Urea, N-(4-chlorophenyl)-N'-(3,4-dichlorophenyl)-: Human health tier II assessment

05 February 2016

CAS Number: 101-20-2

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.

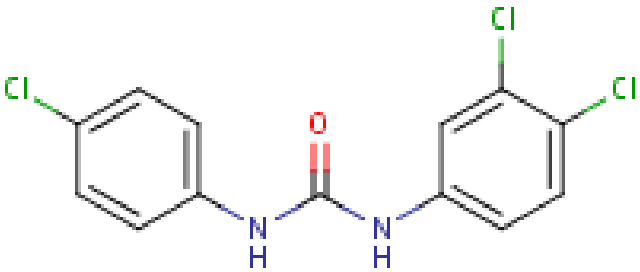
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	3,4,4'-trichlorocarbanilide triclocarban 3,4,4,'-trichlorodiphenylurea TCC Carbanilide
Structural Formula	
Molecular Formula	C13H9Cl3N2O
Molecular Weight (g/mol)	315.59
SMILES	c1(Cl)c(Cl)cc(NC(=O)Nc2ccc(Cl)cc2)cc1

Import, Manufacture and Use

Australian

The following uses have been identified from material safety data sheets (MSDS)s.

The chemical has reported domestic use as antibacterial component in cleaning products including personal care products at concentrations <1.5 %.

International

The following uses were identified through Galleria Chemica, Cosmetic Substances and Ingredients database (CosIng), United States (US) Occupational Health Database (HazMap), US National Toxicology Program (NTP, 2014), Personal Care Products database (INCI), Registration, Evaluation, Authorisation and Restriction of Chemicals dossier (REACH), and European Commission (EC) Scientific Committee on Consumer Products (SCCP, 2005).

The chemical has reported cosmetic uses as an anti-fungal or anti-microbial agent in:

- cosmetics;
- personal care products (toothpaste, soaps and deodorants); and
- disinfectants for skin and mucous membrane.

The chemical has reported domestic uses as an anti-fungal or anti-microbial agent in:

- cleaning products; and
- air fresheners.

Restrictions

Australian

No known restrictions have been identified.

International

Restrictions on the chemical were identified from the Galleria Chemica:

The European Union (EU) specifies that the chemical may be used as a preservative in cosmetic products at concentrations up to 0.2 % (CosIng, Annex V), and it may be used at concentrations up to 1.5 % for purposes other than as a preservative (CosIng, Annex III).

The chemical is included in the Association of Southeast Asian Nations (ASEAN) Cosmetic Directive:

- Annex VI – Part 1 – List of preservatives allowed for use in cosmetic products: 0.2% maximum authorised concentration; and
- Annex III – Part 1 – List of substances which cosmetic products must not contain except subject to restrictions and conditions specified: 1.5 % in rinse-off products.

The chemical is included in New Zealand Cosmetic Products Group Standard:

- Schedule 5 - Components - cosmetic products that must not contain except subject to the restrictions and conditions specified: 1.5 % maximum authorised concentration in the finished rinse-off cosmetic product; and
- Schedule 7: Preservatives - cosmetic products may contain with restrictions - Table 1: List of preservatives allowed: 0.2 % maximum authorised concentration.

The chemical is listed in the Philippines restricted ingredients for use in cosmetics - List of substances which cosmetic products must not contain except subject to the restrictions and conditions specified: 2 % maximum allowable concentration in the finished cosmetic product (deodorants).

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

The most important route for human exposure to the chemical (triclocarban) is through dermal contact. Inhalation exposure is not expected due to the low vapour pressure of the chemical, unless it is used in spray products. There is no anticipated oral exposure under recommended use conditions.

Toxicokinetics

Triclocarban has been detected in 35 % of human adult urine and 44 % of serum samples in the United States (Zhou et al., 2012). A background level of up to 285 nmol/L was detected in the whole blood of a volunteer who routinely used triclocarban-containing personal care products (Schebb et al., 2012). This indicates that frequent application of personal care products containing the chemical may lead to significant internal concentration of the chemical in the body. The chemical was also detected in eight out of 35 cord plasma samples (22.9 %) in a US based study (Pycke et al., 2014).

