

2-Propenoic acid, 3-(4-methoxyphenyl)-, 2-ethylhexyl ester: Human health tier II assessment

10 March 2017

CAS Number: 5466-77-3



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Preface

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

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

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

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

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

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

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

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

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

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Acronyms & Abbreviations

Chemical Identity

Synonyms	2-ethylhexyl 4-methoxycinnamate ethyhexyl methoxycinnamate octinoxate octyl methoxycinnamate
Structural Formula	
Molecular Formula	C ₁₈ H ₂₆ O ₃
Molecular Weight (g/mol)	290.40
Appearance and Odour (where available)	Colourless to light yellow, odourless viscous liquid
SMILES	<chem>C(=O)(C={t}Cc1ccc(OC)cc1)OCC(CCCC)CC</chem>

Import, Manufacture and Use

Australian

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

The following non-industrial use has been identified in Australia:

- as an active agent for therapeutic sunscreens (Therapeutic Goods Administration (TGA), 2016).

International

The following international uses have been identified through Galleria Chemica; 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 US Household Products Database.

The chemical has reported cosmetic use:

- as a UV absorber and UV filter in sunscreens; and
- in various personal care products including hair dyes, shampoos, lipsticks, nail polish and creams at concentrations up to 10 %.

Restrictions

Australian

In the Australian regulatory guidelines for sunscreens, the use of the chemical is restricted up to a maximum concentration of 10 % in therapeutic sunscreens (TGA, 2016).

International

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

- EU Cosmetics Regulation 1223/2009 Annex VI—List of UV Filters Allowed in Cosmetic Products (The chemical may be used at a maximum concentration of 10 % in ready for use preparations); and
- New Zealand Cosmetic Products Group Standard—Schedule 8: UV Filters Cosmetic Products May Contain With Restrictions (maximum authorised concentration of 10 %).

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

The chemical octinoxate or ethylhexyl methoxycinnamate (EHMC) may refer to a composition consisting of four main constituents: the cis- and trans-isomers with the R- and S-stereoisomers of each chemical. The CAS Numbers 5466-77-3 and CAS No. 83834-59-7 are grouped together in Galleria Chemica and are generally named as octinoxate. The European Chemicals Agency (ECHA) has clarified that CAS No. 83834-59-7 is the trans-isomer of CAS No. 5466-77-3 and has assigned it as a different category in the dossiers (REACH; ECHA, 2013).

Commercially available EHMC consists of the trans- and cis-isomers in a ratio of 99:1, under normal conditions. However, the trans-isomer is irreversibly and rapidly converted to the less stable cis-isomer following exposure to UV light (Necasova et. al., 2016). As all toxicological data to date are specific to the trans-isomer, data for CAS No. 83834-59-7 will be considered in this assessment.

Toxicokinetics

Based on available studies, the chemical can be absorbed orally and dermally. No inhalation data are available. Percutaneous absorption studies in humans have indicated slight absorption (1–2 % of applied dose) through the skin when the chemical is applied topically over a 10 hour period (NTP, 2006).

Several studies have been conducted to investigate skin penetration and systemic absorption of sunscreen filters. These sunscreen products include a range of UV-filters (benzophenone-3, methylbenzylidene camphor and octylsalicylate), apart from octinoxate. In a two-week percutaneous absorption study, a sunscreen formulation containing the chemical (10 %) was applied topically (whole-body) at 2 mg/cm² to 32 healthy volunteers daily. The control used was a basic cream formulation without the UV-filters. For the chemical, the maximum plasma concentrations detected were 20 ng/mL for males and 10 ng/mL for females. Hormone changes (testosterone, oestradiol and inhibin B levels) were observed following treatment but were not considered to be biologically significant. Following 1–2 hours of application, the chemical was detected in the parent form both in plasma and in urine (more than 86 % of the applied dose) (NTP, 2006; HSDB).

