

Risk assessment of oxedrine in foods intended to promote weight loss

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Executive summary

A range of foods that are intended to promote weight loss were tested in an analytical survey to ascertain if they contained any pharmaceuticals that are normally only prescribed by qualified medical practitioners. The survey was conducted as a scoping exercise in response to a number of reports internationally showing detectable levels of scheduled pharmaceuticals such as sibutramine and phenolphthalein in foods and supplements intended to promote weight loss.

No pharmaceutical drugs were found in 34 of the 36 products tested. Two products contained oxedrine (synonym: synephrine) equivalent to a dose of 13 and 39 mg, respectively, when taken at the recommended daily intake listed on the product labels. Oxedrine is listed in schedule S4 (Prescription only medicines) of the 'Standard for the Uniform Scheduling of Medicines and Poisons' with a cutoff for preparations labelled with a recommended daily dose greater than 30 mg. Both products list bitter orange (*Citrus aurantium*) or bitter orange extract as ingredients. Bitter orange and other citrus species naturally contain oxedrine at levels up to 0.2% in the fruit.

Concerns have been raised regarding the safety of oxedrine in bitter orange extracts due to potential adverse effects on the cardiovascular system, as documented in several published case reports. These case reports are difficult to interpret because there is a lack of information on levels of oxedrine and confounding from potential effects due to other ingredients in the products. A causal relationship has not been established between the consumption of bitter orange extracts and adverse cardiovascular effects.

The weight of evidence from seven clinical studies on bitter orange extracts, resulting in oxedrine doses of up to 98 mg/day, indicates no concern for potential adverse effects. In a double-blind, placebo-controlled clinical trial of 60 days duration, ingestion of a bitter orange extract, resulting in an oxedrine dose of 98 mg/day (the highest dose tested in published clinical studies), gave no adverse effects. No effects on blood pressure or heart rate were observed.

Dietary exposure to oxedrine from the consumption of citrus fruits and their products (e.g. juices and jams) has been estimated for French and German populations. Oxedrine dietary exposure for mean and high level consumers of citrus fruits and products was estimated to

be 6–7 mg/day and 20–26 mg/day, respectively. Dietary exposure to oxedrine from citrus consumption in Australia/New Zealand populations was estimated using oxedrine concentration data from the French study and Australian or New Zealand food consumption data. Estimated oxedrine dietary exposure for mean and high level consumers of citrus fruits and products was 0.5–14 mg/day and 1.3–35 mg/day respectively across both countries. Additional dietary exposure resulting from consumption of the weight loss product providing the highest daily dose of oxedrine (39 mg/day) would not be expected to result in total dietary exposure exceeding 98 mg/day, a dose that resulted in no effects in a double-blind, placebo-controlled clinical trial of 60 days duration.

It is concluded that the highest oxedrine level determined in a FSANZ analytical survey of foods intended to promote weight loss does not indicate a public health and safety concern.

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1. Introduction

1.1 Background

FSANZ has conducted an analytical survey of foods that are intended to promote weight loss to ascertain if they contained any scheduled pharmaceuticals or their analogues. The survey was undertaken as a scoping exercise to determine whether scheduled pharmaceutical compounds were likely to be present in foods intended for weight loss available in Australia.

The analytical survey is a follow-up to an Implementation Subcommittee for Food Regulation (ISFR) research paper prepared as a part of the ISFR Coordinated Food Survey Plan (CFSP). The research paper noted that there had been a number of international reports indicating that scheduled pharmaceuticals had been reported in foods and supplements intended to promote weight loss. Overall the research paper found that:

- a variety of food and beverage products are marketed in Australia as slimming, or for weight loss purposes
- pharmaceuticals have been reported internationally in over 200 weight loss products, either in foods or beverages, or in capsule and tablet form
- sibutramine and phenolphthalein were the most commonly identified undeclared pharmaceutical ingredients in weight loss products.

1.2 Conduct of the study

A total of 36 products consisting of powders (25 products), pre-mixed drinks (7 products) and bars (4 products) were purchased from supermarkets, pharmacies and sports stores in the Australian Capital Territory (ACT) in April 2015. Regional sampling was not considered necessary as these foods are national foods available throughout Australia and no regional variability in food composition is anticipated.

Preparation and analysis of samples for approximately 500 pharmaceutical compounds and analogues was performed by the Therapeutic Goods Administration (TGA) using ultra high performance liquid chromatography (UPLC) with photo diode array (PDA) detection. The UV spectra and retention time were matched against a library with defined matching parameters and identification was confirmed using gas chromatography or liquid chromatography.

The vast majority of compounds added to the library have been run at an equivalent of 10 ppm when compared to a sample dilution of 1 in 20.

A system suitability solution was run with each analysis to assure acceptable retention time and library matches are achieved for the system suitability compounds, and criteria for peak shape are also assessed.

