Synephrine, Octopamine and Caffeine Health Risk Assessment (HRA) Report

**Overview:** Health Canada, counterpart to the U. S. Food and Drug Administration, has relaxed and redefined its guidelines for the use of *p*-synephrine, the dominant amine in *Citrus aurantium* (bitter orange). The 49-page report reviews *p*-synephrine’s chemistry; receptor binding, in vitro, animal, and human studies; summaries of clinical case reports; and Canadian clinical case reports. The report concludes that 1 to 50 mg of *p*-synephrine per day – and up to 40 mg of *p*-synephrine in combination with a maximum of 320 mg of caffeine per day – for healthy adults “is not likely to cause any adverse health consequences.”
Synephrine, Octopamine and Caffeine Health Risk Assessment (HRA) Report

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<th>Issue</th>
<th>Assessment of the potential risks to health from natural health products containing synephrine and/or octopamine in combination with caffeine.</th>
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<td>HC File Number</td>
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<td>Requested By/Date of Request</td>
<td>Christine Zaczyński, Health Products and Food Branch Inspectorate (HPFBI) 2011-01-27</td>
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<td>Consulted With/Date of Consultation(s)</td>
<td>Marketed Biologicals, Biotechnology and Natural Health Products Bureau, Marketed Health Products Directorate (MHPD) 2011-02-28</td>
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**SUMMARY OF PRODUCT INFORMATION**

<table>
<thead>
<tr>
<th>Name of Product(s) &amp; Identification Number (if any)</th>
<th>various products not licensed for sale in Canada</th>
</tr>
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<tbody>
<tr>
<td>Type of Product</td>
<td>Natural Health Products</td>
</tr>
<tr>
<td>Common Name (if any)</td>
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<tr>
<td>Medicinal/Active Ingredient(s)</td>
<td>Synephrine and/or Octopamine and Caffeine</td>
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<td>Dosage Form(s)</td>
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<td>various</td>
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<tr>
<td>Route of Administration</td>
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</tr>
<tr>
<td>Proposed Indication(s)</td>
<td>Weight loss aid is the primary indication</td>
</tr>
<tr>
<td>Proposed Sub-population(s)</td>
<td>Adults</td>
</tr>
<tr>
<td>Non-medicinal/active Ingredient(s) (if applicable)</td>
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</tr>
<tr>
<td>Manufacturer/Sponsor</td>
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</tr>
<tr>
<td>Manufacturer Site Licence Information and Number (if applicable)</td>
<td>various</td>
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### REVIEWER’S DECISION

| Health Risk Classification & Recommendation | Types III, II and possible I as specified for different product compositions and conditions of use, below. |

### APPROVALS

<table>
<thead>
<tr>
<th>Revised and Approved By</th>
<th>Robin Marles, Director, Bureau of Clinical Trials and Health Sciences, Natural Health Products Directorate (NHPD)</th>
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Executive Summary

Citrus aurantium Peel
Based on the evidence reviewed above, the botanical material Bitter Orange peel, at the doses typically used in herbal medicine and food, is not considered to pose any risk to the health of consumers.

p-Synephrine Alone
At doses up to 50 mg/day in healthy adults, p-synephrine is classified as Type III, except in cases where the necessary cautionary statements (i.e. contraindicated in children, pregnancy, and breast-feeding, do not use if you are taking blood pressure medications (either hypertensives or antihypertensives), thyroid medications, sympathomimetics, or monoamine oxidase inhibitors (MAOIs)) are lacking, which would result in a risk classification of Type II.

At doses above 50 mg/day, p-synephrine approaches the dose used as a prescription drug in Europe for the treatment of hypotension. While it is possible to be exposed to a dietary source of as much as 70 mg of p-synephrine from a cup of Cleopatra mandarin orange juice, this is not a common item in the diet and the dose-response curve for p-synephrine between 50 mg and therapeutic doses of the racemic tartrate are not adequately characterized to be categorical as to safety. Therefore, in the absence of a product-specific review of safety under specific recommended conditions of use, as would be accomplished through assessment of a product licence for market authorization, the application of precaution is a legitimate decision making approach within risk management. Such unauthorized products are therefore classified as a Type II risk to health.

p-Synephrine and Caffeine
Products providing 40 mg/day or less of p-synephrine plus 320 mg/day or less of caffeine, are classified as Type III, except in cases where the necessary cautionary statements (i.e. contraindicated in children, pregnancy, and breast-feeding, do not use if you are taking blood pressure medications (either hypertensives or antihypertensives), thyroid medications, sympathomimetics, or monoamine oxidase inhibitors (MAOIs)) are lacking, which would result in a risk classification of Type II.

Products exceeding either threshold dose or products lacking the cautionary statements (i.e. contraindicated in children, pregnancy, and breast-feeding, do not use if you are taking blood pressure medications (either hypertensives or antihypertensives), thyroid medications, sympathomimetics, or monoamine oxidase inhibitors (MAOIs)), are classified as a Type II risk to health.

p-Synephrine, Caffeine and Other Stimulants
Such products have been implicated in many serious adverse reaction case reports. Causality is not likely due to the p-synephrine content on its own, rather to other ingredients such as octopamine in high doses or thyroid drugs such as iodotyrosine. The risk to human health must be assessed on a case by case basis. Given the nature of the observed adverse reactions, it is probable that some of these products will be assessed as posing a Type I risk to health.
**p-Octopamine**
Based on its known pharmacology, *p*-octopamine at doses up to 50 mg/day in healthy adults is classified as Type III. At doses above 50 mg/day, due to the paucity of human clinical data, in the absence of a product-specific review of safety under specific recommended conditions of use, as would be accomplished through assessment of a product licence for market authorization, the application of precaution is a legitimate decision making approach within risk management. Such unauthorized products are therefore classified as a Type II risk to health.

**Exacerbating Conditions**
Due to the extremely limited evidence for the safety of chronic use of *p*-synephrine at doses higher than 50 mg or in combination with caffeine or other ingredients in vulnerable subpopulations, the following cautionary statements (or words to these effects) should be on product labels to mitigate the risk of potentially serious adverse reactions:

- **Contraindicated in children, pregnancy, and breast-feeding.**
- **Do not use if you are taking blood pressure medications (either hypertensives or antihypertensives), thyroid medications, sympathomimetics, or monoamine oxidase inhibitors (MAOIs).**

**Consistency of Approach with Previous NHP HRAs**
The recommended Health Risk Classification criteria above are consistent with the Health Risk Assessments (Health Hazard Evaluations) previously prepared by Health Canada with respect to the products *Thermonex* (Type I, 2004-04-13), *Slim System 8* (Type II, 2004-12-20), No. 1 *Protocole Minceur* (Type III, 2005-06-10), *MetaSlim* (Type III 2006-02-22), *Synerate* (Type I, 2010-12-31), and *Lipo-6X* (Type I, 2011-01-25).

**Conclusions**
There are a number of limitations that are common to all the available clinical studies, including:

- The sample sizes of the studies are extremely small. Although the possible cardiovascular effects to products in this class are potentially very serious, they are also fairly rare. The available studies are not sufficiently broad in scope to support the safety in a general consumer population, especially when the population targeted for these products consists of largely overweight/obese individuals, who are subject to various co-morbidities. This limitation is inherent to all available randomized, controlled trials. In effect, appropriate evidence for safety, especially for rare adverse events, should come by way of sufficient epidemiological studies;
- In addition to the limited sample sizes, the study populations are also generally healthy, even if some studies include overweight individuals. This adds further to the incomparability of available studies and extrapolation to the general population;
- None of the studies include a justification for their sample sizes, nor an indication of power. This is a critical oversight, as it calls into question all of the findings. Lack of an effect could very well be a genuine lack of an effect, or simply an inability to detect an effect;
- The studies are all of very short duration – another inherent deficiency seen when using randomized, controlled trials to support safety. As the nature of the cardiovascular events could depend on long-term exposure (e.g., chronic sympathetic over-stimulation), the short-term studies are not adequate to support long-term safety. The authors of Seifert et al. (2011) comment that, “longer term studies are required to assess [the effects on heart rate and blood
pressure] under conditions similar to those encountered when using the product in conjunction with a long term weight loss program.”

In summary, this Health Risk Assessment does not address the issue of efficacy, which must be assessed through the product licensing process for each individual product.

However, based on new clinical studies and published reviews of safety information, it has been possible to revise the synephrine and caffeine recommendations prepared previously by Health Canada (2010c) in order to reduce unnecessary compliance actions on products that do not present as serious a risk to health as had been judged previously. This will allow resources to be focused better on compliance and enforcement of more risky products.

**Issue Identification**

In seeking an alternative to ephedra for use in weight-loss products after reports of serious adverse reactions and consequent compliance and enforcement actions by regulatory authorities in various countries, the history of use of citrus fruit consumption for weight loss has been extensively investigated, with much attention focused on Bitter Orange and its proto-alkaloids synephrine and octopamine (Preuss et al. 2002). While there is some preliminary evidence from animal, in vitro, and human studies for limited efficacy and safety of bitter orange, some potential safety issues have been identified with the consumption of synephrine or related sympathomimetics particularly when combined with caffeine. There are unlicensed natural health products (NHPs) currently on the Canadian market and Product Licence Applications (PLAs) currently under review that include synephrine and/or octopamine, or Bitter Orange peel which is a source of these substances, with caffeine or sources of caffeine such as cocoa, cola, guaraná, maté, or green tea.

The purposes of this HRA are to develop risk classifications and relevant risk mitigation strategies, including public communication and guidance for compliance and enforcement actions, for unauthorized products containing synephrine and/or octopamine, with or without caffeine, and with or without additional stimulants.

The HRA will then be used to develop basic assessment requirements for the evaluation of product licence applications for NHPs that include these ingredient combinations.

This HRA is not intended to apply to any product that has already been licensed by the Natural Health Products Directorate (NHPD), unless the marketed product is not in compliance with its approved conditions of use and labelling. Licensed products should be safe and effective when used according to all of the recommended conditions of use.

**Health Risk Assessment**
The main potential cause for concern relates to suspected involvement of human oral consumption of products containing synephrine and/or octopamine, with or without caffeine, in cardiovascular serious adverse reactions.

**Hazard Identification & Characterization**

**Occurrence of Synephrine, Octopamine and Related Substances**

Bitter Orange (also known as Seville Orange, *Citrus aurantium* L., Rutaceae) peel extracts are well-known sources of synephrine and other proto-alkaloids, shown together with ephedrine (mainly coming from *Ephedra* species) and the human neurotransmitters epinephrine and nor-epinephrine (also known as adrenaline and noradrenaline, respectively) in Figure 1 to facilitate comparison of their chemical structures.
Figure 1. Molecular structures of synephrine, octopamine and related adrenergic agonists.

Synephrine has also been isolated from other members of the citrus family (Rutaceae) including sweet orange (*Citrus sinensis* (L.) Osbeck), mandarin orange (*Citrus reticulata* Blanco), Murcott orange (*C. reticulata × C. sinensis*), Satsuma mandarin (*Citrus unshiu* Marcow.), Cleopatra mandarin (*Citrus reshni* hort. ex Tanaka), tangerine (*Citrus tangerina* Tanaka), Mediterranean tangerine (*C. deliciosa* Ten.), tangelo (*Citrus ×tangelo* J. W. Ingram & H. E. Moore), temple
orange (*Citrus temple* hort. ex Yu. Tanaka), Hassaku orange (*Citrus hassaku* hort. ex Tanaka),
common lemon (*C. limon* (L.) Burm. f.), sweet lemon (*Citrus limetta* Risso), rough lemon
(*Citrus jambhiri* Lush.), Meyer lemon (*Citrus meyeri* Yu. Tanaka), manderin lime (*C. limonia* Osbeck),
calamondin (*×Citrofortunella microcarpa* (Bunge) Wijnands), Troyer citrange
(*×Citroncirus webberi* J. W. Ingram & H. E. Moore), evodia (*Evodia rutaecarpa* (A. Juss.)
Benth. reclassified to *Tetradium ruticarpum* (A. Juss.) T. G. Hartley). Synephrine has also been
isolated from plants in other families including the Amaryllidaceae (*Amaryllis vittata* L’Hér. reclassified as
*Hippeastrum vittatum* (L’Hér.) Herb., *Amazon lily Eucharis ×grandiflora* Planch. & Linden, and
Blood lily *Haemanthus katherinae* Baker reclassified as *Scadoxus multiflorus* (Martyn) Raf. subsp. *katherinae* (Baker) Friis & Nordal) and Moraceae (rubber tree
*Ficus bengalensis* L.) (Wheaton and Stewart 1965, 1969, 1970; Hosoda et al. 1990; Blumenthal

Octopamine is present naturally in much lower levels than synephrine (usually less than 0.03 %) in
 citrus juices and extracts; it was below the limit of quantification in fresh and dried fruit of
 Bitter Orange (Pellati et al. 2002). It was detected in trace amounts in temple orange and Murcott
 orange juices, 1 mg/L in Dancy and Robinson tangerine juices, 2 mg/L in Cleopatra mandarin
 juice and 4 mg/L in Meyer lemon juice (Stewart and Wheaton 1964; Wheaton and Stewart
 1965). It has also been isolated from papyrus (*Cyperus papyrus* L., Cyperaceae) leaves at 17
 mg/kg fresh weight and nutgrass (*Cyperus rotundus* L.) leaves at 91 mg/kg fresh weight, leaves
 of the asparagus relative liriope (*Liriope spicata* (Thunb.) Lour., Asparagaceae) at 20 mg/kg
 fresh weight and bell pepper (*Capsicum frutescens* L., Solanaceae) leaves at 234 mg/kg fresh
 weight (Wheaton and Stewart 1970).

