The Physiological Effects of Pseudoephedrine on Endurance Cycling

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Abstract

Background: Pseudoephedrine (PSE) is a mild central nervous system stimulant that when consumed at a high dosage has the potential to alter physiological and psychophysical responses. PSE is widely accessible as over-the-counter medication and despite limited research into PSE at high dosages or its effects on prolonged exercise (>2 hours) is no-longer on the World Anti-Doping Association's banned substance list. Currently unrestricted in sport and with no real understanding of the abovementioned responses during endurance exercise there is a high potential for abuse in sport. A recent study performed in our laboratory found PSE to improve self-paced cycling performance in some individuals, however no physiological measurements were taken

Purpose: The primary purpose of this study was to determine the physiological effects of PSE at a dosage previously shown to improve performance (2.5 mg/kg) in some individuals during prolonged cycling. A secondary purpose of this study was to assess the effect on endurance cycling performance.

Methods: In a randomized, double-blind and counter-balanced design, ten well-trained cyclists participated in two trials, consisting of 120 min of fixed-intensity cycling at 65% $\dot{V}O_{2max}$ followed by a set work, self-paced time-trial (TT) of ~30 min, following ingestion of either 2.5 mg/kg PSE or visual-matched glucose placebo. Venous blood samples were collected before and during exercise, along with body temperatures and heart rate. Perceived effort and expired gas samples were collected during exercise. Exercise and diet was controlled ~48-hours prior to the trials.

Results: Mean heart rate was significantly higher with PSE (P = 0.028) during fixed-intensity exercise. Blood glucose concentrations were significantly lower with PSE (P <0.001) for the first 40 min of fixed-intensity exercise. Respiratory exchange ratio was lower in the final 20-min of fixed-intensity and TT with PSE.

Blood lactate, perceived effort, ventilation, and body temperatures were not significantly different between conditions during exercise, nor was TT performance; however individual response was variable.

Conclusions: PSE ingestion increased heart rate during endurance cycling and initially suppressed carbohydrate release into the bloodstream while increasing fat oxidation in the later stages of exercise. Despite individual responses, endurance cycling performance remained unchanged with PSE ingestion.

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The Central Regional Health and Disability Ethics Committee (CEN/08/04/016) approved testing procedures and written consent was obtained from all participants prior to commencing the study.

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1. Introduction

The use of stimulants in endurance exercise-based sport is not a new or exclusive practice due to the common perception that their use will delay fatigue [1]. While amphetamine and cocaine are the more potent of the known stimulants, they are illegal for non-medical purposes [2]. Pseudoephedrine (PSE) on the other hand is a mild stimulant that shares a pharmacological and structural similarity to amphetamine [3]. PSE is legally accessible in the form of over-the-counter medications [4]. Furthermore, the World Anti-Doping Agency (WADA) removed PSE from its restricted substance list in 2004 citing a lack of evidence for an ergogenic effect [5].

PSE effects the adrenergic system and at high dosages (3 times the maximum therapeutic dosage ~180 mg) has the potential to alter a number of physiological processes during exercise [6]. This dosage may increase heart rate and alter respiratory and cardiovascular functions while potentially improving athletic performance [5-7]. Theoretically, a high dosage of PSE also has the potential to lower an individual's perception of exercise effort and increase core temperature [6, 7], however there is little scientific evidence to support this theory.

Since the removal of PSE from the WADA banned list, anecdotal reports suggest its use has been embraced by athletes [5], including those in endurance based events. The available scientific literature appears to focus on the effect of PSE on endurance exercise of approximately one hour or less in duration [5, 8-10]. Thus, an apparent gap in the literature exists regarding the effect of PSE on exercise of a more prolonged nature. Therefore, it is important to improve the current understanding of the physiological effects of a high dosage of PSE during prolonged endurance exercise.

In the following chapter a brief background into the history, legislation, and physiological effects of each of the major available stimulants in relation to

endurance exercise will be provided. This general background will then be followed by a review of the literature concerning the stimulant PSE. The prevalence of use, current legislation, physiological and neural mechanisms, and the effect on endurance performance and physiological variables i.e. cardio-respiratory, metabolic, psycho-physical, and thermoregulatory, during endurance exercise will be discussed. This review of the literature leads into the aims of the current investigation followed by the main body of the thesis.

2. Literature review

2. 1. Stimulant use in sport

Since the earliest documented athletic competition, athletes have sought ways of gaining a competitive edge [11]. In modern professional sports where physical fitness and genetic ability are similar between competitors, the use of stimulants possibly provides the extra gain that is necessary for success [12]. The use of stimulants within sporting competition has a long, colourful history that can be traced back to the third century writings of the Greek physician Galen. His reports on the ancient Olympic Games of Greece have athletes consuming potions of herbs and seeds thought to hold stimulant properties [1]. Roman gladiators and medieval knights reportedly utilized herbal stimulants to maintain energy levels following injury, and later, swimmers of the Amsterdam canal race during the 19th century were reported to ingest a plethora of stimulants including strychnine, a common pesticide [13]. While the history of stimulant use in athletic competition may be well established, only a few of the stimulants utilized today (table 1) have been thoroughly investigated. Athletes may then, sometimes illegally, use stimulants guided only by questionable information. This can carry significant health implications, the risk of facing legal charges, and prohibition from competition.

In general, stimulant intake causes the release of adrenaline and noradrenaline; hormones which in turn act on the adrenergic receptors eliciting the 'fight or flight' response [14]. This response alters a number of physiological processes, including heightening of the senses and physical ability. Unsurprisingly, those in dangerous situations (e.g. soldiers) or physically competitive environments (e.g. athletes) could stand to benefit from an artificial increase in this response [11].

Ref	Drug	Legal status in sport	Availability
[15]	Amphetamines	Prohibited in competition	Prohibited / Prescription
[15]	Cocaine	Prohibited in competition	Prohibited
[16]	Caffeine	Monitored in competition	Freely available
	Nicotine	-	Freely available
[15]	Ephedrine	Prohibited in competition	Restricted
[16]	Pseudoephedrine	Monitored in competition	Over-the-counter medication

Table 1: Legal classification of common stimulants thought to be exploited in sport and their availability

2. 1. 1. Amphetamines

Amphetamines were initially administered during the 1920's as anti-depressants, appetite suppressants, and for the relief of symptoms from the common cold [17]. Over the next few decades the psychostimulant and addictive properties of amphetamines became apparent and by 1971 the drug was re-classified and restricted (table 1) [2, 18, 19]. During the second world war amphetamines were administered to troops as a way of delaying fatigue and enhancing mental awareness [11]. The U.S. air force also utilized amphetamines during Operation Desert Storm in 1991 due to their ability to enhance flight safety and cockpit performance [20].

Amphetamine abuse in sport appears to be most pronounced in cycling and American football [1, 21, 22], possibly due to the supposed central effects of amphetamine which mask fatigue and increase aggression [23]. However, initial investigators concluded that amphetamine holds little or no ergogenic effect during aerobic exercise, while the ability to tolerate high levels of anaerobic metabolism appeared to marginally increase [21, 24]. More recently, reviewers have described amphetamine to provide an advantage of no more than 1-2% during sporting

competition, a degree of improvement often difficult to detect within the realms of statistical significance [17].

It is the side effects of amphetamine use that appear to be much more pronounced. These include a redistribution of blood flow away from the skin, reducing the athlete's ability to dissipate heat [25]. Therefore, in endurance cycling events that often combine prolonged, high intensity exercise with high ambient temperatures and humidity, a situation of amphetamine-induced heatstroke or, more severely, cardiac arrest can occur [2]. Unfortunately, amphetamine use in endurance sports has reached notoriety with the death of two cyclists, Jenson (heatstroke) and Simpson (cardiac arrest), who died while competing in road cycling events during the 1960 Rome Olympics and the 1967 Tour de France, respectively [2].

2. 1. 2. Cocaine

Derived from the cocoa plant (*Erythroxylon cocoa*), cocaine has been used for centuries in tonics and other preparations to increase vigour and alleviate feelings of fatigue. At the turn of the 20th century cocaine was used as an anaesthetic and available in various medications for many years; it was also a key ingredient in the popular soft drink 'Coca-cola' until 1903, when it was removed [11]. Now known to be a highly addictive substance with severe side-effects (paranoid psychosis, delirium), it is one of the most common illicit and heavily restricted drugs in modern society [26].

Recently, professional cyclist Tom Boonen was banned from the 2008 Tour de France due to testing positive for cocaine [27], again lifting the debate as to its possible ergogenic effects. Unfortunately, the true motivation behind cocaine use in sport is difficult to investigate due to the obscurity in separating abuse for social or athletic reasons [1]. For obvious ethical and legal reasons little researched has been performed on human participants concerning the effects of cocaine on

athletic performance and what is known has often been extrapolated from animal studies [12].

While the actual ergogenic benefits of cocaine are heavily disputed, the risks (beyond possible legal ramifications) appear to be great [1]. Currently, it appears that cocaine is an ergolytic agent for all exercise but that of short duration [28]. Cocaine is thought to increase glycogen metabolism and the sympathetic response to endurance exercise causing premature fatigue [29, 30]. Acute cocaine use has been found to increase heart rate, blood pressure, and left ventricular contractility [31] and is associated with coronary vasoconstriction [32]. Cocaine is also suggested to increase in platelet aggregability [33] facilitating thrombus formation [34]. This cascade of events is often thought to have resulted in a number of cocaine-associated deaths in sporting competition [34]. It is also likely that cocaine increases core temperature [35] and lactate formation during exercise [29], and together with coronary vasoconstriction may lead to fatal cardiac damage [11].

2. 1. 3. Caffeine

As the pharmacologically active substance in coffee, tea, and some soft drinks such as cola, caffeine is one of the oldest and most widely consumed stimulants known [11].

As early as 1907, caffeine was shown to increase work output [36], a discovery that has been supported by researchers over the last century [37].

Caffeine is considered sociably acceptable, medically safe, and is widely available [38]. Of the available stimulants, caffeine has received by far the most investigative attention with reviewers able to provide detailed reports covering physiological and ergogenic effects [37, 39]. While the ergogenic effect of caffeine appears to be well founded, the mechanisms by which it occurs is not so well understood [37]. Caffeine was first proposed to improve endurance sporting performance by enhancing fat utilisation and reducing glycogen breakdown [40, 41], however, more recent investigations fail to support this theory [42]. Another proposed mechanism includes the ability of caffeine to improve the intracellular ionic environment within active muscle improving the development of force production for each motor unit.

However, it is not clear whether these are direct effects on enzymes or due to post-receptor events [43]. Further work has also suggested a role for caffeine to improve motivation and concentration, thereby acting 'centrally' [44].

Caffeine has become a common drug utilized in sport, often referred to in layman publications as a "nutritional strategy". A plethora of sports supplement companies now offer caffeinated sports drinks, energy gels and even pills for use in sport [37, 39]. Once a restricted substance at levels greater than 12 μg ml^{-1} [45], caffeine was removed from the World Anti Doping Agency's (WADA) restricted substance list in 2004. It was concluded that caffeine levels above those already allowed had been shown to decrease performance [38].

2. 1. 4. Nicotine

Nicotine is accepted as the major component in tobacco smoke responsible for addiction [46]. Along with caffeine, nicotine is one of the most widely consumed psychostimulants [47]. Due to the widespread use of nicotine in the form of tobacco smoke and its associated health consequences, research into the effects of nicotine has been focused on the pharmacodynamics of the drug to allow better understanding of its addictive properties to improve smoking cessation rates [46]. It appears that few investigators have considered the effects of nicotine during exercise. Early research focused on nicotine's possible anti-anxiety effects on target-based sporting competitions such as golf [48]. However more recently, a group of investigators have turned focus to endurance exercise. Nicotine administration has reportedly caused an increase in heart rate and blood lactate during treadmill exercise at 60 and 85% $\dot{V}O_{2max}$ [49]. In a recent investigation [50], nicotine administration via a transdermal patch was found to increase time to exhaustion at 65% $\dot{V}O_{2max}$ by 17%. No significant effect was observed on heart rate, lactate or any of the other physiological measures during the experiment, leading the authors to conclude that nicotine prolonged endurance exercise via a central mechanism.

2. 1. 5. Ephedrine

A naturally occurring sympathomimetic drug originally derived from the Chinese herb Ma Huang, ephedrine is structurally similar to amphetamine [2, 3]. Ephedrine has gained a reputation as both an ergogenic aid and a weight-loss adjunct (commercially available as the latter in some countries) [51]. The use of ephedrine in sporting competition has had its share of the limelight with 16 year old, US athlete, DeMont, stripped of his 1972 Olympic gold medal due to a positive test for ephedrine. DeMont later claimed the ephedrine was part of an asthma treatment provided by his doctor [52]. Also, the year 2001 saw the death of American footballer, Wheeler, during training following the ingestion of ephedrine [1].

A recent meta-analysis of published studies concluded ephedrine to promote modest short-term weight loss [51], while the possible ergogenic properties of ephedrine appear to remain elusive [53]. Ephedrine at low dosages has been shown to hold no effect on a number of performance variables, including muscular endurance [54]. Furthermore, Bell et al [55, 56] reported no significant effects on oxygen consumption, time to exhaustion, or carbon dioxide production with ingestion of ephedrine in military personnel. The combination of ephedrine and caffeine however, has been shown to improve performance in a variety of military applications, including a 3.2 km run carrying 11 kg of equipment [56].

2. 2. Pseudoephedrine

Pseudoephedrine (PSE) is a sympathomimetic amine commonly utilized in more than 135 over-the-counter and orally administered prescription medications [19]. When administered at therapeutic levels (60mg), PSE is known to provide relief from sinus congestion and the discomfort associated with many of the symptoms of the common cold, hay fever and upper respiratory tract infections [4, 8, 19]. The drug shares a similarity to that of amphetamine and ephedrine [57].

PSE's pharmacological and structural similarity to amphetamine [57] has led many to suggest that PSE may also hold an ergogenic effect for endurance based athletic pursuits [5, 58]. This, in turn, is based on the assumption that amphetamines exert a simulative effect on the central nervous system, ample to override the sensation of fatigue and enhance or prolong endurance exercise [58]. Both assumptions do not appear to be well supported by the literature [10, 25, 59, 60]. In spite of this, many athletes assume that PSE, along with other stimulants, will delay fatigue [61].

The use of PSE in sport created media headlines during the 2000 Sydney Olympic Games with the positive test of Romanian gymnast Andreea Raducan. Allegedly given a cold remedy containing PSE by her team doctor, the gymnast subsequently had her all-round gold medal striped from her [62]. Whilst Raducan's case has been the most prolific, a recent survey found that in the five years prior to year 2000, 22% of the stimulants used by athletes, as detected by a UK sports drug testing programme, were PSE [63]. Furthermore, Australian sports drug testing agencies collected 11 positive for PSE urine tests for the years 1996-1997 [64] and three for the years 2000-2001, one of which resulted in a three month ban from competition (triathlon) [65].

2. 2. 1. Legislation in sport

PSE urinary concentration levels were initially restricted to 10 μg $ml \cdot l^{-1}$, and then later in 2001 increased to 25 $mg \cdot l^{-1}$ by the International Olympic Committee (IOC) [66]. The scientific rationale for the previously selected cut-off points were never published by the IOC, however it has been suggested that they were not based on experimental evidence [66] but rather an assumption formulated from PSE's chemical similarity to amphetamines [6, 58]. January, 2004 saw the World Anti Doping Agency (WADA) remove PSE from the restricted substance list [5]. The decision to remove PSE from the restricted drug list was met with controversy within mainstream media. A number of sporting (science and coaching) and medical professionals expressed concern at the lack of research into the possible

ergogenic and, more importantly, physiological effects of PSE, especially when consumed at higher-than-recommended dosage levels [67]. Interestingly, the decision to lift the restriction on PSE was based on the same premise; that there was a lack of scientific evidence for an ergogenic effect [5]. WADA currently monitors PSE levels in athletes through urine testing [25].

Prior to 2004, athletes who tested positive for PSE use were often reprimanded for doping, when in reality, many cases could have been a simple mistake on the athletes behalf such as ingesting an over the counter cold treatment containing PSE for genuine medicinal purposes. Therefore, it is important that the effects of PSE at therapeutic dosages should be considered separately from the much higher dosages likely to be used for intentional ergogenic gain. The majority of investigations prior to 2004 were performed using PSE at therapeutic levels (<60 mg) or in a maximal therapeutic regime (60 mg, 6 times over 36 hours) in an effort to understand whether athletes taking the drug for medicinal purposes would gain an ergogenic advantage (Table 2) [8, 9, 58, 68, 69]. However, following PSE's removal from the banned substance list, researchers have since shifted focus to the possible effect of the drug at dosages exceeding therapeutic levels (Table 3) [5-8, 10, 58, 59]. This is important for two reasons; first, at high dosages (60 mg/kg PSE, 4 mg/kg AMP) PSE has been shown to exert similar actions as amphetamine in rodents [19], suggesting the possibility of a dosage effect. And second, many athletes perceive the possible ergogenic effects of a given substance to act in a 'linear' fashion [53].

2. 2. 2. Pharmacokinetics

PSE is readily absorbed from the gastrointestinal tract [66], the majority of which is thought to be excreted unchanged in the urine [70]. However, reported urine concentration levels within 24 hours of ingestion are wide ranging (43 to 96%) with the reasons as yet unknown [66]. A small, varying percentage of PSE (~1 – 6%) is also metabolized through hepatic N-demethylation to norpseudoephedrine [70]. Urinary pH is thought to play a role in the amount metabolized, with more alkaline

urine increasing reabsorption and prolonging retention of the drug within the body, extending the time allowed for metabolism [71]. PSE has a half-life of 9-16 hours [72].

Within humans, PSE begins to exert its effects approximately 60 minutes following ingestion [36] and, based on ingestion of 180 mg, reach peak plasma concentrations in approximately 2 hours [2].

2. 2. 3. Neurophysiology and central actions

When administered orally, the effects of PSE on the adrenergic system can extend beyond its intended therapeutic effects [8]. PSE is currently understood to exert its effect by indirectly increasing neurotransmitter release [5] and/or the direct stimulation of adrenoreceptors (or post-synaptic receptors) at various tissues and organs throughout the body [2].

The primary mechanism of PSE action is indirect [19]. PSE, like all stimulants must cross the blood-brain barrier from cerebral circulation in a sufficient quantity to exert a central pharmacological effect [2]. Compared to amphetamine, PSE has a reduced ability to cross the blood-brain barrier due to its lower lipid solubility, thus limiting its possible effect on the central nervous system [28]. Once across, PSE leads to the release of adrenaline from the adrenal medulla and dopamine from the hypothalamus [72]. Dopaminergic neurons then mediate the indirect stimulation of norepinephrine release from noradrenergic neurons [18, 59], while noradrenaline is released as a neurotransmitter from the majority of sympathetic nerves [25]. Once released into the neuronal synapse, norepinephrine stimulates the various α- and, to a lesser extent, β-adrenergic receptors [5].

The direct, also known as secondary, action of PSE is observed as a weak agonistic effect on the α- and β-adrenergic receptors [5]. These adrenoreceptors throughout the body have differing affinities towards PSE, adding to the already complex nature of PSE's direct effect on adrenoreceptors [73].

The potential central psychostimulant benefits include the reduction of fatigue and an increase in concentration and alertness, whereas the potential peripheral physiological advantage of these agents includes the indirect activation of β-adrenergic receptors and the stimulation of cardiovascular function and metabolic activity [2].

High dosages of PSE (50 - 60 $mg \cdot kg^{-1}$ cf 2.5 $mg \cdot kg^{-1}$; the maximum used in human studies to date) have been documented to share similar actions on the central nervous system to amphetamines. These are described by their effect on locomotor activity and feeding behaviour in rodents [19, 72], presumably because the higher dosage maximises possible cerebral uptake. Using a unilateral lesion of the nigro-neostriatal pathway of rodent brains, investigators administered a series of stimulants to investigate the actions of the stimulants on central dopamine neurons. By observing turning behaviour the authors concluded that while not as potent (10-20 times less) as amphetamine, PSE does hold similar effects on central-dopamine-containing neurons [72].

Dopamine is an important neurotransmitter in the central nervous system, especially in the hypothalamus, which is important for body arousal and is thought to reduce the sensation of fatigue [5]. It is therefore possible that PSE could be ergogenic in a similar manner as amphetamine, stimulating the central nervous system and theoretically masking fatigue [10]. Dopamine is commonly considered to be part of the brain's reward system. Its role in regulating the pleasurable effects (or euphoria) associated with some stimulants is thought to play a large role in the addictiveness or sensation of reduced fatigue commonly reported from stimulants [19].

2. 2. 4. Adrenoceptors.

Adrenaline, noradrenaline (via primary action) and PSE (via secondary action) exert their effects on the body through a group of nine G-protein-coupled receptors

(adrenoreceptors) found in nearly all peripheral tissues and many neuronal populations within the central nervous system [73].

Adrenoreceptors mediate many physiological responses, and as a result are considered an effective target for drug action. The therapeutic effect of PSE occurs via the indirect stimulation of the α-receptors of the nasal mucosa in the nasal cavity, reducing blood flow therein [59, 74]. The possibility for effect often extends beyond therapeutic intentions; the side effects include altering blood pressure, myocardial contractile rate and force, airway reactivity, and a variety of metabolic functions [25]. Furthermore, adrenoreceptors in the locus coeruleus hold multiple effects on the activity of many other neuronal nuclei in the brain [73].

