2-Propenal, 3-phenyl-: Human health tier II assessment

01 July 2016

CAS Number: 104-55-2

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.

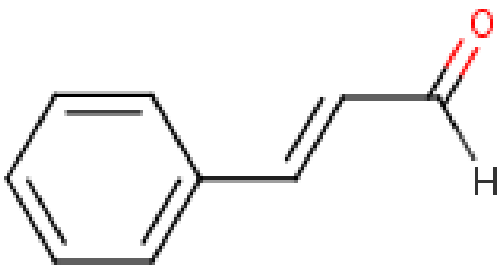
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	cinnamal cinnamaldehyde cinnamic aldehyde cinnamyl aldehyde acrolein, 3-phenyl-
Structural Formula	
Molecular Formula	C9H8O
Molecular Weight (g/mol)	132.2
Appearance and Odour (where available)	yellowish oily liquid with strong odour of cinnamon
SMILES	c1(C={t}CC=O)ccccc1

Import, Manufacture and Use

Australian

The chemical has reported potential domestic use in automotive aftermarket products and reported commercial use in industrial cleaners.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development High Production Volume chemicals programme (OECD HPV); the United States Environmental Protection Agency (US EPA) High Production Volume Information System (US HPVIS); Galleria Chemica; PubChem Compound database; the Substances in Preparations in Nordic countries (SPIN) database; the European Commission (EC) Cosmetic Ingredients and Substances (CosIng) database; the US Personal Care Products Council International Nomenclature Cosmetic Ingredient (INCI) dictionary; the Joint Expert Committee on Food Additives (JECFA, 2001) and National Toxicology Program (NTP, 2004) reports.

The chemical has reported cosmetic uses as:

- a perfuming, flavouring or denaturant agent (personal care products); and
- a shining agent.

The chemical has reported domestic uses in:

- absorbents and adsorbents;
- air care products;
- cleaning and washing agents;
- lubricants and additives; and
- paints and coatings.

The chemical has reported commercial uses in:

- professional cleaning and washing products;
- polishes and wax blends; and
- preparation of corrosion inhibitors.

The chemical has reported site-limited uses in:

- the manufacture of photosensitive chemicals;
- processing aids, specific to petroleum production; and
- solids separation agents.

The chemical has reported non-industrial uses in:

- pharmaceuticals;
- flavouring agents in foods and beverages;
- water treatment agents; and

- pesticides.

Restrictions

Australian

No known restrictions have been identified for the chemical.

International

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

- European Commission (EC) Toy Safety Directive 2009/48/EC: Allergenic fragrances toys shall not contain;
- EC Cosmetics Regulation Annex III (List of substances with restricted use in cosmetic products): The presence of the substance must be indicated in the list of ingredients when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products; and
- the New Zealand Cosmetic Products Group Standard: Schedule 5—Components cosmetic products must not contain except subject to the restrictions and conditions laid down. The presence of the substance must be indicated in the list of ingredients when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products.

The chemical is also included in the International Fragrance Association (IFRA) Standards: the Research Institute for Fragrance Materials (RIFM) Expert Panel established the No Expected Sensitization Induction Level (NESIL) of 590 µg/cm^2 for cinnamaldehyde (IFRA, 2013).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available for the chemical.

International

The US Temporary Emergency Exposure Limits (TEELs) for cinnamaldehyde are 14, 150 and 670 mg/m^3 (Galleria Chemica).

Health Hazard Information

Cinnamaldehyde (CAS No. 104-55-2) is a major component (up to 98 %) of the oil from several plants such as the cinnamon and cassia trees. It can be also synthesised commercially from benzaldehyde and acetaldehyde (FFHPVC, 2005). The chemical

is an α,β-unsaturated aldehyde that is commercially available as a mixture of two geometric isomers, neither of which is individually listed on the Australian Inventory of Chemical Substances (AICS). Cinnamaldehyde predominantly consists of the thermodynamically stable trans-isomer, >97 % trans-cinnamaldehyde (CAS No. 14371-10-9), with up to 1 % cis-cinnamaldehyde (CAS No. 57194-69-1) (NTP, 2004; EFSA, 2015). The isomeric mixture is therefore expected to have a nearly identical profile to the pure trans isomer. Therefore, for toxicity endpoints where the data are incomplete or unavailable for the commercial product (CAS No. 104-55-2), data can be read across from available sources for the purified trans isomer (CAS No. 14371-10-9).