Bitter Orange also contains the protoalkaloids tyramine, hordenine and N-methyltyramine
 (Nelson et al. 2007).

Three positional isomers of synephrine exist (Figure 1): *para-*-, *meta-* and *ortho-*synephrine.
 These isomers differ in the position of the phenolic hydroxyl group, which impacts on the
 pharmacological activity of these compounds (Allison et al. 2005).

In mammals, *p*-synephrine and *m*-synephrine occur naturally in the adrenal gland and probably
 in the nerves of the heart and brain although at extremely low concentrations; *p*-octopamine is
 found at concentrations of 6-60 pmol/g in the sympathetic nervous system with norepinephrine
 (NE), where it functions as a co-neurotransmitter or modulator of NE activity in the sympathetic
 nervous system (Ibrahim et al. 1985; Williams et al. 1987; Brown et al. 1988; Evans et al. 1988).
 The natural occurrence of *o*-synephrine has not been reported to date (James et al. 1983; Allison
 et al. 2005). Both *m-* and *o*-octopamine have also been reported to occur naturally in vertebrates
 (James et al. 1983; Brown et al. 1988; Evans et al. 1988). Octopamine is an important
 neurotransmitter in invertebrates (it was first isolated from the octopus, hence the name) where
 with tyramine it plays the complex variety of roles that epinephrine and norepinephrine play in
 vertebrates (Roeder et al. 2003). *R-*(-)*p*-Synephrine, through its stimulation of NE release, may
 play a role in mental health by providing an endogenous antidepressant-like effect (Kim et al.
 2001). Octopamine may be an important biomarker for certain pathogenic processes, since it has
 been reported to occur at mean levels of 0.2 to 0.4 ng/mL in the plasma of healthy subjects, but
 has been seen as an abnormality at concentrations above 3.2 ng/mL in hepatic encephalopathy.
(Rossi-Fanelli et al. 1976), with rare extremes up to 59.5 ng/mL in cirrhotic patients with hepatic coma (Hörtnagl et al. 1981), and in renal disease at 1.9 ng/mL increasing to 2.7 ng/mL during dialysis (Kinniburgh and Boyd 1979); octopamine production may be deficient in some cases of depression as suggested by urinary output of metabolites (Sandler et al. 1979).

The \( p \)-synephrine found in Bitter Orange should not be confused with \( m \)-synephrine, a synonym for phenylephrine (also known as Neo-Synephrine), a sympathomimetic drug used as a nasal decongestant, miotic and cardiotonic (Sweetman 2007; NIH 2004) that can induce reflex bradycardia (Martindale 2007; Keys and Violante 1942). There is evidence that some manufacturers may be adulterating Bitter Orange extracts with \( m \)-synephrine, since Allison et al. (2005) found both \( m \)- and \( p \)-isomers in a commercial product purportedly containing synephrine from \( C. \) aurantium. Studies at the University of Mississippi found only \( p \)-synephrine in \( C. \) aurantium (Ikhlas Khan, National Center for Natural Products Research, University of Mississippi, e-mail to V. Hurry, 2007-10-02 9:08 AM). Roman et al. (2007), using a single-laboratory validated method, found that octopamine, phenylephrine, tyramine, N-methyltyramine and hordenine were all below the limit of quantification (about 300 µg/g except about 600 µg/g for phenylephrine) in National Institute of Standards and Technology reference samples of \( Citrus \) aurantium powdered lyophilized Bitter Orange raw material and a powdered Bitter Orange fruit extract, while for Nutratech \( C. \) aurantium raw material, octopamine averaged 554 µg/g and N-methyltyramine averaged 1200 µg/g; phenylephrine, tyramine and hordenine were below the limit of quantification in these samples and in two commercial Bitter Orange dietary supplements.

Using chiral HPLC chromatography, Pellati et al. (2002) found \( l \)-synephrine, also known as \((-\)\)-synephrine, the \( R \)-enantiomer, present in all samples analyzed of \( Citrus \) aurantium L. var. amara L. fresh fruits, dried fruits, dried extracts, and herbal products. A significant amount of \( d \)-synephrine, also known as \((+)\)-synephrine, the \( S \)-enantiomer, was found in fresh fruits and some commercial products. They found from a heat stability study that synephrine was not likely to be racemized at temperatures within the range usually used for extraction procedures (refluxed in water at 100°C for 24 h), but in a subsequent investigation (Pellati et al. 2010) they revised this position by concluding that racemization of the naturally occurring \( R-(-)\)-synephrine is possible at high temperature at both acidic and basic pH values, and that the presence of an organic co-solvent also affected racemization.

**Evidence from Animals, in vitro Studies, Models & Bench Testing**

**Mechanisms via Receptor Binding**

Central nervous system biogenic amine systems have been studied extensively with respect to their effects on feeding behaviour, energy balance and weight management (Nelson and Gehlert 2006). Food intake can be stimulated or inhibited depending on which type of adrenergic receptors (ARs) in the brain are affected: NE activation of \( \alpha_1 \)-ARs in the paraventricular nucleus decreases food intake, while NE activation of \( \alpha_2 \)-ARs, which are coupled through G proteins to modulate cyclic adenosine monophosphate and calcium channels, will stimulate food intake, but
specific α₂-AR antagonists have not been shown to have significant or consistent effects on
human body weight. NE stimulation of β₂-ARs in the perifornical area will also decrease food
intake. The β₃-AR plays a key role in thermogenesis, and increased sensitivity of the β₂-AR to
NE stimulation also plays a role in lipolysis (Bray and Greenway 1999). Unfortunately, the
lipolytic effect of selective β₃-AR agonists does not appear to persist in humans due to either lack
of recruitment of β₃-AR responsive tissue, a down regulation of β₃-ARs, or both, so human trials
have been disappointing (Bray and Greenway 2007).

Synephrine has been shown, in vitro, to interact directly with the α₁-ARs and cause contraction
of the rat aorta, anococcygeus (pair of thin sheets of smooth muscle that insert into the rectum),
as well as the guinea pig atria and trachea (Brown et al. 1988). Varma et al. (1995) used
endothelium-denuded strips of rat aorta to show that in the presence of blockade of both α-AR
(by benextramine) and β-AR (by propranolol), significant vasorelaxation (66% to 92%) was
caused by tyramine > l-ephedrine > synephrine > octopamine. p-(−)-Synephrine’s interaction
with α₁- and α₂-ARs, however, is much weaker than phenylephrine, and both are weaker than
NE: phenylephrine is 4 to 150-fold less active than NE, and synephrine is 30 to 1,000 fold less
active than NE, depending on the tissue in which the receptor is located. In all circumstances, the
meta- forms of synephrine have much greater direct binding ability than do the para- forms, and
the (−) levo forms have greater direct activity than the (+) dextro forms generally in 1-3 orders of
magnitude (Brown et al. 1988). Synephrine’s effect at the α₁-ARs is supported by the reversal of
effects with an α₁-antagonist (Prazosin) (Fugh-Berman and Meyers 2004). Further studies have
confirmed that synephrine binds to human α₁A-, α₂A- and α₂C-AR subtypes with relatively low
affinity, acting as a partial agonist at the α₁A-AR (EC₅₀ = 4 µM, maximal response at 100 µM
that was equal to 55.3% of the L-phenylephrine maximum) and as a lower activity partial
antagonist at the α₂A- and α₂C- ARs (Airriess et al. 1997; Ma et al. 2010).

At the β₁-AR in guinea pig atria, the rank order for the activities of the (−)-stereoisomers of the
phenylethylamines was found to be NE > m-synephrine (100 fold) > m-octopamine = p-
octopamine (6000 fold) > p-synephrine (40,000 fold). The (+)-stereoisomers were 1-2
orders of magnitude less active than their (−)-counterparts. At the β₂-AR in guinea pig trachea the
four (−)-stereoisomers were more than four orders of magnitude less active than NE and the (+)-
stereoisomers had no detectable activity in concentrations as high as 10⁻⁴ M (Jordan et al. 1987).

Octopamine has been reported to have lipolytic activity in isolated rat fat cells although only at
concentrations greater than 0.1 µM (Nakano et al. 1969). Despite some evidence for octopamine
stimulation of α₁- and α₂-ARs from animal models (e.g. Brown et al. 1988; Airriess et al. 1997),
it has only a very weak affinity for the human α₂A-AR and can be considered to be devoid of
functional human α₂-AR agonism (Fontana et al. 2000). Visentin et al. (2001) demonstrated that
in rat fat cells, (±)-octopamine stimulated lipolysis and counteracted insulin lipogenic action via
β₃-AR stimulation, but, on the other hand, stimulated glucose uptake by a mechanism dependent
on octopamine’s oxidation by monoamine oxidase or semi-carbazide-sensitive amine oxidase.

Some of the central nervous system effects of octopamine have been attributed to its stimulation
of central dopaminergic and noradrenergic systems, and its reduction of cerebral concentrations
of NE and gamma-aminobutyric acid (GABA); inhibition of the activity of the synthesizing
enzyme glutamate decarboxylase was observed (Jagiello-Wojtowicz and Chodkowska 1984).
Octopamine also has greater sympathomimetic activity associated with the R-(-)-enantiomer than the S, increasing blood pressure and having positive chronotropic and inotropic effects on the heart of experimental animals such as the dog and cat, but is weaker in its effects than norepinephrine (David and Coulon 1985).

Carpéné et al. (1999) reported that synephrine and octopamine exhibited lipolytic effects in rat, hamster, guinea pig and human adipocytes, but only at high concentrations (0.1 to 1 mM). Synephrine’s lipolytic effects have been suggested to be likely attributable to β1-AR and/or β2-AR stimulation since lipolysis could be induced in the guinea pig, a species lacking β3-AR responsiveness, and was suppressed by selective β1-AR and β2-AR antagonists but only poorly by a selective β3-AR antagonist. Synephrine and octopamine had similar levels of intrinsic activity compared to the model β3-AR agonist isoprenaline with a 2-fold lower affinity for human β3-AR than NE. However, the evidence indicates that octopamine is a selective β3-AR agonist.

In a subsequent paper from the same research group, Mercader et al. (2011) reported that their observations of lipolysis appear contradictory to synephrine having α2-AR antagonist activity since it was unable to improve epinephrine-induced lipolysis in human fat cells and did not totally prevent bromoxidine-induced antilipolysis. They noted that partial agonism of α2-ARs by synephrine cannot be excluded but its very poor affinity to the α1-, α2a- and α2c-ARs make resolving this issue of doubtful value. Compared to the 7-fold increase in lipolysis seen as the maximal response (defined 100%) from the β-AR agonist isoprenaline at 10 µM (2.45 µg/mL) in human adipocytes, synephrine provided 33% of the maximal response and octopamine provided 52% of the maximal response, but they had very low potency compared to isoprenaline with activity detected only at concentrations >10 µg/mL. Octopamine was additive to isoprenaline, synephrine was not. The mechanism of action of octopamine is by activation of β3-ARs but unlike rat adipocytes, human fat cells have only a weak β3-AR responsiveness. Tyramine and N-methyltyramine had antilipolytic activity. The authors conclude that based on their in vitro data, although having lower intrinsic activity that octopamine, synephrine has a much higher concentration so it can be considered the predominant active lipolytic component of Bitter Orange. However, the benefit/risk ratio remains to be established due to the high doses needed to achieve an effective concentration in the human adipocytes compared to the toxic dose. The authors recognized that a potential weakness of their study was their use of racemic synephrine rather than the R-(-)-enantiomer but also noted that racemic synephrine is generated by commercial extraction procedures, so their results may in fact be relevant to products on the market. Based on these results, the presence of tyramine and N-methyltyramine in weight-loss products is not desirable.

