P +64 9 477 5420
F +64 9 479 1486
HPSNZ.ORG.NZ

17 ANTARES PLACE
MAIRANGI BAY
AUCKLAND 0632

PO BOX 302 563
NORTH HARBOUR
AUCKLAND 0751

HIGH PERFORMANCE SPORT NEW ZEALAND

14 November 2019

Food Standards Australia New Zealand

To Whom It May Concern,

Re: Call for submissions – Urgent Proposal P1054

Thank you for the opportunity to submit our case regarding Proposal P1054 to amend the Australia New Zealand Food Standards Code (the Code) to prohibit the retail sale of pure and highly concentrated caffeine food products.

Our desire is to support New Zealand athlete performances, their safety and wellbeing.

High Performance Sport New Zealand has a Nutritional Supplements Programme aimed at managing the risks related to dietary supplements, and protecting the health, integrity and wellbeing of New Zealand high performance athletes.

Caffeine use in sport

Internationally, dietary supplement products containing caffeine are widely used at all levels in sport. It is probably the most well-researched ergogenic ingredient.

We would like to direct you to several relevant key papers relating to use of caffeine in sport and specifically, concentrated caffeine products commonly used in sport:

1. Peeling et al 2019. Sports Foods and Dietary Supplements for Optimal Function and Performance Enhancement in Track-and-Field Athletes. International Journal of Sport Nutrition and Exercise Metabolism, 2019, 29, 198-209. This paper refers to use of caffeine in sport, protocols, side effects, safety and dosing.
2. Wickham et al 2019. Administration of caffeine in different forms. Sports Medicine 48 (Suppl 1):S79-S91. This paper specifically refers to use of alternate caffeine modalities including caffeine gum effects and dosing.
3. Whalley et al (2019). The Effects of Different Forms of Caffeine Supplement on 5-Km Running Performance. International Journal of Sports Physiology and Performance, (Ahead of Print). With permission from the author to send this to FSANZ, this paper compares caffeine gum, dissolvable strips and tablet forms in terms of individualised performance, dosing

From 1984 to 2004 caffeine was on the World Anti-Doping (WADA) Prohibited List due to the reported high amounts being used at the time in relation to performance enhancement. Caffeine has subsequently been removed from the Prohibited List due to evidence indicating a beneficial effect at a much lower/safer dose (i.e. 3-6mg/kg) and the inability to separate social and habitual use. Caffeine has remained on a WADA Monitoring Programme to detect patterns of misuse.

Caffeine and high-performance sport in NZ, key points

- At High Performance Sport New Zealand (HPSNZ), athletes are supported by HPSNZ Performance Nutritionists and HPSNZ Medical doctors. When athletes choose to use dietary supplements, individual advice and recommendations

are made in consultation with Performance Nutritionists regarding use of products based on evidence, safety, dosing, timing, protocols, the practicalities of the sport and individual preference. For these reasons, we access a range of products and delivery modes for caffeine.

- Safe use of caffeine (and all supplements) for performance is paramount to athletes and to HPSNZ who's medical and nutrition practitioners advise athletes directly on appropriate use. We do recognise the limits of this approach outside of the high-performance system in New Zealand.

- Foods containing caffeine are known to vary in caffeine content. For this reason, athletes wishing to use appropriate and safe doses of caffeine will choose products that are dose controlled and independently batch tested for banned substances. We would be concerned that removal of such products could increase the use of internet purchasing from foreign sources and obtaining products that are not tested. There is a risk access and use of preferred caffeine products could go 'underground' where product risk is much greater to health and wellbeing (e.g. mixed ingredient products, questionable quality assured doses, and products contaminated/spiked with scheduled substances).

- The HPSNZ Nutritional Supplement Programme provides access to Preferred Suppliers to mitigate risks of accessing contaminated or poor-quality product. Preferred Suppliers meet strict criteria in relation to efficacy, quality, safety and ethical considerations.

- Education regarding the risks of supplement products to athletes (and staff) is a key aspect of the HPSNZ Nutritional Supplement Programme. Education covers inherent risks, product risks and risks of inappropriate or misuse. Alerts and Advisories are also part of HPSNZs strategy to continually educate and update high performance support personnel and athletes in New Zealand about supplement risks and align with regulatory agencies. When FSANZ published the outcome regarding the banning of caffeine powder, HPSNZ promptly supported the distribution of this message via an HPSNZ internal and New Zealand sport wide Alert (Appendix 1).

- Access and availability to product that has been specifically banned substance tested is a constant challenge in NZ. Products are accessed from overseas suppliers that are carefully assessed by HPSNZ to meet quality, safety and Preferred Supplier criteria. Restricting the availability and range of currently suitable products will pose a much greater challenge for NZ athletes and HPSNZ to source quality and appropriately tested product.

- Products in use under supervision within the NZ high performance system include (with links to examples):

  Sports gels with caffeine (e.g. SIS 75ml - 150mg/60ml, Pure Sports Nutrition 30mg/50g)

  Caffeine shots – 150mg/60ml (SIS)

  Caffeine strips – 40-80mg/211g (per strip)

  Caffeine chewing gum – 100mg/piece (Healthspan Elite)

  Tablets (e.g. No doz 100mg/tablet, HealthSpan Elite 50mg/tablet)

  Note: in each case above this is the consumable dose per item/serve.

- The gum and strip delivery systems are based on technological advances that avoid gastrointestinal disturbances commonly experienced by athletes and takes advantage of absorption of caffeine in the oral cavity. Caffeine dose requirements to achieve the same effects may in fact be lower using this delivery system. We note that the proposed 5mg/100g (5% limit) does not reflect technological advances in delivery modalities such as gums and strips.

- In terms of safety and potential for misuse, HPSNZ has focused on the use of products with minimal other ingredients to encourage specificity of use (including dose and timing) and to avoid potential undesirable side effects and interactions with medications. Strips, tablets and gums contain minimal other ingredients.

- High performance athletes who choose to use caffeine in relation to performance, particularly around event situations, are often advised to make use of a caffeine dietary supplement product, independently of food sources, due to the ability to calculate a caffeine dose accurately from food and beverage sources.

- HPSNZ has an adverse reaction reporting system in place for dietary supplements. To date there have been no reports of caffeine adverse reactions specific to any delivery modalities.

- We note Revvies Strips products are available online and in Australia, New Zealand and the United Kingdom. Revvies Energy is an Australian company.

To remove products within months of the Tokyo Olympics poses a disadvantage and a disruption to well-developed strategies that have been practised by NZ athletes. The removal of product options and/or change of individualised strategies (due to product regulatory change) could have a significant impact on athlete preparation and performance at the Tokyo Olympics and beyond due to the above outlined reasons.

We therefore support careful consideration of pure caffeine products used for sport within the FSANZ review. We would be happy to provide more information if required.

Sincerely

Appendix 1: Sample HPSNZ Dietary Supplement Advisory

HPSNZ Dietary Supplement Advisory

Pure Caffeine Powder

Date: October 2019

Recently the Australian Government banned the sale of pure caffeine powder and highly concentrated caffeine food products for retail (personal consumption) sale. This was in response to the tragic death of a young man who consumed pure caffeine powder added to a protein shake in an amount that was reportedly up to 50 times the dose in a cup of coffee. New Zealand is set to follow according to a report by Food Standards Australia and New Zealand (FZANZ).

Caffeine powder is potentially lethal in quantities less than one teaspoon. Measuring out a small quantity accurately is not possible on the average set of kitchen scales and confusion with metric measurements is also possible (grams v milligrams, teaspoons v tablespoons).

A review by FZANZ is currently underway for sports and dietary supplements containing high levels of caffeine.

What you should know:

- Dietary supplement product labels can be misleading and do not always reveal the true content or purity of the product. Caffeine has many physical and mental stimulatory effects and is often used in association with sports performance. Use should be monitored. More is not better and, in this case, could be lethal.
- Young people and children are more sensitive to caffeine and use is not recommended for performance
- HPSNZ advises sports people against sourcing pure or highly concentrated caffeine products
- Extensive caffeine safety studies have concluded that a daily intake of up to 400mg caffeine is considered safe for most people over the age of 18 (excluding pregnant and lactating women).
- Foods and beverages containing caffeine are unlikely to pose any risk because their caffeine level is regulated under the Food Standards Code (e.g. caffeine containing sodas).
- Athletes do not receive benefit from exceeding safe levels of caffeine intake. High levels could be detrimental to health and performance. Advice about caffeine use for performance should always be via a Registered Dietitian, Registered Nutritionist and or General Practitioner.
- Most cases of caffeine toxicity result from co-consumption with alcohol, unintentional overdose, interaction with some medications, or the excess consumption of energy drinks (particularly in individuals aged 13-16 years).
- Excess caffeine can cause abnormally accelerated heart beats (tachycardia) and has led to caffeine related deaths.
- Note that Guarana is another form of caffeine commonly added to food and drinks.
- As with all dietary supplements, athletes are encouraged to check products for safety and contamination risk. Choosing third party tested products reduces the chances of inadvertently consuming a contaminant such as a substance prohibited in sport.

If you have any questions or concerns, please contact your General Practitioner, Registered Dietitian or Registered Nutritionist.

Jeni Pearce and Tanya Hamilton
HPSNZ Performance Nutrition

Bruce Hamilton
HPSNZ Medical Director

Distribution List
HPSNZ website
HPSNZ Perf Nut and Medical

Private Dietitians
DFSNZ

International Journal of Sport Nutrition and Exercise Metabolism, 2019, 29, 198-209
https://doi.org/10.1123/ijsnem.2018 0271

Human Kinetics
SCHOLARLY REVIEW

Sports Foods and Dietary Supplements for Optimal Function and Performance Enhancement in Track-and-Field Athletes

Peter Peeling
The University of Western Australia and Western Australian Institute of Sport

Linda M. Castell
University of Oxford

Wim Derave
Ghent University

Olivier de Hon
Anti-Doping Authority Netherlands

Louise M. Burke
Australian Institute of Sport and Australian Catholic University

Athletes are exposed to numerous nutritional products, attractively marketed with claims of optimizing health, function, and performance. However, there is limited evidence to support many of these claims, and the efficacy and safety of many products is questionable. The variety of nutritional aids considered for use by track-and-field athletes includes sports foods, performance supplements, and therapeutic nutritional aids. Support for sports foods and five evidence-based performance supplements (caffeine, creatine, nitrate/beetroot juice, β-alanine, and bicarbonate) varies according to the event, the specific scenario of use, and the individual athlete's goals and responsiveness. Specific challenges include developing protocols to manage repeated use of performance supplements in multievent or heat-final competitions or the interaction between several products which are used concurrently. Potential disadvantages of supplement use include expense, false expectancy, and the risk of ingesting banned substances sometimes present as contaminants. However, a pragmatic approach to the decision-making process for supplement use is recommended. The authors conclude that it is pertinent for sports foods and nutritional supplements to be considered only where a strong evidence base supports their use as safe, legal, and effective and that such supplements are trialed thoroughly by the individual before committing to use in a competition setting.

Keywords: ergogenic aids, performance nutrition, high performance, athletics

Numerous nutritional products are marketed with claims of optimizing athlete health and function and/or enhancing performance. Products that fall under the banner of "Sports Foods" or "Dietary Supplements," may be used to support performance during training and competition or for enhancing aspects of training adaptation, recovery, immune function, and/or overall athlete health. Effective marketing campaigns and athlete endorsements may convince us that certain sports foods and supplements are fundamental in allowing athletes to reach their sporting goals. However, this approach is naive in understanding the true foundations of athlete success, such as the inherent genetic predisposition for athletic characteristics, the many hours of well-structured/periodized training, appropriate underlying nutrition, adequate sleep and recovery, and of course, good overall physical and mental health. Nevertheless, if these variables are all accounted for, there may be a role for sports foods and dietary supplements in an athlete's training and competition routine, particularly within elite sport where marginal performance gains are pursued. The following review presents general considerations for track-and-field athletes using sports foods and dietary supplements to enhance performance, in addition to exploring the potential therapeutic/prophylactic use of these nutritional aids.

Definition of a Dietary Supplement

Maughan et al. (2018a) recently defined a dietary supplement as:

> A food, food component, nutrient, or non-food compound that is purposefully ingested in addition to the habitually consumed diet with the aim of achieving a specific health and/or performance benefit.

Prevalence

A recent systematic review and meta-analysis of 159 unique studies in athlete populations (Knapik et al., 2016) investigated the prevalence of dietary supplement use (defined using the Federal Drug Administration's Dietary Supplement Health and Education Act of 1994; e.g., sports foods, iron, vitamins, etc.) by sport, sex, and athlete status (i.e., elite vs. nonelite). High variability in supplement use among various sporting groups was reported,

Peeling is with School of Human Sciences (Exercise and Sport Science), The University of Western Australia, Crawley, Western Australia, Australia; and the Western Australian Institute of Sport, Mt Claremont, Western Australia, Australia. Castell is with Green Templeton College, University of Oxford, Oxford, United Kingdom. Derave is with the Dept. of Movement and Sports Sciences, Ghent University, Ghent, Belgium. de Hon is with the Anti Doping Authority Netherlands, Capelle aan den IJssel, The Netherlands. Burke is with the Australian Institute of Sport, Bruce, Australian Capital Territory, Australia; and the Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Victoria, Australia. Address author correspondence to Peter Peeling at peter.peeling@uwa.edu.au.

with the combined group summary prevalence estimate (SPE) ranging from 4 to 62% across various supplement types. When differentiated by athlete status, results showed that elite athlete cohorts (SPE male: ~69% and SPE female: ~71%) presented with greater rates of supplement use than their nonelite counterparts (SPE male: ~48% and SPE female: ~42%). Furthermore, sex differences were apparent, with greater use of supplemental iron reported by female athletes, whereas males used products such as protein, creatine, and vitamin E more often. Although specific supplement use among athlete groups is hard to quantify, these outcomes suggest that service providers (i.e., dietitians, physiologists, sports physicians) working with athlete cohorts should be aware of differences in the incidence and type of supplement use within a given group of athletes, with caliber and sex being discriminating characteristics. For further insights into the prevalence and rationale for use of supplements and sports foods, the reader is directed to recent comprehensive review of the topic (Garthe & Maughan, 2018).

Sports Foods

The term "Sports Foods" generally refers to specifically formulated food products that are commercially developed for use by athletes. The various categories of such foods are outlined in Table 1, with a specific function to target nutritional goals that underpin training adaptation, recovery, and competition performance (Burke & Cato, 2015). Although they often contain nutrients in similar amounts to those found in whole foods and manufactured products in the general food supply (hereafter, called "everyday foods"), sports foods may offer the practical advantage of combining all the nutrients needed for a specific goal in a single source. In addition, the use of novel food and packaging technology can make sports foods easy to transport, store hygienically, prepare, and consume, particularly in situations before, during, or after/between competition events and training sessions. However, although some sports foods resemble "everyday food," they also differ in that they may consist of only a few nutrients compared with the many hundreds of nutrients and phytochemicals found in the former. For that reason, sports foods should not be used as a dietary replacement for athletes, but rather as a supplementary strategy on occasions where a specific combination of key nutrients is required.

The ergogenic properties of sports foods, in general, can be ascribed to four main physiological goals, which they help to support:

a. Hydration: Fluid ingestion for maintaining or restoring hydration status.
b. Fuelling: Carbohydrate provision before, during, and following/between exercise.
c. Anabolism: Protein ingestion to promote amino acid delivery for optimal training adaptation and event recovery.
d. Osmolality: Electrolyte ingestion to replenish loss in sweat.

These goals are generally accepted by the broad sport nutrition scientific community as being determinants of sports performance and training response. Of note, the risk of dehydration and fuel/electrolyte depletion is predominately an issue during longer athletic events, such as distance running and race walking; furthermore, there is ample evidence of the benefits of hydration, carbohydrate fueling, and electrolyte replacements during these events (Burke, 2010; Hoffman et al., 2018). Alternatively, athletic sprint events require a high level of muscle power, and their training-induced muscle hypertrophy relies on adequate protein and amino acids provision around training sessions (Reidy & Rasmussen, 2016). Each sports foods category will contribute to one or more of these physiological goals, yet each in a variable degree. The link between the sports foods categories and their respective goals is summarized in Table 1.

Table 1 Summary of the Roles and Ingredients in Sports Foods

Product	Active ingredient / Physiological goal	Water / Hydration	Carbohydrates / Fueling	Protein / Anabolism	Electrolytes / Osmolality
Isotonic sports drink		✓✓	✓		✓
High energy sports drink		✓	✓✓		✓
Electrolyte supplement (drink form)		✓			✓✓
Sports gel			✓✓		
Protein supplement (drink form)		✓	✓	✓✓	✓
Sports bars			✓	✓	✓
Sports confectionary			✓✓		
Liquid meal supplements		✓	✓✓	✓	✓
Advantages of sports foods		• Sports foods can contain only those ingredients that are actually needed during exercise. Foods in the general food supply, particularly whole foods, will usually contain other nutrients, such as fat and fibers, which are not needed during a race, and may cause gastrointestinal discomfort. • Sports foods may be manufactured to optimize serving size, convenience, digestibility, storage, and transport.			
Concerns about sports foods		• Sports foods are more expensive than "everyday foods" and may drain an unnecessarily large share of the athlete's budget. It should be noted that many sports nutrition goals can easily be met with the use of everyday foods. A typical example is the protein rich recovery drinks that can be adequately replaced by the much cheaper dairy products (e.g., skim milk or yogurt). • An overreliance on sports foods as energy sources may lead to poor nutrient intake and limited dietary variety.			

✓ Can contribute to this goal. ✓✓ Is an important contributor to this goal.

Of course, manufacturers want to claim additional benefits of their specific products and proprietary blends, which usually lack any scientific substantiation, beyond the benefits of each compound in isolation. Of note, some manufacturers add performance supplements or other ingredients to sports foods. For instance, protein shakes can contain creatine, sport drinks or sports bars can contain caffeine, and vitamins can be found in the most unexpected places (e.g., in the so-called "sports/fitness waters" that provide a pleasant tasting drink rather than addressing any unique athlete need). This makes the distinction between sports foods and sports supplements more diffuse, and it also greatly complicates the work of sport nutritionists to keep track of the total daily doses of supplements and micronutrients to which athletes are exposed. To track the total ingestion of such ingredients and to reduce concerns around product contamination via raw ingredients that may be considered at higher risk of this problem, athletes are guided to choose brands of sports foods with the simplest formulations to meet the specific goals for which they are designed; in general, they should focus their use of performance supplements to separate protocols, using separate products, which have preferably been third-party batch tested or are manufactured by large (reputable) food companies. The exception to this might be caffeine, which already has a crossover to the food industry, as it is found in the athlete's diet via their intake of "everyday-consumer" products, such as coffee, tea, iced coffee beverages, and "energy drinks.".

In summary, sports foods may provide a valuable contribution to an athlete's nutrition plan, providing nutrients that support training adaptation (e.g., protein) and promote performance (e.g., carbohydrate and fluid/electrolytes). However, their role should not be overestimated, as many of those goals can, to a large extent, be also obtained by carefully selected "everyday" foods.

Performance Supplements

Although countless supplements are marketed with the claims of directly enhancing athletic performance, only a handful are supported by an evidence base that warrants consideration for trial use by athletes (see Figure 1 relevant to the decision-making process). A recent review of this area categorizes the commonly encountered performance supplements in terms of their research support and level of efficacy (Peeling et al., 2018). In addition, the recent International Olympic Committee consensus statement on supplement use by high-performance athletes (Maughan et al., 2018a) proposes that only five performance supplements have an adequate level of evidence to suggest marginal performance gains *may* be possible for elite athletes (a population where such gains are generally harder to obtain) when added to a bespoke and periodized training and nutrition plan. These supplements are summarized with the mechanism of action and the potential application to track-and-field athletics presented in Tables 2 and 3, respectively.

Caffeine

Caffeine shows well-established benefits for enhancing athletic performance across both endurance-based events and short-term, supramaximal tasks. Caffeine dosages of 3 6 mg/kg of body mass (BM), consumed ~60 min prior to exercise in the form of anhydrous caffeine (i.e., pill or powder form), are commonly shown to result in performance gains (Ganio et al., 2009). However, lower caffeine doses (<3 mg/kg BM, ~200 mg), provided both before and during exercise, have also resulted in an ergogenic benefit (Spriet, 2014). Of note, recent research has suggested that the ergogenic effects of caffeine are influenced by the athlete's variant of a number of genes, including the CYP1A2 gene involved in the liver metabolism of caffeine (Guest et al., 2018). This explains the well-known variability in individual responses to the "social" use of caffeine, confirming the need for athletes both to trial their intended performance uses of caffeine prior to implementation in competition and to take into account their personal history of reactions to caffeine intake in "everyday life" (e.g., effects on heart rate, jitteriness, or sleep quality). Interestingly, larger caffeine doses (≥9 mg/kg BM) do not appear to increase the performance effect (Bruce et al., 2000), and are more likely to increase the risk of *negative side effects* such as nausea, anxiousness, insomnia, and restlessness (Burke, 2008). Caffeine habituation seems to have limited impact on the performance effects of this stimulant (Goldstein et al., 2010); high-habitual daily caffeine users tend to encounter similar performance benefits as those with low and moderate intakes (Gonçalves et al., 2017). Furthermore, studies have shown that athletes need not undertake "caffeine withdrawal" over the days prior to competition use to achieve a performance improvement (Irwin et al., 2011). Earlier studies that suggested a larger performance improvement when caffeine supplementation was preceded by a dehabituation period may have been measuring the reversal of the negative effects of caffeine withdrawal (i.e., headache, fatigue, demotivation; Irwin et al., 2011) on top of the normal performance effect rather than a unique benefit.

