Biphenylol and its sodium salt: Human health tier II assessment

01 September 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
[1,1'-Biphenyl]-2-ol	90-43-7
[1,1'-Biphenyl]-2-ol, sodium salt	132-27-4

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

Grouping Rationale

The chemicals, o-phenylphenol (OPP; CAS No. 90-43-7) and sodium o-phenylphenate (SOPP; CAS No. 132-27-4), have been grouped together in this assessment. The chemical SOPP is the water soluble salt resulting from treating OPP (also referred to as the parent chemical) with a solution of sodium hydroxide. While some physical properties of the chemicals differ (i.e. water solubility), OPP and SOPP are in a pH dependent equilibrium, hence the chemicals are considered together in this assessment report.

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossier;
- the European Commission Cosmetic Ingredients and Substances (CosIng) database;
- Galleria Chemica;
- Haz-Map;
- the Substances and Preparations in Nordic countries (SPIN) database;
- the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary;
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and
- various international assessments (MAK, 1991; IARC, 1999; INCHEM, 1999; CEPA, 2007).

The chemicals in this group have the following reported cosmetics uses:

- as cosmetic preservatives;
- in hair colouring preparations;
- as ingredients in fragrances; and
- as ingredients in cleansing products such as cold creams, cleansing lotions, liquids and pads, and in mud pack pastes.

The chemicals have one or more of the following reported domestic uses, including:

- in lubricants and additives;
- as preservatives in cleaning/washing agents;
- as preservatives in food packaging;
- in paints, lacquers and varnishes;
- in aerosol disinfectant products,
- in automobile polishes, ceramic glazes, laundry starch, inks; and
- as odour agents.

The chemicals have one or more of the following reported commercial uses, including:

- in metal working fluids, such as cutting emulsions;
- in adhesives and binding agents;
- in absorbents and adsorbents;
- in construction materials; and
- in impregnation materials.

One or both of the chemicals have the following reported site-limited uses, including:

- as an accelerator during dyeing of synthetic fibres;
- in manufacturing dyes and thermoplastics (plasticiser); and
- in manufacturing resins and rubber.

The chemicals also have reported non-industrial uses as pesticides and biocides.

Restrictions

Australian

The parent chemical OPP (CAS No. 90-43-7) is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 5 (SUSMP, 2015).

Schedule 5:

'ortho-PHENYLPHENOL'except:

in preparations containing 5 per cent or less of o-phenylphenol'.

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2015).

It should be noted that the Schedule entry for OPP, above, also applies to the salt (SOPP; CAS No. 132-27-4), in accordance with the interpretation of the SUSMP (SUSMP, 2015).

International

The use of the chemicals in cosmetics in the EU is subject to the restrictions described under Annex V/7 of EU Cosmetics Regulation 1223/2009 — biphenyl-2-ol, and its salts may be used as preservatives at maximum concentrations of 0.2 % (as the parent chemical) in ready for use preparations (CosIng).

The chemicals are also listed on the following (the same use restrictions as described above for the EU (Galleria Chemica)):

- the Association of Southeast Asian Nations (ASEAN) Cosmetic Directive—Annex VI—Part 1;
- the New Zealand Cosmetic Products Group Standard—Schedule 7—Table 1; and
- the Philippines Listing of Cosmetic Ingredients—Section III—Table II.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

The parent chemical, CAS No. 90-43-7 is classified as Xi; R36/37/38 (irritation).

The sodium salt, CAS No. 132-27-4 is classified as Xn; R22 (acute toxicity) and Xi; R37/38-41 (irritation and eye damage).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

The toxicokinetics of the chemicals in this group may vary due to differing physical properties, i.e. with the parent chemical (OPP) being relatively insoluble in water (0.8 g/L), and the salt (SOPP) being highly water-soluble (~1200 g/L) (PubChem). However, OPP and SOPP are in a pH dependent equilibrium (INCHEM, 1999), the oral bioavailability and subsequent distribution, metabolism and excretion of the absorbed chemicals are expected to be similar.

The available toxicokinetic data for the chemicals are provided below.