Multiple adrenoreceptor subtypes can coexist in a particular tissue or cell and can create a multitude of opposing, redundant, or synergistic responses [73]. For example, the complex action of adrenaline on blood vessels can be broadly explained by the distribution and relative expression of adrenergic receptor subtypes. In cardiac and skeletal muscle, β-adrenergic receptors are more dominant hence vasodilation is the prevailing response, while α-adrenergic receptors dominate in the skin causing vasoconstriction. This causes an increase in cardiac output and redistribution of blood away from non-essential organs (skin) to skeletal muscle [25] readying the body for physical effort.

To our knowledge, no investigations specifically examining the physiological effects of a high dosage of PSE during endurance exercise have been produced. At best, current knowledge is based on a mixture of extrapolated data from shorter trials or lower dosages [5, 6, 8, 9, 58, 59, 68, 69] and observations made during endurance based performance trials [7, 10].

Theoretically, the effect of PSE on the body's adrenoreceptors could result in a number of physiological changes that may influence endurance exercise, including an increase in cardiac output, glycogenolysis, oxygen consumption, arterial blood

pressure and peripheral vasoconstriction [5, 59, 68]. Holistically, a change in one or a combination of these possible systemic physiological factors could influence athletic performance or contribute to a potentially hazardous health situation.

2. 2. 5. Cardiovascular effects

PSE is appears to have a dosage-dependent inotropic and chronotropic effect on the heart, increasing cardiac output [4]. Furthermore, PSE is suggested to initiate vasoconstriction of cutaneous blood vessels and vasodilation of muscle arterioles [5, 59]. This redistribution of blood combined with the increase in cardiac output [5] could theoretically lead to a greater blood supply to working muscles [6].

At rest it appears that therapeutic levels of PSE causes and increase in heart rate, with a recent meta-analysis [4] of 24 clinical studies finding a minor but significant increase in heart rate (2 – 3.6 beats/min) and systolic blood pressure (0.08 – 1.90 mm Hg). The authors of the meta-analysis also reported a dosage-response relationship ($P < 0.001$) on both heart rate and blood pressure.

PSE's effect on heart rate during exercise does not appear to be so well defined. A number of investigations have observed a strong trend for maximal therapeutic dosages [68] and above [5, 7, 8, 68] to increase heart rate during exercise. They often fail to meet statistical significance however; hence PSE is frequently concluded to hold no effect on the cardiovascular system (see tables 2 and 3). Bright et al [8] suggested a dosage-dependent cardiovascular effect during and after exercise following investigation of two separate dosage levels (60 mg and 120 mg PSE) during various ergometer cycling tests. With the increase in dosage, the investigators observed a slight increase in resting heart rate compared to placebo (PLB) (68 ± 3 PLB 0 mg, 72 ± 3 PSE 60 mg, 75 ± 5 PSE 120 mg), a reduction in time to reach 85% heart rate and a reduction in the time for participants' heart rate to return to resting levels following exercise. Each of these observed changes failed to reach statistical significance however; although the authors did suggest a type II error due to the small number of participants. Interestingly, other low dosage

investigations [9, 68] have shown no effect of PSE on heart rate during constant-load exercise (~20 minutes). Two investigations have considered the effects of a much greater dosage of PSE (2.5 $mg \cdot kg^{-1}$) on heart rate during exercise [5, 7]. Middle distance track running following ingestion of 2.5 $mg \cdot kg^{-1}$ PSE yielded a trend for increased heart rate (+5–7 beats per min) during exercise [5]. Also, research performed in our laboratory using the same dosage of PSE [7] has shown a significant increase in heart rate (+10 beats per min) during TT endurance cycling (>2.5 hours) when compared to a PLB. Both studies suggest a dosage-dependent response however, it must be noted that during both studies exercise was self-paced, making between-participant comparison difficult.

While heart rate appears to slightly increase at rest following PSE ingestion [4], the sympathetic drive that occurs with exercise may override the simulative effect of the drug at lower dosages [9, 68]. It appears possible that higher levels of PSE administration may reveal an additive stimulatory effect, with the sympathetic drive associated with exercise and PSE increasing heart rate further than that of exercise alone [5, 7]. However without constant-load trial data it is difficult to be certain. It is also possible that the observed increase in heart rate may not solely be as a direct result of PSE effect on the heart, but an indirect effect related to the rise in core temperature with exercise and PSE use [7]. Increasing core temperature has experimentally been shown to lower stroke volume, requiring an increase in heart rate to maintain cardiac output [75].

Ref	Participants	Dosage / timing	Protocol	Results					
				Cardio-vascular effects	Body temp	Substrate metabolism	Psycho-physiological	Pulmonary function	Performance
[68]	8 male endurance runners, $\dot{V}O_{2max}$ 65.5 ± 5.6 ml·kg^{-1}·min^{-1}	25mg *PPA* & 60mg *PSE* 6x over 36h, last dosage 4h prior	- 20min SS run @ 70% $\dot{V}O_{2max}$ - 5km *TT* on treadmill	↔ HR_{Peak}, *HR*, *BP* (rest & post exercise)	-	↔ lactate, glucose, *NEFA* (rest & post exercise)	↔ *RPE*	↔ O_2 consumption, $\dot{V}_E$, *RER*,	↔ Time to complete
[9]	11 male, mod trained	60mg, 90min	- Wingate cycle - Submax cycle efficiency test	↔ *HR*	-	-	-	↔ $\dot{V}O_{2max}$, $\dot{V}_E$, *RER*	- ↔ PP, $Work_{Total}$, Fatigue index ↔ efficiency
[69]	10 “healthy” females	60mg	- Graded treadmill test	↑ *HR*, ↔ *BP*	↔ Core	-	↔ *RPE*	↔ $\dot{V}O_{2max}$, *RER*, $\dot{V}_E$, *RR*, *TV*	↔ Exercise time
[8]	6 “healthy” males	60mg, 60min	- Multistage treadmill test to 85% predicted HR_{max}	↔ Rest *HR*, *BP* (rest, exercise & post)	-	↔ glucose, insulin	-	-	↔ Time to reach 85% HR
[58]	10 male cyclists, >50 miles per week	1 mg·kg^{-1} bw, 60min	- $\dot{V}O_{2max}$ test - Time to exhaustion	↔ BP_{max}, HR_{max}	-	-	↔ *RPE*	↔ $\dot{V}O_{2max}$	↔ Time to exhaustion

Table 2: Investigative findings of studies of low/therapeutic PSE dosages during exercise. Results displayed as PSE vs. placebo. Abbreviations: *TT* Time-trial, *MVC* Maximum Voluntary Contraction, ↔ No change (not significantly different $p > .05$), ↑ Increase (significantly different $p < .05$), *RM* Repetition Maximum, *HR* Heart Rate, $\dot{V}_E$ Minute Ventilation, *RER* Respiratory Exchange Ratio, *NEFA* Non-esterified fatty acids, *RPE* Perceived Exertion, *BP* Blood Pressure, *PO* Power Output, *PSE* Pseudoephedrine, *PPA* Phenylpropanolamine, *RR* Respiration rate, *TV* Tidal volume, SS Steady State, PP Peak Power, RM Repetition Maximum.

Ref	Participants	Dosage / timing	Protocol	Results					
				Cardio-vascular effects	Body temp	Substrate metabolism	Psycho-physiological	Pulmonary function	Performance
[10]	10 male cyclists, 402 ± 15 W_{max}	120mg, 120min	- 40km cycle erg *TT* - Max isometric torque *MVC* to fatigue	-	-	↔ lactate	-	-	↔ Time to complete
[59]	10 males & 10 females, described as "healthy"	120 mg, 120min	- *MVC* strength & fatigue in handgrip and ankle dorsiflexion - 30 sec max cycle	-	-	↔ lactate	-	-	↔ Force production or time to fatigue ↔ PO
[8]	6 "healthy" males	120mg, 60min	- Multistage treadmill test to 85% predicted HR_{max}	↔ Rest *HR, BP* (rest, exercise & post)	-	↔ glucose, insulin	-	-	↔ Time to reach 85% HR
[58]	10 male cyclists, >50 miles per week	2 mg·kg^{-1} bw, 60min	- $\dot{V}O_{2max}$ test Time to exhaustion	↔ BP_{max}, HR_{max}	-	-	↔ *RPE*	↔ $\dot{V}O_{2max}$	↔ Time to exhaustion
[5]	7 male "athletes" $\dot{V}O_{2max}$ 68.7 ± 9.2 ml·kg^{-1}·min^{-1}	2.5 mg·kg^{-1} bw, 90min	- 1500-m run (400m outdoor track)	↔ *HR* (trend of ↑ 5-7 bpm)	-	↔ lactate, glucose	-	↔ PCO_2, PO_2, $\%0_2$ saturation	↓ Time to complete
[7]	8 male cyclists, $\dot{V}O_{2max}$ 69.0 ± 2.0 ml·kg^{-1}·min^{-1}	2.5 mg·kg^{-1} bw, 90min	- Cycling erg, work dependent *TT* = 2.5h @ 70% $\dot{V}O_{2max}$	↑ *HR*	-	↔ lactate, glucose	-	-	↔ *TT* (large individual variance)
[6]	22 male intermittent team sports, rec & rep level	180mg, 45min	- 30 sec max cycle - Bench press (max) - Bench press (fatigue) - Isometric knee extension	↑ *HR* post,	-	↔ lactate	-	-	↑ PO_{Peak} ↔ 1 RM bench press & reps to fatigue ↑ $Torque_{max}$

Table 3: Investigative findings of studies of high PSE dosages during exercise. Results displayed as condition vs. placebo. Abbreviations: *TT* Time-trial, *MVC* Maximum Voluntary Contraction, ↔ No change (not significantly different $p < .05$), ↑ Increase (significantly different $p < .05$), *RM* Repetition Maximum, *HR* Heart Rate, $\dot{V}_E$ Minute Ventilation, *RER* Respiratory Exchange Ratio, *NEFA* Non-esterified fatty acids, *RPE* Perceived Exertion, *BP* Blood Pressure, *PO* Power Output, *PSE* Pseudoephedrine, *PPA* Phenylpropanolamine, *RR* Respiration rate, *TV* Tidal volume, SS Steady State, PP Peak Power, RM Repetition Maximum.

2. 2. 6. Substrate metabolism

The results of published research indicate that there is no significant interaction between PSE ingestion and substrate shifts during exercise [5-8, 10, 59, 68].

The measurement of substrate usage via indirect calorimetry has revealed no effect of PSE at therapeutic dosages on fuel oxidation during exercise [9, 68, 69]. Unfortunately, the method has yet to be applied to higher dosages of the drug or to exercise in duration beyond 20 minutes.

The most widely examined metabolite response to PSE use has been that of lactate [5-8, 10, 59, 68]. When compared to a PLB, ingestion of PSE, at any investigated dosage, has not been shown to hold a significant effect on lactate concentrations during or following various modes of exercise, including, isometric hand grip [59], middle-distance running [5, 68], sub-maximal steady-state running [68], 'all-out' anaerobic cycling [6, 59], and prolonged aerobic cycling [7, 10].

Measurements of blood substrate concentrations have revealed no significant interactive effects between sub-maximal exercise and glucose plasma concentrations [5, 7, 8, 68] or insulin levels [8] with PSE ingestion. To date only one study [68] has included the measurement of non-esterified fatty acids, revealing no significant effects of PSE at maximal therapeutic levels.

While non-esterified fatty acids have received little investigative attention, it appears possible that there is a lack of significant interactive effect between PSE, exercise and substrate metabolism and oxidation. Taken together, the results suggest the exclusion of a purely metabolic mechanism for any performance-related effects.

2. 2. 7. Core and surface temperature

It is possible that the redistribution of blood associated with PSE ingestion [6] could stand to alter an exercising individual's ability to dissipate heat, causing an increase in core temperature [75].

There appears to be no systematic investigations available regarding the effects of PSE on core and surface temperature. Investigators have shown therapeutic dosages of PSE to hold no effect on core temperature during a graded exercise test (Bruce protocol) when compared to a PLB [69]. However, given that low dosages of the drug were used the possibility of a dosage-dependent effect has not been ruled out [7].

An investigation recently completed in our laboratory [7] found a reduction in performance following PSE ingestion (2.5 $mg \cdot kg^{-1}$) from two of the participants completing a prolonged cycle TT (> 2 hours). While temperature was not recorded, the participants commented that they felt "hotter" during the trial. It is possible that these two participants experienced a much greater sensitivity toward the PSE dosage, increasing the blood redistribution properties of the drug and resulting in an increased core temperature. Further analysis of the experimental data revealed a significant (P = 0.034) negative linear correlation (R^2 = -0.54) between the metabolic work completed (kJ) and the effect of PSE on performance (see Fig 1). Those participants who completed a higher amount of metabolic work displayed a trend for a reduced ergogenic or even an ergolytic effect. The length and intensity of the experimental trials were calculated by the total work (kJ) required for the participant to complete 150 minutes cycling at 70% of $\dot{V}O_{2max}$, therefore it is possible that those able to work at a higher relative metabolic rate may also be at increased risk of becoming hyperthermic. However, as stated by the author, "without measurement of body temperature during exercise such a theory remains purely speculative." (pg 32 [7])

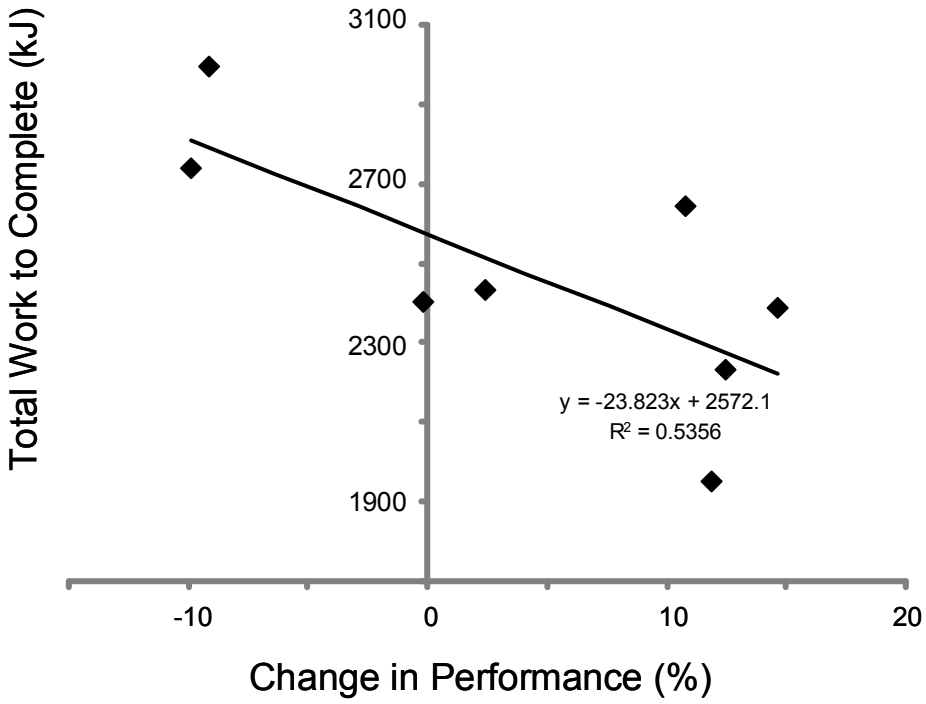

Figure 1: Percentage change in performance vs. metabolic work completed [7]

While there is no definitive data available concerning the possible effect of PSE on body temperature and the only published results show no effect at therapeutic levels over a graded exercise test, the suggestion of an increase in body temperature reported by Betteridge [7] warrants further investigation. Assuming an increase in core temperature did actually take place, it may have been due to the combination of a higher PSE dosage and a more prolonged exercise protocol than in the previous study.

If PSE ingestion does in fact lead to an increase in core temperature during prolonged exercise a number of health issues would be raised. Firstly, heart rate is known to increase as core temperature rises in an effort to maintain cardiac output as stroke volume decreases [75]. This can result in a greater cardiovascular strain

and a reduction in blood flow to the brain and, in severe cases, intestinal organs [76, 77]. Together, this can create a situation of amphetamine-like induced heatstroke or cardiac arrest [2]. Secondly, an increase in brain temperature may reduce central arousal, increase an individual's perception of fatigue, and impair central neuromuscular activation [78].

2. 2. 8. Psycho-physiological correlates

One theory of PSE's possible ergogenic action is an increase in the stimulation of the central nervous system, theoretically masking the central component of fatigue and lowering perceived effort [5, 7]. Given the importance of central fatigue in endurance performance [79], this may be a plausible explanation for PSE's potential ergogenic effect with this type of exercise. Indeed, one group of investigators found high dosages of PSE to improve 1500 metre running performance, later suggesting the improvement was likely to be associated with a psycho-stimulant effect rather than any systemic physiological effects [5]. However, the investigators failed to report any measures of psycho-physiological parameters. While a popular theory, surprisingly few investigators have addressed this possibility within human participants. Perhaps the simplest and most relevant measurement would be that of Borg's ratings of perceived exertion (RPE) during consistent load exercise [80]. Currently, three investigations have measured RPE during PSE trials [58, 68, 69]. PSE ingestion at dosages of 2 $mg \cdot kg^{-1}$ [58] and 60 mg [69] during ramp protocol exercise have shown no effect on RPE. A more recent investigation involved six dosages of 60 mg over 36 hours (maximal therapeutic dosage) prior to a 20 minute set steady state (70% $\dot{V}O_{2max}$) running trial and 5000 meter TT on a treadmill. No significant difference was detected between PSE and PLB conditions [68]. It is possible that the lack of differences may be due to the low dosages tested [5, 68], however investigations utilizing 2 $mg \cdot kg^{-1}$ have also yielded no effect [58]. Another possibility for a lack of effect may lie in the exercise durations examined. It is possible that endurance exercise (>2 hours) combined with high dosages of PSE may elicit such effects. Betteridge [7] found those participants who consumed 2.5 $mg \cdot kg^{-1}$ PSE and performed better during a

>2 hour cycling TT commented that they also felt “stronger” with the drug. While the author failed to report any measure of RPE, it was suggested that future research should quantify participant’s perception of fatigue during such trials.

2. 2. 9. Pulmonary ventilation and gas exchange

While current studies have failed to extensively describe any direct ergogenic benefit of PSE ingestion, there is a strong potential for an indirect benefit by way of an improvement in cardiovascular and respiratory functions due to altered lung function from bronchial dilation [25].

Lung function tests have revealed high dosages of PSE (180 mg) to enable participants to expire slightly more air in one maximal breath (FVC) [6]. These tests have also revealed a significant increase in volume of air expired in the first second of the test (FEV_1) and the total maximal volume of air moved in one breath (FVC), however, these changes have been described as small and likely to be clinically insignificant [6].

Hodges et al [9] examined the effects of 60 mg of PSE on aerobic cycling efficiency approximately 120 minutes following ingestion. No significant difference was observed between drug and PLB administration on $\dot{V}O_2$ or minute ventilation ($\dot{V}_E$) at 40% and 60% peak power (58 ± 8% and 78 ± 11% of $\dot{V}O_{2peak}$ respectively). Similar findings have been published regarding short-term steady state exercise following ingestion of PSE at therapeutic levels with no significant effects on $\dot{V}O_{2max}$, $\dot{V}_E$, respiration rate (RR), or tidal volume (TV) [58, 68, 69]. Hodges et al [5], who observed an improvement in 1500 meter running performance, also found no change in PO_2, PCO_2, and oxygen saturation with high PSE dosages (2.5 $mg \cdot kg^{-1}$). Unfortunately measurements were recorded post-exercise only; therefore an understanding of the possible effects during exercise is unclear.

2. 2. 10. Effect on endurance Performance

PSE is commonly perceived to provide a direct ergogenic effect, improving endurance, strength, and reducing the sensation of fatigue [1]. However, evidence for an ergogenic effect is more ambiguous than anecdotal reports would suggest. A review of the available literature revealed that any proposed ergogenic effect of PSE when consumed at therapeutic levels appears unlikely (see table 2). Investigators have often concluded that, in the case of therapeutic dosages, the stimulant effect of PSE is over-ridden by the sympathetic drive associated with exercise [9, 68]. They also suggest that the lack of ergogenic effect is due to the low dosage of PSE provided [9, 58, 68]. Thus it seems likely that if an ergogenic benefit was sought by individuals, they would most likely ingest a higher than therapeutic dosage.