In vitro diffusion experiments have been conducted on pig flank skin and human abdominal skin to compare the rate of absorption. The chemical remained primarily on the skin surface after 16 hours of treatment. The amount recovered by washing was 81.2 % and 87.7 % for pig flank and human skin, respectively. The chemical was observed to have a high affinity for the stratum corneum compared with the other tested sunscreen ingredient (benzophenone-3) (NTP, 2006). Following a 24 hour application of the chemical in mineral oil to isolated human epidermal membranes, around 95–98 % of the chemical was recovered on the surface of the epidermis. Low levels were also detected in the stratum corneum and viable epidermis (HSDB).

The chemical is lipophilic and is cleaved slowly in vitro by esterases in human blood plasma. In a preliminary in vitro experiment, the hydrolysis of the chemical at 10 µg/mL concentration in human blood was determined. The half-life of the chemical was approximately 10 hours. After 120 hours, the parent compound and 4-methoxycinnamate were found at 17.8 % and 83.3 %, respectively. The consequent alcohol (2-ethylhexanol) was predicted to form in vivo to a limited extent. A male volunteer received a single oral dose of a capsule containing 100 mg (1.6 mg/kg bw) of the chemical. The cumulative excretion in the urine was studied over 24 hours following ingestion. The parent compound and 4-methoxycinnamate were not found in the untreated urine, but after alkaline hydrolysis, 13.2 mg 4-methoxycinnamate was recovered (one fifth of the expected amount for complete transformation) (DSM, 2008; SCC, 2000; HSDB).

In the same study, an oil-in-water (o/w) cream (2 g) containing 10 % of the chemical (~200 mg active ingredient) was applied to the interscapular area of five male subjects. The area was covered with gauze for 12 hours. Blood and urine were collected up to 24 and 96 hours, respectively. No increase in plasma levels was observed. Urine levels were 'physiological' at 100–300 ng/mL. The authors concluded that very little of the compound was dermally absorbed compared with absorption via ingestion (SCC, 2000; HSDB).

Dermal penetration was observed to be dependent on the vehicles, using the tape-stripping technique. Significantly greater amounts were absorbed when the chemical was applied in emulsions than when microencapsulated (HSDB).

Apart from 2-ethylhexanol, another metabolite predicted to form in vivo based on the structure was 2-ethylhexanoic acid. Both of these chemicals have potential to be developmentally toxic (Necasova et. al., 2016).

Acute Toxicity

Oral

Based on the available information, the chemical has low acute toxicity in animals.

The median lethal dose (LD50) was >8 g/kg bw (8000 mg/kg bw) in mice and >20 mL/kg bw (>20200 mg/kg bw) in rats (HSDB).

Dermal

Based on data for CAS No. 83834-59-7, the chemical is considered to be of low acute toxicity at >126.5 mg/kg bw. However, higher doses were not tested and, therefore, the available data are insufficient to determine appropriate hazard classification.

In an acute dermal toxicity study conducted according to OECD Test Guideline (TG) 402, sunscreen cream containing up to 7.5 % of the chemical was applied (occlusively) to the skin of CFY (remote Sprague-Dawley) rats (n = 5/sex) for 24 hours, with observation up to 14 days. The dose was calculated to be 126.3 mg/kg bw. No toxicity symptoms or mortality were observed. A dermal LD50 of >126.5 mg/kg bw was established (REACH)

Inhalation

Based on data for CAS No. 83834-59-7, the chemical is considered to be of low acute inhalation toxicity in rats. Studies with higher tested doses (>0.511 mg/L) are not available and, therefore, the available data are insufficient to determine appropriate hazard classification.

In an acute inhalation study (OECD TG 403), Wistar rats (n = 5/sex) were exposed (nose-only) to an aerosol of the chemical from a spray can at 2 and 5 % for four hours. The mean concentration of the chemical was 0.511 mg/L. The animals were observed for 14 days. A slight decrease in body weight gain was observed in the treated animals, but were not statistically significant. No mortalities or clinical toxicity signs were observed. A median lethal concentration (LC50) of >0.511 mg/L was established. The chemical was considered to be of low toxicity under the conditions of this study (REACH).

