# Mercurate(1-), ethyl(2-mercaptobenzoato(2-)-O,S)-, sodium: Human health tier II assessment

**10 March 2017**

## CAS Number: 54-64-8



## 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.

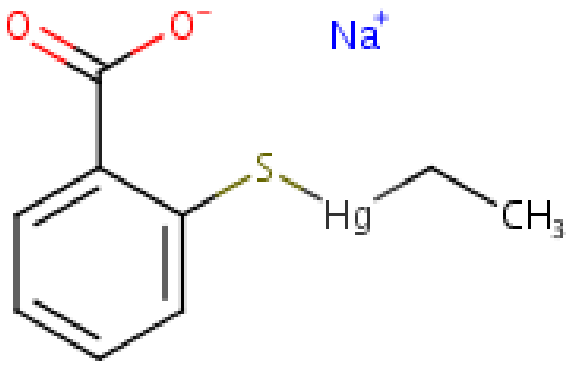
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | ((o-carboxyphenyl)thio)ethylmercury sodium salt<br>sodium ethylmercuric thiosalicylate<br>merthiolate<br>thiomersal<br>thimerosal |
| Structural Formula |  |
| Molecular Formula | C9H9HgO2S.Na |
| Molecular Weight (g/mol) | 404.81 |
| Appearance and Odour (where available) | cream coloured crystalline powder |
| SMILES | C(=O)(c1c(S[Hg]CC)cccc1)O{-}.[Na]{+} |

# Import, Manufacture and Use

## Australian

No specific Australian industrial use, import, or manufacturing information has been identified.

The following non-industrial uses have been identified in Australia:

- the chemical is a constituent in vaccines registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) for use in farm animals; and
- the chemical is a constituent in vaccines registered by the Therapeutic Goods Administration (TGA) for use in humans.

Since the year 2000, vaccines that are part of the National Immunisation Program for children and adolescents have not contained thiomersal (Australian Immunisation Handbook, 10th edition).

## International

The following international uses have been identified through the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the National Toxicology Program (NTP) nomination report for thiomersal (NTP, 2001).

The chemical has reported cosmetic use as a preservative.

The following non-industrial uses have been identified internationally through Galleria Chemica; HSDB; the NTP nomination report for thiomersal (NTP, 2001); and the Substances and Preparations in Nordic countries (SPIN) database.

The chemical has reported non-industrial uses as:

- a bacteriostat, fungistat or anti-infective agent in pharmaceutical products; and
- an agricultural fungicide.

# Restrictions

## Australian

The chemical is covered by general entries for 'MERCURY' (in Schedules 7, 4 and 2, as well as Appendices G and J) and 'MERCURY, organic compounds' (in Appendix E) in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (SUSMP, 2017).

Schedule 7:

'MERCURY except:

a) when separately specified in this Schedule;

b) when included in Schedule 2, 4 or 6;

c) in preparations containing 0.01 per cent or less of mercury in organic form as a

preservative;

d) mercury (metallic) in scientific instruments;

e) dental amalgams; or

f) in a sealed device, for therapeutic use, which prevents access to the mercury.'

Schedule 4:

'MERCURY for cosmetic or therapeutic use except:

a) when separately specified in these Schedules; or

b) in a sealed device which prevents access to the mercury.'

Schedule 2:

'MERCURY for external use in preparations containing 0.5 per cent or less of mercury.'

Schedule 7 chemicals are described as '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'. Schedule 7 chemicals are labelled with 'Dangerous Poison' (SUSMP, 2017).

Schedule 4 chemicals are described as 'Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription'. Schedule 4 chemicals are labelled with 'Prescription Only Medicine or Prescription Animal Remedy' (SUSMP, 2017).

Schedule 2 chemicals are described as 'Substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person'. Schedule 2 chemicals are labelled with 'Pharmacy Medicine' (SUSMP, 2017).

Appendix J, Conditions for availability and use of Schedule 7 poisons:

'MERCURY' is restricted by the following conditions—'Not to be available **except** to authorised or licensed persons'.