Investigations utilizing dosages of PSE above therapeutic levels have provided mixed results (Table 3). Gillies et al [10] were the first to examine the effects of PSE on endurance performance at dosages above therapeutic levels. Administration of 120 mg PSE 2 hours prior to exercise was found to offer no ergogenic effect during the laboratory based, 40 km cycle ergometer time trial (TT) (Mean time ± SD 58.3 ± 1.6 min placebo (PLB), 58.7 ± 1.5 min PSE). Alternatively, ingestion of 2.5 $mg \cdot kg^{-1}$ 90 minutes prior to exercise was shown to significantly improve running performance by 2.1% (273.86 ± 4.36 s PSE, 279.65 ± 4.36 s PLB) over 1,500 meters on an athletics track [5]. Using a similar dosage, Gill et al [6] found a slight but significant improvement in lower-body force development. A recent investigation performed in our laboratory [7], examined the performance effects of PSE ingestion (2.5 $mg \cdot kg^{-1}$) 90 minutes prior to a work-dependent cycle ergometer TT. While mean performance was not significantly improved with PSE ingestion, a large variation in individual response was observed. Four of the eight cyclists improved their individual performance by 10 - 15% (169.16 ± 18.84 min PSE, 193.03 ± 19.13 min PLB). Two participants appeared to have an adverse reaction to PSE, with a reduction in performance of -9% (200.33 ± 32.06 min PSE, 183.03 ± 30.17 min PLB). The remaining two participants showed no significant

change. These findings lead the author to suggest that the performance outcome of a high dosage of PSE may be dependent on individual sensitivity to the drug.

Despite the majority of investigations finding no significant effect of PSE on endurance performance, evidence of an ergogenic effect at higher dosages exists, albeit possibly influenced by individual response [5-7], therefore further investigation is warranted.

2. 3. Summary

PSE is accessible (via over-the-counter medications), unrestricted in sport, and potentially ergogenic at high dosages [5-7], yet despite these factors little is known about the drug's effect on the physiological responses to exercise or its effect on endurance performance. As the current knowledge stands, athletes may be putting themselves at risk by consuming PSE. Alternatively, WADA may have "legalized" a drug that does in fact improve endurance performance.

Clearly there is a paucity of data regarding PSE ingestion at dosages suggested to instigate an ergogenic effect on endurance cycling in some individuals [7]. More specifically, there is scope for a rigorous study of the physiological and performance-related effects of PSE ingestion on endurance exercise.

3. Objective

The primary objective of the investigation was to determine if pseudoephedrine at dosages ingested at three times the therapeutic level would have an effect on the chosen physiological and psycho-physiological variables.

A secondary objective of the investigation was to examine the effect of the same dosage of pseudoephedrine on cycling performance.

4. Methods

4. 1. Study design

All participants completed two trials, one under placebo (PLB) conditions and the other under the pseudoephedrine (PSE) condition. The PSE and PLB were administered in a randomized, double-blind and counter-balanced manner.

4. 2. Participants

Ten male cyclists (29.7 ± 7 years; mean ± SD, 73.5 ± 4.3 kg, 4.86 ± 0.45 l min^{-1} $\dot{V}O_{2max}$) volunteered to take part in the study. All participants were fully informed of the experimental procedures and gave their written consent. The study was approved by the Central Regional Health and Disability Ethics Committee (CEN/08/04/016) (appendix 5). All participants were not habitual PSE users and reported to have no personal health history that may cause complications during intense endurance exercise. All participants completed a health screening form (appendix 4) designed specifically to highlight any drug or detrimental health interactions with the dosage of PSE investigated.

4. 3. Pre-experiment protocol

Participants initially reported to the laboratory at least one week prior to the first performance trial for an incremental sub-maximal oxygen consumption test, followed by a maximal oxygen uptake test ($\dot{V}O_{2max}$) on an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands). Subsequent experimental trials were also conducted using the same Lode ergometer with the same ergonomic measurements tailored for the individual.

Participants completed an incremental sub-maximal test, performed in four sub-maximal workloads (100, 150, 200, and 250 W) in a step wise fashion for six minutes per workload on an electronically braked cycle ergometer (Lode, Groningen, The Netherlands). A self selected cadence was maintained throughout the test. Participants were then given a period of five minutes active recovery in

which they maintained a self selected cadence (~80-100). This was followed by five minutes inactive recovery; that is rest off the cycle ergometer. A maximal oxygen consumption test was then performed with the participants beginning at 100 W and increasing in an incremental fashion at a rate of 40 W per minute until volitional exhaustion or when the participant was no longer able to maintain a cadence of ≥40 rpm.

Expired gas samples were collected for the final 60 seconds of each workload during the sub-maximal test, while 30 second samples were collected in a continuous manner during the latter part of the maximal test. Gas samples where collected via a two-way re-breathing mouthpiece (Hans-Rudolph, USA) into a Douglas bag. Participants wore a nose clip throughout the test.
The collected gas samples were then analysed for fractions of O_2 and CO_2 gas using dedicated gas analysers (AEI Technologies, Naperville, IL, USA), and volume using a dry gas meter (Alphatech System Ltd, Auckland, NZ). Both dedicated gas analyses were calibrated with gases of known composition (0.157 O_2 and 0.05 CO_2) prior to testing. Standard temperature, pressure, dry (STPD) values for $\dot{V}O_2$, $\dot{V}CO_2$, and respiratory exchange ratio, were calculated adjusted for ambient barometric pressure and temperature.

The relationship between oxygen consumption and power output at the sub-maximal intensities was used to formulate a linear regression equation. This equation, in conjunction with $\dot{V}O_{2max}$ calculated from the maximal test, provided a calculation of workloads expressed as power outputs that would elicit 65 and 80% of measured $\dot{V}O_{2max}$. These calculated workloads were used for the experimental trials.

($\dot{V}O_{2max}$ L·min^{-1} – “x axis” / “Y axis”) / 0.65 or 0.80

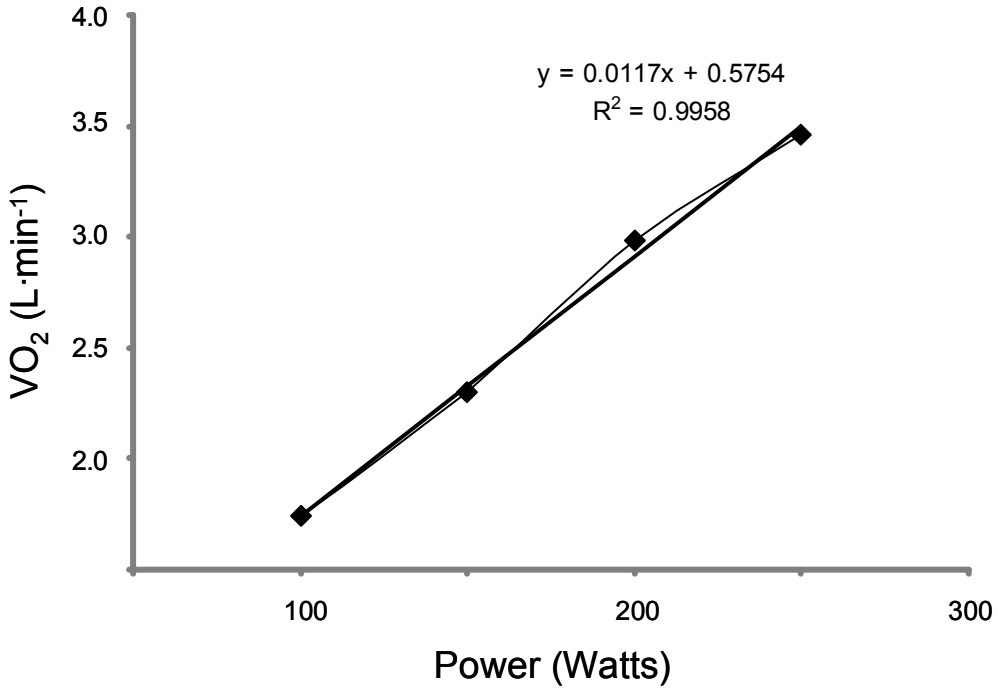

Figure 2: $\dot{V}O_2$ uptake at incremental power outputs

Example from participant showing the linear relationship between the four sub-maximal workloads and corresponding oxygen uptake to form a linear regression equation.

4. 4. Experimental protocol

4. 4. 1. Prior to laboratory entry, 48 hours to 90minutes prior to experimental trials

Exercise was controlled for in the 48 hour period leading up to each experimental trial. For each experimental trial participants were instructed to avoid any exercise in the 48 hours prior to entering the laboratory other than controlled training session at 24 hours. The controlled training session served as a familiarization consisting of 60 minutes cycling on the cycle ergometer at the same workload calculated for the individual participant's constant-load section of the experimental trials (see section 4.3). Participants also recorded their diet during the 24 hour period prior to the first experimental trial, this diet was then repeated for the second

trial to ensure starting glycogen levels remained as close as possible for each experimental trial. CoreTemp temperature measurement pills (CoreTemp, HQInc, Palmetto, FL, USA) were ingested by the participants with 250 ml of water 12 hours prior to the start of each trial to allow for optimal timing of passage through the gastrointestinal tract, as per manufacturer's recommendations.

The two trials were separated by a minimum of 6 days to ensure adequate recovery and drug washout. This protocol has been used by a number of other investigations using similar stimulants and exercise protocols [7, 81].

Four hours prior to arriving at the laboratory for each experimental trial, participants consumed a standardized meal consisting of a "One Square meal" bar (Cookie Time Limited, NZ) and an "Up and Go" liquid meal (Sanitarium Health Food Company, Australia) totalling approximately 3750 kJ (56% carbohydrate, 29% fat, 15% protein). After this, no food was ingested until the trial began. This was to replicate dietary practice of many athletes prior to competition and standardise conditions prior to the trials.

4. 1. 2. Laboratory arrival, 90 minutes to 0 minutes prior to experimental trials

On arrival at the laboratory, participants were fitted with a heart rate monitor (Garmin, Olathe, Kansas, USA) and rested for five minutes. Baseline measurements (at 90 minutes prior to trial) were then taken, including a 5ml venous blood sample, followed immediately by oral ingestion of the PSE or PLB capsule and a muesli bar (Tasti Products Limited, NZ) containing 771 kJ of energy (37% carbohydrate, 51% fat, 12% protein). The participants then rested for 90min. Ten minutes prior to the beginning of exercise, a cannula was inserted into a forearm vein. The cannula was kept clear throughout the trial by regular flushing with saline every 10-20 minutes.

4. 1. 3. Exercise trial and at the end of experimental trial

The exercise consisted of two distinct but consecutive phases: 1) a 120 min cycle at a consistent load calculated to elicit of 65% $\dot{V}O_{2max}$; and 2) a work dependent time trial (TT). During the first phase, the cycle ergometer was set in hyperbolic mode, allowing a consistent workload to be imposed on the participant independent of pedalling rate. At 120 min, the second phase (TT) began uninterrupted with the ergometer automatically switching to linear mode. This allowed workload to be proportional to cadence using the following formula: W = L·(rpm)^2. During the self-paced time-trial participants were required to complete a set amount of work (kJ) calculated as the equivalent of 30 min at the workload calculated to elicit 80% $\dot{V}O_{2max}$. Participants were informed of the endpoint prior to beginning the TT (instructed as ~30 min TT effort or ~20km TT) and instructed to complete the work as quickly as possible, once the participant had begun the TT no external cues were offered as to their progress.

A 7.2% weight/weight glucose polymer drink was provided at a calculated volume of 1g of carbohydrate per kg of body mass per hour during the first 120 min. For a 70kg participant this was consumed at a rate of 324 ml every 20 min [82]. A final drink, the same volume as consumed during the 20 min periods was consumed during the TT.

Trials took place in laboratory conditions with ambient temperature and wind speed held constant (19 ˚C, and 24 km hr^{-1} respectively).

4. 5. Pseudoephedrine / placebo administration

Prior to each of the two trials (-90 minutes) participants ingested either PSE (Sudomyl^{TM}) at a dosage rate of 2.5 mg·kg^{-1} or an equal portion (total mg) of galactose. Both the PSE and PLB were in powder form and placed inside gelatine capsules. This ensured the participant and researcher remained blind as to the trial condition. To exclude the possibility of a training effect and ensure that the trials

were double blind, treatment conditions were randomly assigned by an external party in a balanced (for treatment) manner.

Time delay between dosing and exercise was chosen based on previous findings in which it was suggested that PSE exerts its effect approximately 60 minutes following ingestion [69], and a dosage of 180 mg reaches peak plasma concentration at approximately 120 minutes [83].

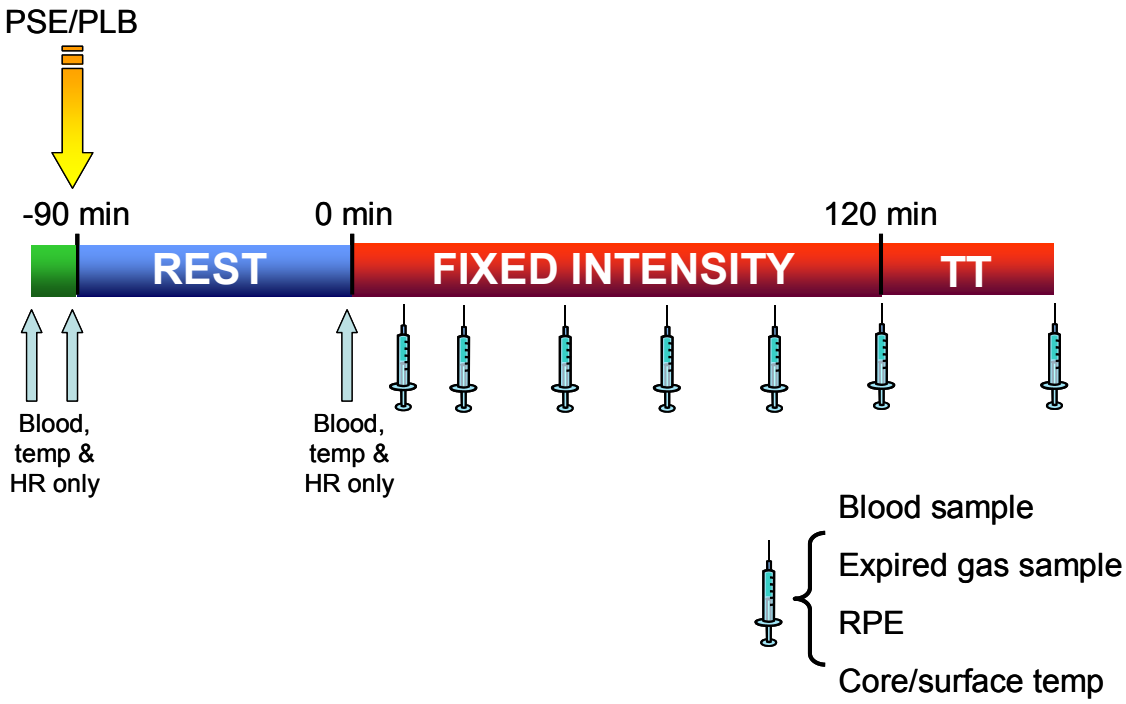

Figure 3. Timeline of experimental protocol.

Furthermore, dosage timing was chosen to replicate the previous investigation [7]. Setting the dosage relative to body mass was used to avoid introducing any bias from differing weights among the current study's participants.

4. 6. Experimental measurements

Unless stated otherwise, all measurements were taken concurrently and at each time point. Prior to treatment administration (-90 minutes) a baseline measurement was taken, including core and surface temperature, blood analysis, and heart rate. The resting measurements were then repeated in the final minute prior to

beginning the exercise portion of the experimental trials, 90 minutes following treatment administration (0 minutes). Exercise measurements were then taken during the experimental trials at the 10, 20, 40, 60, 80, 100 minute and the final minute of the TT. These measurements included core and surface temperature, blood analysis, heart rate, expired gas samples, and perceived exertion. The experimental protocol is illustrated in figure 2.

4. 6. 1. Heart rate

Heart rate was recorded via a heart rate monitor (previously stated) and downloaded with dedicated software (Garmin Training Center®, version 3.3.2, Garmin, US) to computer (Acer, Aspire 3620, US) at the end of each trial. Data of the 1 minute period surrounding the gas and blood measurements was later averaged to give the final heart rate for each measurement point.

4. 6. 2. Blood sampling and analysis

Blood samples were collected prior to ingestion of the PLB or PSE (-90 min), just before the beginning of exercise (0 min) and concurrently with gas analysis. Blood samples were drawn into a 5 ml syringe with 1ml of blood drawn from the collection tube for immediate analysis of lactate and glucose concentration.

The remaining sample was immediately divided into a potassium EDTA (ethylenediamine tetra-acetic acid) vacutainer (4ml) and a vacutainer (3ml) containing heparin. The samples were immediately centrifuged (Ependorf 5804R, Germany) at 2000rpm for 15 minutes. Plasma samples were then frozen at -80˚C for later analysis beyond the current thesis.

4. 6. 3. Biochemical analysis

Concentration of blood lactate was determined using an YSI 1500 lactate auto-analyzer (YSI, Yellow Springs, OH, USA) immediately following extraction. The YSI lactate analyser utilises an electrode containing a film of lactate enzyme immobilised and contained by a membrane. As lactate diffuses through the

membrane hydrogen peroxide is produced. A platinum electrode measures the current created by the produced hydrogen peroxide, which is proportional to the lactate contained within the blood sample (manufacturer's website, www.ysilifesciences.com). The lactate analyser was calibrated prior to every trial using a 5 $mmol \cdot L^{-1}$ standard, following calibration, an accuracy of ± 0.01 $mmol \cdot L^{-1}$ has been reported by the manufacturer.

Blood glucose was also analysed immediately using a HemoCue glucose analyser (HemoCue Glucose 201+, Sweden). Utilising a capillary action, the blood collected in disposable microcuvettes is exposed to dried reagents initiating a glucose dehydrogenase based reaction. The produced coloured formazan allows photometric quantification through a two wave length (660 and 840 nm) method. The HemoCue glucose analyser was calibrated by the manufacturer to an accuracy of ± 0.3 $mmol \cdot L^{-1}$ (manufacturer's web site, www.hemocue.com).

4. 6. 4. Core and surface temperature measurement

Core temperature was measured continuously throughout the trial at 60 second intervals via aforementioned CoreTemp® temperature pills. When swallowed, CoreTemp temperature pills transmit the temperature of an individual's core to a receiver. Core temperature at each time point was recorded during all trials and later compared with the downloaded continuous measurement to correct for human error. All CoreTemp temperature pills were calibrated according to the manufacturer's instructions prior to the trials. The accuracy stated by the manufacturer is ± 0.1˚C (manufacture's website, www.hqinc.net).

Surface temperature was measured using an infrared thermometer (Tyco Healthcare, UK), concurrently with the other measurements at each time point. Three locations on the participants' body were marked prior to the initial measurements. The first location was marked at the most lateral aspect of the upper arm, centred between the acromion process and the top of the ulna, the second, 2 centimetres above the inferior aspect of the sternum, and the third,

centred between the two iliac crests on the lower back. During statistical analysis the average of all three measurement points used to provide overall surface temperature.

Due to the measurement of surface and core temperature, participants wore the same cycling kit for both trials with the cycling shirt open to the inferior aspect of the sternum. The standardization in clothing and skin exposure was for two reasons, firstly, it allowed access for chest surface temperature measurements and secondly to account for the possibility of temperature changes due to a change in the participants clothing micro environment.

4. 6. 5. Subjective rating of exercise exertion

Borg's modified [80] rating of perceived exertion (RPE) scale was used to measure subjective effort. Participants were asked to give an indication as to their perceived effort 1 min prior to each blood and gas sample during exercise. All participants were familiar with the Borg's perceived exertion scale.

4. 6. 6. Expired respiratory gas analysis

Expired respiratory gas samples were collected into Douglas bags for one minute at each time point during exercise. Calibration was performed and gas concentrations were then analysed as previously explained (see section 4.3) for the sub-maximal and maximal pre-experiment tests. The collected data was then used to calculate oxygen consumption ($\dot{V}O_2$), respiratory exchange ratio (RER), and minute ventilation ($\dot{V}_E$).

4. 6. 7. Time trial performance

As a measure of performance the time to complete the aforementioned calculated kilojoules was recorded. Participants were not provided with any form of feedback, only that the TT was calculated to take ~30 minutes and that they should try to complete the TT as fast as possible.

4. 7. Statistical analysis

Data was separated into resting, constant-load exercise and TT. Resting data included -90 min (pre administration) and 0 min blood, heart rate, and core and surface temperature samples. Constant-load exercise data included the 7 measurements taken from 10-120 min and consisted of blood, heart rate, respiratory gas samples, perceived exertion, and core and surface measurements.

TT data included the measurements taken at 120 min and in the final minute of the TT to compare for an interaction effect.

All measures were compared using a two-way repeated measures analysis of variance for treatment and time. If proven significant, T-tests with a bonferroni correction were then performed post-hoc for each time point.

Group data was then split again into those who improved in performance during the TT (group A), those who showed no change (group B) and those who decreased in performance (group C) with the PSE condition. Statistical analysis was then run for each of the groups as performed for the original data set.

All statistical analysis was performed using specialist statistical software (SSPS Inc, Chicago, Il, USA). Statistical significance was accepted at $P \leq 0.05$. All data has been expressed as means ± standard deviation (SD) in the text unless otherwise stated. All data in graphical form has been presented as means ± standard error (SE).

5. Results

All participants successfully completed both trials. One participant became nauseous half way into the time trial (TT) segment of the pseudoephedrine (PSE) trial. The participant chose to complete the trial and vomited on completion. Another participant experienced “light-headedness” throughout the PSE trial, later claiming that it was not sufficient to impair performance.

