# Brucine: Human health tier II assessment

**04 July 2014**



## Chemicals in this assessment

| Chemical Name in the Inventory | CAS Number |
|---|---|
| **Strychnidin-10-one, 2,3-dimethoxy-** | 357-57-3 |
| **Strychnidin-10-one, 2,3-dimethoxy-, sulfate (2:1)** | 4845-99-2 |

## Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

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ACRONYMS & ABBREVIATIONS

## Grouping Rationale

The chemical brucine (CAS No: 357-57-3; referred to as the parent base in this report) is an alkaloid resembling strychnine, but it is much less potent. It occurs in several plant species, the most well known being the *Strychnos nux-vomica* tree, found in South-East Asia. As brucine sulfate (CAS No: 4845-99-2) is a salt of the parent base (brucine—CAS No: 357-57-3), these two chemicals are considered together in this assessment report. The speciation of these chemicals in biological fluids will be dependant on pH, but independent of the original form.

## Import, Manufacture and Use

### Australian

No specific Australian use, import, or manufacturing information has been identified for either chemical.

### International

The following international uses have been identified through the Galleria Chemica; the eChemPortal, the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical brucine sulfate (CAS No: 4845-99-2) has reported cosmetic use, including in soap and cleaning products.

It is also noted that the chemicals in this group have reported uses as denaturants in alcohols and oils. It is likely that this use may lead to low concentrations of brucine and/or brucine sulfate in domestic or cosmetic products.

Although the brucine sulfate (CAS No: 4845-99-2) has reported a minor cosmetic use (frequency of use is only two) in the United States (Personal Care Products Council, 2011), there are no reported domestic uses for either chemical in the US Household Products Database.

The chemicals in this group have reported commercial use, including as additives for lubricants.

The chemicals in this group have reported site-limited use, including as:

- a denaturant in oils and alcohols; and
- a reagent for separating racemic mixtures.

The chemical brucine (CAS No: 357-57-3) has reported non-industrial use, including as:

- homeopathic medicine; and
- a pesticide in agriculture.

## Restrictions

### Australian

The chemical brucine (CAS No: 357-57-3) is listed in the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2013)) in Schedule 7 with the following exemption:

'except in alcohol containing 0.02 % or less of brucine as a denaturant'.

Schedule 7 chemicals are labelled with 'Dangerous Poison'. These are substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.

### International

The chemicals in this group are listed on the following (Galleria Chemica; CosIng):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist"); and

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part I—List of substances which must not form part of the composition of cosmetic products.

## Existing Worker Health and Safety Controls

### Hazard Classification

The chemicals in this group are classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia) T $^{+}$; R26/R28 (Acute toxicity).

### Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

## Health Hazard Information

There is a lack of available test data relating to the chemicals in this group due to their high acute toxicity. As the availability of the chemicals in this group is highly controlled through their listings in the *Poisons Standard* (SUSMP, 2013) in Schedule 7, public as well as occupational exposure are expected to be limited. Thus, the lack of available data was not a limiting factor for the assessment of public and occupational risk characterisation during this assessment.

### Toxicokinetics

No data are available for the chemicals in this group. There are no known structural reasons to indicate that the chemicals would not exhibit dermal or inhalation bioavailability.

Brucine (CAS No: 357-57-3) is known to have similar pharmacological and toxicological effects to strychnine (CAS: 57-24-9), but is less potent (Malone et al., 1992). Data are available for strychnine, a chemically-related alkaloid to the chemicals in this group. Strychnine is rapidly absorbed via the oral, nasal and parenteral routes. Oral absorption of strychnine is affected by food. Strychnine is readily metabolised and excreted in the urine with approximately 10–20 % excreted unchanged in the urine (IPCS, 1997).

### Acute Toxicity

Oral

The chemicals in this group are classified as hazardous with the risk phrase ‘Very toxic if swallowed’ (T $^{+}$; R28) in HSIS (Safe Work Australia). While the available data for brucine (CAS No: 357-57-3) and human case reports support this classification, limited data are available for brucine sulfate (CAS No: 4845-99-2). The acute toxicity of brucine sulfate is expected to be similar to that of brucine.

The reported oral median lethal dose (LD50) for brucine (CAS No: 357-57-3) is 1 mg/kg bw in rats (IPCS, 1990), 150 mg/kg bw in male Swiss-Webster mice, and 4 mg/kg bw in rabbits. Central nervous system depression was noted in all mice prior to the onset of convulsions (Malone et al., 1992; CIR, 2008; HSDB).

Dermal

No data are available.

Inhalation

The chemicals in this group are classified as hazardous with the risk phrase ‘Very toxic by inhalation’ (T $^{+}$; R26) in HSIS (Safe Work Australia). Based on the high acute toxicity of brucine and the ready nasal absorption (based on strychnine—CAS No: 57-24-9), this classification appears appropriate for both chemicals.