Appendix G, Dilute preparations:

'MERCURY' has a concentration cut-off of 1 mg/kg or 1 mg/L.

Appendix E, First aid instructions for poisons:

'MERCURY, organic compounds' and 'MERCURY, organic compounds–in preparations for human external use' must be labelled with the first aid instructions A and S1, and A, respectively. The standard statement for first aid instruction A is 'For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)'. The standard statement for first aid instruction S1 is 'If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water'.

The chemical is an Annex III chemical on the Rotterdam Convention, requiring prior informed consent for importation into Australia (Galleria Chemica).

## International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 7: Preservatives cosmetic products may contain with restrictions;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’); and

- the Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex VI—List of preservatives allowed for use in cosmetic products.

The chemical may be used in eye products at a maximum concentration in ready-for-use preparations of 0.007 % (of mercury (Hg)) and, if mixed with other mercury-containing compounds, the maximum concentration of Hg remains fixed at 0.007 %. Products must also be labelled with 'Contains thiomersal' (CosIng; Galleria Chemica).

The chemical is also restricted by Annex XVII to the REACH Regulations, under the entry for 'Mercury compounds'. The conditions of restriction state that it 'Shall not be placed on the market, or used, as substances or in mixtures where the substance or mixture is intended for use: (a) to prevent the fouling by micro-organisms, plants or animals of: - the hulls of boats, - cages, floats, nets and any other appliances or equipment used for fish or shellfish farming, - any totally or partly submerged appliances or equipment; (b) in the preservation of wood; (c) in the impregnation of heavy-duty industrial textiles and yarn intended for their manufacture; (d) in the treatment of industrial waters, irrespective of their use' (Galleria Chemica).

The World Health Organisation (WHO) recommends that 'total mercury intake should not exceed 5 µg/kg of body weight per week with not more than 3.3 µg/kg per week as methylmercury' (WHO, 1996).

# Existing Work Health and Safety Controls

## Hazard Classification

The chemical is covered by a general entry for 'organic compounds of mercury with the exception of those specified elsewhere in this database' and is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity – category 2; H330 (Fatal if inhaled)
- Acute toxicity – category 1; H310 (Fatal in contact with skin)
- Acute toxicity – category 2; H300 (Fatal if swallowed)
- Specific target organ toxicity (repeated exposure) – category 2; H373 (May cause damage to organs through prolonged or repeated exposure).

## Exposure Standards

### Australian

The chemical is covered by a general entry for 'Mercury alkyl compounds (as Hg)' and has an exposure standard of 0.01 $mg/m^3$ time weighted average (TWA) and 0.03 $mg/m^3$ short-term exposure limit (STEL) (Safe Work Australia).

### International

The following exposure standards are identified for mercury, including alkyl mercury compounds (Galleria Chemica).

An exposure limit of 0.01–0.05 $mg/m^3$ TWA and 0.15 $mg/m^3$ short-term exposure limit (STEL) in different countries such as Japan, Philippines and South Africa.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 0.01 $mg/m^3$ TWA and 0.03 $mg/m^3$ STEL for mercury, alkyl compounds as Hg.

# Health Hazard Information

When data for the chemical being assessed are not available or are limited, health hazard information for compounds of ethylmercury (a metabolite of the chemical) has been included in this report. The IMAP report on (elemental) mercury (NICNAS) complements this report.

## Toxicokinetics

The chemical is an organic alkyl mercury compound, an ethylmercury-sulfidobenzoate, containing approximately 50 % ethylmercury by molecular weight. It is metabolised (or degraded in the presence of sunlight and oxygen) to yield thiosalicylate and the active metabolite, ethylmercury (NCIRS, 2009; ATSDR, 2013; HSDB).