Absorption

Limited studies exist on pharmacokinetics following long-term dermal exposure to the chemical. In human volunteers (6 males and 6 females), the absorption of the chemical was examined after repeated daily application of approximately 260 mg of triclocarban in a 28-day bathing study. The triclocarban level was found to be below the limit of detection (25 ng/mL) in blood and in urine of all volunteers and at all timepoints (Howes & Black, 1976; REACH).

Several studies have examined the dermal absorption of chemical following single topical application in human volunteers. After a single dermal application, blood levels of the chemical ranged from below the limit of detection (10 ng/mL) to a maximum of approximately 167 ng/mL (Scharpf et al., 1975; Schebb et al., 2012). Small amounts of the chemical were also detected in the urine and faeces of the subjects (Schebb et al., 2011). The estimated total average recovery ranged between 0.39 and 0.60 % of the applied dose. These studies suggest that very little chemical is absorbed after a single topical exposure.

In another study, ^{14}C-labelled triclocarban dissolved in acetone was applied topically to the skin (500 cm^2) of five human volunteers at a concentration of 4 µg/cm^2. Urine was collected for ten days. Based on urinary excretion of the radiolabelled chemical, approximately 7 % of the totally administered dose was calculated to have been absorbed through the skin (SCCP, 2005).

In human volunteers (12; sex not specified), the majority of the applied chemical from a single wash with bar soap containing the chemical was removed from the skin by rinsing. An average of 1.4 % of the applied chemical remained on the skin after rinsing (North-Root et al., 1984).

In an in vitro dermal absorption study, the absorption of ^{14}C-labelled triclocarban was evaluated in static and flow-through in vitro skin cell systems using full thickness of human newborn and adult abdominal and foreskin, as well as a monkey's abdominal skin. At 37°C, 2.5 % of the applied dose was absorbed through human newborn foreskin and 0.6 % through human adult foreskin. In human newborn and adult as well as monkey abdominal skin, 0.23–0.29 % of the chemical was absorbed. In the continuous flow system at 23°C, 6 % of the applied dose was reported to be absorbed in the human adult abdominal skin model (SCCP, 2005).

The low dermal absorption of the chemical is supported by the low absorption through the intact skin of rats and guinea pigs (Black et al., 1975; Hiles, 1977). In rats, the absorption of ^{14}C-labelled triclocarban was demonstrated to occur at a constant rate over 72 hours and the flux was calculated to be 0.15 nmol/cm^2/hour (Hiles, 1977). In guinea pigs, ^{14}C-labelled triclocarban was applied to guinea pig skin. After the area was rinsed, most of the chemical was deposited on the skin surface and only small amounts penetrated through the epidermis into the dermis. The chemical was not detected in blood or other tissues following topical application, suggesting very low percutaneous absorption of the chemical (Black et al., 1975).

In a pharmacokinetic study following single oral exposure, human volunteers (six males) received a single oral dose of ^{14}C-labelled triclocarban. The maximum plasma concentration of 3.7 nmol triclocarban/g plasma (approximately 1,200 ng/mL) was detected 2.8 hours after dosing (NDAC, 2014).

In a reproductive and developmental toxicity study, Sprague Dawley (SD) rats (5/group) were exposed to 0.2 % or 0.5 % triclocarban in diet from gestation day (GD) 5 to GD 19. A significant increase in concentrations of triclocarban was detected in amniotic fluid on GD 19. In addition, significantly increased levels of the chemical were detected in maternal milk on postnatal day (PND) 6 and in neonate serum on PND 5 (Kennedy et al., 2015).

Metabolism

Triclocarban is readily metabolised in both humans and experimental animals following oral exposure. The principal metabolites are the sulfate and glucuronide conjugates of 2'-, 3', and 6-hydroxy-triclocarban. There appear to be some differences in triclocarban metabolism between rats and higher primates. The monkey is considered to be the more appropriate model relevant for humans (Birch et al., 1978).

