Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-: Human health tier II assessment

28 June 2019

CAS Number: 1222-05-5

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.

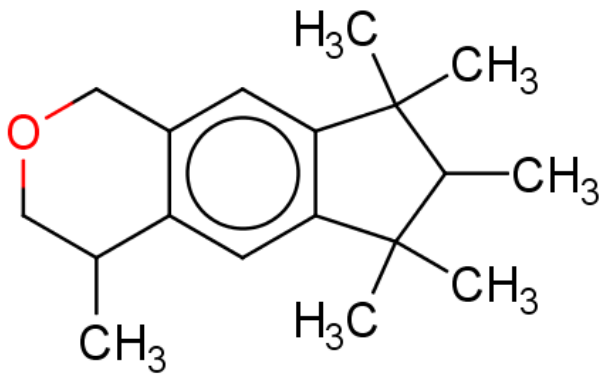
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	galaxolide 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-gamma-2-benzopyran HHCB pearlide
Structural Formula	
Molecular Formula	C18H26O
Molecular Weight (g/mol)	258.40
Appearance and Odour (where available)	Viscous liquid or colourless solid with sweet floral musk odour.
SMILES	C1(C)(C)c2c(C(C)(C)C1C)cc1c(C(C)COC1)c2

Import, Manufacture and Use

Australian

The chemical has reported domestic use in cleaning products, and in marine and automotive aftermarket products such as coatings.

International

The following international uses were identified through Galleria Chemica; the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Substances and Preparations in the Nordic countries (SPIN) database; the United States (US) Environmental Protection Agency (EPA) Chemical and Product Categories (CPCat); the US Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary and Cosmetic Ingredients; Cosmetic Ingredients and Substances (CosIng) database; and European Union Risk Assessment Report (EU RAR, 2008).

The chemical has reported cosmetic uses as a fragrance ingredient in perfumes and personal care products. It is listed on the IFRA transparency list of fragrance materials (IFRA, 2017). The chemical is listed in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011), indicating its use in nine cosmetic products.

The chemical has domestic uses in:

- washing and cleaning products;
- air care products; and
- anti-odour agents.

The chemical has commercial uses in:

- floor and surface treatment products;
- scented clothes and papers;
- car care products;
- photochemicals;
- leather tanning and textile dyes;
- coatings and paints, thinners,
- polishes and wax blends; and
- adsorbents.

The chemical has site-limited uses in the manufacture of paper plastic and rubber products; and industrial detergents.

The chemical has non-industrial use in pesticides and preservatives.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical 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

Toxicokinetics

The available data suggest that dermal absorption of the chemical is poor. No toxicokinetic data are available for oral and inhalation exposure (EU RAR, 2008; US EPA, 2014).

In rats, dermal absorption was estimated to be approximately 16 %. In vitro studies with human epidermal membranes and porcine back skin diffusion model indicated a lower absorption of 5.2 % or 11 %, respectively. Studies in human volunteers (n=3) indicated that absorption might be as low as 0.1 % (EU RAR, 2008; US EPA, 2014; Zhang et al., 2017).

The chemical has rapid, widespread distribution without evidence of significant accumulation. The chemical was found in rat milk up to 17.6 µg/mL after 10 days of oral administration of 20 mg/kg bw/day of the chemical (EU RAR, 2008; US EPA, 2014).

After intravenous administration the chemical was completely metabolised and excreted. No unchanged chemical was detected in urine of rats or pigs. The metabolites are similar in the two species, but not fully characterised. The major excretion route in rats is via the faeces, while it is mostly excreted in urine in pigs (Api et al., 2013; US EPA, 2014).

Biomonitoring

The chemical has been detected in human breast milk, adipose tissue and blood.

The chemical is found in human milk at levels up to 1316 µg/kg of fat (equivalent to 48 µg/kg whole milk based on a measured fat content of 3.67 %) and in adipose tissue at levels ranging from 12–89 µg/kg of fat (EU RAR, 2008; US EPA, 2014; REACH).

