Phenol, 4,4'-(1-methylethylidene)bis-: Human health tier II assessment

01 July 2016

CAS Number: 80-05-7

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.

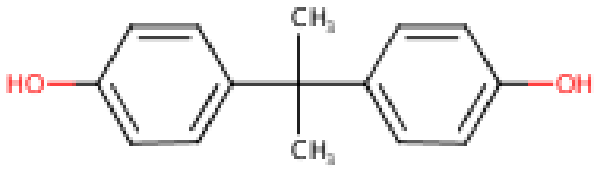
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2,2-bis(4-hydroxyphenyl)propane 4,4-(1-methylethylidene)bis[phenol bisphenol A 4,4'-bisphenol A 4,4'-isopropylidenediphenol
Structural Formula	
Molecular Formula	C15H16O2
Molecular Weight (g/mol)	228.29
Appearance and Odour (where available)	White to brownish crystals or flakes, phenolic odour.
SMILES	c1(C(C)(C)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, including in adhesives (binding agents).

The chemical has reported site-limited uses, including in stabilisers.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was 100–1000 tonnes.

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers;
- the Organisation for Economic Co-operation and Development Screening information data set International Assessment Report (OECD SIAR);
- Galleria Chemica;
- the Substances and Preparations in Nordic countries (SPIN) database; and
- the European Commission Cosmetic Ingredients and Substances (CosIng) database.

The chemical has reported domestic uses, including in:

- adhesives (binding agents);
- cleaning/washing agents;
- corrosion inhibitors;
- fillers;
- insulating materials;
- paints, lacquers and varnishes;
- surface treatment; and
- surface-active agents.

The US Household Products Database states a concentration of up to 5 % (liquid) for home maintenance use and 5–20 % for use inside the home (three products), one liquid and two 2-part dispenser (US Household Products Database).

The chemical has reported commercial uses including in:

- anti-static agents;
- construction materials;
- hydraulic fluids and additives;

- lubricants and additives;
- process regulators;
- reprographic agents;
- softeners; and
- viscosity adjustors.

The chemical has reported site-limited uses, including as:

- an intermediate in manufacturing epoxy, polycarbonate, phenoxy, polysulphone and certain polyester resins, flame retardants, rubber chemicals, and fungicides; and
- stabilisers.

The chemical is reported to be used in heat sensitive paper, for example for credit card receipts. The chemical is also a monomer in some food contact plastics (epoxies and polycarbonates), from which small quantities can leach into food.

The non-industrial use of the chemical has been identified internationally in a non-agricultural pesticide.

Restrictions

Australian

No known restrictions have been identified (SUSMP, 2015).

International

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

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain—Table 1;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’); and
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xi; R37/41 (Irritation)
- Xi; R43 (Sensitisation)

- Xn; R62 (Reproductive Category 3) (Toxic to fertility)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- Bisphenol A (CAS No: 80-05-7) has an exposure limit of 5–10 mg/m³ time weighted average (TWA) in countries such as France, Germany, Ireland, the Netherlands, Norway, Poland, Russia, Spain, and the United Kingdom.
- Bisphenol A (CAS No: 80-05-7) also has an exposure limit of 5–10 mg/m³ short-term exposure limit (STEL) in countries such as Russia and Switzerland.

Health Hazard Information

Bisphenol A is an industrial chemical that is widely used as a chemical intermediate in manufacturing the lining of food contact articles such as reusable beverage bottles, infant feeding bottles, tableware (plates and mugs), storage containers, food and beverage cans and vats. It is also used in non-food products. Small amounts of bisphenol A can migrate into food and beverages from containers (EU RAR, 2003; EU RAR, 2010).

A large amount of data is available on bisphenol A and its reported effects. Food safety authorities around the world have studied bisphenol A extensively. Consideration of the large amount of data available on bisphenol A is beyond the scope of an IMAP Tier II assessment. Therefore, the analyses and conclusions of high quality assessments from other international regulatory agencies have been reviewed to determine the priority for further assessment of the safety of industrial uses associated with bisphenol A as an IMAP Tier III assessment.

The European Food Safety Authority (EFSA) recently released a comprehensive re-evaluation of bisphenol A exposure and toxicity. It is the most recent assessment of exposure and toxicity of bisphenol A and the report was the subject of extensive consultation and engagement process with national authorities and stakeholders to ensure that the ‘widest possible range of scientific views and information were considered’ (EFSA, 2015). The following hazard conclusions are largely drawn from the EFSA report.

The major metabolic pathway in rats involves glucuronide conjugation. In humans, non-human primates and rodents, limited sulphate conjugation can also occur. Comparison of oral and intravenous toxicokinetic data indicated that the available unconjugated bisphenol A in adults is 2.8 % in rats, 0.45 % in mice and 0.9 % in monkeys. Available experimental evidence indicates a 24-hour percutaneous penetration of bisphenol A across human skin of 2.3–8.6 %.

