1,2-Propanediol, 3-(4-chlorophenoxy)-: Human health tier II assessment

05 February 2016

CAS Number: 104-29-0

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.

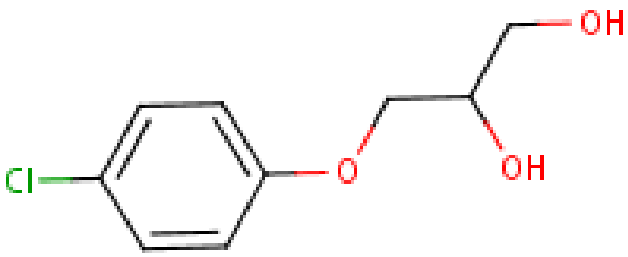
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	3-(4-chlorophenoxy)-1,2-propanediol chlorphenesin p-chlorophenyl glyceryl ether
Structural Formula	
Molecular Formula	C9H11ClO3
Molecular Weight (g/mol)	202.6
Appearance and Odour (where available)	Almost odourless white to off-white powder with a bitter taste
SMILES	c1(Cl)ccc(OCC(O)CO)cc1

Import, Manufacture and Use

Australian

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

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 Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); Household Products Database; and Canada Natural Health Products Ingredients Database (NHPID).

The chemical has reported cosmetic use as a preservative.

The chemical has been reported as being used in a high number (1068) of cosmetic products in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011). The chemical is reported to be present in cosmetic products at low concentrations up to 1 % (CPCat).

Restrictions

Australian

No known restrictions have been identified.

International

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

- The Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex VI—Part 1: List of preservatives allowed for use in cosmetic products;
- the European Union (EU) Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 7: Preservatives cosmetic products may contain with restrictions.

The chemical may be used in cosmetics and personal care products at a maximum concentration of 0.3 % (CosIng).

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

The chemical is well-absorbed following oral and dermal application.

Male Sprague Dawley (SD) rats (four animals) were administered the chemical at a dose of 16.7 mg by oral gavage. The chemical was rapidly absorbed with the maximum blood concentration measured at 30 minutes after administration. When administered intraperitoneally (i.p.) at a dose of 15.2 mg, over half of the administered dose was excreted in the urine after four hours, with the remainder primarily detected in the gastrointestinal tract and carcass. The excreted metabolites identified were 3-p-chlorophenoxylactic acid and p-chlorophenoxyacetic acid (CIR, 2014).

The chemical was applied occlusively to the shaved skin on the back of 16 male SD rats at a dose of 1.14 mg/kg. Up to 57 % of the applied dose was absorbed 96 hours after application. During this time period, approximately 48 % and 0.5 % of the applied dose was excreted in the urine and faeces, respectively, whilst less than 1 % of the applied dose was present in the tissues (CIR, 2014).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from an animal test following oral exposure. The median lethal dose (LD50) in SD rats is 3000 mg/kg bw. Observed sub-lethal effects included dyspnoea, decrease in spontaneous activity, hypotonia, piloerection and loss of reflex (CIR, 2014).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is not considered to be a skin irritant up to a concentration of 1 % (w/v).

The chemical was applied occlusively to the shaved flanks of six male New Zealand albino rabbits at a concentration of 1 % (w/v) in distilled water for 24 hours. Slight, reversible erythema was observed in two animals after patch removal. The chemical was concluded to be a non-irritant with a primary irritation index of 0.1 in this study (CIR, 2014).

A test to determine the maximum non-irritating concentration of the chemical was performed prior to a skin sensitisation study. The chemical was applied occlusively at concentrations of 0.1, 0.25, 0.5 and 1.0 % to the shaved skin of three male albino Dunkin-Hartley guinea pigs for 24 hours. No irritation was observed at any concentration tested (CIR, 2014).

Eye Irritation

The chemical is considered to be a slight eye irritant up to a concentration of 1 % (w/v). The effects observed were not sufficient to warrant hazard classification.

The chemical, at a concentration of 1 % (w/v) in distilled water, was instilled into the right eyes of three New Zealand albino rabbits. Slight conjunctival enanthema (rash), chemosis and lacrimation were observed at one hour after instillation (maximum ocular irritation index of 6). These effects were reversed within 24 hours. The chemical was concluded to be a slight eye irritant in this study (CIR, 2014).

Observation in humans

Based on the available human data, the chemical is not expected to be a skin irritant when used at low concentrations.