The participant who became nauseous naturally slowed during the TT, therefore the statistical analysis was performed both with and without this participant’s TT results. The exclusion of the participant’s test results altered the paired t-test for heart rate, thus both results are presented. Interestingly, the inclusion of this participant’s data did not affect the level of significance of any other measurements.

Following both trials, six of the ten participants correctly guessed the order of PSE/placebo (PLB) administration. Four of which, performed better during the TT section under the PSE condition. Two participants where unsure as to which trial was PSE or PLB.

5. 1. Heart rate

Mean heart rate for the duration of the trial is presented in figure 3.

Rest

Resting heart rate showed a significant interaction effect (treatment*time interaction, P = 0.002) with heart rate increasing significantly between measurement points (-90min, 0min) following pseudoephedrine (PSE) ingestion (P = 0.001) but not with PLB ingestion (0.863). No main treatment effect was detected (P = 0.729).

Constant-load exercise

Heart rate increased significantly during the constant-load section of both trials (P <0.001). However, this increase was not significantly different between trials (P =

0.131). PSE administration showed a significant main effect (*P* = 0.001) with average heart rate during the constant-load exercise in both the PLB and PSE trial at 152 ± 11 and 158 ± 9 beats per minute respectively (figure 3).

Time trial

As expected heart rate increased from the constant-load with the increase in wattage output of the time-trial (*P* = 0.016). Again, the increase was not significant between conditions (*P* = 0.793) but a significant main effect was detected between the conditions (*P* = 0.028) with heart rate higher under the PSE condition (170 ± 8 PLB, 174 ± 7 PSE).

Post hoc t-tests between treatments and the final measurement point revealed no significant difference, however, the removal of the nauseous participants data showed a significant effect (*P* = 0.027).

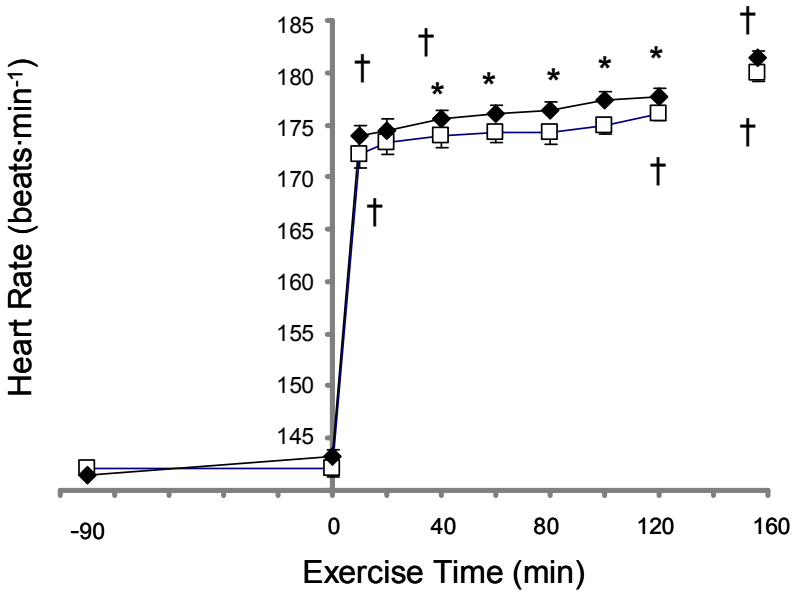

Figure 4: Heart rate during rest and exercise for PLB (□) and PSE (♦)
Rightmost data points indicate TT values at time to complete. * Denotes significant difference between conditions at same time point. † Denotes significant difference from previous time point of same condition.

5. 2. Metabolic factors

Mean plasma glucose and blood lactate concentration for the duration of the trial is presented in figure 11 and 12 respectively.

Rest

Neither plasma glucose or blood lactate concentration levels showed an interaction effect between treatment and time. A time effect was evident for plasma glucose concentration levels as they increased over time (P = 0.030); blood lactate however remained unchanged (P = 0.746). No condition effect was evident for either blood analysis.

Constant-load

There was a significant interaction between treatment and time with plasma glucose concentration (P = 0.029). There was also a highly significant main time and treatment effect (P = <0.001, P = 0.004 respectively). Concentrations of plasma glucose showed a noticeable increase occurring 20 and 40 minutes following the onset of exercise. Post hoc t-tests showed this increase was significantly greater in the PLB group for both the 20 minute and 40 minute time points (P <0.001). Blood lactate concentration levels were similar at rest and, as expected, showed a significant time effect (P<0.001) with concentration levels initially spiking at the commencement of exercise. However, the rate of change was not significantly different between trials (treatment*time interaction, P = 0.773) and no trial effect was detected (P = 0.968).

Time-Trial

Neither plasma glucose or blood lactate concentration levels showed any significant interaction between treatment and time (P = 0.117, P = 0.998 respectively). Unsurprisingly, plasma glucose lowered and blood lactate increased with the change in power output during the TT, hence both showed a significant effect for time (P = 0.022 Glucose, P = 0.004 Lactate). However, neither showed any trial effect (P = 0.556 Glucose, P = 0.706 Lactate).

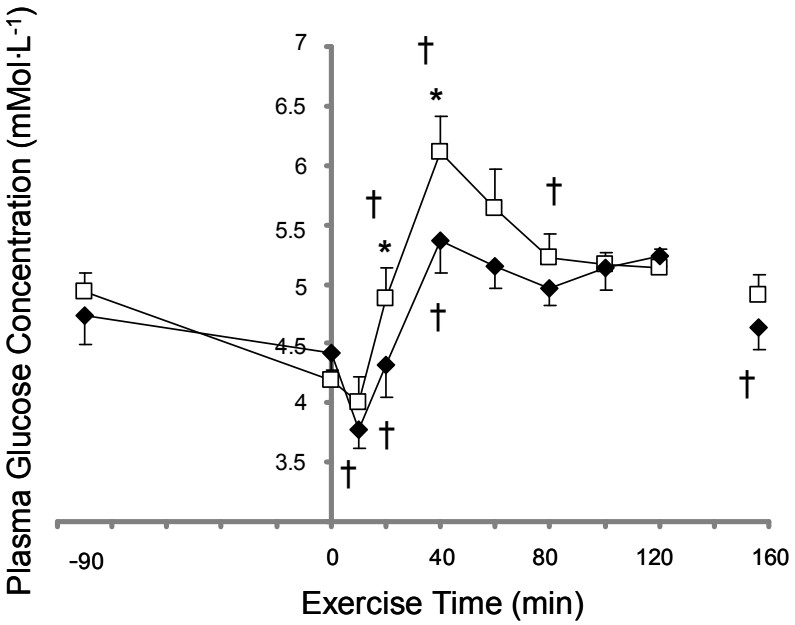

Figure 5: Plasma glucose concentration (mMol·L^{-1}) during rest and exercise for PLB (□) and PSE (♦). Rightmost data points indicate TT values at time to complete. * Denotes significant difference between conditions at same time point. † Denotes significant difference from previous time point of same condition.

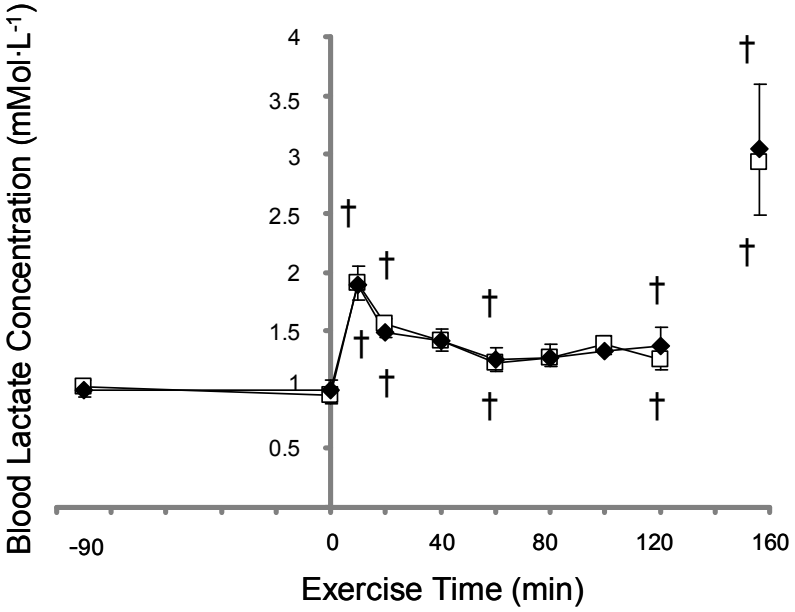

Figure 6: Blood lactate concentration (mMol·L^{-1}) during rest and exercise for PLB (□) and PSE (♦). Rightmost data points indicate TT values at time to complete. † Denotes significant difference from previous time point of same condition.

5. 3. Core and surface temperature

Mean core and surface temperature for the duration of the trial is presented in figure 9 and 10 respectively.

Rest

Neither core nor surface temperature showed a significant interaction between treatment and time (P = 0.770, P = 0.538 respectively). While core temperature did not show any significant time effect (P = 0.189) overall surface temperature did increase significantly (P = 0.032). No significant trial effect was detected for either measurement (P = 0.154 core temperature, P = 0.617 surface temperature).

Constant-load

Both core and surface temperature changed over time during constant-load exercise (P = <0.001 core temperature, P = 0.047 surface temperature). Core temperature exhibited a significant initial increase during the first 40 minutes of exercise (figure 9), then remained relatively stable for the remainder of the constant-load section of the trial. Surface temperature also exhibited a significant effect for time (P = 0.047) with an expected significant (P = <0.001) decrease within the opening 10 minutes of the exercise trial (figure 10) before following a gradual decline. The rate of change for core temperature approached significance (treatment*time interaction, P = 0.089) but not for surface temperature (treatment*time interaction, P = 0.489). No significant condition effect was detected for both core (P = 0.901) or surface temperature (P = 0.142), however post hoc t-tests indicated surface temperature between conditions approached significance at the 20 minute (P = 0.062) and 40 minute (P = 0.070) measurement points.

Time-trial

Core temperature, as expected, showed a significant time effect, increasing with the change from constant-load to the end of the TT (P = 0.001). Alternatively, surface temperature did not show any time effect (P = 0.972). Neither core nor surface temperature showed any significant condition effect (P = 0.528, P = 0.101 respectively).

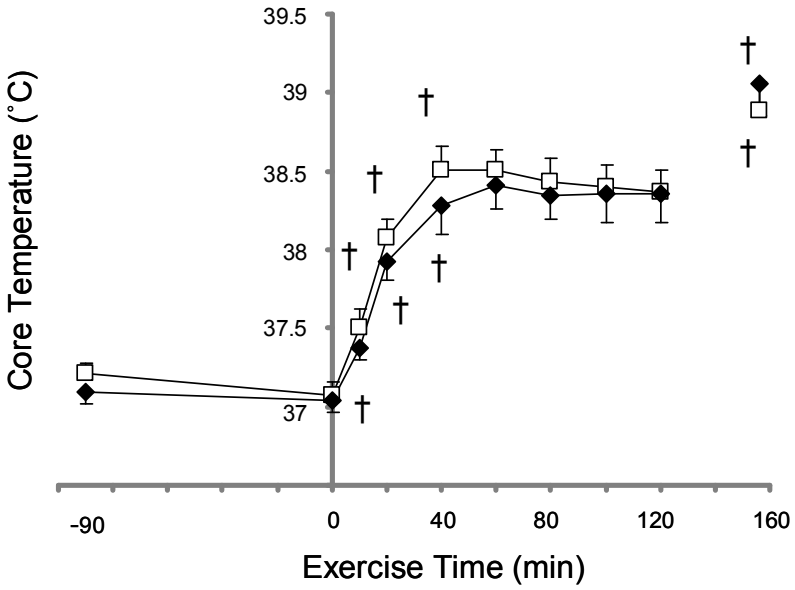

Figure 7: Core temperature during rest and exercise for PLB (□) and PSE (♦)
Rightmost data points indicate TT values at time to complete. † Denotes significant difference from previous time point of same condition.

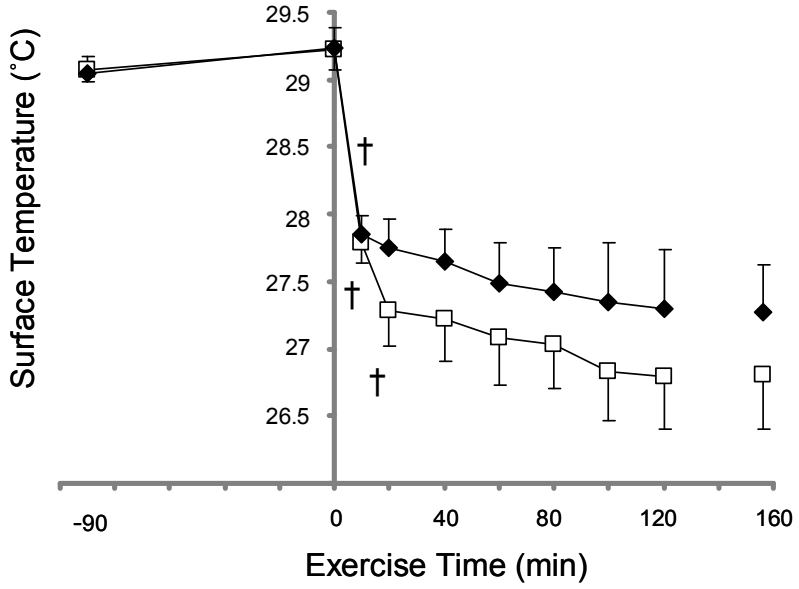

Figure 8: Surface temperature during rest and exercise for PLB (□) and PSE (♦) Rightmost data points indicate TT values at time to complete. † Denotes significant difference from previous time point of same condition.

5. 4. Rating of Perceived Exertion (RPE)

Mean rating of perceived exertion for the exercise portion of the trial is presented in figure 13.

Constant-load

RPE increased over time in both conditions (*P* <0.001), however the rate of increase was not significantly different between conditions (treatment*time interaction, *P* = 0.266). A main effect of the treatment was not apparent (*P* = 0.235).

Time trial

As expected RPE increased with the TT (*P* = <0.001), but no main effect of the treatment on RPE was detected (*P* = 0.864). A post hoc t-test between treatments at the final time-point displayed the condition effect on RPE to near significance (*P* = 0.066).

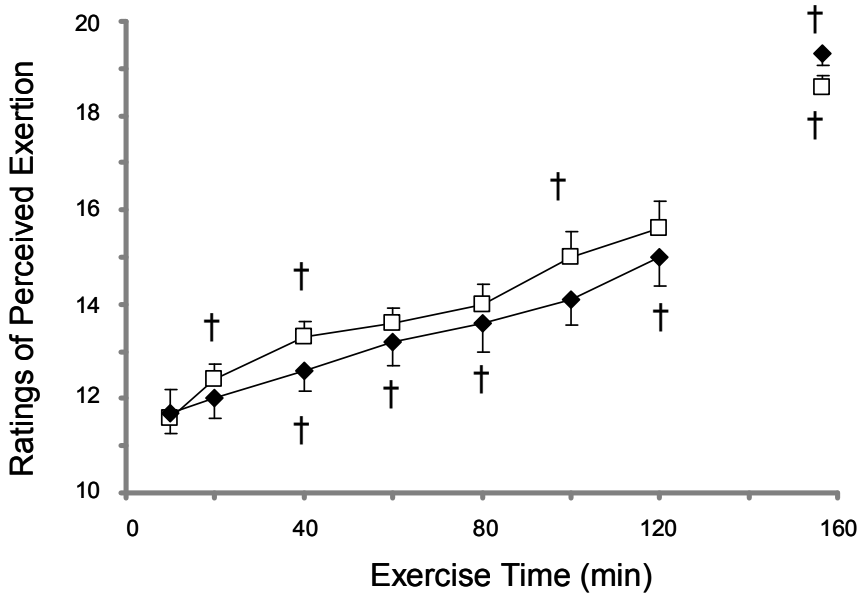

Figure 9: Ratings of perceived exertion during exercise for PLB (□) and PSE (♦) Rightmost data points indicate TT values at time to complete. † Denotes significant difference from previous time point of same condition.

5. 5. Expired respiratory gases

Mean $\dot{V}O_2$, $\dot{V}_E$, respiratory exchange ratio, fat oxidation and carbohydrate oxidation for the exercise portion of the trial is presented in figure 4, 5, 6, 7, and 8 respectively.

$\dot{V}O_2$

Constant-load

$\dot{V}O_2$ did not increase significantly in either trial during the constant-load section (*P* = 0.134). There was no main effect of treatment on $\dot{V}O_2$ during exercise (*P* = 0.134). Mean percentage of $\dot{V}O_{2max}$ was 69.2 and 70.6 for the PLB and treatment trials respectively.

Time trial

$\dot{V}O_2$ increased significantly with the change from constant-load exercise to the TT (*P* = 0.011), however no main effect was detected (*P* = 0.410). Post hoc t-tests revealed no significant condition effect at the final time-point (*P* = 0.174).

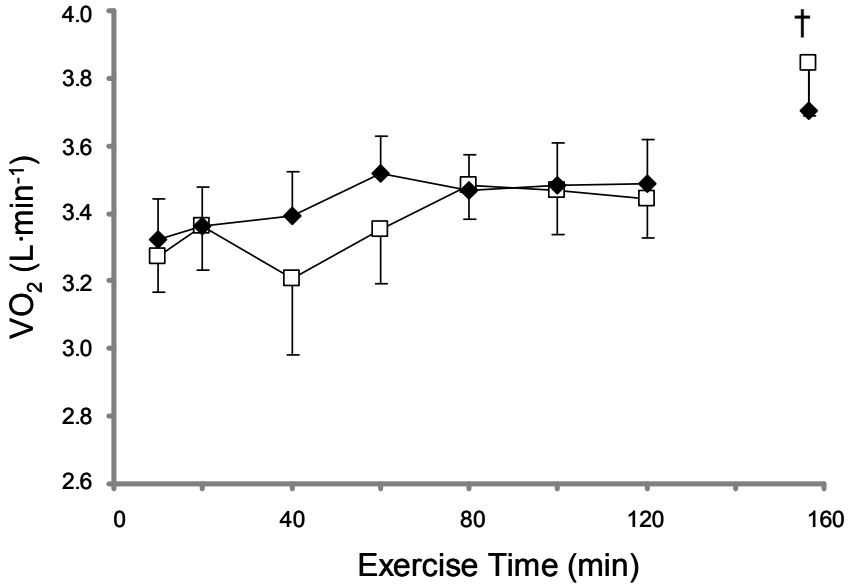

Figure 10: $\dot{V}O_2$ (L·min^{-1}) during exercise for PLB (□) and PSE (♦)

Rightmost data points indicate TT values at time to complete. † Denotes significant difference from previous time point of same condition.

Minute ventilation ($\dot{V}_E$)

Constant-load

Minute ventilation showed a gradual increase over time in both conditions (P = 0.049). However, this change was not due to an interactive effect of treatment conditions (P = 0.384). A weak condition effect was detected (P = 0.096).

Time trial

As expected, minute ventilation increased as work output increased due to the TT (P <0.001). No condition effect was detected (P = 0.368).

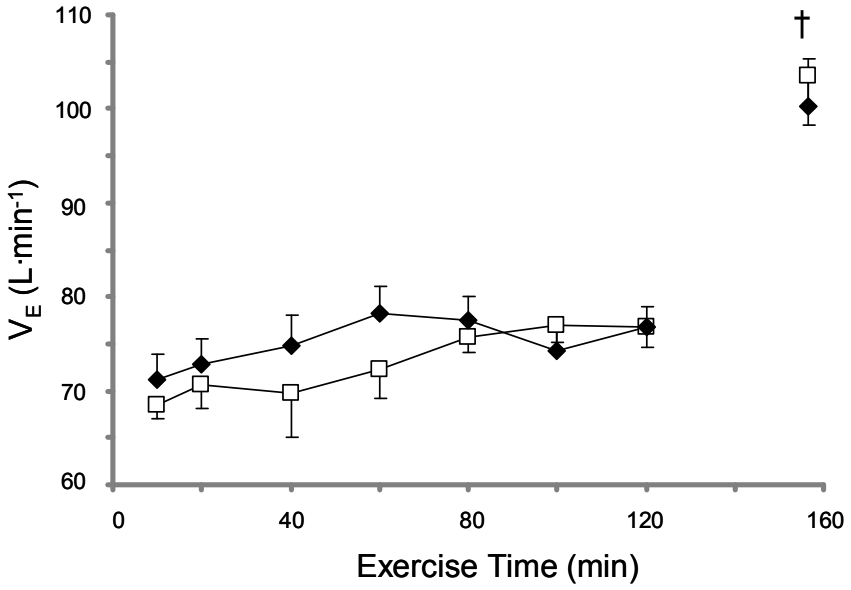

Figure 11: $\dot{V}_E$ (L·min^{-1}) during exercise for PLB (□) and PSE (♦)

Rightmost data points indicate TT values at time to complete. † Denotes significant difference from previous time point of same condition.

Respiratory exchange ratio (RER)

Constant-load

Respiratory exchange ratio declined over time throughout the constant-load exercise (P <0.001). There was no main effect of the conditions on RER (P = 0.676), however, the paired samples t-test showed a weak condition effect at the 100 minute time point (P = 0.086) and a significant condition effect at the 120 minute time point (P = 0.027).

