Benzenepropanal, 4-(1,1-dimethylethyl)-.alpha.-methyl-: Human health tier II assessment

25 November 2016

CAS Number: 80-54-6

- Preface
- Chemical Identity
- Import, Manufacture and Use
- Restrictions
- Existing Work Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References

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.

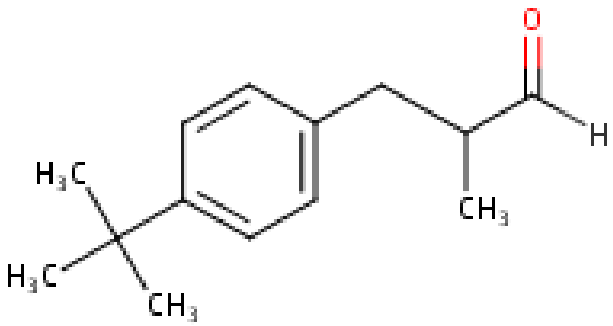
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	lilial 2-(4-tert-butylbenzyl)propionaldehyde p-tert-butyl-alpha-methylhydrocinnamic aldehyde alpha-methyl-p-(tert-butyl)hydrocinnamaldehyde alpha-methyl, beta-(p-tert-butylphenyl)propionaldehyde
Structural Formula	
Molecular Formula	C14H20O
Molecular Weight (g/mol)	204.311
Appearance and Odour (where available)	colourless liquid with a floral odour
SMILES	C(C)(C)(C)c1ccc(CC(C)C=O)cc1

Import, Manufacture and Use

Australian

The chemical has reported cosmetic use as a fragrance ingredient on the Australian Botanical Products catalogue (ABP).

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the International Fragrance Association (IFRA); the European Chemicals Agency (ECHA); and the Scientific Committee for Consumer Safety (SCCS).

The chemical has reported use in cosmetic and personal care products. It is used as a fragrance in various industries (BASF SE, 2013). Maximum concentrations of the chemical (in finished products) were reported to be in (SCCS, 2015):

- hydroalcoholic products: 0.6 % (if used on shaved skin) or 1.9 % (if used on non-shaved skin);

- deodorants: 0.12 %;
- make-up products: 0.05 %;
- liquid foundations: 0.04 %;
- face creams: 0.05 %;
- body lotions: 0.1 %;
- shampoos and conditioners: 0.05 %;
- hair styling products: 0.04 %; and
- shower gels and bath products: 0.1 %.

The chemical has also reported domestic uses in:

- washing and cleaning products; and
- air care products.

The chemical has reported commercial uses in:

- coatings and paints;
- ink/toners; and
- polishes and wax blends.

The chemical has reported non-industrial use as a fragrance ingredient in biocidal products.

Restrictions

Australian

No known restrictions have been identified.

International

Using the chemical in cosmetics in the European Union is subject to the restrictions described in EU Regulation Annex III (Galleria Chemica). This 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 (CosIng).

The International Fragrance Association (IFRA) has established concentrations limits to be used for the chemical in finished cosmetic and personal care products (IFRA, 2015). The maximum concentrations allowed are (IFRA, 2015; SCCS, 2015):

- 0.1 % in lip products;
- 0.2 % in deodorants and antiperspirants;
- 0.6 % in hydroalcoholic products for shaved skin;
- 1.9 % in hydroalcoholic products for unshaved skin;
- 1 % for women's facial creams;
- 3 % (mouthwash and toothpaste products);
- 2 % in make-up products; and
- 2.5 % in shampoos and conditioners.

However, use in oral personal care products is not expected (BASF, 2013).

Existing Work Health and Safety Controls

Hazard Classification

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

In the European Union, the chemical is currently the subject of a proposal for harmonised classification and labelling regarding its reproductive toxicity (BASF SE, 2013).

The main metabolite of the chemical, p-tert-butylbenzoic acid (TBBA) (CAS No. 98-73-7) has been assessed by NICNAS and is classified as hazardous, with the following risk phrases for human health in the HSIS (Safe Work Australia):

- Xn; R22 (acute toxicity)
- T; R48/23/24/25 (repeat dose toxicity)
- Repr. Cat. 2; R60 (reproductive toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

The chemical is a synthetic substance that has not been reported to occur in nature (Arnau et al., 2000).

