered eligible for a TMA in Canada, HC has determined that CEDs should provide no more than 3 g taurine per day (Health Canada 2013).

There are very few publications that report on potential cardiovascular impacts of exposure to both caffeine and taurine. In 1 study (Bichler et al. 2006), where the main objective was to assess the potential impact of CED consumption on short-term memory, the combination of 100 mg caffeine with 1000 mg taurine

caused a significant decline in HR (average decrease of 8.1 beats/min within 45 min following consumption). A significant increase in mean arterial BP (average increase of 2.8 mm Hg following consumption) was observed in subjects only after they took a memory test; the authors suggested a combination effect on BP may occur under stressful circumstances. However, whether the BP effect was a result of a synergistic effect of caffeine and taurine cannot be concluded from this 1 study, since the administration of caffeine alone, combined with psychological stress (e.g., taking a test) has also been shown to increase BP (Bichler et al. 2006).

Most published studies that looked at interactions between taurine and caffeine used CEDs as a comparator (Supplementary File S1[1]). For example, 6 randomized double-blind control trials compared CEDs to caffeine alone when assessing effects on BP (Brothers et al. 2017; Doerner et al. 2015; Fletcher et al. 2017; Franks et al. 2012; Miles-Chan et al. 2015). One study reported significant SBP and DBP increase (Franks et al. 2012) while another reported significant SBP only (Fletcher et al. 2017) associated with CED intake. However, the other trials did not observe significant differences between CEDs and caffeine alone groups (Brothers et al. 2017; Doerner et al. 2015; Miles-Chan et al. 2015). A meta analysis summarizing these results suggests these effects are due to caffeine alone (Shah et al. 2016*a*). Despite limitations such as the small number of studies, limitations in study designs and inconsistency of the results, the available evidence does not support an impact of combined exposure to caffeine and taurine on the etiology of ischemic heart disease via thrombotic events (Higgins 2013; Pommerening et al. 2015; Worthley et al. 2010) or vasospasm (Abebe and Mozaffari 2011; Benjo et al. 2012; Hanan Israelit et al. 2012).

With respect to myocardial performance, several studies that included a caffeine control group (Baum and Weiss 2001; Doerner et al. 2015; Grasser et al. 2014) reported increased myocardial contractility 1–2 hours after consuming 1–2 servings of CED (average amount in 1 serving equivalent to 105 mg caffeine, 1304 mg taurine; 160 mg caffeine, 2000 mg taurine in 2 servings). A double-blind crossover study examined the effect of CEDs on contractile function (stroke volume and fractional shortening) of endurance athletes before and after exercise (Baum and Weiss 2001). In this study, 40 minutes before exercise 13 athletes consumed either the equivalent of 2 typical CEDs (2 × 250 mL, each providing 80 mg caffeine, 1000 mg of taurine), a water beverage containing caffeine (160 mg), a water beverage containing taurine (2000 mg) or sugar water (10.5 g). Contractile function among athletes consuming CEDs was significantly increased with exercise compared with consuming caffeine, taurine or sugar water alone, suggesting a combination effect. In a more recent study (Doerner et al. 2015), myocardial contractility using cardiac magnetic resonance was assessed in 32 healthy volunteers following CED consumption (average 105 mg caffeine, 1304 mg taurine). After a washout period of at least 1 week, 10 participants repeated the same protocol but consumed a beverage containing caffeine only (i.e., 105 mg caffeine, no taurine). The results showed a small, but statistically significant increase in left ventricular contractility, 1 hour after consumption, in volunteers who consumed a CED, but not in individuals who consumed the beverage that contained caffeine only. In summary, while some studies reported a modest increase in myocardial contractility following consumption of CEDs containing both caffeine and taurine supporting a possible synergistic role, the available data are too limited to determine the clinical significance of this observation.