Since synephrine and octopamine are commonly suggested to be pharmacologically similar to ephedrine due to the relatedness of their chemical structures, it is instructive to review the receptor binding of ephedrine. By convention, ephedrine is the name for the two enantiomers with opposite stereochemistry around the two chiral centres (1R,2S and 1S,2R, see Figure 1), while pseudoephedrine has the same stereochemistry around the two chiral centres (1R,2R and 1S,2S). Commercial synthetic ephedrine may be racemic but natural ephedrine is the (-)- or l-stereoisomer, with the (1R,2S) configuration. The stereochemistry is important as it dramatically affects the pharmacology, as demonstrated in the studies below.
The beneficial and adverse effects of ephedrine and related analogues are known to be mediated via the α- and β-ARs and may be elicited by either direct interactions with the receptors as agonists or antagonists or indirectly by either causing a release of endogenous catecholamines and/or by preventing their neuronal reuptake. The relative contribution of these direct and indirect interactions to the pharmacological effects of the ephedrine isomers in humans in vivo has remained controversial (Ma et al. 2007). Rothman et al. (2003) found that (-)-ephedrine’s most potent action was substrate activity at NE transporters. Using cloned human ARs expressed in animal tissues, it has been determined that (-)-ephedrine is generally more potent than its enantiomers to α-ARs (Ma et al. 2007) and β-ARs (Vansal and Feller 1999), and that (-)-ephedrine showed the highest intrinsic activity at human β2-AR and also showed significant agonist activity at β1-AR but probably clinically inconsequential agonist activity at the human β3-AR (Vansal and Feller 1999), and even where β1- and β2-AR activity has been shown, it is still at least an order of magnitude lower than NE due to low affinities for the receptors (Rothman and Baumann 2005). At cloned human a1A, a1B, a1D, a2A, a2B, and a2C-ARs, (-)-ephedrine had only a weak partial agonist activity (at >10⁻⁴ M) and moderate antagonist activities on the α-AR subtypes. This is in contrast to rodent cell lines in which (-)-ephedrine was seen to have an agonist effect on β3-AR and a1A-ARs, possibly related to a greater density of receptors (Ma et al. 2007). Furthermore, in rodents gene knockout techniques provided support for direct mediation through α-ARs of pressor responses to (-)-ephedrine rather than through effects on the release of NE (Liles et al. 2007). In humans, (-)-ephedrine may block a1A-ARs and act as antagonists of presynaptic a2A/a2C-ARs, interfering with presynaptic NE uptake, thus enhancing the synaptic concentration of NE and its effects (Ma et al. 2007).

In a further mechanistic study, Fang et al. (2003) used a model of ventricular myocytes of guinea pigs to show that Citrus aurantium extract could increase the L-type calcium current and promote the opening of the calcium channel at low concentrations or inhibit the L-type calcium channel and depress its opening at high concentrations.

Hibino et al. (2009) studied the effects of a water-extract of Evodia rutaecarpa (standardized to ~20% synephrine) on the contraction of aortic strips, isolated from young (7- or 13-week-old) Wistar rats. When expressed in terms of synephrine content, it was found that a significant increase in contraction (vs. vehicle) was seen at 3 × 10⁻⁷ M, with a maximal effect (i.e., ~90% of the maximum tension induced by 60 mM K⁺) at 1 × 10⁻⁵ M. Hibino et al. (2009) presented evidence from the use of selective antagonists to suggest that synephrine may also have serotonergic activity, primarily at 5-HT₂A receptors (perhaps to a lesser extent at 5-HT₁D), which may contribute to vasoconstrictive activity. Assuming a molecular weight of 167.2 g/mole for synephrine, these concentrations equal 0.05 to 1.7 ng/mL, respectively. These concentrations are similar to maximal blood concentrations of ~2 ng/mL, found in humans, after having consumed 46.9 mg of synephrine (Haller et al., 2005).

With respect to the mechanism of the addition of caffeine to ephedrine or synephrine, caffeine is a non-selective adenosine receptor antagonist, and blockage of adenosine’s pre-synaptic activity would lead to the release of catecholamines, which would act on the adrenergic receptors. Kim et al. (2001) demonstrated the ability of p-synephrine to stimulate NE release. Inhibition of the adenosine receptors in the heart (A₁) would promote contractility and activity in the sinoatrial
node and atrioventricular node (Stiles 1986), and inhibition of adenosine receptors in the smooth muscle vasculature \((A_2)\) would result in vasoconstriction (Mort and Kruse 2008; Higdon and Frei 2006; Mandel 2002; Stiles 1986). In vitro experiments have shown that the sympathomimetic activity of synephrine and octopamine is enhanced upon coadministration of caffeine or other methylxanthines (Kalsner 1971; Fischer and Florey 1987).

At high doses, caffeine may cause hypotension due to \(\beta\)-AR activation and tachycardia due to the release of catecholamines (Benowitz 1990). Caffeine is also suggested to inhibit the enzyme phosphodiesterase, responsible for inactivating cAMP (cyclic 3,5-adenosine monophosphate), leading to increased adrenergic effects (Kalman et al. 2002; Brent et al. 2005). The latter is not thought to occur at doses of caffeine in food or drink; however, this may occur with higher doses of caffeine present in natural health products (Mort and Kruse 2008; Dulloo et al. 1992).

Thus, caffeine and other methylxanthines prevent the body from becoming resistant to the effects of phenylpropamines by inhibiting the adenosine receptor and phosphodiesterase (Bray and Greenway 1999). These results suggest that synephrine and octopamine interactions with caffeine in humans are likely to be similar to the reported ephedrine and caffeine interactions (e.g. Young et al. 1998) although to a much lesser degree, i.e., requiring much higher doses to observe the same effects.

With respect to structure-activity relationships, key differences that affect the three-dimensional structure (steric hindrance) and the distribution of hydrophobic potential across the molecule, both affecting receptor site binding, distribution in the body such as the ability to cross the blood-brain barrier, and activity, include the \textit{para}-hydroxyl functional group of \textit{p}-synephrine and \textit{p}-octopamine which is absent in (-)-ephedrine, the basic carbon skeleton with synephrine and octopamine being phenylethylamines while ephedrine is a 2-methylamino-1-phenylpropanol, and the secondary amine functional group of synephrine and ephedrine while octopamine has a primary amine. For example, the presence of the \textit{para}-hydroxyl functional group and the lack of the additional methyl group on the side chain greatly decrease the lipid solubility of \textit{p}-synephrine compared with ephedrine, resulting in little transport into the central nervous system compared with ephedrine. The larger the size of the alkyl group linked to the amine group of the side chain, the greater the affinity for the \(\beta\)-AR (Rossato et al. 2011). Differences in steric hindrance and receptor binding creating pharmacodynamic differences also apply to positional isomers such as \textit{m}-synephrine compared to \textit{p}-synephrine (Brown et al. 1988; Colker et al. 1999; Stohs et al. 2011a).

In summary, there are both qualitative and quantitative differences in the mechanism of action of ephedrine compared to synephrine, octopamine and related substances, and these differences are further complicated by significant differences between rodent and human receptor experimental models. In humans, ephedrine has \(\beta_1\)- and \(\beta_2\)-AR agonist activity, no significant \(\beta_3\)-AR activity, and \(\alpha_2\)-AR antagonist activity, at least one fold less potent than NE, but due to low affinity for these receptors it acts mainly through increasing presynaptic NE concentration. Synephrine is a partial agonist at \(\alpha_1\)-AR and partial antagonist at the \(\alpha_2\)- and \(\alpha_3\)- ARs, 30 to 1,000 fold less active than NE, and synephrine is also a partial agonist at \(\beta_1\)-, \(\beta_2\)-ARs although it is 40,000 fold less active than NE, and a partial agonist at \(\beta_3\)-ARs although only half as potent as NE.
Synephrine also acts by stimulating NE release. Octopamine is a selective β3-AR agonist, although with a 2-fold lower affinity than NE.

**Preclinical Pharmacology and Toxicology**

In an acute study using a model of portal hypertension in Sprague-Dawley rats (Huang et al. 1995), intravenous unripe Bitter Orange (aqueous extract, 7.5 to 30 mg/kg body weight) and intravenous synephrine (0.57 to 2.28 mg/kg body weight) were shown to significantly increase mean arterial pressure and decrease portal vein pressure in a dose-dependent manner. The increase in mean arterial pressure following Bitter Orange infusion was comparable to that with synephrine. The mechanism was suggested to be by way of arterial vasoconstriction.

In a subchronic study using two models of portal hypertension in Sprague-Dawley rats (Huang et al. 2001), oral synephrine (1 mg/kg body weight per day for 8 days) significantly increased mean arterial pressure (MAP), systemic vascular resistance and portal tributary vascular resistance (n=7 per group, 42 total) (p<0.05). Cardiac index, portal vein pressure, and portal tributary blood flow were significantly decreased (p<0.05). No significant effects in body weight, heart rate, gross changes, or mortality were observed. It was suggested by the authors that the observed effects were due to synephrine’s activation of the α1-ARs, resulting in vasoconstriction of the splanchnic or mesenteric arteries. Although no β stimulatory effects were observed, it was suggested by the authors that this may have been due to species difference, disease state (hypertension), or dosage regimen. As only one dose was used, no dose-dependent effects could be determined.

Calapai et al. (1999) administered hydroethanolic extracts of Bitter Orange (standardized to 4% or 6% synephrine), ranging from 2.5 to 20 mg/kg b.w./day, for 15 days, in Sprague-Dawley rats. It was found that treatment resulted in reduced food intake and body weight gain, in a dose-dependent manner. It was also found that rats given 20 mg/kg b.w./day developed significant anomalies in ECG activity, including ventricular arrhythmias and enlargements of the QRS complex, by the tenth day of treatment. It was not indicated if ECG analysis was performed on rats given lower doses.

Arbo et al. (2008) conducted 6 hour acute oral toxicity studies through administration by gavage of *C. aurantium* unripe fruit extracts (2.5% p-synephrine, 300, 500, 1000, 2500, 3500, or 5000 mg/kg) or p-synephrine (150, 300, 450, 600, 800, 1000, or 2000 mg/kg) versus water control in groups of 8 male albino CF1 mice. Reduction of locomotor activity persisting from 15 min. until 2 h post-treatment was seen at 1000-5000 mg/kg of the Bitter Orange extract and from 15 min. until 1 hr post-treatment at 300 to 2000 mg/kg p-synephrine, which was confirmed in spontaneous locomotor activity tests. Gasping (from 15 min. until 3-4 h) and salivation (from 15 min. until 30 min.) were seen at 150 mg/kg p-synephrine, and gasping, salivation, piloerection (from 15 min. to 2 h), and exophthalmia (from 15 min. to 2 h) were seen at doses of 300 to 2000 mg/kg. There were no deaths and all the effects were reversible. Body weight gain over 14 days following treatment was similar to control and at necropsy there were no alterations in the removed organs. The authors speculated that the toxic effects observed seemed to be related to adrenergic stimulation.
In a subsequent subchronic toxicity study, Arbo et al. (2009) evaluated Bitter Orange extract and p-synephrine in mice, treating groups of 9-10 male albino CF1 mice for 28 days with a commercial *C. aurantium* dried extract (containing 7.5% synephrine) at 400, 2000, or 4000 mg/kg, or *p*-synephrine at 30 or 300 mg/kg, by oral gavage. There were no deaths, clinical signs of toxicity, or changes in relative weights of organs in any of the treatment groups. There was no significant change in body weight during treatment with any of the doses of Bitter Orange extract but both doses of synephrine produced a significant decrease in body weight gain by the 28 day measurement point.

**Experience in Humans**

**Conditions of Use**

Syneprhine is a sympathomimetic (adrenergic agonist). It is used as a vasoconstrictor in circulatory failure (Masten 2004). The tartrate salt is given orally to treat hypotension, and ocularly (hydrochloride salt as well) as an ocular decongestant to constrict blood vessels in the eye in order to reduce hyperaemia (Sweetman 2007).

Octopamine is used as a cardiotonic and to treat hypotension (Masten 2004).

Bitter Orange peel has GRAS status (FDA 2010a) and is often used in marmalade; the dried peel is used in *bouquet garni* and for flavouring certain Belgian white beers, such as Orange Muscat (Facciola 1998).