The majority of the chemical and its metabolites are eliminated through the faeces. When human volunteers (six healthy males) received a single oral dose of ^{14}C-labelled triclocarban (in corn oil), 70 % of the dose was eliminated in the faeces by 120 hours, while 28 % of the dose was eliminated in urine by 80 hours after dosing (Hiles & Birch, 1978).

Only limited data on the metabolism of the chemical following dermal application are available. In human volunteers using bar soap containing triclocarban (details of the frequency or length of time for soap usage was not reported), the major plasma metabolite was a sulfate of 2-hydroxytriclocarban while the major metabolites found in the urine were triclocarban glucuronides (Gruenke et al., 1987).

Acute Toxicity

Oral

The chemical is not considered to be acutely toxic via the oral route. Several studies have reported acute oral median lethal dose (LD50) values of >2000 mg/kg bw (SCCP, 2005).

In a guideline study (OECD Test Guideline (TG) 423), Wistar rats (6 females) were given a single dose of 2000 mg triclocarban/kg bw by gavage. The treatment did not cause mortality. The LD50 was estimated to be >2000 mg/kg bw (REACH).

In another guideline study (OECD TG 401), rats (5/sex) were given a single dose of 2000 mg triclocarban/kg bw by gavage and observed for 14 days. There were no signs of toxicity and no mortality. The median lethal dose (LD50) was reported to be >2000 mg/kg bw (SCCP, 2005).

In a non-guideline study, NMRI (Swiss) mice received the chemical orally at various doses and were observed for seven days. The treatments did not cause mortality. The LD50 was estimated to be >5000 mg/kg bw (SCCP, 2005).

Dermal

The chemical is not considered to be acutely toxic via the dermal route.

In a guideline study (OECD TG 402), the chemical was applied to the skin of Wistar rats (5/sex) at 2000 mg/kg bw under occlusion for 24 hours. No signs of toxicity or deaths were reported (REACH).

In a non-guideline study, the chemical (containing up to 20% of dichloro- and tetrachlorocarbanilide as contaminants), was applied to the clipped, intact skin of New Zealand White rabbits. The treated areas were covered with plastic strips (occlusive) for 24 hours. No deaths occurred at the highest dose of 10000 mg/kg bw (SCCP, 2005).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is not considered to be irritating to the skin.

In a guideline study (OECD TG 404), 500 mg of the chemical (moistened with polyethylene glycol 400) was applied to a hypoallergenic patch (semi-occlusive) placed on the trunk of three New Zealand White rabbits for four hours. The treated skin area was rinsed with water after

application. The chemical was not irritating to the skin according to the Draize scoring system (REACH; SCCP, 2005).

In a non-guideline study, the chemical (containing up to 20 % of dichloro- and tetrachlorocarbanilide as contaminants), was applied to the clipped, intact skin of New Zealand White rabbits as a 25 % suspension in corn oil. The treated areas were covered with plastic strips (occlusive) for 24 hours. The chemical was not irritating to the skin (REACH; SCCP, 2005).

In another study, male albino rabbits and male albino guinea pigs were treated with 0.03 mL of the chemical (diluted in acetone) at concentrations of 0.5, 1 and 3 %. The chemical was applied to a depilated circle of skin (1.5 cm diameter). The sites of topical application (non-occlusiven patch) were observed for 24 and 48 hours. No skin reactions were seen in any animals at any dose. The chemical was considered to be non-irritating to skin (REACH; SCCP, 2005).

Eye Irritation

The chemical is not considered to be irritating to the eye.

In a guideline study (OECD TG 405), 0.1 mL of the chemical (approximately 42 mg of triclocarban) was placed in the conjunctival sac of one eye of each of three New Zealand White rabbits. The eyes were rinsed with saline solution after 24 hours and observed up to 21 days. No irritation effects were observed (SCCP, 2005).

In a non-guideline study, 20 mg of the chemical (containing up to 20 % of dichloro- and tetrachlorocarbanilide as contaminants), was placed in the conjunctival sac of the right eye of each of three albino rabbits. The eyes were rinsed with saline solution after 24 hours and observed for several days. The chemical was considered to be slightly irritating to the eyes (SCCP, 2005).

Two other studies were performed following the principles of OECD TG 405.