Observation in humans

The chemical brucine (CAS No: 357-57-3) has been reported to be very toxic following ingestion and incidences of suicide-related deaths have been reported. A male ingested an unknown concentration of brucine (CAS No: 357-57-3) resulting in death; a concentration of 5 µg/mL of the chemical was found in the blood (Stanaszek & Lechowicz, 2010). In another report, a male ingested an unknown concentration of brucine resulting in death. A concentration of 1.51 and 4.47 µg/mL was found in the femoral and cardiac blood, respectively. A 1 g dose of the chemical was estimated as the lethal dose (Teske et al., 2011; HSDB). Brucine has also been reported to cause convulsions and weakness in vision, as though seeing through a fog; and tinnitus and headache (HSDB).

Limited data are available regarding acute toxicity via the dermal route. However, based on the available information from a phototoxicity test in humans, chemicals in this group are not likely to have acute dermal toxicity or phototoxicity. In a clinical study, brucine sulfate (CAS No: 4845-99-2) was found not to be phototoxic when used as an alcohol denaturant in a sunscreen product. A sunscreen product containing an alcohol denatured with brucine sulfate was applied using an occlusive patch to 22 fair-skinned subjects for 24 hours followed by UVA irradiation. On a scale of zero to five, 16 subjects observed at 24 hours and six observed at 48 hours after exposure had reaction scores of one. All other subjects had a score of zero. No other adverse effects were observed (CIR, 2008).

## Corrosion / Irritation

### Skin Irritation

No data are available.

### Eye Irritation

No data are available.

### Observation in humans

The chemical brucine (CAS No: 357-57-3) has been reported to cause eyes, nose, and throat irritation in humans (HSDB).

## Sensitisation

### Skin Sensitisation

No data are available.

### Observation in humans

Limited data are available. However, based on the available information from a photosensitivity test in humans, chemicals in this group are not likely to be skin sensitisers at the low concentrations present in formulated products.

The following data are available for brucine sulfate (CAS No: 4845-99-2) when used as an alcohol denaturant in a sunscreen product (CIR, 2008).

The ability of the chemical to induce photosensitivity was evaluated using a sunscreen product containing a specially denatured alcohol 40, denatured using brucine sulfate. Occlusive patches containing the sunscreen product were applied to 103 fair-skinned subjects for 24 hours. After removing the patch, the application sites were irradiated with three minimal erythema doses of ultraviolet A/B. Following a challenge phase and the rest period, the test product was determined to not produce photoallergy.

## Repeated Dose Toxicity

### Oral

No data are available.

### Dermal

No data are available.

### Inhalation

No data are available.

## Genotoxicity

Although limited data are available, the available information indicates that chemicals in this group do not have mutagenic or genotoxic potential. In an Ames assay with four strains of *Salmonella typhimurium* (TA100, TA1535, TA1537 and TA98), brucine (CAS No: 357-57-3) showed negative results in all of the strains at the highest tested dose of 6666 µg/plate, with or without metabolic activation ( Zeiger et al., 1987; HSDB).

### Carcinogenicity

No data are available.

### Reproductive and Developmental Toxicity

No data are available.

## Risk Characterisation

### Critical Health Effects

The critical health effects for risk characterisation include very high systemic acute toxicity by the oral and inhalation routes of exposure.

### Public Risk Characterisation

The use of chemicals in this group in cosmetic and domestic products in Australia is not known. Although the chemicals in this group have reported cosmetic and domestic uses overseas (see **Import, manufacture and use**), only limited evidence of use of brucine sulfate (CAS No: 4845-99-2) in cosmetics was available, having been reported in only two products (Personal Care Products Council, 2011). The use of these chemicals as alcohol denaturants may lead to very low concentrations in formulated cosmetic products (CIR, 2008).

It has been noted that the chemicals in this group have been prohibited for use in cosmetic products in other countries (see **Import, manufacture and use**). Therefore, the use of the chemicals in this group in cosmetic and consumer products is not anticipated in Australia. Furthermore, as the availability of the chemicals in this group is highly controlled through their listings in the *Poisons Standard* (SUSMP, 2013) in Schedule 7, public as well as occupational exposure is expected to be limited. Therefore, the chemicals in this group are not considered to pose an unreasonable risk to public health.

### Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemicals might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemicals at lower concentrations can also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking

(PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

Based on the available data, the existing hazard classification in HSIS is considered appropriate.

## NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

### Regulatory Control

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Very toxic if swallowed (T+; R28)* * Very toxic by inhalation (T+; R26)* | Fatal if swallowed - Cat. 1 (H300) Fatal if inhaled - Cat. 1 (H330) |

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

### Advice for consumers

Products containing the chemicals should be used according to the instruction on the label.

### Advice for industry

***Control measures***

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures, which might minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

***Obligations under workplace health and safety legislation***

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemicals has not been undertaken as part of this assessment.