Following ingestion of a single oral dose, OPP and SOPP are absorbed to a similar extent in rats, with approximately 85 % detected as having been absorbed within 24 hours (CEPA, 2007). Dermal exposure to OPP in rats and humans resulted in slower absorption rates than for oral exposure, with dermal absorption calculated to be ~45 %. However, both oral and dermal exposure to OPP resulted in peak plasma concentrations at one hour after dosing.

Radiolabelled OPP or SOPP, administered as a single oral dose to rats, were found not to accumulate significantly in the body, with <8 % and <1 % of the radiolabeled chemicals detected in tissue (including adipose, liver, kidneys and brain) at 24 hrs and 7 days after dosing, respectively. Both chemicals are reported to be rapidly excreted through the urine (CEPA, 2007).

In humans and rodents, absorbed OPP and SOPP both produced similar metabolites including sulfate and glucuronide conjugates of OPP; unconjugated phenylhydroquinone (PHQ); phenylbenzoquinone; and 2,4'-dihydroxybiphenyl (Bartels et al., 1998; Cnubben et al., 2002; IARC, 1999; INCHEM, 1999). The urinary levels of both conjugates and free metabolites were reported to be dose-dependent (Kwok et al., 1999). In the urine, little or no free OPP was identified (Bartels et al., 1998; IARC, 1999). At low doses, the major metabolic pathway for OPP is sulfation in human, rat and mouse (Bartels et al., 1998). In vitro, OPP has been shown to undergo redox cycling facilitated by cytochrome P450 enzymes (IARC, 1999).

Acute Toxicity

Oral

The acute toxicity of the chemicals following oral exposure varies; SOPP is considered more toxic than the parent chemical, OPP.

The chemical SOPP is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data (reported oral median lethal dose—LD50— range of 591-1550 mg/kg bw in rats) support this classification (Bomhard et al., 2002; CEPA, 2007).

The chemical OPP has low acute oral toxicity with LD50 values of >2000 mg/kg bw in rats (Bomhard et al., 2002; MAK, 2012; REACH).

The treatment-related clinical changes observed following ingestion of either chemical included ataxia, rales, coughing (tussis), diuresis, depression, abnormal protusion of the eyeball (exophthalmos), lacrimation, dropping of the upper eyelid (ptosis), and abdominal inflation in rats, reduced spontaneous movement, staggering gait, and low respiratory rate. Pathological effects such as bleeding in the liver, kidney, lungs and alimentary canal were also reported (CEPA, 2007; MAK, 2012).

Dermal

The parent chemical OPP has low acute toxicity based on results from animal tests following dermal exposure. The dermal LD50 is reported to be >2000 mg/kg bw in Wistar rats and New Zealand White rabbits (Bomhard et al., 2002). No treatment-related effects were reported. No data are available for SOPP.

Inhalation

The chemicals have low acute toxicity based on results from animal tests following inhalation exposure. The parent chemical OPP has reported median lethal concentration (LC50) values of >36 mg/m^3 as vapour (four hour inhalation exposure) and >949 mg/m^3 as aerosol (one hour exposure). The chemical SOPP has an LC50 of >1331 mg/m^3 as aerosol dissolved in water (one hour inhalation) (inconclusive due to lack of study details). No treatment-related effects were reported (Bomhard et al., 2002; REACH).

Observation in humans

Ingestion or inhalation of OPP has been reported to be moderately toxic in humans (NTP, 1986). Fatal ingestion of 10 g of OPP was reported in two individuals, resulting in pathological changes in the urothelium of the bladder (NTP, 1986). In another case, intentional ingestion of OPP (in a commercial antiseptic, concentration not specified) by a 39-year-old woman resulted in liver complications, impairment of renal function, severe damage of the lungs including acute respiratory distress syndrome and fibrosis (HSDB). However, it is noted that the woman was also suffering from cervical cancer.

Corrosion / Irritation

Corrosivity

The chemicals are classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). However, available data for OPP support a recommendation to amend the existing classification (**Recommendation** section). Considering the high pH of SOPP (11.2-11.6) and the associated high alkaline reserve, amendment of the classification of this chemical is also recommended (see **Recommendation** section).