Glucuronolactone

There are no human studies regarding potential toxicity of glucuronolactone, which precludes the setting of a maximum level for CEDs. However, glucuronolactone has been used up to 3000 mg/day for chronic treatment of specific conditions, with no evidence of any adverse effects (Rotstein et al. 2013). At levels present in a typical 250 mL CED (up to 1200 mg, Table 1), it is considered unlikely that glucuronolactone would cause adverse effects, notably cardiovascular effects, in the general population. In recent years, there has been a decline in the use of glucuronolactone in CEDs. No relevant studies were identified on physiological effects of glucuronolactone combined with caffeine.

Inositol

While there is insufficient information to establish a maximum level of inositol for CEDs, high doses of inositol appear well tolerated; specifically, a Canadian study established a NOAEL of 18 g inositol per day (Lam et al. 2006), and 4 g per day is commonly prescribed as a safe treatment for polycystic ovary syndrome (Carlomagno and Unfer 2011). Based on the range of levels generally present in CEDs (up to 200 mg per serving, Table 1), inositol is not expected to cause any adverse effects, including cardiovascular effects, for the general Canadian population. As with glucuronolactone, the addition of inositol in CEDs has declined in recent years. No relevant studies were identified that addressed potential interactions of inositol with caffeine.

B vitamins

No significant impacts on the cardiovascular system have been reported for B vitamins at the daily maximum levels permitted in CEDs sold in Canada (Rotstein et al. 2013).

While some studies showed that caffeine may contribute to an increase in the concentration of homocysteine, a risk factor for cardiovascular disease, it is also reported that B vitamins can lower homocysteine levels without any major adverse effects on endothelial function (Maruyama et al. 2019). This combination effect requires further investigation; however, there are no published data available that address the consumption of CEDs and effects on plasma concentrations of total homocysteine.

CED consumption and cardiovascular effects

Published intervention studies looking at potential cardiovascular effects (BP, HR, and ECG parameters) associated with CED consumption were analysed. A total of 19 randomized controlled trials (RCT) and 1 meta-analysis were identified (for more details, refer to Supplementary File S1[1]). All studies had small sample sizes (generally less than 30 participants) and there was high variability in CED intake (56–946 mL) making comparisons difficult. Of the 19 identified studies, 3 different types of study design were used: (*i*) CEDs versus non-caffeinated Energy Drinks, (*ii*) CEDs versus caffeine only, and (*iii*) CEDs versus placebo.

Blood pressure

The RCTs that reported effects of CEDs on BP are summarized in the supplemental material (Supplementary File S1[1]). Overall, available data for BP are consistent with studies showing a modest effect of CEDs increasing both SBP and DBP. It is difficult to precisely quantify the contribution of caffeine to the BP effect that has been reported following CED consumption. However, a meta-analysis published in 2016 (Shah et al. 2016*a*) focused on the impact of CED consumption on BP parameters. It included 15 studies with a total of 340 individuals assessed for SBP effects and 14 studies with a total of 322 individuals for DBP effect. The SBP and DBP increased by 4.44 mm Hg ($IC_{95\%}$ = 2.71 to 6.17) and 2.73 mm Hg ($IC_{95\%}$ = 1.52 to 3.95) on average respectively, which was statistically significant. The authors attributed the increase in BP to the caffeine content. There also appeared to be a dose

[1]Supplementary data are available with the article at https://doi.org/10.1139/apnm-2021-0245.

effect because SBP was elevated by 3.7 mm Hg when the caffeine content of the CED was <200 mg (equivalent to 2 or less CEDs) and by 6.4 mm Hg when ≥200 mg (equivalent to 3 or more CEDs). However, no such dose-related change was observed for DBP. As normal BP is less than 120 mm Hg (SBP) and 80 mm Hg (DBP) a temporary increase of BP such as that observed following intakes of less than 200 mg of caffeine is not expected to be clinically significant for healthy adults.