Toxicokinetics

Absorption

The chemical is rapidly and extensively absorbed from the gastrointestinal tract, based on excretion data in rats and mice (e.g. ~80 % and >90 % excreted in urine and faeces at 24 and 72 hours after exposure, respectively) (Bickers et al., 2005; FFHPVC, 2005). In vitro dermal absorption studies reported that 24 % and 52 % cinnamaldehyde was absorbed through human skin, compared with 34 % and 42 % through rat skin within 72 hours under non-occluded and occluded conditions, respectively (Bickers et al., 2005).

Distribution

After single or multiple dose oral exposure, the chemical is distributed primarily to the gastrointestinal tract, kidney and liver, with a small amount distributed to fat (JECFA, 2001; FFHPVC, 2005).

Metabolism

Cinnamaldehyde undergoes extensive oxidation and conjugation to give a variety of metabolites. The major urinary metabolite of cinnamaldehyde is hippuric acid (glycine conjugate of benzoic acid). After repeated treatment with high doses in rats, benzoic acid was found to be the major metabolite, which could suggest a saturation of the glycine conjugation pathway (Bickers et al., 2005; FFHPVC, 2005).

Excretion

Animal data indicate that cinnamaldehyde is excreted as polar metabolites mainly in the urine and, to a lesser extent, in the faeces (~77–90 % vs 7–16 % at 24 hours). The excretion is independent of dose (up to 250 mg/kg bw), species (rats vs mice), sex or route of exposure (oral vs intraperitoneal (i.p.)) (Adams et al., 2004; Bickers et al., 2005; FFHPVC, 2005).

Acute Toxicity

Oral

Cinnamaldehyde has low acute oral toxicity based on animal studies. The median lethal dose (LD50) in rats is >2000 mg/kg bw.

Osborne-Mendel rats (10 animals/sex/dose) were administered single doses of cinnamaldehyde (1910–2600 mg/kg bw) by gavage. Clinical signs of toxicity included reduced activity, diarrhoea, and thin and bony appearance. The LD50 was reported to be 2200 mg/kg bw (Bickers et al., 2005; FFHPVC, 2005; REACH; US HPVIS, 2009).

Dermal

Cinnamaldehyde has moderate acute dermal toxicity based on animal studies, warranting hazard classification (see **Recommendation** section). The dermal LD50 in rabbits was in the range of 620–1260 mg/kg bw (refer to Bickers et al., 2005; Cocchiara et al., 2005; FFHBVC, 2005; and US HPVIS, 2009 for further information).

Albino rabbits (2 animals/dose) were administered a single dose of cinnamaldehyde (0, 0.25, 0.50, 1.0, 2.0 or 4.0 mL/kg bw—equivalent to 0, 263, 525, 1050, 2100 or 4200 mg/kg bw) by application to intact and abraded skin. All animals in the 1.0 mL/kg

and higher dose groups died after treatment. The LD50 was reported to be 620 mg/kg bw (Cocchiara et al., 2005; FFHPVC, 2005; US HPVIS, 2009; REACH).

A single dose of cinnamaldehyde was applied to the skin of New Zealand White (NZW) rabbits (4 animals/sex/dose) at doses of 0, 0.59, 0.83, 1.00, 1.23 or 1.50 mL/kg bw (equivalent to 0, 620, 872, 1050, 1292 or 1575 mg/kg bw). Two animals in the 0.83 mL/kg bw group, one animal each in the 1.00 mL/kg bw and 1.23 mL/kg bw and all four animals in the 1.50 mL/kg bw group died by day three. Deaths were preceded by decreased faeces, lethargy, ataxia and rales. Abnormalities in the treated skin areas, lungs, liver, kidneys and the gastrointestinal tract, brown staining in the anogenital region and yellow staining of the nose and mouth areas were observed in the necropsy examination. Clinical signs included diarrhoea, decreased faeces, emaciation, ataxia and limited mobility due to severe skin reactions. Increased uterine size was reported; however, the dose level at which this effect occurred was not specified. The reported LD50 was 1260 mL/kg bw (FFHPVC, 2005; US HPVIS, 2009; REACH).