Corrosion / Irritation

Skin Irritation

Based on the limited data available, the chemical is not considered to be a skin irritant.

In a skin irritation study (non-guideline), the chemical (0.5 mL) was applied under occlusion to the abraded skin of Vienna White rabbits (n = 5) for 24 hours, with observation up to 15 days. The mean erythema and oedema scores over 24, 48 and 72 hours after application were 1.7 and 0.2, respectively. Erythema was observed to be fully reversible within 15 days and oedema within

48 hours. Scaling was observed in one animal after eight days. Under these conditions, the chemical was not considered to be irritating to the skin (REACH).

No signs of irritation were observed when the undiluted chemical was applied twice a day to guinea pigs (n = 20) for 16 days (HSDB).

Eye Irritation

Based on the limited data available, the chemical is not considered to be an eye irritant.

In an eye irritation study (non-guideline), undiluted chemical (0.1 mL) was instilled into the conjunctival sac of three groups of three rabbits, with observations made up to 168 hours. Two groups of animals had eyes rinsed after 2 and 4 seconds, respectively. Following treatment, slight irritation of the conjunctivae was observed for a few hours but was reported to be due to the treatment method and not the chemical. No effects were observed after 24 hours. The mean score for conjunctivitis for one hour was 3.3, but this was fully reversed within 24 hours. Based on these results, the chemical was not considered to be an eye irritant (REACH).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is not a sensitiser in animal studies.

In a guinea pig maximisation test (GPMT) (OECD TG 406), female guinea pigs (n = 20) were initially exposed to the chemical intradermally at 5 % in olive oil. Topical induction used undiluted chemical (occluded for 48 hours). The animals were challenged epicutaneously at 75 % concentration in olive oil (occluded for 48 hours) and evaluated 24 and 48 hours after the end of the challenge. Well-defined signs of irritation (grade 2 erythema) were observed in 1/20 animals at both 24 and 48 hour timepoints. No effects were observed in all other treated animals (REACH).

Two poorly documented skin sensitisation studies are available. Guinea pigs (n = 20) were exposed to the undiluted chemical twice a day for 16 days. After a non-treatment period of three days, the animals were challenged once a day for three days. No reactions were observed. In another study with two groups of guinea pigs (n = 4/group), one group was injected with the undiluted chemical at 0.05 mL/day for five days, and another group topically exposed (0.025 mL, 50 %) on the shaved skin. No reactions were observed (SCC, 2000).

Observation in humans

Based on the available data, the chemical is not considered to be a skin sensitiser in humans. There is potential for photosensitivity following UV exposure, but the results are inconclusive.

In a dermal study, the chemical at a concentration of 10 % in dimethyl phthalate was tested on 58 subjects. The subjects were topically induced on their backs for 24 hours (occlusively) then three times/week for a total of nine applications. This was followed by a two-week rest period and further application on a new site on the back for 24 hours (occlusively). Observations were made at 0, 24 and 48 hours post-application. No sensitisation or adverse reactions were observed (HSDB).

Several poorly reported studies are available. No sensitisation was observed in Draize repeated insult patch tests, conducted at a concentration of 2 % in 53 subjects, and at a 7.5 % concentration in 54 subjects. Undiluted chemical applied (occlusively) on 60 subjects (20 with sensitive skin) for 24 hours did not cause any reaction (SCC, 2000).

A number of photosensitisation tests were carried out in humans. These studies involved a range of common UV filters. Photopatch tests were conducted on 82 patients using a set of sunscreen ingredients or common allergens. These allergens were applied to the back of the patients and covered with opaque tape and removed 24 hours later. The right panel was irradiated with UV-A. Readings were obtained at 24 hours after application, and at 24 and 72 hours after irradiation. Octinoxate produced positive photopatch responses in eight out of 82 patients. Positive results were observed in 19.5 % of the patients to

at least one of the allergens in the irradiated panel as well as the non-irradiated site, but these were deduced to be possibly caused by aeroallergens (HSDB).