The chemical has been detected at concentrations up to 4100 ng/L in human blood and up to 98.3 ng/g of fat in umbilical cord serum (EU RAR, 2008; US EPA, 2014; Zhang et al., 2015; REACH).

Acute Toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity. The reported median lethal dose (LD50) values are >2000 mg/kg bw/day.

In a pre-guideline study conducted similarly to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, female Sprague Dawley (SD) rats (5/dose) were administered the chemical (65 % in diethyl phthalate (DEP)) via oral gavage at doses of 140, 300, 650, 1400, 3000 mg/kg bw and observed for 7 days. No treatment-related mortality was observed. An LD50 >3000 mg/kg bw was reported (EU RAR, 2008; REACH).

In another non-guideline study, the chemical (65 % in DEP) was administered to 10 rats (strain and sex unspecified) at a dose of 3250 mg/kg bw. The animals were observed for 14 days. One mortality was observed on day 2. An LD50 >3250 mg/kg bw was reported (EU RAR, 2008; REACH).

An oral LD50 of >3000 mg/kg bw has also been reported in rabbits (EU RAR 2008; REACH).

Dermal

The chemical is expected to have low acute toxicity via the dermal route. The reported LD50 values are >5000 mg/kg bw.

In a dermal acute toxicity study conducted similarly to OECD TG 402, female SD rats (5/dose) were treated with a single application of 300, 650, 1400, 3000 or 6500 mg/kg bw of the chemical (65 % in DEP) onto shaved skin. No mortality occurred at any dose. The LD50 was >6500 mg/kg bw (EU RAR 2008; US EPA, 2014; REACH).

In a pre-guideline dermal acute toxicity study in 7 rabbits administered with a single dose of 3250 mg/kg bw, no mortality was observed (observation period not reported). Slight signs of skin irritation were observed in all animals. The LD50 was >5000 mg/kg bw (EU RAR 2008; US EPA, 2014; REACH).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical may be moderately irritating to skin. The effects are not sufficient to warrant hazard classification.

In three studies conducted similarly to OECD TG 404, 3–4 female New Zealand White (NZW) rabbits received topical applications of the chemical in DEP or benzyl benzoate (BB) under a 6 cm^2 semi-occlusive patch for 4 h on clipped dorsal skin and were observed 1, 24, 48, 72 h and 7 days after patch removal.

The irritation scores for gradings of each individual animal at 24, 48 and 72 h were averaged. No animal had an average score ≥2.3 for either erythema or oedema. One individual animal had a score of 3 for erythema during 24–72 h, all other scores were below 2.3. Irritation scores for the DEP alone were 0–0.2 and 0 for erythema and oedema, respectively. The irritation score for BB were 1.2 and 0.4, for erythema and oedema, respectively. The irritating effect of the chemical was reversible within 7 days in 8/15 animals in the studies (EU RAR 2008; REACH).

Mild to moderate irritation was observed in two non-guideline studies in rabbits after application of the chemical for up to 72 h (EU RAR 2008; REACH).

Several in vivo non-guideline photoirritation studies with limited reported information have been conducted. Positive reactions have been observed in rabbits and guinea pigs at concentrations of the chemical between 3.5–32 % in DEP, while no reactions were reported in mice at 65 % of the chemical in DEP (EU RAR 2008; REACH).

In a phototoxicity assay conducted according to OECD TG 432 (neutral red uptake phototoxicity assay), mouse fibroblast cells were exposed to 50 µL of the chemical in Hank's Balanced Salt Solution (HBSS) containing 0.5 % ethanol at concentrations of 1.77–100 µg/mL for 1 h. This was followed by irradiation for 50 min at a total irradiation dose of 5 J/cm^2. The mean photo effect (MPE) and photoirritation factor (PIF) were both below the threshold values for the chemical to be considered a photoirritant (<0.1 and <5.0, respectively). Therefore, the chemical was not considered to be a photoirritant (SSCNFP, 2002; EU RAR 2008; REACH).

Eye Irritation

The chemical may be slightly irritating to eyes. The effects are not sufficient to warrant hazard classification.