The EFSA report re-confirmed that bisphenol A is a reproductive toxicant at high dose levels. The evidence is not sufficient to infer a causal link between bisphenol A exposure and reproductive effects in humans at current exposure levels. Reproductive or developmental effects at low doses, below the human equivalent dose (HED) of 3.6 mg/kg bw/day, were not assigned overall as being 'likely' to have these effects.

It is also stated that bisphenol A is unlikely to have any neurological, neurodevelopmental, and or neuroendocrine effects. The available data support a conclusion that bisphenol A is not considered to have mutagenic, or genotoxic or carcinogenic potential.

Kidney and liver weight changes at high doses of bisphenol A were considered as critical endpoints for the identification of a systemic no observed adverse effect level (NOAEL). The increased kidney weight was associated with nephropathy at the

highest dose in mice. Liver weight was increased in rats (relative weight) and mice (both absolute and relative weight). The latter species also showed hepatocellular hypertrophy. A benchmark dose lower bound ($BMDL_{10}$) of 8.96 mg/kg bw/day for changes in relative kidney weight was determined from a two generation reproductive study in mice. Although bisphenol A has produced proliferative changes in the mammary gland in animal studies, including a non-human primate study, these were insufficient to conclude a link to cancer development.

Bisphenol A is classified as hazardous with the risk phrases 'Risk of serious damage to eyes' (Xi; R41); 'Irritating to respiratory system' (Xi; R37); ‘May cause sensitisation by skin contact’ (R43); and ‘Possible risk of impaired fertility (R62)’ in the HSIS (Safe Work Australia). The available data generally support this classification (EU RAR, 2003; EU RAR, 2010; REACH). However, for skin sensitisation, human observations supportive of bisphenol A being a skin sensitiser were not supported by results from a modified LLNA test in mice at up to 30 % of the chemical.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects of reproductive toxicity and general toxicity (liver and kidney effects), and local effects of skin sensitisation and eye and respiratory irritation.

Public Risk Characterisation

As the chemical has no reported cosmetic use in Australia and overseas, exposure to the public with respect to cosmetic products is limited.

The major reported public health risk relates to the wide use of the chemical in the lining of food contact materials such as reusable beverage bottles, infant feeding bottles, tableware (plates and mugs), storage containers, and food and beverage cans and vats. Small amounts of bisphenol A can migrate into food and beverages from containers (see **Health Hazard Information**). The review of effects from these types of exposures is outside the remit of NICNAS, although they provide a relevant reference point for comparison of likely industrial exposures with known exposure effects via food.

Food safety authorities around the world have studied bisphenol A extensively and Food Standards Australia New Zealand (FSANZ) has concluded that exposure to bisphenol A in food does not present a significant human health and safety issue at current exposure levels. FSANZ concurred with the previously performed hazard assessment by other regulatory agency and also with the tolerable daily intake (TDI) of 50 µg/kg bw/ per day (Health Canada, 2008; US FDA, 2008; EFSA, 2010). A FSANZ survey of bisphenol A in food and drinks in the Australian market found only a limited number of products with detectable levels of bisphenol A; and no detectable levels of bisphenol A were found in infant formula. FSANZ concluded that Australians of all ages are exposed to extremely low levels (in the range of ng/kg food to µg/kg food) of bisphenol A via such packaged foodstuffs (FSANZ, 2010).

Health Canada (2012) and the US Food and Drug Administration (US FDA, 2014) have drawn similar conclusions.

As previously mentioned, the most recent comprehensive re-evaluation of bisphenol A exposure and toxicity has been completed by EFSA in 2015. The report concluded that bisphenol A poses no health risk to consumers of any age group (including unborn children, infants and adolescents) at the estimated levels of exposure. In addition to dietary exposure, the EFSA report also calculated 'average' and 'high' exposure levels for dust and toys, thermal paper, and cosmetics. Exposure (TDI) from the diet or from a combination of all sources (diet, dust, cosmetics and thermal paper) is considerably under the safe level (EFSA, 2015; see **Health Hazard Information**).

Therefore, the risk to public health is not considered to be unreasonable and further risk management for industrial uses of bisphenol A is not considered necessary for public safety.

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.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. NICNAS will continue to monitor the high quality assessment work that is being conducted by regulators and, unless the conclusions of these regulators are significantly changed in the future, a Tier III assessment is not recommended at this stage.

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]
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)* Irritating to respiratory system (Xi; R37)*	Causes serious eye damage - Cat. 1 (H318) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
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 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 oral, dermal, and ocular exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which could minimise the risk include, but are not limited to:

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

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

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

Obligations under workplace health and safety legislation

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

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical 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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