The parent chemical OPP has been tested for skin irritation in New Zealand White rabbits, conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 404 (REACH). In one test, 0.5 g of OPP (99 % purity) suspended in water was applied onto the skin of the animals (occlusive condition) for four hours, followed by 14 days observation. The following treatment-related changes were observed at different time points after the exposure has ceased:

- slight to severe eschar formation and burns after 30 minutes;
- very slight erythema and slight to severe oedema after 30 minutes and 24 hours; and
- slight to severe oedema after 48 and 72 hours.

The mean scores after 72 hours were 2.8 and 1.3 for erythema and oedema respectively (REACH).

In another study (OECD TG 404), the same mean scores were obtained. In this investigation, an unknown concentration of OPP was applied to the skin of New Zealand White rabbits for four hours with observation for seven days. Moderate to severe erythema in 5/6 animals was noted at day seven (REACH). Skin ulcers were produced on depilated squares on the backs of pigmented young female guinea pigs within a week of exposing the animals to occlusive patches containing 6 % OPP (Bomhard et al., 2002).

Respiratory Irritation

The chemicals are classified as hazardous with the risk phrase 'Irritating to respiratory' (Xi; R37) in HSIS (Safe Work Australia). No available data are available to support this classification.

Eye Irritation

The chemical SOPP is classified as hazardous with the risk phrase 'Risk of serious eye damage' (Xi; R41) in HSIS (Safe Work Australia). However, the high pH of the chemical SOPP and consequent skin irritation potential support a recommendation to amend this classification (see **Corrosivity** and **Recommendation** sections).

The parent chemical OPP is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data and the corrosive potential of OPP following dermal exposure support a recommendation to amend this classification (see **Corrosivity** and **Recommendation** sections).

In a guideline compliant study (OECD TG 405), exposure of New Zealand White rabbits to OPP caused irreversible, serious eye damage. In this test, 0.1 g of the chemical was instilled into the conjuctival sac (right eye) of the lower eyelid of each animal. The treated eye was not washed after exposure. The left eye served as a control. The effects were observed for up to seven days (REACH). The mean eye irritation scores observed after 24, 48 and 72 hours were 2.33, 1, 2.5 and 3.61 for corneal opacity, iritis, conjunctival redness and chemosis respectively (REACH).

Another study in New Zealand White rabbits (similar experimental protocol), also reported serious eye damage following exposure to 0.1 mL of OPP. The average scores recorded at 24, 48 and 72 hours after cessation of exposure were 1.77 for corneal opacity; 0.88 for irititis; 1.66 for conjuctival

redness; 2.22 for chemosis; and 1.66 for eye discharge. All of these chemically-induced effects (except eye discharge) were not reversible after eight days from termination of exposure (REACH).

Moderate eye irritation was also reported after exposing rabbit eyes to 100 mg (species and exposure duration not specified) of OPP (Bomhard et al., 2002). No other details were supplied.

Sensitisation

Skin Sensitisation

The potential for the chemicals to induce skin sensitisation has been tested in guinea pigs. In these studies, negative results were found (Bomhard et al., 2002; INCHEM, 1999; REACH).

In a guinea pig maximisation test, solutions of 0.5 % and 5 % OPP (in propylene glycol) or 5 % SOPP (in water) were injected into the skin of female Ssc:Al guinea pigs for intradermal induction. This was followed by topical induction using 25 % OPP or SOPP under an occlusive condition. For the challenge exposure, the animals were exposed topically to 5 % OPP or SOPP (in petrolatum) 21 days after the induction exposure. No dermal reactions were observed in animals after exposure to either OPP or SOPP (Bomhard et al., 2002; REACH).

The Buehler test was also used to investigate the skin sensitisation potential of the chemicals. In this test, the skin of ten male Hartley guinea pigs was exposed (epicutaneously) to 0.4 g of neat OPP or 0.4 g SOPP (moistened with 0.2 mL water). This induction exposure was conducted under an occlusive condition on shaved skin for six hours, once a week for 21 days. The challenge was conducted two weeks after the last induction exposure by applying 0.4 g of neat OPP and or 0.4 mL of a solution containing 7.5 % SOPP suspended in water. The results showed that neither OPP nor SOPP induces skin sensitisation (Bomhard et al., 2002; REACH).