In the first study, 0.1 mL of test solution (a bar soap containing 0.55 % triclocarban in a 10 % w/v aqueous solution) was placed into the conjunctival sac of one eye of six New Zealand White rabbits. Three rabbits had their eyes rinsed with lukewarm water four seconds after application, and the other eyes remained unwashed. Two out of three rabbits in the unrinsed group had corneal epithelial peeling, which reversed in four to seven days. Rinsing of the eyes reduced the effects.

In the second study, 10 µL of a liquid hand soap containing 0.15 % of the chemical was applied directly into the cornea of six New Zealand White rabbits. The eyes of three rabbits were rinsed with lukewarm water four seconds after application and the other eyes remained unwashed. Clear discharge, capillary haemorrhage (petechiae) and corneal dulling over 40 % of the eye were noted one day after treatment in all the rabbits with unrinsed eyes, but the effects cleared by four days. Following rinsing of the eyes, redness of the conjunctivae was noted in only one rabbit at one day after application which cleared by the second day (SCCP, 2005).

In both studies, the findings indicate that the formulation containing the chemical was mildly irritating to the unrinsed eyes of rabbits (SCCP, 2005).

Observation in humans

The chemical at concentrations of 1, 3, 6 or 9 % in petrolatum was applied by patch test (occlusive) to the paraspinal skin of white male volunteers for 21 days. One out of 10 subjects had a minor positive response to 3 % triclocarban from10 days after application. No other effects were reported. The chemical was not considered to be irritating to the human skin (REACH; SCCP, 2005).

The cumulative skin irritation effect of a liquid hand soap (containing 1.5 or 1.35 % triclocarban) was investigated in a three patch application test (3-PAT) as a 2 % aqueous solution (approximatley 0.03 or 0.027 % triclocarban). Human volunteers (10–12 volunteers) were treated with patches (occlusive) on the upper arms (max eight patches per person, four per arm) for 24 hours, three times a week for total of one week. The skin was graded (grades 0–4) for irritation after 24–48 hours following removal of the patches. The mean average skin grading scores were 1.36 and 1.32 for 0.03 % and 0.027 %, respectively. This was similar to the irritation scores observed for control products (SCCP, 2005).

The phototoxicity of the chemical was evaluated in ten white males following application on both forearms of 9 % triclocarban in petrolatum for one hour. The test site on one forearm was UV irradiated for 45 minutes. No positive responses were observed in any of the test subjects (SCCP, 2005).

Sensitisation

Skin Sensitisation

The chemical is not considered to be a skin sensitiser.

In a guideline study (OECD TG 406), the sensitisation potential of the chemical (as a suspension with Cremophor EL (2 % v/v) in physiological saline solution) was evaluated in the guinea pig maximisation test. The treatment group (20 male guinea pigs) was injected with 0.1 mL of the solution with: (a) 1:1 mixture of Freund's complete adjuvant (FCA) and physiological saline solution; (b) 5 % test substance formulated with Cremophor solution and, (c) 5 % test substance in a 1:1 mixture of FCA. The control animals were treated similarly but without the test substance. A week later, a patch containing 0.5 mL of a 50 % solution of the test substance was placed over the injection area for 48 hours in the treatment group while the control groups received 0.5 mL of Cremophor solution alone. Three weeks after the induction phase, the back and the flanks of the treated and the control animals were shaved and an occlusive challenge patch containing 50 % test substance formulation was applied to the left flank of the animals for 24 hours and observed for up to 72 hours. Under the test conditions, the chemical did not induce skin sensitisation in guinea pigs (SCCP, 2005).

Photosensitisation of the chemical was evaluated in guinea pigs (6–10 per group). The chemical was applied to the left side of the back. The right side served as solvent control. Animals were irradiated either with both UVB and UVA, or UVA alone. The guinea pigs received six successive treatments and irradiations, followed by a three week recovery period. After recovery, a non-phototoxic challenge dose was administered to determine photoallergy. Triclocarban at a concentration of 4 % did not exhibit photoallergic activity in guinea pigs (SCCP, 2005).