Based on the available data, the chemical is expected to have low percutaneous absorption in humans (max. 2.4 %), but cream formulations containing the chemical may increase the absorption rate (SCCS, 2015). The SCCS stated that the maximum amount of chemical expected to be dermally absorbed was 5 % in ethanolic formulations and 25 % in cream formulations (SCCS, 2015).

In three human volunteers dermally exposed for six hours to the chemical at 70 % (in ethanol), 0.8–2.4 % of the applied dose was excreted in the urine within 24 hours (BASF SE, 2013).

In vitro dermal absorption studies showed that the chemical applied in different formulations had a much higher absorption rate in naked rat skin compared with mini pig skin. Mini pig skin is reported to be more comparable to human skin (SCCS, 2015). The chemical applied to excised skin of mini pigs had a greater bioavailability in cream formulations (25 %) than in methylcarbitol (0.8 %) or ethanol (4.9 %). Based on these results, the SCCS concluded that the chemical 'might also better penetrate human skin when it is applied in cream formulations' (SCCS, 2015). The SCCS will publish a reassessment of the chemical that will include additional information on dermal absorption through human skin.

In general, the chemical is expected to have high bioavailability via the oral route. In rats, the chemical is distributed predominantly to the liver after dermal exposure. The same behaviour is expected following oral administration (BASF SE, 2013).

In a plasma pharmacokinetic study in rats, single oral doses of 25 or 100 mg/kg bw resulted in peak plasma levels of 52 µg equivalent/mL at 1.75 hours and 14.3 µg equivalent/mL at 3.5 hours, respectively. These levels were compared to those obtained in humans dermally exposed to 16 g of the chemical (estimated to represent a high-level exposure from a cosmetic application). This comparison led to the conclusion that "the adverse effect levels were at least three orders of magnitude greater than levels of exposure in humans under condition of use" (FFHPVC, 2005).

In urinary excretion, two metabolites were identified in rats, mice, rabbits and humans: p-tert-butylbenzoic acid (TBBA) and p-tert-butylhippuric acid (TBHA), deriving from TBBA (BASF SE, 2013).

In vitro data showed that TBBA formation was predominant in rat hepatocytes when compared with other species. The levels of TBBA in human hepatocytes were four times lower than in rat hepatocytes at corresponding incubation concentrations. After incubation with doses of the chemical eliciting testicular toxicity in rats, TBBA levels in human hepatocytes were comparable to those found in rabbits, indicating humans to be less sensitive compared with rats (BASF SE, 2013).

Acute Toxicity

Oral

The chemical has moderate acute oral toxicity in rats, warranting hazard classification.

In an acute oral toxicity study, compliant with the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 401, the chemical was administered as single doses of 681, 1000, 1470, 2150 or 3160 mg/kg bw to Sprague Dawley (SD) rats. The median lethal dose (LD50) was reported to be 1390 mg/kg bw (REACHa; SCCS, 2015). Observed sublethal effects included somnolence (general depressed activity) and dyspnoea (difficulty breathing).

Dermal

The chemical has low acute dermal toxicity in rats and rabbits.

In an acute dermal toxicity study (equivalent to OECD TG 402), the LD50 in SD rats was reported to be >2000 mg/kg bw, as there were no animal deaths during the 14-day observation period of the study. Observed clinical effects and local effects (all reversible) included dyspnoea, agitation, apathy, staggering, rough fur coat, lacrimation, poor general condition and slight erythema/oedema followed by desquamation (REACHa; SCCS, 2015).

In another dermal toxicity study, the LD50 in rabbits (n = 3/sex) was reported to be 4700 mg/kg bw, as there were no animal deaths during the 14-day observation period. Clinical signs included erythema and thickened wrinkled skin but no systemic effects were reported (SCCS, 2015).

Inhalation

Only limited data are available.

In an inhalation hazard test, SD rats (n = 6/sex) were exposed (whole-body) to an atmosphere saturated with vapours of the chemical (at 20°C) for seven hours. At the concentration of 0.18 mg/L, there were no mortalities observed in rats, but signs of systemic toxicity were observed (details not available) (REACHa; SCCS, 2015).