1.3 Results

No pharmaceutical drugs or analogues were found in 34 of the 36 products tested. Two products contained oxedrine (synephrine¹) at levels which would result in doses of 13 and 39 mg, respectively, when taken at the recommended daily dose listed on the product labels. The labels on both products list bitter orange (*Citrus aurantium*)² or bitter orange extract as ingredients.

¹ The term oxedrine, as used by the TGA, is used throughout this document. However, most of the cited studies use the term synephrine.

² Bitter orange is also known as Seville orange, sour orange, or marmalade orange.

Bitter orange and other citrus species such as *Citrus sinensis* (sweet orange) and *Citrus limon* (lemon) naturally contain oxedrine at levels up to 0.2% in the fruit (Arbo et al 2008).

Oxedrine is scheduled S4 (Prescription only medicines) for preparations labelled with a recommended daily dose greater than 30 mg (TGA 2015). In New Zealand, oxedrine is also prescription only for medicines containing more than 30 mg per recommended daily dose.

The Australian National Drugs and Poisons Schedule Committee (NDPSC³) first considered oxedrine in 2002 (TGA 2002). It was noted that there was a significant number of products being sold on the internet containing *Citrus aurantium* and extracts from various parts of the plant. Products containing oxedrine included supplements stated to support metabolism, burn body fat, and aid weight loss. The Committee noted that it appeared that such products were illegally supplied as therapeutic goods and that a 28-year-old man experienced a myocardial infarction following abuse of oxedrine tablets in Australia. The NDPSC concluded that additional information on the following should be sought for consideration at the February 2003 meeting: (i) extent to which oxedrine is being used as an active ingredient; (ii) purposes for which oxedrine is being used; (iii) oxedrine dose versus risk of toxicity including cardiovascular effects; and (iv) pharmacology of oxedrine (TGA 2002).

At the February 2003 NDPSC meeting, the Committee agreed to include oxedrine for internal human use in Schedule 4 of the SUSDP except when the total daily dose is 30 mg or less. Based on the therapeutic dose of oxedrine for the treatment of hypotension of "about 100 mg three times daily" (i.e. 300 mg/day) quoted in *Martindale: The Complete Drug Reference*, the NDPSC concluded that a scheduling exemption for products at 30 mg or less total daily dose would provide a ten-fold safety factor which was considered to be adequate (TGA 2003).

The TGA is currently reviewing the safety of therapeutic goods containing both caffeine and oxedrine (TGA 2013).

1.4 Risk assessment

This is an assessment of the potential risks to public health and safety arising from the consumption of the foods containing oxedrine at the measured levels in this survey. While it is noted that a majority of these products contain other ingredients, such as caffeine, these constituents have not been specifically considered as part of this assessment.

2. Chemistry and pharmacology

Oxedrine is structurally related to phenylephrine and adrenaline (epinephrine) (Figure 1), but exhibits comparatively weak binding to adrenergic receptors. The compound has one chiral carbon and the (-)-enantiomer is naturally present in bitter orange (Pellati et al 2005; Stohs and Preuss 2012). In plants, (-)-oxedrine is synthesized from the amino acid L-tyrosine (Bartley et al 2010). Small amounts of (+)-oxedrine can be produced during extraction from plant material depending on the procedures and conditions used such as temperature and pH (Stohs and Preuss 2012). CAS registry numbers and molecular weights are shown in Table 1.

³ In 2010, the NDPSC was replaced by the Advisory Committee on Medicines Scheduling (ACMS) and the Advisory Committee on Chemicals Scheduling (ACCS)

Table 1: CAS registry numbers and molecular weights

Substance	CAS number	Molecular weight
(-)-oxedrine	614-35-7	167.2
(+)-oxedrine	532-80-9	
(±)-oxedrine	94-07-5	
(±)-oxedrine tartrate	67-04-9	484.5

As shown in Figure 1, oxedrine has a hydroxyl group at the para position. Some reports indicate that the pharmacologically more active meta isomer (i.e. phenylephrine, also known as neo-synephrine) is also present at substantial levels in bitter orange raw materials and extracts (e.g. Allison et al 2005), however this has subsequently been shown not to be the case (Roman et al 2007). Octopamine (oxedrine without the N-methyl group) has been shown to be present at low levels relative to oxedrine in bitter orange and its extracts.