Time trial

Respiratory exchange ratio did not change significantly between the 120 minute time point and the TT time points (P = 0.715). A significant condition effect was detected (P = 0.006). A post hoc t-test also showed the final time point to hold a significant condition effect (P = 0.028).

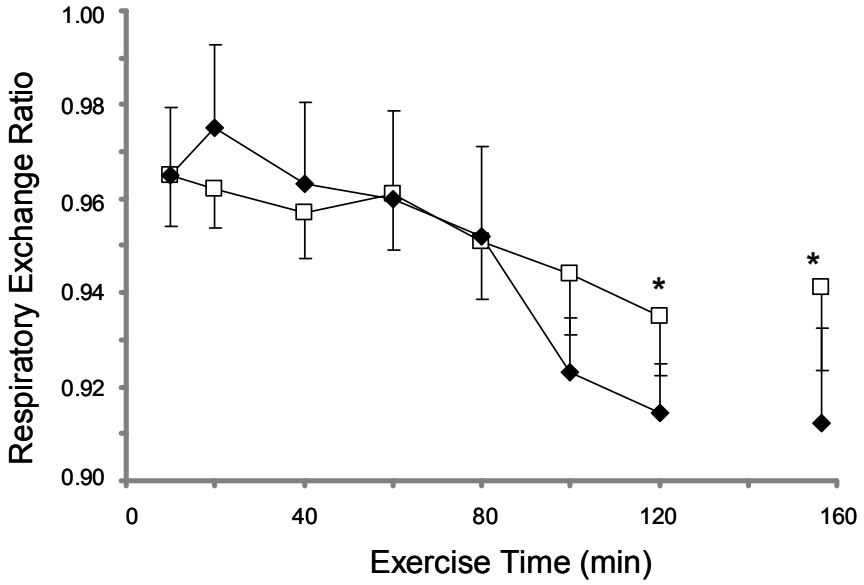

Figure 12: RER during exercise for PLB (□) and PSE (♦)

Rightmost data points indicate TT values at time to complete. * Denotes significant difference between conditions at same time point.

Fat oxidation

Constant-load

Respiratory gas analysis revealed fat oxidation to increase over the duration of the constant-load exercise (P <0.001), but the rate of increase was not significant between conditions (treatment*time interaction, P = 0.277). No trial effect was detected (P = 0.532). A post hoc t-test between treatments at the 120 minute time-point displayed the condition effect on fat oxidation to near significance (P = 0.055).

Time trial

A t-test between treatments for the final time-point showed a condition effect during the TT (P = 0.041).

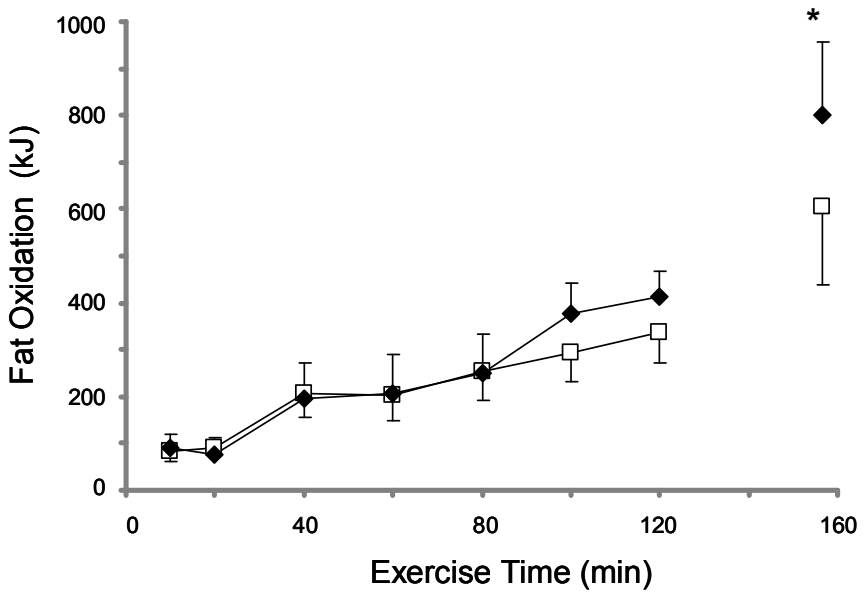

Figure 13: Fat oxidation during exercise for PLB (□) and PSE (♦)
Rightmost data points indicate TT values at time to complete. * Denotes significant difference between conditions at same time point.

Carbohydrate oxidation

Constant-load

Carbohydrate oxidation increased with constant-load exercise (P <0.001), however the rate of increase was not significant between conditions (P = 0.211). There was no significant trial effect detected for carbohydrate oxidation (P = 0.610). A post hoc t-test revealed a significant condition effect at the 100 minute time-point (P = 0.011) and near significant condition effect at the 120 minute time-point (P = 0.068).

Time trial

T-test between treatments at the final time-point showed a condition effect during the TT (P = 0.024).

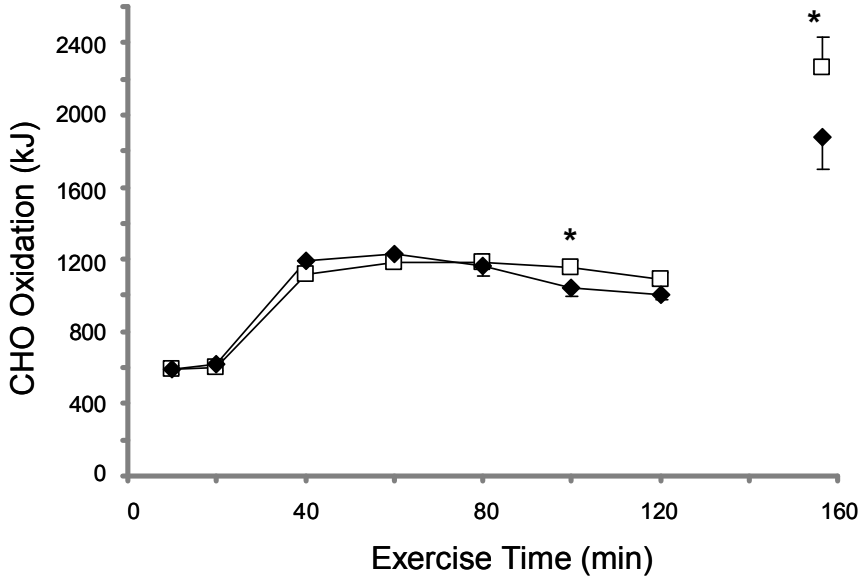

Figure 14: CHO oxidation during exercise for PLB (□) and PSE (♦)
Rightmost data points indicate TT values at time to complete. * Denotes significant difference between conditions at same time point.

5. 6. Time trial performance

Mean power output during the constant-load section, work required to complete the TT section, and total work and time taken to complete the experimental trials is shown in table 1 (mean ± SD). Mean total PSE consumption is also shown.

Table 4 Mean pseudoephdrine consumption, work and power data for all subjects

Workload at 65% $VO_{2\,max}$ (W)	*Work required to complete TT (kJ)*	*Mean total work done (kJ)*	*Mean total test time (min:sec)*
226.0 ± 27.3	544.1 ± 65.8	2170.8 ± 262.3	156:54 ± 4:50

Abbreviations: $VO_{2\,max}$, maximal oxygen uptake; TT, time trial, W, watts; PSE, pseudoephdrine.

Mean time to complete the PLB and PSE TTs were 36.9 ± 5.2 and 36.9 ± 4.0 min (mean ± SD) respectively. No significant difference was detected between conditions (P = 0.967).

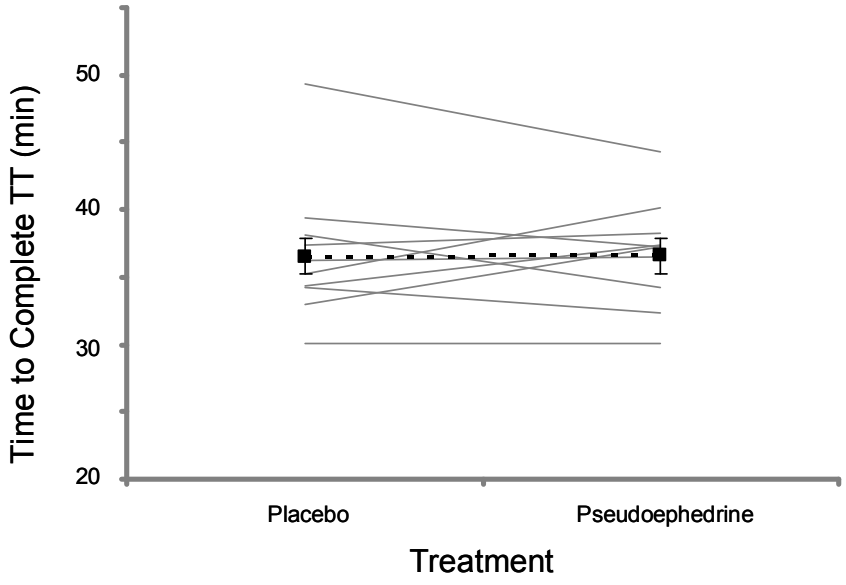

Figure 15: Time to complete the TT section for PLB and PSE

Solid gray lines indicate individual change in TT completion time. Broken black line indicates mean change in TT completion time.

6. Discussion

The current investigation is the first to examine the effect of pseudoephedrine (PSE) ingestion on physiological variables i.e. cardio-respiratory, metabolic, psycho-physical, and thermoregulatory, during prolonged constant-load exercise at dosages previously shown to elicit performance changes in some individuals [5-7].

The most important findings were that heart rate was higher throughout the PSE trial while there was an initial decrease in plasma glucose levels during constant-load exercise, furthermore respiratory exchange ratio (RER) decreased in the final stage of the constant-load exercise and time trial (TT) revealing an increase in fat oxidation. It was apparent that the PSE condition had no significant effect on oxygen consumption or carbon dioxide production, pulmonary ventilation, core or surface temperature, blood lactate concentration, perceived exertion, or TT performance.

Our investigation was developed from questions that arose from a previous study [7] performed in our laboratory in which a 2.5 $mg \cdot kg^{-1}$ dose of PSE was shown to have no effect on endurance cycling performance, as measured by a work-dependent TT. There was, however, large individual variation in performance change ($^{-}9\%$ - $^{+}15\%$). Furthermore, the previous investigators suggested the possibility of an increase in core temperature due to the participants commenting that they felt “hotter” during the PSE trial [7]. A negative linear correlation between the total work to complete and percentage change in performance (see figure 1) with PSE ingestion was reported. It was hypothesised that those participants able to work at a higher absolute metabolic rate for a prolonged period of time may be at increased risk of reaching a limiting core temperature with PSE ingestion. Due to the performance focus of this previous study, limited physiological data was collected. Also, because exercise was self-paced, between-participant comparison was difficult as each person had different pacing strategies and time to completion. The current study was therefore designed to primarily examine the effects of PSE in a controlled, constant-load exercise trial of similar duration. Secondly, the

investigation was designed to replicate the previous performance based trial by utilizing a TT segment immediately following the 120 minute constant-load exercise period. This format has been successfully used to gain physiological and performance data by previous investigators [81, 82].

6. 1. Observations and side-effects

Similar to the observations of Betteridge [7] the current investigation found no evidence of the cautioned side effects (e.g. restlessness, tachycardia, decreased ability to concentrate) during the 90 minute rest period following PSE ingestion. Furthermore, in the present study the window of observation was extended to 48 hours following drug administration, during which no participants experienced any side effects commonly associated with PSE ingestion. This is in contrast to the findings of Chester et al [66] who observed a multitude of minor side effects (headache, dry mouth, sleeplessness, anxiety and nausea) in participants who had ingested six dosages of 60mg PSE spread over 36 hours. It is possible the multiple dosing protocol used may have compounded the effects of PSE within those individuals [66]. The co-ingestion of food and PSE, followed by the exhaustive exercise in the previous [7] and current studies may have minimised any side-effects. While one participant became nauseous during the TT and another experienced “light-headedness” under the PSE condition in the current study, it appears that a dosage of PSE three times the maximally-prescribed therapeutic level can be well tolerated and therefore may not present a health issue as previously anticipated [4]. However, as with most studies employing a relatively small sample size, larger and more heterogeneous study populations would be needed to confirm these observations.

6. 2. Justification for experimental approach

Previous investigations have provided limited physiological data due to the focus on performance parameters; employing either self paced TT protocols [5-7, 10] or incremental exercise tests [8, 58].

To our knowledge, only two previous studies have specifically addressed the physiological effects of PSE using controlled, fixed intensity exercise. However, these investigations were based on therapeutic dosage levels [58, 68] and only a few variables were tested over a short exercise duration [58].

While the use of constant-load exercise may not be the most ecologically valid, it allows for the collection of reliable physiological data. The addition of a work-dependent TT segment (of ~30 min) after the steady state period provided the opportunity to collect performance measurements and further physiological data. This type of protocol has been successfully employed elsewhere in the investigation of the effects of nutrition and pharmacological supplements on both performance and physiological parameters [81, 82].

6. 3. Cardiovascular effects

While no main condition effect was detected for heart rate at rest, possibly due to a higher pre-administration heart rate in the placebo (PLB) trial, resting heart rate did increase (~5 bpm) within the PSE trial. The observed increase is comparative to those reported in the previously mentioned meta-analysis of 24 trials [4].

During the 120 minute constant-load section of the exercise trial cardiac drift was experienced by all participants regardless of condition. Heart rate was significantly higher for the PSE condition over the 120 minutes of constant-load exercise (average of 6 bpm). These observations are consistent with our previous investigation using the same PSE dosage level and similar exercise duration [7]. Similarly, a recent study [5] noted a trend for an increase of 5-7 bpm at the same dosage but this failed to reach significance. Gill et al [6] reported an increase in heart rate under PSE conditions following a maximal cycling effort of 30 seconds duration. In contrast, with the exception of one study [69], investigations using lower dosages (< 2 $mg \cdot kg^{-1}$) have failed to show any effect on heart rate during exercise [8, 9, 58, 68].

Taken together, the evidence suggests that a dose of at least ~2.5 $mg \cdot kg^{-1}$ is required to exert an influence over and above the sympathetic drive associated with exercise. The mechanism may be explained by previous research showing PSE, at high dosages, to stimulate the sympathetic nervous system [5-9, 68, 69]. As a sympathomimetic amine, PSE also acts directly and indirectly on the heart, having an inotropic and chronotropic effect [69], although, as illustrated at lower drug dosages, the sympathetic drive associated with exercise can overshadow the effects of PSE on heart rate [8, 68].

Whilst heart rate displayed a tendency to be higher (~4 bpm) under the PSE condition during the TT in the current study, there was a lack of statistically clear effect. It is possible that the observed lack of effect on heart rate during the TT may be due to the increase in exercise intensity and therefore sympathetic drive. Another more likely explanation lies in the previously mentioned participant who became nauseous half way into the TT. The removal of this participants data reveals heart rate to be significantly higher than PLB during the TT (P = 0.027). It is likely that due to nausea, this participant slowed during the TT and as a result recorded a lower heart rate, affecting the overall results.

6. 4. Substrate metabolism

While RER did not show any condition effect during the majority of the constant-load section of the experimental trial, PSE administration was associated with a lower RER during the latter stages (100 and 120 minute) of the constant-load section and TT when compared to PLB. Estimates of whole body substrate use via indirect calorimetry revealed fat oxidation to be higher at the TT measurement point with PSE ingestion (605 kJ PLB, 800 kJ PSE). Carbohydrate oxidation was lower during the TT measurement (2266 kJ PLB, 1878 kJ PSE). Normally, during strenuous self-paced exercise, reduced carbohydrate oxidation is associated with reduced power output; however during the present study this was not evident.

PSE did not appear to induce any effect on blood glucose or lactate concentration during the 90 minutes of rest, these results are mirrored by the previous study [7]. In contrast, the PSE condition appeared to blunt the increase in glucose concentration during the first 40-60 minutes of constant-load exercise, after which, blood glucose levels began to stabilize.

We believe that this is the first investigation to demonstrate that PSE ingestion alters glycaemic control during exercise. It is possible that previous investigations have not observed such differences due to the lower dosages studied [8, 68], timing of measurements (post exercise) [5] or having not controlled for exercise intensity [5, 7, 8].

This finding is a little puzzling as adrenaline is known to stimulate glucose release from the liver [84], and therefore one would expect an increase in blood glucose concentration with PSE ingestion. Furthermore, no difference was detected between conditions in fuel selection via indirect calorimetry in the first half of the constant-load exercise section of the experimental trials. Suggesting that although blood glucose concentration was initially lower during the constant-load section of the PSE trial it was unlikely to be due to increased carbohydrate uptake and oxidation by the working muscles. A carbohydrate-containing beverage was ingested during both trials to replicate normal athletic practice (see section 4.4). It may be possible therefore that PSE altered the absorption of the glucose polymer from the gastrointestinal tract, and this may indeed have explained the nausea felt by one participant. However, none of the participants indicated that they experienced diarrhoea or any other form of gastrointestinal distress, indicating that the entire glucose polymer was absorbed.

The lack of effect on blood lactate concentration levels during the constant-load exercise or the TT further supports previous investigations showing blood lactate to be unaffected by PSE ingestion regardless of dosage, exercise mode, or duration [6-10, 59, 68].

6. 5. Core and surface temperature

The hypothesis that PSE ingestion increased core temperature during exercise [7] cannot be supported by the findings of our study. No difference in core or surface temperature was detected between conditions at rest, during constant-load exercise or the TT. Furthermore, unlike the previous investigation [7], no participants commented that they felt “hotter” under either condition. This finding is also consistent with the investigation performed by Clemons and Crosby [69] who used therapeutic doses prior to incremental exercise.

Betteridge [7] suggested that the increase in heart rate found during exercise with PSE ingestion may be related to an increase in core temperature, however in that study core temperature was not measured. Although the current study also observed an increase in heart rate there was no change in measured core temperature. Therefore the hypothesis that the observed increase in heart rate could, in part, be due to an increase in core temperature [7] appears false.

6. 6. Perceived exertion (RPE)

The results of the current investigation provide no support to the theory that PSE ingestion alters perceived exertion during exercise. This finding concurs with previous investigations that have also found PSE at therapeutic [68, 69] and above [58] levels to have no effect on ratings of perceived exertion (RPE) during short term endurance exercise.

The present investigation is not only the first to measure RPE during more prolonged exercise following PSE ingestion, but also the first to address dosages of PSE that have been shown to alter exercise performance [5, 7]. Both Betteridge [7] and Hodges et al [5] suggested a reduction in perceived exertion, due to an increase in central nervous system stimulation, to be one possible explanation for the changes in performance observed in some individuals during their experiments. However, given the current findings this hypothesis cannot be supported. While RPE did not show significant differences between conditions during the constant-

load section of the experiment, the final TT measurement did approach statistical significance, with the PSE condition associated with a higher level of exertion.

6. 7. Pulmonary ventilation and gas exchange

Our study is also the first to investigate pulmonary ventilation, gas exchange, and indirect estimates of whole body substrate use during exercise at high dosages of PSE. The results indicate high dosages of PSE have no effect on $\dot{V}O_2$ or $\dot{V}_E$ during endurance exercise. Previous investigations using lower dosages also found no effect [9, 68, 69].

A recent review of the drug's action on the β-adrenergic system [25] suggested that PSE may exert an ergogenic effect on respiratory and cardiovascular function, stimulating the cardiovascular system to provide sufficient O_2 to working muscles. Therefore, one might anticipate a change in oxygen consumption or $\dot{V}_E$ during exercise, however, the lack of effect on both parameters observed in the current study do not support such a hypothesis.

6. 8. Time trial performance

PSE ingestion showed no main effect on performance measured as time to complete the TT section of the trial. The findings of this investigation support the lack of main effect observed in the previous performance based study performed in our laboratory [7]. Gillies et al [10] also observed no effect on cycling performance over simulated 40 km TT in the laboratory with a dosage of 120 mg, as have other studies with lower dosages [8, 9, 58, 68, 69] or shorter duration exercise [58, 59].

Our results are at odds with a previous investigation where equally high dosages of PSE were associated with improved 1500 metre running performance [5]. However, the differences in exercise protocol compared to the current study (mode, duration and intensity) make direct comparisons difficult.

The lack of an overall ergogenic effect found in the current investigation may be due, in part, to the variation in individual response to PSE. Performance increased with PSE ingestion by >10% in two of the participants while two other participants under-performed by a similar proportion, one becoming nauseous as discussed previously (figure 16). This variation in individual response is consistent with the results from the previous investigation of Betteridge [7], performed in the same laboratory, which showed the same dosage level over similar duration endurance cycling to produce variations in performance of similar proportions ($^{-}10$ – $^{+}15\%$). As with the previous study, day to day variation in performance is unlikely to explain the observed variability, when a low coefficient of variation within cyclists (1.7%) has been described using an exercise protocol of similar duration [85]. The careful control of exercise 48 hours prior to the experimental trials and the repetition of each participant's diet in the final 24 hours prior to each experimental trial provides further support for the notion that the variations in individual response are due to differing responses of individuals to PSE.