Heart rate

Most of the 19 RCTs reported no significant change in HR after consuming CEDs (refer to Supplementary File S1[1]). These results were confirmed by Shah et al.'s meta-analysis (Shah et al. 2016*a*) where HR data for 340 individuals showed no significant change after CED consumption compared with baseline (0.8 beats/min; $IC_{95\%}$ = −1.26 to 2.87). Changes observed in HR in some of the RCTs are consistent with moderate consumption of caffeine; however, these effects are expected to have no clinical impact, except when caffeine doses are greater than 400–450 mg/day. At these doses, symptoms such as tachycardia or palpitations can occur, which are endpoints most often reported in observational studies.

ECG parameters

CEDs have been linked to several adverse effect reports, notably cardiovascular arrhythmias. In a review of published case-reports of adverse cardiovascular events after consumption of CEDs (Goldfarb et al. 2014), 15 cases were identified, including 5 atrial arrhythmias, 5 ventricular arrhythmias, 1 QT prolongation and 4 ST segment elevations; a predisposing cardiac abnormality was not identified in the majority of cases. One study reported QT interval prolongation at a relatively high volume of CED consumption (950 mL consumed over a 45-minute period, providing 320 mg caffeine) (Shah et al. 2014) in healthy volunteers. Other case reports of cardiovascular symptoms, in patients with long QT syndrome (LQTS), were reported but at much higher doses (1500 to 1900 mL of a CED, providing 480 to 640 mg caffeine within 4 hours) (Berger and Alford 2009; Rottlaender et al. 2012).

Of the 19 RCTs identified, 7 investigated the impact of CED intake on ECG corrected QT interval (QTc), to allow comparison of QT values over time at different heart rates and improve detection of patients at increased risk of arrhythmias. Of those 7, 1 study (Gray et al. 2017) investigated a small population of patients (n = 24) with pre-existing genetically confirmed Long QT Syndrome (LQTS) and did not observe any significant differences in the QTc nor in any other ECG parameters in comparing patients who consumed CEDs (250 mL × 2 within 30-min interval; equivalent to 160 mg caffeine, 2 g taurine) versus a placebo. Three individuals either with a severe history of cardiovascular incidents or severe phenotype of LQTS (QTc interval >500 ms) presented with an increased QT interval of at least 50 ms following CED consumption, indicating these sensitive individuals may be at increased risk when consuming 2 typical 250 mL CEDs within 30 min. However, there are several limitations with this study (Gray et al. 2017) that make these conclusions difficult to interpret. Notably the fact that 83% of the patients were being treated with beta-blockers during the study, the small sample size, the absence of plasma concentration-time curves for caffeine and taurine, and only 1 dose of CEDs was provided to patients, thus a dose effect cannot be confirmed. Lastly, the existence of several LQTS pathogenic variants in the selected study population, with possible differences in LQTS severity, greatly limits any extrapolation of these results to the general population. Given the limitations of the data, this genetically confirmed population should likely exercise caution when consuming CEDs.

The other 6 studies looked at young adult populations (average 20–29 years) with no identified underlying disease. Significant changes in QT interval was reported in 2 trials (Fletcher et al. 2017; Shah et al. 2016*c*), 2 hours after consuming a high volume of CEDs (950 mL ≈ 4 cans of 250 mL, composition not provided). The first study (Fletcher et al. 2017) observed that the change in QTc from baseline in the CED group (950 mL) was significantly higher than the caffeine-alone group but only at the 2-hour time point following consumption (0.44 ± 18.4 ms vs −10.4 ± 14.8 ms; p = 0.02). No difference was observed at any other time period (1, 4, 6 or 24 hours following consumption). In the second study (Shah et al. 2016*c*), an increase in QTc interval of 3.4 ms, 2 hours after CED consumption (950 mL) was observed compared with a decrease of −3.2 ms in the placebo group (p = 0.03). Similar to the first study, the results were not significant at any other time period (1, 3.5 or 5.5 hours following consumption). For comparison, the U.S. Food and Drug Administration's guidance for clinical evaluations of QT/QTc interval prolongation associated with drugs indicates additional follow-up is needed only when a change in QTc interval of greater than 10 ms is observed on ECG (FDA 2005, 2017). For the 2 studies cited (Fletcher et al. 2017; Shah et al. 2016*c*), despite the significant differences reported between each group, the increase in QTc intervals from baseline, 2 hours after consumption of CEDs, was less than 10 ms suggesting that the effect was transient and reversible with no long term clinical impact. The remaining 4 studies that explored QT intervals did not report any significant changes between CEDs and caffeine only (Brothers et al. 2017) nor CEDs and placebo (Basrai et al. 2019; Ragsdale et al. 2010; Shah et al. 2016*b*). Based on the available data, there is some evidence that higher CED intakes (equivalent to 4 servings of a typical 250 mL CED) in healthy adults may increase QTc intervals; however, the clinical significance of these observations is unclear. Additional studies are required to investigate the potential electrocardiographic effects of CEDs in people with pre-existing cardiac diseases and, to a lesser extent, in healthy adults.