Corrosion / Irritation

Respiratory Irritation

Limited information is available.

In a respiratory irritation study, albino female mice (n = 4/dose) were exposed (nose-only) to the chemical at concentrations of 69.8, 256.9 or 815.4 µg/L for one to five minutes. The respiration rate was recorded for 30 seconds, at three, five and 15 minutes post-exposure. A concentration-related decrease in respiration rate was observed (2.6, 15.2 and 41.2 % decrease at 69.8, 256.9 and 815.2 µg/L, respectively) (SCCS, 2015).

Skin Irritation

The chemical is a skin irritant, warranting hazard classification.

In a study performed in accordance with the OECD TG 404, undiluted chemical applied to the shaved skin of New Zealand White (NZW) rabbits (n = 3) produced moderate erythema (score of 2) and oedema (score of 2.6) after four hours of exposure (mean scores for all animals after 24, 48 and 72 hours). After seven days, the exposed areas had effects that were not reversed in at least two animals with well-defined erythema and slight oedema (REACHa; SCCS, 2015).

In a skin irritation study, four rabbits were exposed (semi-occlusive applications) to undiluted chemical for four hours. The mean oedema and erythema scores (after 24, 48 and 72 h) were 1.7 and 1.9, respectively. Desquamation was observed in all animals after seven days (SCCS, 2015).

In another skin irritation study, six female rabbits were exposed on both flanks (one abraded, the other intact) to a solution containing the chemical at 0.2 % in propylene glycol for 24 hours under occlusive dressing. No oedema was observed. One hour after removing the patch, very slight (in 3/6 animals) to well defined (in 1/6 animals) erythema was observed on both flanks and disappeared within 48 hours. The primary irritation score was 0.5 (SCCS, 2015). The chemical is not irritating to the skin at 0.2 %.

Eye Irritation

The chemical is considered slightly irritating to the eyes.

In an eye irritation study (performed according to FDA Register 38. No. 187, Para. 1500.41, S27029), undiluted chemical instilled into one eye of each of three Vienna white rabbits induced slight redness in all animals within 24 hours. Redness persisted in one rabbit 48 hours after instillation and

disappeared by 72 hours after exposure. No other effects were observed (mean scores for cornea, iris and chemosis were 0) (REACHa).

In another study (compliant with OECD TG 405), the chemical was found to cause 'mild and transient effects' in rabbit eyes (SCCS, 2015). Three NZW rabbits were exposed to the chemical (undiluted or at 10 or 30 % in diethyl phthalate) by instillation into one eye of each rabbit. No corneal or iris effects were observed. Undiluted chemical caused conjunctival redness (score: 1) and chemosis (score: 1) up to 72 and 24 hours post-exposure, respectively. At 10 and 30 %, the chemical induced conjunctival redness, up to 24 hours post-exposure. All effects were reversible within seven days (SCCS, 2015).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is considered to be a skin sensitiser, warranting hazard classification.

In a local lymph node assay (LLNA), four female CBA/Ca mice were exposed to the chemical at 0, 1, 2.5, 10, 25 or 50 % (in a mix of acetone/olive oil at 4:1, v/v). The reported stimulation index (SI) values were: 1, 1.3, 2.47, 2.02, 3.71 and 9.26 respectively. The concentration required to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated as 18.7 %, indicating the chemical as a weak skin sensitiser (Basketter et al., 2001; SCCS, 2015).

In another LLNA study conducted in male CBA/Ca mice, the chemical was tested at concentrations of 0, 1, 3, 10, 30 or 50 % in diethyl phthalate (DEP) or ethanol (EtOH) and at concentrations of 0, 0.3, 1, 3, 10 or 30 % in a mix of EtOH:DEP (at 1:3 or 3:1). The calculated EC3 values were 4.2, 3, 13.9 and 8.8 %, for the corresponding vehicles (DEP, EtOH, 1:3 EtOH:DEP and 3:1 EtOH:DEP, respectively). Regardless of the type of vehicle used in the assay, the chemical showed a potential for skin sensitisation. The strongest result, obtained with EtOH, indicated the chemical to be a moderate skin sensitiser while the use of a mix of vehicles resulted in weak sensitising potential. According to the study authors, the combination of EtOH and DEP should be the preferred vehicle option to extrapolate results to humans (Lalko, 2004).

