Phenol, 4-chloro-2-(phenylmethyl)-: Human health tier II assessment

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CAS Number: 120-32-1

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.

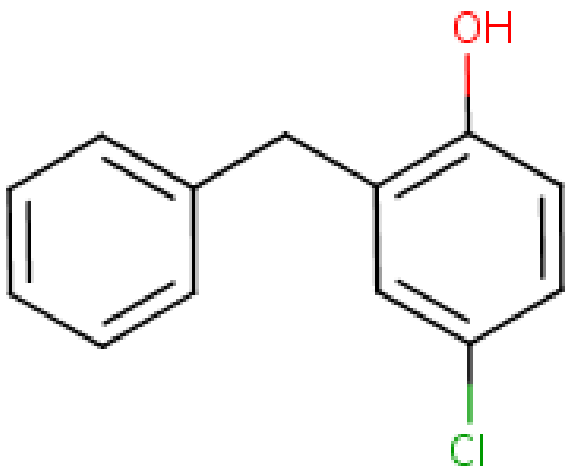
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	chlorophene (chlorofene) o-cresol, 4-chloro-alpha-phenyl- p-chloro-o-benzol phenol o-benzyl-p-chlorophenol 2-benzyl-4-chlorophenol
Structural Formula	
Molecular Formula	C13H11ClO
Molecular Weight (g/mol)	218.68
Appearance and Odour (where available)	White to light tan or pink flakes, slightly phenolic odour.
SMILES	c1(O)c(Cc2ccccc2)cc(Cl)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 Substances and Preparations in Nordic countries (SPIN) database; 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); Cosmetic Ingredient Review, and the Handbook of Preservatives (Ash and Ash, 2004).

The chemical has reported cosmetic use as an antimicrobial and preservative. Although it is listed as a preservative allowed for use in cosmetics in the EU CosIng Directive and is also included in the INCI Dictionary, the Cosmetic Ingredient Review (CIR, 2004) states that it is no longer used in cosmetics. It is not listed in the Compilation of Ingredients Used in Cosmetics in the United States of America (USA) (ed. Bailey, 2011). There is limited evidence that chlorophene has cosmetic use as an antibacterial in hand soaps.

The chemical has reported domestic and commercial uses in cleaners and disinfectants.

Non-industrial uses of the chemical have been identified internationally in microbiocides and germicides for agricultural applications.

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products. Using the chemical in cosmetics in the EU is subject to the restrictions described in the EU Regulation Annex V. This chemical may be used in cosmetics and personal care products at a maximum concentration of 0.2% (CosIng);
- New Zealand Cosmetic Products Group Standard—Schedule 7: Preservatives Cosmetic Products May Contain With Restrictions—Table 1: List or Preservatives Allowed; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’).

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 absorption, distribution, metabolism and excretion of ^{14}C-labelled chlorophene were studied in male Fischer 344 (F344) rats. The test substance was administered via gavage, intravenous (i.v.) injection and dermal application. Higher relative percentages of chlorophene were excreted in the faeces following oral treatment compared to i.v. administration. After dermal application, a high percentage of the total dose of chlorophene was present at the application site. These findings indicated that chlorophene was incompletely absorbed through both intestine and skin. Oral absorption was estimated to be 70 % by comparing oral and i.v. administration of the test substance (measurement of net test substance present in urine plus expired air plus carcass by each of the two routes). Based on the levels of the chemical in urine, faeces and tissues, dermal absorption of chlorophene was determined in two studies to be 60 and 62% (ECHA, 2014).

Most of the administered chlorophene was excreted and the tissue levels were generally low within three days following administration (except for the dermal study where 32 % of the total dose was found at the skin site). The highest concentration of chlorophene-derived radioactivity was found in the kidney during the whole measuring period. The affinity of renal tissue for chlorophene is likely to play a role in the suggested nephrotoxicity of this compound. In addition, the studies indicated that enterohepatic circulation was involved in chlorophene disposition. The major in vivo metabolites detected following radioactively-labelled chlorophene exposure were glucuronide conjugates of chlorophene and hydroxy-chlorophene in faeces and urine (ECHA, 2014).

Acute Toxicity

Oral

The chemical has low acute toxicity following oral exposure.

In a study conducted similarly to OECD Test Guideline (TG) 401, the chemical was administered by gavage to CD-Sprague Dawley (SD) rats (5/sex/dose) as single doses at 1500, 2500, 3150, 3969 and 5000 mg/kg bw. The median lethal oral dose (LD50) was 3852 mg/kg (ECHA, 2014).