The toxicokinetics of ethylmercury compounds differ from methylmercury compounds, another organic alkyl mercury type. Methylmercury compounds are considered to be more potent than ethylmercury compounds, as they have a longer half-life and are metabolised to inorganic mercury relatively slower, allowing them to accumulate in the body to a greater extent than ethylmercury compounds (Clarkson & Magos, 2006; NCIRS, 2009; ATSDR, 2013). Note that most mercury toxicity reports relate to methylmercury, not the ethylmercury form found in thiomersal.

In general, organic mercury compounds are lipid-soluble and almost completely absorbed (90–100 %) via oral exposure. Absorption following respiratory and dermal exposure is also considered to readily occur, although data are limited. Organic mercury compounds are distributed throughout the body (including the brain and foetus), with the highest mercury accumulation in the kidneys and the liver (ATSDR, 1999).

In adult Squirrel monkeys, thiomersal was administered at doses equivalent to 1 or 6 µg ethylmercury/kg bw/day. The chemical was converted to inorganic mercury, was detected in the kidneys and to a lesser extent in the brain, but did not induce any histopathological changes (NTP, 2001). No further details are available.

In a descriptive study in human infants aged 2 or 6 months, the metabolism of the chemical was assessed in children who received a routine vaccine that contained thiomersal (n = 40) compared with children who received a thiomersal-free vaccine (n = 21). Blood, urine and stools were collected 3–28 days after immunisation for the determination of total mercury. Mean total mercury exposure was 45.6 µg in 2-month-old infants and 111.3 µg in 6-month-old infants who received a vaccine that contained thiomersal. Blood total mercury concentration was 3.75–20.55 nmol/L (or parts per billion, ppb) in 2-month-old infants and <7.50 nmol/L (ppb) in 6-month-old infants who received a vaccine that contained thiomersal. Concentrations were described as 'uniformly low', with 'highest levels … recorded soon after vaccination'. In infants who were immunised with thiomersal-free vaccines, blood total mercury concentrations were below the reliable quantitation limit for all samples except one, which was 4.65 nmol/L (ppb). Urinary total mercury was low or not quantifiable in all samples. Stool total mercury concentrations were slightly higher in the 2-month-old infants compared with the 6-month-old infants and mercury was primarily in the inorganic form. It was noted that 'All children remained healthy throughout the study and during 24–36 months of follow-up'. It was determined that the blood half-life of ethylmercury is seven days and that it is primarily excreted in faeces as inorganic mercury. Total blood mercury in the children immunised with vaccines that contained thiomersal did not exceed the concentration (29 nmol/L or ppb) thought to be safe in cord blood (Pichichero et al., 2002).

## Acute Toxicity

### Oral

Organic mercury compounds (which includes this chemical) are classified as hazardous with hazard category 'Acute toxicity – category 2' and hazard statement ‘Fatal if swallowed’ (H300) in the HCIS (Safe Work Australia). While the limited available data do not support this classification, in the absence of more comprehensive information, and considering that organic mercury

compounds are almost completely absorbed after oral exposure (see **Toxicokinetics** section), there is insufficient evidence to support a recommendation to amend this classification.

The following oral median lethal dose (LD50) values were available (HSDB; RTECS):

- 75 mg/kg bw in rats; and
- 91 mg/kg bw in mice.

No other details are available.

### Dermal

Organic mercury compounds (which includes this chemical) are classified as hazardous with hazard category 'Acute toxicity – category 1' and hazard statement ‘Fatal in contact with skin’ (H310) in the HCIS (Safe Work Australia). Organic mercury compounds are readily absorbed after dermal exposure (see **Toxicokinetics** section). No other data are available to evaluate or to support a recommendation to amend this classification.

### Inhalation

Organic mercury compounds (which includes this chemical) are classified as hazardous with hazard category 'Acute toxicity – category 2' and hazard statement ‘Fatal if inhaled’ (H330) in the HCIS (Safe Work Australia). Organic mercury compounds are readily absorbed after inhalation exposure (see **Toxicokinetics** section). No other data are available to evaluate or to support a recommendation to amend this classification.