In Traditional Chinese Medicine (TCM), there are two medicinal materials, *zhi qiao* prepared from the mature but still green Bitter Orange fruit peel collected in July and *zhi shi* prepared from the immature fruit collected in May or June. They are both used to treat the TCM condition of *qi* stagnation. With respect to Western diagnoses, both are added to multiple ingredient formulas to treat indigestion, abdominal distension, tenesmus (urgent feeling of need and painful straining to defecate or urinate, but that is not effective) distention and full sensation in the chest and epigastric region of the body (Blumenthal 2004-2005). In contemporary use in China, it is injected for the treatment of toxic shock and anaphylactic shock, weak heart conditions and cardiac exhaustion. The peel is also used in TCM (Wichtl 2004), similarly to the whole dried immature fruit (Wichtl 2004; Sweetman 2007).

Bitter Orange peel from ripe (Wichtl 2004; Council of Europe 2010) or either ripe or unripe fruit (Fugh-Berman and Myers 2004) is used in modern herbalism and in the Eclectic medical movement (Blumenthal 2004-2005) as a bitter aromatic digestive tonic to stimulate secretion of gastric juice and the appetite in gastric hypoacidity disorders and as a flavouring agent for other medicines.

Bitter orange peel is also used in South American folk medicine to treat anxiety, insomnia, and as an anticonvulsant (Carvalho-Freitas and Costa 2002).
In dietary supplements and natural health products, Bitter Orange peel and its extracts are used orally for weight loss, increasing lean body mass, body building, improving athletic performance, nasal congestion, allergic rhinitis, and chronic fatigue syndrome (NMCD 2011). Bitter Orange extracts are often standardized for its synephrine content for thermogenic action (Costa et al. 2011).

**Dose Response**

**Ephedrine and Caffeine**
Since Bitter Orange extracts, synephrine and octopamine have been investigated so much as substitutes for Ephedra and ephedrine, the clinical evidence for Ephedra or ephedrine with caffeine, for weight loss and athletic performance, will be briefly summarized to provide context.

Ephedrine combined with methylxanthines has been used in the treatment of asthma for decades. A Danish physician noted weight loss in his patients on this regimen. The combination of 200 mg caffeine and 20 mg ephedrine three times per day was subsequently approved and marketed for more than 10 years as a prescription medication for weight loss in Denmark (Bray and Greenway 2007). Human clinical trials of ephedrine and caffeine for weight loss have been reviewed by Bray and Greenway (1999) and Schekelle et al. (2003). Key findings were that none of the weight loss trials assessed a duration of greater than 6 months, that weight loss in comparison to placebo for the combination of ephedrine plus caffeine was 1.0 (CI95% 0.4-1.3) kg/month, and safety data from 50 trials yielded an estimate of 2.2- to 3.6-fold increases in the odds of psychiatric, autonomic, or gastrointestinal symptoms, and heart palpitations (Shekelle et al. 2003).

Since those reviews were published, there have been a couple of clinical trials and an observational study involving more than six months exposure to ephedrine plus caffeine.

Greenway et al. (2004) enrolled 12 healthy male and female adult subjects in a pilot study to assess the effect of a multiple-ingredient product containing Ephedra (12 mg ephedrine), kola and tea extracts (35 mg caffeine total), plus various other herbs and minerals, at a dose of 2 pills on an empty stomach, on resting metabolic rate: 8% higher in treatment than control. Next, those 12 plus 28 more subjects were enrolled for a placebo-controlled trial of three months at the same dose of product providing 24 mg ephedrine and 70 mg caffeine per day: weight loss at 12 weeks was significant at 3.5 ± 0.6 kg with treatment vs. 0.8 ± 0.5 kg with placebo and fat loss was also significant 7.9 ± 2.9% vs. 1.9 ± 1.1% and adrenergic symptoms from treatment including blood pressure did not exceed placebo although 5 patients lost to follow-up could have failed to return because of adrenergic symptoms. Finally, there was an open-label phase for 6 months: after a total of 6 months treatment those in the treatment arm of the second phase of the study had lost 7.8 ± 1.9% of their body weight and those from the placebo arm had lost 7.3 ± 1.9%. The authors noted that weight loss reached a plateau after 6 months of treatment and there were no serious adverse events or clinical signs of toxicity.
Hackman et al. (2006) conducted a 9-month trial of a multiple-ingredient dietary supplement containing Ephedra herb extract (500 mg containing 40 mg ephedrine alkaloids), guarana extract (550 mg containing 100 mg caffeine), plus other herbs, amino acids, fatty acids, plant extracts and isolates, vitamins and minerals. Of 61 obese (BMI 29-37 kg/m²) but otherwise healthy (e.g. hypertension excluded), pre-menopausal women enrolled, 41 completed the study. The treatment group lost significantly more body weight (-7.18 kg) and body fat (-5.33 kg) than the controls (-2.25 and -0.99 kg respectively), and showed significant declines in heart rate, serum cholesterol, triglycerides, cholesterol to high-density lipoprotein ratio, glucose, fasting insulin, and leptin. Blood pressure, electocardiograms, and other clinical chemistry, blood histology and urinalysis results were similar to controls. Adverse effects reported as minor included dry mouth, insomnia, nervousness and palpitations. The authors concluded that a supplement containing a low potency ephedra/caffeine mixture could be used safely and effectively for loss of weight and body fat under physician supervision.

Hallas et al. (2008) conducted a controlled observational study (registry-based case-crossover study design) of data on 257,364 Danish patients prescribed an ephedrine (20 mg) and caffeine (200 mg) combination product (Letigen), 1-3 tablets per day, for weight loss, over the period from 1995 until 2002 when its marketing was suspended after reports suggesting a safety problem. They found that under physician supervision, use of this specific quality-controlled pharmaceutical ephedrine/caffeine product was not associated with adverse cardiovascular outcomes over a wide range of patient subgroups, different cardiovascular outcomes (death outside hospital, myocardial infarction, and stroke were the composite endpoint), different assumptions about exposure, and different utilization patterns. There was nothing in the case-control analysis to suggest a delayed effect with continuous exposure e.g. mediated through a hypertensive effect, or an increased risk among naive users or users with large cumulative doses. The authors noted the implication that spontaneous reporting of adverse effects can “snowball” where a product has acquired a poor reputation that generates new adverse reports.

Clinical trials of an ephedrine 20 mg/caffeine 200 mg combination observed side effects of increased systolic blood pressure, tremor, insomnia and dizziness that were transient and after 8 weeks of treatment had reached placebo levels (Astrup et al. 1992, 1995; Astrup and Toubro 1993). A possible mechanism for this lack of significant adverse effects under physician supervision is that caffeine combined with ephedrine stimulates both α- and β-ARs. The α-, β1- and some of the β2-ARs down-regulate with time, while the β3- and some of the β2-ARs do not. This allows ephedrine with caffeine to become a selective β2/β3-AR agonist over time as the tremor, tachycardia, and nervousness lessen or disappear (Bray and Greenway 1999).

**Synephrine**

Despite the reported hypertensive effect of synephrine when used at doses of 100-150 mg, three times daily, to treat hypotension (Sweetman 2007), and the evidence from animal-based models, there is controversy in the literature as to whether or not synephrine from C. aurantium extracts, used in amounts typically found in marketed weight-loss products, elicits hemodynamic responses on its own.

Penzak et al. (2001) reported no effects on hemodynamic measures (systolic, diastolic blood
Bui et al. (2005) reported increases in systolic blood pressure and heart rate for at least 6 hours, versus placebo, in healthy adults, following a single dose of 900 mg of *C. aurantium* extract standardized to 6% synephrine (~54 mg). In contrast, using the same product, Min et al. (2005) found no hemodynamic effect associated with a single dose of 900 mg of *C. aurantium* extract, standardized to 6% synephrine, in healthy adults. Gougeon et al. (2005) found no hemodynamic effect associated with a single dose of *C. aurantium* extract providing 26 mg of synephrine, in healthy and overweight adults. Major limitations to these studies are that they all included measurements after a single dose, so long-term effects cannot be extrapolated, and the study populations are all healthy (even if overweight) normotensive individuals. Therefore, possible responses in a hypertensive population are unknown. In addition, a placebo group was not included in the study by Gougeon et al. (2005).

Shara et al. (cited in Stohs and Shara 2011) conducted a randomized, placebo-controlled double-blind crossover study involving 16 healthy subjects administered one capsule of 50 mg *p*-synephrine or placebo daily for 14 days. Blood pressure, heart rate, and electrocardiograms were determined at 30 min., 60 min., 90 min, 2 h, 4 h, 6 h, 8 h, and then after one week and two weeks. There was no significant effect on blood pressure or heart rate and there were no cardiovascular abnormalities.

Stohs et al. (2011b) assessed the thermogenic effects of *p*-synephrine alone (Advantra Z providing 50 mg of synephrine) and in combination with the flavonoids hesperidin and naringin (0 mg + 600 mg; 100 mg + 600 mg; 1,000 mg + 600 mg, respectively) in a pilot double-blind, randomized, placebo-controlled trial with 10 healthy subjects/group. Resting metabolic rate (RMR), blood pressure and heart rate were measured and subjects’ self-reported mood/energy levels were recorded while resting, at baseline and 45 min. and 75 min. after treatment. The placebo group had a small decrease in RMR as anticipated due to continued fasting, while all treatment groups showed an increase in RMR statistically greater than placebo, with a maximal response vs. placebo of +183 kcal in group 4 (synephrine 50 mg, hesperidin 100 mg, naringin 600 mg). A dose of 1,000 mg hesperidin produced a much less than optimal increase in RMR. No increases in systolic or diastolic blood pressure or heart rate were observed. There were no significant effects relative to placebo in the self-reported symptoms including energy level, concentration or adverse reactions.

**Caffeine**

Caffeine levels peak (T\text{max}) 30-120 min. after oral intake and the half-life (T\text{1/2}) is 3-6 h. Blood pressure changes occur within 30 min. of ingestion, peak in 1-2 h, and may persist for more than 4 h. Changes are usually in the range of an increase of 3-15 mm Hg systolic and 4-13 mm Hg diastolic.
diastolic. Caffeine tolerance diminishes the acute effect of caffeine on blood pressure. Hypertensive individuals are more susceptible to blood pressure changes (Mort and Kruse 2008).

**Synephrine + Caffeine**

Haller et al. (2005) conducted a randomized, double-blind, 3-arm crossover study in 10 healthy adults with Xenadrine EFX, a multiple-ingredient product including vitamins C, B₆, and B₅, magnesium, L-tyrosine, acetyl-L-tyrosine, green tea extract, cocoa extract (containing phenylethylamine, tyramine and theobromine), yerba mate, d-methionine, ginger root, 3,3’,4’,5-7-pentahydroxyflavone, 3,3’,4’,7-tetrahydroxyflavone, 2-dimethylaminoethanol, grape seed extract, and Bitter Orange extract (providing synephrine, n-methyl-tyramine, hordenine, octopamine and tyramine). Some ingredients are sources of caffeine, and other ingredients are relevant to sympathetic nervous activity, e.g., phenylethylamine is a chemical precursor for other sympathomimetic agents (Katzung 2001); parenteral administration of tyramine has an indirect sympathomimetic action by causing a release of stored catecholamines (Katzung 2001); and hordenine has positive inotropic activity (Hoffman 2003). Xenadrine EFX was chemically analyzed and found to contain per 2-capsule dose 5.5 mg synephrine, 5.7 mg octopamine, and 239.2 mg caffeine, in addition to other herbal extracts and isolates, vitamins and minerals, with Advantra Z analyzed to provide 46.9 mg synephrine per 3 tablet dose, versus placebo. With respect to pharmacokinetics, synephrine’s T<sub>max</sub> was 75 min., T<sub>1/2</sub> was 3.1 ± 2.2 h, C<sub>max</sub> was 2.85 ± 0.86 ng/mL. Caffeine’s T<sub>max</sub> was 90 min., T<sub>1/2</sub> was 7.8 ± 3.1 h, C<sub>max</sub> was 5.1 ± 1.3 µg/mL. Octopamine’s pharmacokinetics could not be measured since 99% of the plasma samples measured were below the limit of quantitation of 0.2 ng/mL. Xenadrine EFX significantly raised mean systolic (+9.6 ± 6.2 mm Hg) and diastolic (+9.1 ± 7.8 mm Hg) blood pressure with a maximal increase 2 h after ingestion. Heart rate was significantly elevated compared with placebo only at the 6 hour time point after dosing. Advantra Z did not raise systolic or diastolic blood pressure but showed a similar increase in heart rate at the 6 h point. However, at 8 h post-treatment, placebo and both treatment groups had similar elevated levels of heart rate but these were all well within the normal range of heart rate increase associated with normal activities undertaken by healthy adults (McGuffin 2007). Haller and Benowitz (2007) replied that the mean peak heart rate increases observed with bitter orange alone or the bitter orange-plus-caffeine were approximately 2-fold higher than the heart rate increase observed with placebo and was a statistically significant difference seen while subjects were at rest. Stohs et al. (2011a) noted that this increase in heart rate does not coincide with the pharmacokinetics of p-synephrine but with the thermic effect of food. Whatever the cause, the maximum difference of 16 beats/min. with the Xenadrine EFX treatment may not be clinically significant.