Dermal

The chemical has low acute toxicity following dermal exposure.

In a limit test conducted similarly to OECD TG 402, chlorophene was applied dermally to CD-SD rats (5/sex/dose) at 2000 mg/kg bw for 24 h. The LD50 was >2000 mg/kg bw (ECHA, 2014).

Inhalation

The chemical has moderate acute toxicity based on results from animal tests following inhalation exposure and warrants hazard classification (see **Recommendation** section). The four hour median lethal concentration (LC50) in rats is 2.43 mg/L as dust.

In a test similar to OECD TG 403, CD-SD rats (number unspecified/sex/dose) were administered a single dose of chlorophene nose-only at 2.07, 2.40 and 3.13 mg/L for 4 h. The LC50 was 2.43 mg/L. Following inhalation, increased lung weights were noted in the decedents, indicating pulmonary irritation and respiratory failure caused by oedema. Three cases of hydronephrosis, four cases of enlarged cervical lymph nodes and one case of hepatic nodules were observed in the decedents after exposure through inhalation (ECHA, 2014).

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is a skin irritant and warrants hazard classification (see **Recommendation** section).

Two of the three available studies followed OECD TG 404 without major deviations.

In one guideline skin irritation study, the chemical was applied to the skin of three rabbits (strain unspecified), producing strong erythema and oedema after 4 hours. Mean scores for erythema and oedema were: 3 and 4 for the first rabbit; 2.7 and 4 for the second rabbit; and 2.7 and 4 for the third. Effects reversed within 14 days in two of the rabbits and 21 days for the third. At 72 and 96 h, the erythema had a necrotic appearance in all three rabbits (ECHA, 2015).

In a second guideline study, the chemical was reported to cause reversible exfoliation and eschar formation but the scores were not high enough to warrant classification for irritation (average scores for erythema and oedema were 1.22 and 0.22 respectively) (ECHA, 2015). Available information does not provide an explanation for the differences between the outcomes of this study and the previous one.

The third study was not conducted in accordance with OECD TGs and lacked important study details (ECHA, 2015).

Additional information on the skin irritant potential of chlorophene can be taken from the skin sensitisation studies (see the **Skin Sensitisation** section). In one study, moderate to strong erythema reactions were observed at the sites treated with 10 % w/v chlorophene mixture during the induction phase (ECHA, 2015).

Eye Irritation

Based on the available data, the chemical causes serious, irreversible damage to eyes and warrants hazard classification (see **Recommendation** section).

In a study performed in accordance with OECD TG 405, chlorophene was placed in the eyes of three albino rabbits, producing lesions of the cornea and iris as well as conjunctival redness and chemosis, all of which persisted until the end of the observation period. The study was terminated 72 h after treatment in light of the deteriorating condition of the treated eyes, especially the corneae. It was considered that significant resolution of the treatment effects was most improbable within the period of extended observation allowed by the OECD test method. Mean scores were: 2.7 (corneal opacity), 1 (iris lesion), 2.7 (redness of the conjunctivae), and 2 (chemosis) for the first rabbit; 3 (corneal opacity), 0.7 (iris lesion), 2.7 (redness of the conjunctivae), and 2 (chemosis) for the second rabbit; and 2.7 (corneal opacity), 1 (iris lesion), 2.7 (iris lesion), 2.7 (redness of the conjunctivae), and 1.3 (chemosis) for the third rabbit (ECHA, 2014).

Sensitisation

Skin Sensitisation

Based on the available data from three animal studies and human observations, the chemical is a skin sensitiser and warrants hazard classification (see **Recommendation** section).

In a Buehler test conducted according to OECD TG 406, chlorophene was reported to be positive for skin sensitisation in guinea pigs (strain not specified). After induction using 10 % chlorophene solution, a challenge dose of 5 % chlorophene solution was applied to the animals. Out of 20 animals tested, 19 showed faint to moderate redness (ECHA, 2015).

In a second Buehler test conducted according to OECD TG 406, chlorophene was reported to be positive for skin sensitisation in guinea pigs (strain not specified) following induction and challenge using a 50 % concentration in 45 % (9/20) of the animals. The result suggests moderate potency, but a higher potency cannot be excluded from this result (ECHA, 2015).

A third Buehler test was conducted in guinea pigs (strain not specified, 10/group) using 0.5 % in ethanol/water (80/20) for induction and 0.25 % (acetone) for the challenge. Very faint erythema was seen (score 0.5) in the induced animals (4/10) and two of the control animals (2/10) (ECHA, 2015).