The individual response to the drug may be due to a differing level of sensitivity. A dose rate lower than administered in this and the previous study may have been beneficial for those with greater sensitivity to the drug.

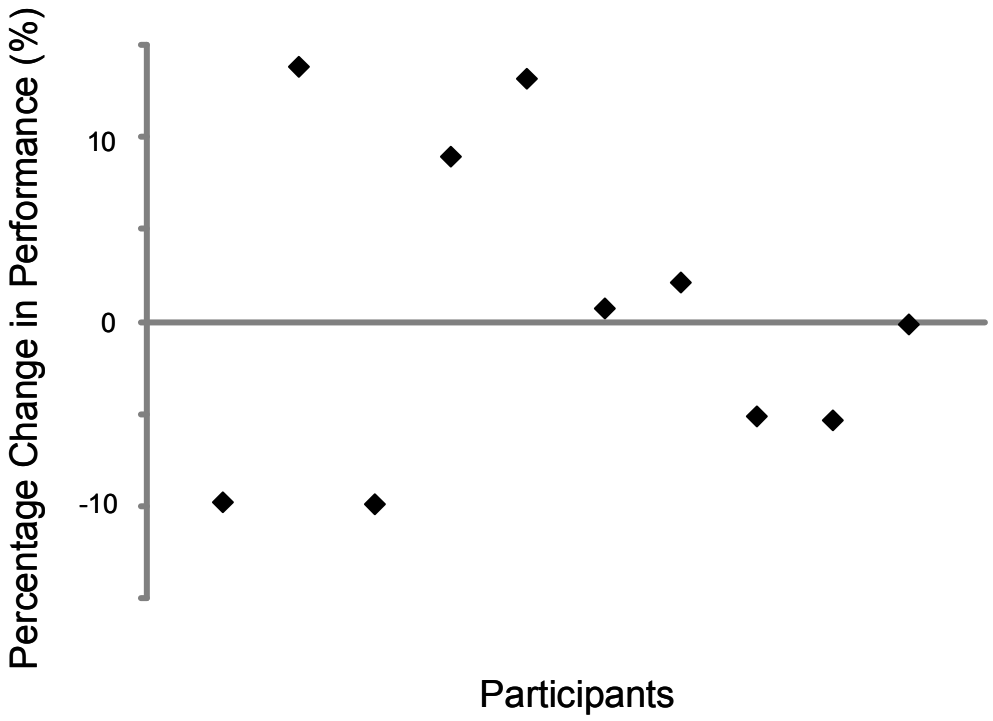

Figure 16: Percentage change in performance with pseudoephedrine compared to placebo.

Assuming a differing level of sensitivity towards the drug, one may expect to observe differing physiological responses to steady state exercise in those who experienced an ergogenic or ergolytic effect. However, division of the data into those who improved in TT performance (group A), those who experienced no change (group B), and those who decreased in performance (group C), showed no difference in the physiological responses (table 5).

Group	HR		Glucose		Lactate		Core Temp		Surface Temp	
	PLA	PSE	PLA	PSE	PLA	PSE	PLA	PSE	PLA	PSE
A	157 ± 10	161 ± 8	5.4 ± 0.8	5.0 ± 0.8	1.5 ± 0.2	1.6 ± 0.2	38.17 ± 0.67	38.16 ± 0.69	27.7 ± 2.8	28.6 ± 3.2
B	150 ± 11	163 ± 4	4.7 ± 0.3	4.6 ± 0.1	1.6 ± 0.5	1.7 ± 1.0	38.49 ± 0.19	38.42 ± 0.51	27.9 ± 1.4	27.9 ± 1.1
C	156 ± 7	163 ± 4	5.3 ± 0.3	4.9 ± 0.4	1.7 ± 0.1	1.5 ± 1.3	38.40 ± 0.12	38.24 ± 0.22	27.6 ± 2.2	29.0 ± 1.0

Group	RPE		$\dot{V}O_2$		$\dot{V}_E$		RER		Fat Oxidation		CHO Oxidation	
	PLA	PSE	PLA	PSE	PLA	PSE	PLA	PSE	PLA	PSE	PLA	PSE
A	15.0 ± 1.4	14.3 ± 1.9	3.62 ± 0.41	3.74 ± 0.26	79.2 ± 8.5	80.8 ± 8.8	0.95 ± 0.04	0.94 ± 0.03	278 ± 233	323 ± 158	1226 ± 210	1142 ± 167
B	13.0 ± 0.3	13.0 ± 1.4	3.21 ± 0.39	3.21 ± 0.36	76.4 ± 4.6	81.6 ± 3.4	0.96 ± 0.05	0.98 ± 0.06	210 ± 247	133 ± 260	1110 ± 84	1155 ± 159
C	14.5 ± 0.4	14.3 ± 1.1	3.39 ± 0.36	3.38 ± 0.40	73.9 ± 6.3	70.6 ± 5.4	0.94 ± 0.03	0.91 ± 0.04	283 ± 199	417 ± 227	1082 ± 75	919 ± 122

Table 5: Mean physiological data during exercise of the three performance response groups. Group A (4 participants - improved), B (3 participants – no change) and C (3 participants - decreased) all exhibiting similar responses across testing parameters.

6. 9. Practical implications and health issues

While PSE did not appear to have a main effect on core temperature, one participant did attain a core temperature in excess of 40˚C during the PSE trial. This occurred even though ambient temperature was controlled to thermoneutral conditions and a fan was provided at all times. While this was only one participant, it is worth noting that in combination with increased heart rate and typical race environments (comprising of hot, humid conditions and long duration, exhaustive exercise) some individuals may be at risk of suffering heat illness if they ingest PSE at the dosages examined.

With no restriction of PSE imposed by a governing body and the common perception that the drug improves performance, it is likely that some athletes would choose to take PSE, creating unknown and potentially unsafe situations. While athletes are known to take great risks (health and otherwise) for sporting performance it is a somewhat ironic and needless risk for what appears to only be a misconception of improved performance. Ideally, research such as the current study will be communicated to athletes via the correct channels in an effort to educate and encourage safe competition.

Those choosing to utilize PSE during endurance exercise should be aware of the influence the drug has on heart rate. Due to the strong possibility of a dose-dependent effect on the heart, dosages greater than those currently investigated may cause greater tachycardia in a similar fashion to ephedrine [86], which in situations of abuse have been observed to cause a myocardial infarction [87]. Putting aside possible health issues, athletes would need to be aware that for the same power output heart rate would be higher, possibly affecting pace judgement if a heart rate monitor is used to dictate intensity.

Furthermore the use of PSE in high concentrations can lead to a high concentration of cathine (pseudonorephedrine) in the urine. As a metabolite of PSE, cathine acts as an indirect sympathomimetic and is prohibited when its urine

concentration is greater than 5mg ml^{-1} [25]. Therefore, athletes still risk inadvertently "failing" a drug test when consuming PSE.

6. 10. Considerations / limitations

The study design was a double-blind, controlled design similar to previous successful studies [81, 82], and our participants formed a homogenous group of ten participants. While individual variation in response to the administered drug is a possible investigation limitation, the controls for participant diet, exercise, and circadian rhythms were implemented in the current study. Therefore, the results of the current study are presented with the utmost confidence that any difference, or lack thereof, between conditions is due to drug administration.

Participants did mention, after participation, that not having feedback as to the endpoint of the TT was difficult. It is possible that by not providing clear feedback as to TT progress, test-retest reliability may have suffered. However, due to similar RPE, $\dot{V}O_2$, and lactate concentration an effect on the results appears unlikely.

While all studies of this nature have the possibility of a type II error, the statistical results appear to be very decisive; with the exception of the $\dot{V}_E$ data during constant-load exercise. $\dot{V}_E$ results may have been slightly different with the addition of more participants (P = 0.096) during the steady-state portion of the trial.

6. 11. Future research

Interestingly, like the previous study [7] a large individual variation in performance change was observed. It may be that individual sensitivity to the drug influences performance outcomes; therefore future research may consider investigating the effect of various dosages on individuals.

While core temperature was not altered by PSE ingestion, in the field athletes compete in ambient temperatures well in excess of those currently investigated.

Further research considering the effects of PSE on core temperature during endurance exercise at higher ambient temperatures would be valuable.

The current study considered the use of PSE exclusively, however athletes have been reported to employ combinations of stimulants to gain a performance edge [88]. Known as “stacking”, the combination of ephedrine and caffeine was a practice of the US military during the Second World War [1]. The combination of ephedrine and caffeine has previously been shown to improve performance beyond that reported for caffeine or ephedrine alone [53, 55, 56]. With ephedrine restricted during competition by WADA it would be reasonable to assume athletes may turn to a “legal” alternative, such as PSE, to recreate the effect. With both PSE and caffeine off the WADA restricted substance list, further research investigating the physiological and possible ergogenic effects of their combination appears to be an area greatly in need of research.

7. Conclusions

This is the first study to consider the physiological effects of PSE ingestion prior to exercise at dosages well in excess of therapeutic recommendations. Ingestion of 2.5 $mg \cdot kg^{-1}$ PSE 90 minutes prior to exercise clearly increases heart rate during endurance cycling and may initially suppress carbohydrate release into the bloodstream. Blood lactate, perceived effort and core and surface temperature during exercise were not affected by PSE ingestion. Two studies have now provided no statistical evidence of performance enhancement over prolonged endurance cycling (>2.5 hours) with PSE ingestion (2.5 $mg \cdot kg^{-1}$), however individual sensitivity remains.

8. References

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9. Appendix 1: Characteristic data

Participant	Age	Weight (kg)	$\dot{V}O_{2max}$ L/min	Workload @ 65% $\dot{V}O_{2max}$ (W)	Work required to complete TT (kJ)	Total work to complete (kJ)	Pseudoephedrine dosage (mg)
1	23	77	4.85	211	507.2	2023.8	195
2	28	71.4	5.24	265	638.1	2546.1	172
3	27	70.6	5.00	242	582.6	2324.6	173.5
4	35	68.8	4.61	224	539.2	2151.3	172
5	40	73.8	4.19	187	451.3	1800.6	172
6	22	77.8	4.95	224	538.4	2148.3	194.5
7	41	72	4.78	226	545.2	2175.2	180
8	32	82.2	5.65	248	596.1	2378.6	205
9	24	70	4.88	252	607.3	2423.1	175
10	25	71	4.30	181	435.2	1736.6	177.5
Mean	29.7	73.5	4.80	226	544.1	2170.8	181.7
SE	2.01	1.23	0.12	7.89	18.98	75.73	3.47

10. Appendix 2: Raw data, means and standard error (SE)

A2. 1. Heart rate

Placebo

Participant	-90	0	10	20	40	60	80	100	120	TT_{End}	Mean during constant-load ($Mean_{CL}$)	$Mean_{Total}$
1	65	62	146	146	151	150	151	151	158	163	150	134
2	55	53	160	163	162	162	161	163	165	172	162	142
3	57	56	157	163	163	167	166	169	168	150	165	142
4	55	45	139	149	152	151	153	154	158	172	151	133
5	61	58	139	146	149	150	148	149	153	173	148	133
6	62	65	160	158	158	160	159	160	167	171	160	142
7	47	57	132	141	143	147	146	151	153	176	145	129
8	45	48	133	133	139	141	145	147	153	170	142	125
9	70	73	170	170	168	167	168	163	165	174	167	149
10	45	48	129	132	132	135	129	142	144	179	135	122
Mean	56.2	56.5	146.5	150.1	151.7	153	152.6	154.9	158.4	170	152	135.0
SE	2.48	2.48	4.13	3.76	3.29	3.12	3.35	2.45	2.25	2.36	3.12	2.44

Pseudoephedrine

Participant	-90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	58	63	148	149	149	153	153	157	157	170	152	136
2	59	61	166	167	167	167	167	164	168	159	167	145
3	52	54	154	160	164	170	168	171	175	170	166	144
4	53	57	151	156	159	164	166	168	171	184	162	143
5	61	64	145	154	155	153	159	158	160	177	155	139
6	56	61	162	164	162	165	165	168	168	171	165	144
7	41	55	140	142	149	150	150	154	157	179	149	132
8	47	50	148	140	151	152	151	158	159	178	151	133
9	62	72	167	167	169	166	167	174	167	178	168	149
10	53	60	140	136	142	141	148	151	151	176	144	130
Mean	54.2	59.7	152.1	153.5	156.7	158.1	159.4	162.3	163.3	174.2	158	139.4
SE	1.88	1.77	2.88	3.28	2.57	2.74	2.35	2.24	2.18	2.01	2.49	1.86

A2. 2. Glucose

Placebo

Participant	- 90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	4.7	4.8	3.7	3.8	5.9	4.7	5.2	5.5	5.2	5.3	4.9	4.9
2	5.5	3.6	4.0	5.0	6.3	5.1	4.7	4.9	5.1	4.7	5.0	4.9
3	5.8	4.1	4.1	4.8	5.2	5.1	4.9	5.2	4.6	4.3	4.8	4.8
4	4.9	3.8	3.8	5.6	5.9	5.5	5.3	5.7	5.7	6.4	5.4	5.3
5	4.6	4.5	4.4	5.3	7.3	5.8	5.0	5.2	5.4	4.6	5.5	5.2
6	4.7	4.4	4.1	4.4	5.7	5.8	5.2	5.2	5.4	4.5	5.1	4.9
7	4.9	3.9	3.6	4.1	5.2	5.5	5.1	5.0	4.4	4.8	4.7	4.7
8	4.0	4.0	3.7	4.6	6.9	5.9	5.3	5.0	4.9	4.7	5.2	4.9
9	5.4	5.8	5.8	6.9	8.0	8.5	7.1	5.4	6.1	4.9	6.8	6.4
10	4.9	3.0	2.9	4.3	4.7	4.5	4.4	4.6	4.6	4.9	4.3	4.3
Mean	4.9	4.2	4.0	4.9	6.1	5.6	5.2	5.2	5.1	4.9	5.2	5.0
SE	0.15	0.22	0.22	0.26	0.30	0.32	0.21	0.09	0.15	0.17	0.20	0.16

Pseudoephedrine

Participant	- 90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	3.1	3.7	3.0	4.1	4.7	4.7	4.6	5.1	4.9	4.9	4.4	4.3
2	5.3	5.5	4.1	3.9	4.7	4.5	4.8	4.7	3.8	3.8	4.5	4.5
3	5.4	4.6	3.9	3.5	4.6	5.0	5.0	4.6	4.7	4.7	4.5	4.5
4	6.0	4.2	4.0	4.4	5.6	5.4	5.1	5.6	4.8	4.8	5.1	5.1
5	4.2	4.6	4.0	5.3	5.8	5.6	5.4	5.2	4.6	4.6	5.2	5.2
6	5.4	4.9	3.5	2.9	4.6	5.4	5.1	5.0	4.0	4.0	4.6	4.6
7	3.7	3.9	3.0	3.8	5.8	4.3	5.1	4.3	5.1	5.1	4.5	4.5
8	4.7	4.2	3.5	4.2	5.7	5.0	5.2	5.2	3.9	3.9	4.9	4.9
9	4.7	4.5	4.7	6.2	7.5	6.6	5.7	6.6	5.8	5.8	6.2	6.2
10	4.9	4.1	4.0	4.9	4.6	5.0	3.7	5.0	4.7	4.7	4.6	4.6
Mean	4.7	4.4	3.8	4.3	5.4	5.2	5.0	5.1	5.2	4.6	4.8	4.8
SE	0.25	0.15	0.15	0.27	0.27	0.19	0.16	0.18	0.09	0.18	0.16	0.13

A2. 3. Lactate

Placebo

Participant	- 90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	0.96	0.65	1.36	1.39	1.47	1.15	1.26	1.37	0.97	1.43	1.28	1.20
2	0.66	0.88	2.56	1.92	1.33	1.66	1.14	1.27	1.11	4.04	1.57	1.66
3	0.81	0.6	2.43	2.43	2	1.54	1.7	1.6	1.41	0.66	1.87	1.52
4	0.79	1.03	1.58	1.15	1.01	0.86	1.51	1.73	1.51	3.75	1.34	1.49
5	0.92	1.11	1.8	1.45	1.4	1.25	1.19	1.09	1.15	4.29	1.33	1.57
6	1.39	0.94	1.5	1.31	1.48	1.12	1.08	1.09	1.5	1.6	1.30	1.30
7	1.48	1.52	2.26	1.61	1.46	1.51	1.36	1.71	1.82	5.62	1.68	2.04
8	0.90	1.04	1.64	1.49	1.5	1.17	1.23	1.01	1.05	2.49	1.30	1.35
9	1.05	0.98	2.64	1.79	1.68	1.29	1.46	1.14	1.14	2.1	1.59	1.53
10	1.24	0.85	1.28	1.06	0.83	0.79	0.81	1.9	0.93	3.31	1.09	1.30
Mean	1.02	0.96	1.91	1.56	1.42	1.23	1.27	1.39	1.26	2.93	1.43	1.49
SE	0.08	0.07	0.15	0.12	0.09	0.08	0.07	0.09	0.08	0.44	0.07	0.07

Pseudoephedrine

Participant	-90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	0.89	1.04	1.83	1.56	0.96	1.13	1.18	1.18	1.09	2.61	1.28	1.35
2	0.86	0.91	2.73	1.81	1.57	1.64	1.34	1.31	1.48	2.63	1.70	1.63
3	0.76	1.02	2.19	1.95	1.8	1.6	1.54	1.68	1.7	1.66	1.78	1.59
4	0.79	0.8	1.42	1.19	1.15	0.96	1.05	1.55	1.25	1.84	1.22	1.20
5	0.99	1.04	1.99	1.55	1.45	1.31	1.22	1.12	0.98	2.49	1.37	1.41
6	1	0.6	2.02	1.44	1.57	1.17	1.15	0.95	1.1	1.32	1.34	1.23
7	1.85	1.62	2.36	1.86	1.97	1.64	2	2.06	2.67	8.08	2.08	2.61
8	0.8	1.13	1.56	1	1.27	1	1.06	0.96	0.8	3.73	1.09	1.33
9	0.86	1.16	1.98	1.77	1.64	1.47	1.58	1.76	1.84	3.5	1.72	1.76
10	1.11	0.71	0.87	0.69	0.74	0.66	0.59	0.74	0.8	2.56	0.73	0.95
Mean	0.99	1.00	1.90	1.48	1.41	1.26	1.27	1.33	1.37	3.04	1.43	1.51
SE	0.09	0.08	0.15	0.12	0.11	0.10	0.11	0.12	0.17	0.56	0.11	0.13

A2. 4. Core temperature

Placebo

Participant	- 90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	37.15	36.82	36.98	37.25	37.21	37.42	37.04	37.18	37.05	37.38	37.16	37.15
2	37.06	37	37.63	38.25	38.47	38.39	38.49	38.52	38.54	39.11	38.33	38.15
3	37.02	36.79	37.88	38.58	39.13	39.13	39.01	38.77	38.7	38.55	38.74	38.36
4	37.52	36.68	36.71	37.55	38.32	38.54	38.54	38.63	38.66	39.28	38.14	38.04
5	37.44	37.28	37.69	38.35	38.79	38.65	38.6	38.55	38.54	38.89	38.45	38.28
6	37.12	37.47	37.74	38.33	38.75	38.36	38.44	38.64	38.46	38.87	38.39	38.22
7	37.02	37.06	37.58	38.29	39.07	38.79	38.68	38.61	38.72	39.83	38.53	38.37
8	37.15	37.24	37.86	38.31	38.46	38.46	38.43	38.43	38.45	38.79	38.34	38.16
9	37.57	37.51	37.78	38.05	38.55	38.75	38.71	38.15	38.07	38.84	38.29	38.20
10	37.12	36.89	37.15	37.82	38.28	38.62	38.39	38.56	38.47	39.34	38.18	38.06
Mean	37.22	37.07	37.50	38.08	38.50	38.51	38.43	38.40	38.37	38.89	38.26	38.10
SE	0.06	0.08	0.12	0.12	0.16	0.13	0.15	0.13	0.14	0.18	0.12	0.10

Pseudoephedrine

Participant	- 90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	36.75	36.9	37	37.67	37.59	38.04	37.96	38.1	38.04	38.33	37.77	37.64
2	37.09	37.01	37.41	38.27	38.51	38.44	38.49	38.53	38.43	38.66	38.30	38.08
3	36.86	36.52	37.36	38.19	38.81	38.96	38.82	38.88	38.84	38.67	38.55	38.19
4	37.07	36.82	37.13	37.79	38.38	38.44	38.46	38.52	38.62	39.8	38.19	38.10
5	37.2	37.02	37.46	37.95	38.19	38.18	37.84	37.95	37.87	38.47	37.92	37.81
6	37.06	37.12	37.4	37.96	38.63	38.86	38.96	39.01	38.91	39.37	38.53	38.33
7	36.81	37.11	37.6	38.42	38.94	38.88	38.75	38.77	38.78	40.18	38.59	38.42
8	37.34	37.1	37.32	37.2	37.15	37.53	37.48	36.91	36.99	38.26	37.23	37.33
9	37.65	37.56	37.87	38.37	38.9	38.99	38.9	39.04	39.08	39.92	38.74	38.63
10	37.15	37.13	37.17	37.42	37.66	37.78	37.84	37.88	38.00	38.94	37.68	37.70
Mean	37.10	37.03	37.37	37.92	38.28	38.41	38.35	38.36	38.36	39.06	38.15	38.02
SE	0.08	0.08	0.07	0.12	0.18	0.15	0.15	0.19	0.18	0.20	0.14	0.12