Safety signals and population surveillance data for CEDs

Canadian post-market surveillance data

In Canada, post-market surveillance data on reports of suspected adverse reactions to CEDs has been collected via 2 different regulatory frameworks. From 2004 until 2012, when CEDs were regulated as NHPs, adverse reactions were captured under the Canada Vigilance Program, which has been in place since 1965. Since their transition to the food regulatory framework in 2012, manufacturers and distributors of CEDs who have been issued TMAs are required to annually report all consumption incidents associated with their products to HC.

Between approximately 2004 (the date of licensing of the first CED as an NHP) and 2012, 74 adverse reaction reports were reported in the Canadian Vigilance Program (Table 2). Cardiac disorders were reported in 35% of the cases (n = 47).

Since their transition to the food framework in 2012, 113 adverse reactions (referred to as consumption incidents for food products) related to CEDs were reported to HC under the TMA process (Table 3). Cardiac symptoms were reported in 9 cases (7.9% of total cases) and 3 were reported as serious incidents. Two were fatal due to cardiac arrhythmia and acute coronary artery thrombosis, and involved use of alcohol and recreational drugs. The third serious case was a pericarditis. This latter case reported consuming only 1 can (250 mL) of CED with alcohol. The symptoms reported in the other 6 non-serious cardiac cases, included irregular heart rhythm (1 case), chest pain (4 cases), and increased heart rhythm (1 case).

Regardless of the reporting system (Canadian Vigilance Program or TMAs), adverse event reports following CED consumption present many limitations. The reports often lack information on demographics, quantity or details of CEDs consumed, chronic versus acute exposure to CEDs, involvement in strenuous activities, other substances consumed with CEDs, and pre-existing medical conditions. Although the reporting of adverse reactions associated

Table 2. Summary of adverse reaction reports for caffeinated energy drinks (CEDs) in the Canadian Vigilance Program (2004–2012).

Variable	*n* (%)
Total number of adverse reaction reports*	74
Mean age, years†	26.0
Median age, years	18.0
Sex	
Female	17 (23)
Male	50 (67.6)
Not specified	7 (9.5)
Serious outcomes and reasons for seriousness	41 (55.4)
Congenital	0
Death	3 (4.1)
Disability	4 (5.4)
Hospitalization required	18 (24.3)
Life-threatening	5 (6.8)
Other medically important conditions	24 (32.4)
Summary of reported adverse reactions‡	
Cardiac disorders	47 (35.1)
Gastrointestinal disorders	46 (33.8)
General disorders and administration site conditions	55 (40.5)
Nervous system disorders	53 (39.2)
Psychiatric disorders	38 (28.4)
Respiratory/thoracic/mediastinal disorders	9 (6.8)
Skin and subcutaneous tissue disorders	13 (9.5)
Vascular disorder	9 (6.8)

*Multiple CEDs may be involved in a single adverse reaction report. Reports could indicate 1 or more symptoms.

†Missing age data for $n = 16$ (21.6%).