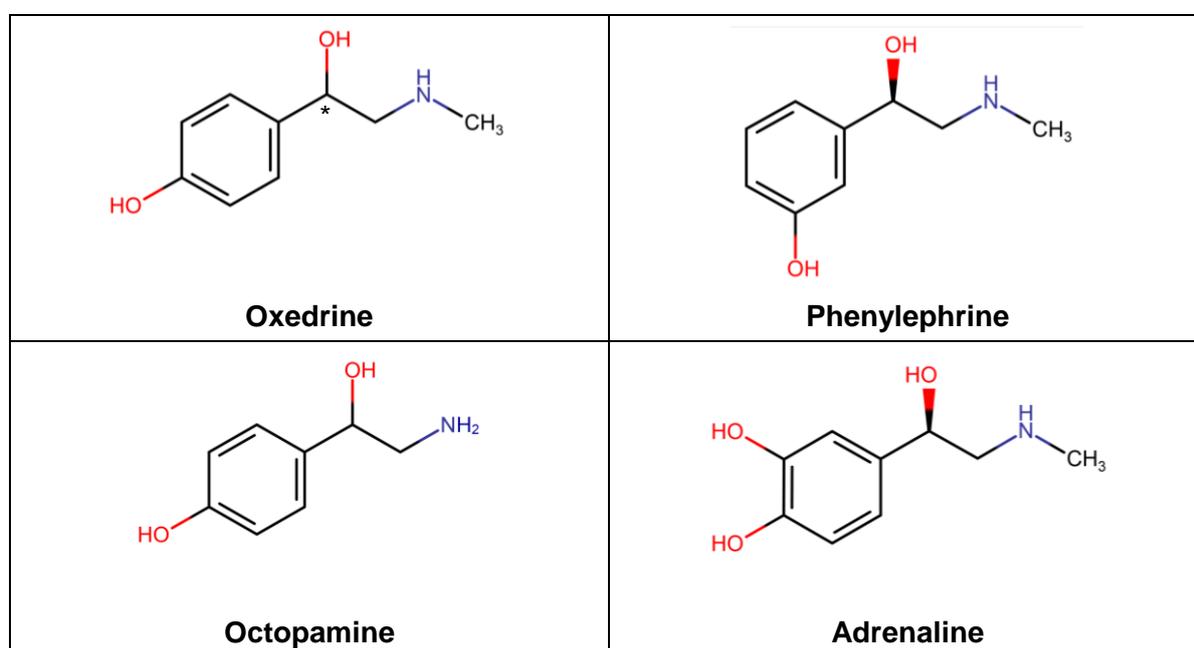


Figure 1: Chemical structures of oxedrine, phenylephrine, octopamine and adrenaline (epinephrine). The chiral carbon is labelled on the oxedrine structure with an asterisk. Phenylephrine is also known as meta-synephrine or neo-synephrine.

Oxedrine is a weak alpha-adrenergic agonist. Receptor binding studies have shown that oxedrine binds to adrenoceptors with much lower affinity than adrenaline and noradrenaline. (+)-Oxedrine binds with weaker affinity than the naturally occurring (-)-oxedrine. Brown et al (1988) examined the binding activities of the (-)- and (+)-oxedrine to α -adrenoceptors in rat and rabbit aorta and vein. (-)-Oxedrine was 1000-fold less active in binding to both α 1- and α 2-adrenoceptors than noradrenaline. (+)-Oxedrine exhibited over 100-fold weaker binding activity than (-)-oxedrine. The binding of phenylephrine to α -1 and α -2 adrenoceptors was 6-fold and 150-fold less, respectively, than norepinephrine. (-)-Octopamine exhibited binding activity that was similar to (-)-oxedrine.

Oxedrine binds very weakly to β 1-adrenoceptors. In guinea pig atria and trachea, (-)-oxedrine and (-)-octopamine bound to β 1-adrenoceptors 40,000- and 6000-fold less readily than noradrenaline, respectively. (+)-Oxedrine exhibited approximately 100-fold weaker binding than (-)-oxedrine. (-)-Oxedrine was about 10,000-fold less active in binding to β 2-adrenoceptors than noradrenaline, while the (+)-form exhibited no detectable binding. In contrast, phenylephrine was ~100-fold less active than noradrenaline in binding to β -1 and β -2 adrenoceptors (Jordan et al 1987).

3. Hazard Assessment

3.1. Evaluation of data

A search of the scientific literature using PubMed⁴, TOXNET⁵ and Google Scholar⁶ identified a number of published journal articles on the biological effects of oxedrine. The articles include reports of toxicity studies in laboratory animals, case reports of adverse effects in humans, and clinical studies examining the safety and potential efficacy of bitter orange extracts containing oxedrine. Non-oral studies (e.g. Huang et al 1995) and studies on bitter orange extracts which provide no information on oxedrine content (e.g. Parra et al 2001) were excluded.

Laboratory animal studies

Acute toxicity

Male CF-1 mice (8/group) received single oral gavage doses of (\pm)-oxedrine (synephrine; Aldrich; purity 99%) at dose levels of 0 (water control), 150, 300, 450, 600, 800, 1000 or 2000 mg/kg bw. Piloerection and exophthalmia were evident within 15 min after administration of 300–2000 mg/kg bw and persisted for 2 h. Reduction of locomotor activity was evident 15 min after administration of 300–2000 mg/kg bw and the effect persisted for 1 h. Salivation was observed within 15 min at all tested doses and persisted for 30 min, while gasping was evident at the same time in all tested doses and persisted for 3-4 h. The incidence and severity of the clinical signs for each group was not reported. There were no unscheduled deaths over the 14-day study period. Bodyweight gain was similar among the groups. At necropsy, organs examined (heart, liver, kidneys and adrenals) appeared normal (Arbo et al 2008).