Observation in humans

The allergic contact sensitisation potential of the chemical was tested according to the Shelanski repeated insult patch test method. Human volunteers (n=50) were treated on the back with 15 semi-occlusive patches containing approximately 50 mg of undiluted triclocarban for 24 hours, and the skin examined for irritation reactions. After 24 hours' rest, the patches were reapplied for another 24 hours and the sites examined on removal. After a second patch, the site was allowed to recover for two weeks, followed by a final 24 hour challenge application of 50 mg undiluted test substance. No skin reactions were observed after any treatments. The chemical was considered not to be a primary skin irritant or a skin sensitiser. However, the solubility of the test substance was questioned (SCCP, 2005).

In four separate studies, 0.06 to 0.12 % of triclocarban was applied on the skin of human volunteers (97-114) under semi-occlusive patches (as an aqueous solution of bar soap) for 24 hours, three times a week for three weeks at the same skin site. After a two week rest period, a final 24 hour challenge was applied and the skin reaction was evaluated after 48, 72 and 96 hours. There was no evidence of skin sensitisation in any of the volunteers at any concentration after the challenge test (SCCP, 2005).

In another study, 0.05 % of triclocarban was applied on the skin of human volunteers (n=107) under semi-occlusive patches (aqueous solution of bar soap) for 24 hours, three times a week for three weeks at the same skin site. After a 12-20 days' rest period, a final 24 hour challenge was applied and the skin reaction was evaluated after 48 and 72 hours. There was no evidence of skin sensitisation in any of the volunteers after the challenge test (SCCP, 2005).

In a Draize method study, the chemical was applied to the upper portion of the arm of male volunteers (n=88). In the induction phase, the chemical (1.5 or 10 %) was repeatedly applied to the skin for three and a half weeks, followed by a rest period of two weeks. In the challenge phase, 1 % triclocarban was applied to the arm for 72 hours. There was no evidence of skin sensitisation.

In a modified Draize method study, 9 % triclocarban was applied to the upper lateral portion of the arm of male volunteers (n=185), three times a week for 48 or 72 hours. Each individual received ten applications. The induction period was followed by a two week rest phase. A challenge consisted of a patch of 9 % triclocarban applied for 72 hours with skin reactions evaluated 96 hours after removal of the patch. No positive responses were observed in any of the test subjects.

Dermatitis patients (total 2200 patients) were treated with 1 % triclocarban in petrolatum in the routine test battery in dermatitis screening programme. One patient reacted to 1 % concentration, and was confirmed by repeat patch testing. However, this patient did not react positively to a following test with twice daily application of triclocarban soap (containing 1.5 % triclocarban in bar soap) for a week, which suggests that triclocarban is not a strong sensitiser even within sensitive populations (SCCP, 2005).

Repeated Dose Toxicity

Oral

Based on the effects reported in various repeated dose toxicity studies, repeated oral exposure to the chemical is not considered to cause serious damage to health.

In a chronic oral toxicity study performed based on a protocol approved by the US Food and Drug Administration (US FDA), SD rats (80/sex) received 0, 25, 75 or 250 mg/kg bw/day of triclocarban in diet for two years. Signs of laboured breathing, emaciation and rales as well as increased mortality were observed in controls and treated males in weeks 64 – 86 and 70 – 83, respectively . The authors considered these effects as not treatment-related but attributed to a respiratory infection present predominantly in males during this time period. Slightly reduced body weight was seen at 75 mg/kg bw/day. Significant increase in liver weight was observed at 75 and 250 mg/kg, increased spleen weight at 75 (males) and 250 mg/kg bw/day (males and females), and increased testes and heart weights in males at 250 mg/kg bw/day. However, the

organs were microscopically normal and, therefore, the effects on organ weights were reported to not be of biological significance. No effects on food consumption were observed. Based on these findings, the no observed effect level (NOEL) and the lowest observed effect level (LOEL) of 25 and 75 mg/kg bw/day were determined, respectively (SCCP, 2005).

In another chronic oral toxicity study, rats (strain not specified) received 1000, 3000 or 10000 ppm (approximately 100, 300, or 1000 mg/kg bw/day) triclocarban in diet for two years. Testicular toxicity was detected at 3000 ppm and above (see Reproductive toxicity). No testicular lesions were present in rats fed 1000 ppm (approximately 100 mg/kg bw/day). No other chemical-related gross, biochemical, haematological, central nervous system or histopathological effects were observed in the study (SCCP, 2005).