‡Adverse reactions are coded to terms in Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Table 3. Summary of consumption incidents reports for caffeinated energy drinks (CEDs) from Temporary Marketing Authorizations (2012–2018).

Variable	*n* (%)
Total number of consumption incident reports*	113
Mean age, years†	30.4
Median age, years	25.5
Sex	
Female	14 (12.4)
Male	79 (69.9)
Unknown	20 (17.7)
Serious outcomes‡	9 (7.9)
Death	4 (3.5)
Seizure	2 (1.7)
Anaphylaxis reaction	1 (0.8)
Reaction and skin discoloration	1 (0.8)
Chest pain	1 (0.8)
Most commonly cited symptoms§	
Stomach discomfort	2 (1.7)
Vomiting	30 (26.5)
Chest pain	4 (3.5)
Nausea	4 (3.5)
Gastrointestinal distress	5 (4.4)
Dizziness	3 (2.6)
Headache	2 (1.7)
Irregular/increased heart rhythm	2 (1.7)

*Multiple CEDs may be involved in a single consumption incident report. Reports could indicate 1 or more symptoms.

†Missing age data or provided age range, $n = 39$ (34.5%).

‡Serious consumption incident: requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is life-threatening or results in death.

§As reported in consumption incident reports.

with CEDs is mandatory for TMA holders, reporting is voluntary for consumers and health professionals. Most of the adverse reactions are reported directly by consumers and are in most cases not validated by a physician. Therefore, this data is not sufficient to support the establishment of a cause and effect relationship between CEDs and the reported adverse reaction.

Poison information centre data

From 2012 to 2018, 852 calls related to multiple exposure (i.e., not only CEDs) and 281 calls related to single exposure involving CEDs, were received by Canadian poison information centres. For both types of exposure, the number of calls per year was relatively consistent between 2012 and 2016, with an increase in the number of calls in 2017 and 2018 (data not shown). Among the 281 single exposure calls, 1.1% reported a major effect, 7.8% a moderate effect, 14.2% a minor effect, and 77% reported minimal clinical effects. However, it was not possible to obtain data on specific clinical outcomes or symptoms. No fatal case was reported for single exposures. Among the 852 multiple exposure reports, similar clinical outcome numbers are reported, and there was 1 fatal case caused by an intentional overdose resulting in cardiac arrest where the caffeinated beverage was considered a co-exposure (CED was used to ingest the overdose drugs).

The reason for exposure was reported to be unintentional in 80.4% and 51.4% of the calls, for single and multiple exposures, respectively. Most of the calls were reported in children younger than 5 years of age, and represent 49.1% and 30.8% of total calls, for both types of exposure. This high proportion of cases involving unintentional exposures by children aged less than 5 years has also been reported in the US (Seifert et al. 2013).

Several other international studies (Borron et al. 2018, Gunja and Brown 2012; Markon et al. 2019, Seifert et al. 2013) provide analysis of adverse reactions related to CED exposures based on calls to poison information centres. A study based on the Texas poison center network (TPCN) reported data from single substance exposures to CED (multiple product types or CEDs in combination with other substances such as alcohol were excluded) from 2010 to 2014 (Borron et al. 2018). Over this 5-year period, 855 documented CED exposures were reported out of a total of 752 279 calls to the TPCN, or 0.11%. An Australian study analysed data from calls to the New South Wales (NSW) poisons information centres, a mean frequency of 0.04% of CED related-calls were reported to the NSW poisons information centre (297 incidents for 770 000 calls) between 2004 and 2010 (Gunja and Brown 2012).