As a no observed adverse effect level (NOAEL) was not evident in the above study, a follow-up study was conducted with a bitter orange extract to give oxedrine doses below 150 mg/kg bw. Male CF-1 mice (8/group) received single oral gavage doses of a bitter orange extract (containing 2.5% oxedrine) at dose levels of 0 (water control), 300, 500, 1000, 2500, 3500 or 5000 mg/kg, resulting in oxedrine doses ranging from 7.5–125 mg/kg bw. The extract was obtained by maceration of unripe fruit with 50% methanol for 24 h followed by filtration and concentration in a rotary evaporator (no other details were provided). The only effect attributable to treatment was reduced locomotor activity which was evident 15 min after administration of extract doses of 1000–5000 mg/kg bw (oxedrine doses 25–125 mg/kg bw) and persisted for 2 h (incidence and severity not reported). The acute NOAEL for the bitter orange extract was therefore 500 mg/kg bw, corresponding to an oxedrine dose of 12.5 mg/kg bw (Arbo et al 2008).

⁴ <http://www.ncbi.nlm.nih.gov/pubmed>

⁵ <http://toxnet.nlm.nih.gov/>

⁶ <http://scholar.google.com.au/>

In a follow-up study to quantitatively assess locomotor activity, groups of male CF-1 mice (8–10/group) received the following by oral gavage: water (control), oxedrine (purity 99%; 300 mg/kg bw) or bitter orange extract (5000 and 10,000 mg/kg bw). The bitter orange extract was produced by maceration of unripe fruit with 50% methanol (as above), however this extract had an oxedrine content of 3.0%. The oxedrine doses resulting from administration of this extract were therefore 150 and 300 mg/kg bw. Cages equipped with photocells automatically recorded the number of animal crossings. Monitoring commenced 30 min after treatments and crossings were recorded for 15 min. All three treatments (oxedrine 300 mg/kg bw and bitter orange extract, 5000 and 10,000 mg/kg bw), significantly decreased locomotor activity ($p < 0.01$). Locomotor activity scores were 31%, 37% and 15%, respectively, of the control group score (Arbo et al 2008).

Arbo et al (2008) also reported that single oral gavage doses of oxedrine (300 mg/kg bw) or bitter orange extract (5000 and 10,000 mg/kg bw; 3.0% oxedrine) had no effect on body temperature in male CF-1 mice (6/group).

Repeat-dose toxicity

Arbo et al (2009) evaluated bitter orange extract and oxedrine in CF-1 mice, treating groups of 9–10 males for 28 days with a bitter orange extract (containing 7.5% oxedrine) at 0 (water control), 400, 2000, or 4000 mg/kg bw/day (oxedrine doses 30–300 mg/kg bw/day), or oxedrine at 30 or 300 mg/kg bw/day, by oral gavage. The bitter orange extract was a commercial product obtained from Galena (Campinas, Brazil). It was stated to be a methanolic extract, however no other information was provided on its method of production or composition (apart from oxedrine content). The purity of oxedrine test article was 99%, however the enantiomeric form was not stated. There were no deaths, clinical signs of toxicity, or changes in bodyweight-relative weights of organs (heart, liver, brain, spleen, kidneys and adrenals) in any of the treatment groups. There was no statistically significant change in bodyweight resulting from treatment with bitter orange extract but both dose levels of oxedrine produced a statistically significant ($p < 0.05$) decrease in bodyweight gain by day 28, however the effect was not dose-dependent. Bodyweight gains for the control group and the oxedrine 30 and 300 mg/kg bw groups were approximately 8.5%, 1.8% and 2.9%, respectively. Several haematology and clinical chemistry parameters were evaluated and no treatment-related effects were observed for any group.

Male Sprague-Dawley rats (8/group) were dosed daily by oral gavage with two different bitter orange extracts at doses of 0 (saline control), 2.5, 5, 10 or 20 mg/kg bw/day for 15 days. It was stated that commercially available *Citrus aurantium* fruit hydroalcoholic extracts from India and the USA, standardized to oxedrine content of 4% and 6%, respectively, were used. No other information was provided on methods of production or composition of the extracts. There were dose-dependent reductions in food intake and bodyweight gain. No clinical signs of toxicity were evident, however deaths were observed in all treatment groups (up to 50% for the 20 mg/kg bw/day, 6% extract, corresponding to an oxedrine dose of 1.2 mg/kg bw/day). No effects on blood pressure were detected. However, ventricular arrhythmias with QRS complex extension were observed in both of the 20 mg/kg bw/day groups (4% and 6% extracts). It was not indicated if ECG analysis was performed on rats given lower doses (Calapai et al 1999).