Hoffman et al. (2006) examined the effects of JavaFit™, which is a source of synephrine and caffeine, in healthy, physically active subjects, who were all regular coffee drinkers, following a single dose, providing 450 mg of caffeine, 1200 mg of Garcinia cambogia (standardized to 50% hydroxycitric acid), 360 mg of C. aurantium extract (standardized to 6% synephrine alkaloids = 21.6 mg), and 225 µg of chromium polynicotinate. The control group was a placebo group which included a standardized coffee drink. The study included a cross-over design, for an effective sample size of 10 per group. The authors reported a statistically significant increase in systolic blood pressure in the JavaFit™ group, versus coffee alone.
Fugh-Berman and Myers (2004) have suggested that overweight individuals may be particularly susceptible to the effects of synephrine + caffeine: overweight individuals are commonly hypertensive and may react differently to vasopressors.

On the other hand, there is evidence that supports the absence of cardiovascular responses to products providing synephrine and caffeine or, possibly, that tolerance may develop to the hemodynamic effects, over time as were observed for ephedrine/caffeine. Although no data are provided, Colker et al. (1999) reported no significant effects on blood pressure and heart rate (not the primary end points) in a 6-week double-blind, randomized, placebo-controlled trial in subjects (n = 9) who received 975 mg *C. aurantium* extract (6% synephrine = 58.5 mg), caffeine 528 mg, and St. John’s Wort 900 mg/day. Acute hemodynamic effects could have been missed since subjects were evaluated only at baseline, week 3 and week 6.

Greenway et al. (2006), in an 8-week pilot study, randomized eight subjects to a multi-component supplement (18 mg synephrine/ day + ≥ 400 mg caffeine) or placebo and also found no effects on blood pressure and heart rate (measured at baseline, 2, 4 and 8 weeks). However, the authors confused *m*-synephrine/phenylephrine with *p*-synephrine as the active constituent of *C. aurantium*, so it is not clear what was actually tested in this clinical trial.

Zenk et al. (2005) examined the effects of the multiple-ingredient herbal supplement Lean System 7 on metabolic rate and other hemodynamic parameters, in generally healthy, but overweight adults (n=24), versus placebo (n=23). The supplement provided, daily, 102 mg of 3-acetyl-7-oxo-dehydroepiandrosterone, 600 mg of *C. aurantium* extract (36 mg of synephrine), 300 mg of *Coleus forskohlii* extract (60 mg forskolin), 1000 mg of yerba mate and ~1400 mg of guarana (308 mg of caffeine). While persons with “uncontrolled hypertension” were excluded, the mean baseline blood pressures (supplement group: systolic blood pressure of 125.8 ± 13.7 mm Hg, diastolic blood pressure of 74.3 ± 10.9 mm Hg; placebo group: SBP of 128.8 ± 17.9 mm Hg, DBP of 78.6 ± 10.4 mm Hg) suggest that at least some subjects were hypertensive. The treatments were administered over a period of 8 weeks. There were no statistically significant differences in the changes in blood pressure or heart rate between groups. With respect to adverse events, the authors comment that there were no differences in the number of adverse events experience between groups, but the supplement group experienced 2 incidences of nausea and 1 incidence of urticaria that were considered possibly related to treatment. While this study does tend to support the safety of synephrine + caffeine in an overweight population, it is still limited by the relatively small study population, and the relatively short duration of study. The results cannot be used to justify long-term safety.

Sale et al. (2006) examined the acute effects of ingestion of a commercial formula containing extracts of Bitter Orange (synephrine 6 mg/dose), green tea and guarana (caffeine 150 mg/dose, catechin polyphenols 150 mg/dose) on the metabolic rate and substrate utilization in overweight, adult males (n=5 per treatment or placebo arm) at rest and during treadmill walking. Although systolic and diastolic blood pressure were consistently slightly higher in the treatment than in the placebo group, the differences were not significant for risks or benefits in this very small single-dose study.
Haller et al. (2008) studied the effects of Ripped Fuel Extreme Cut®, in healthy adults, after single dose of product, providing 21 mg of synephrine (from *C. aurantium*), 303.8 of caffeine (from green tea leaf, guarana seed and caffeine), 40 mg of niacin, 150 µg of biotin, 12 mg of pantothenic acid, and undeclared amounts of ginger root extract, cocoa seed extract, cayenne fruit, quercetin, wasabi extract, naringin complex, white willow bark extract, l-tyrosine, catuaba bark, and citrus bioflavonoids. The study was three-arm (test product + moderate-intensity exercise vs. test product + rest vs. placebo + exercise), double-blind, placebo-controlled crossover study. Diastolic blood pressure was statistically significantly increased in the test product + exercise group vs. placebo + exercise group. In these same groups, systolic blood pressure was reportedly elevated, but not to a statistically significant degree (P < 0.077).

Recently, Seifert et al. (2011) examined the acute hemodynamic effects of a supplement in 23 mildly overweight (overall BMI 26.6 ± 3.8) subjects, three of whom were pre-existing hypertensives (systolic blood pressure > 140 mm Hg). The study involved a placebo-controlled crossover design. Each product capsule provided 13 mg of synephrine (from a *C. aurantium* extract), 176 mg of caffeine, 55.5 mg of a green tea extract, 1 mg of bee pollen, 1 mg of white willow bark powder, 2 mg of *Panax ginseng* root, 2 mg of *Garcinia cambogia* extract and 0.15 µg of vanadium. Three capsules were taken on the day prior to examination, and the last capsule after a 12-hour overnight fast. Following the last dose, measurements were taken after a 60-minute relaxation period. There were no reported differences in heart rate, blood pressure or respiratory exchange ratio, in the treatment vs. placebo groups. A major limitation to this study is that the last dose was administered after a 12-hour fast. Given the clearance of synephrine and caffeine (the authors estimated 60 min. to maximal blood levels), the effects of the product, or lack thereof, should only be attributed to the last single dose of the product, and not all 4 doses over the preceeding 24 hours. Another limitation is that this study was done at rest, thus the effects the stimulant ingredients may have had in an excited state (e.g., such as when exercising) would not have been seen.

**Adverse Reaction Reports**

Case reports do not demonstrate causation or association but repeated co-occurrences can be considered signals used to generate hypotheses and potentially, to raise safety concerns.

Public and regulator concerns over reports of serious adverse reactions to products containing *Citrus aurantium* were triggered by an April 11, 2004, article in the New York Times citing an unidentified U.S. Food and Drug Agency spokesperson that there had been 85 adverse reactions and 7 deaths. By June of 2004 the FDA reports rose to 147 cases and by July 169 cases. However, subsequent investigations into these reports revealed that there were many apparent duplicates and very incomplete reports, at least 82 reports did not identify a Bitter Orange ingredient in the associated product but were products with ephedrine-containing ingredients, 40 were cases in which not only Bitter Orange but also caffeine was present, and only one adverse reaction report involved a product in which the only ingredient was Bitter Orange. In that case, there were three separate herbal formulas prescribed by a Chinese herbalist, not a commercial product, and there were several concomitiant prescription drugs that may have contributed to the
adverse effects (McGuffin 2004, 2006a). FDA’s Center for Food Safety and Applied Nutrition made some corrections to its adverse event reporting procedures for bitter orange following this miscalculation of the number of AERs tied to the ingredient (Anonymous 2004).

Stohs (2010a) reviewed 22 adverse reaction reports received by the FDA from April 2004 to October 2009 and the 10 clinical case reports from the literature involving adverse events associated with products labelled as containing Bitter Orange extracts or \( p \)-synephrine. Reported adverse events included acute lateral-wall myocardial infarction, exercise-induced syncope associated with QT prolongation, ischemic stroke, variant angina, ischemic colitis, coronary spasm and thrombosis, vasospasm and stroke, ST segment elevation myocardial infarction, ventricular fibrillation, and a suggestion of masking of bradycardia and hypotension while exacerbating weight loss in an individual with anorexia nervosa. Stohs’ conclusions were that “All products involved in these reports were poly-herbal and poly-alkaloidal in composition. The conclusion that BOE and \( p \)-synephrine are responsible for adverse events presented in these reports is unjustified, based on the presence of confounding factors, the paucity of detailed information in many reports, current knowledge of the pharmacokinetic and adrenoreceptor binding properties of \( p \)-synephrine, the high probability of concurrent but independent events, knowledge of dose–response relationships, and the widespread use of BOE containing supplements and \( p \)-synephrine containing juice and food products.”

Stohs (2010a), Stohs and Shara (2011), Stohs and Preuss (2011) and Stohs et al. (2011a) have noted that many of the products linked by the various authors to these case reports contained 5 to 12 alkaloidal and protoalkaloidal ingredients in addition to \( p \)-synephrine, including yohimbine and ephedrine, plus large doses of caffeine. Underlying conditions that may have contributed to the adverse events included morbid obesity, asthma, diabetes, hypertension, hyperlipidemia, heart attack, stroke, pneumonia, alcoholism, drug abuse, depression, anxiety, and nicotine use, as well as dehydration during use.

Rossato et al. (2011) have also recently reviewed the evidence for safety of synephrine. Stohs (2011) has criticized this review for its lack of clarity on \( p \)- versus \( m \)-synephrine as the active constituent of \textit{Citrus aurantium} and consequent relevance to assessment of adverse reaction reports, and for other weaknesses. Rossato (2011) replied to point out that adulteration of dietary supplements with \( m \)-synephrine has been reported by several authors so their discussion of this positional isomer is relevant.

Inchiosa (2011) has also recently reviewed the safety and efficacy of sympathomimetic agents for weight loss, including brief sections on synephrine and ephedrine.

Keeping in mind the comments of Stohs and colleagues, cited above, and the review by McGuffin, regarding the reliability of the adverse reaction case reports in the literature and from the FDA, the literature case reports and Health Canada’s domestic adverse reaction reports are nevertheless summarized below to present as complete a picture as possible of the information available upon which to base an assessment of the potential for synephrine alone or in combination with other substances to present risks to health.
Cardiovascular Adverse Reaction Case Reports from the Literature

A case report of myocardial infarct due to coronary spasm was reported in a 28-year-old male who was a heavy smoker, and abusing oxedrine (synephrine) tablets; the dose of synephrine was not disclosed (Keogh and Baron 1985). A case of unremitting tachycardia was reported in a 55-year-old woman, following a single dose of Bitter Orange for weight loss (500 mg Bitter Orange, standardized to 6% synephrine, providing 30 mg synephrine); the individual was also taking concomitant thyroxine (Firenzuoli et al. 2005). This case report suggests that even at doses of 30 mg synephrine, concomitant use with thyroxine may predispose certain individuals to adverse health effects.

In a case study involving Xenadrine EFX, Nasir et al. (2004) reported the possibility of the product being associated with exercise-induced syncope, associated with QT prolongation. A 22-year-old woman had taken Xenadrine EFX for 1 year, stopped for 3 months prior to the incident, and resumed her routine the day before the incident. She reported taking 1 tablet 45 minutes before running. Near the end of a 3.5-mile run, she reported feeling light-headed, sensing a rapid heart rhythm and then losing consciousness and falling. Examination in hospital revealed sinus tachycardia with QT prolongation, which normalized within 4 hours. A heart murmur was identified on admission, but further investigation revealed no evidence of valvular heart disease, normal ventricle size normal systolic function, normal wall thickness and no wall abnormalities. The following day, an exercise stress-test was administered and no cardiac abnormalities were observed. However, certain doubts of a causal association were raised by Hamilton (2005), who pointed out that the patient’s anion gap acidosis and ketosis are consistent with starvation, which may have contributed to the adverse event.

Gray and Woolf (2005) suggested that the adrenergic agonist properties of a C. aurantium (325 mg standardized to 6% synephrine alkaloids) + guarana (800 mg standardized to 22% caffeine) supplement may have masked bradycardia and hypotension while exacerbating weight loss in a 16-year-old woman with anorexia nervosa.