The caffeine supplementation literature shows strong evidence of improved performance when it is consumed before events varying in duration from 5 to 150 min (Ganio et al., 2009). Furthermore, low moderate doses of caffeine (100 300 mg) consumed *during* endurance exercise (after 15 80 min of activity) have also been shown to enhance endurance performance by a range of 3 7% (Paton et al., 2015; Talanian & Spriet, 2016). When considering short-term, supramaximal tasks, the ingestion of 3 6 mg/kg BM of caffeine taken 50 60 min preexercise relates to performance gains of >3% for anaerobic activities of 1 2 min in duration (Wiles et al., 2006). Therefore, there is support for high-performance track-and-field athletes in the longer sprints, middle distance, and endurance/ultraendurance events to consider competition use of caffeine. Furthermore, shifting the "social" intake of caffeine to target its effects to training sessions may help to improve the quality of some workouts, particularly if rehearsing competition practices or undertaking sessions in a fuel-depleted state (Lane et al., 2013).

Creatine Monohydrate

Creatine monohydrate (CM) supplementation increases muscle creatine and phosphocreatine stores, sustaining exercise that is otherwise limited by the inability of phosphocreatine resynthesis to keep pace with exercise fuel demands, for example, single and repeated bouts of high-intensity exercise (<150 s duration), with the most pronounced effects evident during tasks <30 s (Branch, 2003; Lanhers et al., 2017). Indeed, creatine supplementation received widespread attention in 1992 when the first report on successful loading protocols (Harris et al., 1992) was published at the same time as anecdotes emerged from the Barcelona Olympic Games regarding its use by gold-medal winning British track-and-field sprinters. In addition, chronic training adaptations, such as lean mass gains and improvements to muscular strength and power, have also been noted with both direct and indirect mechanisms proposed (Table 2). Less commonly, performance advantages for endurance athletes have also been suggested, including such

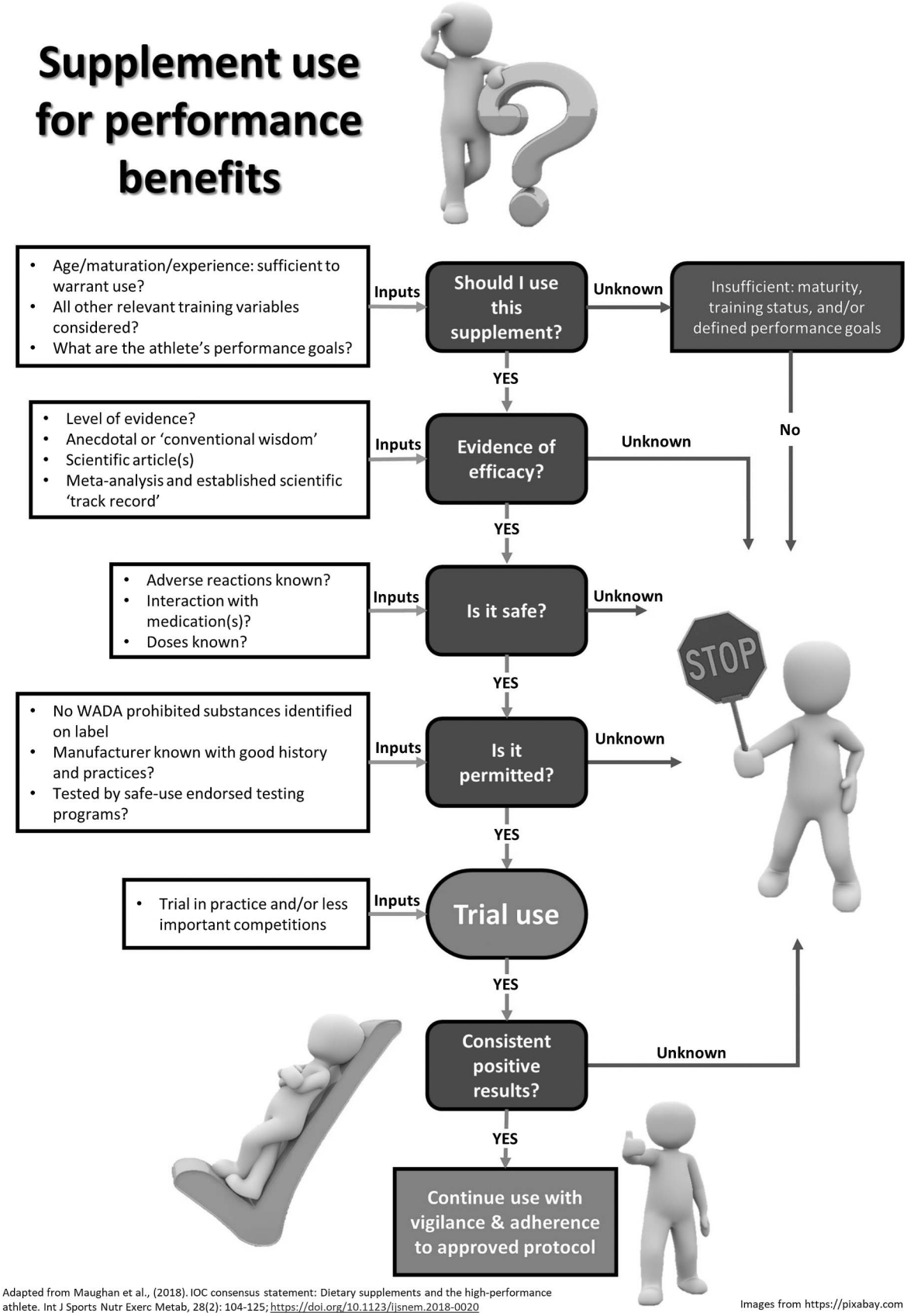

Figure 1 A pragmatic approach to making decisions about supplement use to optimize function and performance in athletes. Adapted from "IOC consensus statement: Dietary supplements and the high performance athlete," by R. J. Maughan, L. M. Burke, J. Dvorak, D. E. Larson Meyer, P. Peeling, S. M. Phillips, ... L. Engebretsen, 2018a, *International Journal of Sport Nutrition and Exercise Metabolism, 28*(2), pp. 104 125.

Table 2 Roles and Challenges of Evidence-Based Performance Supplements

Supplement	Mechanism of action	Challenges around use in track-and-field events (Burke, 2017)
Caffeine	Caffeine acts as an adenosine receptor antagonist, with many effects on different organs and systems. Actions include increases in epinephrine release, improvements in neuromuscular function, vigilance and alertness, and a masking of pain and perception of effort during exercise (Burke, 2008; Spriet, 2014).	• High degree of individual variability includes potential for negative response, minimal response, positive response, and super response; thorough practice is needed. • Repeated use for events within the same day (e.g., heptathlon and decathlon) requires careful planning of the timing and amount of doses, including whether a top up dose is even needed. • Use on successive days (e.g., heats and finals of many events in major meets) requires consideration of the effect on sleep and overall recovery, especially when the first event has a late night schedule. • Interactions with the efficacy or side effects of other supplements used concurrently needs careful consideration and experimentation; this is a likely scenario in many events (see Table 3).
Creatine monohydrate	Supplementation with creatine monohydrate increases muscle creatine stores and augments the rate of PCr resynthesis, thereby enhancing short term, high intensity exercise capacity (Buford et al., 2007) and the ability to perform repeat high intensity bouts. Chronic effects of increased muscle size and strength might be explained by indirect benefits (allowing the athlete to train harder) as well as the direct benefits of upregulation of cellular signaling and protein synthesis due to changes in cellular osmolality (Safdar et al., 2008). Benefits of additional muscle storage of glycogen and water might be of interest to endurance events (Twycross Lewis et al., 2016).	• Weight gain of 1 2 kg associated with creatine supplementation (Buford et al., 2007) may be counterproductive for weight sensitive events, such as jumps and distance races. However, a low dose approach that avoids the CM "loading phase" may avoid such issues (Rawson et al., 2011). • Interactions with the efficacy or side effects of other supplements used concurrently needs careful consideration and experimentation (see Table 3). Indeed, there has been lengthy but unclear speculation that the independently achieved performance benefits of creatine supplementation might be negated by caffeine supplementation (Trexler & Smith Ryan, 2015).
Nitrate	Nitrate enhances NO bioavailability via the NO_3^- nitrite NO pathway, which plays an important role in the modulation of skeletal muscle function (Jones, 2014). This pathway augments exercise performance via an enhanced function of Type II muscle fibers (Jones et al., 2016a), a reduced ATP cost of muscle force production, an increased efficiency of mitochondrial respiration, increased blood flow to the muscle, and a decrease in blood flow to VO_2 heterogeneities (Bailey et al., 2010).	• As for caffeine, responsiveness to nitrate supplementation is individual, and protocols for repeated use within the same day need planning. Furthermore, various research suggests a lack of response for athletes with a well developed aerobic capacity (i.e., VO_2max >60 ml/kg; Jones, 2014). • Interactions with the concurrent use of other performance supplements require consideration; at present, this has been investigated in relation to use with caffeine with unclear results (Burke, 2017).
β Alanine	β Alanine is a rate limiting precursor to carnosine, an endogenous intracellular (muscle) pH buffer during exercise (Lancha Junior et al., 2015). Chronic, daily supplementation increases skeletal muscle carnosine content (Saunders et al., 2017).	• Concurrent use of β alanine and sodium bicarbonate supplementation is logical when maximal buffering capacity is needed; however, literature support for combined benefits is premature.
Sodium bicarbonate	Sodium bicarbonate acts as an extracellular (blood) buffer, aiding intracellular pH regulation by raising the extracellular pH and HCO_3^- concentrations (Katz et al., 1984; Lancha Junior et al., 2015). The resultant pH gradient between the intracellular and extracellular environments leads to efflux of H^+ and La^- from the exercising muscle (Katz et al., 1984; Mainwood & Worsley Brown, 1975).	• Potential for gut disturbances is high risk in running based events, likely due to the increased sodium content and large fluid intake required to consume the supplement. • Protocols for repeated use within the same day or successive days need planning. • Interactions with the concurrent use of other performance supplements require consideration; concurrent use with caffeine supplementation has been investigated in other sports and often seen to counteract the benefits of the former due to gastrointestinal side effects (Burke, 2017).

Note. PCr phosphocreatine; CM creatine monohydrate; NO nitric oxide; ATP adenosine triphosphate.

benefits as enhanced glycogen storage and thermoregulation secondary to the changes in the cellular environment associated with the additional storage of creatine and water (Cooper et al., 2012; Kreider et al., 2017); however, the potential negative influence of minor weight gain from such mechanisms should be considered in the context of event-specific performance requirements (see Table 2).

Effective supplementation protocols generally encompass a "loading phase" of ~20 g/day (divided into 4 equal 5 g doses/day), for 5 7 days, followed by a "maintenance phase," typically involving a single daily CM dose of 3 5 g for the duration of the supplementation period (Hultman et al., 1996). Alternative approaches propose lower doses of CM (2 5 g/day), consumed for approximately 4 weeks (Rawson et al., 2011), based on the concept that low doses of CM provided over an adequate time period can increase muscle creatine levels (Hultman et al., 1996). Of note, consuming CM concurrently with a mixed protein/carbohydrate source (~50 g of protein and carbohydrate) may enhance muscle creatine uptake via insulin stimulation (Steenge et al., 2000), while it takes ~4 6 weeks following the cessation of supplementation for muscle stores to return to baseline levels.

No negative health effects have been noted with the long-term use of CM (up to 4 years) when appropriate loading protocols are followed (Schilling et al., 2001), and in some instances, potential anti-inflammatory effects are proposed (Deminice et al., 2013). Therefore, creatine supplementation consumed according to the previously mentioned protocols shows strong efficacy for both

Table 3 Performance Supplements That May Achieve a Marginal Performance Gain in Track-and-Field Events as Part of a Bespoke and Periodized Training and Nutrition Plan

Event	Caffeine	Creatine	Nitrate	β-Alanine	Bicarbonate
Sprints: 100 m, 100 m hurdles, 110 m hurdles, and 200 m	✓	✓			
Sustained sprints: 400 m and 400 m hurdles	✓	✓		✓	✓
Middle distance: 800 m, 1,500 m, 3,000 m, and steeple chase	✓		✓	✓	✓
Long distance: 5,000 m, 10,000 m, cross country, 20 km race walk, half marathon, marathon, 50 km race walk, and mountain/ultra running	✓		✓		
Jumps and throws: high jump, long jump, triple jump, pole vault, discus throw, hammer throw, javelin throw, and shot put	✓	✓			
Multievents: heptathlon and decathlon	✓	✓	✓	✓	✓

Readers are referred to Burke et al. (2019), da Costa et al. (2019), Slater et al. (2019); Stellingwerff et al. (2019), and Sygo et al. (2019).

acute and chronic performance gains, where power, strength, and short-repeated bouts of high-intensity exercise are encountered.

Nitrate

Nitrate supplementation has been shown to promote improvements in exercise tasks that predominately stress the aerobic energy system, such as time to exhaustion (4 25% increased performance) and sport-specific events (1 3% increased performance) lasting <40 min (Jones, 2014; McMahon et al., 2017). In addition, nitrate supplementation is proposed to enhance Type II muscle fiber function (Bailey et al., 2015) resulting in the improvement (3 5%) of high-intensity exercise efforts (Thompson et al., 2015; Wylie et al., 2016). Current evidence is equivocal for such benefit to exercise tasks lasting <12 min (Reynolds et al., 2016; Thompson et al., 2016), although more work is needed in this area.

Nitrate-rich foods include leafy green and root vegetables (i.e., spinach, rocket, celery, beetroot, etc.), although *beetroot juice* is the more popular supplement choice for exercise settings (McMahon et al., 2017). Acute performance benefits are generally seen within 2 3 hr following a NO_3^- bolus of 5 9 mmol (310 560 mg) (Hoon et al., 2014; Peeling et al., 2015); however, chronic periods of NO_3^- intake (>3 days) also appear beneficial to performance (Thompson et al., 2015, 2016).

There appears to be few side effects or limitations to nitrate supplementation other than the potential for minor gastrointestinal upset in some gut-sensitive athletes. In addition, an upper limit to the benefits of NO_3^- consumption has been shown (i.e., no greater benefit from 16.8 mmol [1,041 mg] vs. 8.4 mmol [521 mg]; Wylie et al., 2013), and it might also be considered that performance gains appear harder to obtain in elite athletes, with limited to no benefits generally seen in athletes with a maximal oxygen uptake (VO_2max) > 60 ml/kg (Jones, 2014). Therefore, individual trials of this supplement prior to use in competition are recommended to ensure its use is effective.

β-Alanine

β-Alanine supplementation is associated with the improved tolerance for maximal exercise in the range of 30 s to 10 min (Saunders et al., 2017), with small but potentially meaningful performance benefits (~0.2 3%) shown during both continuous and intermittent exercise tasks of this duration (Baguet et al., 2010; Chung et al., 2012). β-Alanine supplementation increases the muscle content of carnosine, an intracellular dipeptide with buffering, antioxidant, and anti-inflammatory properties. Of these effects, enhanced buffering is believed to explain the main performance benefit. β-Alanine dosing strategies typically involve the consumption of 3.2 6.4 g/day, ingested via a split-dose regimen (i.e., 0.8 1.6 g every 3 4 hr) over an extended supplement time frame of 4 12 weeks (Saunders et al., 2017). Regardless, a positive correlation between the magnitude of muscle carnosine change and performance benefit remains to be established (Saunders et al., 2017). Of note, the effectiveness of this supplement has also been shown in well-trained athletes (Bex et al., 2014; Saunders et al., 2017), although the performance margins for improvement are evidently smaller (Bellinger, 2014). A possible negative side effect of skin paresthesia should be considered, although sustained release tablets are noted to prevent this outcome and are reported to result in lower urinary loss of the supplement, possibly resulting in improved whole-body β-alanine retention (Decombaz et al., 2012). Finally, large interindividual variations in muscle carnosine synthesis have been reported with the use of β-alanine (Stautemas et al., 2018), and therefore, an individualized approach to supplementation must be considered.

Sodium Bicarbonate

Sodium bicarbonate ($NaHCO_3$) supplementation is proposed to enhance the performance (~2%) of short-term, high-intensity sprints lasting ~60 s in duration, with a reduced efficacy as the effort duration exceeds 10 min (Carr et al., 2011a). In contrast to β-alanine supplementation, which achieves a chronic elevation in intracellular buffering capacity, $NaHCO_3$ ingestion (consumed at a dose of 0.2 0.4 g/kg BM) achieves an acute increase in extracellular/blood buffering (Carr et al., 2011a) with peak blood bicarbonate levels occurring after 75 180 min (when consuming 0.3 g/kg BM $NaHCO_3$), which appear to decrease by 3-hr postsupplementation (Jones et al., 2016b). However, split doses (i.e., several smaller doses) taken over a 30- to 60-min time period (Krustrup et al., 2015) or serial loading with three to four smaller doses per day for two to four consecutive days prior to an event (Burke, 2013) has been proposed as methods to overcome the well-established gastrointestinal distress associated with this supplement. Further strategies used to minimize gastrointestinal distress include the coingestion of $NaHCO_3$ with a small carbohydrate-rich meal (~1.5 g/kg BM CHO; Carr et al., 2011b) or the use of the less effective but more gut-friendly sodium citrate as an alternative (Requena et al., 2005).

In summary, despite the relatively robust evidence base to support the consideration for use of these five supplements by well-trained athlete populations, the potential side effects and negative individual tolerance must be considered, and therefore, any supplement use should be thoroughly trialed in training before competition. Notwithstanding, as can be seen in Table 2, there are potential challenges for the use of these supplements within

track-and-field events, including issues of repeated use and the potential for interaction when several potentially useful supplements are used together (Burke, 2017). The current literature relevant to such use is not well understood and requires more research.

Therapeutic Nutritional Supplements and Prophylactic Aids

In the context of this review, "therapeutic/prophylactic supplements" are considered as nutritional aids that can be used either to (a) correct a deficiency, (b) assist in the *possible* prevention of illness and/or injury, or (c) help in the recovery from the stress of physical workloads via an anti-inflammatory effect. For instance, it is well known that iron deficiency can impair hematologic adaptation, which left untreated can negatively impact on athletic performance (Garvican et al., 2011). However, nutritional correction of this issue via various intervention strategies has been regularly shown to have a positive impact on correcting the underlying deficiency and enhancing athlete performance (Dawson et al., 2006; Garvican et al., 2011; Woods et al., 2014).

Regarding illness, there is strong evidence to suggest that immunodepression can occur as a result of strenuous exercise (Castell et al., 2019; Peake et al., 2017), and a high incidence of upper respiratory tract illness is frequently reported (Drew et al., 2018; Nieman, 1994), before and particularly after endurance events. Low-energy availability has been identified as a key nutritional factor in such illness (Drew et al., 2018; Heikura et al., 2018); however, the provision of nutritional supplements to alleviate exercise-induced immunodepression and to aid more rapid recovery in athletes has also been well studied. Sometimes certain supplements initially appear promising, but further intensive investigation fails to provide sufficient evidence of consistent beneficial effects on some aspects of exercise-induced immunodepression. As different nutritional supplements become unfashionable, whether targeting immunodepression or performance, others take their place; however, the pros and cons of these need to be carefully studied. For instance, probiotic supplementation has been investigated in recent years (as have prebiotics), with preliminary evidence of positive effects on immune function (Cox et al., 2010) that might support the consistency of training and competition. However, the effects of such supplementation are dependent on appropriate doses of live bacteria of specific strains (e.g., *Lactobacillus, Bifidobacterium*), and larger studies are still needed to provide definitive evidence that probiotics benefit the immune function of athletes. Glutamine and branched chain amino acids, which are often marketed to support bodybuilding and postexercise recovery, also have an unclear role in supporting immune function in athletes (Bermon et al., 2017). Clearly, immunonutrition is an emerging and important area for consideration in the use of dietary supplements for athlete populations, and as such, the reader is directed to recent reviews in this area (Bermon et al., 2017; Castell et al., 2019), in addition to the comprehensive paper on feeding the immune system (Calder, 2013).

