# Phenol, 4,4'-sulfonylbis-: Human health tier II assessment

**01 September 2015**

## CAS Number: 80-09-1



## 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.

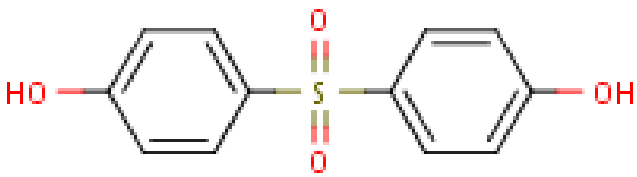
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | 4,4'-bisphenol S<br>diphone C<br>4,4'-sulfonyldiphenol<br>bisphenol S<br>BPS |
| Structural Formula |  |
| Molecular Formula | C12H10O4S |
| Molecular Weight (g/mol) | 250.2 |
| Appearance and Odour (where available) | odourless white powder |
| SMILES | c1(S(=O)(=O)c2ccc(O)cc2)ccc(O)cc1 |

# Import, Manufacture and Use

## Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported domestic uses as a flame retardant and fire-preventing agent.

## International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Cooperation and Development (OECD) Screening information data set International Assessment Report (SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the OECD High Production Volume chemical program (HPV); the United States (US) Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR) and the US National Library of Medicine's (NLM) Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic uses as a flame retardant and fire-preventing agent.

The chemical has reported commercial uses including:

- as a dye fixative;
- in thermal paper;
- in can linings; and
- in plastics for food storage.

The chemical has reported site-limited uses as:

- an intermediate in manufacture of thermal paper;
- an intermediate in manufacture of vinyl chloride plastics;
- a monomer for manufacture of thermoplastics;
- a raw material for industrial chemicals; and
- a raw material for photographic coupler.

# Restrictions

## Australian

No known restrictions have been identified.

## International

No known restrictions have been identified.

# Existing Work Health and Safety Controls

## Hazard Classification

The chemical is not listed on the Hazardous 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 chemical is a close analogue of the extremely widely studied bisphenol A (phenol, 4,4'-(1-methylethylidene)bis- (CAS No. 80-05-7)). Given the close structural similarity and similar uses of the two chemicals, studies are underway to better characterise the hazard of the chemical (NTP). Until better quality data become available, information about bisphenol A, particularly for the critical reproductive toxicity endpoint, should be considered relevant.

## Toxicokinetics

Limited data are available on the absorption, distribution, metabolism and excretion of the chemical. Available data suggest oral absorption and distribution to different organs in rats. Changes to the caecum, liver, thymus, adrenal, spleen, bone marrow and kidney were observed in the pathological examinations in a 28-day repeat dose oral toxicity study in rats (OECD, 2013).

In the human general population in the United States, China, India, Japan, Korea, Kuwait, Malaysia, and Vietnam, the chemical was found in 81 % of 315 urine samples at concentrations ranging from 0.02 ng/mL to 21.0 ng/mL (OECD, 2013; NTP, 2014; HSDB; REACH).

## Acute Toxicity

### Oral

The chemical has low acute toxicity based on the results from animal tests following oral exposure. The median lethal dose (LD50) in rats is > 2000 mg/kg bw.

In a study conducted similarly to OECD Test Guideline (TG) 401, the chemical dissolved in Lutrol was administered to groups of 10 male rats/dose at 1000, 1500, 2000, 3100, 3500, 4000, 5000 or 5500 mg/kg bw/day. Clinical signs included increased diuresis, salivation, sedation, dyspnoea, lateral and prone positions, decrease body weight gain and bad general condition. The reported LD50 was 2830 mg/kg bw (OECD, 2013; HSDB; REACH).

In another animal study conducted according to OECD TG 401, the chemical was administered to five male and five female (Tif:RAIf(SPF), F3-crosses of RII 1/Tif x RII 2/Tif) rats. Clinical signs included dyspnoea, exophthalmos, ruffled fur and curved

body position. The LD50 was reported to be > 5000 mg/kg bw (OECD, 2013).

### Dermal

No data are available for the chemical.

### Inhalation

No data are available for the chemical.