Female Sprague-Dawley rats (13–14/group) were dosed daily by gavage for 28 days with two different bitter orange extracts nominally containing 6% and 90% oxedrine, respectively. The extracts were purchased from Modern Nutrition and Biotech (Appleton, WI, USA). Analysis showed that the nominally 6% oxedrine extract contained 7.25% oxedrine, 0.63% hordenine, 0.10% octopamine and 0.09% tyramine by weight. The nominally 90% oxedrine extract contained 95.0% oxedrine, 0.05% hordenine, 0.39% octopamine, and 0.02% tyramine by weight.

The oxedrine doses for each extract were 0 (control: 0.25% methyl cellulose), 10 and 50 mg/kg bw/day. Telemetry was used to monitor heart rate, blood pressure, body temperature and QT interval in all rats at 1, 2, 4 and 8 h after each dose. There were no treatment-related deaths, signs of toxicity, differences in bodyweight gain or food consumption. Systolic blood pressure was increased at 50 mg/kg bw/day for both extracts at 1–4 h post-dose (maximum increase 6 mmHg). This effect was greatest at the end of week 1 of dosing and gradually decreased by week 2 and 3. There were some statistically significant differences in diastolic blood pressure, heart rate and body temperature at some time-points, however the differences were small and not dose-dependent. There were no statistically significant differences in QT interval (Hansen et al 2012).

Female Sprague-Dawley rats were dosed daily by gavage for 28 days with the two different bitter orange extracts administered in the study by Hansen et al (2012). Each extract was administered to give oxedrine doses of 10 or 50 mg/kg bw/day. Rats were subjected to 30 minutes of physical activity (treadmill running), three days per week. Heart rate, blood pressure, body temperature, and QT interval were monitored. Both doses of both extracts statistically significantly increased systolic and diastolic blood pressure for up to 8 h after dosing. Maximum increases in systolic blood pressure were 4.7 mmHg and 7.5 mmHg, observed 4 h after administration of 10 and 50 mg/kg bw/day, respectively. For diastolic blood pressure, maximum increases were 3.7 and 6.0 mmHg, observed 8 h after administration of 10 and 50 mg/kg bw/day, respectively. There were no treatment-related effects on body temperature, heart rate or QT interval (Hansen et al 2013).

Developmental toxicity

Daily oral gavage administration of two different bitter orange extracts (described above: Hansen et al 2012), resulting in oxedrine doses of up to 100 mg/kg bw/day, to pregnant Sprague-Dawley rats (25/group) from gestation days 3–20 resulted in no signs of maternal toxicity and did not affect fetal growth or development (Hansen et al 2011).

Human case reports

Several case reports have associated intake of products containing bitter orange extracts with various adverse effects, such as myocardial infarction (Nykamp et al 2004; Thomas et al 2009), ischemic stroke (Bouchard et al 2005), angina (Gange et al 2006), vasospasm and stroke (Holmes and Tavee 2008), ventricular fibrillation (Stephensen and Sarlay 2009), ischemic colitis (Sultan et al 2006), and apical ballooning syndrome, a reversible cardiomyopathy (Chung et al 2013). The products consumed in these case reports typically contained a number of other pharmacologically active extracts/substances at unspecified levels, including caffeine. Information on oxedrine doses was generally lacking.

Regarding the Australian case report cited by the NDPSC (TGA 2002), it is noted that the 28 year old man who experienced a myocardial infarction was abusing oxedrine tablets, however no information was provided on estimated doses and it was stated that the man smoked heavily (Keogh and Baron 1985).

Clinical studies

Minimal information has been located on the use of oxedrine in the treatment of hypotension. *Martindale* states that the oxedrine tartrate has been used in the treatment of hypotension in oral doses of about 100 to 150 mg three times daily, however no references to supporting clinical studies are provided in the three editions of *Martindale* that were consulted (published in 1999, 2002 and 2014). No papers in English were located that contained relevant information on clinical use/dosing of oxedrine tartrate in the treatment of hypotension.

Four potentially relevant papers in German were consulted, however, these papers lacked information directly relevant to this issue (Hansen and Juhl 1965; Hengstmann and Aulepp 1978; Hengstmann 1983; Schönborn 1986).

Several human studies have been published investigating the effects of bitter orange extracts containing known levels of oxedrine, as summarised below.