With respect to the inflammatory response, there is a growing body of work that is investigating anti-inflammatory and antioxidant aspects of various foods and supplements. For instance, food polyphenols possess strong antioxidant and anti-inflammatory properties (Tsao, 2010) that may be beneficial to exercise recovery. Specifically, the high-anthocyanin content of tart Montmorency cherries is proposed to reduce the inflammatory and oxidative stress responses to strenuous exercise, such as a marathon (Dimitriou et al., 2015; Howatson et al., 2010), or consecutive days of intermittent high-intensity activity (Bell et al., 2014). This may be particularly relevant to the heavy training loads of many high-performance athletes, as well as the competition recovery in multievents in track-and-field athletics or the programs of middle-distance runners with heats and finals across several events at major competition. Other anti-inflammatory nutrients include flavonoids such as quercetin and green tea extract, plus fish oil, each of which may have a beneficial effect on delayed onset muscle soreness (Ranchordas et al., 2018). Consumption of highly colored vegetables/fruit is often advised; this advice is appropriate for elite athletes (previously mentioned), as these flavonoids (including blueberries, blackcurrants, and cherries) have a beneficial effect on exercise-induced inflammation, muscle damage, and illness (Bermon et al., 2017). In addition, it is proposed that some of these foods may also have the ability to reduce exercise-induced oxidative stress; however, there is currently some controversy about whether high-dose antioxidant supplementation (in the form of pills, powders, and tablets) is advisable to alleviate exercise-induced generation of reactive oxygen/nitrogen species. Emerging evidence suggests that antioxidant supplementation mitigates important exercise-induced adaptations, which may also extend to the immune system (Bermon et al., 2017).

In summary, there are various roles for nutritional supplements for what may be considered "therapeutic applications"; however, much more work is needed in this area to assess the efficacy of these supplements and to determine their true effect on athletic performance.

Disadvantages of Sports Foods and Dietary Supplements

The decision to take a supplement will always involve an attempt to gain a functional advantage, in most cases being health protection/improvement, physique management or enhanced recovery, or a direct performance enhancement. Contrary to these potential benefits, is the consideration that the supplement inherently possesses certain risks against its use; such risks can be divided into three categories.

Risks of Labeled Content

All supplements worldwide are legally bound to be sold in packages that contain a listing of the ingredients. Some national legislations may be stricter than others in setting and enforcing the list of permitted ingredients in supplements, but any consumer, and certainly, athletes who consider taking supplements to support their athletic performance should not consume a product with ingredients that cannot be recognized in a basic Internet search. A so-called "proprietary-blend" listing exotic names and claiming commercial Intellectual property cannot be considered a transparent listing of ingredients.

Even when supplement contents are clearly listed, they cannot necessarily all be considered safe. In many countries, the regulations covering supplements do not require specific testing before going to market but rely on notification of adverse events to remove unsafe products from sale. This has led to the inclusion of toxic substances in highly popular products, for example, the bodybuilding and weight loss supplement OxyELITE Pro (USPlabs, Hermosa Beach, CA) was found to be associated with at least one death and a cluster of serious liver complications, attributed to the ingredient 1,3-dimethylhexanamine (also known as DMAA; Johnston et al., 2016). This was subsequently removed from the list of ingredients

that may be included in supplements across many countries. Even where some ingredients might have been considered to be "safe use," basic toxicology laws dictate that any substance has the potential to lead to health-deteriorating effects when used by some individuals in specific scenarios or doses. For athletes, this is often preceded by decreased performance.

Risks of Undeclared or Unlabeled Content

Despite existing legislations, some supplements have been found to contain contaminants or health hazards, such as molds, glass, or animal feces (Benedict et al., 2016; Katz, 2013). A specific risk for competitive athletes is the undeclared presence of substances that are banned under the World Anti-Doping Agency (WADA) anti-doping code. Of course, these substances are sometimes identified on product labels, but athletes are either unaware that they are banned or are confused by technical/chemical names. For example, DMAA is a banned substance and has been included in supplements under a variety of other names including geranium oil/extract or geranamine; this no doubt contributed to many publicized and less well-known cases of anti-doping rule violations.

This risk of inadvertent doping from supplement use has been known for at least 30 years but is still very much present (de Hon & Coumans, 2007; Geyer et al., 2004; Martinez-Sanz et al., 2017). Indeed, the list of prohibited substances that have been detected in supplements includes stimulants, anabolic agents, selective androgen receptor modulators, diuretics, anorectics, and β2 agonists (Martinez-Sanz et al., 2017). When the amounts of banned substances in supplements are large enough to generate a direct effect (e.g., stimulant symptoms), this is an obvious sign of potential contamination to a consumer and sometimes an indicator of intentional but undeclared manufacturing practices (Geyer et al., 2008; Parr et al., 2007, 2008). But the risks of unintentional contamination from adulterated raw ingredients or cross-contamination of machinery, even by the most careful manufacturers, should not be underestimated and will never be zero (Judkins et al., 2010; Maughan et al., 2018b). Because of the ever-improving analytical capabilities in antidoping laboratories, trace amounts of prohibited substances can be found in biological samples taken at doping control. As a result, it cannot be stressed enough that athletes need to be aware that the WADA rules of strict liability mean that the detection of a prohibited substance in an athlete's specimen will be treated as an anti-doping rule violations, irrespective of the intentions behind it (Abbott, 2004; Hughes, 2015). Furthermore, it should also be understood that coaches, support personnel, parents, friends, and anyone else involved in the life of an athlete can also be implicated in an anti-doping rule violations, with WADA imposed sanctions (i.e., suspensions from sport) applicable. Using only products that have been audited by a third-party testing program and found to be free of banned substances will help to lower, but not completely eliminate, this risk. However, the general avoidance of the high-risk multi-ingredient supplements promoted as preworkouts or weight loss and bodybuilding products is recommended.

Noncontent-Related Risks

Some final concerns or issues regarding use of supplements and sports foods need to be considered. First, athletes should realize that any benefit of legal supplementation is bound to be small. Expecting too much of an intervention that addresses only the top end of one aspect of athletic performance may lead to disappointments and distract from other, more powerful, aspects of elite athletic training. Second, expense must also be considered, especially when finite resources could have been used in other areas of the preparation of an elite athlete's life. Finally, concerns have been raised that supplement use may be a stepping stone to taking other substances, including those prohibited by antidoping regulations (Backhouse et al., 2013). With this in mind, attention should be directed toward the ethical challenges of athlete product marketing and the influence of such approaches on encouraging undue supplement use, especially on young/developing athletes.

In summary, the very real risks of taking supplements should be carefully considered by competitive athletes. Of note, Castell et al. (2015) published an A Z Guide on 140 nutritional supplements in exercise and health; this includes efficacy tables ranging from those supplements shown to be ergogenically effective to those banned by WADA as being harmful or illegal. Readers might find it useful to consult this book prior to embarking on a course of supplements.

Conclusion: A Pragmatic Approach to Making Decisions about Supplements

In the past, athletes and coaches often worked in a parallel universe to their expert groups (e.g., governing bodies of sport) and service teams (e.g., sports scientists, dietitian, and physicians) with regard to performance supplements, with the former favoring supplement use based on their interest in performance gains and the latter being risk averse and dismissive of such products. The modern landscape, at least for high-performance athletes, has seen a unification of effort and intent, with many parties now working together to take a pragmatic approach to managing a risk:benefit audit around the use of sports foods, therapeutic/prophylactic supplements, and performance supplements. This has been led by organizations such as the International Olympic Committee and the Australian Institute of Sport, that have produced expert statements (Maughan et al., 2018a) and education resources (Burke & Cato, 2015) to guide a proactive but evidence-based consideration of the use of these products. In the case of sports foods, track-and-field athletes are guided to seek the expertise of an appropriately qualified sports nutrition professional who can help them balance the expense of using these specialized products with the scenarios in which they offer genuine performance benefits. Therapeutic/prophylactic supplements should involve the expertise of a sports physician, especially when a diagnosis of medical issues and nutrient deficiencies is needed. A decision-tree approach to the use of performance supplements (Figure 1), especially in collaboration with sports science/nutrition experts, will help to ensure that any products that are used are appropriate to the athlete's age and maturation in their event, integrated into the athlete's plan according to evidence-based protocols and appropriate scenarios, and chosen on the basis of being at low risk of contamination with banned or harmful ingredients. Ultimately, it is pertinent that sports foods and nutritional supplements should only be considered where a strong evidence base supports their use as safe, legal and effective and that such supplements are trialed thoroughly by the individual before committing to use in a competition setting.

References

Abbott, A. (2004). Dutch set the pace in bid to clean up diet supplements. *Nature, 429*(6993), 689. PubMed ID: 15201875 doi:10.1038/429689a

Backhouse, S.H., Whitaker, L., & Petroczi, A. (2013). Gateway to doping? Supplement use in the context of preferred competitive situations, doping attitude, beliefs, and norms. *Scandinavian Journal of*

Medicine & Science in Sports, 23(2), 244 252. doi:10.1111/j.1600 0838.2011.01374.x

Baguet, A., Bourgois, J., Vanhee, L., Achten, E., & Derave, W. (2010). Important role of muscle carnosine in rowing performance. *Journal of Applied Physiology, 109*(4), 1096 1101. doi:10.1152/japplphysiol. 00141.2010

Bailey, S.J., Fulford, J., Vanhatalo, A., Winyard, P.G., Blackwell, J.R., DiMenna, F.J., . . . Jones, A.M. (2010). Dietary nitrate supplementa tion enhances muscle contractile efficiency during knee extensor exercise in humans. *Journal of Applied Physiology, 109*(1), 135 148. doi:10.1152/japplphysiol.00046.2010

Bailey, S.J., Varnham, R.L., DiMenna, F.J., Breese, B.C., Wylie, L.J., & Jones, A.M. (2015). Inorganic nitrate supplementation improves muscle oxygenation, O_2 uptake kinetics, and exercise tolerance at high but not low pedal rates. *Journal of Applied Physiology, 118*(11), 1396 1405. doi:10.1152/japplphysiol.01141.2014

Bell, P.G., Walshe, I.H., Davison, G.W., Stevenson, E., & Howatson, G. (2014). Montmorency cherries reduce the oxidative stress and inflam matory responses to repeated days high intensity stochastic cycling. *Nutrients, 6*(2), 829 843. PMID: 24566440 doi:10.3390/nu6020829

Bellinger, P.M. (2014). Beta alanine supplementation for athletic per formance: An update. *The Journal of Strength and Conditioning Research, 28*(6), 1751 1770. doi:10.1519/JSC.0000000000000327

Benedict, K., Chiller, T.M., & Mody, R.K. (2016). Invasive fungal infections acquired from contaminated food or nutritional supple ments: A review of the literature. *Foodborne Pathogens and Disease, 13*(7), 343 349. doi:10.1089/fpd.2015.2108

Bermon, S., Castell, L.M., Calder, P.C., Bishop, N.C., Blomstrand, E., Mooren, F.C., . . . Nagatomi, R. (2017). Consensus statement immunonutrition and exercise. *Exercise Immunology Review, 23*, 8 50. PubMed ID: 28224969

Bex, T., Chung, W., Baguet, A., Stegen, S., Stautemas, J., Achten, E., & Derave, W. (2014). Muscle carnosine loading by beta alanine sup plementation is more pronounced in trained vs. untrained muscles. *Journal of Applied Physiology, 116*(2), 204 209. doi:10.1152/ japplphysiol.01033.2013

Branch, J.D. (2003). Effect of creatine supplementation on body compo sition and performance: A meta analysis. *International Journal of Sport Nutrition and Exercise Metabolism, 13*(2), 198 226. doi:10. 1123/ijsnem.13.2.198

Bruce, C.R., Anderson, M.E., Fraser, S.F., Stepto, N.K., Klein, R., Hopkins, W.G., & Hawley, J.A. (2000). Enhancement of 2000 m rowing performance after caffeine ingestion. *Medicine & Science in Sports & Exercise, 32*(11), 1958 1963. doi:10.1097/00005768 200011000 00021

Buford, T.W., Kreider, R.B., Stout, J.R., Greenwood, M., Campbell, B., Spano, M., . . . Antonio, J. (2007). International society of sports nutrition position stand: Creatine supplementation and exercise. *Journal of the International Society of Sports Nutrition, 4*, 6. PubMed ID: 17908288 doi:10.1186/1550 2783 4 6

Burke, L., Jeukendrup, A., Jones, A., Bosch, A., & Mooses, M. (2019). Nutrition for long distance athletes. *International Journal of Sport Nutrition and Exercise Metabolism,29*(2). doi:10.1123/ijsnem.2019 0004

Burke, L.M. (2008). Caffeine and sports performance. *Applied Physiology, Nutrition, and Metabolism, 33*(6), 1319 1334. doi:10.1139/H08 130

Burke, L.M. (2010). Fueling strategies to optimize performance: Training high or training low? *Scandinavian Journal of Medicine & Science in Sports, 20*(Suppl. 2), 48 58. doi:10.1111/j.1600 0838.2010.01185.x

Burke, L.M. (2013). Practical considerations for bicarbonate loading and sports performance. *Nestle Nutrition Institute Workshop Series, 75*, 15 26. PubMed ID: 23765347 doi:10.1159/000345814

Burke, L.M. (2017). Practical issues in evidence based use of performance supplements: Supplement interactions, repeated use and individual responses. *Sports Medicine, 47*(Suppl. 1), 79 100. doi:10.1007/ s40279 017 0687 1

Burke, L.M., & Cato, L. (2015). Dietary supplements and nutritional ergogenic aids. In L.M. Burke& V. Deakin (Eds.), *Clinical sports nutrition* (5th ed.). Sydney, Australia: McGraw Hill.

Calder, P.C. (2013). Feeding the immune system. *The Proceedings of the Nutrition Society, 72*(3), 299 309. PubMed ID: 23688939 doi:10. 1017/S0029665113001286

Carr, A.J., Hopkins, W.G., & Gore, C.J. (2011a). Effects of acute alkalosis and acidosis on performance: A meta analysis. *Sports Medicine, 41*(10), 801 814. doi:10.2165/11591440 000000000 00000

Carr, A.J., Slater, G.J., Gore, C.J., Dawson, B., & Burke, L.M. (2011b). Effect of sodium bicarbonate on [HCO_3], pH, and gastrointestinal symptoms. *International Journal of Sport Nutrition and Exercise Metabolism, 21*(3), 189 194. doi:10.1123/ijsnem.21.3.189

Castell, L.M., Nieman, D.C., Bermon, S., & Peeling, P. (2019). Exercise induced illness and inflammation: Can immunonutrition and iron help? *International Journal of Sport Nutrition and Exercise Metabolism,29*(2). doi:10.1123/ijsnem.2018 0288

Castell, L.M., Stear, S., & Burke, L.M. (2015). *Nutritional supplements in sport, exercise and health: An A Z guide*. Abingdon, United Kingdom: Routledge.

Chung, W., Shaw, G., Anderson, M.E., Pyne, D.B., Saunders, P.U., Bishop, D.J., & Burke, L.M. (2012). Effect of 10 week beta alanine supplementation on competition and training performance in elite swimmers. *Nutrients, 4*(10), 1441 1453. PubMed ID: 23201763 doi:10.3390/nu4101441

Cooper, R., Naclerio, F., Allgrove, J., & Jimenez, A. (2012). Creatine supplementation with specific view to exercise/sports performance: An update. *Journal of the International Society of Sports Nutrition, 9*(1), 33. PubMed ID: 22817979 doi:10.1186/1550 2783 9 33

Cox, A.J., Pyne, D.B., Saunders, P.U., & Fricker, P.A. (2010). Oral administration of the probiotic Lactobacillus fermentum VRI 003 and mucosal immunity in endurance athletes. *British Journal of Sports Medicine, 44*(4), 222 226. doi:10.1136/bjsm.2007.044628

da Costa, R., Knechtle, B., Tarnopolsky, M., & Hoffman, M. (2019). Nutrition for ultra marathons and mountain running. *International Journal of Sport Nutrition and Exercise Metabolism,29*(2). doi:10. 1123/ijsnem.2018 0255

Dawson, B., Goodman, C., Blee, T., Claydon, G., Peeling, P., Beilby, J., & Prins, A. (2006). Iron supplementation: Oral tablets versus intramus cular injection. *International Journal of Sport Nutrition and Exercise Metabolism, 16*(2), 180 186. doi:10.1123/ijsnem.16.2.180

Decombaz, J., Beaumont, M., Vuichoud, J., Bouisset, F., & Stellingwerff, T. (2012). Effect of slow release beta alanine tablets on absorption kinetics and paresthesia. *Amino Acids, 43*(1), 67 76. PubMed ID: 22139410 doi:10.1007/s00726 011 1169 7

de Hon, O., & Coumans, B. (2007). The continuing story of nutritional supplements and doping infractions. *British Journal of Sports Medicine, 41*(11), 800 805; discussion 805. doi:10.1136/bjsm.2007.037226

Deminice, R., Rosa, F.T., Franco, G.S., Jordao, A.A., & de Freitas, E.C. (2013). Effects of creatine supplementation on oxidative stress and inflammatory markers after repeated sprint exercise in humans. *Nutrition, 29*(9), 1127 1132. PubMed ID: 23800565 doi:10.1016/j.nut.2013.03.003

Dimitriou, L., Hill, J.A., Jehnali, A., Dunbar, J., Brouner, J., McHugh, M.P., & Howatson, G. (2015). Influence of a montmorency cherry juice blend on indices of exercise induced stress and upper respiratory tract symptoms following marathon running A pilot investigation. *Journal of the International Society of Sports Nutrition, 12*, 22. doi:10.1186/s12970 015 0085 8

Drew, M., Vlahovich, N., Hughes, D., Appaneal, R., Burke, L.M., Lundy, B., . . . Waddington, G. (2018). Prevalence of illness, poor mental health and sleep quality and low energy availability prior to the 2016 Summer Olympic Games. *British Journal of Sports Medicine, 52*(1), 47 53. doi:10.1136/bjsports 2017 098208

Ganio, M.S., Klau, J.F., Casa, D.J., Armstrong, L.E., & Maresh, C.M. (2009). Effect of caffeine on sport specific endurance performance: A systematic review. *The Journal of Strength and Conditioning Research, 23*(1), 315 324. doi:10.1519/JSC.0b013e31818b979a

Garthe, I., & Maughan, R.J. (2018). Athletes and supplements: Prevalence and perspectives. *International Journal of Sport Nutrition and Exer cise Metabolism, 28*(2), 126 138. doi:10.1123/ijsnem.2017 0429

Garvican, L.A., Lobigs, L., Telford, R., Fallon, K., & Gore, C.J. (2011). Haemoglobin mass in an anaemic female endurance runner before and after iron supplementation. *International Journal of Sports Physiology and Performance, 6*(1), 137 140. doi:10.1123/ijspp.6.1.137

Geyer, H., Parr, M.K., Koehler, K., Mareck, U., Schanzer, W., & Thevis, M. (2008). Nutritional supplements cross contaminated and faked with doping substances. *Journal of Mass Spectrometry, 43*(7), 892 902. doi:10.1002/jms.1452

Geyer, H., Parr, M.K., Mareck, U., Reinhart, U., Schrader, Y., & Schanzer, W. (2004). Analysis of non hormonal nutritional supple ments for anabolic androgenic steroids Results of an international study. *International Journal of Sports Medicine, 25*(2), 124 129. doi:10.1055/s 2004 819955

Goldstein, E.R., Ziegenfuss, T., Kalman, D., Kreider, R., Campbell, B., Wilborn, C., . . . Antonio, J. (2010). International society of sports nutrition position stand: Caffeine and performance. *Journal of the International Society of Sports Nutrition, 7*(1), 5. PubMed ID: 20205813 doi:10.1186/1550 2783 7 5

Gonçalves, L.S., Painelli, V.S., Yamaguchi, G., Oliveira, L.F., Saunders, B., da Silva, R.P., . . . Gualano, B. (2017). Dispelling the myth that habitual caffeine consumption influences the performance response to acute caffeine supplementation. *Journal of Applied Physiology, 123*(1):213 220. doi:10.1152/japplphysiol.00260.2017

Guest, N., Corey, P., Vescovi, J., & El Sohemy, A. (2018). Caffeine, CYP1A2 genotype, and endurance performance in athletes. *Medicine & Science in Sports & Exercise, 50*(8), 1570 1578. doi:10.1249/MSS. 0000000000001596

Harris, R.C., Soderlund, K., & Hultman, E. (1992). Elevation of creatine in resting and exercised muscle of normal subjects by creatine supple mentation. *Clinical Science, 83*(3), 367 374. doi:10.1042/cs0830367

Heikura, I.A., Burke, L.M., Bergland, D., Uusitalo, A.L.T., Mero, A.A., & Stellingwerff, T. (2018). Impact of energy availability, health, and sex on hemoglobin mass responses following live high train high alti tude training in elite female and male distance athletes. *International Journal of Sports Physiology and Performance, 13*(8):1090 1096. doi:10.1123/ijspp.2017 0547

Hoffman, M.D., Stellingwerff, T., & Costa, R.J.S. (2018). Considerations for ultra endurance activities: Part 2 Hydration. *Research in Sports Medicine,* 1 13. PubMed ID:30056755 doi:10.1080/15438627.2018. 1502189