Bouchard et al. (2005) reported the occurrence of ischemic stroke, presumably of vasospastic origin, in a 38-year-old male who smoked 5 cigarettes per day but with no other major risk factors for atherosclerotic disease and no concomitant medications, who consumed 1-2 capsules of Stacker 2 Ephedra-free dietary supplement for one week prior to presentation. This multiple-ingredient product contains 6 mg synephrine and 200 mg caffeine per capsule. The authors concluded that the stroke was “probably secondary to synephrine.”

A case of possible myocardial infarction (MI) was reported in a 55-year-old woman following use of a Bitter Orange containing supplement (Nykamp et al. 2004). The supplement contained 300 mg Bitter Orange (dose of synephrine not disclosed), in addition to 250 mg carnitine, 400 µg chromium, 300 mg Citramax® (hydroxycitric acid, from Garcinia cambogia), 250 mg chitosan, and sources of caffeine including guarana seed extract (250 mg) and green leaf tea extract (30 mg). The amount of synephrine was not specified. Although the patient did not have an underlying history of hypertension, coronary artery disease, or hyperlipidemia, she did have a lesion in the left main coronary artery and had a history of 1.5 pack/day smoking habit. Synephrine was said to be possibly associated with this event.
A case report of variant angina involving the right coronary artery was reported in a 57-year-old male, following use of a Bitter Orange- and green tea-containing product for 35 days (1 tablet twice daily; 125 mg/tablet of a Bitter Orange and green tea proprietary blend) (Gange et al. 2006a). No previous adverse reactions were reported by the patient during prior use of the product, and the product was last taken 17 hours prior to the AR. The patient did have a history of hypertriglyceridemia, gastro esophageal reflux disease, and a 60-pack per year smoking history, but had quit 7 years previously. He denied illicit drug use, but did consume 3-4 alcoholic drinks per day. Medications included fenofibrate, omeprazole, aspirin, a multi-vitamin, vitamin B complex and vitamin E. A temporal link between the product and the adverse reaction was proposed by the authors; however, due to the gap in time between the last time the product was taken (17 hours previously), and the patient experiencing further chest pain 4 months after discontinuation of the product, the cardiovascular effects may not have been product-related. McGuffin (2006b) has criticized this report for attributing a causal relationship to the Bitter Orange peel extract (5% synephrine) which together with green tea leaf extract constituted 125 mg of a “Leptiplex” mix (thus perhaps 3 mg synephrine), when the product, CortiSlim, also contained chromium polynicotinate, vanadyl sulfate, magnolia bark extract, L-theanine, bamboo leaf extract, beta-sitosterol, calcium and vitamin C, and there were concomitant medications and regular alcohol consumption. Gange et al. replied (2006b) that the hypertension could be attributed to the subjects underlying factors of alcohol intake and obesity, but maintained that the dietary supplement may have exacerbated the variant angina.

A case report of acute myocardial infarct (MI) was reported in a bodybuilder, following use of a supplement containing synephrine, octopamine, tyramine and caffeine (Smedema and Müller 2008). The 39-year-old bodybuilder presented with new-onset angina pectoris and vegetative symptoms during a bodybuilding competition. The individual did not have any previous medical history or cardiovascular risk factors including atherosclerosis plaque, and denied using anabolic steroids. He had been taking the product for ‘several years’, and in the 3 months preceding the competition, had taken a daily dose of the product providing 40 mg synephrine, 400 mg caffeine, and unknown levels of octopamine and tyramine; the product also contained St. John’s Wort. The individual had also restricted fluid intake, and increased carbohydrate intake prior to the competition. The authors concluded that the MI was probably caused by a coronary spasm and thrombosis due to use of the product, in combination with dehydration and impaired renal function.

A case report of vasospasm and stroke was reported in a previously healthy 36-year-old woman, following the use of a synephrine- and caffeine-containing supplement (Xenadrine EFX) for purposes of weight loss ‘for a few months’ leading up to the AR (Holmes and Tavee 2008). The individual experienced right upper extremity weakness, difficulty speaking, in addition to facial droop and severe headache, 1 hour later. The neurological deficits resolved a few hours later, however, the headache persisted. There was no previous history of migraine headache, thrombophilia, hyperlipidemia, tobacco use, or oral contraceptive use. The only concomitant health product was an iron supplement. There was no pertinent medical history, or abnormal results from general and neurological exams, except for mild flattening of the right nasolabial fold. An MRI and MRA (magnetic resonance angiography) revealed a left middle cerebral artery infarct, consistent with a vasospasm. All other medical and laboratory exams were normal. Two weeks after discontinuation of the supplement, and intervention with aspirin, there was resolution.
of the vasospasm, and facial weakness completely resolved after 1 month. The authors suggested that the vasospasm and stroke was related to the use of the synephrine-containing product, given the lack of stroke risk factors, normal inflammatory market profile and resolution of the vasospasm after the supplement was discontinued.

Stephensen and Sarlay (2009) reported a case of ventricular fibrillation that they associated with use of a dietary supplement containing synephrine. However, the product, Lipodrene, has multiple other ingredients that may have contributed to the adverse reaction (Stohs 2010b).

Thomas et al. (2009) attributed a case of ST-segment-elevation myocardial infarction (STEMI) in a previously healthy 24 year old man to consumption of a dietary supplement, Nutrex Lip-6X and its constituent, synephrine. Stohs (2010c) pointed out that this multi-ingredient product contains at least 7 alkaloids and that the evidence does not support pharmacological properties of synephrine being similar to ephedrine. Thomas et al. (2010) replied that they agreed it is not possible to know with certainty the precise agent or synergistic interaction that caused the myocardial infarction in the subject but they still believed synephrine was the most likely cause.

Non-cardiovascular Adverse Reaction Case Reports from the Literature

Although Bitter Orange/synephrine-containing products have been predominantly associated with adverse cardiovascular reactions, a case report of ischemic colitis, as well as a case of rhabdomyolysis have been associated with use of two multi-ingredient Bitter Orange-containing products.

A case report of ischemic colitis was reported in a 52-year-old woman, following the use of a Bitter Orange-containing supplement for weight loss for 1 week leading up to the adverse reaction (Sultan et al. 2006). The product did contain other ingredients, including, per capsule, 300 mg Garcinia cambogia, 250 mg L-Carnitine, 250 mg Chitosan, and 200 µg chromium arginate (3 capsules per dose recommended); however, the authors posited that the other ingredients did not mediate these effects, and that the adverse event was due to synephrine’s vasoconstrictive effects resulting in decreased portal tributary blood flow, which has been observed with synephrine in a rat model of portal hypertension (Huang et al. 2001).

A case of rhabdomyolysis was reported in a previously healthy obese 22-year-old male with sickle cell anaemia, following his use of a synephrine- and caffeine-containing dietary supplement (Burke et al. 2007). The patient presented with fatigue, light-headedness and myalgia, which developed during an exercise test, and was diagnosed with exercise-induced rhabdomyolysis with heat exhaustion. Several weeks later, the patient resumed the exercise tests without medical clearance, and experienced a second episode of rhabdomyolysis and heat exhaustion while running. He presented with hypotension, tachycardia, tachypnea, and myalgia. The individual also experienced muscle hypoxia and ischemia. The patient further developed hypovolemic shock, respiratory failure and acute renal failure. Despite extensive medical intervention, the patient sustained permanent bilateral sensory and motor neurological deficits in both distal lower extremities. Following the second episode of rhabdomyolysis, the patient admitted to the use of a synephrine and caffeine-containing supplement twice daily during the last 3 months leading up to the AR; the product also contained yohimbine HCl. Reports of
rhabdomyolysis have been associated with large doses of caffeine; the contribution of synephrine in this case report is unclear, as no other reports of rhabdomyolysis have been documented to be associated with synephrine. Confounders in this case report include the sickle cell anaemia trait and intense physical exercise in a warm climate.

*Canadian Domestic Adverse Reaction Case Reports*

From January 1, 1998, to March 31, 2008, Health Canada received 61 domestic case reports of adverse reactions suspected to be associated with Bitter Orange (*Citrus aurantium*)- and synephrine-containing natural health products. At the time of the initial causality assessments, only 51 reports had been entered into the Canada Vigilance database. Of these 51 reported cases, 44 were assessed for causality; 18 out of the 25 adverse reactions reported from 1998–2004 were reviewed based on suspected cardiovascular adverse reactions. Post-2004, all adverse reaction reports associated with Bitter Orange/synephrine were reviewed.

Of the 44 analyzed reports:
- Bitter orange/synephrine was noted to be typically part of a multi-ingredient formulation, most often for the indication of weight loss;
- 35 of the 44 case reports were cardiovascular in nature, of which 27 were classified as “serious”. An additional report of “chest pain” was assessed as “serious”; however, its cardiovascular origin was not assessable;
- 2 out of the 44 case reports had “death” as an outcome, 20 cases had “recovered without sequelae”; 2 cases “recovered with sequelae”; 1 “not yet recovered”, and 19 cases had outcome as “unknown”;
- The 2 fatal case reports involved a 21 year-old male and a 29 year-old female. Both of these cases were associated with Bitter Orange/synephrine-containing products that also contained *Ephedra*/ephedrine and caffeine. Causality for these cases has been assigned “possible” for synephrine’s contribution;
- 3 of the 44 cases involved misuse (abuse or suicidal attempt);
- 10 of the 44 cases had Bitter Orange/synephrine with concomitant *Ephedra*/ephedrine and caffeine ingredients. Causality for these cases was assigned as “possible” for synephrine’s contribution to the adverse events;
- 33 of the 44 cases had Bitter Orange/synephrine with concomitant caffeine or sources of caffeine (without *Ephedra*/ephedrine) in the suspect product(s). Causality for these cases has been assigned as follows: 30 “possible”, 1 “probable”, 1 “unassessable”, 1 “unlikely” for synephrine’s contribution to the adverse events;
- The causality for the role of synephrine was “possible” in most case reports. It was not “probable”, since almost all of the suspect products contained Bitter Orange/synephrine in combination with sources of caffeine;
- Only one case can be identified as having synephrine without concomitant *Ephedra*/ephedrine alkaloids or caffeine. Causality for this case has been assigned as “probable” for synephrine’s contribution to the adverse events. This case involved a 43 year old patient (gender not specified) who developed tachycardia and dyspnea after having ingested 4 doses of Slim Essentials Weight Loss Formula over a period of 3 days. The patient required 3 days of hospitalization. The clinical events in this case had a positive temporal relationship, and positive dechallenge. The patient had no prior history of coronary artery
disease, no concomitant medications and the laboratory and thallium test were reported normal in hospital;

- In 14 of the 44 cases, the standardized level of synephrine in the Bitter Orange products was specified but the actual dosage of Bitter Orange was not reported, so the dose of synephrine cannot be calculated;

- The nature of the cardiovascular adverse reactions associated with Bitter Orange/synephrine were variable: tachycardia, hypertension, syncope, breathing difficulty, chest pain, ventricular fibrillation, cardiac arrest, and death. For Bitter Orange-containing NHPs, 46.2% of reported reactions involved gastrointestinal disorders, followed by 42.3% nervous system disorders, 34.6% general disorders and administration site conditions, and 30.8% cardiac disorders;

- In terms of demographics, as weight loss is the predominant indication of the suspect products, the main at risk population are women (29 out of the 44 cases involved women, 14 involved men; in 1 report, gender was not specified), and young adults (19 cases involved patients in the 20s; age ranged from 16-64 years old).

A recent search of the Canada Vigilance databases has indicated that there have been 5 new adverse reaction case reports for products containing caffeine and synephrine (excluding ephedra) have been identified since March 31, 2008. Only one of the adverse reactions is cardiovascular in nature (chest pain), but this was associated with Slimming Coffee, which was subject to a Public Warning on January 14, 2010, as it was adulterated with sibutramine. The other four adverse reaction reports, all from multi-ingredient products, included: rhabdomyolysis (CPK > 10,000) associated with Green Tea Fat Burner; seizure (new onset) associated with Thermo-lean; increased liver function tests associated with Greens + and Xenadrine; and allergic reaction associated with Happy Planet Shots-Energy and Glow. This recent search does not provide additional information for cardiovascular risk assessment with respect to synephrine-containing products.