Observation in humans

The available information from clinical tests shows that chlorophene has the potential to elicit skin sensitisation reactions in people. However, the data are limited and do not include any useful information on induction exposure or potency (ECHA, 2015). Limited patch data and case studies have been reported (CIR, 2004).

Repeated Dose Toxicity

Oral

Based on the treatment-related effects reported from repeated dose toxicity studies, repeated oral exposure to the chemical is not considered to cause serious damage to health.

Gavage studies were conducted in rats and mice for 16 days, 90–95 days and 2 years in studies similar to OECD TG 407, 408 and 451 respectively. Across the studies, rats were more sensitive to chlorophene than mice and the kidney was the main target organ in rats. Effects observed at the lowest levels in mice were increased liver weights in females and decreased kidney weights in males. Among rats and mice, males were more prone to chlorophene-induced nephropathy compared to females. In the 95-day study in F344 rats (doses administered at 0, 30, 60, 120, 240 and 480 mg/kg bw/day), there was a dose-related increase in incidence and severity of nephropathy starting at 30 mg/kg bw/day (minimal to mild effects at this dose) in males with the incidence of nephropathy increasing significantly at 120 mg/kg bw/day, also in males. A no observed adverse effect level (NOAEL) was established in this study at 60 mg/kg bw/day, as effects seen at 30 and 60 mg/kg bw/day were not considered adverse. Increased absolute and relative kidney weights and microscopic kidney lesions were observed at 60 mg/kg bw/day with an equivalent exposure duration in male Wistar rats in the 2-generation study (doses administered at 0, 60, 180 and 540 mg/kg bw/day). In a two-year oral study performed in F344/N rats (doses administered at 0, 30, 60, 120 mg/kg bw/day) with interim sacrifices at 13 and 65 weeks, a NOAEL was established at 60 mg/kg bw/day for females. Effects on the kidneys of male rats were observed at the lowest dose. Severe, time- and dose-related nephropathy was observed in both sexes, occurring after only three months of exposure. Males were most sensitive. At the three-month interim evaluation, absolute and relative kidney weights of male rats receiving 120 mg/kg bw/day and female rats receiving 240 mg/kg bw/day of chlorophene were significantly higher than those of the controls. Time- and dose-dependent increases in heart rates were also observed. In male rats dosed for as long as 2 years, secondary hyper-parathyroidism developed, with parathyroid gland hyperplasia, mineralisation of the kidney and glandular stomach, and fibrous osteodystrophy occurring in the high-dose group (ECHA, 2014).

Dermal

Based on the treatment-related effects reported from repeated dose toxicity studies, repeated dermal exposure to the chemical is not considered to cause serious damage to health.

Chlorophene was administered to the skin of rabbits in four studies for five days, 21 days (two studies) and 28 days. Severe local effects were observed at the site of application. Kidney lesions were generally observed at doses ≥ 100 mg/kg bw/day. There was evidence of increased incidence and severity of histopathological lesions at 160 mg/kg bw/day in one of the three week studies. Increased incidence of tubular calcinosis was observed at 40 mg/kg bw/day in the same study in female rabbits (3/5 rabbits versus 0 in controls), but this was not dose-dependent. This effect was graded as weak and the finding was not replicated in any of the other studies. There were no changes in clinical chemistry or urinalysis values in the affected animals in the group (ECHA, 2015).

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

The potential genotoxicity of chlorophene has been studied in vitro in both bacteria and mammalian cells, and in vivo in a mouse micronucleus test, a comet assay and a mouse dominant lethal test.

In vitro

Clear negative result were reported in:

- bacterial reverse mutation tests in *Salmonella typhimurium strains* TA98, TA100, TA1535 and TA1537 exposed at 0.1–100.0 μg with and without metabolic activation; and
- a test for chromosome aberrations in Chinese hamster ovary cells exposed at 1.3–20 μg/mL and 4–60 μg/mL with and without metabolic activation respectively.

Neither of these tests conformed to the relevant guidelines available today. Nevertheless, they do not provide any indications of mutagenic potential.

The results from two mammalian cell mutation assays were equivocal:

- a gene mutation assay with L5178Y lymphoma cells exposed at 0–35 μg/mL, with and without metabolic activation; and
- a gene mutation assay with mouse L5178Y and human TK6 cells exposed at 0–45 μg/mL and 0–40 μg/mL respectively.