Hoon, M.W., Jones, A.M., Johnson, N.A., Blackwell, J.R., Broad, E.M., Lundy, B., . . . Burke, L.M. (2014). The effect of variable doses of inorganic nitrate rich beetroot juice on simulated 2,000 m rowing performance in trained athletes. *International Journal of Sports Phys iology and Performance, 9*(4), 615 620. doi:10.1123/ijspp.2013 0207

Howatson, G., McHugh, M.P., Hill, J.A., Brouner, J., Jewell, A.P., van Someren, K.A., . . . Howatson, S.A. (2010). Influence of tart cherry juice on indices of recovery following marathon running. *Scandina vian Journal of Medicine & Science in Sports, 20*(6), 843 852. doi:10.1111/j.1600 0838.2009.01005.x

Hughes, D. (2015). The world anti doping code in sport: Update for 2015. *Australian Prescriber, 38*(5), 167 170. doi:10.18773/austprescr. 2015.059

Hultman, E., Soderlund, K., Timmons, J.A., Cederblad, G., & Greenhaff, P.L. (1996). Muscle creatine loading in men. *Journal of Applied Physiology, 81*(1), 232 237. doi:10.1152/jappl.1996.81.1.232

Irwin, C., Desbrow, B., Ellis, A., O'Keeffe, B., Grant, G., & Leveritt, M. (2011). Caffeine withdrawal and high intensity endurance cycling performance. *Journal of Sports Sciences, 29*(5), 509 515. doi:10. 1080/02640414.2010.541480

Johnston, D.I., Chang, A., Viray, M., Chatham Stephens, K., He, H., Taylor, E., . . . Park, S.Y. (2016). Hepatotoxicity associated with the dietary supplement OxyELITE pro Hawaii, 2013. *Drug Testing and Analysis, 8*(3 4), 319 327. doi:10.1002/dta.1894

Jones, A.M. (2014). Dietary nitrate supplementation and exercise perfor mance. *Sports Medicine, 44*(Suppl. 1), S35 S45. doi:10.1007/ s40279 014 0149 y

Jones, A.M., Ferguson, S.K., Bailey, S.J., Vanhatalo, A., & Poole, D.C. (2016a). Fiber type specific effects of dietary nitrate. *Exercise and Sport Sciences Reviews, 44*(2), 53 60. doi:10.1249/JES.0000000000000074

Jones, R.L., Stellingwerff, T., Artioli, G.G., Saunders, B., Cooper, S., & Sale, C. (2016b). Dose response of sodium bicarbonate ingestion highlights individuality in time course of blood analyte responses. *International Journal of Sport Nutrition and Exercise Metabolism, 26*(5), 445 453. doi:10.1123/ijsnem.2015 0286

Judkins, C.M., Teale, P., & Hall, D.J. (2010). The role of banned substance residue analysis in the control of dietary supplement contamination. *Drug Testing and Analysis, 2*(9), 417 420. doi:10.1002/dta.149

Katz, A., Costill, D.L., King, D.S., Hargreaves, M., & Fink, W.J. (1984). Maximal exercise tolerance after induced alkalosis. *International Journal of Sports Medicine, 5*(2), 107 110. doi:10.1055/s 2008 1025890

Katz, M.H. (2013). How can we know if supplements are safe if we do not know what is in them? Comment on "the frequency and character istics of dietary supplement recalls in the united states". *JAMA Internal Medicine, 173*(10), 928. doi:10.1001/jamainternmed.2013. 415

Knapik, J.J., Steelman, R.A., Hoedebecke, S.S., Austin, K.G., Farina, E.K., & Lieberman, H.R. (2016). Prevalence of dietary supplement use by athletes: Systematic review and meta analysis. *Sports Medi cine, 46*(1), 103 123. PubMed ID: 26442916 doi:10.1007/s40279 015 0387 7

Kreider, R.B., Kalman, D.S., Antonio, J., Ziegenfuss, T.N., Wildman, R., Collins, R., . . . Lopez, H.L. (2017). International society of sports nutrition position stand: Safety and efficacy of creatine supplementa tion in exercise, sport, and medicine. *Journal of the International Society of Sports Nutrition, 14*, 18. doi:10.1186/s12970 017 0173 z

Krustrup, P., Ermidis, G., & Mohr, M. (2015). Sodium bicarbonate intake improves high intensity intermittent exercise performance in trained young men. *Journal of the International Society of Sports Nutrition, 12*, 25. doi:10.1186/s12970 015 0087 6

Lancha Junior, A.H., de Salles Painelli, V., Saunders, B., & Artioli, G.G. (2015). Nutritional strategies to modulate intracellular and extracel lular buffering capacity during high intensity exercise. *Sports Medi cine, 45*(Suppl. 1), S71 S81. doi:10.1007/s40279 015 0397 5

Lane, S.C., Areta, J.L., Bird, S.R., Coffey, V.G., Burke, L.M., Desbrow, B., . . . Hawley, J.A. (2013). Caffeine ingestion and cycling power output in a low or normal muscle glycogen state. *Medicine & Science in Sports & Exercise, 45*(8), 1577 1584. doi:10.1249/MSS. 0b013e31828af183

Lanhers, C., Pereira, B., Naughton, G., Trousselard, M., Lesage, F.X., & Dutheil, F. (2017). Creatine supplementation and upper limb strength

performance: A systematic review and meta analysis. *Sports Medicine, 47*(1), 163 173. PubMed ID: 27328852 doi:10.1007/s40279 016 0571 4

Mainwood, G.W., & Worsley Brown, P. (1975). The effects of extracellular pH and buffer concentration on the efflux of lactate from frog sartorius muscle. *The Journal of Physiology, 250*(1), 1 22. doi:10.1113/jphysiol.1975.sp011040

Martinez Sanz, J.M., Sospedra, I., Ortiz, C.M., Baladia, E., Gil Izquierdo, A., & Ortiz Moncada, R. (2017). Intended or unintended doping? A review of the presence of doping substances in dietary supplements used in sports. *Nutrients, 9*(10), 1093. doi:10.3390/nu9101093

Maughan, R.J., Burke, L.M., Dvorak, J., Larson Meyer, D.E., Peeling, P., Phillips, S.M., . . . Engebretsen, L. (2018a). IOC consensus statement: Dietary supplements and the high performance athlete. *International Journal of Sport Nutrition and Exercise Metabolism, 28*(2), 104 125. doi:10.1123/ijsnem.2018 0020

Maughan, R.J., Shirreffs, S.M., & Vernec, A. (2018b). Making decisions about supplement use. *International Journal of Sport Nutrition and Exercise Metabolism, 28*(2), 212 219. doi:10.1123/ijsnem.2018 0009

McMahon, N.F., Leveritt, M.D., & Pavey, T.G. (2017). The effect of dietary nitrate supplementation on endurance exercise performance in healthy adults: A systematic review and meta analysis. *Sports Medicine, 47*(4):735 756. doi:10.1007/s40279 016 0617 7

Nieman, D.C. (1994). Exercise, upper respiratory tract infection, and the immune system. *Medicine & Science in Sports & Exercise, 26*(2), 128 139. doi:10.1249/00005768 199402000 00002

Parr, M.K., Geyer, H., Hoffmann, B., Kohler, K., Mareck, U., & Schanzer, W. (2007). High amounts of 17 methylated anabolic androgenic steroids in effervescent tablets on the dietary supplement market. *Biomedical Chromatography, 21*(2), 164 168. doi:10.1002/bmc.728

Parr, M.K., Koehler, K., Geyer, H., Guddat, S., & Schanzer, W. (2008). Clenbuterol marketed as dietary supplement. *Biomedical Chromatography, 22*(3), 298 300. doi:10.1002/bmc.928

Paton, C., Costa, V., & Guglielmo, L. (2015). Effects of caffeine chewing gum on race performance and physiology in male and female cyclists. *Journal of Sports Sciences, 33*(10), 1076 1083. doi:10.1080/02640414.2014.984752

Peake, J.M., Neubauer, O., Walsh, N.P., & Simpson, R.J. (2017). Recovery of the immune system after exercise. *Journal of Applied Physiology, 122*(5), 1077 1087. doi:10.1152/japplphysiol.00622.2016

Peeling, P., Binnie, M.J., Goods, P.S.R., Sim, M., & Burke, L.M. (2018). Evidence based supplements for the enhancement of athletic performance. *International Journal of Sport Nutrition and Exercise Metabolism, 28*(2), 178 187. doi:10.1123/ijsnem.2017 0343

Peeling, P., Cox, G.R., Bullock, N., & Burke, L.M. (2015). Beetroot juice improves on water 500 m time trial performance, and laboratory based paddling economy in national and international level kayak athletes. *International Journal of Sport Nutrition and Exercise Metabolism, 25*(3), 278 284. doi:10.1123/ijsnem.2014 0110

Ranchordas, M.K., Rogerson, D., Soltani, H., & Costello, J.T. (2018). Antioxidants for preventing and reducing muscle soreness after exercise: A Cochrane systematic review. *British Journal of Sports Medicine*. doi:10.1136/bjsports 2018 099599

Rawson, E.S., Stec, M.J., Frederickson, S.J., & Miles, M.P. (2011). Low dose creatine supplementation enhances fatigue resistance in the absence of weight gain. *Nutrition, 27*(4), 451 455. PubMed ID: 20591625 doi:10.1016/j.nut.2010.04.001

Reidy, P.T., & Rasmussen, B.B. (2016). Role of ingested amino acids and protein in the promotion of resistance exercise induced muscle protein anabolism. *The Journal of Nutrition, 146*(2), 155 183. doi:10.3945/jn.114.203208

Requena, B., Zabala, M., Padial, P., & Feriche, B. (2005). Sodium bicarbonate and sodium citrate: Ergogenic aids? *The Journal of Strength and Conditioning Research, 19*(1), 213 224. PubMed ID: 15705037 doi:10.1519/13733.1

Reynolds, C., Halpenny, C., Hughes, C., Jordan, S., Quinn, A., & Egan, B. (2016). Acute ingestion of beetroot juice does not improve repeated sprint performance in male team sport athletes. *Proceedings of the Nutrition Society, 75*(OCE3), E97. doi:10.1017/S0029665116001129

Safdar, A., Yardley, N.J., Snow, R., Melov, S., & Tarnopolsky, M.A. (2008). Global and targeted gene expression and protein content in skeletal muscle of young men following short term creatine monohydrate supplementation. *Physiological Genomics, 32*(2), 219 228. doi:10.1152/physiolgenomics.00157.2007

Saunders, B., Elliott Sale, K., Artioli, G.G., Swinton, P.A., Dolan, E., Roschel, H., . . . Gualano, B. (2017). Beta alanine supplementation to improve exercise capacity and performance: A systematic review and meta analysis. *British Journal of Sports Medicine, 51*(8), 658 669. doi:10.1136/bjsports 2016 096396

Schilling, B.K., Stone, M.H., Utter, A., Kearney, J.T., Johnson, M., Coglianese, R., . . . Stone, M.E. (2001). Creatine supplementation and health variables: A retrospective study. *Medicine & Science in Sports & Exercise, 33*(2), 183 188. doi:10.1097/00005768 200102000 00002

Slater, G., Sygo, J., & Jorgensen, M. (2019). Nutrition for sprints. *International Journal of Sport Nutrition and Exercise and Metabolism,29*(2). doi:10.1123/ijsnem.2019 0273

Spriet, L.L. (2014). Exercise and sport performance with low doses of caffeine. *Sports Medicine, 44*(Suppl. 2), S175 S184. doi:10.1007/s40279 014 0257 8

Stautemas, J., Lefevere, F., Everaert, I., & Derave, W. (2018). Pharmacokinetics of β alanine using different dosing strategies. *Frontiers in Nutrition, 5*:70. doi:10.3389/fnut.2018.00070

Steenge, G.R., Simpson, E.J., & Greenhaff, P.L. (2000). Protein and carbohydrate induced augmentation of whole body creatine retention in humans. *Journal of Applied Physiology, 89*(3), 1165 1171. doi:10.1152/jappl.2000.89.3.1165

Stellingwerff, T., Whitfield, J., & Bovim, I. (2019). Nutrition for middle distance athletes. *International Journal of Sport Nutrition and Exercise Metabolism,29*(2). doi:10.1123/ijsnem.2019 0241

Sygo, J., Kendig, A., Killer, S., & Stellingwerff, T. (2019). Fueling for the field: Nutrition for jumps, throws, and combined events. *International Journal of Sport Nutrition and Exercise Metabolism,29*(2). doi:10.1123/ijsnem.2019 0272

Talanian, J.L., & Spriet, L.L. (2016). Low and moderate doses of caffeine late in exercise improve performance in trained cyclists. *Applied Physiology, Nutrition, and Metabolism, 41*(8), 850 855. doi:10.1139/apnm 2016 0053

Thompson, C., Vanhatalo, A., Jell, H., Fulford, J., Carter, J., Nyman, L., . . . Jones, A.M. (2016). Dietary nitrate supplementation improves sprint and high intensity intermittent running performance. *Nitric Oxide, 61*, 55 61. PubMed ID: 27777094 doi:10.1016/j.niox.2016.10.006

Thompson, C., Wylie, L.J., Fulford, J., Kelly, J., Black, M.I., McDonagh, S.T., . . . Jones, A.M. (2015). Dietary nitrate improves sprint performance and cognitive function during prolonged intermittent exercise. *European Journal of Applied Physiology, 115*(9), 1825 1834. doi:10.1007/s00421 015 3166 0

Trexler, E.T., & Smith Ryan, A.E. (2015). Creatine and caffeine: Considerations for concurrent supplementation. *International Journal of Sport Nutrition and Exercise Metabolism, 25*(6), 607 623. doi:10.1123/ijsnem.2014 0193

Tsao, R. (2010). Chemistry and biochemistry of dietary polyphenols. *Nutrients, 2*(12), 1231 1246. PubMed ID: 22254006 doi:10.3390/nu2121231

Twycross Lewis, R., Kilduff, L.P., Wang, G., & Pitsiladis, Y.P. (2016). The effects of creatine supplementation on thermoregulation and physical (cognitive) performance: A review and future prospects. *Amino Acids, 48*(8), 1843 1855. PubMed ID: 27085634 doi:10.1007/s00726 016 2237 9

Wiles, J.D., Coleman, D., Tegerdine, M., & Swaine, I.L. (2006). The effects of caffeine ingestion on performance time, speed and power during a laboratory based 1 km cycling time trial. *Journal of Sports Sciences,* 24(11), 1165 1171. doi:10.1080/02640410500457687

Woods, A., Garvican Lewis, L.A., Saunders, P.U., Lovell, G., Hughes, D., Fazakerley, R., . . . Thompson, K.G. (2014). Four weeks of IV iron supplementation reduces perceived fatigue and mood disturbance in distance runners. *PLoS ONE, 9*(9), e108042. PubMed ID: 25247929 doi:10.1371/journal.pone.0108042

Wylie, L.J., Bailey, S.J., Kelly, J., Blackwell, J.R., Vanhatalo, A., & Jones, A.M. (2016). Influence of beetroot juice supplementation on inter mittent exercise performance. *European Journal of Applied Physiol ogy, 116*(2), 415 425. doi:10.1007/s00421 015 3296 4

Wylie, L.J., Kelly, J., Bailey, S.J., Blackwell, J.R., Skiba, P.F., Winyard, P.G., . . . Jones, A.M. (2013). Beetroot juice and exercise: Pharma codynamic and dose response relationships. *Journal of Applied Physiology, 115*(3), 325 336. doi:10.1152/japplphysiol.00372.2013

International Journal of Sports Physiology and Performance, (Ahead of Print)
https://doi.org/10.1123/ijspp.2019 0287

Human Kinetics
ORIGINAL INVESTIGATION

The Effects of Different Forms of Caffeine Supplement on 5-Km Running Performance

Peter J. Whalley, Chey G. Dearing, and Carl D. Paton

Purpose: Caffeine is frequently used by athletes as an ergogenic aid. Various alternate forms of caffeine administration are available, which may produce different effects. This investigation compares the effects of different forms of caffeine supplementation on 5-km running performance, and the relationship between athlete ability and degree of enhancement attained. ***Methods:*** Fourteen amateur runners completed a series of self-paced outdoor time trials following unknown ingestion of a placebo (P) or one of 3 alternate forms of caffeine supplement. Trials were randomized in a crossover design with caffeine (approximately 3 4.5 mg·kg ^{1}) administered 15 minutes before each trial via chewing gum (CG), dissolvable mouth strips (CS), or tablet (CT). ***Results:*** Compared with P, all caffeine supplements led to worthwhile enhancements in running performance with a mean (±95% confidence limit) overall effect across all supplements of 1.4% ± 0.9%. Individual caffeine treatment effects (CG = 0.9% ± 1.4%, CS = 1.2% ± 1.0%, and CT = 2.0% ± 1.1%) were not significantly different ($P > .05$) from each other; however, CT trials produced the largest gain and was significantly different ($P = .02$) compared with P. There was no significant difference in heart rate or rate of perceived exertion across the performance trials. The magnitude of caffeine enhancement was also strongly correlated ($r = .87$) with no-treatment performance time. ***Conclusions:*** The findings showed that irrespective of delivery form, moderate dose of caffeine supplementation produces worthwhile gains in 5-km running performance compared with a P. Furthermore, the magnitude of caffeine enhancement is highly individualized, but it appears related to athlete performance ability.

Keywords: athletes, ergogenic aid, genetics, nutrition, time trial

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed of all psychoactive drugs and is frequently used by athletes as a performance-enhancing ergogenic aid. A number of previous reviews have comprehensively documented the performance-enhancing effects of caffeine for both aerobic-[1,2] and anaerobic-based sporting activities.[3,4] Caffeine exerts its ergogenic effects via both physiological and psychological mechanisms[5]; the most likely mechanisms impacting actual physical performance are an increase in central nervous system drive, increased catecholamine release, and enhancements in muscle recruitment and contractility (see Graham[6] and Davis and Green[7] for detailed caffeine mechanism reviews).

Q1 Although caffeine is most frequently consumed via oral administration (beverages such as coffee and energy drinks or as tablets [CT] and gels), there also exists a variety of sublingual or buccal administration products including chewing gum (CG), dissolvable mouth strips (CS), and aerosols. Oral caffeine products are typically ingested 60 minutes or more before exercise to allow for sufficient absorption and metabolism via the hepatic system. In contrast, sublingual- or buccal-administered products may produce more rapid effects as they are absorbed directly into the bloodstream[8] and avoid the first-pass metabolism of orally ingested products. Indeed, a study by Kamimori et al[9] comparing equal doses of caffeine administered in traditional CT form or via CG reported that plasma caffeine levels reached peak values in less than 30 minutes for gum but was closer to 90 minutes for CTs. Evidence for the rapid effects of caffeinated gum has been reported in 2 performance-based cycling studies. Paton et al[10] found that CG taken midway between repeated exercise sets rapidly reversed the accumulation of fatigue in the latter sets compared with a placebo (P). In a more recent study, Paton et al[11] reported an improvement in cycling time-trial performance within 20 minutes of an initial dose of caffeinated gum during a ~60-minute time trial. However, neither of these previous studies compared the effects of buccal delivery forms of caffeine against oral supplementation.

The majority of available evidence indicates caffeine supplementation enhances performance across sporting events by a modest but potentially worthwhile 1% to 3%. However, research also indicates a wide range of individual responses to caffeine ingestion.[2] Several factors may account for these individual variations including the extent of habitual consumption, length of abstention before an event, the timing of ingestion, and participant ability.[12] Furthermore, recent research suggests that an individual's genotype and variations in the enzyme responsible for caffeine metabolism cytochrome P450 1A2 (CYP1A2) may also influence an individual's response to caffeine ingestion,[13] particularly when using orally consumed products requiring hepatic absorption. If first-pass metabolism of caffeine can be avoided by using different caffeine forms, then it is possible that buccal delivery will produce different effects from oral delivery products in individual subjects. Furthermore, if different forms of caffeine produce different effects, it may be possible to individualize the use of caffeine supplements to gain larger effects.[14] To our knowledge, there is currently no published research comparing the effects of different caffeine delivery forms on exercise performance. Therefore, the primary aim of this study was to investigate the ergogenic effects of different forms of caffeine supplementation on 5-km running performance. The study also determined the reproducibility of

Whalley and Paton are with the School of Health and Sport Science, Eastern Inst of Technology, Napier, New Zealand. Dearing is with the School of Nursing, Eastern Inst of Technology, Napier, New Zealand. Paton (cpaton@eit.ac.nz) is corresponding author.

caffeine effects along with examining any relationship between athlete ability and the magnitude of caffeine's ergogenic effect.

Methods

Sixteen amateur runners initially volunteered to participate in this study. All runners gave their written informed consent to participate in the study, which was approved by the Eastern Institute of Technology Human Research Ethics committee in accordance with the Declaration of Helsinki. Two runners failed to complete the study: one due to an unrelated injury and other due to noncompliance with scheduled testing. At the initial briefing, runners were told that they would be taking part in a study to test the efficacy of 4 different commercially available caffeine supplements. The presence of the fake P condition was not disclosed until the study was completed. A total of 14 runners completed this study (mean [SD]; age = 40 [8] y; weight = 69 [11] kg; height = 177 [11] cm). The cohort consisted of 10 males (40 [9] y; 73 [10] kg; 181 [10] cm) and 4 females (41 [9] y; 167 [7] cm; 59 [2] kg). Prestudy training and food questionnaires indicated that runners regularly trained between 3 and 10 hours per week, and that 10 identified as moderate caffeine users (100 400 mg·d ^{1}), while 4 identified as low caffeine users (<100 mg·d ^{1}).