In a study conducted similarly to OECD TG 405, 0.1 mL of the chemical was applied to one eye of 6 male NZW rabbits while the other eye served as the control. Four of the rabbits displayed no signs of ocular irritation. The irritation scores of the two remaining rabbits were 2 and 0 for corneal opacity; 1 and 0 for iris irritation; and 1 and 1 for conjunctival redness. These effects were mainly seen at the 24 h time-point and had cleared up completely after 72 h (EU RAR, 2008; REACH).

In an eye irritation study (limited information available), 0.1 ml of the chemical (65 % in DEP) was tested in the eyes of three rabbits with observation up to 168 h. No irritation was seen in any of the rabbits (EU RAR, 2008; REACH)

Evidence of slight eye irritation was reported from two studies with limited information available. However, in both these studies ethanol (a potential eye irritant) was used to dilute the chemical. Therefore, the relevance of these studies is questionable (EU RAR, 200; REACH).

Observation in humans

The chemical did not cause irritation in a human repeated insult patch test (HRIPT). In the test, the chemical (neat) was applied semi-occlusively to the upper arms of 42 subjects for 24 h, 3 times a week for 3 weeks. No irritation was observed in any of the subjects (EU RAR, 2008).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is not a sensitiser or a photosensitiser.

Both sensitisation and photosensitisation studies in animals and humans were negative (see ***Observation in humans*** section). There were no structural alerts for skin sensitisation using the OECD QSAR Toolbox; and, Chemtunes ToxGPS (Molecular Networks Altamira) predicted the chemical as negative for skin sensitisation.

In a non-guideline guinea pig maximisation test (GPMT), 10 (6 male, 4 female) Dunkin Hartley guinea pigs received a 0.325 % intradermal injection [(v/v in 0.01 % dodecylbenzene sulfonate in 0.9 % saline (DOBS/saline)] and 0.1 mL (50 %) of Freund's complete adjuvant in 0.9 % saline. This was followed one week later by a 65 % topical application of the chemical (induction). Two weeks after topical induction, 16.25 % of the chemical (in 70 % acetone/30 % PEG 400) was applied to a naive site for 24 h under occlusion (challenge). Two repeat challenges at weekly intervals were conducted. Only one equivocal reaction was reported (EU RAR, 2008; REACH).

The (quantitative) structure activity relationship [(Q)SAR] modelling for skin sensitisation using the OECD QSAR Toolbox (version 4.2) indicates that there are no alerts for skin sensitisation for either the chemical or its metabolites (skin metabolism and autoxidation).

Chemtunes ToxGPS (version 1.2) predicted the chemical to be negative for skin sensitisation. The prediction was within the applicability domain of the model.

Photosensitisation studies

In a GLP-compliant photo-GPMT study, 12 Hartley guinea pigs received topical applications of the chemical (65 % in DEP) followed by irradiation with ultraviolet light (UV) (ca. 1.8 mW/cm^2; 10 J/cm^2) (induction). The induction was followed by challenges at a naive site with up to 1 % of the chemical and UV light. One animal displayed mild erythema after the challenge. The chemical was considered negative for photo-sensitisation (EU RAR, 2008).

Observation in humans

No sensitisation reactions were reported in three separate human repeated insult patch test (HRIPT) studies at concentrations between 3.75–100 % in a total of 125 human subjects, in two human maximisation tests with 65 % solutions of the chemical or in patch test studies using 1–25 % solutions of the chemical in 334 dermatological patients (EU RAR, 2008).

Repeated Dose Toxicity

Oral

The chemical is not expected to cause serious damage to health from repeated oral exposure, based on the low severity of the reported effects.