In a retrospective analysis of positive photopatch reactions from an environmental dermatology database, 111 out of 2715 patients were found to exhibit positive results, with UV filters accounting for 52 positive reactions. Among these UV photoallergens, octinoxate caused two photoallergic reactions in a span of 12 years of testing. The authors concluded that photoallergic reactions to UV filters were rare (HSDB).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not considered to cause serious damage to health from repeated oral exposure.

In a repeated dose oral toxicity study (OECD TG 408), SPF (specific pathogen-free) rats (n = 12/sex/dose) were administered the chemical in the diet at doses of 0, 200, 450 or 1000 mg/kg bw/day for 90 days, with a recovery period of 5 weeks. No mortalities occurred. At the highest dose, observed effects included soiled tails, slightly increased kidney weights in males, reduced liver glycogen (with slight shrinkage of hepatocytes), and slight non-significant increase in iron positive material in Kupffer cells. High dose females had increased plasma activity and glutamate dehydrogenase (GLDH). Most of these effects were reversed during the recovery period and organ weight changes were considered to be adaptive changes. The no observed adverse effect level (NOAEL) was established as 450 mg/kg bw/day, based on the minor and reversible changes at 1000 mg/kg bw/day (HSDB; REACH).

In a short-term repeated dose oral toxicity study, rats were administered the chemical (gavage) at 0, 0.3, 0.9 or 2.7 mL/kg bw/day (approximately 300, 900 or 2700 mg/kg bw/day) for 21 days. At the highest dose, reduced body weight, thymus weight (relative and absolute), left kidney weight (absolute) in males and heart weight (absolute) in females were observed. Increases in the absolute weight of the pituitary were observed at the lower doses but these were not considered to be biologically significant by the authors. A NOAEL of 900 mg/kg bw/day was determined (SCC, 2000).

The chemical is suspected to possibly have oestrogenic properties and several studies have been conducted to specifically evaluate oestrogenic effects in rats. These studies were conducted at high doses.

In an oral study with female Wistar rats, the chemical was administered at a single dose of 1000 mg/kg bw/day in the diet for 35 days. The oestrous cycle and selected hormones (triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), prolactin, follicle-stimulating hormone (FSH), luteinising hormone (LH), estradiol (E2) and progesterone) were evaluated. A slight but statistically significant increase in T4 levels was observed but there were no changes in the other hormone levels. One animal developed a cyst in the ovaries but this was considered not to be treatment related. The lowest observed effect level (LOEL) was 1000 mg/kg bw/day (REACH).

In other studies with ovariectomised rats, female Sprague Dawley (SD) rats administered the chemical at 2.5 or 12.5 g/kg bw/day (2500 or 12500 mg/kg bw/day) for 12 weeks displayed a slight increase in liver malic enzyme activity, compared with the significant increase by the positive control E2. Other effects included a significant reduction in hepatic 5'-deiodinase activity, decreased T4, and increased TSH (at the low dose). A 5-day gavage study at 1000 mg/kg bw/day showed significantly increased uterine weights and up-regulation of the oestrogen receptor (Er β), significant increase of the TERP1 gene in the pituitary, decreased cholesterol, low-density lipoprotein (LDL) and triglyceride serum levels (NTP, 2006).

Dermal

Based on the available studies, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a 90-day repeated dose dermal study, SD rats (n = 10/sex/dose) were treated with the chemical in mineral oil on the shaved skin at doses of 0, 55.5, 277 or 555 mg/kg bw/day, five days/week. The highest applied dose was stated as 135 times the amount used daily by the average consumer. No mortalities were observed. Slight scaliness of the skin (attributed to the vehicle) was observed at the application site for all animals. At the highest dose, elevated (but non-significant) serum alanine

phosphatase (SAP) levels and increased relative liver weight were observed. Liver effects were not observable upon microscopic examination. There were no changes in haematological parameters. The NOAEL was determined to be 555 mg/kg bw/day based on no significant adverse effects at the highest treated dose (SCC, 2000).