These independent studies assessed mammalian mutagenesis at two different loci (HPRT and TK), reporting indications of increased mutation frequencies in the absence of metabolic activation. However, both studies had limitations that reduced confidence in the conclusions (ECHA, 2015).

In vivo

Negative results were reported for the following in vivo studies in somatic cells (ECHA, 2015):

- a comet assay in ICR(CD-1) male mice exposed to two doses of the chemical (in corn oil) at 90, 180, 360 mg/kg bw; and
- a micronucleus assay in bone marrow erythrocytes of CD-1 mice exposed to single oral doses of the chemical at 500, 1000 and 2000 mg/kg bw in males and 250, 500 and 1000 mg/kg bw in females (OECD TG 474).

Negative results in germ cells were reported for a dominant lethal test in male mice (strain unspecified) following single intraperitoneal (i.p.) doses of the chemical at 100 and 200 mg/kg bw (ECHA, 2015).

Carcinogenicity

The available data provide evidence of the carcinogenic effects of chlorophene, warranting classification as carcinogenic (see **Recommendation** section).

Two carcinogenicity studies in rats (similar to OECD TG 453) and mice (similar to OECD TG 451) were available with supporting information from a non-guideline dermal initiation/promotion study and a short-term dermal carcinogenicity study in transgenic mice.

In a two-year carcinogenicity gavage study in F344 rats (50/sex/group), males were treated orally with chlorophene at 0, 30, 60 or 120 mg/kg bw/day and females with 0, 60, 120 or 240 mg/kg bw/day. No effects on survival or mean body weights were seen. In a standard evaluation, one female from the mid dose group and one female from the highest dose group were found to have a rare carcinogenic tumour of the renal transitional epithelium. Historical control data from the US National Toxicology Program (NTP) database showed that there were no incidences of this tumour out of 1068 controls; thus, the likelihood that these tumours were spontaneous was low and the study provided equivocal evidence of carcinogenicity (ECHA, 2014). The evidence is considered equivocal because the tumour incidence is low, there is no evidence of chlorophene being genotoxic (see the **Genotoxicity** section) and there is no clear relationship established between treatment-related toxicity (e.g. renal transitional cell hyperplasia) and susceptibility of animals to this tumour type. Nevertheless, there is no evidence to suggest that the results are irrelevant to humans. Thus the available information cannot be discounted (ECHA, 2015).

In a two-year carcinogenicity gavage study, B6C3F1 mice (50/sex/group) were treated orally with chlorophene at 0, 120, 240 or 480 mg/kg bw/day. At the end of the 2-year experimental period, an extended evaluation was performed using step sections of the kidney. Renal tubule adenomas were observed in male mice, dose-dependently across all study groups, reaching statistical significance at 480 mg/kg bw/day (5/50 (10 %) versus 0 in controls). Renal tubule carcinoma was evident in two males at 240 mg/kg bw/day (2/50 (4%)) and in one male at 480 mg/kg bw/day (1/50 (2%)). The incidence of adenoma and carcinoma combined reached statistical significance at doses ≥ 240 mg/kg bw/day. Renal tubular hyperplasia was also observed in all treated groups but in the absence of a dose-response relationship. These effects were observed at doses all greater than the maximum tolerated dose (MTD) with reductions in body weight of 20, 26 and 32 % at necropsy for dose groups 120, 240 and 480 mg/kg bw/day, respectively. Increased severity of nephropathy was observed at these doses (grading 0.8, 2.0, 2.4 and 2.4 for 0, 120, 240 and 480 mg/kg bw/day, respectively). No neoplasms were observed in female mice. There was limited evidence of carcinogenicity in this study. Increased nephropathy and mortality were related to tumour incidence and no tumours were observed in females. However, as there is no clear mechanistic basis to discount the finding in males, they should be considered of potential relevance to humans (ECHA, 2015).

In the initiation/promotion study, chlorophene (10 mg/animal) was applied topically to Swiss CD-1 mice (50/sex/group) as an initiator. Repeated topical applications of 0.1, 1 or 3 mg per animal were then applied three times a week for a year. When chlorophene treatment was followed by promotion using the phorbol ester tetradecanoyl phorbol acetate (TPA), chlorophene was not found to exert any initiating activity. However, there was a dose-related increased incidence of papilloma in both males and females following chlorophene treatment after initiation with dimethylbenzanthracene (DMBA). In conclusion, chlorophene did not act as a skin tumour initiator or as a complete carcinogen but did have activity as a weak skin tumour promoter (ECHA, 2015).