A 24-hour occlusive patch test was performed with the chemical at a concentration of 2 % on 30 subjects and the mean irritation score was calculated to be 0.17. In a cumulative skin irritation test, 15 subjects were tested with mixture formulations (a) containing 0.2 % methylparaben, 0.1 % propylparaben and 0.25 % of the chemical, and mixture formulations (b) containing 0.2 % methylparaben, 0.1 % propylparaben, 0.3 % phenoxyethanol and 0.25 % of the chemical. Each formulation was applied to the subjects three times per week for three weeks. The highest reported total cumulative irritation mean scores were 0.40 and 0.87 for formulations (a) and (b), respectively. In a sensory irritation test on 16 subjects, the chemical at a concentration of 0.4 % had a mean score of 0.54 for irritation potential compared with 0.22 for the controls. An acute skin irritation test was performed with the chemical at a concentration of 0.3 % in 25 subjects for 48 hours. Minimal erythema was observed in 3/25 subjects (CIR, 2014).

In a skin irritation and sensitisation study on a test material containing the chemical at concentrations of 12–17 %, 1/53 subjects developed mild erythema (score of 1) on day 22 of induction. The response was considered to be clinically insignificant. In a patch test study to identify preservative allergens, 8/30 subjects had positive irritation readings to 0.5 % of the chemical at day four of the study. The authors concluded that the maximum use concentration of the chemical should be less than 0.5 % to avoid skin reactions (CIR, 2014).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is not considered to be a skin sensitiser up to a concentration of 1 % (w/v).

In a modified guinea pig maximisation test with 30 female albino Dunkin-Hartley guinea pigs, the sensitisation potential was tested at a concentration of 1 % intradermally, and 1 % topically. A topical challenge was then applied occlusively with 0.5 or 1 % chemical in distilled water for 24 hours. The chemical did not give positive reactions in the animals at either challenge concentration (CIR, 2014).

Observation in humans

A human repeated insult patch test using the chemical at concentrations of 5-9 % did not result in sensitisation reactions. In a separate study using a test material containing 12–17 % of the chemical, no evidence of skin sensitisation was observed in the subjects (CIR, 2014).

Several case reports have indicated that the chemical might be a skin sensitiser. Positive reactions were observed in patch test results using the chemical at concentrations of 0.5–1 % following symptoms of skin sensitisation after the use of cosmetic products by consumers (CIR, 2014).

Repeated Dose Toxicity

Oral

The available data suggest that the chemical has low repeated dose toxicity based on results from an animal test following oral exposure. The effects observed were not sufficient to warrant hazard classification.

In a repeated dose toxicity study, the chemical was administered to Charles River Crl:CD(SD) BR rats (eight animals/sex/group) at doses of 10, 100 or 1000 mg/kg bw/day by gavage for 28 consecutive days. Hunched posture, abnormal gait, paleness, lethargy, drooping eyelid, badly-groomed appearance, brown staining of the fur, noisy respiration and piloerection were observed at 1000 mg/kg bw/day. Significant reductions in body weight gain and haemoglobin levels were observed at 1000 mg/kg bw/day. A significant reduction in haemoglobin levels was also observed in the males treated with 100 mg/kg bw/day of the chemical. Biochemical changes, including significant increases in alanine aminotransferase (ALT), IgG and IgM serum levels (females only), and significant reductions in potassium and calcium ion concentrations (females only) were observed at 1000 mg/kg bw/day. Significant reductions in the absolute spleen (both sexes) and thymus (males only) weights were observed at 1000 mg/kg bw/day. At 1000 mg/kg bw/day, treatment-related kidney effects (renal tubular dilatation and necrosis of the papillary tip) were observed in a male rat euthanised during week four of the study. A no observed adverse effect level (NOAEL) of 10 mg/kg bw/day, based on haemoglobin level changes in the males at 100 mg/kg bw/day, was established in this study (CIR, 2014).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available in vitro mutagenicity studies, the chemical is not considered to be mutagenic.

A bacterial gene mutation assay was conducted in five *Salmonella typhimurium* strains (TA98, TA100, TA1535, TA1537 and TA1538) up to a maximum concentration of 5000 µg/plate of the chemical, in the absence or presence of a metabolic activation system. Negative findings were reported in this study. In a separate bacterial gene mutation assay, *S. typhimurium* strain TA102 and *Escherichia coli* strain WP2uvrA were tested with the same conditions as the previous assay. Negative findings were also reported in this study (CIR, 2014).

A mammalian cell gene mutation assay was conducted in Chinese hamster ovary (CHO) cells (hypoxanthine-guanine phosphoribosyl transferase (hprt) locus). The chemical was tested up to a maximum concentration of 1500 µg/mL in the

absence or presence of a metabolic activation system. The chemical was concluded to be non-mutagenic in this study (CIR, 2014).

Carcinogenicity

No data are available on the carcinogenicity of the chemical. However, several studies have indicated that the chemical may have anti-tumourigenic potential.