Each runner completed five 5-km running time trials over a 4 to 9 week period with a minimum of 4 days and a maximum of 10 days between the trials. During the 24 hours preceding any trial, runners were required to prepare as though it were a competition and to abstain from caffeine consumption. Runners were also required to keep a record of their dietary intake in the 24 hours preceding the first trial and replicate this as closely as possible for subsequent trials. All trials took place on an outdoor 400-m synthetic running track under stable environmental conditions. Q3 The facility met the international IAAF Tier 1 standard for athletics and had grandstand seating and a raised stop bank around the perimeter to provide shelter from the wind. Weather details, including wind speed temperature and humidity, were checked at the start of each trial using a TESA Pro WS1151 wireless weather station (Fine Offset Electronics, Shenzhen, China). Before each trial, runners conducted a prescribed 25-minute warm-up of low- to moderate-intensity running, dynamic stretching, technique drills (including heel flicks and skipping), and gradually accelerated Q4 sprints. All runners initially completed a familiarization trial without any treatment to establish their baseline performance. For subsequent trials, runners were assigned to one of 4 supplement treatments (see below for details). Supplement administration occurred during the warm-up period, 15 minutes before the commencement of each time trial.

All trials were performed at a self-paced maximal effort. Trial timing was conducted using Webscorer software (Webscorer Inc, Woodinville, WA), loaded onto a portable tablet device. Heart rate was recorded at 1 Hz during the trials using a telemetry system (Garmin 920 XT; Garmin International, Olathe, KS). On completion of each trial, runners were asked to estimate their average rate Q5 of perceived exertion using the Borg 6 20 scale (Borg, 1982).

Experimental treatments were randomized using a 4 × 4 Latin square model. Given the different nature of the caffeine products, it was not feasible to blind the runners to the treatment condition. All caffeine doses were administered dependent on the runner's prestudy body mass. Runners less than 65 kg received a caffeine dose of 200 mg (females: n = 4 and males: n = 2), while runners more than 65 kg received a dose of 300 mg (males: n = 8); this regime ensured all runners received a moderate dose of ~3 to 4.5 mg·kg ^{1}. Caffeine was provided in 3 different forms: caffeine CG was administered as 100 mg of caffeine per piece (Military Energy Gum; Marketright Inc). Caffeine-dissolvable CS was administered as 40 mg of caffeine per piece (Revvies Energy Strips, NSW, Australia), and CT was administered as 100 mg of caffeine per tablet (NoDoz, Cedar Rapids, IA). The P was administered as a fixed 300-mg dose of glucose powder in an opaque gelatin capsule. Q6

Statistical Analyses

Date are reported as mean (SD). The magnitude of the effect of caffeine on performance time and physiological measures was determined using a made for purpose spreadsheet,[15] in accordance with recommendations by Batterham and Hopkins.[16] Briefly, the mean effect of caffeine and its 95% confidence limits (CLs) were estimated using the unequal-variance, *t*-statistic computed for change scores between the treatments. Measures were log transformed to reduce bias arising from nonuniformity of error and back-transformed to obtain changes in means as percents. The effects of caffeine on performance time were interpreted qualitatively using magnitude-based inference: Unclear effects were those with the possibility (>25% chance) of benefit, but unacceptable risk of harm (>5%). All other effects were clear and reported with a probability of benefit/harm using the following scale: 25% to 74% (possibly), 75% to 94% (likely), and 95% (very likely). The spreadsheet used computes these chances when a value for the smallest practical, worthwhile change is provided. We used a conservative value of 0.5% for performance time, as previous research suggests that this value is consistent with the estimated smallest worthwhile enhancement for runners competing over the 3- to 10-km distance.[17] As a secondary analysis, we also performed a 1-way repeated-measure analysis of variance, followed by Bonferroni-corrected Tukey post hoc analysis (version 4; GraphPad, San Diego, CA), to compare differences between the caffeine and P supplements. In addition, a linear regression and Pearson *r* correlations were performed to assess the relationship between the mean percentage changes in performance for all caffeine trials combined compared with the P condition. All statistical differences ($P < .05$) and correlations ($\alpha < .05$) were considered significant.

Results

The mean (SD) for all measured variables across each trial are shown in Table 1. The only significant difference ($P = .02$) observed was for finish time between the P and CT condition. Differences in finish time, heart rate, or perceived exertion between all caffeine supplements were deemed trivial and nonsignificant ($P > .05$). In comparison with the P condition, the finish time (mean ± 95% confidence limit) decreased by −1.0% ± 1.4%, −1.2% ± 1.0%, and −2.0% ± 1.1% for CG, CS, and CT treatments, respectively (Figure 1). The average effect on finish time of all caffeine treatments combined was −1.4% ± 0.9%. The estimated magnitudes (chances) of benefit of each caffeine treatment compared with P was 75% (likely), 93% (likely), and 99% (very likely) for CG, CS, and CT, respectively; the average chance of effectiveness was 97% for all treatments combined.

Figure 2 shows the mean (SD) percentage change in performance time for the caffeine treatments relative to the P condition for each individual. The majority (10/14) of runners reported similar (±1%) responses to the various caffeine forms. Four runners reported larger than expected (>1%) variations in caffeine response.

Table 1 Comparison of 5-Km Running Performance, Time Heart Rate, and Perceived Exertion, Mean (SD) Q7

Treatment	5-Km time, min:s	Heart rate, bpm	Rate of perceived exertion
Familiarization (F)	20:46 (3:12)	163 (13)	16.6 (0.8)
Placebo (P)	20:45 (3:12)	164 (11)	16.0 (0.8)
Gum (CG)	20:30 2:43)	165 (12)	16.3 (1.0)
Strips (CS)	20:29 (2:59)	166 (11)	15.8 (2.0)
Tablets (CT)	20:19 (2:52)*	165 (12)	16.1 (1.0)

*Significantly different (P .02) from placebo.

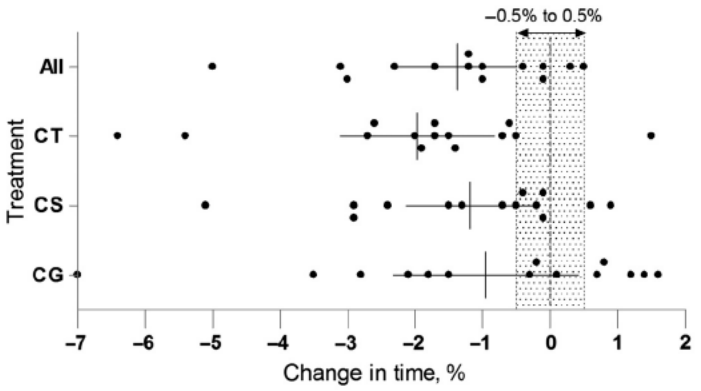

Figure 1 Mean (±95% confidence limit) change in 5 km performance time as percent (%) for different caffeine forms and all combined. Shaded area indicates the smallest effect range (±0.5%). Closed circles (•) indicate individual runner responses to the treatments; CG, chewing gum, CS, dissolvable mouth strips; CT, tablet.

There was a strong correlation ($r = .87$, $P < .001$) between baseline performance time and the magnitude of enhancement (expressed as a percent) across the group.

Discussion

The main aim of this study was to examine the effects of different forms of caffeine delivery on 5-km running performance. Our main finding was that caffeine in a moderate dose (approximately 3 4.5 mg·kg ^{1}) provides a likely to very likely beneficial (>75%) enhancement to 5-km performance irrespective of delivery form. There were only small (nonsignificant) differences in the magnitude of performance enhancement between caffeine forms. Caffeine provided in CG, dissolvable CS, and CT forms led to performance gains of between 1% and 2% with an average effect across all forms of ~1.4%. Supplementary findings of our study were a large interindividual response to caffeine and a strong correlation ($r = .87$) between no-treatment performance and the magnitude of the response to caffeine. Thus, slower runners experienced greater performance benefit from caffeine compared with faster runners.

The overall magnitude of performance enhancements reported in our study is similar to previous running studies, which reported ~1% improvements in performance over a 5-km run[18] and gains of 1.3% in an 8-km run[19] in similarly trained runners. Furthermore, our observed enhancement is consistent with that reported in several reviews examining caffeine's effects across various duration endurance events.[2,20] The mechanism responsible for the performance enhancement in our study is speculative due to limited physiological measures. Potential mechanisms responsible for caffeine's positive effects include enhanced lipid metabolism, increased central nervous system drive, or reduced perception of effort.[6] Given the short duration (~20 min) of exercise involved, it is unlikely that enhancements in lipid metabolism could account for the enhancement reported. The most likely reason for the enhanced performance in our study, therefore, appears to be a reduced perception of effort (facilitated by caffeine's antagonism of adenosine receptors) as we found no significant difference in runners perceived exertion despite the faster run times in the caffeine trials.

A unique aspect of our study was the comparison of the effects of different forms of caffeine delivery. Traditionally, caffeine is administered orally 60 to 90 minutes before activity to allow

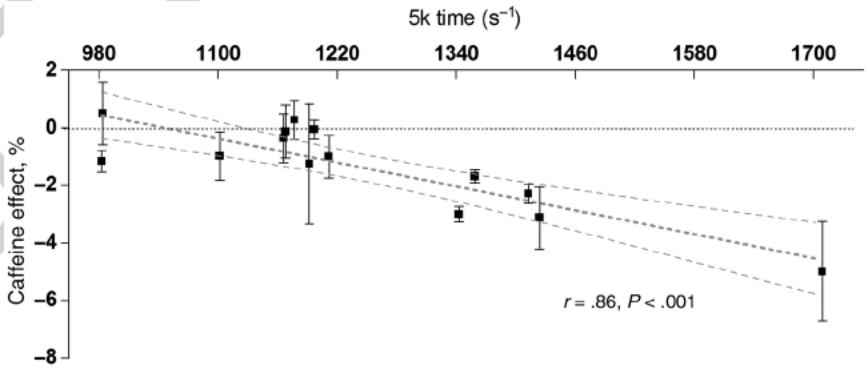

Figure 2 The relationship between baseline (P) performance and percent (%) change in performance time with caffeine. Individual error bars indicate the mean (SD) response for each individual. Dashed lines indicate the ±95% confidence limit.

sufficient time for absorption and proposed enhancements to occur. However, previous research[9] has demonstrated that buccal-absorbed caffeine gum reaches peak values faster than ingested caffeine and, therefore may, provide a more rapid boost to performance. Our study, therefore, purposely used a short intervening period (<20 min) between the administration and the performance trial to test the hypothesis that caffeine absorbed via the mouth (CG and CS forms) would act more rapidly and produce a larger enhancement than caffeine (CT) requiring slower hepatic absorption. However, our results did not support this hypothesis as there were similar (<1%) in effects between the various caffeine supplements, and surprisingly, the greatest enhancement was reported with CT. The small differences in the effects of the caffeine delivery forms may be due to random sampling variation. However, the unexpected larger effect observed with CT we speculate may be attributed to participant familiarity with the particular tablet product used. The prestudy questionnaire indicated that the majority of runners ingested caffeine via the same CTs used in the study, and none reported previous use of either CG or CS products. Therefore, it is plausible that the true ergogenic effect of CT was supplemented by an element of familiarity or prior belief similar to the P effect. Interestingly, however, there was no evidence of any benefit when runners ingested a true P despite them being told they were ingesting caffeine.

Another unique aspect of our study is that it provides an examination of the reliability of an individual's response to caffeine across 3 repeated trials. To our knowledge, the only previous study examining the reliability of caffeine's ergogenic effect was for cycling performance across 2 trials.[21] In their study, Astorino et al[21] found that 77% (7/9) of subjects experienced a consistent enhancement in performance across the repeated caffeine trials. By comparison, we estimate that ~71% (10/14) of runners in our study (Figure 2) report a consistent effect of caffeine given that runners have a typical variation in run times of ±1%.[17] Also, similar to the Astorino study, we found substantial interindividual responses to caffeine ingestion. Recent research[13,22] suggests that an individual's variation in metabolic genotype (CYP1A2) may explain this observed variability seen in many caffeine studies. Unfortunately, due to our inability to perform a genetic assessment, we cannot confirm if genotype played a role in the individual responses seen in the current study. However, it is possible that the large variation in response seen in some runners, using the different caffeine forms, is related to differences in the way oral- and buccal-administered caffeine is metabolized in these individuals.

Finally, our study also examined the relationship between performance ability and the magnitude of caffeine's effect. Our results show a large correlation ($r = .87$) between baseline performance and the level of enhancement, with lower ability runners gaining the most benefit. This finding is similar to a recent study,[23] which reported greater improvement with lower ability cyclists during a high-intensity 3-km cycling time trial. The reason for the lack of improvement in higher ability athletes is unclear, but this may reflect that they are already physiologically close to their maximal performance limit and have little room left for further enhancement effects due to caffeine. However, in contrast to our findings, other studies[18,24] have reported no apparent relationship between performance ability and level of enhancement from caffeine. However, these latter studies only performed cross-sectional analysis over composite groups (eg, trained and untrained) and did not specifically examine the strength of the relationship across a range of individuals making direct comparisons with the current study difficult.

Practical Applications

We observed that a caffeine dose of ~3 to 4.5 mg·kg ^{1} improved 5-km running performance by 1% to 2% irrespective of delivery form or absorption method. Although the magnitude of enhancement was small, it would prove beneficial in events of similar duration with closely matched competitors. We also found that caffeine delivered in tablet form exerted its ergogenic properties far quicker than is traditionally believed, and therefore, it is appropriate for use when the time period between delivery and the required effect is limited.

Conclusions

In summary, our findings indicate that caffeine supplementation leads to small but potentially worthwhile enhancements in 5-km running performance irrespective of delivery form. Furthermore, the effects of caffeine delivered in different forms on individual runners are relatively consistent, despite large interindividual responses. Finally, there is a significant relationship between the magnitude of performance gain from caffeine and runner ability. Further research is needed to better elucidate the reasons for the differences in individual responses to caffeine and also to identify and optimize strategies for using different caffeine forms to enhance performance with individual athletes.

Acknowledgments

The authors would like to acknowledge the runners for their participation and visiting research scholars Mathias Vangsoe and Jonas Kvoltrup for their valuable assistance in data collection. This research was supported by internal institutional funds. The results of the current study do not constitute endorsement of the products by the authors or the journal.

References

1. Doherty M, Smith PM. Effects of caffeine ingestion on exercise testing: a meta analysis. *Int J Sport Nutr Exerc Metab*. 2004;14:626 646. PubMed ID: 15657469 doi:10.1123/ijsnem.14.6.626
2. Ganio M, Klaus J, Casa D, et al. Effect of caffeine on sport specific endurance performance: a systematic review. *J Strength Cond Res*. 2009;23:315 324. PubMed ID: 19077738 doi:10.1519/JSC.0b013e31818b979a
3. Astorino TA, Roberson DW. Efficacy of acute caffeine ingestion for short term high intensity exercise performance: a systematic review. *J Strength Cond Res*. 2010;24(1):257 265. PubMed ID: 19924012 doi:10.1519/JSC.0b013e3181c1f88a
4. Warren GL, Park ND, Maresca RD, McKibans KI, Millard Stafford ML. Effect of caffeine ingestion on muscular strength and endurance: a meta analysis. *Med Sci Sports Exerc*. 2010;42(7):1375 1387. PubMed ID: 20019636 doi:10.1249/MSS.0b013e3181cabbd8
5. Burke L, Desbrow B, Spriet L. *Caffeine for Sports Performance*. Champaign, IL: Human Kinetics; 2013.
6. Graham TE. Caffeine and exercise: metabolism, endurance, and per formance. *Sport Med*. 2001;31(11):785 807. doi:10.2165/00007256 200131110 00002

7. Davis JK, Green JM. Caffeine and anaerobic performance: ergogenic value and mechanisms of action. *Sports Med*. 2009;39(10):813 832. PubMed ID: 19757860 doi:10.2165/11317770 000000000 00000
8. Wickham KA, Spriet LL. Administration of caffeine in alternate forms. *Sport Med*. 2018;48:79 91. doi:10.1007/s40279 017 0848 2
9. Kamimori GH, Karyekar CS, Otterstetter R, et al. The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. *Int J Pharm*. 2002;234:159 167. doi:10.1016/S0378 5173(01)00958 9
10. Paton C, Lowe T, Irvine A. Caffeinated chewing gum increases repeated sprint performance and augments increases in testosterone in competitive cyclists. *Eur J Appl Physiol*. 2010;110(6):1243 1250. PubMed ID: 20737165 doi:10.1007/s00421 010 1620 6
11. Paton C, Costa V, Guglielmo L. Effects of caffeine chewing gum on race performance and physiology in male and female cyclists. *J Sports Sci*. 2015;33(10):1076 1083. PubMed ID: 25517202 doi:10.1080/02640414.2014.984752
12. Astorino TA, Cottrell T, Talhami Lozano A, Aburto Pratt K, Duhon J. Effect of caffeine on RPE and perceptions of pain, arousal, and pleasure/displeasure during a cycling time trial in endurance trained and active men. *Physiol Behav*. 2012;106(2):211 217. PubMed ID: 22349482 doi:10.1016/j.physbeh.2012.02.006
13. Guest N, Corey P, Vescovi J, El Sohemy A. Caffeine, CYP1A2 genotype, and endurance performance in athletes. *Med Sci Sports Exerc*. 2018;50:1570 1578. PubMed ID: 29509641 doi:10.1249/MSS.0000000000001596
14. Pickering C, Kiely J. Are the current guidelines on caffeine use in sport optimal for everyone? Inter individual variation in caffeine ergogenicity, and a move towards personalized sports nutrition. *Sport Med*. 2018;48(1):7 16. doi:10.1007/s40279 017 0776 1
15. Hopkins WG. Spreadsheets for analysis of controlled trials, cross overs and time series. *Sportscience*. 2017;21:1 4. http://sportsci.org/2017/wghxls.htm. Accessed 26 February 2019
16. Batterham AM, Hopkins WG. Making meaningful inferences about magnitudes. *Int J Sports Physiol Perform*. 2006;1(1):50 57. PubMed ID: 19114737 doi:10.1123/ijspp.1.1.50
17. Malcata RM, Hopkins WG. Variability of competitive performance of elite athletes: a systematic review. *Sports Med*. 2014;44:1763 1774. doi:10.1007/s40279 014 0239 x
18. O'Rourke MP, O'Brien BJ, Knez WL, et al. Caffeine has a small effect on 5 km running performance of well trained and recreational runners. *J Sci Med Sport*. 2008;11(2):231 233. doi:10.1016/j.jsams.2006.12.118
19. Bridge CA, Jones MA. The effect of caffeine ingestion on 8 km run performance in a field setting. *J Sports Sci*. 2006;24(4):433 439. PubMed ID: 16492607 doi:10.1080/02640410500231496
20. Doherty M, Smith PM. Effects of caffeine ingestion on rating of perceived exertion during and after exercise: a meta analysis. *Scand J Med Sci Sports*. 2005;15(2):69 78. PubMed ID: 15773860 doi:10.1111/j.1600 0838.2005.00445.x
21. Astorino TA, Cottrell T, Lozano AT, Aburto Pratt K, Duhon J. Increases in cycling performance in response to caffeine ingestion are repeatable. *Nutr Res*. 2012;32:78 84. PubMed ID: 22348455 doi:10.1016/j.nutres.2011.12.001
22. Southward K, Rutherford Markwick K, Badenhorst C, Ali A. The role of genetics in moderating the inter individual differences in the ergogenicity of caffeine. *Nutrients*. 2018;10:1352 1364. doi:10.3390/nu10101352
23. Boyett JC, Giersch GEW, Womack CJ, et al. Time of day and training status both impact the efficacy of caffeine for short duration cycling performance. *Nutrients*. 2016;8(10):E639. PubMed ID: 27754419 doi:10.3390/nu8100639
24. Astorino TA, Cottrell T, Lozano AT, Aburto Pratt K, Duhon J. Ergogenic effects of caffeine on simulated time trial performance are independent of fitness level. *J Caffeine Res*. 2011;1:179 185. doi:10.1089/jcr.2011.0022

Queries

Q1. Please note that "gum," "strips," and "tablets" changed to "CG," "CS," and "CT" throughout the text is correct.

Q2. Please ensure author information is listed correctly here and within the byline.

Q3. Please provide expansion for "IAAF."

Q4. Please note that "trail" has been changed to "trial" in the sentence "All runners initially . . . ." Please check if the change made is correct.

Q5. Please provide complete details of "Borg (1982)" to be included in the reference list.

Q6. Please provide manufacturer location (city, state [if USA], and country name) details for "Marketright Inc."