Observation in humans

Rare cases of allergic dermatitis caused by OPP exposure have been reported in humans (Bomhard et al., 2002). The use of the chemical in medical hand cream and/or coolant has been associated with three cases of dermatitis. This was confirmed by positive reactions observed following patch tests with 0.5 % and 1 % of the chemical.

The chemical OPP was implicated in the contact urticaria reported in a 19-year-old woman after topical application (to intact skin) of 1 % of OPP in plaster casts. In a large scale study, allergic reactions to OPP were also identified in few individuals following patch tests involving dermatitis patients at 1 % formulation (Bomhard et al., 2002).

In a broader study, no skin sensitisation reactions were observed in 200 individuals patch-tested with 5 % OPP and 0.1 % SOPP (REACH).

Repeated Dose Toxicity

Oral

The repeat dose oral toxicity of the chemicals in this group was investigated in rats and mice. Based on the results, only high doses of the chemicals caused treatment-related effects. The chemicals are not considered to cause serious damage to health (NTP, 1986; IARC, 1999; MAK, 2012; REACH).

In albino rats, exposure to diet at approximately 50-500 mg/kg bw/day OPP, five days a week for six months resulted only in slight increases in liver and kidney weights. No histopathological changes were observed. However, degenerative changes of the renal tubules and atrophy of the renal cortex were observed following the exposure of Fischer 344 (F344) rats to 1000-1500 mg/kg bw/day OPP for three months (MAK, 2012).

Changes in the bladder epithelium were also observed in F344 rats exposed to 1000-1500 mg/kg bw/day of SOPP in the diet for three months (MAK, 2012). Pyelonephritis (kidney inflammation) was reported in F344/DuCrj rats following oral exposure to 2450 mg/kg bw/day SOPP (MAK, 2012).

In B6C3F1 mice, exposure to diet containing SOPP at time weighted average doses of 1581, 3529 and 5375 mg/kg bw/day for males and 1926, 4294 and 6349 mg/kg bw/day for females for three months resulted in significant reduction of bodyweight and decreased urinary specific gravity (CEPA, 2007; MAK, 2012). In a longer term study, exposure to a diet containing 2 % SOPP for 36 weeks did not cause any structural changes in the bladder of male B6C3F1 mice (Bomhard et al., 2002).

Dermal

Limited data are available. Dermal application of 500 and 1000 mg/kg bw/day OPP to F344 rats daily, for 21 days, resulted in notable changes at the application site. The observed effects were not attributed to systemic toxicity but rather to the local irritant potential of the chemical (Bomhard et al., 2002; REACH).

No chemically-related effects were reported following dermal exposure of Swiss Webster CFW mice to 5.95, 11.4, 20.8, 35.7 or 55.5 mg/kg bw/day of OPP, three times a day for four weeks (REACH). In another study, dermal exposure of Swiss CD-1 mice to 55.5 mg/0.1 mL (acetone) OPP for two years

caused local effects at the site where the chemical was applied, including inflammation, ulceration, hyperkeratosis, and acanthosis (NTP, 1986).

Inhalation

No data are available.

Genotoxicity

Based on the available data from the in vitro and in vivo genotoxicity studies, the chemicals OPP and SOPP are considered to be genotoxic. Hence, the chemicals are recommended for classification (see **Recommendation** section).

The parent chemical, OPP was reported to cause damage to chromosomes and DNA in vivo and vitro studies.

In vitro, OPP was mutagenic in the following:

- bacterial reverse mutation assay (weak mutagenicity) in *Salmonella typhimurium* strain TA 1535 without metabolic activation and TA 98 (activation details not specified);
- forward mutation assay in mouse lymphoma L5178Y cells (thymidine kinase locus) with or without metabolic activation;
- sister chromatid exchanges in Chinese hamster ovary (CHO) cells without metabolic activation (NTP, 1986; CEPA, 2007);
- chromosomal aberration in CHO and human fibroblast cells;
- chromosomal aberration in human fibroblast cells; and
- gene mutation in human RSA cells (Na^+/K^- ATPase locus).