Inhalation

No data are available for the chemical.

Corrosion / Irritation

Respiratory Irritation

Limited animal data are available for the chemical. Inhalation of nebulised cinnamaldehyde produced irritating effects in the upper airways of humans in a single study (see **Observation in Human**s section). A NTP review also described the chemical as causing respiratory irritation in humans (NTP, 1989; Birrell et al., 2009). Hazard classification for respiratory irritation is recommended (see **Recommendation** section)

Respiratory irritation was assessed in CF-1 female mice by recording their respiratory rate following exposure to nebulised cinnamaldehyde for 1 minute, either through nose-only breathing or via a tracheal cannula. Marked respiratory depression with nose-only inhalation was observed. The ED25 (dose providing a 25 % reduction in respiratory rate) was calculated to be 241 µg/L. No significant effects were observed when inhalation was through the tracheal cannula (Cocchiara et al., 2005).

Skin Irritation

The available information from animal and human studies (see **Observation in Humans** section) suggests that cinnamaldehyde causes irritation to the skin, warranting hazard classification (see **Recommendation** section).

Cinnamaldehyde produced severe irritation in rabbits when applied undiluted, mild irritation in mice and guinea pigs at concentrations of 3–5 %, and was non-irritating to rabbits at 1 % (Bickers et al., 2005). The US EPA considers cinnamaldehyde a strong skin irritant in guinea pigs (no study details provided) (US HPVIS, 2009).

Eye Irritation

The available information from animal and human studies (see **Observation in Humans** section) suggests that cinnamaldehyde causes irritation to the eyes, supporting a recommendation for hazard classification (see **Recommendation** section).

Several international agencies have concluded that cinnamaldehyde is an eye irritant (US HPVIS, 2009; REACH), and a number of notifications to the Classification and Labelling Inventory by industry in the European Union have indicated the chemical as irritating to the eyes (ECHA C&L).

In NZW rabbits, eye irritation was observed with undiluted cinnamaldehyde, and effects were not completely reversed after 7 days (Cocchiara et al., 2005). In three separate experiments, concentrations of 0.125 %, 1 % and 1.25 % cinnamaldehyde were instilled in rabbit eyes. Intense to mild conjunctival irritation was observed and, at the highest concentration (1.25 %), severe

chemosis and considerable discharge were observed. The effects were reversible after a week at all concentrations except the highest (Bickers et al., 2005; Cocchiara et al., 2005).

Observation in humans

Dermal

The chemical has been shown to cause skin irritation in humans in a number of reports. The chemical produced irritation in 10/63 volunteers at 3 % in diethyl phthalate/ethanol (ratio of 3:1). Severe skin irritation was observed in 5/5 volunteers treated with 8 % cinnamaldehyde in petrolatum (Bickers et al., 2005). In another study, doses of 40 and 48 mg of cinnamaldehyde in petrolatum (concentrations not reported) were applied under occlusive conditions to human skin for 48 hours. The chemical was concluded to be severely irritating to human skin (REACH). A review carried out by the RIFM Expert Panel reported that cinnamaldehyde produced no skin irritation effects in 171 volunteers at concentrations of 0.125–1.25 % in a variety of vehicles (Bickers et al., 2005).

Eye

In a limited data eye irritation study, a solution of 8 % cinnamaldehyde was instilled in human eyes. The chemical produced slightly irritating effects. It was noted that the cornea was not affected; however, no further details were described (US HPVIS, 2009; REACH).

Respiratory

Cinnamaldehyde induced coughing in all ten human subjects following inhalation of nebulised chemical (dose levels from 125–800 mM), with a distinct dose-response relationship observed—the response being the number of coughs recorded after exposure to the chemical. The chemical was found to be a specific agonist of the TRPA-1 receptor, and induced cough due to chemaesthesis of the airways (Birrell et al., 2009).