Q7. Please check if the edits made to Table 1 are correct.

Q8. Originally, Refs. 6 and 21 were identical. Hence the duplicate has been removed from the reference list and the subsequent references have been renumbered both in text and in reference list. Please verify.

Sports Med (2018) 48 (Suppl 1):S79 S91
https://doi.org/10.1007/s40279 017 0848 2

REVIEW ARTICLE

Administration of Caffeine in Alternate Forms

Kate A. Wickham[1] · Lawrence L. Spriet[1]

Published online: 24 January 2018

Abstract There has been recent interest in the ergogenic effects of caffeine delivered in low doses (~ 200 mg or ~ 3 mg/kg body mass) and administered in forms other than capsules, coffee and sports drinks, including chewing gum, bars, gels, mouth rinses, energy drinks and aerosols. Caffeinated chewing gum is absorbed quicker through the buccal mucosa compared with capsule delivery and absorption in the gut, although total caffeine absorption over time is not different. Rapid absorption may be important in many sporting situations. Caffeinated chewing gum improved endurance cycling performance, and there is limited evidence that repeated sprint cycling and power production may also be improved. Mouth rinsing with caffeine may stimulate nerves with direct links to the brain, in addition to caffeine absorption in the mouth. However, caffeine mouth rinsing has not been shown to have significant effects on cognitive performance. Delivering caffeine with mouth rinsing improved short-duration, high-intensity, repeated sprinting in normal and depleted glycogen states, while the majority of the literature indicates no ergogenic effect on aerobic exercise performance, and resistance exercise has not been adequately studied. Studies with caffeinated energy drinks have generally not examined the individual effects of caffeine on performance, making conclusions about this form of caffeine delivery impossible. Caffeinated aerosol mouth and nasal sprays may stimulate nerves with direct brain connections and enter the blood via mucosal and pulmonary absorption, although little support exists for caffeine delivered in this manner. Overall, more research is needed examining alternate forms of caffeine delivery including direct measures of brain activation and entry of caffeine into the blood, as well as more studies examining trained athletes and female subjects.

✉ Lawrence L. Spriet
lspriet@uoguelph.ca

[1] Human Health and Nutritional Sciences, University of Guelph, Guelph, ON N1G 2W1, Canada

1 Introduction

Caffeine is a socially acceptable drug that has been used as an ergogenic aid or performance enhancer in athletic circles for many years. It is a currently legal method of enhancing performance in training sessions and athletic competitions as it does not appear on the World Anti-Doping Agency's banned or restricted substances list. Over the last 10 years, numerous reviews have examined different aspects of the efficacy of caffeine as an ergogenic aid [1 6] and a book was published to "describe a framework that might help the world of sport to develop a sensible and unified view of caffeine use by athletes" [7]. The contemporary approach is to use low doses of caffeine which exert ergogenic effects through interactions with the central nervous system (CNS) and have minimal effects on the physiological responses to exercise and caffeine-related side effects [6].

The traditional form of caffeine administration in research and athletic settings has been to ingest tablets/capsules along with water or to drink coffee. The caffeine is quickly swallowed and the majority absorbed into the blood from the intestine, with the possibility that a small amount is absorbed in the buccal mucosa. Caffeinated sports drinks have also been studied for many years, with most reports demonstrating that caffeine added to a sports drink has a further performance enhancing effect above that of a carbohydrate (CHO)-electrolyte solution alone, as reviewed by Kovacs et al. [8], Cureton et al. [9], and Spriet [6]. These findings will not be reviewed here,

but include studies that examined the effects of caffeinated sports drinks on cycling [10 12], running [13], golf [14] and soccer [15, 16] performance.

Caffeine is now also available in gels, bars, gums, lozenges and energy drinks, which may affect how quickly the caffeine is absorbed into the blood from the buccal mucosa and intestines. There is also recent evidence that mouth rinsing with caffeine may activate sensors in the oral cavity with direct connections to the brain that could ultimately affect athletic performance. Lastly, manufacturers are also suggesting that the delivery of caffeine in mouth and nasal aerosol sprays may activate sensors with neural links in the nose and provide a direct route for absorption in the lungs, although no research has examined this possibility. Given the interest in these so-called "alternate forms of delivery," this paper aims to examine (1) how they affect the rate of caffeine entry into the blood versus traditional tablet or coffee administration, (2) if they stimulate direct connections between caffeine sensors in the oral and nasal cavities and the brain, and (3) if they are ergogenic in training and competition situations.

2 Caffeinated Bars and Gels

Over the last decade, few studies have explored the potential ergogenic effects of caffeinated bars and gels. To date, only Hogervorst et al. [17] have tested the effects of repeated dosing with caffeinated energy bars on cycling performance and a battery of cognitive tests in 24 trained men. The subjects completed 150 min of submaximal cycling at 60% maximal oxygen consumption (VO_{2max}) followed by a 5-min rest, and a time to exhaustion protocol at 75% VO_{2max}. Additionally, the subjects underwent a cognitive battery at baseline, at 70 and 140 min into the submaximal cycle, and again at exhaustion. The conditions were a caffeinated bar with 100 mg caffeine and 45 g CHO, a non-caffeinated bar with 45 g CHO, or 300 mL of a non-caloric placebo beverage, administered immediately before and at 55 and 115 min into the submaximal cycling protocol. The cognitive battery assessed complex cognitive function through a Stroop test, a rapid visual information processing (RVIP) task and a visual search test, and simple cognitive function through an immediate recall task. Saliva samples were collected at baseline and immediately following exhaustion for determination of caffeine concentrations. Supplementation with a caffeinated bar increased salivary caffeine (5.93 μg/mL) compared to baseline (0.25 μg/mL) (ratio of salivary to plasma concentrations $= 0.74 \pm 0.08$ [18]). Supplementation with caffeinated bars improved reaction time on the Stroop test and RVIP test during steady-state exercise and following exhaustion and improved speed and accuracy on a visual search test at the end of exhaustive exercise compared to the other two conditions. The caffeinated bars also improved time to exhaustion (1600 s) versus the non-caffeinated CHO bars (1150 s) and the placebo beverage (850 s) [17].

Surprisingly, only two studies have explored the effects of caffeinated gels on athletic performance. Cooper et al. [19] investigated the effects of repeated dosing with caffeinated gels on performance of four blocks of an intermittent sprint test (IST) in 12 recreationally active males. The participants consumed either a CHO (25 g), CHO (25 g) and caffeine (100 mg), or placebo gel 1 h prior to the first IST block, immediately prior to the first IST block and at the end of the second IST block. The authors reported no significant difference between the conditions for best sprint time, but there was a trend for faster sprint performance in the CHO and caffeine group when compared with the CHO-only and placebo gel groups. Additionally, following the third block of sprints, the CHO and caffeine group demonstrated a significantly decreased fatigue index and a lower rating of perceived exertion compared to the CHO-only and placebo gel groups. In a second study, Scott et al. [20] demonstrated that ingestion of a CHO (21.6 g) and caffeine gel (100 mg), 10 min before a 2000-m rowing task, significantly improved performance compared to a CHO-only gel in 13 male collegiate athletes (CHO 471 s vs. CHO/caffeine 466 s).

Taken together, these studies suggest that bars and gels with 100 mg caffeine improved cognitive function, time to exhaustion, and time trial (TT) performance. Lacking from these studies were plasma caffeine measurements, although it could be assumed that increases would mimic the findings from caffeine tablet and coffee consumption. More research in this area is needed as caffeinated bars and gels are key caffeine sources for athletes during training and competition, and there is presently no work examining female subjects.

3 Caffeinated Chewing Gum

Much of the important early work with the delivery of caffeine in chewing gum was conducted with a military purpose. Studies had demonstrated the ability of caffeine delivered in capsules to reverse the prolonged wakefulness-induced decrements in alertness, mood and performance [21 23]. However, there is a time delay of 20 30 min before significant amounts of caffeine leave the gut, reach the blood and affect the CNS. Therefore, in military settings where it is important to restore alertness and performance as quickly as possible, it was hypothesized that delivering caffeine in a chewing gum may speed the rate of caffeine delivery to the blood by absorption through the

buccal mucosa as well as the gut [24]. Absorption of drugs other than caffeine in a gum form had been demonstrated to be more rapid through the buccal cavity, in part because of the extensive vascularization in this region [24, 25]. In addition, absorption through the buccal mucosa/cavity avoids the first-pass metabolism which may occur in the intestines or liver when absorbed through the gut. Therefore, any increase in the rate of caffeine absorption with gum could lead to a faster biological effect in the body.

To test this hypothesis, a landmark study by Kamimori et al. [24] examined the rate of caffeine absorption by measuring plasma caffeine concentrations at several time points following the ingestion of capsules or chewing gum containing either 50, 100 or 200 mg of caffeine. Each condition had a separate group of 12 healthy male subjects who consumed less than 300 mg caffeine/day and had abstained from caffeine intake for 20 h and fasted for 3 h. Blood samples were taken at 5, 15, 25, 35, 45, 55, 65 and 90 min and 2, 3, 4, 6, 8, 12, 16 and 29 h post ingestion/chewing. The time to reach the maximal caffeine concentration was faster in the gum trials (44.2 80.4 min) versus the capsule trials (84 120 min). However, the maximal caffeine concentrations between capsule and gum conditions and the area under the entire concentration time curves were not different at each of the three doses (Fig. 1). The markedly faster rate of absorption with the gum is seen when examining the 200-mg dose, as a large increase in plasma caffeine concentration occurred between 5 and 15 min and to a lesser extent from 15 to 25 min (Fig. 2). The largest increases in caffeine concentration with the capsules were delayed until 25 35 and 35 45 min. This study demonstrated the efficacy of delivering caffeine more quickly with gum versus capsules, in part by uptake in the buccal cavity along with absorption from swallowing while chewing gum. A second study from the same group demonstrated that plasma caffeine levels were maintained and increased in a dose-dependent manner with three repeated caffeine doses, each 2 h apart, when delivered in gum form with either 50, 100 and 200 mg of caffeine [26]. These pharmacokinetic findings are useful in military and sport situations where rapid caffeine effects are required and need to be maintained over a known time span. It is also possible that chewing gum may have an additional advantage over capsule delivery during intense exercise where splanchnic blood flow may be reduced and slow the absorption of caffeine in the gut, but this has not been studied to date.

3.1 Caffeinated Gum and Athletic Performance

3.1.1 Aerobic Endurance Cycling

Several studies have now examined the potential ergogenic effect of caffeinated gum administration on aerobic-based cycling. Ryan et al. [27] administered two sticks of caffeinated chewing gum (200 mg total) to college-age, physically active males at either 35 or 5 min before exercise, or 15 min into cycling at 85% VO_{2max} to exhaustion (~30 35 min). A placebo was given at the other two time points and all three points during the control trial. The caffeinated gum did not improve endurance performance at any of the administration times [27]. In a follow-up study,

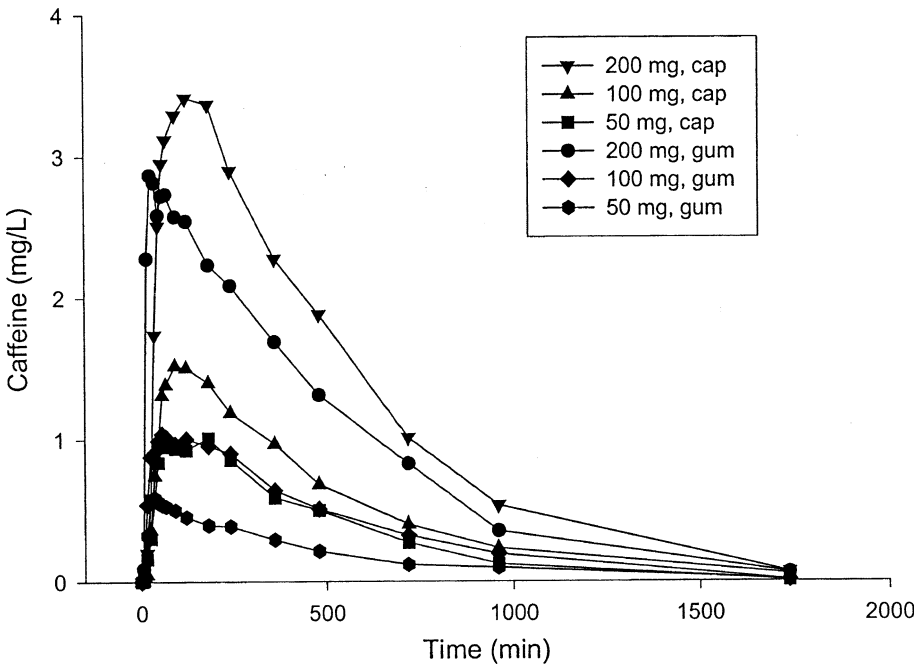

Fig. 1 Mean caffeine plasma concentration profiles following a 50 , 100 or 200 mg dose of caffeine, delivered as either a capsule or gum formulation to healthy male volunteers (12 subjects in each of the seven treatment groups) Reproduced from Kamimori et al. [24], with permission

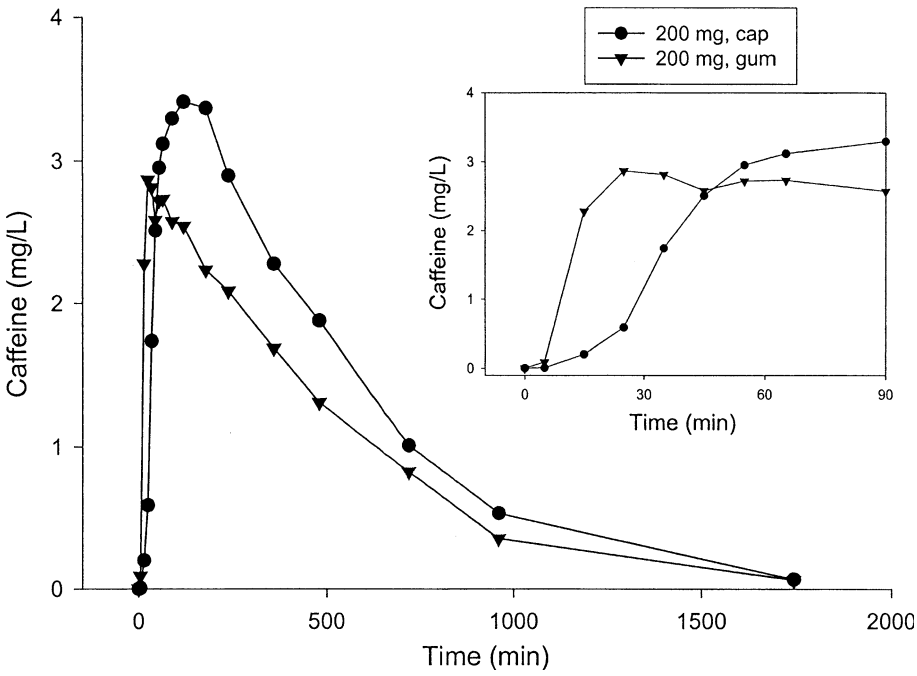

Fig. 2 Mean caffeine plasma concentration profiles following a 200 mg dose of caffeine as a capsule or gum formulation to healthy male volunteers (12 subjects in each of the two treatment group). Inset shows plasma concentration profiles of the 200 mg dose delivered in capsule or gum formulation up to 90 min after caffeine administration Reproduced from Kamimori et al. [24], with permission

Ryan et al. [28] gave caffeinated gum (300 mg) or non-caffeinated gum to well-trained male cyclists at either 120, 60 or 5 min before cycling at 75% VO_{2max} for 15 min, followed by a TT where 7 kJ/kg body mass (BM) of work was completed as fast as possible. Caffeine improved cycling TT performance only in the trial where the caffeine was administered 5 min before exercise [28]. Lane et al. [29] examined the effects of 3 mg/kg BM of caffeine delivered in chewing gum to 12 well-trained males and 12 well-trained females during a TT that simulated the cycling course at the 2012 London Olympic Games (females 29.35 km, males 43.83 km), lasting 50 60 min. The athletes chewed caffeinated gum with 2 mg/kg BM for 10 min, starting at 40 min before the TT, and another 1 mg/kg BM in the 10 min before the TT. In the placebo trial, subjects chewed non-caffeinated gum. The subjects also underwent two additional trials, one with beetroot juice (BRJ) and one with BRJ and caffeine. The results were similar for females and males, and caffeine ingestion in the caffeine trial alone and in the caffeine + BRJ trial significantly improved TT performance by 3 4% versus placebo (Fig. 3). BRJ did not affect performance.

Oberlin-Brown et al. [30] had 11 well-trained male cyclists ride for 90 min at 63% VO_{2max}, followed by a 20-km TT on four occasions to test placebo, caffeine, CHO, and caffeine with CHO. The caffeine was administered in 50-mg sticks of gum at the start of the TT and at the completion of 5, 10 and 15 km for a total dose of 200 mg (2.7 mg/kg BM). There were no significant differences in TT performance between conditions, with all times between 32:20 and 32:27 min:s. It is possible that the use

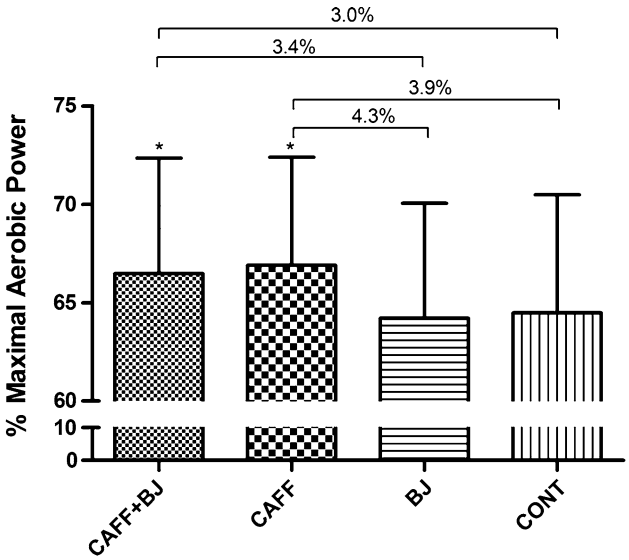

Fig. 3 Mean power output combined for males and females during cycling time trial. Data are presented as mean ± standard deviation. *BJ* beetroot juice, *CAFF* caffeine, *CAFF + BJ* caffeine with beetroot juice, *CONT* placebo. *Different from CONT and BJ ($p < 0.01$) Reproduced from Lane et al. [29], with permission

of small 50-mg caffeine doses administered only at the start of the TT and every ~ 8 min thereafter limited the ergogenic effect of caffeine in this study. Paton et al. [31] studied the effects of administering caffeinated (200 300 mg) or non-caffeinated gum at the 10-km mark of a 30-km TT in ten well-trained female and ten well-trained male cyclists. There also was a 0.2-km sprint (~ 15 s) at the end of each 10-km section. There were no

differences in performance during the initial 20 km of the TT, but caffeine improved mean power by 3.8 ± 2.3% and increased speed by 1.9% in the final 10 km and improved sprint power by 4.0 ± 3.6% during the final sprint. Females and males increased mean power over the final 10 km by 4.3 ± 3.4 and 3.2 ± 3.0% and increased sprint time by 1.9 ± 5.0 and 6.2 ± 5.2%, respectively.

These studies suggest that caffeine delivered in chewing gum in a dose of ~ 200 300 mg is ergogenic in well-trained females and male cyclists when delivered prior to or during an endurance event. However, it should be noted that no study has compared the effects of chewing gum versus the traditional caffeine capsule ingestion on aerobic performance in the same group of subjects.

3.1.2 Sprint Cycling and Power Events

Paton et al. [32] gave caffeinated chewing gum to nine competitive male cyclists who completed four sets of 30-s maximal sprints (with 30 s of active recovery at 100 W), with five sprints/set. Subjects cycled for 5 min at 100 W following sets 1 and 3. Following set 2, subjects cycled for 10 min at 100 W and caffeinated (240 mg/3 mg/kg BM) or placebo gum was administered. The rate of power output decline in sets 3 and 4 (ten sprints) was significantly reduced by the caffeinated gum versus placebo. A second study reported that standing shot-put performance was improved following the administration of 100 mg caffeine in chewing gum in nine collegiate shot-put athletes [33]. The subjects chewed the gum immediately before attempting six throws (with 1 min between throws), and the performance of the first throw and the overall performance of all six shot-put throws was improved with caffeine. Although this study utilized a small sample size, the results suggested that caffeinated gum improved performance in sprint and power events.

There was also one study that assessed the ergogenic effects of a caffeinated lozenge, and while this is not gum, the lozenge is held in the mouth for several minutes [34]. The lozenge contained 420 mg of nitric oxide (NO) and 70 mg of caffeine compared to a non-caloric placebo lozenge. The treatment was administered to 15 moderately trained cyclists (eight males, seven females) 10 min prior to the beginning of a cycling protocol where subjects cycled for 8 min at 50%, 6 min at 65% and 6 min at 75% VO_{2max}, and then rested for 5 min before completing a 21.15-km TT. TT performance was significantly faster (2.1%) with the caffeinated lozenge (2424 s) compared to placebo (2477 s). In this study, the authors could not distinguish between the effects of NO and caffeine, and therefore could not be certain that caffeine was the only active ingredient [34].