## References

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at **http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf**

ChemID Plus Advanced. Accessed May 2014 at **http://chem.sis.nlm.nih.gov/chemidplus/**

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Teske J, Weller J-P, Albrecht U-V and Fieguth A 2011. Fatal Intoxication Due to Brucine. Journal of Analytical Toxicology (35) pp. 248-253.

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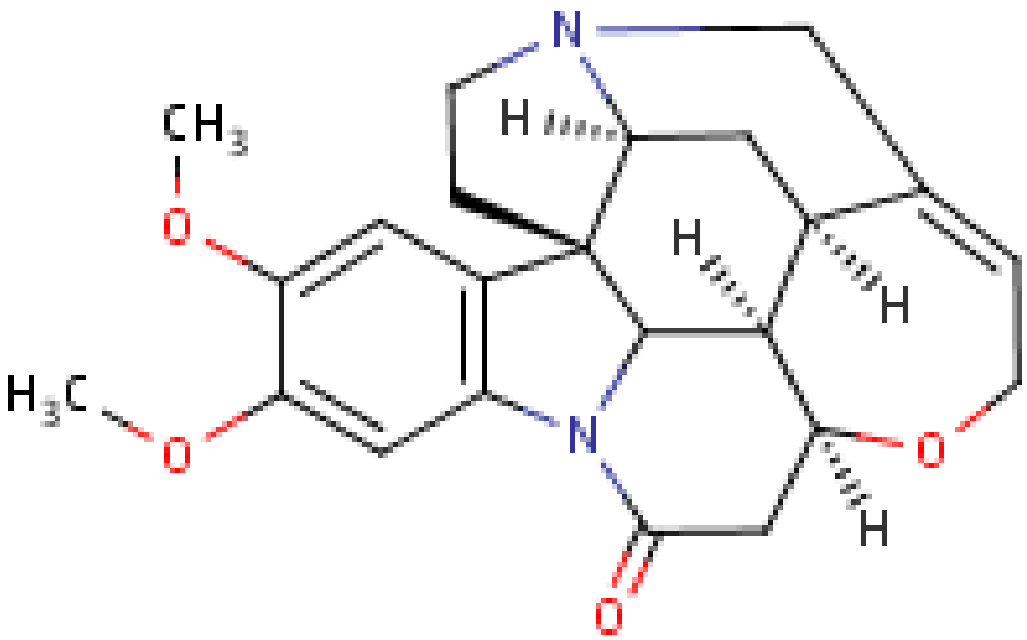
Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K and Speck, W 1987. Salmonella mutagenicity tests. III. Results from the testing of 225 chemicals Environ. Mutagen. Vol. 9 (Suppl 9) pp. 1-109.

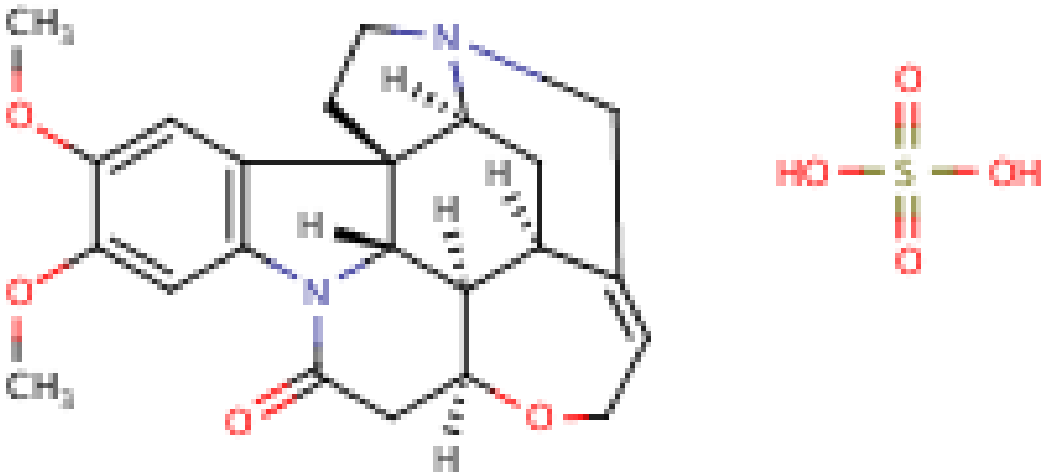
Last Update 04 July 2014

## Chemical Identities

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Strychnidin-10-one, 2,3-dimethoxy-**<br>Brucine<br>(-)-Brucine<br>Brucinum<br>10,11-Dimethoxystrychnine<br>Dimethoxy strychnine |
| CAS Number | 357-57-3 |
| Structural Formula | |

| | |
|---|---|
| |  |
| Molecular Formula | C23H26N2O4 |
| Molecular Weight | 394.47 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Strychnidin-10-one, 2,3-dimethoxy-, sulfate (2:1)**<br>Brucine sulfate (2:1) |
| CAS Number | 4845-99-2 |
| Structural Formula | |



| | |
|---|---|
| Molecular Formula | C23H26N2O4.1/2H2O4S |
| Molecular Weight | 492.55 |

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