In the second dermal study, female Tg.AC transgenic mice (13 – 20/group) were dosed dermally with chlorophene (0.1, 1, 3 mg per animal) three times per week for over 20 weeks. The results showed a significant increase in skin tumours in animals treated with chlorophene (3 mg/animal) over the vehicle controls (84 % versus 29 % respectively). Survival decreased at 20 weeks in a dose-dependent manner with 86 %, 77 % and 68 % survival noted in the low, medium and high dose groups, respectively (ECHA, 2015).

Reproductive and Developmental Toxicity

Based on the available data, the chemical showed specific reproductive effects, warranting hazard classification for reproductive toxicity (see **Recommendation** section). Developmental effects were only observed secondary to maternal toxicity.

Reproductive toxicity

Wistar rats were exposed to chlorophene in a two-generation reproduction study performed according to OECD TG 416 in compliance with good laboratory practice. The chemical was administered orally by gavage at 60, 180, 540 mg/kg bw/day (30/sex/group). The animals in the parental generation (F0) were mated to produce offspring (F1), which were subsequently mated to produce a second generation (F2). Results confirmed that the kidney is the target organ for general chlorophene toxicity in rats. Increases in absolute and relative kidney weights were observed in all treated males of both generations. These findings were associated with macro- and microscopic renal lesions. Reductions in body weight gain during gestation were observed in dams at 540 mg/kg bw/day in the F0 generation and at 180 and 540 mg/kg bw/day in the F1 generation. Body

weights of the F1 pups were reduced at 180 and 540 mg/kg bw/day at lactation day 7, 14 and 21. Maternal body weights were unaffected at 60 and 180 mg/kg bw/day. No treatment-related changes in food intake were recorded in the dams. Body weights of F2 pups were reduced during lactation in the 540 mg/kg bw/day group. At the same dose level, some effects on maternal bodyweight were recorded on lactation day 1. Delayed ear and eye opening at 540 mg/kg bw/day and incisor eruption at 180 mg/kg bw/day were observed in both F1 and F2 pups. Significantly lower female fertility indices were observed in the F0 generation at 540 mg/kg bw/day (76.7 % compared to 93.3 % in controls) and at 180 and 540 mg/kg bw/day in the F1 generation (90 and 83.3 % respectively compared to 100 % in controls), and reduced fecundity was observed at 540 mg/kg bw/day in the F1 generation. Historical control data provided by the laboratory that conducted the study showed that the range previously observed in similar studies was 80–100 %. Significant increases in oestrus cycle length (4.5 days) were observed in the F1 females after treatment at 540 mg/kg bw/day.

The NOAEL for adverse effects on sexual function and fertility was 60 mg/kg bw/day, based on reduced female fertility indices observed in the F1 generation. A parental NOAEL of 180 mg/kg bw/day was established for females, with a lowest observed adverse effect level (LOAEL) of 60 mg/kg bw/day for males, based on the kidney effects in both generations. The overall NOAEL for adverse effect on development of the offspring is 60 mg/kg bw/day based on the reductions in body weight in the F1 pups at 180 mg/kg bw/day. The increased oestrous cycle durations observed in the F1 females of the highest dose group were significantly greater than controls (4.5 days versus 4.1 days respectively). However, the oestrus cycle lengths of the concurrent control animals and the animals in the two lowest dose groups (4.1, 4.0 and 4.1 respectively) were lower than the historical control range (4.3–4.5). Consequently, the significance of these findings is not clear. The reductions in fertility indices were found to occur in a dose-dependent manner which was reproducible in both F0 and F1 generations. There was a clear reduction in both generations when compared to historical control data, indicative of a weak adverse effect on fertility (ECHA, 2015).

Charles River albino rats (10 males/group and 20 females/group) were exposed orally to chlorophene at 0, 50, 150 mg/kg bw/day by gavage in a one-generation study similar to OECD TG 415. The animals in the parental generation (F0) were mated to produce offspring (the F1 generation). In this study, male body weight gains were reduced in the high-dose group (150 mg/kg/bw/day) during the pre-mating period. The body weight reductions continued until the end of the study. Females of either dose group were not affected. There were no effects on the number of implantation sites, resorption sites and corpora lutea. Reproductive performance was not affected in any treatment groups. All delivered pups were normal in appearance. Dose-dependent reductions in the 4-day survival and lactation indices (79.1 and 61.1 % in the 50- and 150-mg/kg bw/day groups, compared with the control value of 80.4 mg/kg bw/day) were observed. Body weights of male weanlings in the 50- and 150-mg/kg bw/day groups were significantly lower than in control weanlings. The parental NOAEL in this study was considered to be 50 mg/kg bw/day for the males based on the reduced body weights. Since there were no effects observed in the dams, the maternal NOAEL was ≥150 mg/kg bw/day. The LOAEL for the F1 generation pups was 50 mg/kg bw/day, based on the reductions in body weight in the male weanlings. The maternal NOAEL in this study was higher than the NOAEL for the weanlings and it cannot be excluded that the effect observed are treatment-related. The reduced body weights in the male weanlings were not dose-dependent and individual data were not reported (ECHA, 2015).