Reference and study design	Results
<p>Gurley et al (2004)</p> <p>Randomised, open-label, four-arm crossover study in 12 healthy adults.</p> <p>Subjects received extracts of either bitter orange (two capsules once per day providing a total oxedrine dose of 31 mg/day), <i>Echinacea purpurea</i>, milk thistle or saw palmetto daily for 28 days with washout periods of 30 days.</p> <p>The extract, nominally containing 4% oxedrine, was a product of General Nutrition Corp (Pittsburgh, PA, USA). No information was provided on its method of production. The extract was analysed for octopamine (not detected) and oxedrine (determined to be 4.4% w/w).</p>	<p>No treatment-related adverse effects were reported in subjects receiving bitter orange extract. None of the treatments affected pre-supplementation activities of cytochrome P450 (CYP) 1A2, 2D6, 2E1 or 3A4, the major drug-metabolizing cytochrome enzymes.</p>
<p>Haller et al (2005)</p> <p>Randomized, double-blind, placebo-controlled, three-arm crossover study in 10 healthy adults.</p> <p>Subjects received either a single dose of bitter orange extract (three tablets providing a total oxedrine dose of 47 mg), Xenadrine EFX (a multi-component formulation providing 5.5 mg oxedrine, 240 mg caffeine) or placebo, with 1 wk washout periods.</p> <p>The extract, 'Advantra Z', was a product of Nutratech Inc (Wayne, NJ, USA). No information was provided on the method of production. The product was analysed for caffeine (not detected), octopamine ('trace' amount) and oxedrine (15.6 mg/tablet).</p>	<p>Analysis of plasma levels of oxedrine following oral administration of bitter orange extract (47 mg oxedrine) resulted in T_{max}, C_{max} and $T_{1/2}$ of 75 min, 2.9 ng/mL and 3.1 h, respectively.</p> <p>Bitter orange extract had no effect on systolic or diastolic blood pressure (SBP, DBP). Xenadrine EFX increased SBP and DBP at 2 h post-dose. Both treatments increased heart rate (HR) from baseline at 6 h post-dose (17 beats/min with Xenadrine EFX, $p = 0.01$; 11 beats/min with bitter orange extract, $p = 0.03$). There was no effect on HR at the other time points (1, 1.5, 3, 4 and 8 h post dose). Bitter orange extract had no effect on self-reported rating of physical symptoms, moods, and emotions. Xenadrine EFX resulted in an increased score for alertness, which the authors considered attributable to caffeine.</p>

Reference and study design	Results
<p>Min et al (2005)</p> <p>Randomized, double-blind, placebo-controlled, two-arm crossover study in 18 healthy adults.</p> <p>Subjects received either a single dose of bitter orange extract (a single tablet containing 27 mg oxedrine) or placebo, with a 1 wk washout period.</p> <p>The extract, nominally containing 6% oxedrine, was a product of Nature's Way (Springville, UT, USA). No information was provided on the method of production. Apart from oxedrine content no other compositional information was provided.</p>	<p>There were no clinical signs or symptoms related to treatment. Bitter orange extract had no effect on SBP or DBP or QT interval at any time point post-dose (1, 3, 5, and 8 h after ingestion). No data on HR was provided.</p>
<p>Bui et al (2006)</p> <p>Randomized, double-blind, placebo-controlled, two-arm crossover study in 15 healthy adults.</p> <p>Subjects received either a single dose of bitter orange extract (two capsules providing a total oxedrine dose of 54 mg) or placebo, with a 1 wk washout period.</p> <p>The extract was a product of Nature's Way (Springville, UT, USA), as described above for Min et al (2005).</p>	<p>Bitter orange extract increased SBP at 1-5 h post-dose ($p < 0.0001$; peak difference 7.3 ± 4.6 mmHg). DBP was increased at 4-5 h post-dose ($p \leq 0.02$; peak difference 2.6 ± 3.8 mmHg). HR was increased at 2-5 h post-dose ($p < 0.01$; peak difference 4.2 ± 4.5 beats/min).</p>
<p>Gougeon et al (2005)</p> <p>Single dose of bitter orange extract (26 mg oxedrine) administered to 30 healthy adults.</p> <p>The extract, 'ZhiThin', was a product of Fyto Research (Lachine, Canada). Method of production was not described. Other than oxedrine, the extract provided doses of 4 mg octopamine, 3.6 mg N-methyltyramine, and 2.9 mg tyramine and hordenine.</p>	<p>Bitter orange extract had no effect on pre-dose SBP, DBP, or HR.</p>
<p>Stohs et al (2011a)</p> <p>Randomized, double-blind, placebo-controlled, parallel study (five groups with 10 healthy adults per group). Single dose.</p> <p>Group 1: placebo; Group 2: bitter orange extract (50 mg oxedrine); Groups 3-5 received the same as Group 2 plus 600 mg naringin (Group 3); 100 mg hesperidin and 600 mg naringin (Group 4); 1000 mg hesperidin and 600 mg naringin (Group 5). Treatments were administered in vegetable juice ("V-8").</p> <p>The bitter orange extract, 'Advantra Z' (NutraTech Inc, West Caldwell, NJ, USA) contained 60 % oxedrine. Method of production and components other than oxedrine were not described.</p>	<p>None of the treatment groups exhibited changes in HR or BP relative to the control group. There were no differences in self-reported ratings of 10 common symptoms between the treatment groups and the control group (anxiety, hunger, tension, sleepiness, energy, nervousness, headache, upset stomach, concentration or general discomfort).</p>