### Observation in humans

In a suicide attempt, ingestion of 83 mg/kg bw of the chemical (which is well in excess of the WHO recommendation of intake not exceeding 5 µg/kg bw/week) by a 44-year old male resulted in gastritis (stomach lining inflammation), renal tubular failure, dermatitis (skin inflammation), gingivitis (gum inflammation), delirium, coma, polyneuropathy (generalised peripheral nerve degeneration) and respiratory failure. Death was prevented with clinical intervention (FDA; HSDB).

## Corrosion / Irritation

### Skin Irritation

No data are available.

### Eye Irritation

No data are available.

## Sensitisation

### Skin Sensitisation

No animal data are available.

### Observation in humans

Based on the available data in humans, the chemical is considered to be sensitising, warranting hazard classification (see **Recommendation** section).

Thiomersal is reported to be a contact allergen. Delayed-type hypersensitivity reactions (e.g. redness and swelling) have been observed in some individuals at injection sites following immunisation with vaccines that contained thiomersal. Retrospective analyses of several human patch test studies conducted in contact-sensitised individuals reported positive responses to thiomersal in 1.3–25 % of cases (NTP, 2001; NCIRS, 2009; FDA; HSDB).

In a questionnaire in current and previous car mechanics (n = 801 males, age range 18–63 years), the prevalence of eczema in the last 12 months was self-reported to be 15 % (n = 120). Dermatological examination in 105 of these individuals confirmed irritant contact dermatitis, allergic contact dermatitis, unclassifiable hand eczema and dry skin in 55 %, 19 %, 14 % and 10 % of cases, respectively. In patch-testing, 35 individuals had positive reactions to a range of chemicals and thiomersal was found to be the most common allergen (9 % of cases). The basis for exposure to thiomersal in car mechanics was considered not related to a specific occupational use of the chemical, but from prior immunisation with vaccines that contained thiomersal (Meding et al., 1994).

In subjects (n = 125, 72 females and 53 males, age range 3–65 years) participating in a study to examine thiomersal tolerance, 57 were identified as being sensitised to thiomersal by open or closed patch test using the chemical at 0.05 % in petrolatum vehicle. All subjects were then subjected to intradermal injection of 0.1 mL of the chemical at 100 µg/mL and a positive response was elicited in 24 subjects, all of whom were identified as sensitised by the previous patch test. Intramuscular challenge with 0.1, 0.5 and 1.0 mL of the chemical at 100 µg/mL conducted in all subjects elicited mild local reactions in five subjects, four of whom were identified as sensitised by previous testing. It was concluded that thiomersal in vaccines is 'relatively safe' since more than 90 % of allergic individuals in this study tolerated intramuscular injection of the chemical at similar concentrations to those present in vaccines (Audicana et al., 2002).

Infants in Italy (n = 5, 2 females and 3 males, age range 7–28 months) with atopic dermatitis presented with exacerbated eczema following immunisation with vaccines that contained thiomersal. Positive sensitisation reactions were seen with patch testing using thiomersal in petrolatum at 0.01 % (3/5), 0.05 % (3/5) and 0.1 % (5/5). This sensitisation response did not prevent these children from completing their mandatory immunisations (Risher et al., 2002).

Temporary laryngeal (throat) obstruction, requiring tracheostomy for treatment, was reported in an adult 30 hours after using a spray containing the chemical to treat a minor sore throat. Patch testing using thiomersal was positive (Risher at al., 2002).

## Repeated Dose Toxicity

### Oral

No data are available.

### Dermal

No data are available.

### Inhalation

No data are available.

### Observation in humans

Toxicity in humans has occurred following repeated exposure to the chemical or a metabolite (compounds of ethylmercury) at high doses. At concentrations used in vaccines that contain thiomersal, toxicity does not occur with repeated exposure (see **Toxicokinetics**, **Reproductive and developmental toxicity** and **Other health effects: Neurotoxicity** sections).