Observational and cross-sectional studies

Observational studies identified in the literature search were obtained from emergency department visits and cross-sectional studies focusing on cardiac-related events following CED consumption in specific populations. The data collected relies on adverse reactions reported by patients who also reported consuming CEDs (Bashir et al. 2016; Busuttil and Willoughby 2016; Kamijo et al. 2018; Nordt et al. 2012, 2017). In these retrospective studies, subjects were questioned about previous consumption of CEDs, but the adverse effects reported as related to CEDs were not necessarily the reason for their visit to the emergency department. In 2 separate studies on emergency visits for possible cardiac-related issues related to CED consumption, palpitations were self-reported in 12%–16% of the participants who also reported having a history of CED consumption, chest pain in 3%–5% and dyspnea in 4% (Nordt et al. 2012, 2017). As for all retrospective investigations, these studies presented several biases, namely recall bias, since these symptoms may not be causally related to CED consumption only. In addition, these symptoms were self-reported by patients and not validated by physicians, which makes this type of survey at higher risk of

over-interpretation. Lastly, other potential sources of caffeine intakes were not queried in some of these studies.

To avoid these biases, 1 study (Busuttil and Willoughby 2016) investigated 60 patients presenting in an emergency department with a complaint of palpitations (defined as "awareness of a fast or erratic heartbeat") to determine the impact of CED clinical presentations in healthy adolescents and adults (13–40 years). Results showed that DBP was slightly higher in CED consumers while SBP and HR were not significantly different. In contrast, the percentage of abnormal ECG findings in CED consumers was lower than non-consumers, but this difference was not significant.

Ad hoc cross-sectional studies are often limited by small sample size (Kamijo et al. 2018; Pensa et al. 2016). To mitigate this issue, other studies (Attipoe et al. 2018; Hammond et al. 2018; Wiggers et al. 2019) have used online surveys with relatively large sample sizes, including a Canadian study (Hammond et al. 2018), which assessed potential adverse effects associated with CED consumption among youth (12–17 years) and young adults (18–24 years). This study found that 41.5% of the respondents reported experiencing at least 1 adverse reaction after consuming CEDs, while 30.6% reported experiencing at least 1 adverse reaction after drinking coffee. Of the possible adverse effects captured in the survey, the only cardiac-related effect, "fast heartbeat", was reported in 24.7% for CED consumers versus 10.5% for coffee consumers. The difference between self-reported adverse effects among CED and coffee consumers was considered significant. In an Australian study (Costa et al. 2016), 399 adolescents (12–18 years) from 4 secondary schools completed a self-report electronic survey of consumption patterns and symptoms related to CEDs. Here the participants were presented with 8 short-term symptoms related to cardiovascular effects and possibly associated with CED consumption, including "racing heart" and "palpitations". Overall, the response rate was 68% with 56% reporting lifetime CED consumption (n = 224) and, among them, 53.2% of adolescent consumers reported experiencing at least 1 of these symptoms following CED consumption. "Racing heart" was the primary symptom reported (41%), with 16% reporting "heart palpitations". However, use of online survey tools are sometimes based on convenience samples, which maybe subjected to ascertainment bias and sampling errors (lack of quality random sampling). Further, low response rates observed (e.g., 5% in the Hammond study (Hammond et al. 2018) and 7% in the Attipoe study (Attipoe et al. 2018)) limit the generalizability of the data.

Overall, palpitations and tachycardia were generally the most frequently reported categories of cardiac symptoms reported by CED consumers. Although the results of the observational studies indicate that the proportion of participants who experience adverse effects following consumption of CEDs is frequent and/or common, the findings are not necessarily representative of the general population or of the specifically targeted populations such as young adults and adolescents due to the limitations of the observational studies. Furthermore, while the number of reported adverse reactions and the average annual frequency of CED-related calls to poison information centres are underestimated and insufficient to support a cause effect relationship; a rough comparison with the number of CED units sold each year in Canada (320 million units sold in 2019; source: HC internal document, 2019) provides a contrasting perspective on the frequency of occurrence of adverse effects following consumption of CEDs. More comprehensive data are needed to more fully understand the occurrence of adverse effects are following consumption of CEDs.