Negative results were reported in other chromosomal aberration assays (NTP, 1986).

In vivo, OPP caused micronuclei formation in the urinary bladder of male F344 rats following oral exposure to 2 % OPP in the diet (Balakrishnan et al., 2002). High sodium salt concentrations exacerbated chromosomal damage. The OPP-induced protein binding was also reported in the urinary bladder of rats following oral exposure (Kwok et al., 1999). In another study, OPP was positive for DNA ^{32}P-post-labeling (quantifying DNA adducts) in the urinary bladder of rats in vivo, at doses 570 and 940 mg/kg bw/day (INCHEM, 1999). However, another similar study yielded a negative result (Kwok et al., 1999).

Negative results were found in the sex-linked recessive lethal mutations in vivo in *Drosophila melanogaster* (NTP, 1986).

In vitro, SOPP was positive *Aspergillus nidulans* gene mutation assay. However, the chemical gave negative results in *S.typhimurium* assays and in other in vitro tests (CEPA, 2007).

In vivo, SOPP induced DNA adduct formation, DNA breaks and cell transformation in the urinary bladder of male F344 rats (CEPA, 2007). Formation of DNA adducts was also reported in CD-1 mice following dermal exposure. Results from a modified in vivo comet assay demonstrated DNA breaks in isolated nuclei obtained from several ddY mouse tissues (CEPA, 2007).

The metabolites of the chemicals, PHQ and phenylbenzoquinone have been shown to induce clastogenic and aneugenic effects in chromosomes in vitro. These metabolites also caused covalent DNA damage including adduct formation, single strand breaks, oxidation and sister chromatid exchange. The genotoxicity of these biologically active metabolites was suggested to be enhanced by increased pH and increased metal ion concentration (NTP, 1986; INCHEM, 1999; CEPA, 2007; MAK, 2012).

Following oral exposure to rodents, both metabolite chemicals were reported to induce macromolecular binding in the bladder, the liver and kidney (IARC, 1999). These metabolites are known to cleave DNA (Bartels et al., 1998; ChemIDplus). The ionisation of PHQ semiquinone has been suggested to be an important step towards pH-dependent formation of reactive species (INCHEM, 1999).

Carcinogenicity

The carcinogenic potential of the chemicals has been evaluated in several long-term oral and dermal studies in rats and mice. In these studies, the carcinogenic effects were more prominent in male rats than in mice. The commonly observed cancer-related effects are benign or malignant tumours (papillomas and carcinomas) in the urinary bladder of rats. The chemical SOPP was reported to be a more potent tumour initiator and tumour promoter than OPP (NTP, 1986; IARC, 1999). Sufficient data are available to support the recommendation for carcinogenicity classification for the chemicals (see **Recommendation** section).

SOPP

The International Agency for Research on Cancer (IARC) has classified the chemical, SOPP, as ‘Probably carcinogenic to humans’ (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animal testing.

Oral exposure of Fischer 344/DuCrj rats to 0 % to 2 % (males) SOPP (in diet) for up to 104 weeks resulted in urinary bladder tumours in rats. Although most of the tumours observed were carcinomas, several treated rats had papillomas (IARC, 1999).

Urinary bladder tumours were also reported in SOPP-treated F344/DuCrj rats in two long term (104 weeks) dietary studies. In the first study, rats (50/sex/group) were treated with SOPP at 0.7 or 2 % for males (approximately equivalent to 350 and 1000 mg/kg bw/day, respectively) and 0.5 or 1 % for females (approximately equivalent to 250 and 500 mg/kg bw/day, respectively). In the second study, rats (25/sex/group) were treated with SOPP at 0.25, 0.7 or 2 % for males (approximately equivalent to 125, 350 and 1000 mg/kg bw/day, respectively) and 0.25, 0.5 or 1 % for females (approximately equivalent to 125, 250 and 500 mg/kg bw/day, respectively). Based on the results, a significant number of male rats from high dose groups had urinary bladder tumours: 47/50 in the first study; and 23/25 in the second study. Very few tumours were found in female rats (IARC, 1999).