## Corrosion / Irritation

### Skin Irritation

Based on the available data, the chemical is not a skin irritant.

In a skin irritation study conducted according to OECD TG 404, no irritation was observed after occlusive application of 0.5 g of the chemical to male New Zealand White rabbits. All three animals showed normal body weight development. The test was finished after three observation days due to lack of any effects (OECD, 2013; REACH).

In an in vitro human skin irritation test conducted according to OECD TG 431, approximately 15 mg of the chemical applied to a reconstructed three dimensional human epidermis model (EpiDerm$^{TM}$) did not induce mitochondrial dehydrogenase activity (MTT). The chemical was considered not to be a skin irritant (OECD, 2013; REACH).

### Eye Irritation

Based on the available data, the chemical is not an eye irritant.

In an eye irritation study according to OECD TG 405, 0.1 g of the chemical applied to the conjunctival sac of the right eye of New Zealand White rabbits did not cause any irritation (OECD, 2013; REACH).

In another eye irritation study performed similarly to OECD TG 405, 50 mg of the chemical applied to the conjunctival sac of the eye of one male and one female rabbit showed slight short term irritation due to mechanical stress. No other eye irritation effects were seen (REACH).

## Sensitisation

### Skin Sensitisation

The available animal data suggest that the chemical is not a skin sensitiser.

In a mouse local lymph node assay (LLNA) conducted according to OECD TG 429 and EU method B.42, the chemical did not show skin sensitising potential following topical application to CBA mice up to 25 % (w/v) (OECD, 2013; REACH).

In a guinea pig maximisation test conducted according to OECD TG 406, the chemical caused mild grade reactions in 20 to 25 % of Pirbright White guinea pigs following intradermal induction phase (30 % of the chemical in Vaseline) and challenge phase (10 % of the chemical in Vaseline) (REACH).

## Repeated Dose Toxicity

### Oral

The available data suggest that the chemical has harmful effects following repeated oral dosing based on results from animal tests. However, the effects were not sufficient to warrant hazard classification.

In a 28-day study conducted similarly to OECD TG 407, the chemical was administered to male and female Crj:CD(SD) rats (six animals/sex/dose) by oral gavage at 0, 40, 200 or 1000 mg/kg bw/day. During the treatment period, two males of the highest dose group died due to haemorrhaging in the intestinal tract centred around the caecum. Females in the highest dose group showed abdominal distension in the second half of the dosing period reflecting the dilatation of the caecum seen at necropsy and significantly decreased body weight gain and food consumption. Blood chemistry examination at the highest dose revealed a decrease in total cholesterol in both sexes, increased alkaline phosphatase and decreased lactate dehydrogenase in males, and increases in total protein, calcium and albumin in females. Increases in protein and urobilinogen and significant increases in the incidence of decreased pH at 200 and 1000 mg/kg bw/day in both sexes were observed at urinalysis. Histopathological examination showed hypertrophy of centrilobular hepatocytes and significantly increased atrophy of the thymus at 1000 mg/kg bw/day in both sexes. Males at 1000 mg/kg bw/day showed significantly increased hypertrophy of cortical zona fasciculata cells in the adrenals of both males and females at 1000 mg/kg bw/day and showed significantly increased spongy bone in the femur. Significant increases in mucosal hyperplasia and single cell necrosis in the mucosal epithelium in the caecum and significantly increased kidney weight were observed at 200 mg/kg bw/day. The changes in the kidney were present after the 14-day recovery period. The spleen showed significant increase in extramedullary haematopoiesis in the high dose group animals. The no observed adverse effect level (NOAEL) established was 40 mg/kg bw/day for both males and females (OECD, 2013; NTP, 2014; REACH).