Reference and study design	Results
<p>Kaats et al (2013)</p> <p>Randomized, double-blind, placebo-controlled, parallel study (three groups with 25 healthy adults per group). Dosed two times per day for 60 days.</p> <p>Group A: Bitter orange extract (49 mg oxedrine per dose in capsule form: 98 mg oxedrine/day) with hesperidin (200 mg/day) and naringin (1150 mg/day); Group B: Bitter orange extract (as for Group A) alone; Group C: placebo.</p> <p>The bitter orange extract was as per Stohs et al (2011a), above.</p>	<p>No adverse effects were reported by any of the subjects and no significant differences between groups were observed in responses to an 84-item Quality of Life questionnaire completed at base line and after 60 days.</p> <p>There were no treatment-related effects on clinical chemistry or haematology parameters.</p> <p>No significant differences were observed after 60 days with respect to SBP or DBP between either of the two treatment groups and the placebo group or between the two treatment groups. No significant difference in HR was observed between the oxedrine only and placebo groups.</p>

3.2 Hazard assessment - discussion and conclusions

The limited animal toxicity data available on purified oxedrine or bitter orange extracts provides some evidence for treatment-related increases in blood pressure and heart rate, however the data are insufficient for defining a no observed adverse effect level (NOAEL) for either of these end-points. Few other endpoints have been investigated in repeat-dose animal studies. One rat study investigated several haematology and clinical chemistry parameters with no effects evident at oxedrine doses up to 300 mg/kg bw/day (the top dose) for 28 days (Arbo et al 2009). Bitter orange extract administered to pregnant rats, giving oxedrine doses of up to 100 mg/kg bw/day, resulted in no signs of maternal toxicity and did not affect fetal growth and development (Hansen et al 2011). A study in mice involving oral administration of a methanol extract of bitter orange showed large reductions in locomotor activity at oxedrine doses ≥ 25 mg/kg bw. However, it was unclear if the extract was completely dried and the effect on activity could be due to residual methanol in the extract.

Concerns have been raised regarding the safety of bitter orange extracts due to potential adverse effects on the cardiovascular system, as documented in several published case reports. These case reports suffer from a number of weaknesses including a lack of information on levels of oxedrine in the ingested supplements, the supplement doses ingested, and confounding from potential effects due to other ingredients in the products (e.g. caffeine). As discussed in several published articles, a causal relationship has not been established between the consumption of bitter orange extracts and the adverse effects documented in case reports (Stohs 2010a, 2010b, 2014).

Six published clinical studies have specifically investigated potential effects on blood pressure and heart rate following administration of bitter orange extracts with known oxedrine levels, resulting in single oxedrine doses ranging from 26 to 54 mg and a study using twice daily doses of 49 mg (i.e. 98 mg/day) for 60 days. No treatment-related clinical signs or symptoms were evident in these studies. Only one study reported an effect on blood pressure. This was a crossover study in which 15 healthy adults received either a single dose of bitter orange extract (54 mg oxedrine) or placebo (Bui et al 2006). Systolic blood pressure was increased at 1–5 h post-dose (peak difference 7.3 ± 4.6 mmHg) with a smaller effect on diastolic blood pressure (peak difference 2.6 ± 3.8 mmHg) that was only evident at 4-5 h post-dose. This study also reported a small increase in heart rate at 2–5 h post-dose (peak difference 4.2 ± 4.5 beats/min). These transient increases in blood pressure and heart rate are relatively small and are not considered to be clinically relevant. Another study of similar design reported an increase in heart rate following administration of bitter orange extract (oxedrine dose 47 mg).

However, the increase was statistically significant only at 6 h post-dose with no effect at the other timepoints (1, 1.5, 3, 4 and 8 h post-dose) (Haller et al 2005).

In a recently published double-blind, placebo controlled study, healthy adults (n=25) received twice daily doses of bitter orange extract for 60 days. Each dose of bitter orange extract contained 49 mg oxedrine, resulting in a daily oxedrine dose of 98 mg. No statistically significant differences were observed after 60 days with respect to systolic or diastolic blood pressure and heart rate between the treated and placebo groups. No adverse effects were reported by any of the subjects and there were no treatment-related effects on clinical chemistry or haematology parameters (Kaats et al 2013).

In a study in 12 healthy adults, bitter orange extract (oxedrine dose 31 mg/day for 28 days) had no effect on the major drug-metabolizing cytochrome enzymes suggesting that oxedrine has a low potential for such drug interactions (Gurley et al 2004).