Sensitisation

Skin Sensitisation

The available information from animal and human studies (even with low concentrations of the chemical; see **Observation in Humans** section), suggests that cinnamaldehyde causes sensitisation to the skin, supporting a recommendation for hazard classification (see **Recommendation** section).

The chemical was considered to be a moderate to strong skin sensitiser based on the positive results in several local lymph node assays (LLNA). The EC3 value (concentration required to provoke a 3-fold increase in lymph node cell proliferative activity compared with controls) was reported to be as low as 0.2 % (SCCS, 2012).

In a study equivalent to OECD TG 429, cinnamaldehyde was reported to be positive for skin sensitisation in an in vivo mouse LLNA. The mice were administered 0, 0.1 %, 0.3 %, 1.0 %, 3.0 % or 10.0 % (w/v) of the chemical in ethanol/diethyl phthalate (ratio of 3:1). Stimulation indices (SI) were not reported; however, the EC3 was determined to be 0.2 % (SCCS, 2012). A similar study with the chemical, at doses of 0, 0.5 %, 1.0 %, 2.5 %, 5 % and 10 % in acetone/olive oil (ratio of 4:1), reported positive results for skin sensitisation with SI of 1, 1.4, 0.9, 1.9, 7.1 and 15.8 respectively. An EC3 of 3.1 % was calculated (Basketter et al., 2001; SCCS, 2012).

The chemical has also been reported as sensitising at almost all concentrations (0.1–20 %) studied in various guinea pig sensitisation tests (Bickers et al., 2005; Danish EPA, 2016; NTP, 2004; US HPVIS, 2009; REACH). A recent review of cinnamaldehyde by the Danish EPA reported skin sensitisation effects in 90–100 % of animals tested at a concentration of 0.75 % in three separate guinea pig maximisation tests (GPMTs). Strong sensitisation effects were also reported with 3 % cinnamaldehyde, although further study details were not provided (see Danish EPA, 2016 for review). In a modified Draize test, an injection challenge concentration of 0.25 % cinnamaldehyde with a 20 % topical application challenge dose resulted in sensitisation effects after the challenge was repeated a week later. In addition, concentrations of 0.1–1.0 % cinnamaldehyde in acetone have resulted in skin sensitisation effects at all doses (Bickers et al., 2005).

A 3-day application of 10 % cinnamaldehyde on the ear dorsum in mice resulted in a high differentiation index (DI) of 8.7, according to OECD standards. The DI is defined as a ratio of maximum response percentages in lymph node activation and skin inflammation, where a DI >1 indicates an allergic reaction pattern (REACH).

Observation in humans

Cinnamaldehyde is a well-recognised and frequently reported consumer contact allergen (SCCNFP, 1999; RIVM, 2009; SCCS, 2012; IFRA, 2013). It is one of eight components of the diagnostic test, the fragrance mix, used by dermatologists to determine if a patient has allergies to common chemicals used in fragrances. It is an established contact allergen in humans according to the Scientific Committee on Consumer Safety (2012), and accounts for 5–36 % of the reactions to the fragrance mix (SCCNFP, 1999).

A number of human repeat insult patch tests (HRIPTs) have been undertaken to determine the skin sensitisation potential of cinnamaldehyde in healthy volunteers, as well as groups of subjects suspected of skin allergies to fragrances (SCCNFP, 1999; NTP, 2004; Cocchiara et al., 2005). Although fewer cases of sensitisation were found when the concentration of the chemical was less than 1 %, positive allergic responses have been reported in cases where the administered concentration of cinnamaldehyde was as low as 0.2 % (Cocchiara et al., 2005). Skin irritation effects were generally predominant at concentrations above 3 % cinnamaldehyde, and often impeded the interpretation of results from the patch testing (SCCNFP, 1999; NTP, 2004).