An initiation-promotion study was conducted on female mice (30 animals/group) to assess the anti-tumourigenic activity of the chemical. Thirty animals were given applications of 7,12-dimethylbenzanthracene (DMBA), a tumour initiator, to the interscapular area and after three weeks, croton oil, a tumour promoter, was applied to the skin twice weekly for 20 weeks. A second group of animals was given the same treatments with additional two i.p. injections of 2.5 mg of the chemical at the same time as croton oil was applied. The chemical was found to inhibit tumourigenesis in this study when administered during tumour promotion (CIR, 2014).

In a published study, Swiss mice (18–20 females/group) previously injected with Rauscher murine leukaemia virus (RMLV) or Friend murine leukaemia virus (FMLV) were administered i.p. injections of 0 or 100 mg/kg of the chemical, twice a day up to seven days. No evidence of systemic cytotoxicity was observed in the animals following chemical treatment. The chemical reduced mortalities due to leukaemia after the animals were infected with the viruses (Spencer et al., 1972; CIR, 2014).

In preliminary clinical trials conducted by the Clinical Screening Group of the European Organisation for Research on Treatment of Cancer, thirty-one cancer patients were given oral treatment with the chemical for up to six weeks. The oral doses range between 1–6 g/day, with the usual dose being 4 g/day. Treatment with the chemical was ineffective in 16 cases of carcinoma (including basal cell, cervix, uterus, tonsil, oesophagus and lung) and four cases of sarcoma. However, complete remission was observed in 1/9 patient with squamous cell carcinoma of the skin and incomplete but substantial remission was observed in 4/9 patients (Spencer et al., 1972; CIR, 2014).

Reproductive and Developmental Toxicity

While there are limited data for the chemical, based on the available data, there is no evidence of reproductive and developmental toxicity.

In a reproductive and developmental toxicity study, the chemical was administered to Specific Pathogen Free (SPF) rats (25 adult females/group) by oral gavage at doses of 0, 10, 50 or 100 mg/kg bw/day on days 6–15 post-coitum. The animals were euthanised on day 20. At 100 mg/kg bw/day, increased fur loss and transient post-dosing salivation were observed but the effects were not likely to be due to treatment. No effects on maternal or developmental toxicity were observed in the study. A NOAEL of 100 mg/kg bw/day for both maternal and foetal toxicity was established in this study (CIR, 2014).

Risk Characterisation

Critical Health Effects

No critical health effects for risk characterisation were identified for the chemical. However, the chemical could possess hazardous properties such as skin sensitisation, and skin and eye irritation when used at concentrations above 1 % (w/v).

Public Risk Characterisation

The chemical is used only as a preservative in cosmetics (CosIng) and therefore cosmetic use is not expected to expose the public to high concentrations. If the concentrations in cosmetics are low, critical health effects are not expected. 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 and ocular exposure of workers to the chemicals may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations may 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.

At low concentrations, an unreasonable risk to workers is not expected. However, at high concentrations, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal and ocular exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

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 is not recommended for classification and labelling under the current approved criteria and adopted GHS. This does not consider classification of physical hazards and environmental hazards. No recommendations or further assessment is required.

Regulatory Control

Advice for industry

Control measures

Control measures to minimise the risk from dermal and ocular 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:

- 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.

References

Bailey, JE (ed.) 2011, Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 1st Edition, Personal Care Products Council, Washington, D.C.

Canada Natural Health Products Ingredients Database (NHPID). Accessed October 2015 at http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/online-enligne/nhpid-bipsn-eng.php

ChemID Plus Advanced. Accessed October 2015 at http://chem.sis.nlm.nih.gov/chemidplus/

Cosmetic Ingredient Review (CIR, 2014). Final Report on the Safety Assessment of Chlorphenesin as Used in Cosmetics. International Journal of Toxicology 33(Supp.2):5-15. Accessed October 2015 at http://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR612.pdf

European Commission Cosmetic Ingredients and Substances (CosIng) Database. Accessed October 2015 at http://ec.europa.eu/consumers/cosmetics/cosing/

Galleria Chemica. Accessed October 2015 at http://jr.chemwatch.net/galleria/

Stephen HJ, Runser RH, Berger FM, Tarnowski GS and Mathe G (1972). Attenuation of certain neoplasias by chlorphenesin (36631). Proceedings of the Society for Experimental Biology and Medicine. 140(4):1156-1161.

United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary. Accessed October 2015 at http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp

US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR). Accessed October 2015 at http://actor.epa.gov/actor/faces/ACToRHome.jsp

US Environmental Protection Agency's Chemical and Product Categories (CPCat). Accessed November 2015 at http://actor.epa.gov/cpcat/faces/search.xhtml

US National Library of Medicines, Household Products Database, Health& Safety Information on Household Products. Accessed October 2015 at http://householdproducts.nlm.nih.gov/

Last update 05 February 2016

Share this page