In a 90-day OECD TG 408 oral study, SD rats (15/sex/dose) received the chemical via diet resulting in an average daily intake of the chemical 5.4, 15.7, 51.8 or 155.8 mg/kg bw/day for males and 5.1, 15.6, 51.9 or 154.6 mg/kg bw/day for females. After the treatment period, 3 males and 3 females from the control and the high dose groups were maintained for a treatment-free period of 4 weeks. No mortality or adverse clinical signs of toxicity were observed. Body weight and food consumption were similar to that of the control group. There were no statistically significant differences in absolute bodyweight or organ weights (except liver) at the end of the study. Relative liver weights were increased in males at all doses, but not in females. There were no significant histopathological findings at any dose. Any haematology and blood chemistry changes were minimal and not dose-dependent and; therefore, not considered adverse. The reported NOAEL values were 155.8 mg/kg bw/day for males and 154.6 mg/kg bw/day for females (Api, 1999; EU RAR, 2008, US EPA, 2014; REACH).

In a 2-week range finding study, SD rats (5/sex/dose) received the chemical via diet at average daily doses of 0, 341, 598, or 679 mg/kg bw/day for males and 0, 352, 633 or 980 mg/kg bw/day for females. There was a dose-related decrease in body weight in the two highest dose groups of both sexes. Dose-related increases in absolute and relative liver weights were observed at all doses in both sexes. This was accompanied by moderate centrilobular hypertrophy in the liver of one male and two females receiving the highest dose (Api, 1999; EU RAR, 2008, US EPA, 2014; REACH).

In a dose range finding developmental toxicity study, pregnant SD rats received the chemical on days 7–17 of pregnancy (see ***Reproductive and developmental toxicity*** section). The highest dose (1000 mg/kg bw/day) was lethal to three dams. Decreased motor activity, localised alopecia and urine stained fur were observed in dams receiving 1000 and 500 mg/kg bw/day. The highest dose group had a red perioral substance, ungroomed coat and changes in defecation (soft or liquid faeces). In the follow-up developmental toxicity study dams receiving 500 mg/kg bw/day showed excess salivation, urine-stained abdominal fur, red or brown substance on the forepaws and alopecia (Christian et al., 1999; EU RAR, 2008; US EPA, 2014; REACH).

Dermal

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

In a 13-week non-guideline study, female Crl:CD (SD) rats (15/dose) received topical applications of the chemical at 1, 10 or 100 mg/kg bw/day as a 2 % (w/v) solution in ethanol. There were no reported adverse clinical signs, no variation in biochemistry or

haematological parameters, no effects on bodyweight and no histological changes at any dose. Increases in absolute and relative liver weights in the highest dose group were reported; however, details of the magnitude of these changes are not available (EU RAR, 2008; REACH).

In 26-week non-guideline study, SD female rats (20/dose) received topical applications of the chemical at 9, 18, or 36 mg/kg bw/day as a 2 % (w/v) solution in ethanol. There were no reported adverse clinical signs, no variation in biochemistry or haematological parameters and no histological changes at any dose (EU RAR, 2008; REACH).

In another 26-week non-guideline study, SD rats (15 male and 35 or 38 females) received topical applications of the chemical at 50, 100, 200 mg/kg bw/day (with 6 and 13 week interim sacrifices). One group was dosed for 13 weeks and left to recover until autopsy at 26 weeks. At the highest doses (100 and 200 mg/kg bw/day) some rats displayed scabbed areas and appearance of a white or brown crusty material. No statistically significant effects were observed on body weights, haematology, biochemical parameters or urinalysis. Organs were unaffected except for an increase in relative liver weight in females at week 26 (11 and 23 % in the 100 and 200 mg/kg bw/day groups) and kidney weights (37 %) in males receiving the highest dose. However, no histopathological defects were noted in liver or kidney (EU RAR, 2008; REACH).

No measures were taken to prevent oral ingestion of the chemical in the dermal studies described above. Therefore, it is not possible to determine the actual exposure to or NOAEL for the chemical. No further information is available for these studies.

Inhalation

Limited data are available.

In a study similar to OECD TG 413, SD rats were exposed to aerosolised complex fragrance mixtures containing up to 132 $\mu g/m^3$ of the chemical for 4 h per day, 5 days per week for 13 weeks. Exposure to the aerosolised fragrance mixtures did not result in toxicologically significant effects on animal survival, behaviour, body weights, organ weights, or in haematology, clinical chemistry, or urinalysis parameters. No gross pathological or histopathological findings related to test material exposures were observed (EU RAR, 2008; REACH).