In two other murine LLNA, the following results were reported (SCCS, 2015):

- four female CBA mice were tested at concentrations of 1, 2.5, 5, 10 or 25 % of the chemical in acetone: oil; the chemical was positive (SI>3) at 25 % concentration only; and
- the chemical was found positive for skin sensitisation at all concentrations tested (10, 25 or 50 % in EtOH, or undiluted chemical). Values for SI were 3.3, 9.8, 24.3 and 38.5, respectively.

Guinea pig maximisation tests (GPMTs) showed contradictory results with the chemical. Overall, the chemical has a sensitising potential.

In a GPMT (OECD TG 406), Dunkin/Hartley guinea pigs (n = 5/sex) were administered the chemical by intradermal injection at 1 % (induction phase) and followed by topical induction with undiluted chemical for 48 hours under occlusive dressing. After 12–14 days, the chemical was topically applied at 25 % in acetone/PEG 400 for 24 hours (challenge phase). Reactions were observed in all treated animals. A rechallenge was conducted a week later with 0.25 or 2.5 % in acetone/PEG 400. Reactions were observed in 1/10 and 9/10 animals respectively, indicating a 'clear sensitising potential' (SCCS, 2015).

In another GPMT study following OECD TG 406, female Himalayan spotted guinea pigs were administered the chemical by intradermal injection at 5 % (induction phase) and followed by topical induction with the undiluted chemical in occlusive patches for 48 hours. After 14 days, the chemical was topically applied at concentrations of 10, 30 or 100 % for 24 hours (challenge phase). No reactions were observed in the test animals (REACHb; SCCS, 2015).

Observation in humans

Isolated episodes of allergic reactions to the chemical have been reported.

A 22-year old man had dermatitis after using a roll-on antiperspirant containing a fragrance mixture including the chemical; while the patch test was negative for the fragrance mixture, the patient was shown to respond to the chemical alone (Larsen, 1983).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause serious damage to health through repeated oral exposure. However, there were some effects related to fertility reported in male rats, rabbits and dogs (see **Reproductive and Developmental Toxicity** section).

In a subchronic toxicity study compliant with OECD TG 408, albino rats (n = 14/sex/dose) were administered the chemical by gavage (in rapeseed oil) at doses of 0, 2, 5, 25 or 50 mg/kg bw/day, five days/week, for 13 weeks. A satellite group of 14 animals per sex treated with the highest dose was included for a post-treatment period of four weeks. No treatment-related effects were reported for the following parameters: mortality, body weight gain, food intake and haematology. Treatment-related clinical signs of toxicity included alopecia (hair loss) at 50 mg/kg bw/day in females. Reversible dose-dependent increases in absolute and relative weights of liver and adrenals were observed for both sexes at 25 and 50 mg/kg bw/day, compared with

controls. At the highest dose, the fat content in the liver was increased compared with the other dose groups, in both sexes, but this effect was reversible. Cholesterol concentrations were significantly decreased in the 25 and 50 mg/kg bw/day treated groups but this was not considered an adverse effect by the study authors. Other statistically significant changes observed in clinical chemistry parameters were not considered to be treatment-related. Two females dosed at 50 mg/kg bw/day showed hypertrophy of the zona fasciculata of the adrenals, but the significance of this effect was not assessed. There was an increased frequency of testicular atrophy (6/14 vs. 1/10 in controls, no other details available) and spermatocoeles (spermatic cysts) (13/14 vs. 0/10 in controls) in males at 50 mg/kg bw/day. Both of these persisted after the treatment. A no observed adverse effect levels (NOAEL) of 25 mg/kg bw/day for testicular toxicity was determined (BASF, SE, 2013; FFHPVC, 2005; REACHa; SCCS, 2015).

In another subchronic toxicity study, compliant with OECD TG 409, Beagle dogs (n = 3/sex/dose) were orally administered the chemical in capsules at 0, 4.4, 22.3 or 44.6 mg/kg bw/day, seven days/week, for 13 weeks. No treatment-related effects were reported for the following parameters: mortality, body weight gain, urinalysis, haematological and clinical chemistry, gross pathology and histopathology. No changes in the reproductive organs were seen (BASF, SE, 2013; FFHPVC, 2005; SCCS, 2015).