4 Caffeine Mouth Rinsing

Caffeine mouth rinsing is a relatively new form of caffeine supplementation. This modality gained traction alongside the emerging interest associated with the potential ergogenic effects of CHO mouth rinsing [35, 36]. It was originally proposed that caffeine mouth rinsing for 5 20 s elicited its ergogenic effects by allowing caffeine molecules to competitively inhibit adenosine through binding to adenosine receptors located in the mouth [37, 38]. This interaction was thought to increase permeability of the buccal mucosa therefore triggering caffeine absorption into the blood stream [39]. However, the time for this to occur would be short and the only study examining caffeine mouth rinsing that measured blood caffeine concentrations reported no increase in blood caffeine concentrations [40]. Evidently, a more feasible mechanism of action has been proposed to explain the performance benefits associated with caffeine mouth rinsing. The oral cavity is decorated with bitter taste receptor cells specifically located in the oropharyngeal epithelia [41], and these have been shown to be activated when exposed to caffeine [42]. It has been proposed that activation of these bitter taste receptors can activate gustatory neural pathways [41] and ultimately stimulate regions of the brain associated with information processing and reward [43, 44]. These same regions are shown to be activated when participants are administered a CHO mouth rinse [36, 43].

4.1 Cognitive Performance

Using functional magnetic resonance imaging (fMRI), De Pauw and colleagues [45] identified in ten healthy males that caffeine mouth rinsing increased activity in the dorsolateral prefrontal cortex and the orbitofrontal cortex, which are brain regions associated with problem solving and reward, respectively. Furthermore, this group demonstrated that caffeine (1.2%) mouth rinsing, when administered as a 25-mL solution for 20 s, improved reaction time on an incongruent Stroop task (where the color of the word and the meaning do not match) compared to a CHO (6.4%) mouth rinse, and a placebo rinse. There was no significant difference on incongruent Stroop task performance between the CHO and placebo conditions [45]. Pomportes et al. [46] tested the effects of caffeine (67 mg), CHO (7%), and guarana (0.4 g) mouth rinses on cognitive function during 40 min of submaximal cycling versus a placebo rinse in 24 physically active participants (16 males, six females). The subjects were instructed to mouth rinse with 25 mL of the treatment for 20 s immediately before cycling. After 1 min of cycling, the subjects completed a duration-production task (to assess time

perception) lasting 3 min, continued to cycle for 7 min, then completed the Simon task (to assess cognitive control and information processing) lasting another 3 min. This cognitive battery was repeated two more times with a 20-s mouth rinse occurring between batteries. The results showed that mouth rinsing with caffeine, CHO, or guarana resulted in more consistent responses during the duration-production task compared to placebo and shorter production durations, meaning that participants underestimated the duration of the task compared to placebo. There were also no differences between the caffeine, CHO or guarana treatments for variability or production durations. These authors suggest that mouth rinsing with caffeine, CHO, or guarana may increase brain activation and arousal compared to placebo. Interestingly, the authors also noted a smaller difference between mean incongruent reaction time and mean congruent reaction time during the Simon task in the caffeine condition (24 ms) compared to placebo (30 ms), CHO (29 ms) and guarana (29 ms) conditions, indicating improved cognitive control. There were no differences in errors between conditions.

Although there is minimal evidence to support the effects of caffeine mouth rinsing on cognitive performance, the evidence presented here suggests there may be a beneficial effect on reaction time and cognitive control. However, additional work is required with direct measures of brain activation and plasma caffeine concentrations.

4.2 High-Intensity Repeated Cycle Sprinting

Beaven et al. [37] investigated the effects of caffeine mouth rinsing on repeated sprint cycling performance in 12 recreationally active males. The first experiment compared the effects of a 6% CHO mouth rinse solution, a 1.2% caffeine rinse solution, and a placebo rinse. The subjects completed a 5-min warm up before swirling 25 mL of the rinse solution around their mouths for 5 s and then expelling the solution. Immediately following the mouth rinse, subjects completed a 6-s all out sprint against a resistance equal to 10% of their BM. The subjects then received a 24-s rest period in which they were instructed to mouth rinse again for 5 s. The 6-s sprint and subsequent rest period with mouth rinsing was repeated a total of five times. The authors found that caffeine and CHO mouth rinses improved mean power in the first sprint compared to placebo. Furthermore, 50% of the participants elicited their greatest maximal power during the first two sprints in the caffeine mouth rinse condition when compared to the CHO and placebo rinses [37]. In the second experiment, the authors investigated the effects of a combined caffeine and CHO mouth rinse versus a CHO-only mouth rinse using the same exercise protocol as the first experiment. The combined caffeine and CHO mouth rinse elicited an increase in peak power during the first sprint and increased mean power during the last sprint compared to the CHO only rinse.

Kizzi et al. [47] employed the same exercise protocol as Beaven et al. [37], but induced a state of glycogen depletion (estimated at 30% of resting glycogen levels) prior to the repeated sprint protocol. This group explored the effects of mouth rinsing with 25 mL of a 2% caffeine solution versus a placebo rinse in a glycogen-depleted state in eight recreationally active males. The mouth rinse was performed for 10 s before the first sprint and in the rest periods between each subsequent sprint. The protocol was also repeated in a no-rinse, glycogen-rich state to provide a control group. As expected, the authors found that mean and peak power were highest in the control group for the first three sprints (Fig. 4). Furthermore, in the third sprint, mean and peak power were higher in the caffeine rinse group compared to placebo. Interestingly, there was no significant difference between the control group and the caffeine mouth rinse group for mean and peak power during sprints 4 and 5, and mean and peak power were significantly lower in the placebo group. Similarly, subjects' perceived pain was lower for the first three sprints in the control condition, and perceived pain was lower in the caffeine condition compared to placebo during the third sprint [47]. There was no difference in perceived pain during sprints 4 and 5 when comparing the control condition to caffeine mouth rinse (Fig. 4). However, perceived pain was significantly higher in the placebo versus control and caffeine rinsing during sprints 4 and 5. It should be noted that no measures of muscle glycogen or plasma caffeine levels were made in this study.

It appears that short-duration, high-intensity, repeated-bout sprinting is improved with caffeine mouth rinsing in normal and glycogen-depleted states.

4.3 Aerobic Exercise

The evidence surrounding the ergogenic effects of caffeine mouth rinsing and aerobic exercise performance is equivocal. Sinclair and Bottoms [48] investigated the effects of a tasteless 6.4% CHO mouth rinse, a tasteless 0.032% caffeine rinse, and a water rinse during a 30-min arm crank TT in 12 healthy males. The subjects rinsed with a 25-mL solution for 5 s immediately before starting the TT, and repeated the mouth rinse procedure every 6 min throughout the TT. The results indicated a greater distance covered during a 30-min arm crank TT when utilizing caffeine or CHO mouth rinses ($\sim$ 15 km) compared to a water rinse ($\sim$ 13 km). This greater distance was achieved by higher power outputs and revolutions per min in the caffeine and CHO rinse conditions.

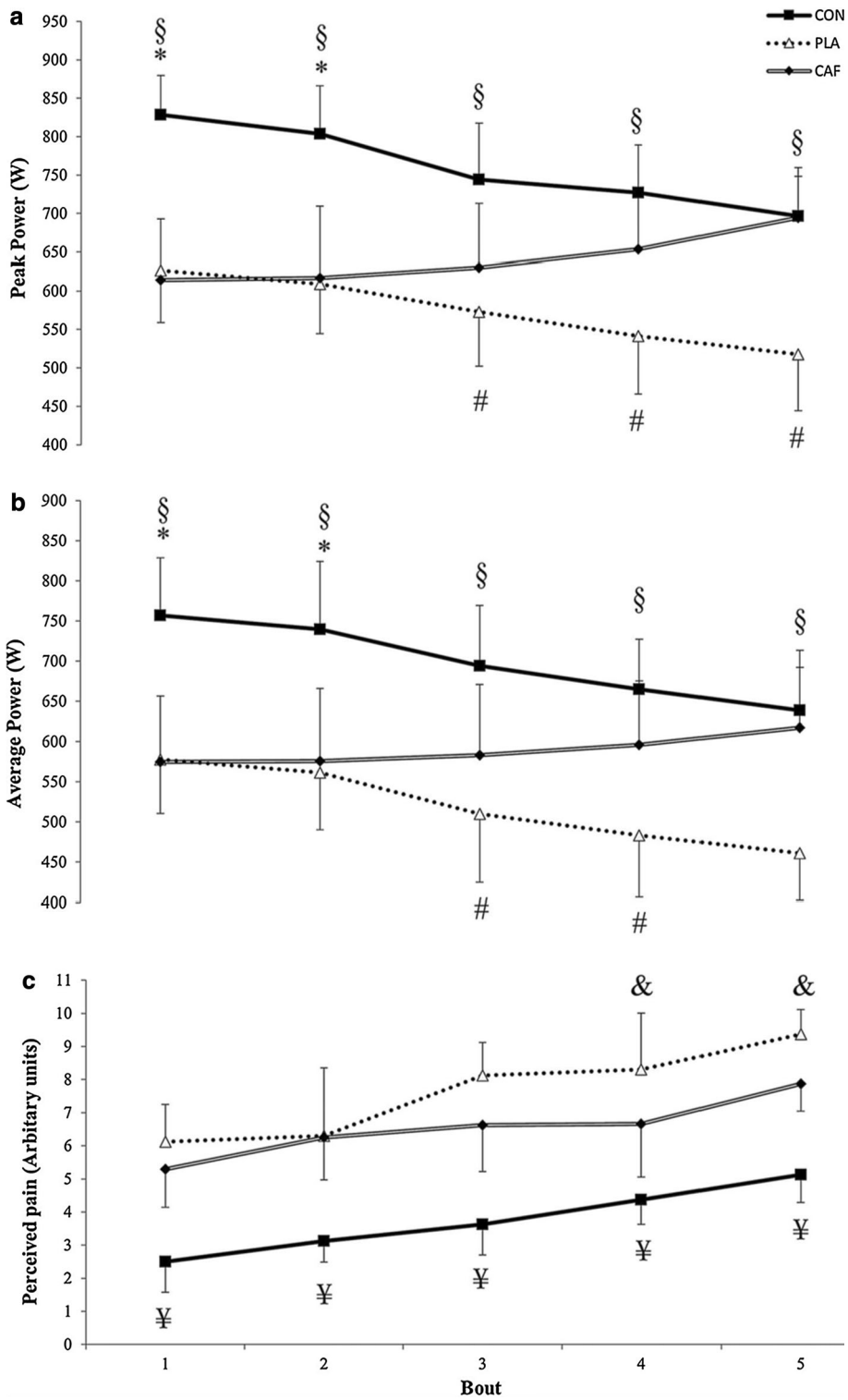

Fig. 4 Peak and average power profiles and ratings of perceived pain for five, 6 s sprints separated by 24 s active rest in control (CON), glycogen depletion and placebo (PLA), and glycogen depletion and caffeine (CAF) conditions. **a** Peak power; **b** mean power; and **c** perceived pain. Data are presented as mean ± standard deviation. [§]CON significantly greater than PLA ($p < 0.05$); # CON significantly greater than CAF ($p < 0.05$); [#]CAF significantly greater than PLA ($p < 0.05$); [¥]CON significantly less than PLA ($p < 0.05$); [&]CAF significantly less than PLA ($p < 0.05$) Reproduced from Kizzi et al. [47], with permission

Conversely, Doering et al. [40] found no effect of a caffeine mouth rinse in ten well-trained male cyclists performing a TT in which they had to complete the work equivalent to 75% of peak power output for 1 h (lasted ~ 65 min). These subjects were administered a 25-mL solution containing 35 mg of caffeine or a placebo rinse immediately before the TT and at 25, 50, 75 and 90% completion of the TT, and were instructed to rinse the solution around their mouths for 10 s before expelling the solution.

Pataky et al. [49] investigated the effects of caffeine capsule ingestion, caffeine mouth rinsing, and the

combination on 3-km cycling TT performance in 38 recreationally trained cyclists (25 males, 13 females). This group also explored the effects of caffeine mouth rinsing on TT performance with respect to caffeine metabolizer genotype and time of day. It is important to note that the subjects were divided into two genotypes: AA homozygous ($n = 21$), who typically experience greater ergogenic effects with caffeine due to a quicker accumulation of caffeine metabolites, and AC heterozygotes ($n = 17$) [50]. To assess the effect of time of day on caffeine mouth rinsing and 3-km TT performance, 15 participants completed all of their trials before 10 a.m. and 23 subjects completed all of their trials after 10 p.m. The treatment conditions included a placebo capsule with a placebo 25-mL mouth rinse, a 6-mg/kg caffeine capsule with a 25-mL placebo rinse, a placebo capsule with a 25-mL caffeine rinse containing 300 mg of caffeine, and a 6-mg/kg caffeine capsule with a 25-mL caffeine mouth rinse containing 300 mg of caffeine. The capsule was ingested 1 h before the exercise protocol, and the mouth rinse was administered immediately before a 5-min warm up and again at the end of the warm up just before the TT.

These authors found a 3% improvement in 3-km cycling TT performance with caffeine capsule ingestion and in the caffeine capsule with mouth rinsing condition when compared to placebo and the caffeine rinse condition [49]. Since there was no benefit of caffeine mouth rinsing alone, it is suggested that the ergogenic effects were solely attributed to caffeine capsule ingestion. Interestingly, these researchers found a positive effect of caffeine mouth rinsing only when the exercise protocol was performed in the morning compared to the evening, suggesting a diurnal effect. Lastly, these authors found that caffeine capsule ingestion was ergogenic for AC heterozygous caffeine metabolizers, and caffeine rinse and capsule ingestion was likely ergogenic for both AA homozygous and AC heterozygous caffeine metabolizers. However, it was also found that caffeine mouth rinsing was possibly detrimental to performance in AA homozygous caffeine metabolizers. More work will be needed to confirm these findings. It is important to consider the possibility that caffeine administered in forms that avoid absorption in the gut and first pass metabolism, such as caffeinated gum, mouth rinsing, or aerosol sprays, may lead to more consistent responses across subjects as genetic variability in caffeine metabolism can account for some of the individual responses demonstrated in many caffeine studies.

Lesniak et al. [51] investigated the effects of a CHO mouth rinse, a caffeine rinse, and a combined CHO and caffeine rinse on TT performance in seven recreationally active females. Subjects completed the work equivalent to 60% of their maximum work rate for 1 h as fast as possible (TT lasted $\sim$ 61 min). These authors found no differences between the conditions. However, there was no placebo group to determine if caffeine mouth rinsing improved performance over baseline. Dolan et al. [52] studied the effects of caffeine mouth rinsing on intermittent exercise performance in ten competitive college lacrosse players. These researchers utilized the Yo Yo Intermittent Recovery Test to mimic stop-and-go sports performance. The participants were instructed to rinse their mouth with 25 mL of either a 6% CHO solution, a 1.2% caffeine solution, a combined CHO and caffeine solution, or a water rinse. There was also a no rinse condition. There were no significant differences in intermittent sport performance between any of the conditions [52].

Currently, most of the literature indicates no ergogenic effect of caffeine mouth rinsing for 5 20 s on aerobic exercise performance [40, 49, 51, 52]. The study by Sinclair and Bottoms [48] is the only study supporting a beneficial effect of caffeine mouth rinsing on aerobic exercise performance.

4.4 Resistance Exercise

Clarke et al. [38] explored the effects of a caffeine mouth rinse (1.2%), a CHO rinse (6%), a combined caffeine and CHO mouth rinse, a placebo rinse, and a water rinse on resistance exercise performance in 15 recreationally resistance-trained males. The subjects were instructed to rinse 25 mL of the treatment solution around their mouth for 10 s immediately prior to performing a bench press at 60% of their 1 repetition maximum (RM) until failure. There were no significant differences in the total weight lifted between CHO mouth rinsing ($\sim$ 1100 kg), caffeine rinsing ($\sim$ 1100 kg), combined CHO and caffeine rinsing ($\sim$ 1050 kg), water rinsing ($\sim$ 1050 kg), or control conditions ($\sim$ 1050 kg). As this is the only study assessing the effects of caffeine mouth rinsing on resistance exercise performance, more research is needed.

4.5 Mouth Rinse Summary

The only exercise situation where it has been shown that caffeine mouth rinsing is ergogenic is with short-duration, high-intensity, repeated-bout cycling protocols. Similarly, it seems that caffeine mouth rinsing may prove beneficial in states of glycogen depletion, and earlier in the day compared to later in the afternoon. Future research should examine if rinsing for a longer duration promotes absorption of caffeine through the buccal mucosa and measure the pharmacokinetics of plasma caffeine concentrations in these situations. More research is needed to examine the effects of caffeine mouth rinsing in females, as only one study investigated caffeine mouth rinsing in women [51],

and also in trained subjects, as only two studies examined trained populations [40, 52].

5 Caffeinated Energy Drinks

While energy drinks are not generally designed for use during sporting activities, they are used before, during and after physical activity [53]. The active ingredients in energy drinks are high levels of CHO (~ 10 12%) and moderate levels of caffeine (~ 80 mg caffeine/250 mL). There are also suggestions that taurine (1000 mg/250 mL) is an active ingredient, although little research support exists [54]. Energy drinks also contain many other ingredients. Over the past 2 decades numerous studies have examined the potential ergogenic effects of caffeinated energy drinks on athletic performance [55]. However, most of these studies did not assess the ergogenic effects of the individual ingredients in caffeinated energy drinks. This makes it impossible to assess the relative importance of each potential active ingredient to any ergogenic effects seen.

This review will discuss the three studies that attempted to examine the potential ergogenic effects of individual ingredients [56 58]. Geiss et al. [56] investigated the effects of 500 mL of Red Bull (160 mg caffeine, 2000 mg taurine, 10.5 g glucose) versus Red Bull with just the caffeine and glucose versus Red Bull with just glucose on cycling performance in ten endurance-trained males. However, there were no trials with just caffeine or just taurine. The exercise protocol consisted of 60 min at 70% VO_{2max} immediately followed by 50 W increases every 3 min until volitional exhaustion. The Red Bull beverage was administered halfway through the submaximal exercise. In addition, 24 h later, subjects returned to complete a cycling protocol starting at 50 W and increasing by 50 W every 3 min until volitional exhaustion. The subjects had a prolonged time to exhaustion in the taurine and caffeine condition (857.8 ± 236.4 s) compared to the caffeine and glucose condition (689 ± 92.35 s) and the glucose only condition (791.8 ± 188.52 s). Time to exhaustion in the exercise bout 24 h later was also significantly longer only with the drink that contained taurine. These authors suggested that taurine was the main ergogenic ingredient in Red Bull and that caffeine and glucose had no effect, as times to exhaustion were prolonged in the taurine condition compared to the taurine-free conditions. However, this study did not test the individual effects of caffeine or taurine. The results imply some synergistic effect of having taurine, glucose and caffeine in the same drink, as studies examining the effects of taurine alone on TT performance and incorporation into skeletal muscle have seen no effect [54, 59].

Kammerer et al. [58] improved on the previous work and recruited 14 male soldiers to test the effects of 250 mL of a placebo beverage, a caffeinated beverage (80 mg caffeine), a taurine beverage (1000 mg taurine), a caffeine and taurine beverage, and a commercially available energy drink (Red Bull: 27 g CHO, 80 mg caffeine, 1000 mg taurine) administered 45 min before three physical tests and two cognitive tests. The physical tests consisted of a VO_{2max} test where time to exhaustion was recorded, a maximum handgrip strength test using both right and left hands, and three vertical jumps. The participants completed a focused attention task in which they were required to point out the numbers 1 38 randomly allocated on a grid with different sized digits, and a digit span test to assess attention and immediate auditory memory. This test required participants to repeat strings of nine numbers in forward order and strings of eight numbers in reverse order. The results demonstrated no significant differences between conditions on any of the physical or cognitive tests, suggesting no ergogenic effect of caffeine, taurine, or the combination with glucose on aerobic capacity, handgrip strength, jump performance or cognitive performance.

A study by Eckerson et al. [60] assessed the effects of 500 mL of sugar-free Red Bull (160 mg caffeine, 2000 mg taurine), a sugar-free drink containing only caffeine (160 mg caffeine), and a placebo beverage on bench press strength and endurance in 17 physically active men. Subjects performed repetitions to failure at a weight equivalent to 70% of their 1 RM. The results indicated that sugar-free Red Bull (114.9 ± 16.2 kg) and the caffeinated sugar-free drink (115.1 ± 16.2 kg) had no significant effect on 1 RM compared to placebo (114.1 ± 5.5 kg) and no effect on muscular endurance during this test (sugar-free Red Bull 1164.1 ± 147.0 kg; caffeinated sugar-free drink 1173 ± 170.6 kg; placebo 1141.5 ± 193.4 kg). This study suggested there was no benefit of sugar-free Red Bull (caffeine and taurine) or a caffeinated sugar-free drink on resistance exercise performance.