A2. 5. Surface temperature

Placebo

Participant	- 90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	32.7	31.4	29.7	29.9	30.1	29.9	29.7	29.2	29.6	30.5	29.7	30.3
2	32.2	33.4	29.8	29.5	29.7	29.9	30.2	29.7	30.2	30.3	29.9	30.5
3	31.7	31.8	28.4	27.5	25.5	25.1	24.3	22.7	22.2	22.0	25.1	26.1
4	31.4	30.9	28.5	27.8	28.4	27.5	27.6	27.2	24.1	25.3	27.3	27.9
5	31.9	31.8	27.3	26.3	27.2	24.0	24.4	25.3	26.4	24.4	25.9	26.9
6	31.2	32.4	29.8	28.8	28.0	28.8	28.5	28.5	29.0	29.6	28.8	29.5
7	30.7	31.2	28.8	25.3	24.5	26.2	27.3	26.9	25.9	25.3	26.4	27.2
8	32.3	34.1	31.1	30.8	31.1	30.9	30.3	30.3	29.6	28.0	30.6	30.9
9	31.2	31.2	28.6	26.0	26.0	24.8	25.0	24.0	25.0	27.7	25.6	27.0
10	31.1	31.3	28.7	28.7	28.8	29.4	28.3	27.8	28.8	27.9	28.7	29.1
Mean	31.65	31.94	29.07	28.07	27.94	27.67	27.57	27.16	27.09	27.11	27.80	28.53
SE	0.18	0.31	0.30	0.52	0.62	0.71	0.66	0.72	0.79	0.80	0.57	0.50

Pseudoephedrine

Participant	- 90	0	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	31.1		29.9	30.3	31.1	31.7	31.4	31.7	31.2	30.6	31.0	31.0
2	33.2	33.4	29.8	29.6	30.2	29.9	29.6	29.9	30.8	28.8	30.0	30.5
3	31.0	31.8	27.6	26.7	25.0	24.0	23.6	21.6	20.7	22.4	24.2	25.4
4	30.7	31.3	29.7	28.6	28.4	27.6	26.8	27.5	26.8	27.4	27.9	28.5
5	31.5	31.7	29.0	29.6	28.9	29.6	29.8	29.9	29.4	29.6	29.5	29.9
6	32.1	33.0	29.7	29.3	28.9	28.4	29.1	29.4	28.2	28.1	29.0	29.6
7	31.1	31.1	28.2	27.3	27.7	27.0	26.7	24.7	26.1	26.2	26.8	27.6
8	33.0	33.3	30.2	31.5	30.5	30.2	30.4	29.5	30.1	29.9	30.3	30.8
9	31.2	30.6	30.0	29.0	28.7	28.6	28.0	30.1	29.2	29.6	29.1	29.5
10	31.3	31.7	27.7	28.1	28.5	27.7	28.2	27.8	28.5	28.0	28.1	28.7
Mean	31.60	31.98	29.19	29.01	28.79	28.47	28.36	28.21	28.09	28.05	28.59	29.16
SE	0.25	0.29	0.28	0.41	0.49	0.61	0.65	0.87	0.88	0.69	0.57	0.49

A2. 6. Perceived exertion (RPE)

Placebo

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	12	13	14	15	16	17	17	19	14.9	15.4
2	13	13	14	14	15	16	16	18	14.4	14.9
3	15	14	16	16	16	18	20	19	16.4	16.8
4	12	13	13	13	13	14	15	19	13.3	14.0
5	12	13	13	14	15	16	15	19	14.0	14.6
6	7	10	12	13	13	15	16	17	12.3	12.9
7	11	12	12	12	12	13	13	18	12.1	12.9
8	10	11	13	13	14	14	15	19	12.9	13.6
9	12	13	13	13	14	15	16	18	13.7	14.3
10	12	12	13	13	12	12	13	20	12.4	13.4
Mean	11.6	12.4	13.3	13.6	14	15	15.6	18.6	13.6	14.3
SE	0.60	0.34	0.33	0.34	0.43	0.53	0.58	0.24	0.39	0.35

Pseudoephedrine

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	12	13	13	14	15	16	17	19	14.3	14.9
2	12	12	12	12	12	12	13	20	12.1	13.1
3	15	15	15	16	17	17	19	20	16.3	16.8
4	13	13	14	14	15	16	16	20	14.4	15.1
5	12	12	14	15	15	15	16	19	14.1	14.8
6	10	12	13	14	15	15	16	20	13.6	14.4
7	10	10	10	10	10	12	13	18	10.7	11.6
8	11	11	12	13	13	13	13	19	12.3	13.1
9	11	11	11	12	12	13	13	18	11.9	12.6
10	11	11	12	12	12	12	14	20	12.0	13.0
Mean	11.7	12	12.6	13.2	13.6	14.1	15	19.3	13.2	13.9
SE	0.43	0.41	0.43	0.51	0.61	0.55	0.61	0.24	0.48	0.43

$\dot{V}O_2$
Placebo

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	3.15	3.41	3.37	3.46	3.39	3.52	3.45	3.69	3.39	3.43
2	3.63	3.51	3.63	3.61	3.57	3.55	3.68	4.13	3.60	3.66
3	3.25	3.73	3.74	3.73	3.64	3.8	3.76	3	3.66	3.58
4	3.51	3.47	3.56	3.36	3.5	3.52	3.44	3.76	3.48	3.52
5	2.74	2.74	2.96	2.95	2.86	2.88	2.97	3.78	2.87	2.99
6	3.09	3.16	3.3	3.29	3.44	3.32	3.4	3.55	3.29	3.32
7	3.28	3.42	3.53	3.5	3.49	3.53	3.53	3.97	3.47	3.53
8	3.74	4.03	4.06	4.1	4.24	4.3	4.18	5.12	4.09	4.22
9	3.6	3.65	1.27	3.47	3.46	3.56	3.37	3.81	3.20	3.27
10	2.72	2.52	2.66	2.04	3.25	2.68	2.67	3.63	2.65	2.77
Mean	3.27	3.36	3.21	3.35	3.48	3.47	3.45	3.84	3.37	3.43
SE	0.10	0.13	0.23	0.16	0.10	0.13	0.12	0.16	0.12	0.11

Pseudoephedrine

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	3.25	3.24	3.45	3.67	3.52	3.53	3.49	4.08	3.45	3.53
2	3.67	3.76	3.67	3.68	3.57	3.6	3.86	2.94	3.69	3.59
3	3.65	3.54	3.69	3.97	3.8	3.96	3.95	3.98	3.77	3.77
4	3.48	3.62	3.53	3.64	3.57	3.66	3.66	3.85	3.59	3.63
5	2.78	2.89	2.88	2.85	3	2.92	2.86	3.1	2.88	2.91
6	3.43	3.18	3.37	3.45	3.41	3.27	3.43	3.44	3.36	3.37
7	3.23	3.37	3.5	3.39	3.39	3.35	3.51	3.9	3.39	3.46
8	3.75	3.87	4	4.14	4.1	4.15	4.12	4.72	4.02	4.11
9	3.55	3.55	3.42	3.35	3.53	3.65	3.76	3.78	3.54	3.57
10	2.45	2.63	2.43	3.04	2.79	2.74	2.76	3.54	2.69	2.80
Mean	3.32	3.37	3.39	3.52	3.47	3.48	3.49	3.71	3.44	3.47
SE	0.12	0.11	0.13	0.11	0.11	0.12	0.13	0.15	0.11	0.11

$\dot{V}_E$
Placebo

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	70.75	76.89	78.04	86.63	82.04	84.18	84.12	112.76	80.38	84.43
2	73.15	74.83	77.13	77.28	77.46	78.37	83.31	107.7	77.36	81.15
3	64.85	77.83	78.16	79.04	77.35	79.04	86.24	73.49	77.50	77.00
4	65.98	64.34	68.16	64.25	69.73	68.57	69.37	85.64	67.20	69.51
5	57.29	54.84	67.78	66.32	67.73	69.35	72.24	112.79	65.08	71.04
6	66	69.42	72.79	72.97	73.86	70.84	73.68	80.7	71.37	72.53
7	68.3	70.7	79.66	79.84	79.04	79.76	83.47	111.16	77.25	81.49
8	74.06	83.47	78.49	80.69	79.88	86.17	80.45	134.89	80.46	87.26
9	74.42	74.05	25.4	62.16	66.41	78.97	63.24	101.64	63.52	68.29
10	69.82	60.39	71.69	53.29	84.12	74.14	72.17	114.81	69.37	75.05
Mean	68.46	70.68	69.73	72.25	75.76	76.94	76.83	103.56	72.95	76.78
SE	1.51	2.51	4.67	2.99	1.76	1.74	2.22	5.36	1.85	1.90

Pseudoephedrine

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	80.14	85.07	94.44	88.34	85.82	90.89	81.95	109.68	86.66	89.54
2	75.22	81.41	74.51	74.28	73.42	76.39	84.51	74.45	77.11	76.77
3	74.88	71.59	76.5	84.51	81.96	80.81	82.31	110.23	78.38	78.38
4	62.6	63.33	62.69	64.71	66.01	67.74	68.97	89.71	65.15	68.22
5	56.27	58.87	60.93	63.75	67.3	59.49	65.74	102.11	61.76	66.81
6	79.99	73.16	83.1	75.61	81.44	75.17	77.77	80.7	78.03	78.37
7	71.18	78.59	83.51	78.47	76.46	80.34	85.08	127.81	79.09	85.18
8	82.36	81.49	82.22	88.12	86.66	80.2	81.65	102.43	83.24	85.64
9	60.11	62.09	61.01	70.47	67.77	63.89	77.5	94.43	66.12	69.66
10	69.33	73.4	69.06	93.39	88.27	67.99	68.17	121.24	75.66	81.36
Mean	71.21	72.90	74.80	78.17	77.51	74.29	76.82	100.28	75.12	77.99
SE	2.61	2.61	3.26	2.96	2.46	2.73	2.13	5.09	2.35	2.25

RER

Placebo

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	1	0.99	1	1.03	1.01	0.98	0.99	1.05	1.00	1.01
2	0.94	0.95	0.94	0.93	0.92	0.91	0.91	0.87	0.93	0.92
3	0.93	0.93	0.92	0.93	0.92	0.9	0.91	0.87	0.92	0.91
4	0.94	0.95	0.93	0.93	0.92	0.91	0.91	0.92	0.93	0.93
5	0.97	0.94	0.99	0.99	0.99	0.99	0.98	1	0.98	0.98
6	0.98	0.97	0.95	0.96	0.93	0.92	0.91	0.9	0.95	0.94
7	0.94	0.93	0.94	0.94	0.92	0.92	0.92	0.91	0.93	0.93
8	0.93	0.96	0.93	0.94	0.92	0.91	0.89	0.95	0.93	0.93
9	0.97	0.98	0.95	0.93	0.95	0.97	0.91	0.93	0.95	0.95
10	1.05	1.02	1.02	1.03	1.03	1.03	1.02	1.01	1.03	1.03
Mean	0.97	0.96	0.96	0.96	0.95	0.94	0.94	0.94	0.95	0.95
SE	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.01

Pseudoephedrine

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	1.01	1.03	1.04	0.98	0.98	0.99	0.95	0.95	1.00	0.99
2	0.95	0.97	0.93	0.92	0.90	0.90	0.89	0.79	0.92	0.91
3	0.94	0.93	0.93	0.94	0.92	0.90	0.89	0.80	0.93	0.93
4	0.90	0.89	0.88	0.87	0.87	0.86	0.85	0.89	0.87	0.88
5	0.96	0.95	0.95	0.98	0.99	0.94	0.95	0.97	0.96	0.96
6	0.98	0.99	1.00	0.94	0.95	0.93	0.91	0.85	0.96	0.94
7	0.96	0.99	0.96	0.96	0.95	0.95	0.93	0.93	0.96	0.95
8	0.98	0.97	0.95	0.95	0.93	0.89	0.89	0.89	0.94	0.93
9	0.90	0.92	0.91	0.94	0.92	0.90	0.90	0.91	0.91	0.91
10	1.07	1.11	1.08	1.12	1.11	0.97	0.96	1.03	1.06	1.06
Mean	0.97	0.98	0.96	0.96	0.95	0.92	0.91	0.91	0.95	0.95
SE	0.01	0.02	0.02	0.02	0.02	0.01	0.01	0.02	0.01	0.01

Fat oxidation

Placebo

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	0.0	19.3	0.0	-130.2	-13.7	112.5	70.3	-430.3	8.3	-46.5
2	140.5	112.5	322.1	361.4	388.2	418.9	473.1	1234.1	316.7	431.4
3	162.5	169.0	417.8	356.5	400.5	528.1	484.9	1301.5	359.9	477.6
4	137.8	129.0	341.6	300.5	384.4	435.2	428.7	737.0	308.1	361.8
5	52.6	105.4	45.3	66.5	56.6	46.3	84.5	0.0	65.3	57.1
6	49.6	58.0	231.0	170.6	345.4	355.0	430.7	905.0	234.3	318.2
7	131.2	171.2	312.2	306.7	369.6	436.5	404.3	937.9	304.5	383.7
8	167.0	111.5	393.3	337.0	466.9	532.5	618.1	654.5	375.2	410.1
9	74.6	61.8	84.8	342.6	232.9	171.5	435.2	767.8	200.5	271.4
10	-75.8	-20.2	-71.8	-81.7	-112.4	-86.7	-73.8	-57.6	-74.6	-72.5
Mean	84.0	92.0	207.6	203.0	252.0	295.0	335.6	605.0	209.8	259.2
SE	22.81	17.87	51.26	54.28	58.44	62.76	64.87	166.81	45.44	58.85

Pseudoephedrine

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	-20.2	-49.9	-174.2	133.3	129.5	45.7	247.4	472.3	44.5	98.0
2	112.3	83.2	327.9	385.2	438.5	456.2	531.3	1595.3	668.1	491.2
3	161.8	160.7	330.7	337.2	421.0	550.8	612.7	1476.2	649.8	327.0
4	226.7	271.0	557.2	607.1	597.6	709.1	717.8	1104.7	725.3	598.9
5	86.0	109.9	223.7	75.8	57.1	262.6	195.4	290.2	610.7	162.6
6	45.1	23.6	13.4	255.6	222.9	314.7	413.2	1231.4	654.1	315.0
7	93.3	38.6	205.3	167.1	238.0	236.9	320.6	681.6	704.8	247.7
8	54.6	94.6	299.9	306.8	416.6	585.1	609.2	1097.8	810.1	433.1
9	243.2	197.8	420.1	291.2	396.7	506.0	507.0	908.6	744.3	433.8
10	-104.8	-184.9	-232.0	-486.2	-400.3	114.2	160.3	-183.4	573.4	-164.6
Mean	89.8	74.5	197.2	207.3	251.8	378.1	411.4	799.8	618.5	294.3
SE	30.61	37.22	73.37	82.38	81.10	62.52	56.03	156.80	61.44	63.86

Carbohydrate oxidation

Placebo

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	656.3	690.6	1405.6	1583.5	1430.6	1350.1	1363.6	3397.1	1211.5	1484.7
2	605.4	611.9	1167.1	1117.3	1071.3	1031.2	1026.4	1700.5	947.2	1041.4
3	503.8	595.3	1110.0	1172.7	1088.9	1019.1	1076.6	1685.6	938.0	1031.5
4	583.0	584.7	1118.8	1078.9	1045.3	998.7	975.7	1899.0	912.2	1035.5
5	515.4	457.3	1186.4	1157.8	1131.8	1150.4	1149.6	2599.3	964.1	1168.5
6	591.0	597.0	1126.4	1187.7	1064.8	1003.2	956.8	1711.7	932.4	1029.8
7	543.9	528.7	1165.3	1128.3	1060.3	1255.8	1036.1	2088.1	959.8	1100.8
8	600.3	720.9	1268.7	1348.8	1267.0	1222.7	1079.9	2943.2	1072.6	1306.4
9	670.9	695.5	439.5	1079.6	1190.8	1301.9	981.0	2299.7	908.4	1082.3
10	648.4	547.8	1187.2	957.2	1477.5	1212.5	1216.0	2338.7	1035.2	1198.2
Mean	591.8	603.0	1117.5	1181.2	1182.8	1154.6	1086.2	2266.3	988.1	1147.9
SE	16.62	23.65	73.29	49.86	45.90	38.36	36.52	166.27	27.22	42.98

Pseudoephedrine

Participant	10	20	40	60	80	100	120	TT_{End}	$Mean_{CL}$	$Mean_{Total}$
1	701.4	732.4	1634.6	1392.7	1335.0	1430.2	1194.6	2415.2	1203.0	1354.5
2	599.3	649.0	1086.6	1030.2	931.3	924.0	942.4	597.5	880.4	845.0
3	583.9	561.2	1177.4	1286.9	1172.4	1053.6	1113.8	2124.6	972.6	972.6
4	472.0	452.4	851.5	844.1	823.3	830.0	760.9	1780.2	719.2	851.8
5	497.4	494.0	1016.1	1125.6	1211.4	957.6	1039.4	2129.7	905.9	1058.9
6	640.8	614.3	1339.0	1112.3	1133.2	975.4	933.2	1198.3	964.0	993.3
7	560.8	648.8	1210.2	1208.0	1132.5	1117.8	1092.5	2324.2	995.8	1161.8
8	716.9	698.7	1333.9	1382.4	1250.6	1088.9	1050.9	1974.6	1074.6	1187.1
9	501.0	551.5	1020.5	1126.3	1090.6	1024.1	1070.1	2053.9	912.0	1054.7
10	627.5	751.2	1267.7	1798.3	1602.9	1027.7	987.0	2428.7	1151.8	1311.4
Mean	590.1	615.3	1193.8	1230.7	1168.3	1042.9	1007.9	1878.0	977.9	1079.1
SE	24.32	28.81	63.19	74.58	61.50	46.12	35.36	176.95	40.45	50.41

TT time to complete (min:sec)

Participant	Placebo	Pseudoephedrine
1	38.08	34.23
2	35.18	40.10
3	49.31	44.36
4	34.35	37.41
5	33.00	37.20
6	36.29	36.45
7	37.42	38.29
8	34.18	32.32
9	39.33	37.26
10	30.06	30.03
Mean	36.52	36.56
SE	1.31	1.10

11. Appendix 3: Statistical analysis

11. 1. ANOVA results

Results of statistical analysis performed for n = 10.