In a non-guideline study, SD rats (10/sex/dose) were dosed with 25 % aqueous solution of the chemical at 0 (controls), 500 or 1000 mg/kg bw/day by gavage, five days a week for 30 days. Based on food consumption, growth data and tissue examination, the NOAEL was determined to be > 1000 mg/kg bw/day. No other study details are available (SCCP, 2005).

In another non-guideline study, SD rats (35/dose) received 25, 75 or 250 mg/kg bw/day of the chemical in diet for eight weeks. No control group was included in the study. There were no signs of toxicity or treatment related mortalities throughout the study. Mean body weight and food consumption were lower in the highest dose group, although the significance is unknown due to lack of a control group. The no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) were reported to be 75 and 250 mg/kg bw/day, respectively (SCCP, 2005).

Dermal

No data are available.

Genotoxicity

The chemical is not considered to be mutagenic or genotoxic.

In a bacterial reverse mutagenicity assay (OECD TG 471), the chemical (up to 5000 µg/plate) was negative with or without metabolic activation in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA1538 (REACH; SCCP, 2005).

In an in vitro mammalian chromosome aberration test (in accordance with US Environmental Protection Agency (EPA) guidelines) using Chinese hamster ovary (CHO) cells, the chemical (up to 2000 µg/mL) gave negative results with or without metabolic activation (SCCP, 2005).

Carcinogenicity

The chemical is not considered to be a carcinogen.

In a chronic oral toxicity study based on a protocol approved by the US Food and Drug Administration (FDA), SD rats (80/sex) received doses of 0, 25, 75 or 250 mg/kg bw/day of the chemical in diet for two years. There was no evidence of a dose-related increase in tumour incidence (SCCP, 2005).

In another chronic oral toxicity study, rats (strain not specified) received doses of 1000, 3000 or 10000 ppm (approximately 100, 300 or 1000 mg/kg bw/day) triclocarban in their diet for two years. There was no evidence of carcinogenicity reported in the study. However, the information available was not considered sufficient to evaluate the quality and reliability of the reported study results (SCCP, 2005).

Reproductive and Developmental Toxicity

While there is an indication of possible reproductive and developmental toxicity, the limited information available is insufficient to warrant classification for the chemical.

Reproductive toxicity

In a three-generation study (oral feed), Charles River CD rats (12/group; males and 24/group; females, respectively) received 0, 250, 500, 1000 or 3000 ppm (0, 25, 50, 100 or 300 mg/kg bw/day) of the chemical in their diet. No treatment-related clinical observations or mortality were reported throughout the study. Body weight and food consumption were not adversely affected by treatment throughout the study. Mating indices and male fertility were not adversely affected by treatment in any generations. At the highest dose group, the mean number of live pups at birth was lower than the controls for the first generation, but not in the following generations. No effect on length of gestation was detected. The NOAEL for the parental (F0), first (F1) and second (F2) generations was reported to be 3000, 1000 and 3000 ppm (approximately, 300, 100, and 300 mg/kg bw/day), respectively (REACH; SCCP, 2005).

In a chronic oral toxicity study, rats (strain not specified) recieved 1000, 3000 or 10000 ppm (approximately 100, 300 or 1000 mg/kg bw/day) triclocarban in diet for two years. At 3000 and 10000 ppm, testicular toxicity with degeneration of the germinal epithelium lining of the seminiferous tubules, atrophy of the tubules, and oligospermia, after six months of exposure were reported. No testicular lesions were present in rats at 1000 ppm (approximately 100 mg/kg bw/day). Therefore, the NOAEL for testicular effects was 1000 ppm (100 mg/kg bw/day) (SCCP, 2005).

In a chronic oral toxicity study performed in accordance with the US Food and Drug Administration (FDA), SD rats (80/sex) received 0, 25, 75 or 250 mg/kg bw/day of the chemical in diet for two years. Increased incidence of small and flaccid testes was observed in males at 250 mg/kg bw/day. The NOAEL for testicular effects was 75 mg/kg bw/day (SCCP, 2005).