Many cases of skin sensitisation have occurred following occupational and consumer exposure to the chemical. Workers in spice manufacturing plants, hairdressing salons and bakeries have reported cases of contact dermatitis that were traced back to cinnamaldehyde. In addition, exposure of consumers to toothpaste, cosmetics and perfumes containing the chemical as a fragrance ingredient have resulted in a number of case studies identifying cinnamaldehyde as an agent responsible for the allergic reactions (see SCCNFP, 1999; NTP, 2004; Cocchiara et al., 2005 for review).

Repeated Dose Toxicity

Oral

Cinnamaldehyde is 'generally regarded as safe' (GRAS) for use as a flavour ingredient by the US Food and Drug Administration (US FDA, 2015), reflecting the low level of concern regarding its potential for long-term toxicity via the oral route. Considering the no observed adverse effect levels (NOAELs) of 68–200 mg/kg bw/day, based on 17-week to 2-year rat studies (read across), and no toxicologically significant treatment-related effects reported in various studies, repeated oral exposure to the chemical is not considered to cause serious damage to health.

In a 17-week study, rats dosed with cinnamaldehyde at 68 mg/kg bw/day showed no significant differences from the control animals (Adams et al., 2004; REACH).

In a 12-week repeated oral toxicity study, rats (20 animals/sex/dose) were fed a diet containing estimated doses of cinnamaldehyde of 0, 50, 100 or 200 mg/kg bw/day. No significant changes were observed in the treated groups. There were no adverse histopathological findings, although gross examination revealed an occasional occurrence of respiratory infections in treated animals. A NOAEL of 200 mg/kg bw/day was reported (JECFA, 2001; Adams et al., 2004; FFHPVC, 2005; REACH).

In a 2-year combined toxicology and carcinogenicity study, Fischer 344 (F344/N) rats (50 animals/sex/dose) were fed microencapsulated trans-cinnamaldehyde (CAS No. 14371-10-9) at doses of 0, 1000, 2100 or 4100 ppm daily (equivalent to 0, 50, 100 or 200 mg/kg bw/day). There were no clinical findings related to trans-cinnamaldehyde exposure. The NOAEL for non-neoplastic effects was determined to be 200 mg/kg bw/day (NTP, 2004; REACH).

Dermal

Based on the limited data available, the chemical is not considered to cause serious damage to health by repeated dermal exposure.

In a short-term repeat dose dermal toxicity study, mice (strains not reported) were treated with cinnamaldehyde at 250 mg/kg bw/day for three days. A TDLo and lowest observed adverse effect level (LOAEL) of 250 mg/kg bw/day were reported based on sensitisation effects; however, no details on systemic toxicity were reported (REACH).

Inhalation

No data are available for the chemical.

Genotoxicity

The chemical cinnamaldehyde contains an α,β-unsaturated aldehyde group, a common structural alert for genotoxicity due to the ability of the chemical to form DNA adducts. However, based on the available data, the chemical is not considered to be genotoxic.

The chemical cinnamaldehyde and the isomer trans-cinnamaldehyde (CAS No. 14371-10-9) were negative for point mutations in almost all strains of *Salmonella typhimurium* in the Ames test. A positive result was found only with TA100 strain, and in only two out of eleven tests. Evidence of genotoxic activity was also observed in isolated mammalian cells. However, these results were weakly positive and observed at cytotoxic concentrations. A sex-linked recessive lethal test in *Drosophila melanogaster* demonstrated that systemically-available chemical (administered via injection) could enter germ cells and induce mutations; however, oral dosing did not produce the same effect. Importantly, the reported activity in in vitro and insect studies did not translate into significant genotoxic activity in mammalian systems in vivo.

In vitro

In a bacterial gene mutation assay, *S. typhimurium* strains TA97, TA98, TA100, TA1335 and TA1537 were treated with cinnamaldehyde at 100 µL/plate with and without metabolic activation. No mutagenic activity was observed in the majority of strains tested; however, a positive result was seen in strain TA100, with and without metabolic activation. In another study, trans-cinnamaldehyde (CAS No. 14371-10-9) also gave a weakly positive result in *S. typhimurium* strain TA100 (300 µL/plate) with metabolic activation, and negative results in all other strains tested (TA102, TA104). These positive results were not confirmed in similar studies on the same strain of *S. typhimurium* with the chemical or the purified trans isomer.