In a 90-day study conducted according to OECD TG 408, male Wistar rats (10 animals/sex/dose) were administered the chemical daily by oral gavage at 0, 100, 300 or 1000 mg/kg bw/day. The dose of 1000 mg/kg bw/day was lowered to 600 mg/kg bw/day from day 70 onwards in male rats, due to severely decreased body weight. Clinical signs of toxicity were observed at 300 mg/kg bw/day and above in males and at 1000 mg/kg bw/day in females. No mortalities were reported. All the high dose males showed dilated caecum and the high dose females showed liver enlargement. Observations in the high dose animals showed increased extramedullary haematopoiesis in the spleen with decreased red blood cell counts, decreased haemoglobin values, decreased haematocrit values in females, higher reticulocyte counts and decreased total bilirubin levels in males. Atrophy in the mammary gland was seen in males at 300 and 600 mg/kg bw/day, while the females had increased liver weights with dose-dependent centrilobular hypertrophy. The NOAELs were 100 mg/kg bw/day in males and 300 mg/kg bw/day in females (REACH).

### Dermal

No data are available.

### Inhalation

No data are available.

## Genotoxicity

Based on the available data, the chemical is not genotoxic. Both in vitro and in vivo assays gave negative results.

***In vitro studies***

In a reverse gene mutation test conducted according to OECD TG 471, the chemical was tested in *Salmonella typhimurium* TA98, TA100, TA1535 and TA 1537 strains at dose concentrations in the range of 78.1 to 5000 µg/plate and *Escherichia coli* WP2 *uvrA* strains at dose concentrations in the range of 156 to 5000 µg/plate with and without S9 mix. Growth inhibition was seen at 5000 µg/plate and no increase in the number of revertants was observed at any dose concentration (OECD, 2013; REACH).

In a structural chromosome aberration test conducted according to OECD TG 473, and a mammalian cell gene mutation test conducted similarly to OECD TG 476, the chemical in dimethyl sulfoxide (DMSO) was tested in the Chinese hamster ovary (CHO) and hypoxanthine-guanine phosphoribosyltransferase (HGPRT) mutation assays, respectively, in the absence and presence of metabolic activation with Aroclor-induced rat liver S9. The chemical at concentrations in the range of 62.5-1000 µg/mL was used in the initial assay and at 31.25-600 µg/mL in the confirmatory assay with or without S9 mix. The chemical gave negative results in the absence and presence of exogenous metabolic activation (OECD, 2013; REACH).

In a L5178Y mouse lymphoma assay, the chemical was tested for genotoxicity at concentrations of 100, 150, 200, 250 or 300 µg/mL both without metabolic activation and with liver S9 preparation from Sprague Dawley (SD) rats. The chemical gave negative results for genotoxicity in the presence or absence of metabolic activation (REACH; OECD, 2013).

***In vivo studies***

In a micronucleus test conducted according to OECD TG 474 in Crlj:CD1(ICR) mice (six males/group), the chemical was tested at dose levels of 0, 500, 1000 or 2000 mg/kg bw/day administered twice by oral gavage at 24-hour interval. The incidence of micronucleated polychromatic erythrocytes (MNPCE) was not increased (OECD, 2013).

In another micronucleus assay conducted according to OECD TG 474 and EU-method B.12 (REACH), the chemical was dissolved in DMSO and emulsified in corn oil and administered by a single oral dose to male NMRI mice (five males/group) at dose levels of 0, 500, 1000 or 2000 mg/kg bw/day. Animals in the 500 and 1000 mg/kg bw/day dose groups were sacrificed at 24 hours and in the 2000 mg/kg bw/day dose group were sacrificed at 48 hours post-administration. No increase in the number of polychromatic erythrocytes was seen. The chemical had no clastogenic effect and no aneugenic activity in the bone marrow cells of the NMRI mice (OECD, 2013; REACH).

## Carcinogenicity

Based on the available data, the chemical is not considered to be carcinogenic.

The chemical has no structural features that present an alert for binding to deoxyribonucleic acid (DNA) based on the profiling functionality of the OECD Quantitative Structure-Activity Relationship (QSAR) Toolbox v.3.2.

The chemical has structural and biological similarity to its analogue, bisphenol A. Data on bisphenol A suggest that it is not considered to have a carcinogenic potential (NICNAS).

## Reproductive and Developmental Toxicity

Based on the available data, the chemical showed specific reproductive effects, warranting a hazard classification for reproductive toxicity. Developmental effects were only observed secondary to maternal toxicity.