In reproductive and teratogenic studies, female New Zealand White rabbits were given topical or oral doses of a 2:1 mixture of triclocarban and 3-trifluoromethyl-4,4'-dichlorocarbanilide (TFC) from day seven to day 18 of gestation (GD 7– 18). The topical treatment groups were 250, 500 or 1000 mg/kg bw/day and the oral treatment groups were 50, 100, or 250 mg/kg bw/day. Topical treatments produced very mild skin irritation at the application site. The oral doses caused dose-related maternal toxicity, including weight losses, abortions, and death (SCCP, 2005).

Developmental toxicity

In a three-generation study (oral feed), male and female Charles River CD rats (12/group and 24/group, respectively) received 0, 250, 500, 1000 or 3000 ppm (approximately 25, 50, 100 or 300 mg/kg bw/day) of triclocarban in diet. No mortality was observed throughout the study. Parental body weight and food consumption were not adversely affected by treatment throughout the study. Reduced mean pup weight at day 21 was observed from the first generation with similar trends detected in the following generations (SCCP, 2005).

In a reproductive and developmental study, SD rats (5 females/group and 4 (sex unspecified in control group) received 0, 0.2 or 0.5 % triclocarban (w/w; approximately 200 or 500 mg/kg bw/day) in their diet on GD5 until GD19 or at weaning on postnatal day (PND) 21. A cross-fostering experiment was performed with each dam (5 females/group) raising two of their own pups and two pups from each of the other two treatment groups (total of six pups/dam) to identify the susceptible windows of gestational and postnatal triclocarban exposure to offspring. The maternal body weight and the serum level of triiodothyronine (T3) were significantly reduced at 0.5 % dose on GD19. No effects were detected on the implantation number or circulating levels of oestradiol, progesterone, testosterone, thyroxine (T4) or thyroid-stimulating hormone (TSH). No effect was detected on the number of live births or pup weight at birth. However, neonatal survival after birth was significantly reduced in the 0.5 % treatment group with none of the pups surviving beyond PND 8. In a cross-fostering study, no effect on body weight or pup survival was observed following in utero only exposure to triclocarban. However, the pup survival and average body weight were significantly reduced in pups nursed by triclocarban-supplemented dams (lactational exposure). No pups raised by dams receiving 0.5 % dose survived beyond PND 5. Histopathological analysis of pups showed small acute gastric ulcers and fatty vacuolation of hepatocytes. On PND 21, the body weights of the surviving pups (13%) raised by dams receiving 0.2 % dose was reduced by approximately 50 %. No significant differences were detected in the anogenital distance, age of vaginal opening or organ weights. Further confirmation of these results is warranted due to a low number of experimental animals used in the study (Kennedy et al., 2015).

In another reproductive and developmental study, Charles River CD rats (5/sex/dose) were fed a diet containing 0, 0.05, 0.1, 0.2 or 0.25 % per day of 2:1 mixture of triclocarban and TFC (as above). At 0.25 % dose (approximately 250 mg of mixture/kg bw/day), significant reductions were observed in the number of pups born to those that did conceive, in the number of pups that survived until weaning, and in the pup body weights at weaning. No teratogenic effects were detected. No reproductive or developmental effects were observed at diet containing 0.2 % (approximately 100 mg of mixture/kg bw/day) dose or less (SCCP, 2005).

Other Health Effects

Endocrine Disruption

Recent studies suggest that the chemical can cause perturbations to the endocrine system by altering the steroid hormone (androgen and oestrogen) activity.

In a short-term toxicity study, male SD rats received either a normal diet or a diet supplemented with the chemical (0.25 % in diet; approximately 250 mg/kg bw/day) for 10 days. No mortalities were observed. The chemical significantly increased the body weight and liver weight of treated animals compared with control animals. The weights of the androgen dependent organs (seminal vesicles, ventral prostate, levator ani/bulbocavernosus (LABC) muscle, and glans penis) were significantly larger in the treated group compared with the control group. However, there were no macroscopic or microscopic abnormalities of any of the accessory sex glands, penis or testes in treated animals (Duleba et al., 2011).