In a 28-day repeated dose dermal study (OECD TG 410), the chemical was applied occlusively on the abraded skin of SD rats (n = 5/sex/dose) at doses of 0, 500, 1500 or 5000 mg/kg bw/day, six hours/day. No mortalities were observed. No systemic effects, body weight changes, ocular defects, haematology effects or changes in blood chemistry parameters were observed. All animals showed low grade epidermal proliferation. This effect was dose dependent and appeared to be more prominent in males. Dermal inflammatory or fibrotic responses were not significant. The chemical was considered as a low grade irritant under the conditions of this study. A NOAEL of 5000 mg/kg bw/day was established (REACH).

In a 21-day repeated dose dermal study (conducted according to EPA guidelines), the chemical was applied occlusively on the abraded skin of New Zealand White rabbits (n = 10/sex/dose) at doses of 500, 1500 or 5000 mg/kg bw/day, six hours/day. Mortalities occurred in three animals treated with high doses. At the highest treatment dose, lethargy, hunched posture, hair loss, soiled coats, emaciation, increased respiration, swelling of the conjunctivae, and reproductive effects (retardation of testicular growth) were observed. After three weeks, haematological changes in high dose animals included increased neutrophils and urea nitrogen, and decreased lymphocytes and alkaline phosphatase activity. Dermal irritation effects (erythema, oedema, desquamation, cracking and atonia) were observed at all doses but were more severe at the highest dose. Histopathology of the skin sites showed an epidermal proliferative response with low grade inflammatory reaction. This effect was dose-related and was more pronounced in the rabbits at the highest dose. No systemic toxicity was observed at doses <1500 mg/kg bw/day. The NOAEL was determined to be 1500 mg/kg bw/day (REACH).

Inhalation

No data are available.

Genotoxicity

Based on the available studies, the chemical does not have genotoxic potential.

Negative results were observed in the following vitro assays (HSDB; REACH):

- bacterial reverse mutation assays in several strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium* at concentrations up to 5000 µg/plate, with or without metabolic activation;
- mammalian cell transformation assay in BALB/c-3T3 clone A31-11 cells at concentrations up to 10 µg/mL;
- chromosome aberrations in human peripheral blood lymphocytes (OECD TG 473). No chromosomal aberrations were induced up to 50 µg/mL (with metabolic activation), and up to 20 µg/mL (without metabolic activation);
- mammalian cell gene mutation assay (OECD TG 476) in Chinese hamster lung fibroblasts (V79) up to 20 µg/mL, with or without metabolic activation;
- DNA damage and repair assay (unscheduled DNA synthesis) (OECD TG 482) in rat hepatocytes at concentrations up to 20 µg/mL;

Negative results were observed in an in vivo micronucleus assay (OECD TG 474) in bone marrow polychromatic erythrocytes from mice, that were orally treated with the chemical at doses up to 5000 mg/kg bw (REACH).

A study indicated that the chemical induced sex-linked recessive lethal mutations in *Drosophila melanogaster*, but the authors stated that the positive results were due to some trace contaminant. Negative results were obtained in feeding tests for adults and larvae, and in somatic mutation and combination tests examining wing structure (SCC, 2000; NTP, 2006).

Two photomutagenic studies were conducted on the chemical in vitro, and the results indicated a 'protective effect' (SCC, 2000):

- negative results were found when cells of *Saccharomyces cerevisiae* were exposed to the chemical at doses ranging from 0.05–625 µg/mL, with radiation up to 50000 mJ/cm² UVA and up to 1200 mJ/cm² UVB/ The UV rays were found to be mutagenic and the chemical protected against this in a dose-dependent manner; and

- the chemical was not photoclastogenic in a chromosomal aberration assay in Chinese hamster ovary (CHO) cells at doses ranging from 5–25 µg/mL, and radiation from 200–2000 mJ/cm² (UVA) and 4–25 mJ/cm² (UVB). The UV irradiation was clastogenic in CHOs at the top dose, but the active ingredient exhibited a protective effect.

Carcinogenicity

No guideline studies for carcinogenicity are available. The chemical has not been shown to be a tumour initiator in photocarcinogenesis studies in mice, but is shown to delay tumour development. No genotoxic potential was observed (see **Genotoxicity**).