When B6C3F1 mice were treated with diet containing SOPP at 0.5, 1 or 2 % (approximately equivalent to 750, 1500 and 3000 mg/kg bw/day, respectively) for 96 weeks (followed by normal diet for further eight weeks), cancer-related effects were not seen. The tumours reported in animals at the end of the study were present in both SOPP-treated and control animals (Hagiwara et al., 1984).

Results from several long term studies (32-103 weeks) in Swiss CD-1 mice and F344 rats indicated that SOPP is a more potent promoter than OPP (NTP, 1986; IARC, 1999). In these studies, bladder tumours were initiated by freeze-ulceration or by pre-exposing the animals to known carcinogens via dermal or oral routes (feeding or drinking water) prior to treatment with SOPP or OPP. These included dimethylbenz[*a*]anthracene (DMBA), N-nitrosobutyl-(4-hydroxybutyl)amine (NBHBA), and N-methyl-N-nitrosourea (MNU). SOPP has not been reported as a complete carcinogen following a dermal route of exposure (NTP, 1986; IARC, 1999).

The high pH of the sodium salt has been suggested to influence the toxicity of SOPP due to the carcinogenic effect following supplementation of the diet with $NaHCO_3$ to increase urinary pH and sodium ion concentration (CEPA, 2007).

OPP

Considering the limited evidence of carcinogenicity, IARC has listed OPP as ‘not classifiable as to its carcinogenicity to humans (Group 3).' However, IARC has also stated that there is limited evidence for carcinogenicity in animal testing, and OPP and SOPP are excreted to be interconvertible at the fixed points seen in various body compartments. This is sufficient to warrant recommending classification for this chemical.

Invasive and non-invasive urinary bladder tumours were reported in F344/DuCrj rats (20-24 rats/group) exposed to OPP in the diet for 91 weeks. The tumours identified were three papillomas, 15 non-invasive carcinomas and five invasive carcinomas in rats. However, these effects were only observed in animals exposed to high doses of OPP (1. 25 %) (IARC, 1999).

The toxicity of OPP has been thought to be enhanced by its biologically active metabolite, PHQ. In the bladder, where PHQ is eventually excreted, this metabolite undergoes pH-dependent auto-oxidation to produce phenylbenzoquinone and reactive oxygen species. At pH of above seven, the rate of auto-oxidation is increased (IARC, 1999). Given its electrophilic nature, phenylbenzoquinone can bind to protein sulfhydryls and other cellular nucleophiles (US EPA, 2001).

The mechanism of action in the carcinogenic effects induced by OPP and SOPP has been suggested to operate through the following:

- in vitro and in vivo genotoxicity (see **Genotoxicity** section);
- in vivo and in vitro DNA binding of the chemicals and their metabolites;
- DNA damage mediated by reactive oxygen radicals during the conversion of PHQ to phenylbenzoquinone (IARC, 1999); and
- cell proliferation arising from chemically-induced cytotoxicity in the rat urothelium (Balakrishnan et al., 2002).

The chemicals OPP and SOPP were reported to induce macromolecular binding in the bladder, the liver and kidney following oral exposure in rodents (IARC, 1999).

The sensitivity of males to the bladder effects of both chemicals is attributed to the difference in oxidative metabolism. The male specific isoform of cytochrome P450 (CYP2C11) has been shown to play a role in the metabolic activation of OPP to PHQ in the rat (US EPA, 2001). Additionally, the activation of PHQ by the prostaglandin (H) synthase in the rat urinary bladder transitional epithelium and kidney medullary papillae to reactive intermediates has been suggested to be responsible for the organ-specific carcinogenicity of the chemicals (INCHEM, 1999). Additionally, SOPP is metabolised to a greater extent in male rats than in females (IARC, 1999).

Overall, considering the ready interconversion of OPP and SOPP, the malignant and benign tumours observed in rats exposed to SOPP, the genotoxic effects of the chemicals and their metabolites (PHQ and phenylbenzoquinone) in vivo and in vitro, and its tumour-promoting potential, recommendation for classification is warranted (see **Recommendation** section).