Potential Citrus aurantium/Synephrine – Drug Interactions

Fugh-Berman and Myers (2004) cited a potential for drug interactions between Bitter Orange and drugs based on the ability of C. aurantium juice to inhibit the key cytochrome P450 drug metabolizing enzyme CYP3A4 in the intestinal wall. Bitter Orange juice was found to contain furanocoumarins such as bergamottin at 5 µM/L and 6',7'-dihydroxybergamottin at 36 µM/L, which are potent CYP3A4 inhibitors, and Bitter Orange juice did interact with the model CYP3A4 substrate felodipine (Malhotra et al. 2001). C. aurantium has been shown in vitro to inhibit CYP3A4 (Guo et al. 2001). However, comparing juice consumption with dietary supplement use may not be appropriate, nor is directly relating effects from intravenous administration to oral administration (Dentali 2005). Fugh-Berman and Myers (2005) replied to Dentali that furanocoumarins are present in the rind and so would be expected to be found in rind extracts. Phytochemical analysis of dietary supplements containing C. aurantium found no detectable 6',7'-dihydroxybergamottin, probably due to the commercial method of extraction with water in which these furanocoumarins are extremely poorly soluble, and an in vivo assessment in 12 healthy volunteers treated for 28 days found no changes in the enzymes CYP3A4, CYP1A2, CYP2E1 or CYP2D6 (Gurley et al. 2004). Therefore, in contrast to the
juice, dietary supplement extracts of *C. aurantium* are not likely to cause any clinically significant interaction with drugs through the cytochrome P450 system.

However, the physiological effects of Bitter Orange and its phenylpropanoid constituents may be exacerbated by monoamine oxidase inhibitors (MAOIs), potentially causing hypertension. Synephrine, as well as octopamine and tyramine, are MAO substrates (Suzuki et al. 1979; Visentin et al. 2001). The mechanism depends on the mode of action of the sympathomimetic: with a predominantly direct-acting sympathomimetic such as phenylephrine (subject to gut wall metabolism by monoamine oxidase), MAOIs increase absorption (Elis et al. 1967); with indirect-acting sympathomimetics, MAOIs increase the amount of NE stored in adrenergic nerve endings (Sweetman 2007). Interactions may also occur with tricyclic antidepressants since they block the inactivation of epinephrine and NE by uptake into the nerve endings and may increase their effect; hypertension and arrhythmias may occur (Sweetman 2007).

Elevated thyroid hormone concentrations may enhance adrenoceptor sensitivity (Sweetman 2007). Larger doses of thyroid hormone may produce serious or even life-threatening manifestations of toxicity when given in association with sympathomimetic amines (Genpharm 2005). Firenzuoli et al. (2005) reported unremitting tachycardia in a patient taking *C. aurantium* (30 mg synephrine daily) and thyroxine; the tachycardia resolved upon de-challenge and recurred upon re-challenge a month later. The arrhythmia again resolved upon discontinuation of Bitter Orange. A report of cardiac arrest in a 29-year old woman taking a synephrine-containing product and Synthroid was also received by Health Canada in 2002 (Health Canada 2007).

**Exposure**

Citrus fruit is the only potential dietary source of synephrine (Wheaton and Stewart 1970). Frozen concentrated orange juice may contain up to 5% Bitter Orange juice by volume (FDA 2010b). Synephrine occurs naturally in citrus juices at concentrations of 2 mg/L in Meyer lemon, 11 mg/L in rough lemon, 20 mg/mL in sweet lemon, 15 to 30 mg/L in several varieties of sweet orange juice, 27 to 43 mg/L in temple orange, 46 mg/L in the Orlando variety of tangelo, 50-52 mg/mL in Murcott orange, 58 mg/L in the Robinson variety of tangerine juice, 97 to 152 mg/L in the Dancy variety of tangerine juice, 73 to 158 mg/L in Satsuma mandarin, and 280 mg/L in Cleopatra mandarin orange juice. Synephrine is below quantification limits in common lemon, lime, and grapefruit juices (Stewart and Wheaton 1964; Wheaton and Stewart 1965; Dragull et al. 2008). The concentration of synephrine is highest in immature citrus fruits and decreases proportionally with increasing diameter of the fruit as they mature (Hosoda et al. 1990).

A typical dose used in TCM, for example in the Jianpi Wan formulation is 1.25 g dry herb (peel) per day (PPRC 2000) which at a concentration of ~0.25% of synephrine, would amount to 3.1 mg/day. The dose of dried fruit in decoctions ranges from 3-10 grams/day (Blumenthal 2004-2005).

In modern European herbal medicine, Bitter Orange peel is used at a dose of 4-6 g, 2-3 g in tincture, and 1-2 g in extract (Blumenthal 1998).
Bitter Orange extracts naturally contain up to 4% synephrine. Commercially available extracts commonly contain 4%, 6%, 10% or ≥ 30% synephrine; some manufacturers boost the synephrine content to 90-95% (Masten 2004; FDA 2005; NDPSC 2003).

Gregory (2007) found that of 36 dietary supplements marketed as “ephedra-free,” 32 (89%) contained a methylxanthine such as caffeine or theobromine, 21 (58%) contained synephrine, and 20 (56%) contained both a methylxanthine and synephrine. Avula et al. (2005) found that in dietary supplements claiming to contain *Citrus aurantium*, there were significant differences in their composition and that in 6 of the 8 products where the quantity of Bitter Orange herb or extract was listed (85 to 900 mg), that quantity did not correlate with the content of synephrine even though it was the major amine present. The highest concentration of synephrine seen was 18.62% and the lowest concentration was 0.073%. N-methyltyramine was detected in the range of 0.13% to 0.16% in six of the products. Trace levels of octopamine were detected in four of the products, traces of tyramine in two, and traces of hordenine in three.

NMCD (2011) lists 537 dietary supplements containing Bitter Orange but many of these are cosmetics with orange oil and TCM products not relevant to this analysis. Of the weight loss or body building types of dietary supplements, many avoid specifying the content of Bitter Orange, synephrine, caffeine or other ingredients by listing a “proprietary blend” where ingredients are named but not quantified. Where quantities were provided, the dose of Bitter Orange ranged from 20 mg to 5500 mg, the dose of synephrine according to the labels ranged from 3 mg to 72 mg, and the dose of caffeine ranged from 16 mg to >1000 mg. Common ingredients that are additional sources of caffeine included green tea, kola, guaraná, maté, and cacao, often standardized to methylxanthines (caffeine, theophylline, theobromine). Some products contained octopamine at 100 mg or 200 mg per dose. NMCD applied a blanket cautionary statement to all Bitter Orange containing products, whether or not there was any evidence for the presence of synephrine.

Products of this type investigated by Health Canada have generally contained a similar range of active ingredients. The product providing the highest dosages seen so far is Thermonex, for which the labelled maximum daily dose provides 1000 mg anhydrous caffeine plus green tea extract (1500 gm) and yerba maté (800 mg), 800 mg octopamine HCl, 80 mg synephrine, 200 mg naringin, 160 mg of the cardioactive alkaloid evodiamine, plus the thyroid action modulating ingredients L-tyrosine (1200 mg), iodotyrosine (400 µg) and diiodotyrosine (400 µg). Health Canada issued a Public Health Warning regarding this product in May of 2004 (Health Canada 2004).

Stohs (2010a) estimates that more than 100 million doses of products containing Bitter Orange extract or *p*-synephrine have been consumed in the U.S. in the past 15 years.

Synephrine has been marketed as a drug under the name Oxedrine since 1927 (Haaz et al. 2006). It is a sympathomimetic given as the tartrate in the treatment of hypotensive states in doses of 100 to 150 mg three times daily by mouth; it has also been given by subcutaneous, intramuscular, or intravenous injection. Oxedrine is also used in eye drops as an ocular decongestant, usually as the tartrate in a concentration of 0.5% in combination preparations. The hydrochloride has also been used. Currently marketed single ingredient preparations include:
Sympatol (Germany, Italy), Sympalept (Switzerland), Sympathomim (Hungary), Ocuton (Hong Kong). Currently marketed multi-ingredient preparations include Dacrin and Pasuma-Drages (Austria), Dacryne, Dacryboraline, Polyfra, Posine, and Sedacollyre (France) (Pharmacopoeia Site 2011). Oxedrine tartrate is not marketed in the United States or Canada. Note that Sympatol is racemic \( p \)-synephrine tartrate in which the natural (\(-\))-enantiomer of \( p \)-synephrine comprises 34.5% of the dose, i.e. 100 to 150 mg of Sympatol supplies 34.5 to 51.8 mg of (\(-\))-\( p \)-synephrine (Inchiosa 2011).

**Risk Characterization and Classification**

*Citrus aurantium Peel*

Based on the conditions of use in foods and traditional medicines, and the exposure from these products which are readily available in the Canadian market, it is highly unlikely that the botanical material, Bitter Orange peel, *Citrus aurantium*, and its natural content of \( p \)-synephrine (e.g. up to approximately 4%), will pose any risk whatsoever to the health of Canadian consumers.

*p*-Synephrine Alone

With respect to \( p \)-synephrine in single ingredient natural health products (dietary supplements) for weight loss and body composition management, the risk of cardiovascular adverse effects in healthy people has been overstated in the literature and probably incorrectly linked causally to case reports. While \((\pm)-p\)-synephrine tartrate has been used successfully to treat hypotension in the dose range of 300 to 450 mg/day (equivalent to approximately 100 to 150 mg of \((-)\)-\( p \)-synephrine/day), clinical trials in healthy humans subject to acute to subchronic dosing (14 days) at up to 50 mg/day \( p \)-synephrine have generally not shown any significant increase in blood pressure or other cardiovascular effects. Receptor binding assays have shown that \( p \)-synephrine has a low affinity, very low potency partial agonism at \( \alpha_{1A} \)-AR and partial antagonism at the \( \alpha_{2A} \)- and \( \alpha_{2C} \)- ARs (30 to 1,000 fold less active than NE) responsible for vasoconstriction, and \( p \)-synephrine has extremely weak partial agonism at \( \beta_1 \)-ARs (40,000 fold less active than NE) responsible for increased heart rate. Therefore, in contrast to ephedrine, at typical supplement doses which are much lower than the hypotension therapeutic dose, \( p \)-synephrine is not likely to trigger cardiovascular adverse events in healthy individuals.

*p*-Synephrine and Caffeine

The risk of cardiovascular adverse events is more difficult to assess due to the fact that most clinical studies have used multi-ingredient products rather than just synephrine plus caffeine. There is some evidence that caffeine may potentiate adverse effects from synephrine. At high doses caffeine itself can trigger cardiovascular adverse events and may be the ingredient most likely linked causally to some of the adverse reactions in the case reports. In the clinical studies the dose of synephrine ranged from 6 mg to 59 mg and the dose of caffeine ranged from 150 mg to 528 mg. While there is up to 6 weeks exposure evidence for the safety of combinations of synephrine up to 50 mg plus caffeine up to 528 mg, and the human body may be able to
accommodate to the combined effect as has been seen for the combination of ephedrine plus caffeine, most of the studies have been acute dosing in healthy populations and it is likely that the risk of cardiovascular adverse events increases as levels of caffeine exceed Health Canada’s recommended maximum daily intake for adults of 400 mg from all sources. To account for dietary sources of caffeine, a reasonable risk mitigation approach is to limit the dose of caffeine in natural health products to 80% of the recommended daily maximum for adults, i.e. 320 mg/day. Given the limited evidence for safety beyond six weeks and the likelihood that weight loss products will be taken for longer than six weeks, coupled with the evidence of a potential synergy between synephrine and caffeine, it would be consistent with the majority of the available clinical trial evidence on \( p \)-synephrine plus caffeine combinations to apply an 80% threshold for synephrine too. This would result in a reasonable level of confidence in the safety, without unnecessarily compromising potential efficacy, of a combination of 40 mg of \( p \)-synephrine plus 320 mg of caffeine. Such a recommendation does not preclude the submission of evidence for higher doses or longer durations for assessment in a product licence for market authorization in Canada.

\( p \)-Synephrine, Caffeine and Other Stimulants
In the majority of adverse reaction case reports involving products that contain Bitter Orange or synephrine, other potential stimulants in addition to caffeine are present, including octopamine, tyramine, N-methyltyramine, hordenine, ephedrine, yohimbine, thyroid stimulating agents such as iodotyrosine, etc. The likelihood of a risk to the health of consumers increases significantly with the presence of these additional ingredients which may more probably be linked causally to the adverse event than the \( p \)-synephrine content (Stohs and Shara 2011). Such products need to be assessed for their risk to health on a case-by-case basis, with a clear understanding of the unique pharmacology of each ingredient rather than assumptions of similar structures providing similar activities.