Studies are available for evaluating the inhibition of UV-induced tumours. In a repeated dose and carcinogenicity study, hairless mice were exposed to doses of UV stimulating the solar energy spectrum (duration and radiation not stated). After a non-exposure period (duration not stated), 12-O-tetradecanoyl phorbol-13-acetate (a potent tumour promoter) was applied to the skin 3 times per week. The initial applied dose on the promoter was 10 µg/mL, but this was reduced to 2 µg/mL due to irritation. The treated mice were observed to be completely protected by the chemical at 50 % concentration, and a 7.5 % concentration was observed to be equivalent to reducing the solar exposure four-fold. There was no evidence of the chemical being a promoter of carcinogenicity. No other details are available (SCC, 2000).

In a dermal UV carcinogenicity study in hairless mice, the chemical was implicated as a potential tumour initiator. The dorsum of the animals was painted daily for nine-weeks, treated with low doses of UV light, followed by treatment with croton oil (a tumour promoter). Tumours were observed (number not stated) and statistical analysis indicated that the chemical may initiate tumours in this strain of mice (NTP, 2006). However, subsequent UV carcinogenicity studies in hairless mice failed to reproduce this result (IARC, 1992).

In a photocarcinogenesis study, mice were exposed to UV radiation 5 days/week for 40 weeks. Some animals were pre-treated with a sunscreen preparation containing the chemical at 5 % concentration (as a UVB filter). Sunscreen was applied before UV exposure 3 days/week and after exposure on the other two days. The chemical was observed to delay the median latent period for tumour development of the skin by two weeks (Fourtanier A, 1996).

Quantitative Structure-Activity Relationship (QSAR) modelling gave an alert for potential non-genotoxic carcinogenicity, but no details are available (OECD QSAR Toolbox ver.3.2).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to be reproductively or developmentally toxic at doses relevant to human exposure.

In a two-generation reproductive toxicity study (OECD TG 416), Wistar rats (n = 25/sex/dose) were administered the chemical in the diet at dose levels of 0, 150, 450 or 1000 mg/kg bw/day. The parental (F0) generation was exposed throughout pre-mating period (73 days), mating (21 days), gestation (21 days), and up to weaning of the F1 offspring (21 days). The duration of exposure for the F1 generation was similar to F0. No adverse effects were observed on the reproductive performance (oestrous cycles, sperm and follicle parameters, mating, fertility), morphology and motility, gestation and parturition. At the highest dose in parental animals, observed effects included reduced food consumption and body weight, increased liver weight and hepatic cytoplasmic eosinophilia related to hepatic enzyme induction, and increased ulceration of the glandular stomach mucosa. Decreased implantation was observed in F0 and F1 dams, however, the number of implantation sites was abnormally high in F0 and F1 female controls. This was considered to be an incidental effect and not directly related to treatment. In the offspring, reduced lactation weight gain and organ weights, and slightly delayed sexual maturation (vaginal opening and preputial separation) were observed at the highest dose. A NOAEL of 450 mg/kg bw/day was established for fertility and reproduction parameters, and for systemic parental and developmental toxicity (Schneider et. al., 2005; REACH).

In a developmental toxicity study conducted according to FDA guidelines, pregnant female rabbits (n = 20/dose) were orally administered the chemical at doses of 80, 200 or 500 mg/kg bw/day on gestation days (GD) 7–20. Foetuses were removed on GD 30 and tested for 24 hour viability. For the dams, the only effects observed were slightly decreased body weight gain and slightly increased frequency of constipation and anorexia at the highest dose. Reproductive parameters were not affected. The foetuses did not show any skeletal or visceral abnormalities. The median individual body weight of foetuses were decreased at 500 mg/kg bw/day, but were within the range of other doses and the controls. It was not clear if this effect was due to direct

intrauterine drug action or to reduced body weight gain of the dams. The 24 hour survival rate of the foetuses was not affected by treatment of the dams. The maternal and developmental NOAELs were determined to be 500 mg/kg bw/day (REACH).