The following subacute studies were available:

- Rats exposed to the chemical by gavage doses of 25 to 100 mg/kg bw/day for five days exhibited clinical signs of toxicity, body weight loss and changes in the liver starting from 50 mg/kg bw/day, along with testicular toxicity (BASF SE, 2013).
- SPF albino male mice and SPF Himalayan spotted male guinea pigs exposed to a daily dose of the chemical at 100 mg/kg bw for five consecutive days showed no signs of systemic toxicity, including testicular toxicity (BASF SE, 2013).
- Rabbits (n = 5) treated for 15 days with the chemical at 30, 100 or 300 mg/kg bw/day showed no treatment-related effects on clinical observations, body weight and food consumption; one animal in the low dose group showed a moderate degeneration of the seminiferous tubules, moderate oligospermia and moderate inflammation in the epididymis; another rabbit showed reduced testicular and epididymal size. Severe degeneration of seminiferous tubules and severe atrophy with aspermia in the epididymides occurred at 100 mg/kg bw/day. These effects were not considered treatment-related by the study authors (BASF SE, 2013).
- Beagle dogs given oral doses of the chemical at 0, 40, 200 or 1000 mg/kg bw/day for two weeks had increased liver weight (30–40 % higher than controls) and centrilobular hypertrophy of hepatocytes at doses ≥200 mg/kg bw/day and one dog showed massive degeneration of seminiferous tubules, hyperplasia of Leydig cells in testes and aspermia and epithelial vacuolation in the epididymids at 200 mg/kg bw/day (BASF SE, 2013; SCCS, 2015); further evaluation in a follow-up study showed that administration of 200 mg/kg bw/day for two weeks led to severe body weight loss, anaemia, changes in the liver and male reproductive organs, altered sperm quality and reduced sperm motility (BASF SE, 2013; SCCS, 2015).
- Rhesus monkeys *Macaca mulatta* (n = 2) treated with the chemical at 100 mg/kg bw/day for five days did not exhibit any general adverse effects or testicular toxicity (BASF SE, 2013).

In a one-generation study in Wistar rats (see **Reproductive and developmental Toxicity** section), 400 ppm (14.5 mg/kg bw/day) was suggested to be a NOAEL in males and a LOAEL in females in regard to systemic toxicity (SCCS, 2015).

In a developmental toxicity study with the chemical in rats (see **Reproductive and developmental Toxicity** section), maternal toxicity signs (female mice body weight changes and chemistry effects) were observed from 15 mg/kg bw/day in dams (BASF SE, 2013).

Dermal

Based on the available data, the chemical is not expected to cause serious damage to health through repeated dermal exposure, apart from the effects on the male reproductive system at very high doses (2000 mg/kg bw/day).

In a subacute study, the undiluted chemical was applied (as occlusive patches) on the back of albino rats for six hours, at doses of 0, 250, 500, 1000 or 2000 mg/kg bw/day for five consecutive days. No treatment-related effects were reported for the following parameters: mortality, clinical signs and gross pathology. The mean body weight decreased immediately after the first administration at the highest dose (2 % decrease compared to controls). Marked atrophy of the testes was reported at 2000 mg/kg bw/day, consisting in spermatocoeles, seminiferous tubules with disorganisation of the epithelial structure, a decreased number of germ cells and an increased number of degenerating germ cells (inclusive giant cells). Based on these effects, a NOAEL of 1000 mg/kg bw/day was established (REACHa; SCCS, 2015).

Inhalation

No data are available.

Genotoxicity

The available data are not adequate to derive a conclusion about the genotoxic potential of the chemical. Although several genotoxicity studies indicate the chemical to be non-genotoxic, one in vivo study in mice indicates positive results at high doses of 600 mg/kg bw. The SCCS will publish a reassessment of the chemical with additional genotoxicity data.