In other mutation assays, cinnamaldehyde was found to be negative for genotoxicity in *Escherichia coli* strain WP2 uvrA at 600 µg and 800 µg per plate. The chemical was also not mutagenic in ten different assays in *Bacillus subtilis* H17 Rec+ and Chinese hamster V79 cells at concentrations ranging from 0.05 to 5000 µg/plate in the presence and absence of metabolic activation (Adams et al., 2004; FFHPVC, 2005; REACH).

Tests for the induction of sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells exposed to cinnamaldehyde produced negative results at low concentrations, and weakly positive results at concentrations approaching cytotoxic levels, suggesting only weak SCE activity. The chemical was also reported to induce chromosomal aberrations at low concentrations (<15 µg/mL) in Chinese hamster lung fibroblasts and B241 cells tested with and without metabolic activation. However, in another study, higher concentrations (up to 100 µg/mL) were negative in CHO cells, with and without metabolic activation. Chromosomal aberrations were not detected in human HAIN-55 fibroblast cells (Adams et al., 2005; EFSA, 2009; Bickers et al., 2005).

In vivo

In a mouse bone marrow micronucleus assay, male ddY mice were administered cinnamaldehyde via i.p. injection at doses of 0, 125, 250, 500 and 1000 mg/kg bw. The frequency of micronucleated polychromatic erythrocytes did not increase at any dose up until the end of study, 3 days following administration (US HPVIS, 2009).

In two mammalian tests, cinnamaldehyde was administered to male F344/N rats and male and female B6C3F1 mice at oral doses of 0, 50, 200 or 1000 mg/kg bw/day. No evidence of an increase in unscheduled DNA synthesis or S-phase synthesis was observed in either species (Adams et al., 2004; FFHPVC, 2005; US HPVIS, 2009).

In a micronucleus assay in male albino Sprague Dawley (SD) rats and male Swiss mice, doses of 0, 550, 1100 and 1650 mg/kg bw (rats) and 0, 850, 1700 and 2550 mg/kg bw (mice) of cinnamaldehyde were administered by oral gavage. The highest doses in each study were found to be lethal in some animals. No increases in the frequency of micronuclei in erythrocytes were

observed in either species up to doses of 1100 mg/kg bw (rats) and 1700 mg/kg bw (mice). However, induction of micronuclei in hepatocytes (both species) and forestomach mucosal cells (rats) was observed. These positive results were attributed to the method of gavaging with large bolus doses of the chemical, resulting in high exposure of the stomach and liver. The chemical was not considered to be clastogenic in this study (Bickers et al., 2005; FFHPVC, 2005; US HPVIS, 2009).

In a sex-linked recessive lethal mutation test in *Drosophila melanogaster* males, no effects were observed following oral feeding of cinnamaldehyde (800 ppm). However, the chemical was found to induce sex-linked recessive lethal mutations (but not reciprocal translocation mutations) following injection of cinnamaldehyde (20 000 ppm) (Bickers et al., 2005).

Carcinogenicity

Based on the limited data available for cinnamaldehyde and trans-cinnamaldehyde (CAS No. 14371-10-9), the chemical is not expected to have carcinogenic potential.

In a two-year carcinogenicity study, groups of F344/N rats and B6C3F1 mice (50 animals/sex/dose) were fed microencapsulated trans-cinnamaldehyde (CAS No. 14371-10-9) by daily gavage at doses of 0, 1000, 2100 or 4100 ppm (equivalent to 0, 50, 100 or 200 mg/kg bw/day). Increased incidences of preputial and prostate gland adenomas and mononuclear cell leukaemia were considered to be within the historical range in controls, or likely to represent biological variations unrelated to exposure to the chemical. No other treatment-related neoplasms or non-neoplastic lesions were reported in either species (Adams et al., 2004; NTP, 2004; REACH; US HPVIS, 2009).