Octopamine
Due to its specificity for the \( \beta_3 \)-AR but low potency and very poor bioavailability, octopamine is not likely to cause any serious adverse consequences at the doses studied clinically (e.g. 5 mg) but its effects at doses of 100 mg or more are unknown.

Susceptible Subpopulations
In addition to the standard susceptible subpopulations of children and pregnant or breastfeeding women, there are some other subpopulations likely to be at great risk from combinations of synephrine, caffeine, and other stimulants.

According to Eckel et al. (2005), overweight individuals are susceptible to developing metabolic syndrome: a multi-faceted disease, characterized by glucose intolerance (e.g., type 2 diabetes, impaired fasting glycemia), insulin resistance, central obesity, dyslipidemia, and hypertension. When taken together, these pathologies are associated with an increased risk of cardiovascular disease. It is difficult to estimate the prevalence of metabolic syndrome due to the various definitions used to characterize the syndrome; though the prevalence may be \( \sim 24\% \) in American
men, though varying by ethnicity and age. The syndrome has been classically seen as an adult’s disease; but with the increasing prevalence of obesity in young people, the syndrome may be evident even in young children. Reportedly, “each half-unit increase in [Body Mass Index] was associated with an increase in the risk of the metabolic syndrome in overweight and obese people (odds ratio 1.55)” (Eckel et al. 2005).

The prevalence of hypertension in an overweight population is of special concern with respect to sympathomimetic stimulant use, as these people do not respond to pressor agents as healthy individuals do (Fugh-Berman and Myers 2004). In the setting of metabolic syndrome including insulin resistance, it should be noted that insulin acts as a vasodilator in healthy individuals; therefore, the absence of a vasodilatory effect due to insulin resistance, coupled with a vasopressor effect provided by the sympathomimetic agent(s) may result in a further elevation in blood pressure (Eckel et al. 2005). There is evidence to suggest that individuals with essential hypertension demonstrate increased alpha adrenergic vasoconstriction, compared to normotensive controls. Egan et al. (1987) compared 24 overweight, hypertensive men (mean systolic blood pressure of 145 ± 3; mean diastolic blood pressure of 100 ± 2) against 18 overweight, normotensive men (mean SBP: 122 ± 3; mean DBP: 78 ± 2). After intravenous injection of norepinephrine, it was found that the hypertensive participants demonstrated a statistically significant greater response in forearm vascular resistance. As synephrine is a known vasoconstrictor with alpha adrenergic activity, the pressor responses to synephrine could be elevated in sensitive, overweight individuals consuming weight-loss products.

Overweight individuals are at an increased risk of having these metabolic disorders and may not have been previously diagnosed. In addition, weight-loss products would likely be taken long-term— at least for periods longer than are used in the clinical studies used to support safety of synephrine, alone or in combination with other stimulants. For instance, the resulting chronic sympathetic stimulation could theoretically lead to a progressive deterioration of health, as would long-term hypertension.

Other vulnerable populations would be those consumers being treated with monoamine oxidase inhibitors or thyroid medications, as they will be particularly susceptible to substances that may affect pressor responses. Since synephrine has limited affinity and potency at implicated receptors, this is more likely to occur via its effects on the NE transporter stimulating NE release.

**Risk Classifications**

*Citrus aurantium* Peel
Based on the evidence reviewed above, the botanical material Bitter Orange peel, at the doses typically used in herbal medicine and food, is not considered to pose any risk to the health of consumers.

*p-Synephrine Alone*
At doses up to 50 mg/day in healthy adults, *p*-synephrine is classified as Type III, meaning that the use of, or exposure to, a single-ingredient *p*-synephrine product under these conditions is not
likely to cause any adverse health consequences, except in cases where the necessary cautionary statements (i.e. contraindicated in children, pregnancy, and breast-feeding, do not use if you are taking blood pressure medications (either hypertensives or antihypertensives), thyroid medications, sympathomimetics, or monoamine oxidase inhibitors (MAOIs)) are lacking, which would result in a risk classification of Type II. The definitions of Type II and III are set out in the Health Products and Food Branch Inspectorate - Recall Policy (POL-0016) (Health Canada 2006).

At doses above 50 mg/day, p-synephrine approaches the dose used as a prescription drug in Europe for the treatment of hypotension. While it is possible to be exposed to a dietary source of as much as 70 mg of p-synephrine from a cup of Cleopatra mandarin orange juice, this is not a common item in the diet and the dose-response curve for p-synephrine between 50 mg and therapeutic doses of the racemic tartrate are not adequately characterized to be categorical as to safety. Therefore, in the absence of a product-specific review of safety under specific recommended conditions of use, as would be accomplished through assessment of a product licence for market authorization, the application of precaution is a legitimate decision making approach within risk management. Such unauthorized products are therefore classified as a Type II risk to health, meaning that the use of, or exposure to, such a product may cause temporary adverse health consequences or where the probability of serious adverse health consequences is remote (Health Canada 2006). A “serious adverse reaction” means a noxious and unintended response to a natural health product that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death (Government of Canada 2011).

p-Synephrine and Caffeine
Products providing 40 mg/day or less of p-synephrine plus 320 mg/day or less of caffeine, are classified as Type III, except in cases where the necessary cautionary statements (i.e. contraindicated in children, pregnancy, and breast-feeding, do not use if you are taking blood pressure medications (either hypertensives or antihypertensives), thyroid medications, sympathomimetics, or monoamine oxidase inhibitors (MAOIs)) are lacking, which would result in a risk classification of Type II (Health Canada 2006).

Products exceeding either threshold dose or products lacking the cautionary statements (i.e. contraindicated in children, pregnancy, and breast-feeding, do not use if you are taking blood pressure medications (either hypertensives or antihypertensives), thyroid medications, sympathomimetics, or monoamine oxidase inhibitors (MAOIs)), are classified as a Type II risk to health.

p-Synephrine, Caffeine and Other Stimulants
Such products have been implicated in many serious adverse reaction case reports. Causality is not likely due to the p-synephrine content on its own, rather to other ingredients such as octopamine in high doses or thyroid drugs such as iodotyrosine. The risk to human health must be assessed on a case by case basis. Given the nature of the observed adverse reactions, it is
probable that some of these products will be assessed as posing a Type I risk to health, meaning that there is a reasonable probability that the use of or exposure to such a product will cause serious adverse health consequences or death (Health Canada 2006).

\textit{\textbf{p-Octopamine}}

Based on its known pharmacology, \textit{p}-octopamine at doses up to 50 mg/day in healthy adults is classified as Type III. At doses above 50 mg/day, due to the paucity of human clinical data, in the absence of a product-specific review of safety under specific recommended conditions of use, as would be accomplished through assessment of a product licence for market authorization, the application of precaution is a legitimate decision making approach within risk management. Such unauthorized products are therefore classified as a Type II risk to health.

\textbf{Exacerbating Conditions}

Due to the extremely limited evidence for the safety of chronic use of \textit{p}-synephrine alone or in combination with caffeine or other ingredients in vulnerable subpopulations, the following cautionary statements (or words to these effects) should be on product labels to mitigate the risk of potentially serious adverse reactions:

- \textit{Contraindicated in children, pregnancy, and breast-feeding.}
- \textit{Do not use if you are taking blood pressure medications (either hypertensives or antihypertensives), thyroid medications, sympathomimetics, or monoamine oxidase inhibitors (MAOIs).}

\textbf{Recommendations for Managing the Risk}

\textit{\textbf{Consistency of Approach with Previous NHP HRAs}}

The recommended Health Risk Classification criteria above are consistent with the Health Risk Assessments (Health Hazard Evaluations) previously prepared by Health Canada with respect to the products Thermonex (Type I, 2004-04-13), Slim System 8 (Type II, 2004-12-20), No. 1 Protocole Minceur (Type III, 2005-06-10), MetaSlim (Type III 2006-02-22), Synerate (Type I, 2010-12-31), and Lipo-6X (Type I, 2011-01-25).

\textit{\textbf{Consistency of Approach with Similar Drugs}}

Sympathomimetic agents have a poor history of long-term success in the treatment of obesity. From earlier experiences with amphetamine and its analogs, to more recent drugs with direct effects on adrenergic receptors or indirect effects from release of catecholamines or inhibition of reuptake, cardiovascular toxicity (strokes and cardiac arrhythmias) has been the major concern (Inchiosa 2011). For example, the European Medicines Agency on January 1, 2010, advised against continuing to prescribe sibutramine based on serious cardiovascular adverse reactions (Inchiosa 2011). Health Canada (2010a,b) and the FDA (2010c) also saw the voluntary withdrawal of all marketed sibutramine drugs for that reason. Thus, it was appropriate to
thoroughly assess the potential risks to health of \textit{p}-synephrine alone and in combination with caffeine and other stimulants, particularly considered the large number of reported adverse reactions but poor quality of those reports.

\textbf{Limits for Synephrine in Other Jurisdictions}

The Therapeutic Goods Administration (TGA) has established a 30 mg total daily dose for synephrine (synonym oxedrine) content in OTCs (NDPSC 2003). The 30 mg limit, which was also adopted by New Zealand (Medsafe 2003), was based on the therapeutic dose for oxedrine tartrate for hypotension as described in Martindale of 100-150 mg three times daily (Sweetman 2007). The National Drugs and Poisons Schedule Committee found little evidence of harmful effects at dosage levels of 30 mg per day or less, in divided doses, and considered a 10-fold safety factor to be an adequate safety margin. Members highlighted that there was sufficient evidence to suggest the significant potential for oxedrine to cause cardiotoxicity at low dose levels. Furthermore, the Committee also noted that a 28-year old Australian man suffered a large myocardial infarction while abusing oxedrine tablets, although no data on the dosage level was provided in the case report. In consequence to the cut-off limit of 30 mg/day, an entry in Schedule 4 of the \textit{Standard for the Uniform Scheduling of Drugs and Poisons} (now the \textit{Standard for the Uniform Scheduling of Medicines and Poisons}) has been included: “Oxedrine [synephrine] for human internal use except in preparations labelled with a recommended daily dose of 30 mg or less of oxedrine.” Schedule 4 includes ingredients intended for use by prescription only (Poisons Standard 2010).

The Food Safety Commission of Malta also permits a 30 mg maximum per day in foodstuffs (corresponding to 800 mg \textit{C. aurantium} with 4\% synephrine); foodstuffs exceeding this dose must be sold from a pharmacy. The content of synephrine must be stated on the label along with a warning against use by patients with cardiovascular disease and/or hypertension, and recommendations not to be used during pregnancy or lactation or by children under 12 years (Government of Malta 2007).

The Italian Ministry of Health also uses a limit of 30 mg synephrine and requires that the label state the synephrine content at the advised dosage as well as warnings against use in the presence of cardiovascularopathies and/or arterial hypertension (Mattoli et al. 2005).

\textbf{Conclusion/Risk Management Strategy}

There are a number of limitations that are common to all the available clinical studies, including:

- The sample sizes of the studies are extremely small. Although the possible cardiovascular effects to products in this class are potentially very serious, they are also fairly rare. The available studies are not sufficiently broad in scope to support the safety in a general consumer population, especially when the population targeted for these products consists of largely overweight/obese individuals, who are subject to various co-morbidities. This limitation is inherent to all available randomized, controlled trials. In effect, appropriate
evidence for safety, especially for rare adverse events, should come by way of sufficient 
epidemiological studies;

- In addition to the limited sample sizes, the study populations are also generally healthy, even 
  if some studies include overweight individuals. This adds further to the incomparability of 
  available studies and extrapolation to the general population;
- None of the studies include a justification for their sample sizes, nor an indication of power. 
  This is a critical oversight, as it calls into question all of the findings. Lack of an effect could 
  very well be a genuine lack of an effect, or simply an inability to detect an effect;
- The studies are all of very short duration – another inherent deficiency seen when using 
  randomized, controlled trials to support safety. As the nature of the cardiovascular events 
  could depend on long-term exposure (e.g., chronic sympathetic over-stimulation), the short-
  term studies are not adequate to support long-term safety. The authors of Seifert et al. (2011) 
  comment that, “longer term studies are required to assess [the effects on heart rate and blood 
  pressure] under conditions similar to those encountered when using the product in 
  conjunction with a long term weight loss program.”

In summary, this Health Risk Assessment does not address the issue of efficacy, which must be 
assessed through the product licensing process for each individual product.

However, based on new clinical studies and published reviews of safety information, it has been 
possible to revise the synephrine and caffeine recommendations prepared previously by Health 
Canada (2010c) in order to reduce unnecessary compliance actions on products that do not 
present as serious a risk to health as had been judged previously. This will allow resources to be 
focused better on compliance and enforcement of more risky products.

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