The following in vitro data were reported for the chemical (REACHa; REACHb; SCCS, 2015):

- negative results in an Ames test (following OECD TG 471) conducted using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 97, TA 98, TA 100 and TA 102 with doses up to 0.5 µL/plate, with or without metabolic activation; cytotoxicity was observed at concentrations ≥0.125

µL/plate;

- negative results in another bacterial reverse mutation assay (following OECD TG 471) on *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and *Escherichia coli* strain WP2 uvrA at concentrations up to 750 µg/plate (*S. typhimurium*) or 5000 µg/plate (*E. coli*); cytotoxicity was observed at ≥333 µg/plate in *S. typhimurium* and ≥3333 µg/plate in *E. coli*;
- ambiguous results in a mammalian cell gene mutation assay (compliant with OECD TG 476) using Chinese hamster lung fibroblasts (V79), with doses up to 128 µg/mL; significant increases in mutant frequency were reported (SCCS, 2015) but they were not reproducible, thus results were considered overall as negative (REACHa);
- negative results in another mammalian cell gene mutation test (compliant with OECD TG 476) using mouse lymphoma L5178Y cells exposed to concentrations up to 72 µg/mL, with or without metabolic activation (REACHb);
- negative results in a non-guideline micronucleus assay on human lymphocytes tested with concentrations up to 50 µM (Di Sotto et al., 2014);
- no DNA damage in a non-guideline comet assay on human colonic epithelial cells (HCEC) exposed to concentrations up to 100 µM (Di Sotto et al., 2014); however, no result was reported at the highest concentration of 300 µM;
- positive results in a mammalian chromosome aberration test (OECD TG 473) using Chinese hamster ovary (CHO) cells; concentrations of the chemical from 30 µg/mL induced statistically significant increases in the number of structural aberrations without metabolic activation.

Only one in vivo micronucleus study, following OECD TG 474, is available. The chemical injected intraperitoneally (i.p.) to ICR mice (n = 5/sex/dose) at a dose of 150, 300 or 600 mg/kg bw in corn oil induced a statistically significant increase in micronucleated polychromatic erythrocytes (PCE) in the high-dose male group, 48 hours after exposure. A non-significant increase was also reported in the high-dose female group, 24 hours post-exposure (REACHa; SCCS, 2015). However, these results were reported as not biologically significant as they were within the range of historical solvent controls (REACHa). This study was reported to be inadequate to 'draw a firm conclusion' on genotoxicity in vivo (SCCS, 2015).

Carcinogenicity

No animal carcinogenicity data are available. Based on the available genotoxicity data and mechanistic information, the chemical is not expected to be carcinogenic.

The Quantitative Structure–Activity Relationship (QSAR) modelling using OASIS–TIMES (Optimized Approach based on Structural Indices Set–Tissue MEtabolism Simulator) predicted negative results for both in vitro and in vivo genotoxicity. However, the chemical was out of the applicability domain for all but the Ames test model used for these predictions. If a prediction is out of the applicability domain of the model, it indicates that there is greater uncertainty about the reliability of the results derived from the model. Thus, only QSAR Ames test model predictions for this chemical can be included in the weight of evidence analysis of the carcinogenic potential of the chemical.

On structural analysis, the chemical is an aldehyde, which has the ability to bind to proteins through a Schiff base formation mechanism (Gerner et al., 2004; Roberts et al., 2007; Verhaar et al., 1992). The positive results obtained in the in vitro mammalian chromosome aberration test may be due to the protein binding ability of the mono-carbonyl group of this chemical. However, it has been demonstrated that the shorter the carbon chain attached to the carbonyl group, the more toxic the aldehyde is likely to be (Jenkins, 1978). Larger aldehydes such as cinnamaldehyde and hexylcinnamaldehyde assessed under IMAP were not considered to be carcinogens. Therefore, compared with other aldehydes, the chemical has a lower likelihood of being a carcinogen.

The chemical has shown 'no evidence from repeated dose toxicity studies that it is able to induce hyperplasia or neoplasia' (SCCS, 2015).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is considered toxic to fertility, warranting hazard classification. The formation of the metabolite p-tert-butylbenzoic acid (TBBA) (CAS No. 98-73-7) may be a possible mode of action for testicular toxicity (BASF SE, 2013). This metabolite has been assessed separately under the IMAP program and testicular toxicity was confirmed (NICNAS). Developmental effects were observed at doses causing maternal toxicity and are considered as secondary effects.

