

# Imported food risk statement

## Supplementary sports foods and octopamine

**Scope:** Supplementary sports foods, including liquid forms, powders, and other solid forms

Recommendation and rationale
<p>Does octopamine in imported supplementary sports foods (sports supplements) present a potential medium or high risk to public health:</p> <p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><b>Rationale:</b></p> <ul style="list-style-type: none"> <li>• Octopamine is an <math>\alpha</math>-adrenergic agonist that may have adverse effects on blood pressure. It may also alter the metabolism of some drugs.</li> <li>• Octopamine has no history of safe use in Australia or New Zealand as a food at the levels, or in the forms reported to being added to sports supplements.</li> <li>• The available evidence in the public literature does not support that octopamine has been tested adequately for safety in animal studies or in humans.</li> </ul>

General description
<p><b>Nature of the analyte/toxin:</b></p> <p>Octopamine has reportedly been added as an ingredient to sports supplements marketed as “fat burners”. It may be listed as an ingredient under a number of synonyms, such as norsynephrine.</p> <p>Octopamine has a similar chemical structure to adrenaline and noradrenaline. It exists in multiple forms, known as ortho-, meta- and para-isomers (o, m, p). Each of these three isomers can also exist either in the (+) or (-) forms; making a total of six different forms<sup>1</sup>.</p> <p>It is an <math>\alpha</math>-adrenergic agonist which can cause vasoconstriction and an increase in blood pressure. The (-) m-isomer (norfenefrine) is likely to be the most pharmacologically active based on studies investigating cardiovascular effects and binding potency to <math>\alpha</math>-adrenergic receptors<sup>2</sup>.</p> <p>Octopamine has been used as a treatment for hypotension although it is not registered on the Australian Register of Therapeutic Goods. Reported therapeutic oral doses to treat hypotension range from 40-600 mg/day<sup>1</sup>.</p> <p>p-Octopamine is found naturally at low levels in both plants e.g Meyer lemon, bitter orange, and animals. m-Octopamine is reported to only occur in animals; and o-octopamine has not been reported to occur naturally. All forms or different combinations may be present if the source of octopamine is a synthetic preparation<sup>1</sup>.</p>
<p><b>Adverse health effects:</b></p> <p>Limited information on the toxicity of octopamine is available from studies in animals or humans.</p> <p>A number of clinical studies of limited design and reporting were identified in the literature. It was reported that a single oral intake of 100 mg m-octopamine in 2 subjects was associated with an increase in blood pressure<sup>4</sup>. In other studies which investigated lower doses of 9.85 to 90 mg, no effects were observed on blood pressure<sup>1,4,5,6,7</sup>.</p> <p>These studies are not sufficient to draw conclusions on the safety of octopamine used in sports foods at the proposed levels.</p> <p>It has been suggested that an inhibitory effect of octopamine on enzyme CYPc11<sup>8</sup>, might alter metabolism of prescribed medications although the clinical relevance is unclear at levels that have been reported in sports foods.</p>

## General description

### Consumption patterns:

In Meyer lemon, p-octopamine has been found at concentrations of around 16 µg/mL<sup>3</sup>. Bitter orange is sometimes cited as a source of octopamine, however where investigated concentrations of p-octopamine have generally been below the limit of detection or very low, e.g. around 0.22 mg/kg of bitter orange<sup>1</sup>. Therefore, current exposure to octopamine occurring naturally in the food supply is likely to be very low.

Based on the instructions on the supplementary sports food labels the daily intake of octopamine could be assumed to be in the range 30-90 mg/day.

### Risk factors and risk mitigation

The available evidence in the public literature does not support that octopamine has been tested adequately for safety in animal studies or in humans. This would need to be conducted in a pre-market safety assessment.

Consumption of octopamine is of greatest risk to people with pre-existing blood pressure disorders.

(+) *m*-Octopamine is the most pharmacologically active form, therefore for risk assessment purposes it should be assumed that this is the form present, if another form is not identified on the label, or there are doubts as to the accuracy of the labelling.

Caffeine, synephrine and/or higenamine, all which have potential to affect blood pressure, may also be present in sports supplements containing octopamine<sup>3</sup>. The effects of the combination of these substances are not well understood.

### Surveillance information:

There is a paucity of surveillance information on the use of octopamine, including when used as an ingredient of sport supplements.

### Illness associated with consumption of supplementary sports foods formulated to contain octopamine

A search of the scientific literature via EBSCO, PubMed and Google Scholar to February 2020 did not identify any case reports of adverse effects clearly attributable to octopamine. A case of acute myocardial infarct in a 39-year old male bodybuilder, was reported following use of a supplement containing octopamine. However, the supplement also contained synephrine, tyramine and caffeine, and St. John's Wort. The levels of caffeine and synephrine in the product were 40 and 400 mg, respectively, with unknown amounts of octopamine, tyramine and St. John's Wort<sup>3</sup>.

### Data on the prevalence of octopamine in supplementary sports foods

A review by Health Canada<sup>3</sup> showed octopamine content in sport supplement products can vary from trace levels to 800 mg.

A review of adulterated food supplements in the Netherlands<sup>10</sup> found that the mean, median, minimum and maximum daily doses of octopamine were: 0.07, 0.05, 0.005 and 0.3 mg, respectively.

An internet search for sports supplements containing octopamine, carried out November/December 2019, using the terms octopamine and sports supplements, found four products listing octopamine on the ingredient list (Shred FX by Genetix, Elemental Shredding Stack, Maxs T-Dex Ripp'd and RedCon1 Double Tap). All of these products were identified as "fat burners". The form of octopamine present was not stated. Based on the label instructions the daily serving of octopamine varied from 30-60 mg/daily. The available information is not sufficient to draw conclusions on the form of octopamine present in the products, or the safety of octopamine in the products at the reported levels.

Of the 4% of supplements found to contain octopamine in the 2018 National Measurement Institute survey of sports supplements<sup>9</sup>, one product contained just octopamine, whilst three others contained synephrine with or without higenamine.

## Standards or guidelines

Octopamine at the levels and in the form reported in sports foods does not have a history of safe use as a food in Australia or New Zealand. It is not explicitly permitted as a novel food in the Australia New Zealand Food Standards Code.

Octopamine is not scheduled by the Therapeutic Goods Administration, and is banned for use in competitive sports by the World Anti-Doping Agency (WADA)<sup>12</sup>, as it is on the prohibited list as a specified stimulant, with a threshold for reporting of 1000 ng/mL in human urine.

### Management approaches used by overseas countries

Health Canada classifies *p*-octopamine\* at doses up to 50 mg/day in healthy adults as a Type III risk. Due to a paucity of data, doses above 50 mg/day are classed as Type II risk to health.

Type II risk is a situation in which the use of, or exposure to, a product may cause temporary adverse health consequences or where the probability of serious adverse health consequences is remote. Type III risk is a situation in which the use of, or exposure to, a product is not likely to cause any adverse health consequences.

\* Note this limit only applies to *p*-octopamine, as the Health Canada review focused on bitter orange as a source of octopamine, rather than consideration of other forms which may be present in synthetic octopamine.

US FDA – Octopamine is listed on the “Dietary Supplement Ingredient Advisory List”<sup>11</sup>. This list is intended to quickly alert the public when the FDA identifies ingredients that do not appear to be a lawful ingredient in dietary supplements. Presence on the list indicates the US FDA have undertaken a preliminary evaluation and is intending to do further evaluation.

The US FDA Dietary Supplement Ingredient Advisory List does not mention different forms of octopamine, it merely uses the term “octopamine”.

**This risk statement was compiled in:** July 2020

### References

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