An 18-month old female with tympanostomy (ear) tubes was administered 1.2 L of an ear irrigation solution, containing the chemical at 0.1 %, over a six-week period to treat an ear infection. Secondary ingestion occurred via draining of the solution to the nasopharynx, with a total chemical exposure of 127 mg/kg bw. Ataxia, stupor and coma occurred at six weeks, followed by death at 140 days after treatment commenced (Risher et al., 2002).

In 13 infants, systemic absorption occurred following dermal exposure to a tincture containing the chemical at 0.1 %. Infants were administered the tincture between 9 and 48 times for the treatment of exomphalos (abdominal wall weakness), resulting in 10 deaths. High levels of mercury (5152–11330 ppb) were detected in liver, kidney, spleen and heart tissues (FDA; HSDB).

Ethylmercury (not thiomersal) poisoning was reported in a mother and her three children who consumed meat from an animal inadvertently fed with seed that had been treated with two fungicides containing ethylmercury chloride at 1 or 2.5 %. Symptoms were noted in all four cases at least 10 days after meat ingestion, and initially included headache, fever, vomiting, diarrhoea and muscle pain. Other common lesions included impaired heart rhythms and neurological effects (see **Other health effects: Neurotoxicity**). In two of the children (both males, aged 10 and 15 years), respiratory lesions (e.g. pneumonia) necessitated artificial ventilation, and death occurred due to cardiac arrest within 1.5 months of the onset of symptoms. Upon autopsy, myocarditis (heart muscle inflammation), nephritis (kidney inflammation), muscle wastage and neurological damage (see **Other health effects: Neurotoxicity**) were observed (Cinca et al., 1980).

Ethylmercury poisoning was also reported in people from rural Iraqi populations who consumed, over a period of weeks to months, bread that had been prepared with ethylmercury fungicide (ethylmercury *p*-toluene sulfanilamide) treated wheat. Kidney damage, skin lesions (e.g. pruritus or itchiness), skeletal muscle pain and gastrointestinal lesions (e.g. vomiting, diarrhoea, constipation) were reported. In severe cases, cardiac lesions (e.g. irregular pulse, bradycardia or slow heart rate), neurological abnormalities (see **Other health effects: Neurotoxicity**) and death occurred (Jalili & Abbasi, 1961).

## Genotoxicity

Based on the limited available data, the chemical is not expected to be genotoxic.

Point mutations were not observed in *Salmonella typhimurium* strains TA100, TA98, TA 1535 and TA1537 exposed to the chemical at 100–10000 µg/plate, with or without metabolic activation (NTP, 2001).

Aneuploidy was not observed in bone marrow or spermatocytes of mice exposed to the chemical by intraperitoneal (i.p.) injection (doses not available), in assays conducted in different laboratories. Overall, negative results were obtained in three assays, and weakly positive results in one assay (NTP, 2001).

Compounds containing ethylmercury (details not specified), have been reported to give inconclusive results for in vivo chromosomal aberration and aneuploidy assays in human lymphocytes. However, ethylmercury chloride caused spindle disturbances in human HeLa cells exposed to the chemical at 1 µg/mL in vitro, without (but not with) metabolic activation (IARC, 1993).

## Carcinogenicity

Based on the limited available data, the chemical is not expected to be carcinogenic.

In a combined toxicology and carcinogenicity study, Fischer 344 (F344) rats were administered the chemical twice weekly by subcutaneous injection at 0.03, 0.1, 0.3 or 1 mg/kg bw (n = 10, 20, 30 and 40/sex/dose, respectively) for one year. Other groups of rats were untreated (negative control; n = 60/sex) or injected with saline (vehicle control; n = 60/sex). Nickel sulfide ($Ni_3S_2$) at 3.3 or 10 mg/kg bw (n = 20/sex/dose) was used as a positive control, for the induction of local inflammation leading to sarcoma formation. Animals were euthanised 12 or 18 months after their first injection. Cumulative mortality was not considered different between thiomersal and control rats. In rats exposed to thiomersal at the highest dose, body weight was reduced by an average of 10 % (range 5–14 %) at 12 months and 22 % (range 20–23 %) at 18 months, compared with control rats. Weight gain at the lower doses was similar with controls. Dose-related increases in bronchopneumonia were observed in thiomersal-treated rats