Genotoxicity

Based on the available data the chemical is not expected to be genotoxic (EU RAR, 2008; US EPA, 2014; REACH).

In vitro

The chemical was negative in:

- point mutation studies in *Salmonella typhimurium* strains TA98 TA100, TA1535, 1537 and the *Escherichia coli* WP2 uvrA strain at concentrations up to 5000 µg/plate, with and without metabolic activation;
- point mutation studies in *S. typhimurium* strains TA97, TA98, TA100 and TA102 at concentrations up to 500 µg/plate, with and without metabolic activation;
- a chromosome aberration assay in Chinese hamster ovary (CHO) cells at concentrations up to 20 µg/mL for 4, 20 and 44 h without metabolic activation, and at concentrations up to 34.5 µg/mL for 4 and 24 h and up to 30 µg/mL for 44 h with metabolic activation;
- an in vitro unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes at concentrations up to 15 µg/mL
- two micronucleus tests in human peripheral lymphocytes and human hepatoma cells at concentrations up to 94 µM and 194 µM, respectively for 48 h, with and without metabolic activation; and
- a sister chromatid exchange (SCE) assay in human lymphocytes at concentrations up to 48.5 µM for 2 h with metabolic activation and for 24 h without metabolic activation.

In vivo

The chemcial was negative in an OECD TG 474 micronucleus test. No significant increases in micronucleated polychromatic erythrocytes of Swiss albino (ICR) mice (5/sex/dose) were observed at 24, 48 and 72 h after administration of a single intraperitoneal dose of the chemical at 376, 750 or 1500 mg/kg bw.

Carcinogenicity

No data are available for the chemical.

Reproductive and Developmental Toxicity

The chemical was not found to have specific reproductive or developmental toxicity.

No effect on reproductive organs including prostate, seminal vesicles and testes of males, and the ovaries, mammary gland, uterus and vagina of females were reported in a 13-week oral toxicity study (see ***Repeated dose toxicity*** section) at doses up to 156 mg/kg bw/day. No effects on reproductive performance were found in a peri/postnatal toxicity study. Developmental effects were only observed secondary to maternal toxicity.

In a developmental toxicity study conducted similarly to OECD TG 414, pregnant SD rats (25/dose) were orally administered the chemical by gavage at 0, 50, 150 or 500 mg/kg bw/day in corn oil on days 7–17 of pregnancy. The study was terminated on day 20 of pregnancy. No abortions, premature deliveries or mortality occurred during the study. At two highest doses the maternal body weight gains were significantly and dose-dependently reduced for the entire dosage period (days 7 to 18 gestation) to 78 % and 91 % of body weight gain in controls, respectively. At gestation day 20, litter means for number of corpora lutea, implantations, live foetuses or resorption sites did not differ significantly between control and treated groups. Mean body weights of live foetuses were significantly decreased in the highest dose group (500 mg/kg bw/day). This dose group also had an increase in axial skeleton (vertebral/rib) malformations and decreased ossification of sternal centra and metatarsals. The reported maternal NOAEL was 50 mg/kg bw/day based on reductions in body weight gain during the dosing period. The developmental NOAEL was 150 mg/kg bw/day based on skeletal malformations at the highest dose (Christian et al., 1999; EU RAR, 2008; US EPA, 2014; REACH).

In a dose range finding developmental toxicity study, pregnant SD rats (8/dose) were orally administered the chemical by gavage at 0, 100, 250, 500 or 1000 mg/kg bw/day in corn oil on days 7–17 of pregnancy. Dams on all dose-levels showed reduced body weight gain during the treatment period (day 7–18 of gestation). Food consumption was reduced in all treated groups. Mean foetal body weights were reduced to 89.3% of controls in dams receiving the 1000 mg/kg bw/day (Christian et al., 1999; EU RAR, 2008; US EPA, 2014; REACH).