In a reproductive and developmental toxicity screening study conducted according to OECD TG 421, the chemical was administered in Crj:CD (SD) rats at 0, 10, 60 or 300 mg/kg bw/day. Male rats received treatment for 45 days in total, from 14 days before mating to the day of necropsy and the female rats were treated for a total of 40 to 46 days, from 14 days before mating to day three of lactation including the mating period, gestation period and delivery. No treatment related changes in the copulation index, delivery index, gestation index, number of corpora lutea, length of gestation period, delivery condition or lactation behaviour were seen at the top dose. There was a significant prolongation of the oestrous cycle and increase in the number of animals that showed prolonged dioestrus period and a decrease in the implantation index at 300 mg/kg bw/day. A tendency towards decrease in fertility index was reported at 300 mg/kg bw/day. Effects in offspring at 300 mg/kg bw/day included decreased total number of offspring delivered, decreased number of live offspring, and decreased number of offspring alive on day four of lactation. All these effects were considered to be due to decreased implantation index. No other effects were observed in the 300 mg/kg bw/day group. No treatment-related changes in parent animals or offspring were observed at the 10 and 60 mg/kg bw/day dose groups. The NOAEL for reproductive toxicity was considered to be 60 mg/kg bw/day based on prolongation of oestrous cycle and dioestrus period, decreased fertility index and decreased implantation index (OECD, 2013; REACH).

In a developmental toxicity study conducted according to OECD TG 414, the chemical was administered to Wistar female rats (25 animals//dose) at 0, 30, 100 or 300 mg/kg bw/day by oral gavage from gestation day six to 19. No treatment related mortality and no systemic toxicity was seen at any of the tested doses. Significant decreases in food consumption and body weight gain

were observed at 300 mg/kg bw/day. No treatment-related changes were seen in the foetal weight and sex distribution of the foetuses. The NOAEL for developmental toxicity was the high dose of 300 mg/kg bw/day (REACH).

The analogue bisphenol A was found to be a reproductive toxicant at higher dose levels with a benchmark dose lower bound (BMDL)10 of 8.96 mg/kg bw/day for changes in relative kidney weight in mice (NICNAS). Bisphenol A is classified as hazardous with the risk phrase 'Possible risk of impaired fertility (R62)' in the HSIS (Safe Work Australia).

Reproductive and developmental toxicity studies on the chemical are currently being conducted by the US National Toxicology Program (NTP) to further characterise the hazards based on the high structural similarity of the chemical to bisphenol A and the chemical's potential for oestrogenic activity (NTP, 2014).

Given the low quality of the available data for the chemical compared with bisphenol A for this critical endpoint, the data from testing bisphenol A in high quality multi-generation tests should be considered relevant to the chemical.

### Other Health Effects

Endocrine Disruption

Based on the available information, the chemical has potential for oestrogenic activity (see **Reproductive and Developmental toxicity)**.

## Risk Characterisation

### Critical Health Effects

The data available for the chemical are extremely limited compared to its analogue, bisphenol A. Studies are currently underway to better characterise the hazards for the chemical (NTP, 2014). In the absence of these data, the hazard data for bisphenol A (NICNAS) should be considered relevant.

The critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity and developmental toxicity).

### Public Risk Characterisation

The chemical is structurally-similar to bisphenol A. Concerns for bisphenol A mostly relate to its wide use in the lining of food contact materials. Given the similarity of both the use and chemical structures between bisphenol A and the chemical, risk conclusions for bisphenol A should be considered relevant. Risk assessments by several regulatory agencies (Health Canada, 2012; US Food and Drug Administration, 2014; European Food Safety Authority, 2015) found no health risk to consumers at the estimated levels of exposure to bisphenol A. Based on the findings of these reports, NICNAS found no concerns from industrial use of bisphenol A (NICNAS) and accordingly no concerns are anticipated from industrial use of the chemical.

### Occupational Risk Characterisation

During product formulation, oral, dermal and ocular 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 local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal and ocular exposure are implemented. The chemical should be

appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

# NICNAS Recommendation

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. NICNAS will continue to monitor the high quality assessment work that is being conducted by regulators on both the chemical and bisphenol A and further assessment may be required.

## 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] |
|---|---|---|
| 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 oral 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;
- 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 01 September 2015

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