compared with control rats. Structural and functional lesions (no details available) were seen on gross pathology and histopathology assessment, respectively. Since mortality was not affected, the lesions were deemed to be slight and cumulative. Testicular tumours were significantly reduced in a dose-dependent manner in thiomersal-treated rats compared with control rats. The incidence of other tumour types was not affected (Mason et al., 1971; NTP, 2001).

## Reproductive and Developmental Toxicity

Based on the available data in humans, the chemical does not cause developmental toxicity in humans at concentrations used in vaccines that contain thiomersal. The limited developmental toxicity data available in animals are not from guideline studies. No data are available on reproductive toxicity related to industrial use of the chemical.

The Global Advisory Committee on Vaccine Safety (GACVS) recently reviewed vaccine safety in pregnancy and lactation and concluded that 'the data remain very reassuring for the use of vaccines during pregnancy, with no evidence of adverse fetal outcomes identified' (WHO, 2012).

Pregnant Wistar rats (n = 10/dose) were exposed to the chemical at 0, 0.2 or 2 % in physiological saline by i.p. injection of a 1 mL volume, from gestation day (GD) 6 to GD 18. Rats were euthanised on GD 20. In the 2 % treatment group, one maternal rat was found to not be pregnant, and another maternal rat died. There were 94, 108 and 70 live foetuses in the 0, 0.2 and 2 % groups, respectively. Congenital malformations were not observed in live foetuses from any treatment group. There were 1, 17 and 39 non-viable (dead or aborted or reabsorbed) foetuses in the 0, 0.2 and 2 % groups, respectively (Gasset et al., 1975; NTP, 2001).

Pregnant New Zealand White rabbits were exposed to the chemical at 0 % (n = 5) or 2 % (n = 7) in physiological saline by eye instillation on GD 6–18. Rats received two drops per eye, eight times a day on GD 6, followed by two drops per eye, four times a day from GD 7–18. Rabbits were euthanised on GD 29. Two and three rabbits were found to not be pregnant in the 0 and 2 % groups, respectively. There were 33 and 34 live foetuses in the 0 and 2 % groups, respectively. Clubbing of the forelegs was observed in one live foetus from each treatment group. There were 6 and 22 non-viable (dead or aborted or reabsorbed) foetuses in the 0 and 2 % groups, respectively (Gasset et al., 1975; NTP, 2001).

The non-viable rat and rabbit foetuses in both studies above were not directly attributed to either foetal or maternal toxicity and it is stated that 'it is impossible to determine whether these embryos which were reabsorbed might have been malformed had they survived in utero for longer periods of time' (Gasset et al., 1975).

## Other Health Effects

### Neurotoxicity

Organic mercury compounds (including this chemical) are classified as hazardous with hazard category 'Specific target organ toxicity (repeated exposure) – category 2' and hazard statement 'May cause damage to organs through prolonged or repeated exposure (H373)' in the HCIS (Safe Work Australia). Considering the toxicokinetics of the chemical and limited data available for a metabolite of the chemical (compounds of ethylmercury), this classification is supported for any potential industrial exposure. At concentrations used in vaccines that contain thiomersal, neurotoxicity does not occur.

In the IOM report, Immunization Safety Review: Vaccines and Autism (2004), it was concluded that 'the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism'. In a more recent review by the GACVS, it was concluded that 'animal or human toxicity studies suggest that the levels of ethyl mercury attained in the blood and brain from cumulative doses of vaccines do not reach toxic levels, making biologically implausible any relation between thiomersal in vaccines and neurological toxicity' (WHO, 2012).