		Time Effect	Trial Effect	Interaction Effect
Heart rate	Rest (-90 – 0min)	p = 0.059	p = 0.729	p = 0.002
	Constant-load (10 – 120min)	p < 0.001	p = 0.001	p = 0.131
	Time trial (120 – TT_{end})	p = 0.016	p = 0.028	p = 0.793
Glucose	Rest (-90 – 0min)	p = 0.030	p = 0.952	p = 0.175
	Constant-load (10 – 120min)	p < 0.001	p = 0.004	p = 0.029
	Time trial (120 – TT_{end})	p = 0.022	p = 0.556	p = 0.117
Lactate	Rest (-90 – 0min)	p = 0.746	p = 0.905	p = 0.445
	Constant-load (10 – 120min)	p < 0.001	p = 0.968	p = 0.773
	Time trial (120 – TT_{end})	p = 0.004	p = 0.706	p = 0.998
Core temperature	Rest (-90 – 0min)	p = 0.189	p = 0.154	p = 0.770
	Constant-load (10 – 120min)	p < 0.001	p = 0.901	p = 0.089
	Time trial (120 – TT_{end})	p = 0.001	p = 0.528	p = 0.976
Surface temperature	Rest (-90 – 0min)	p = 0.032	p = 0.617	p = 0.538
	Constant-load (10 – 120min)	p = 0.047	p = 0.142	p = 0.489
	Time trial (120 – TT_{end})	p = 0.972	p = 0.101	p = 0.910
Perceived exertion	Constant-load (10 – 120min)	p < 0.001	p = 0.235	p = 0.266
	Time trial (120 – TT_{end})	p < 0.001	p = 0.864	p = 0.070
$\dot{V}O_2$	Constant-load (10 – 120min)	p = 0.134	p = 0.134	p = 0.481
	Time trial (120 – TT_{end})	p = 0.011	p = 0.410	p = 0.079
$\dot{V}_E$	Constant-load (10 – 120min)	p = 0.049	p = 0.096	p = 0.384
	Time trial (120 – TT_{end})	p < 0.001	p = 0.368	p = 0.243
RER	Constant-load (10 – 120min)	p < 0.001	p = 0.676	p = 0.100
	Time trial (120 – TT_{end})	p = 0.715	p = 0.006	p = 0.438
Fat oxidation	Constant-load (10 – 120min)	p < 0.001	p = 0.532	p = 0.277
Carbohydrate oxidation	Constant-load (10 – 120min)	p < 0.001	p = 0.610	p = 0.211

11. 2. Paired t-test results

Sig. (2-tailed)

Between conditions

Resting and time trial results

	Resting			Time trial
	-90 min	0 min		TT_{End}
Heart rate	p = 0.268	p = 0.122	Heart rate	p = 0.166
			Heart rate without participant 2	p = 0.076
Glucose	p = 0.480	p = 0.458	Glucose	p = 0.253
Lactate	p = 0.672	p = 0.597	Lactate	p = 0.822
Core temperature	p = 0.106	p = 0.412	Core temperature	p = 0.512
Surface temperature	p = 0.941	p = 0.888	Surface temperature	p = 0.158
			Perceived exertion	p = 0.066
			$\dot{V}O_2$	p = 0.174
			Minute ventilation	p = 0.273
			Respiratory exchange ratio	p = 0.028
			Fat oxidation	p = 0.041
			Carbohydrate oxidation	p = 0.024
			Time to complete time trial	p = 0.967

Between conditions

Constant-load exercise results

	Constant-load exercise						
	10 min	20 min	40 min	60 min	80 min	100 min	120 min
Heart rate	p =0.018	p =0.024	p =0.005	p =0.004	p =0.006	p <0.001	p =0.004
Glucose	p =0.245	p =0.036	p =0.008	p =0.051	p =0.162	p =0.823	p =0.434
Lactate	p =0.934	p =0.393	p =0.965	p =0.509	p =0.975	p =0.691	p =0.431
Core temperature	p =0.208	p =0.324	p =0.194	p =0.937	p =0.624	p =0.504	p =0.573
Surface temperature	p =0.736	p =0.062	p =0.070	p =0.289	p =0.243	p =0.235	p =0.110
Perceived exertion	p =0.811	p =0.343	p =0.111	p =0.309	p =0.479	p =0.095	p =0.260
$\dot{V}O_2$	p =0.411	p =0.436	p =0.420	p =0.142	p =0.792	p =0.647	p =0.144
Minute ventilation	p =0.318	p =0.374	p =0.247	p =0.173	p =0.228	p =0.241	p =0.614
Respiratory exchange ratio	p =1.000	p =0.404	p =0.642	p =0.941	p =0.934	p =0.086	p =0.027
Fat oxidation	p =0.817	p =0.593	p =0.865	p =0.947	p =0.999	p =0.153	p =0.055
Carbohydrate oxidation	p =0.950	P =0.717	p =0.334	p =0.615	p =0.707	p =0.011	p =0.068

Within conditions, between time points
Resting and time trial results for placebo condition

	Resting		Time trial
	-90 - 0 min		120 min - TT_{End}
Heart rate	p = 0.863	Heart rate	p = 0.029
Glucose	p = 0.824	Glucose	p = 0.249
Lactate	p = 0.490	Lactate	p = 0.006
Core temperature	p = 0.182	Core temperature	p = 0.001
Surface temperature	p = 0.308	Surface temperature	p = 0.965
		Perceived exertion	p = 0.002
		$\dot{V}O_2$	p = 0.032
		Minute ventilation	p = 0.002
		Respiratory exchange ratio	p = 0.604

Within conditions, between time points
Constant-load exercise results for placebo condition

	Constant-load exercise						
	0 - 10min	10 - 20min	20 - 40min	40 - 60min	60 - 80min	80 - 100min	100 - 120 min
Heart rate	p<0.001	p=0.024	p=0.087	p=0.070	p=0.648	p=0.144	p=0.002
Glucose	p=0.001	p=0.003	p=0.018	p=0.007	p<0.001	p=0.123	p=0.033
Lactate	p<0.001	p=0.005	p=0.078	p=0.042	p=0.677	p=0.376	p=0.287
Core temperature	p=0.002	p<0.001	p=0.001	p=0.917	p=0.239	p=0.524	p=0.771
Surface temperature	p<0.001	p=0.023	p=0.639	p=0.522	p=0.670	p=0.085	p=0.850
Perceived exertion	-	p=0.037	p=0.010	p=0.081	p=0.104	p=0.001	p=0.051
$\dot{V}O_2$	-	p=0.185	p=0.545	p=0.562	p=0.309	p=0.792	p=0.524
Minute ventilation	-	p=0.299	p=0.869	p=0.579	p=0.296	p=0.538	p=0.959
Respiratory exchange ratio	-	p=0.627	p=0.529	p=0.373	p=0.052	p=0.132	p=0.193

Within conditions, between time points
Resting and time trial results for pseudoephedrine condition

	Resting		Time trial
	-90 - 0 min		120 min - TT_{End}
Heart rate	p = 0.001	Heart rate	p = 0.014
Glucose	p = 0.192	Glucose	p = 0.008
Lactate	p = 0.892	Lactate	p = 0.008
Core temperature	p = 0.024	Core temperature	p = 0.030
Surface temperature	p = 0.072	Surface temperature	p = 0.897
		Perceived exertion	p < 0.001
		$\dot{V}O_2$	p = 0.242
		Minute ventilation	p = 0.007
		Respiratory exchange ratio	p = 0.899

Within condition, between time points
Constant-load exercise results for pseudoephedrine condition

	Constant-load exercise						
	0 – 10min	10 - 20min	20 - 40min	40 - 60min	60 - 80min	80 - 100min	100 - 120 min
Heart rate	p<0.001	p=0.386	p=0.029	p=0.177	p=0.196	p=0.016	p=0.353
Glucose	p=0.003	p=0.041	p=0.001	p=0.356	p=0.363	p=0.445	p=0.476
Lactate	p<0.001	p<0.001	p=0.383	p=0.020	p=0.815	p=0.363	p=0.625
Core temperature	p=0.069	p=0.032	p<0.001	p=0.003	p<0.001	p<0.001	p<0.001
Surface temperature	p<0.001	p=0.506	p=0.420	p=0.115	p=0.493	p=0.712	p=0.713
Perceived exertion	-	p=0.193	p=0.024	p=0.005	p=0.037	p=0.052	p=0.004
$\dot{V}O_2$	-	p=0.614	p=0.200	p=0.096	p=0.272	p=0.626	p=0.122
Minute ventilation	-	p=0.256	p=0.303	p=0.287	p=0.545	p=0.213	p=0.155
Respiratory exchange ratio	p=0.128	p=0.058	p=0.790	p=0.790	p=0.070	p=0.062	p=0.051

12. Appendix 4: Participant screening and information

12. 1. Participant information sheet

Participant Information Sheet

Project Title : The physiological effects of pseudoephedrine ingestion on endurance cycling.

"This project has been reviewed and approved by the Central Ethics Committee Application CEN/08/04/016. If you have any questions or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Telephone: (NZ wide) 0800 555 050 Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)
Email (NZ wide): advocacy@hdc.org.nz"

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This research will form part of a thesis required for the completion of a Masters of Science degree for Joshua Mouatt.

Introduction
Pseudoephedrine is a mild stimulant that partially mimics the actions of noradrenaline and adrenaline, and is found in over the counter drugs to relieve nasal and sinus congestion. Pseudoephedrine was removed from the banned substance list by the World Anti Doping Agency (WADA) from January 2004 as it was felt there was little evidence for an performance enhancing effect despite there being little research investigating its effect on sporting performance, and no research on endurance performance (>2hr). In a previous study performed at Massey University (results yet to be published) no effect was observed on

endurance cycling performance (>2hr). However, several physiological changes were evident despite no effect on endurance performance eg: HR increased 10 bpm, subjects reported that they "felt hotter". During the previous performance trials workload was not held constant between the trials (athletes where self-paced) and few physiological measurements were taken, thus making any physiological analysis difficult. Therefore the present follow up study aims to identify whether pseudoephedrine at this level has an effect on physiological characteristics during endurance cycling.

Participation

We are recruiting fit and healthy male cyclists 18-40 years of age, who train on average more than 200 km a week and regularly competes at club level, to participate in this study. All participation is voluntary and you may withdraw from participating in the study at any time. If you agree to participate, you will be asked to participate in 3 trials during which time you will be exercising on a cycle ergometer for 2 trials and your blood will be sampled. You will also be asked to adhere to certain dietary and exercise controls in the 24 hours preceding the trials. These sessions will take place under supervision in the Human Performance Laboratory (HPL), the Institute of Food, Nutrition and Human Health (IFNHH) at Massey University.

The names and contact details of the researchers undertaking this project are given above. Please do not hesitate to contact any one of them if you have any questions about this project at any time.

Testing

Prior to the first pseudoephedrine performance trial a number of baseline and calibratory measurements will be made including resting measurements. You will also be required to perform a maximal ($\dot{V}O_{2max}$) exercise test on a cycle ergometer where the workload will be increased until you are no longer able to maintain a pedaling cadence of at least 40 rpm i.e. your maximum effort. If you are unfamiliar with this type of cycle testing we will arrange a familiarization session for you, exercising on the cycle ergometer in the HPL and using the measuring equipment required.

Thereafter, on two separate occasions at least 6-days apart, you will be asked again to attend the laboratory. Upon arriving at the laboratory, you will be weighed, and then be asked to lie down while a small (5ml) blood sample is taken from a vein on the front of your forearm. You will then be given either pseudoephedrine at a dose equating to 2.5mg per kg of body weight or a placebo containing glucose to be ingested. Seventy five minutes after ingestion you will again be asked to lie down whilst a cannula is inserted into a vein on the back of your forearm opposite to which your first blood sample was taken from. The place where the cannula is inserted will be in the opposite arm each trial. A 10-minutes warm up will be performed just prior to beginning the exercise trial. Exactly 90 minutes after the ingestion of the placebo or pseudoephedrine you will begin the exercise trial, which will consist of two parts. During the first part you will be cycling at a fixed intensity

(65% of your $\dot{V}O_{2max}$) for 120 minutes; and during the second part you will be cycling at a work dependent self-paced time trial for approx 30 minutes.

During Part one, we will collect a small (6ml) blood sample from the cannula at 5, 10, 20, 40, 60, 80, 100 and 120 min. And another single sample at the end of your time trial. Between blood samples the cannula will be regularly flushed with saline. Just before each blood sample is taken during part one, expired respiratory gas samples will be collected from your mouth using the Pulmolab gas analysis system and sterilized mouthpeices. This equipment measures volumes of air and oxygen passing into and out of your lungs and from this we can determine various values including the rate at which you use oxygen. During part two, we will collect gas samples every five minutes, as well as power output which is measured directly by the computer system controlling the ergometer. Heart rate is measured electronically using the commonly available Polar® chest band and wristwatch combination. Once the time trial is complete, the cannula will be removed form your hand and you will be able to warm down before having a complementary lunch.
To ensure that everyone performs each test with a similar metabolic profile, your food intake and physical activity will be controlled for the 24 hours prior to testing. This will involve provision of a meal, which will be required to be consumed 4 hours prior to the test and a laboratory controlled sub-maximal exercise bout 24 hours prior to each test. This will also be performed in the Human Performance Laboratory.

In summary, you will be required to come to the laboratory to perform the following:

1) $\dot{V}O_{2max}$ test
2) Trial 1 - Ingestion of pseudoephedrine or placebo (glucose) 90 minutes prior to performing trial.
3) Trial 2 - Ingestion of pseudoephedrine or placebo (glucose) 90 minutes prior to performing trial.

Potential risks and discomforts

The procedures involved in participating in this study are of low risk. Nevertheless, as in any invasive and exercise procedures, there are small risks and some discomfort may be experienced:

Venous cannula

Needle insertion into a vein is required for collecting the initial blood sample via syringe as well as for the placement of the cannula, and you will feel minor to moderate discomfort as a result. However with the placement of the cannula, the needle is quickly removed and only a flexible plastic tube remains in your vein for the duration of blood sampling (approximately 2 ½ hours). In order to reduce the

risks of infection, we made need to clip any body hair from a small area on your arm, surgical gloves will be worn and the area will be cleaned with an isopropyl alcohol wipe before we insert the needle. When the cannula is removed, direct pressure will be applied to the area to reduce the changes of bruising. Cannulas are routinely placed into veins of participants in clinical research studies and in hospital patients. The risks of IV cannulation are low, but occasionally significant bruising or infection can occur. Both Dr. Stannard and Dr. Mundel are qualified and experienced in venous cannula placement and the use of aseptic techniques. Blood samples are disposed of in their vacutainers or storage tubes into biohazard bags, which are autoclaved at 121°C and disposed of by Nuplex medical waste. Alternatively, you can request to have any/all portions of your samples returned to you.

Exercise

You are likely to experience the fatigue associated with strenuous exercise, particularly during the time trial. Nevertheless, as in any physical activity, there is a very small possibility of injuries that include, but are not restricted to, muscle, ligament or tendon damage, breathing irregularities and dizziness. However, all protocols are commonly performed in exercise physiology laboratories and potential risks to participants have been minimised.

Pseudoephedrine

As a common over-the-counter drug pseudoephedrine is a key ingredient within many decongestant medications available in New Zealand (Claratyne, Codral, Coldrex, and some Orthoxical products).

At higher dose rates there is some evidence suggesting a possible performance enhancing effect of pseudoephedrine, therefore, the dosage of pseudoephedrine will be higher than that commonly consumed in over-the-counter medications (175mg for a 70kg male compared to 2 Coldrex tablets containing 60mg).

There are possible side effects associated with the ingestion of pseudoephedrine. The most common side effects are nervousness, restlessness, and trouble sleeping. Other less common side effects include difficult or painful urination, dizziness or lightheadedness, headache, nausea, rapid or pounding heartbeat, trembling, weakness and drowsiness. Very rare and more severe side effects include hallucinations, irregular or slow heartbeat, seizures and trouble breathing.

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as

whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.
If you have any questions about ACC, contact your nearest ACC office the chief investigator or supervisors of the study.

Participants' rights

No material which could personally identify you will be used in any reports on this study. You can ask questions on any aspect of the project at any time, and we will do our best to answer them to your satisfaction. As a participant in the study you will provide information on the understanding that your name will not be used unless you give permission to the researcher. You have the right to view your own data at any stage and have it explained to you. Individual results will remain confidential. You have the right to have any blood samples returned to you after they have been analysed. You will also be given access to a summary of the project findings when it is concluded. You can withdraw from the project at any time, without giving any reason and without penalty.

Exclusion Criteria
If any of the following apply:

- ***You have a history of gastrointestinal discomfort after the ingestion pseudoephedrine***
- ***You have any known heart or cardiovascular condition or if a member of your family died below the age of fifty (50) as a result of a heart condition.***
- ***You have asthma or any respiratory disease.***
- ***In the last six months you have suffered from any painful injury or condition that lasted more than one week.***
- ***You have ever had an injury or any medical condition that you think may affect your ability to sense pain or discomfort.***
- ***You have ever had persistent or regular lower back pain.***
- ***You are taking prescribed medication.***
- ***You have cultural or religious sensitivities about human body measurements.***
- ***You have any other reason to consider that you are not in good health and of average, or better than average, fitness.***
- ***You commonly have trouble sleeping***

…you should <u>NOT</u> participate in this project.

Thank you for your time and cooperation.

12. 2. Consent form

CONSENT FORM

Experiment Title: *The physiological effects of Pseudoephedrine on endurance cycling.*

I have read the Participant Information Sheet for the above experiment and had the procedures and potential risks explained to me by the researchers. I am satisfied that my concerns and questions have been addressed fully.

Yes ☐ No ☐

I understand that I have the right to withdraw my consent for being a participant at any time without giving reasons and without penalty.

Yes ☐ No ☐

I have read the information sheet describing this project and I have no known medical or other condition which would exclude me from being a participant in this experiment.

Yes ☐ No ☐

I would like my blood samples returned to me after analysis

Yes ☐ No ☐

I have been given one week to consider my involvement in the project.

Yes ☐ No ☐

I agree to participate as an experimental subject

Yes ☐ No ☐

I understand that thereafter I can withdraw at any time without reason and without penalty.

Yes ☐ No ☐

Signed: …….

Name: …….

Date: …….

12. 3. Pre-exercise health screening questionnaire

Pre-Exercise Health Screening Questionnaire

Name:_____

Address: _____

Phone: _____

Age: _____

Please read the following questions carefully. If you have any difficulty, please advise the medical practitioner, nurse or exercise specialist who is conducting the exercise test.

Please answer all of the following questions by ticking only one box for each question:

This questionnaire has been designed to identify the small number of persons (15-69 years of age) for whom physical activity might be inappropriate. The questions are based upon the Physical Activity Readiness Questionnaire (PAR-Q), originally devised by the British Columbia Dept of Health (Canada), as revised by [1]Thomas *et al.* (1992) and [2]Cardinal *et al.* (1996), and with added requirements of the Massey University Human Ethics Committee. The information provided by you on this form will be treated with the strictest confidentiality.

Qu 1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?

Yes ☐ No ☐

Qu 2. Do you feel a pain in your chest when you do physical activity?

Yes ☐ No ☐

Qu 3. In the past month have you had chest pain when you were not doing physical activity?

Yes ☐ No ☐

Qu 4. Do you lose your balance because of dizziness or do you ever lose consciousness?

Yes ☐ No ☐

Qu 5. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?

Yes ☐ No ☐

Qu 6. Do you have a bone or joint problem that could be made worse by vigorous exercise?

Yes ☐ No ☐

Qu 7. Do you know of any other reason why you should not do physical activity?

Yes ☐ No ☐

Qu 8. Have any immediate family had heart problems prior to the age of 60?

Yes ☐ No ☐

Qu 9. Are you now, or have you been recently on any anti-depression medication?

Yes ☐ No ☐

Qu 10. Have you been hospitalised recently?

Yes ☐ No ☐

Qu 11. Do you have any infectious disease that may be transmitted in blood?

Yes ☐ No ☐

Qu 12. Do you have any allergies to dairy products or products containing milk proteins?

Yes ☐ No ☐

Qu 13. This test may include the taking of blood for blood glucose, insulin, free fatty acid and lactate testing. Do you have any objection to this?

Yes ☐ No ☐

Qu 14. This test may require you to ingest commercial dairy-based products. Do you have any objection to this?

Yes ☐ No ☐

Qu 15. Does consuming carbohydrate based sports drinks cause you severe gastrointestinal discomfort?

Yes ☐ No ☐

You should be aware that even amongst healthy persons who undertake regular physical activity there is a risk of sudden death during exercise. Though extremely rare, such cases can occur in people with an undiagnosed heart condition. If you have any reason to suspect that you may have a heart condition that will put you at risk during exercise, you should seek advice from a medical practitioner before undertaking an exercise test.

I have read, understood and completed this questionnaire.

Signature: _____ Date: _____

References

1. Thomas S, Reading J and Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). *Can J Sport Sci* 17(4): 338-345.
2. Cardinal BJ, Esters J and Cardinal MK. Evaluation of the revised physical activity readiness questionnaire in older adults. *Med Sci Sports Exerc* 28(4): 468-472

13. Appendix 5: Letter notifying ethics approval

Health and Disability Ethics Committees

Central Regional Ethics Committee
Ministry of Health
Level 2, 1-3 The Terrace
PO Box 5013
Wellington
Phone (04) 496 2405
Fax (04) 496 2191

24 April 2008

Mr Joshua Mouatt
Massey University
30 Stanley Avenue
Palmerston North

Dear Joshua

The physiological effects of pseudoephedrine ingestion on endurance cycling.
Mr Joshua Mouatt, Dr Toby Mundel
Massey University
CEN/08/04/016

The above study has been given ethical approval by the **Central Regional** Ethics Committee. A list of members of this committee is attached.

Approved Documents
- Information sheet and consent form version 1, dated 2008
- Advertisement version 1, dated 24 April 2008
- Pre Exercise Questionnaire version 1, dated 2008

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Final Report *(for studies less than 1 year)*
The study is approved until **25 October 2008**. A final report is required at the end of the study. The report form is available on http://www.ethicscommittees.health.govt.nz and should be forwarded along with a summary of the results. If the study will not be completed as advised, please forward a progress report and an application for extension of ethical approval one month before the above date.

Requirements for SAE Reporting
The Principal Investigator will inform the Committee as soon as possible of the following:
- Any related study in another country that has stopped due to serious or unexpected adverse events
- withdrawal from the market for any reason
- all serious adverse events occurring during the study in New Zealand which result in the investigator breaking the blinding code at the time of the SAE or which result in hospitalisation or death.
- all serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

As part of the conditions of approving a proposal, committees may require an independent review or audit of approved research or innovative practice at any time.

Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

Yours sincerely

Jiska van Bruggen
Central Regional Ethics Committee Administrator
Email: jiska_van_bruggen@moh.govt.nz

Health and Disability Ethics Committees

Central Regional Ethics Committee
Ministry of Health
Level 2, 1-3 The Terrace
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Mr Joshua Mouatt
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Central Regional Ethics Committee Members		
Name	**Member category**	**Term (Appointed)**
Helen Colebrook (Chair)	Lawyer	3 years (Dec 06) Reappointed 2 years (Feb 08)
Mark Weatherall	Biostatistician	3 years (Feb 08)
Nicholas Agar	Ethicist	3 years (Feb 08)
Diana Martin	Researcher	3 years (Feb 08)
Elaine Papps	Health Practitioner	3 years (Dec 06)
Joe Asghar	Pharmacist/pharmacologist	3 years (Dec 06)
Maureen Holdaway	Researcher	2 years (Dec 06)
Jacqueline Renouf	Consumer Representative	3 years (July 05)
Hilary Stace	Consumer Representative	3 years (Feb 08)
Anne Tuffin	Community Representative	3 years (Dec 06)
Carolyn Collins	Community Representative	3 years (Feb 08)