In conclusion, the weight of evidence from clinical studies on bitter orange extracts of known oxedrine content indicates minimal concerns for potential adverse effects. Ingestion of bitter orange extract resulting in oxedrine doses approaching 100 mg/day for 60 days, the highest dose tested in published clinical studies, was not associated with adverse effects (Kaats et al 2013).

4. Dietary exposure assessment

Dietary exposure to oxedrine naturally present in Citrus species

The French Agency for Food, Environmental and Occupational Health & Safety has recently reviewed data on oxedrine levels in Citrus species and their products (including juices and jams) (Table 2; ANSES 2014). These data were used in conjunction with consumption data to estimate dietary exposure to oxedrine in the French population. It was noted that oxedrine has not been detected in some Citrus species such as grapefruit (*C. paradisi*), citron (*C. medica*) and pomelo (*C. maxima*) (Avula et al 2005; Bartley et al 2010).

Table 2: Minimum and maximum oxedrine concentrations (in mg/g) in citrus fruits, used to estimate dietary exposure in the adult French population (ANSES 2014).

Synephrine concentrations in mg/g	Species	Minimum (in mg/g)	Maximum (in mg/g)	References
Oranges	<i>C. sinensis</i>	0.013	0.035	Matolli et al. (2005)
Orange juice	Orange / <i>C. sinensis</i> Tan.	0.00365	0.085	Avula et al. (2007) / Uckoo et al. (2011)
Mandarins/Clementines	<i>Citrus</i> hybrids	0.008	0.054	He et al. (2011)
Mandarin juice	<i>C. unshiu mikan</i> / <i>C. reshni hort.</i> Ex Tanaka <i>C. reticulata</i> ?	0.0355	0.28	Kusu et al. (1996) / Wheaton and Stewart (1965)
Lemons	<i>C. limon</i>	0.37	0.45	Arbo et al. (2008)
Lemon juice	Citron / <i>C. limon</i> Tan.	0.002	0.00275	Wheaton and Stewart (1965) / Uckoo et al. (2011)
Jams	<i>C. aurantium</i> / <i>Citrus</i>	0.0009	0.121	Avula et al. (2007) / Kusu et al. (1996)

Estimated dietary exposure to oxedrine for mean and high consumers (95th percentile) was 6.2 and 20 mg/day, respectively. A similar analysis was conducted by the German Federal Institute for Risk Assessment, resulting in estimated dietary exposure to oxedrine for mean and high consumers (95th percentile) of 6.7 and 26 mg/day, respectively (Bfr 2012).

The estimated dietary exposure to oxedrine for Australian and New Zealand populations was also in the same range, based on the minimum and maximum concentration values reported by France in Table 2. For Australia, estimated dietary exposure to oxedrine was 0.5-14 mg/day for mean consumers and 1.3-35 mg/day for high consumers (90th percentile). For New Zealand estimated dietary exposure to oxedrine was 0.7-11 mg/day for mean consumers and 2.5-26 mg/day for high consumers (90th percentile). The slightly higher values based on maximum oxedrine concentrations for the Australian and New Zealand populations compared to estimates for the French or German populations are likely due to the fact that all citrus products, including use as an ingredient in recipes, were incorporated in our dietary exposure assessments, hence it is a more conservative estimate.

Dietary exposure to oxedrine in weight-loss products

FSANZ has conducted an analytical survey of undeclared pharmaceuticals in foods promoted for weight loss. Products were purchased from supermarkets, pharmacies and sports stores in the ACT. No pharmaceutical drugs were found in 34 of the 36 products tested. Two products contained oxedrine at levels which would result in oxedrine doses of 13 and 39 mg, respectively, when taken at the recommended daily dose listed on the product labels (Table 3).

Table 3: Oxedrine concentrations and resulting doses in weight loss products purchased in the ACT.

Product name and form	Batch Number	Oxedrine concentration	Oxedrine dose[#]
BodyWar Nutrition BodyShred Mango Punch (powder)	8946670666	2.0 mg/g	12.8 mg
FatBlaster raspberry ketone (pre-mixed drink)	183512742	0.42 mg/mL	39.3 mg

[#] Oxedrine dose resulting from ingestion of the recommended serving size of the product.

5. Risk characterisation

In France and Germany, dietary exposure to oxedrine from the consumption of citrus fruits and their products (e.g. juices and jams) was estimated to be 6–7 mg/day for average consumers and 20–26 mg/day for high consumers. Estimated dietary exposure to oxedrine for Australian and New Zealand populations was in the same range, from 0.5-14 mg/day for average consumers and from 1-35 mg/day for high consumers. Additional dietary exposure resulting from consumption of the product providing the highest daily dose of oxedrine (39 mg/day) would not be expected to result in total dietary exposure exceeding 98 mg/day, a dose that resulted in no effects in a double-blind, placebo-controlled clinical trial of 60 days duration.

6. Conclusions

The highest oxedrine level determined in a FSANZ analytical survey of foods intended to promote weight loss does not indicate a public health and safety concern.

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