In rats, the chemical was shown to enhance testosterone-induced androgen receptor (AR)- mediated responses in vitro and in vivo. In vitro, the effects of the chemical were evaluated in a cell-based human AR-mediated bioassay system and in prostate cancer cells lines transfected with AR-dependent luciferase reporter system. Triclocarban was shown to augment testosterone induced AR-mediated transcriptional activity, while the chemical alone had no effect (Ahn et al., 2008; Chen et al., 2008; Duleba et al., 2011). Similarly, following androgen deprivation in castrated rats, triclocarban in the presence of testosterone significantly increased androgen responsive male reproductive organ weights when compared to either the chemical or testosterone alone (Chen et al., 2008).

Triclocarban enhanced oestradiol-dependent activation of oestrogen receptor (ER)-responsive gene expression in recombinant human ovarian cells (Ahn et al., 2008). The chemical was shown to have anti-oestrogenic potential in vitro. High concentrations (1.6 μM) of triclocarban significantly reduced the luciferase activity in the ER Calux assay in T47Dluc cells. However, the mechanism is uncertain as triclocarban did not have an effect on oestradiol production in H295R cells. The anti-oestrogenic activity was not due to the increased cytotoxicity as confirmed by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay in T47Dluc cells (Simon et al., 2014).

Triclocarban has been studied in vitro as part of NTP Tox21 High Throughput Screening Program (Tox21). Based on Tox21, the chemical has been classified as mitochondrial toxicant, ER- and farnesoid-X-receptor antagonist as well as aryl hydrocarbon receptor, and antioxidative response element agonist (NTP, 2014).

Risk Characterisation

Critical Health Effects

The analysis of existing data demonstrate that triclocarban has low acute and chronic toxicity profile. Information regarding dermal exposure (the most relevant route for human exposure) is mostly lacking. However, data are available indicating possible testicular toxicity and hormonal perturbations in animals treated with triclocarban.

Public Risk Characterisation

In Australia, the chemical has reported domestic use as antibacterial component in cleaning products including personal care products at concentrations of <1.5 %. Triclocarban is also used in bar and liquid soaps and shower gels overseas. In these instances, the general public may be exposed to the chemicals through the dermal route. Currently, there are no restrictions for use in Australia. However, various overseas countries have placed restrictions on the use of the chemical as a preservative in cosmetics, rinse-off products and for purposes other than cosmetics (See Restrictions - International).

Based on the evaluation of margins of safety (MOS), the worst-case scenario for dermal exposure from the combined use of these products containing up to 1.5 % triclocarban resulted in an estimated systemic exposure dose of 0.032 mg/kg bw/day (SCCP, 2005). This value is significantly lower than the internal NOEL of triclocarban of 6.75 mg/kg bw/day (calculated based on the NOEL of 25 mg/kg bw/day from a chronic two year feeding study and corrected for an oral bioavailability of 27 %) deriving a MOS of > 200 (i.e. adequate safety margin) (SCCP, 2005). In addition, cosmetic products containing triclocarban in which the substance has been used as an antimicrobial active ingredient (e.g. bar soap), have been in the market for more than 45 years and significant adverse effects have not been reported (SCCP, 2005).

Provided that normal precautions are taken to avoid prolonged skin contact, the risk to the public posed by domestic products containing the chemical is not considered to be unreasonable at concentrations below 1.5 %.

Occupational Risk Characterisation

During product formulation, 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 maintenance of equipment. Worker exposure to the chemicals at lower concentrations may also occur while using formulated products containing the chemicals. While the data are insufficient to fully characterise the hazards of the chemical, the chemical should be treated as if it is a hazardous substance.

NICNAS Recommendation

Based on the current available data, there are indications of effects associated with testicular toxicity and hormonal perturbations in animals treated with the chemical. However, the available data do not conclusively demonstrate the potential of the chemical to cause adverse effects from current uses. NICNAS will continue to monitor the high quality assessment work that is being conducted by regulators on the chemical and further assessment may be required.

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

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2014).

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

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

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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Last update 05 February 2016

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