Imported food risk statement

Supplementary sports foods and higenamine

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

Recommendation and rationale
Does higenamine in imported supplementary sports foods (sports supplements) present a potential medium or high risk to public health: ☑ *Yes* ☐ *No* **Rationale**: • Higenamine is a potent β2-adrenergic agonist that inhibits constriction of airways and dilates blood vessels in muscles. It may have adverse effects on heart rate and blood pressure, and has the potential to interfere with blood clotting and with metabolism of prescribed drugs. • Higenamine has no history of safe use as a food in Australia. Higenamine has not been tested adequately for safety in animal studies or humans, particularly with regard to oral exposure. • Consumption of a small amount of higenamine is likely to result in a urinary higenamine concentration that exceeds the level permitted by the World Anti-Doping Agency (WADA), which indicates that higenamine is bioavailable by the oral route.

General description
Nature of the microorganism/analyte/toxin: Higenamine is being added as an ingredient to some sports supplements marketed as stimulants or 'fat burners'. It may be listed as an ingredient under a number of synonyms, such as norcoclaurine. Higenamine is an alkaloid produced by a variety of plants, including edible and toxic species, but none of the plants are typically consumed in Australia. Extracts from plants are likely to be mixtures of the pharmacologically active *S*-enantiomer and the inactive *L*-enantiomer whereas higenamine synthesized in a laboratory may be primarily *S*-enantiomer. Synthesized higenamine may therefore be more potent, and more hazardous to consume, than higenamine extracted from plants. Administered parenterally, higenamine increases heart rate and force of contraction of the heart, reduces constriction of major airways, and causes dilation of blood vessels[1]. It also inhibits platelet aggregation[2] which is a critical step in normal blood coagulation.
Adverse health effects: Higenamine is a potent β2-adrenergic agonist that has been shown to cause nausea, dizziness[3], insomnia[4], racing heart-rate, and sudden changes in blood pressure[5] in studies in which it was administered parenterally. These effects are consistent with its pharmacology. Higenamine inhibits platelet aggregation[2] and might pose risk of haemorrhage in people with haemophilia, people taking anticoagulant medications, and people who require surgery. Higenamine inhibits some liver enzymes[6] and might alter metabolism of prescribed medications. The thresholds for these adverse effects following oral exposure cannot be determined from the available literature.

General description
Consumption patterns: In a survey completed in 2018, the Australian Sports Drug Testing Laboratory[7] found higenamine in 10% of randomly selected "pre-workout" or "fat burner" supplements.
Risk factors and risk mitigation Consumption of higenamine is of greatest risk to people with pre-existing disorders of heart rate or blood pressure, and may also increase risk of haemorrhage in people with clotting disorders, who are taking anticoagulant medications, or are scheduled for surgery. When higenamine is listed on the label of a sports supplement, it should be assumed that all higenamine present is the active S-enantiomer. Higenamine is frequently included in sports supplements in association with other substances that affect blood pressure, such as caffeine. The effects of such combinations are unknown.
Surveillance information: There is a lack of quantitative surveillance information on the use of higenamine. **Illness associated with consumption of supplementary sports foods formulated to contain higenamine** A search of the scientific literature via EBSCO, PubMed and Google Scholar to February 2020 identified that there has been one case reported of acute breakdown of skeletal muscle that was possibly associated with higenamine[8]. **Data on the prevalence of higenamine in supplementary sports foods** Supplementary sports foods that contain higenamine may not specify the concentration of higenamine on the label, and the claimed concentration may not be accurate[9]. A study that analysed dietary supplements for sale in the USA that listed higenamine or norcoclaurine on the label found evidence of inaccurate labelling. Of the twenty four products analysed, only five made specific claims concerning the amount of higenamine present, but none were accurately labelled and the actual amount was up to 200% the amount stated.

Standards or guidelines
Higenamine does not have a history of safe use as a food in Australia. It is not explicitly permitted as a novel food in the Australia New Zealand Food Standards Code. Higenamine is not scheduled by the Therapeutic Goods Administration, and is banned for use in competitive sports by the World Anti-Doping Agency[10].

Management approaches used by overseas countries
Higenamine was included on the *FDA Dietary Supplement Ingredient Advisory List* from the List's inception in April 2019, as an ingredient that does not appear to be lawful in dietary supplements. In October 2021 the FDA reclassified higenamine as a new dietary ingredient (NDI) for which an NDI application is required however one has not been submitted to date[11].

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References

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