A series of studies were conducted in rodent and non-rodent species to assess the effects of the chemical on reproductive organs and development (BASF SE, 2013). In repeat dose toxicity studies, while no adverse systemic effects were demonstrated for major organs at the doses tested, the chemical showed testicular toxicity in male rats and male dogs (see **Repeat Dose Toxicity: Oral** section). Testicular toxicity was reported from 50 mg/kg bw/day in rats, independent of exposure duration (BASF SE, 2013).

In a one-generation study on Wistar rats (n = 10 per sex/dose), the chemical (microencapsulated for practical reasons) was given to the animals (F0) in the feed at concentrations of 400, 800, 1700 or 3400 ppm, equivalent to 14.5, 28.7, 62.6 and 119.7 mg/kg bw/day respectively. After six weeks of treatment, animals were mated to produce the F1 litter, and F1 dams were given the chemical at concentrations of 200, 400, 850 or 1700 ppm in feed during gestation and lactation.

In male rats, testicular toxicity and spermatotoxicity were observed at 1700 and 3400 ppm, with decreased relative testes and cauda epididymis weights (30–45 % and 30–40 % less compared with control, respectively), testes degeneration and aspermia (absence of sperm) of the epididymis. In the 3400 ppm male group, there was also a decrease of seminal vesicle and prostate weights (10 and 20 % less compared with control, respectively) and hyperplasia of Leydig cells. Therefore, a NOAEL of 800 ppm (~29 mg/kg bw/day) for testicular toxicity was suggested (SCCS, 2015), in line with the results from repeat dose toxicity studies (see **Repeat Dose Toxicity: Oral** section).

In the 1700 ppm female group, only 1/8 became pregnant and no viable offspring was produced by the two highest dose groups, consistent with the testicular effects in males at these doses. There were no effects on gestation, live birth indices, viability and lactation index at 800 ppm (28.7 mg/kg bw/day), apart from a slight decrease in the mean number of delivered pups per dam (7.9 in the 800 ppm group compared with 9.4 in the control group) and pup survival (94 % in the 800 ppm group compared with 99 % in the control group). These results are consistent with a lowest observed adverse effect level (LOAEL) of 1700 ppm (62.6 mg/kg bw/day) for reproductive toxicity (BASF SE, 2013).

In females, significant changes in clinical chemistry (including increased levels of gamma glutamyltransferase, decreased levels of serum cholinesterase) were seen at all doses. Signs of developmental toxicity were also observed in the 400 and 800 ppm groups. There was a significant reduction in birth weights (19 % and 22 % below control, respectively) and pup weights at weaning (17 and 21 % below control, respectively). Pup weight gain was also reduced in these two groups (16 and 21 % below control, respectively) (BASF SE, 2013).

In a developmental toxicity study (following OECD TG 414), Wistar rats were orally administered the chemical at nominal doses of 0, 5, 15 or 45 mg/kg bw/day (equivalent to measured dose levels 0, 4.1, 12.7 and 40.7 mg/kg bw/day, respectively), from day 6 to 20 post-coitum (p.c.). The following parameters were not affected by the treatment: number of corpora lutea, implantation sites, pre-implantation loss, sex distribution and placental weights. However, mean post-implantation losses (early resorptions) were significantly increased in the 45 mg/kg bw/day group (15.1 % compared with 4.4 % in the control group). At this dose, there was a decrease in the mean number of foetuses and live foetuses per dam (7.4 compared with 8.1 in the control group), slightly below the historical controls for mean number of foetuses per dam. No dead foetuses, abortions or premature births were observed. In all dose groups, skeletal variations were observed, consisting in delays and minor disturbances in ossification of the skull, sternebrae and pelvic girdle. Litters were affected in a statistically significant manner in regard to the percentage of affected foetuses per litter (89.1, 92, 99.1 and 98.3 %, respectively with increasing doses), although within the historical control range. At 15 and 45 mg/kg bw/day, unossified or incompletely ossified structures were significantly increased compared to the control group, coinciding with decreased mean foetal body weight (10 and 20 % below controls, respectively). The incidences of supernumerary thoracic vertebrae (30 % litters compared with 4.3 % in controls) and misshapen sacral vertebrae (39 % compared with 8.7 % in controls) were significantly increased at the highest dose, above the historical control range (0-16.7 %). Maternal toxicity signs were clearly observed from 15 mg/kg bw/day, including significant decreases in maternal weight gain (56 % below controls), increased levels of alanine aminotransferase (20-30 % above controls) and decreased levels of serum cholinesterase (20-45 % below controls) and increased liver weight (absolute and relative). At the highest dose, transient salivation, slight but significant reduction in food consumption, significant decreased mean body weight gain (32 % below controls), increased levels of glutamate dehydrogenase (79 % above controls) and reduced mean uterus weight (20 % below controls) were observed. A correlation was established between the observed skeletal variations, the significantly decreased foetal body weights and maternal adverse effects. A NOAEL of 4.1 mg/kg bw/day was established for maternal and prenatal developmental toxicity (BASF SE, 2013).