Canadian CED consumption patterns

Data from the 2015 Canadian Community Health Survey (CCHS 2015) (Statistics Canada 2015), which is the most relevant source of food consumption data for the Canadian population, was considered. The CCHS 2015 is a cross-sectional survey representative of the population across the 10 Canadian provinces that collected information on food and beverage consumption with a 24-hour dietary recall, which allows for estimations of dietary exposure to caffeine (19 670 respondents). While caffeine exposure modelling based on this data indicated that most are within their respective RMDI, only 103 of the CCHS 2015 respondents surveyed reported consuming CEDs; too few to reliably estimate caffeine exposure from CEDs alone or determine their contribution to total daily caffeine intakes for the Canadian population. Therefore, HC's current risk management measures for CEDs were evaluated by comparing levels of ingredients in a typical CED to data on potential adverse cardiovascular outcomes.

However, other Canadian studies have looked at the frequency of CED consumption among specific age groups. One study conducted in 2013 on behalf of a trade organization representative of CED manufacturers (IPSOS 2013) showed that 16% of the 15 151 surveyed consumers (aged 12 years or over), had reported consumption of 2 or more CEDs (250 mL) in their lifetime. On those days when they did consume CEDs, between 5% and 6% of youth 12–18 years reported consuming 2 servings (250 mL) of CEDs, and 1% of youth 12–18 years reported consuming up to 5 servings (250 mL) of CEDs. The proportion of adults 19–30 years who consumed 2 servings (250 mL) of CEDs was slightly higher with 8%, while those who consumed 4 servings represented 2% and those who consumed 5 servings (250 mL) represented 1%. According to a recent survey (Institut Léger 2019), 15% of Canadians consumed CEDs in 2019. Another Canadian study from 2017 (Reid et al. 2017), based on a consumer panel of 2040 teenagers (aged 12–17 years, n = 1013) and young adults (aged 18–24 years, n = 1027), reported 73.6% of the respondents as having "ever having consumed CEDs". Among them, 10.2% reported CED consumption in the last 24 hours, 15.6% in the past week and 6.9% reported having consumed 4 servings (cans) or more in a day. The proportion of individuals from this survey who consumed more than 2 servings per day was estimated to 16% (Reid et al. 2017). European findings indicated that 24% of teenagers and 19% of adult CED consumers reported drinking more than 2 cans in a single occasion (Zucconi et al. 2013).

Discussion

The current evidence suggests that caffeine and taurine are the main CED ingredients that may affect the cardiovascular system. In healthy adult populations, the effect of single-occasion intakes of caffeine higher than 250–400 mg (3 or more servings of a typical CED 250 mL sold in Canada) on increased arterial BP is well-documented. However, current evidence indicates that daily moderate consumption (500 mL) of CEDs is not associated with clinically significant increases in BP, nor an increased risk of cardiovascular disease following habitual caffeine consumption in individuals with hypertension. Slight changes in HR observed following CED consumption have been attributed to moderate, single-occasion doses of caffeine (≤400 mg), but these transitory effects are not expected to have any clinical impact. Higher doses of caffeine (≥400 mg) may lead to symptoms such as tachycardia or palpitations. The available information confirms that the current limits and caution statements for caffeine in CEDs, which are based on consideration of HC's RMDI for caffeine, are protective, including for cardiovascular endpoints.

Currently, HC's daily maximum level for taurine in CEDs is 3 g. Taurine alone has not been associated with any clinically significant adverse effects, including on cardiovascular endpoints, in human studies up to 6 g per day. There is scant published scientific data on the potential for synergistic or antagonistic effects between taurine and caffeine. While some studies reported a small increase in BP following consumption of CEDs containing both caffeine and taurine, other studies have attributed this to the presence of caffeine alone. More data on the potential for synergistic effects of caffeine and taurine are needed as some studies

reported a modest increase of myocardial contractility following consumption of more than 1 CED containing both caffeine and taurine. However, the current weight of evidence does not indicate any safety concerns, including increased risk of ischemic heart disease via thrombotic events or vasospasm, related to the presence of these ingredients in a typical (250 mL or 473 mL) CED on the Canadian market.