Reproductive and Developmental Toxicity

The chemicals OPP and SOPP do not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In an OECD TG 414-compliant study, pregnant SD rats were exposed daily to OPP via oral gavage at doses 100, 300, 700 mg/kg bw/day for 15 days. The exposure period was from gestation day six to 21 (REACH). Foetuses showed minor skeletal variations and delayed ossification of sternebrae and occurrence of a foramen in the skull bones (collectively known as skeletal variations) at 700 mg/kg bw/day of OPP. Maternal toxicity was also observed at this dose including significant liver impairment and body weight changes. The reported no observed adverse effect levels (NOAELs) for maternal toxicity and teratogenicity was 300 mg/kg bw/day (REACH).

Maternal toxicity and teratogenecity were examined in a separate study (OECD TG 414) conducted in Wistar rats. In this study, pregnant rats were orally exposed to 150, 300, 600, 1200 mg/kg bw/day of OPP (gavage) for 10 days. Exposure to the lowest dose (150 mg/kg bw/day) did not cause any changes. However, the rats displayed dose-dependent ataxia from 300 mg/kg bw/day of OPP. Increase in foetal resorptions and decrease in dam body weights were observed at 600 mg/kg bw/day dose. The highest dose (1200 mg/kg bw/day) was lethal in 11/12 animals. The reported NOAELs for maternal toxicity and teratogenicity were 150 mg/kg bw/day and 300 mg/kg bw/day respectively (REACH).

The chemical SOPP was examined in another study in Jcl:ICR mice. In this study, mice were exposed to SOPP via oral gavage at doses 100, 200 or 400 mg/kg bw/day from gestation days (GD) seven to 15 and were sacrificed at GD 18. The results showed maternal deaths occurring at GD 11-18 in groups exposed to 200 and 400 mg/kg bw/day (CEPA, 2007). Foetal effects were also reported at doses 200 and 400 mg/kg bw/day, including reduced body weight and decrease in the number of implantation sites per dam. Whilst increased incidences of cervical ribs and external deformities were also observed in the treated mice, these changes were not statistically significant (CEPA, 2007).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects following oral exposure (SOPP), and the local effect of corrosivity. The chemicals could be carcinogens at high doses following long-term repeated exposure. A genotoxic mode of action cannot be excluded. The chemicals could also cause respiratory irritation.

Public Risk Characterisation

Although use in cosmetic and/or domestic products in Australia is not known, the chemicals are reported to be used in these products overseas.

The chemical OPP (and its salt, SOPP) are currently listed on Schedule 6 of the SUSMP, with a number of warning statements, first aid instructions and safety directions applying to the use of these chemical. The current controls are considered adequate to minimise the risk to public health posed by domestic products containing the chemicals, therefore, the chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

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

Given the critical systemic local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal exposure are implemented. In addition, organic peroxides are strong oxidising agents and highly unstable when heated, and this could cause serious explosion and fire hazards. Hence, chemicals 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 HSIS (Safe Work Australia) (refer to **Recommendation** section.

NICNAS Recommendation

Assessment of these chemical are 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.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2015).

Work Health and Safety

The chemicals are 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.

Note that the classification for acute toxicity only applies to the chemical SOPP (CAS No. 132-27-4).

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Irritating to respiratory system (Xi; R37)* Causes burns (C; R34)	May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335) Causes severe skin burns and eye damage - Cat. 1 (H314)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)

[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 consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, inhalation, dermal and ocular 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 chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- air monitoring to ensure control measures in place are working effectively and continue to do so;
- health monitoring for any worker who is at risk of exposure to the chemical[s], 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