Rat studies conducted using the metabolite TBBA (CAS no. 98-73-7) have shown "clear evidence of adverse testicular and spermatotoxic effects, being identical in quality" (BASF SE, 2013) to the effects induced by the chemical. It is classified as Repr. Cat. 2 R60 under the CLP Regulation. The conversion of the chemical into TBBA could give rise to the species specificity of this effect: TBBA formation in human hepatocytes in vitro was reported to be low compared with rat hepatocytes, but similar to the levels found in rabbits, described as a less sensitive species regarding testicular toxicity (BASF SE, 2013).

The chemical is listed on the "Universe of Chemicals list for potential endocrine disruptor screening and testing" (US EPA, 2012). Under the Community Rolling Action Plan (CoRAP), the European Chemicals Agency (ECHA) has requested additional studies to assess the potential of the chemical to cause oestrogenic effects and pre and post natal developmental effects (ECHA, 2014). Results will be available in the updated REACH dossier and SCCS reassessment of the chemical.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity).

The chemical can also cause:

- local effects (skin sensitisation and skin irritation); and
- systemic acute effects from oral exposure.

Public Risk Characterisation

Considering the widespread range of domestic, cosmetic and personal care products that may contain the chemical, the main route of public exposure is expected to be through the skin, and inhalation from products applied as aerosols.

As a fragrance ingredient, the chemical is expected to be used at very low concentrations. The human odour threshold for the chemical has been set at 1–2 ppb, which implies that effective concentrations of the chemical regarding toxicity "would be perceived as rather unpleasant" (BASF SE, 2013). In addition, the chemical has low vapour pressure (0.25 Pa), indicating low volatility (BASF SE, 2013). Therefore, repeated or prolonged exposure via inhalation to doses inducing systemic toxicity seems unlikely.

The chemical is expected to be widely distributed for use as raw fragrance material. The restriction of the chemical under the IFRA Standard is expected to mitigate the public risks associated with chemical exposure through fragrances (e.g. concentration limit in finished products of 0.1–3 % of the chemical).

However, the SCCS opinion stated that the chemical was 'not safe for use as fragrance ingredient in cosmetic leave-on and rinse-off products' at the concentrations set up by IFRA (SCCS, 2015). The SCCS will publish a reassessment of the chemical by the end of 2016, taking into account additional information on dermal absorption, genotoxicity and developmental toxicity. NICNAS may reconsider the hazard profile of the chemical following the SCCS reassessment.

Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products.

Given the critical health effects identified, in particular reproductive toxicity and skin sensitisation, further assessment of the chemical may be required following finalisation of the SCCS reassessment.

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 and dermal exposure are implemented. Given the low dermal absorption and low volatility of the chemical, exposure via dermal and inhalation routes is expected to be minimal. 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 hazard classification of the chemical (refer to **Recommendation** section**)**.

NICNAS Recommendation

Sufficient information is available to recommend that risks for workplace health and safety be managed through changes to classification and labelling.

The chemical is recommended for Tier III assessment following finalisation of the SCCS reassessment and ECHA evaluation.

Regulatory Control

Public Health

The need for regulatory control for public health will be determined as part of the Tier III assessment.

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 if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Irritating to skin (Xi; R38)	Causes skin irritation - Cat. 2 (H315)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)	Suspected of damaging fertility - Cat. 2 (H361f)

[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;
- 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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