In a prenatal developmental toxicity study (OECD 414), female albino rats were orally administered (gavage) the chemical at a single dose of 1000 mg/kg bw/day on GD 7–16. No maternal, embryotoxic or teratogenic effects were observed (REACH). In another pilot study, groups of rats (n = 36) were orally treated with the chemical at 0, 250, 500 or 1000 mg/kg bw/day during GD 6–14. At the highest dose, resorption rates were relatively higher compared with the other treated groups. However, this effect was related to an unusually low level of resorption in the other groups. No other effects were observed (HSDB).

Other Health Effects

Endocrine Disruption

In an in vivo uterotrophic assay, the chemical was observed to cause a dose-dependent increase of uterine weights in immature Long-Evans rats. The animals were exposed orally from day 21–24 (NTP, 2006). The EU Commission evaluated this information and found deviations in the methodology and discrepancies in the results. In another uterotrophic assay (performed under GLP conditions), female immature Wistar rats were orally administered the chemical for three consecutive days up to doses of 1000 mg/kg bw/day in olive oil. No uterotrophic effect and histopathologic changes in the uteri were observed (SCCNFP, 2001)

A Hershberger assay was conducted on castrated Wistar rats to investigate the anti-androgenic properties of the chemical. The rats were treated orally with 0, 300 or 1000 mg/kg bw/day for 10 consecutive days. Serum testosterone levels were significantly decreased and LH concentrations slightly increased compared to the controls treated with a reference androgen. There were no significant changes on testosterone, dihydrotestosterone and LH concentrations at the highest dose, compared to the respective control. A significant decrease in the absolute weight of the ventral prostate was observed, but was considered due to the slightly reduced terminal body weights and not compound-related (REACH).

A neurodevelopmental study was conducted to investigate endocrine changes in rat offspring. Wistar dams were dosed with the chemical at 0, 500, 750 or 1000 mg/kg bw/day during gestation and lactation. Thyroid hormone levels were measured for both dams and offspring. Serum T4 levels were significantly decreased in all treated dams, but were less affected in the offspring. High dose male offspring showed reduced relative prostate and testes weights and a decrease in testosterone levels on postnatal day (PND) 16. At eight months of age, reduced sperm counts in all treated groups and reduced prostate weights at the highest dose were observed. All offspring were evaluated after weaning in behavioural and neurophysiological tests. Observed effects included decreased motor activity levels in all exposed female offspring groups, and improved spatial learning abilities in low and high dose male offspring. These behavioural changes differed from effects expected for developmental hypothyroxinemia. The authors concluded that perinatal exposure to the chemical may affect reproductive and neurological development of rat offspring (HSDB).

The chemical was also reported not to display androgenic or anti-androgenic activity on androgen receptors in the human breast carcinoma cell line, MDA-kb2 at a concentration range of 1 nM–10 µM. The chemical stimulated proliferation on MCF-7 human breast adenocarcinoma cell line in vitro, with median effective concentration (EC50) value of 2.37 µM. However, secretion of the oestrogen-regulated protein pS2 in the cells was not significant (Schneider et. al., 2005).

Risk Characterisation

Critical Health Effects

The chemical is not toxic in mammalian studies. Academic studies of endocrine-related toxicity are inconclusive. The hydrolysis product, 2-ethylhexanol, is a weak developmental toxicant.

Public Risk Characterisation

Although the public could be exposed to the chemical through potential cosmetic and domestic uses, given the low hazard of the chemical, the chemical is not considered to pose an unreasonable risk to public health. Absorption through the skin is low and will not be at levels leading to developmental, toxic levels of 2-ethylhexanol.

The chemical is reported to be used in cosmetic products overseas at concentrations up to 10 %. In Australia, the chemical is currently regulated by the TGA at concentrations up to 10 % in therapeutic sunscreens.

Occupational Risk Characterisation

During product formulation, dermal 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.

Based on the available data, the lack of hazard classification in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

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

Regulatory Control

Advice for industry

Control measures

Control measures to minimise the risk from 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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