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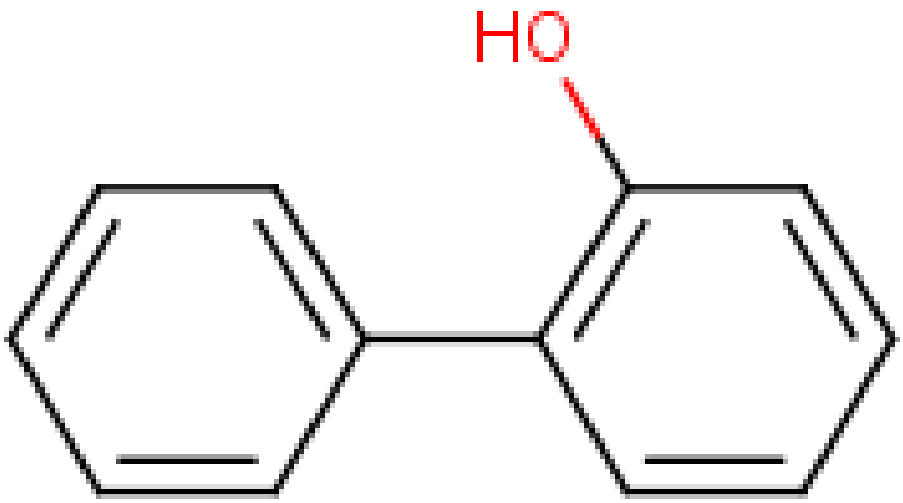
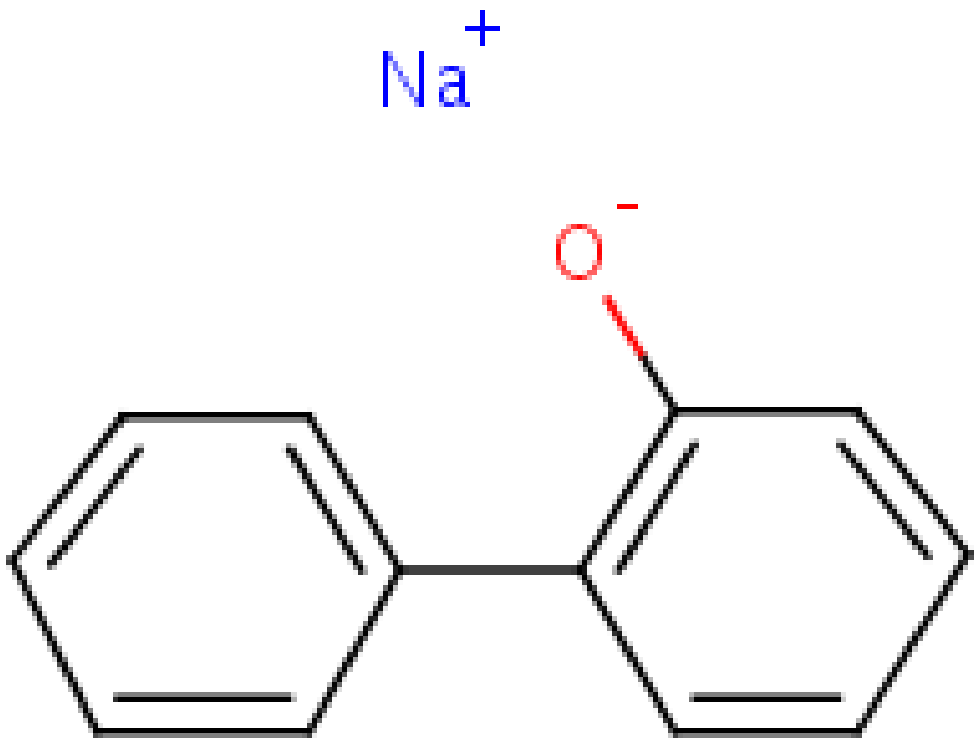
Last Update 01 September 2015

Chemical Identities

Chemical Name in the Inventory and Synonyms	**[1,1'-Biphenyl]-2-ol** o-phenylphenol OPP 1-hydroxy-2-phenylbenzene Anthrapole 73 Dowicide A
CAS Number	90-43-7
Structural Formula	
Molecular Formula	C12H10O
Molecular Weight	

Chemical Name in the Inventory and Synonyms	**[1,1'-Biphenyl]-2-ol, sodium salt** 2-hydroxybiphenyl, sodium salt sodium orthophenylphenoxide SOPP

	o-phenyl phenol sodium salt sodium o-phenylphenate
CAS Number	132-27-4
Structural Formula	
Molecular Formula	C12H10O.Na
Molecular Weight	192.19

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