In a non guideline study with limited details reported, albino rats (17–19 females/group) were exposed orally to the chemical by gavage at 0, 50 and 150 mg/kg bw/day from day 15 of gestation throughout gestation and lactation. At ≥50 mg/kg bw/day, both the 12-day survival index and the 21-day lactation index were reduced. A parental NOAEL was established at 150 mg/kg bw/day and the LOAEL for the offspring was 50 mg/kg bw/day (ECHA, 2014).

Developmental toxicity

There were three oral studies in rats and four in rabbits, one of which in each species was a dose range finding study.

The available studies in rats with treatment from gestation day 6–15 do not provide any findings to justify classification of chlorophene for developmental toxicity. Foetal body weight and an increased incidence of non-ossified phalangeal nuclei were evident at 375 mg/kg bw/day, concomitant with reduced body weight and food intake in dams. In a second study, at comparable doses, no adverse effects were seen in foetuses (ECHA, 2015).

In two studies similar to OECD TG 414, no clear adverse foetal effects were seen. In the first study, New Zealand White rabbits were treated with chlorophene on gestation day 6–19 at 0, 10, 30 and 100 mg/kg bw/day (14–16/group) by gavage. In the second study, they were treated with the chemical on gestation day 7–19 at 0, 40, 80, 160 mg/kg bw/day. No adverse effects were reported in the third study, a range finding study (ECHA, 2015).

A fourth study in rabbits was reported to show increased post-implantation loss and an increased incidence of ectopic kidney, ectopic testes and malformed kidneys in foetuses at 100 mg/kg bw/day. However, no information was available regarding the incidence or severity of these effects or the presence of maternal toxicity (ECHA, 2015).

There were also relevant findings in the oral two-generation study conducted in rats (see the **Reproductive toxicity** section). No overt signs of toxicity were seen in foetuses. Pup body weights were slightly reduced during the lactation period, measured on post natal day (PND) 1, 4, 7, 14 and 21 at 540 mg/kg bw/day in both generations. These reductions appeared to be associated with reduced body weight gains of dams during the gestation period (by 20–30 % and 5–15 % compared to controls at 540 and 180 mg/kg, respectively). At 540 mg/kg bw/day, there were delays in incisor eruption, ear openings and eye openings in both generations. Delayed incisor eruptions were also evident at 180 mg/kg bw/day. These slight delays in the acquisition of developmental landmarks was suggestive of an overall pattern of slight developmental delay in the offspring of rats exposed to chlorophene. However, these observations correlated closely with the reduced body weight gains of dams in the treated groups and do not indicate a significant adverse effect on development (ECHA, 2015).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, reproductive toxicity), systemic acute effects (acute toxicity from inhalation exposure) and local effects (skin irritation, skin sensitisation and severe eye damage).

Public Risk Characterisation

Although the use in cosmetic or consumer products in Australia is not known, limited information suggests the chemical may have cosmetic use in antibacterial hand soaps (<10 %) and domestic or commercial use in disinfectants (1–10 %). The chemical has been used in the past as a preservative in cosmetics at low concentrations ($\leq$ 0.2 %) (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. The chemical has reported domestic use in disinfectants and cleaners up to 10 % (US Household Products Database). In these instances, the general public may be exposed to the chemical by the dermal routes.

Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products (such as disinfectants). The identified critical health effect for public risk characterisation is skin sensitisation (local effect). However, there is little evidence of human sensitisation to the chemical. Exposure is not expected to be high given its limited use. The chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term and acute local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the Hazardous Substances Information System (HSIS) (Safe Work Australia) (refer to **Recommendation** section.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Additional regulatory controls could be required should information become available to indicate that the chemical is used in cosmetic products in Australia

Regulatory Control

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful by inhalation (Xn; R20)	Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41) Irritating to skin (Xi; R38)	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)	Suspected of damaging fertility - Cat. 2 (H361f)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;

- 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 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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