In a neonate nursing study, pregnant SD rats (28/dose) were orally administered the chemcial by gavage at 0, 2, 6 or 20 mg/kg bw/day from day 14 of pregnancy through to weaning on day 21 after birth. There were no treatment related effects in any of the treated parent females (F0) during pregnancy or lactation. The females were allowed to produce a litter and from these litters 24 males and females (F1 generation) were retained to maturity and assessed for behavioural changes and reproductive capacity. The F1 generation were only exposed to the chemical in utero and through mother’s milk. No adverse effects were noted on the development of the F1 generation during the late prenatal phase or on postnatal growth. After approximately 84 days of observations, the F1 generation were mated. Reproductive capacity and litter size (F2 generation) in the F1 generation were normal. The F2 generation was observed until 21 days after birth. No changes in post weaning behavioural tests or mating performance were observed. No abnormalities were seen in the F2 pups. The amount of the chemical in mother's milk was not measured in the study. However, the level of the chemical in the milk can be estimated to be ~ 18 µg/mL after daily dosing of 20 mg/kg bw/day, based on results from a pharmacokinetic study in lactating rats (see ***Toxicokinetics*** section) (EU RAR, 2008; US EPA, 2014; REACH).

Other Health Effects

Neurotoxicity

No behavioural or histological evidence of neurotoxicity was seen at any dose level in one 13 and two 26-week dermal repeat dose toxicity studies in rats (see ***Repeated dose toxicity*** section).

Endocrine Disruption

In vitro and zebrafish studies suggest that the chemical has weak endocrine activity by binding to steroid hormone receptors. However, no effects were seen in an in vivo uterotrophic assay in mice. There is no evidence of these weak endocrine activities causing adverse effects in mammals or humans.

In vitro

Various in vitro assays have demonstrated that the chemical can have estrogenic or anti-estrogenic activity depending on the study. However, the agonistic effects were seen only at concentrations about 6 orders of magnitude greater than for the natural estrogen receptor (ER) agonist 17-beta-oestradiol. The chemical also shows marginal antagonistic effects on androgen and progesterone receptors in vitro; however, at concentrations much higher than the androgen receptor (AR) antagonist vinclozolin and the progesterone receptor (PR) antagonist mifepristone. There is also some evidence of the chemical inhibiting steroidogenesis (progesterone and cortisol production) in vitro (Cavanagh et al., 2018; Li et al., 2013; Scheurs et al., 2005; Seinen et al., 1999; Witorsch et al., 2010).

In vivo

In a 2-week uterotrophic assay, female Balb/c mice (6/dose) received 6 or 40 mg/kg bw/day of the chemical in the diet. The chemical had no significant effects on uterine weights, indicating that the chemical does not have oestrogenic activity in mice (EU RAR, 2008; Seinen et al., 1999).

In a study in transgenic zebrafish expressing zebrafish ER beta and gamma, the chemical did not show any oestrogenic effects at concentrations of 0.01, 0.1 and 1 µM. Dose-dependent antagonistic effects were observed at concentrations of 0.1 and 1 µM (EU RAR, 2008; Schreurs et al., 2004).

Based on a *Xenopus laevis* metamorphosis assay, the chemical may cause an imbalance in the thyroid hormone axis (Pablos et al., 2015).

Risk Characterisation

Critical Health Effects

No critical health effects associated with the chemical have been established.

Public Risk Characterisation

Considering the range of domestic, cosmetic and personal care products that could contain the chemicals, the main route of public exposure is expected to be through the skin, inhaled from products applied as aerosols, and potential oral exposure from lip and oral hygiene products. Infants could also be exposed to the chemicals via breast milk.

Available data do not indicate any hazards associated with exposure to the chemical. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, dermal, oral and ocular exposure might 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the lack critical health effects, the risk to workers from this chemical is not considered to be unreasonable. Information in this report can be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls. The chemical currently has no hazard classification for worker health and safety; this is considered appropriate based on the available data.

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.

The chemical has been shown to have weak endocrine activity. However, the available data do not demonstrate the potential of the chemical to cause adverse effects via this endocrine activity. NICNAS will continue to monitor the availability of high quality data emerging on the chemical and determine if a further assessment is required.

Regulatory Control

Work Health and Safety

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

Advice for industry

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 is 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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