Reproductive and Developmental Toxicity

Based on the limited data available, the chemical is not expected to have the potential for reproductive or developmental toxicity. Any developmental effects were only observed secondary to maternal toxicity.

In a two-generation study in rats (strains not reported), cinnamaldehyde (absolute dose 2 mg—route not specified) was dosed every two days for 223 and 210 days and did not have any effects on body weight gain, reproductive ability, development or viability of offspring (NTP, 2004).

Cinnamaldehyde in olive oil was administered to female SD rats via oral gavage at doses of 0, 5, 25 or 250 mg/kg bw/day on gestation days (GD) 7–17. Treatment-related, increased incidence of defective cranial ossification in all dose groups was observed. Renal abnormalities including dilated pelvis and reduced papilla and dilated ureters were observed at low and mid doses, but not at high dose. Offspring at ≥25 mg/kg bw/day had significantly increased instances of reduced ossification of the tympanic bulla. An increase in the incidence of abnormal sternebrae was also reported in the 25 mg/kg bw/day group. However, these effects were not found to be dose-related and may be attributed to a decrease in maternal weight gain that was noted in the mid- and high-dose groups. A LOAEL of 5 mg/kg bw/day for developmental toxicity was reported based on the reduced cranial ossification and kidney variations. A LOAEL of 25 mg/kg bw/day was reported for maternal toxicity based on the reduced weight gain observed in the dams (Adams et al., 2004; NTP, 2004; US HPVIS, 2009; HSDB; REACH).

No signs of toxicity were reported in the dams or in the offspring of CD-1 mice after exposure to 1200 mg/kg bw/day during GD 6–13 (cinnamaldehyde) or GD 7–14 (trans-cinnamaldehyde) (NTP, 2004; US HPVIS, 2009; REACH).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation. Other observed health effects include systemic acute effects (acute toxicity from dermal exposure) and local effects (eye/skin/respiratory irritation).

Public Risk Characterisation

Considering the range of domestic, cosmetic and personal care products that may contain the chemical, the main route of public exposure is expected to be dermal. There is also possible ocular and inhalation exposure from products applied as aerosols. At the applied concentrations, the irritant effects of cinnamaldehyde are unlikely to present a risk. However, there are recorded cases of human skin sensitisation attributed to fragrance use.

The risk of skin sensitisation could be mitigated by implementing concentration limits and restricting uses to limit dermal exposure. The restrictions on the use of the chemical in cosmetic products in New Zealand and the European Union (see **International restrictions**) are considered appropriate to mitigate the risk.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalational 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 systemic acute and local effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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 HSIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products be managed through changes to poisons scheduling, risks to work health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered sufficient provided that risk management recommendations are implemented and all requirements are met under work health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

It is recommended that the chemical should be included in the *Poisons Standard* (the Standard for the Uniform Scheduling of Medicines and Poisons) with appropriate restrictions on the sale, supply and use of the chemical in domestic and cosmetic products.

Consideration should be given to the following:

- the chemical is an established contact allergen in humans;
- the chemical is a potential strong skin sensitiser, based on an LLNA-derived EC3 value of 0.2 %;
- the existing overseas restrictions (New Zealand, EU) on the use of the chemical in cosmetic products, where the presence of the chemical must be indicated in the list of ingredients when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products;
- the most recent SCCS opinion on cinnamaldehyde recommends a concentration limit of 0.01 % for safe use of the chemical as a fragrance in cosmetic products (SCCS, 2012); and
- the current IFRA guidelines restrict use of the chemical to concentrations of 0.02 % in lip care and deodorant/anti-perspirant products, 0.04 % in intimate wipes, 0.4 % in mouthwashes and 0.05 % in all other personal care products

including fragrances (IFRA, 2013).

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful in contact with skin (Xn; R21)	Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Irritating to eyes (Xi; R36) Irritating to skin (Xi; R38) Irritating to respiratory system (Xi; R37)	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[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 industry

Control measures

Control measures to minimise the risk from dermal, ocular 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:

- 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;
- 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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Last update 01 July 2016

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