The current literature does not support the ergogenic effects of caffeine supplementation administered in the form of energy drinks. However, there is a need for additional studies examining the effectiveness of the individual components of caffeinated energy drinks on performance.

6 Caffeinated Nasal and Mouth Aerosol Sprays

Caffeine nasal and mouth sprays are the latest alternative method of caffeine supplementation. It has been reported that nasal administration of drugs may affect the brain through several mechanisms. First, it is possible that some of the drug enters the systemic circulation, ultimately reaching the brain and crossing the blood brain barrier.

The nasal epithelium is an extremely permeable membrane that allows molecules with a mass cut off lower than 1000 Da to rapidly access the brain via the blood stream [61]. Caffeine molecules could easily cross the nasal epithelium and ultimately affect the CNS through nasal spray delivery since they have a low molecular weight of 194 Da [62]. However, it could be argued that the time for this to occur is too short to have a meaningful impact. Secondly, the drug can be transported directly from the nasal cavity to the cerebrospinal fluid and brain tissue via intracellular axonal transport through the olfactory and trigeminal neural pathways [61, 63]. This method of delivery requires small molecules to travel along axons spanning from the nasal epithelium to the brain [63], but there is no information on the time course of this phenomenon. Thirdly, it has been shown that there are bitter taste receptors in the nasal cavity, akin to those found in the mouth [64]. It is possible that caffeine nasal sprays can activate bitter taste receptors located in the nasal cavity, which form connections with the trigeminal nerve and ultimately stimulate regions of the brain associated with reward and information processing [64]. Lastly, aerosols could deliver caffeine directly to the lungs where absorption into the blood would be expected, thereby delivering caffeine directly to the heart. However, the exact mechanism(s) are not presently established.

The first study in this field examined the efficacy of caffeine and glucose nasal sprays in affecting brain activity and cognitive performance in ten healthy males [62]. Participants completed a Stroop task immediately before and after administering a nasal spray containing 15 mg/mL caffeine, a spray containing 80 mg/mL glucose, or a distilled water placebo spray. The nasal spray was dispensed twice in each nostril to optimally disperse the treatment, and was administered for a total duration of 20 s. These authors measured brain activity through electroencephalogram and event-related potential (P300). Interestingly, treatment with both the caffeine and glucose nasal sprays increased activation of the primary somatosensory cortex (receives and interprets touch), motor cortices (planning, execution and control of motor movements), dorsolateral prefrontal cortex (information processing and working memory), orbitofrontal cortex (information processing and decision making), posterior cingulate cortex (learning and motivation), insular cortex (emotional awareness), and supramarginal gyrus (language perception and processing) compared to the placebo nasal spray [62]. It is also important to note that treatment with a caffeine nasal spray also resulted in a significantly greater activation of the dorsolateral prefrontal cortex and orbitofrontal cortex than the glucose spray. The Stroop task is designed to test a subject's information processing, decision making, and attention [65]. However, it is surprising that despite increasing the activation of these brain regions, there was no effect of caffeine nasal spray on cognitive efficiency as measured by P300 amplitude and latency during a Stroop task [62].

De Pauw et al. [66] performed a follow-up study on 11 moderately trained males, assessing the effects of a caffeine nasal spray, a glucose spray, or a placebo spray on Stroop task performance, Wingate sprint cycling performance, and a 30-min cycling TT. The Stroop task was performed before and after both exercise components and a 15-min rest occurred between exercises. Before each exercise test and at 25, 50 and 75% completion of the cycling TT, the subjects were administered a nasal spray containing either 15 mg/mL caffeine, 80 mg/mL glucose, or a placebo distilled water spray. The nasal spray was dispensed twice in each nostril for 20 s. Furthermore, these authors performed an additional trial to collect venous blood samples at baseline and 20 s after administering the caffeine nasal spray to measure plasma caffeine concentrations. There was no significant increase in blood caffeine concentrations 20 s after administration of the nasal caffeine spray, and it is not clear why serial samples were not taken. There was no effect of caffeine or glucose nasal sprays on mean or peak power output during the Wingate test (peak power 1069 W with placebo, 1046 W with glucose, 1082 W with caffeine). The caffeine nasal spray also had no effect on the 30-min cycling TT (caffeine 206 W, placebo 207 W). Lastly, caffeine and glucose nasal sprays had no impact on reaction time during the Stroop task compared to placebo at any time point throughout the protocol. These authors argued that the effects of a caffeine nasal spray on the brain may be too small to significantly improve exercise performance and/or the dose of caffeine may be too small to elicit an ergogenic effect.

There are few investigations of the efficacy of caffeine nasal sprays, and more work needs to be done to expand the literature in this area. More detailed measurements of plasma caffeine levels following repeated nasal spray doses could establish the efficacy of this procedure. If positive results were found, it is conceivable that caffeine nasal sprays could be applied to many exercise situations, most notably those that incorporate a large information-handling and cognitive component, such as stop-and-go team sports.

It is also important to mention the prevalence of caffeinated aerosols administered directly in the mouth and/or under the tongue. These products are readily on the market and are flaunted for their ability to "boost energy levels throughout the day". Some of the most common products on the market include AeroShot Pure Energy, which claims to deliver 100 mg caffeine/spray [67], Instavit Instant Energy, which claims to deliver 30 mg caffeine/four sprays [68], or Primer Caffeinated Breath Spray, which claims to deliver 33 mg caffeine/spray [69]. However, there is no

current research examining these claims. Additionally, similar to caffeine nasal sprays, there is some concern about the safety of these products. If caffeine is administered as an aerosol in much larger doses than recommended, it could be quickly absorbed into the circulation in high amounts allowing rapid delivery to the heart and the potential for an overdose, similar to what can happen with overdosing with oral caffeine.

Furthermore, Revvies manufactures a caffeinated mouth strip claimed to deliver 40 mg caffeine/strip. Revvies advertises rapid caffeine delivery, as the strip dissolves on the tongue in just 30 s [70]. Lastly, Sprayable Energy claims to deliver 12.5 mg of caffeine/four sprays, and touts the benefit of sustained, slow release energy due to the prolonged absorption of caffeine through the skin [71]. However, there is no research to support these claims.

7 Conclusions

Caffeine in chewing gum can be effectively administered at doses up to 200 mg, and higher with repeated dosing. Caffeine delivered via chewing gum is absorbed quicker through the buccal mucosa compared with capsule delivery and absorption in the gut, although total caffeine absorption over time is not different. Delivering caffeine in chewing gum improved endurance cycling performance, and there is limited evidence that repeated sprint cycling and power production are improved. Mouth rinsing with caffeine may stimulate nerves with direct links to the brain, in addition to any caffeine absorption that occurs in the mouth. However, caffeine mouth rinsing has not been shown to improve cognitive performance, although there is limited support for improvements in reaction time and cognitive control. It appears that delivering caffeine with mouth rinsing improved short-duration, high-intensity, repeated sprinting in normal and depleted glycogen states, while the majority of the literature indicated no ergogenic effect on aerobic exercise performance, and any effects on resistance exercise have not been adequately examined. Studies with caffeinated energy drinks have generally not examined the individual effects of caffeine on performance, as other documented (CHO) and potential (taurine) active ingredients are present. Caffeinated aerosol mouth and nasal sprays are gaining popularity as caffeine may stimulate nerves with direct brain connections and enter the blood via mucosal and pulmonary absorption. However, there is little support for any ergogenic effects as the delivery and/or effectiveness of caffeine delivered in this manner may be too small. Overall, direct measures of brain activation and entry of caffeine into the blood are generally limited or lacking when examining alternate forms of caffeine delivery in doses that are ≤ 200 mg. There is also a lack of research examining trained athletes and female subjects receiving alternate forms of caffeine delivery. Future research should also consider assessing the caffeine content of commercially available products prior to experimentation, as there may be a large variation in caffeine content within and between products.

Acknowledgements This article was published in a supplement supported by the Gatorade Sports Science Institute (GSSI). The supplement was guest edited by Lawrence L. Spriet, who attended a meeting of the GSSI expert panel in October 2016 and received honoraria from the GSSI for his participation in the meeting and the writing of a manuscript. He received no honoraria for guest editing the supplement. Dr. Spriet selected peer reviewers for each paper and managed the process, except for his own paper, which was managed by Dr. Roger Olney, an editor for *Sports Medicine*. The views expressed in this manuscript are those of the author and do not nec essarily reflect the position or policy of PepsiCo, Inc.

References

1. Burke LM. Caffeine and sports performance. Appl Physiol Nutr Metab. 2008;33:1319 34.
2. Ganio MS, Klau JF, Casa DJ, et al. Effect of caffeine on sport specific endurance performance: a systematic review. J Strength Cond Res. 2009;23:315 24.
3. Davis JK, Green JM. Caffeine and anaerobic performance: ergogenic value and mechanisms of action. Sports Med. 2009;39:813 32.
4. Astorino TA, Robertson DW. Efficacy of acute caffeine ingestion for short term high intensity exercise performance: a systematic review. J Strength Cond Res. 2010;24:257 65.
5. Spriet LL. Caffeine. In: Maughan RJ, editor. The encyclopaedia of sports medicine: an IOC medical commission publication. Sports Nutrition. 19th ed. Oxford: Wiley; 2013. p. 313 23.
6. Spriet LL. Exercise and sports performance with low caffeine doses of caffeine. Sports Med. 2014;44:S175 84.
7. Burke L, Desbrow B, Spriet LL. Caffeine for sports performance. Champaign: Human Kinetics; 2013.
8. Kovacs EMR, Stegen JHCH, Brouns F, et al. Effect of caffeinated drinks on substrate metabolism, caffeine excretion, and perfor mance. J Appl Physiol. 1998;85:709 15.
9. Cureton KJ, Warren GL, Millard Stafford ML, et al. Caffeinated sports drink: ergogenic effects and possible mechanisms. Int J Sport Nutr Exerc Metab. 2007;17:35 55.
10. Van Nieuwenhoven MA, Brummer RJM, Brouns F, et al. Gas trointestinal function during exercise; comparison of water, sports drink, and sports drink with caffeine. J Appl Physiol. 2000;89:1079 85.
11. Cox GR, Desbrow B, Montgomery PG, et al. Effect of different protocols of caffeine intake on metabolism and performance. J Appl Physiol. 2002;93:990 9.

12. Talanian JL, Spriet LL. Low and moderate doses of caffeine late in exercise improve performance in trained cyclists. Appl Physiol Nutr Metab. 2016;41:850 5.
13. Van Nieuwenhoven MA, Brouns F, Kivacs EM, et al. The effect of two sports drinks and water on GI complaints and performance during an 18 km run. Int J Sports Med. 2005;26:281 5.
14. Stevenson EJ, Hayes PR, Allison SJ, et al. The effect of a car bohydrate caffeine sports drink on simulated golf performance. Appl Physiol Nutr Metab. 2009;34:681 8.
15. Gant N, Ali A, Foskett A. The influence of caffeine and carbo hydrate coingestion on simulated soccer performance. Int J Sports Nutr Exerc Metab. 2010;20:191 7.
16. Guttierres APM, Alfenas RC, Lima JRP, et al. Metabolic effects of a caffeinated sports drink consumed during a soccer match. Motriz Rio Claro. 2013;19:688 95.
17. Hogervorst E, Bandelow S, Schmitt J, et al. Caffeine improves physical and cognitive performance during exhaustive exercise. Med Sci Sports Exerc. 2008;40:1841 51.
18. Newton R, Broughton L, Lind M, et al. Plasma and salivary pharmacokinetics of caffeine in man. Eur J Clin Pharmacol. 1981;21:45 52.
19. Cooper R, Naclerio F, Allgrove J, et al. Effects of a carbohydrate and caffeine gel on intermittent sprint performance in recre ationally trained males. Eur J Sport Sci. 2014;14:353 61.
20. Scott AT, O'Leary T, Walker S, et al. Improvement of 2000 m rowing performance with caffeinated carbohydrate gel ingestion. Int J Sports Physiol Perform. 2015;10:464 8.
21. Kamimori GH, Penetar DM, Headley DB, et al. Effect of three caffeine doses on plasma catecholamines and alertness during prolonged wakefulness. Eur J Clin Pharmacol. 2000;56:537 44.
22. Kaplan GB, Greenblatt DJ, Ehrenberg BL, et al. Dose dependent pharmacokinetics and psychomotor effects of caffeine in humans. J Clin Pharmacol. 1997;37:693 703.
23. Penetar D, McCann U, Thorne D, et al. Caffeine reversal of sleep deprivation effects on alertness and mood. Psychopharmacology. 1993;112:359 65.
24. Kamimori GH, Karyekar CS, Otterstetter R, et al. The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. Int J Pharm. 2002;234:159 67.
25. Shargel L, Yu ABC. Applied biopharmaceutics and pharma cokinetics. 4th ed. Stamford: Appleton and Lange; 1999.
26. Syed SA, Kamimori GH, Kelly W, et al. Multiple dose phar macokinetics of caffeine administered in chewing gum to normal healthy volunteers. Biopharm Drug Dispos. 2005;26:403 9.
27. Ryan EJ, Kim CH, Muller MD, et al. Low dose caffeine administered in chewing gum does not enhance cycling to exhaustion. J Strength Cond Res. 2012;26:844 50.
28. Ryan EJ, Kim CH, Fickes EJ, et al. Caffeine gum and cycling performance: a timing study. J Strength Cond Res. 2013;27:259 64.
29. Lane SC, Hawley JA, Desbrow B, et al. Single and combined effects of beetroot juice and caffeine supplementation on cycling time trial performance. Appl Physiol Nutr Metab. 2014;39:1050 7.
30. Oberlin Brown KT, Siegel R, Kilding AE, et al. Oral presence of carbohydrate and caffeine in chewing gum: independent and combined effects on endurance cycling performance. Int J Sports Physiol Perfom. 2016;11:164 71.
31. Paton C, Costa V, Guglielmo L. Effects of caffeine chewing gum on race performance and physiology in male and female cyclists. J Sports Sci. 2015;33:1076 83.
32. Paton CD, Lowe T, Irvine A. Caffeinated chewing gum increases repeated sprint performance and augments increases in testos terone in competitive cyclists. Eur J Appl Physiol. 2010;110:1243 50.
33. Bellar D, Kamimori G, Judge L. Effects of low dose caffeine supplementation on early morning performance in the standing shot put throw. Eur J Sports Sci. 2012;12:57 61.
34. Lee J, Kim HT, Solares GJ, et al. Caffeinated nitric oxide re leasing lozenge improves cycling time trial performance. Int J Sports Med. 2015;36:107 12.
35. Carter JM, Jeukendrup AE, Jones DA. The effect of carbohydrate mouth rinse on 1 h cycle time trial performance. Med Sci Sports Exerc. 2004;36:2107 11.
36. Chambers ES, Bridge MW, Jones DA. Carbohydrate sensing in the human mouth: effects on exercise performance and brain activity. J Physiol. 2009;587:1779 94.
37. Beaven CM, Maulder P, Pooley A, et al. Effects of caffeine and carbohydrate mouth rinses on repeated sprint performance. Appl Physiol Nutr Metab. 2013;38:633 7.
38. Clarke ND, Kornilios E, Richardson DL. Carbohydrate and caf feine mouth rinses do not affect maximum strength and muscular endurance performance. J Strength Cond Res. 2015;29:2926 31.
39. Rubinstein I, Chandilawa R, Dagar S, et al. Adensoine A_1 receptors mediate plasma exudation from the oral mucosa. J Appl Physiol. 2001;91:552 60.
40. Doering TM, Fell JW, Leveritt MD, et al. The effect of a caf feinated mouth rinse on endurance cycling time trial perfor mance. Int J Sport Nutr Exerc Metab. 2014;24:90 7.
41. Matsumoto I. Gustatory neural pathways revealed by genetic tracing from taste receptor cells. Biosci Biotechnol Biochem. 2013;77:1359 62.
42. Meyerhof W, Batram C, Kuhn C, et al. The molecular receptive ranges of human tas2r bitter taste receptors. Chem Senses. 2010;35:157 70.
43. Zald DH, Hagen MC, Pardo JV. Neural correlates of tasting concentrated quinine and sugar solutions. J Neurophysiol. 2002;87:1068 75.
44. Gam S, Guelfi KJ, Fournier PA. Mouth rinsing and ingesting a bitter solution improves sprint cycling performance. Med Sci Sports Exerc. 2014;46:1648 57.
45. De Pauw K, Roelands B, Knaepen K, et al. Effects of caffeine and maltodextrin mouth rinsing on P300, brain imaging, and cognitive performance. J Appl Physiol. 2015;118:776 82.
46. Pomportes L, Brisswalter J, Casini L, et al. Cognitive perfor mance enhancement induced by caffeine, carbohydrate and guarana mouth rinsing during submaximal exercise. Nutrients. 2017;9:589.
47. Kizzi J, Sum A, Houston FE, et al. Influence of a caffeine mouth rinse on sprint cycling following glycogen depletion. Eur J Sport Sci. 2016;16:1087 94.
48. Sinclair J, Bottoms L. The effects of carbohydrate and caffeine mouth rinsing on arm crank time trial performance. J Sports Res. 2014;1:34 44.
49. Pataky MW, Womack CJ, Saunders MJ, et al. Caffeine and 3 km cycling performance: effects of mouth rinsing, genotype, and time of day. Scand J Med Sci Sports. 2016;26:613 9.
50. Womack CJ, Saunders MJ, Bechtel MK, et al. The influence of a CYP1A2 polymorphism on the ergogenic effects of caffeine. J Int Soc Sports Nutr. 2012;9:7.
51. Lesniak AY, Davis SE, Moir GL, et al. The effects of carbohy drate, caffeine and combined rinses on cycling performance. J Sport Human Perform. 2016;4:1 10.
52. Dolan P, Witherbee K, Peterson K, et al. The effect of carbo hydrate, caffeine and carbohydrate + caffeine mouth rinsing on intermittent running performance in collegiate male lacrosse athletes. J Strength Cond Res. 2017;31:2473 9.
53. Ballard SL, Wellborn Kim JJ, Clausen KA. Effects of commer cial energy drink consumption on athletic performance and body composition. Phys Sportsmed. 2010;38:107 17.

54. Spriet LL, Whitfield J. Taurine and skeletal muscle function. Curr Opin Clin Metab Care. 2015;18:96 101.
55. Souza DB, Del Coso J, Casonatto J, et al. Acute effects of caf feine containing energy drinks on physical performance: a sys tematic review and meta analysis. Eur J Nutr. 2017;56:13 27.
56. Geiss KR, Jester I, Falke W, et al. The effect of a taurine con taining drink on performance in 10 endurance athletes. Amino Acids. 1994;7:45 56.
57. Rutherford JA, Spriet LL, Stellingwerff T. The effect of acute taurine ingestion on endurance performance and metabolism in trained cyclists. Int J Sports Nutr Exerc Metab. 2010;20:322 9.
58. Kammerer M, Jaramillo JA, Garcia A, et al. Effects of energy drink major bioactive compounds on the performance of young adults in fitness and cognitive tests: a randomized controlled trial. J Int Soc Sports Nutr. 2014;11:44 50.
59. Galloway SDR, Talanian JL, Shoveler AK, et al. Seven days of oral taurine supplementation does not increase muscle taurine content or alter substrate metabolism during prolonged exercise in humans. J Appl Physiol. 2008;105:643 51.
60. Eckerson JM, Bull AJ, Baechle TR, et al. Acute ingestion of sugar free Red Bull energy drink has no effect on upper body strength and muscular endurance in resistance trained men. J Strength Cond Res. 2013;27:2248 54.
61. Jogani V, Jinturkar K, Vyas T, et al. Recent patents review on intranasal administration for CNS drug delivery. Recent Pat Drug Deliv Formul. 2008;2:25 40.
62. De Pauw K, Roelands B, Van Cutsem J, et al. Electro physio logical changes in the brain induced by caffeine or glucose nasal spray. Psychopharmacology. 2017;234:53 62.
63. Pardeshi CV, Belgamwar VS. Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood brain barrier: an excellent platform for brain targeting. Expert Opin Drug Deliv. 2013;10:957 72.
64. Finger TE, Böttger B, Hansen A, et al. Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration. Proc Natl Acad Sci USA. 2003;100:8981 6.
65. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18:643 62.
66. De Pauw K, Roelands B, Van Cutsem J, et al. Do glucose and caffeine nasal sprays influence exercise and/or cognitive perfor mance? Int J Sports Physiol Perform. 2017;12:1186 91.
67. Aeroshot, http://www.blessthisstuff.com/stuff/living/misc living/aeroshot pure energy/. Accessed 26 Nov 2017.
68. Instavit, https://instavit.com/product/instant energy/. Accessed 26 Nov 2017.
69. Primer, http://www.itsgotime.com/. Accessed 26 Nov 2017.
70. Revvies, http://www.revviesenergy.com/our products/. Accessed 26 Nov 2017.
71. Sprayable Energy, https://sprayable.wpengine.com/media/. Acces sed 26 Nov 2017.