Potential effects on ECG parameters in people with pre-existing cardiac diseases warrants further investigation given some evidence that CED consumption could prolong QTc intervals in these individuals. Overall, it is recommended that individuals with known Long QT syndrome should exercise caution and consult a Long QT expert before consuming CEDs.

The low number of CED respondents in the most recent CCHS survey could be due to the consumption pattern of these products, as CEDs may not be consumed daily like other food products, which makes it difficult to capture them in a 24-hour recall-based survey. While other surveys provided some information on CED consumption among Canadians, the data overall does not allow for an accurate estimate of CED consumption. These limitations highlight that ad hoc robust surveys could support an improved characterization of CED consumption. Despite this data gap, it was possible to re-evaluate the adequacy of HC's existing risk management approach for CEDs by comparing potential cardiovascular effects identified in the literature to the ingredient composition of a typical Canadian (250 or 473 mL) CED.

With a focus on CED ingredients that have the potential to impact the cardiovascular system, typical CEDs sold in Canada are defined as either 250 or 473 mL, providing a caffeine and taurine content of 80 or 160 mg and 1000 or 2000 mg, respectively (Table 1). The maximum number of servings per day indicated on the CED label is determined by the daily maximum level established for ingredients. Based on taurine content, a typical 473 mL-sized CED would require a "do not consume more than 1 can/day" statement, providing a similar daily amount of caffeine and taurine as 2 servings of a typical 250 mL-sized CED (approximately 160 mg and 2000 mg, respectively).

Both caffeine and taurine exposures are well below HC's safe reference values (RMDI, 400 mg/day and 3 g/day), respectively. Estimated combined intakes of caffeine and taurine are unlikely to cause any cardiovascular risk in healthy adults, including women of childbearing age. Similarly, it continues to be recommended that healthy adolescents (aged 14–18 years) consume no more than the equivalent of 2 servings of a typical 250 mL-sized CED per day. The taurine content associated with moderate CED consumption is unlikely to cause any cardiovascular risk in healthy adolescents. In the absence of adequate safety data to establish a separate RMDI of caffeine for adolescents, HC has taken a precautionary approach and recommends the RMDI value for children (2.5 mg/kg bw/day) also apply to this age group. This recommendation is considered to be conservative, as there is no compelling safety reason to suggest that older and heavier adolescents can consume no more than 2.5 mg/kg bw/day of caffeine whereas adults can consume 6 mg/kg bw/day (equivalent to 400 mg/day). Maximum daily intakes of caffeine could increase from 2.5 to 6 mg/kg bw/day as adolescents approach 19 years of age and would not be expected to result in significant health risks. Nonetheless, HC's 2013 risk assessment did account for the more conservative RMDI applied to adolescents in setting caffeine restrictions for CEDs. HC considered the concentration of caffeine in CEDs sold in smaller formats (e.g., 250 mL), of which up to 2 could be consumed in 1 occasion, and a limit on the total caffeine content of CEDs sold in larger formats (e.g., 473 mL) that could be consumed as a single serving, in order to minimize the caffeine intake from CEDs to a level considered acceptable for adolescents. Furthermore, based on caffeine alone, HC continues to recommend that CEDs should not be consumed by children and pregnant and/or breastfeeding women. In Canada, CEDs are already required to carry these caution statements.

HC has updated its 2013 health risk assessment with an emphasis on the potential for adverse cardiovascular effects associated with the consumption of CEDs authorized for sale in Canada. The results indicate that for the healthy population of adults and adolescents, moderate consumption (equivalent to up to 500 mL per day) of a typical CED is not associated with an increased risk of cardiovascular effects, and reference values used by HC to set limits for both caffeine and taurine are considered adequate to manage their safety from a cardiovascular perspective. Despite potential under-reporting, available surveillance data also show that the number of reported consumption incidents related to CEDs is low compared with the number of products sold in Canada, and cannot be attributed to moderate (equivalent to up to 500 mL per day) CED consumption alone.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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