Organic mercury compounds are lipophilic and can therefore cross the blood-brain barrier. Mercury can be retained in the brain more than other organs, with mercury ions becoming oxidised to inorganic divalent mercury and trapped. This can result in neurotoxicity with prolonged or repeated exposure, as the level of mercury accumulates over time, damaging the brain (ATSDR, 1999; NICNAS). However, this would only be expected to occur at levels of exposure higher than that recommended for the general public. Furthermore, the toxicokinetics of ethylmercury makes it less toxic than other forms of alkyl mercury (particularly

methylmercury), as accumulation is less likely to occur due to a shorter half-life in blood and the brain, and rapid excretion in the faeces (see **Toxicokinetics** section).

In case studies of occupational exposure to ethylmercury compounds (not thiomersal) during their production, neurotoxicity was reported. A 29-year old male developed leg weakness, ataxia, dysarthria (motor speech disorder) and bilateral deafness after seven weeks of exposure to ethylmercury chloride during the manufacture of insecticides. Death occurred at 25 weeks following the initial exposure, and severe brain atrophy was observed on autopsy, in regions associated with vision. Elevated inorganic mercury was measured in the liver, kidney and various regions of the brain (Hay et al., 1963). A 50-year old male worker exposed to Fusariol (an ethylmercury cyanide) developed paraesthesia (tingling or numbness), a constricted visual field, dysarthria and symptoms typical of mercury vapour exposure that persisted during an 18 year follow-up period (Schmidt & Harzmann, 1970; cited in Risher et al., 2002). No other details are available.

In a mother and her three children who consumed meat from an animal inadvertently fed with seed that had been treated with two fungicides containing ethylmercury chloride at 1 or 2.5 %, neurological impairments included gait disturbance, ataxia, agitation, speech difficulties, visual disturbances and altered reflexes. The poisoning was fatal in two children, and autopsy revealed nerve cell loss in the brain, demyelination of spinal motor neurones and peripheral nerve damage. Elevated inorganic mercury was found in various organs, including in many regions of the brain and nervous system (Cinca et al., 1980).

In people from rural Iraqi populations who consumed, over a period of weeks to months, bread that had been prepared with ethylmercury fungicide (ethylmercury *p*-toluene sulfanilamide) treated wheat, neurological lesions were reported. These included difficulty or inability to walk, ataxia, speech disturbances, loss of reflexes and restriction of the visual field or loss of vision. Elevated mercury was found, when measured, in the organs (including liver, but others not specified) of the deceased (Jalili & Abbasi, 1961).

# Risk Characterisation

## Critical Health Effects

The critical health effects for risk characterisation include skin sensitisation (local effects) and toxic systemic effects following a single exposure through the oral, dermal and inhalation routes.

The chemical can also cause harmful cumulative effects following repeated exposure at high levels.

## Public Risk Characterisation

The chemical is covered by general entries for 'MERCURY' (in Schedules 7, 4 and 2, as well as Appendices G and J) and 'MERCURY, organic compounds' (in Appendix E) in the SUSMP (SUSMP, 2017). The current controls are considered adequate to minimise the risk to public health posed by cosmetic products containing the chemical; therefore, the chemical is not considered to pose an unreasonable risk to public health.

## Occupational Risk Characterisation

During product formulation, oral, dermal and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. 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 could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal and inhalation exposure 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 the appropriate controls.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

# NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

## Regulatory Control

### Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2017).

### Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Not Applicable | Fatal if swallowed - Cat. 2 (H300)* Fatal in contact with skin - Cat. 1 (H310)* Fatal if inhaled - Cat. 2 (H330)* |
| Sensitisation | Not Applicable | May cause an allergic skin reaction - Cat. 1 (H317) |
| Other Health Effects | Not Applicable | May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)* |

[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 chemical should be used according to the instructions on the label.

## Advice for industry

***Control measures***

Control measures to minimise the risk from oral, dermal and inhalation exposure to the chemical 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 that could 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 help meet 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 chemical has not been undertaken as part of this assessment.

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