Australian Government
Department of Health, Disability and Ageing
Australian Industrial Chemicals Introduction Scheme

Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-

Evaluation statement (EVA00176)

1 April 2026

Draft

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AICIS evaluation statement (EVA00176)

Subject of the evaluation

Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-

Chemical in this evaluation

CAS name	CAS number
Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-	96-69-5

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

Based on international use information, the chemical has functional use as an antioxidant. The chemical is primarily used in the manufacture of plastic and polymer products including articles intended for food contact. It also has reported commercial use in adhesives and lubricants. No Australian or international cosmetic or domestic uses have been identified.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical.

Based on the available toxicological data, the chemical:

- has low acute oral and dermal toxicity
- is likely to be slightly irritating to skin and eyes
- is not likely to have genotoxic potential
- is not likely to be carcinogenic.

The chemical is a skin sensitiser based on animal and limited human data. In a mouse local lymph node assay (LLNA), a 3-fold increase in lymphocyte proliferation (EC3) value of 0.23 was reported, indicating strong sensitisation potential. In a Guinea Pig Maximisation Test

(GPMT), at 0.5% intradermal induction, a high response rate of positive reactions (70% of the animals) was reported.

The oral repeat dose toxicity studies indicate that the chemical can produce adverse health effects following repeated exposure. The main reported effects were in the liver, kidney and haematopoietic system in both mice and rats. A non-guideline study in mice indicated that the chemical may have effects on the immune system. However, the effects occurred mainly at high doses and were not severe enough to warrant hazard classification.

The available data are not sufficient to draw conclusions of effects on fertility or developmental toxicity. There are limitations in the data due to study design or non-availability of detailed study results. There is some indication of effects on the male reproduction system. The relevance of developmental effects was uncertain due to severe observed maternal toxicity.

No data are available for inhalation toxicity. For further details of the health hazard information see **Supporting Information.**

Hazard classifications relevant for worker health and safety

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Skin sensitisation	Skin Sens. 1A	H317: May cause an allergic skin reaction

Summary of health risk

Public

Based on the available use and end use information, public exposure to the chemical is expected to be minimal.

The public could potentially be exposed to the chemical through migration from food-contact materials into food. The limited available data indicates that migration from plastic food-contact materials into food is below internationally established regulatory migration limits. The Government of Canada considered the probable daily intake of the chemical from use in food-contact materials was negligible.

Therefore, there are no identified risks to the public that require risk management.

Workers

During product formulation and packaging, dermal, inhalation and ocular exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. The level and route of exposure will vary depending on the method of application and work

practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the sensitisation potential and potential for critical systemic long-term health effects, the chemical could pose a risk to workers. Control measures to minimise dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section). Controls in place due to the sensitisation classification should minimise the potential risks relating to other toxicity endpoints including reproductive and developmental toxicity.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety (see **Summary of health hazards** section).

Information relating to safe introduction and use

The information in this statement, including recommended hazard classifications, should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Recommended control measures that could be implemented to manage the risk arising from dermal and inhalation exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate, or manage risk arising from storing, handling and using this hazardous chemical depend on the physical form and how this chemical is used.

These control measures may need to be supplemented with conducting:

- Health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.
- Air monitoring to ensure control measures in place are working effectively and continue to do so.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

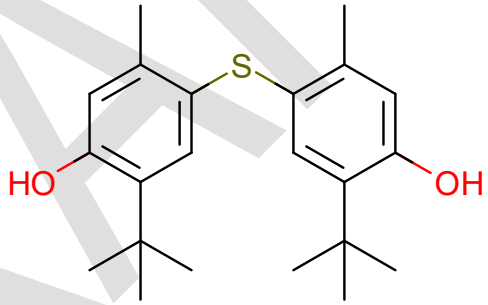
The Executive Director proposes to be satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.
2. A person introducing this chemical should be aware of their obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	96-69-5
CAS name	Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-
Molecular formula	$C_{22}H_{30}O_2S$
Associated names	4,4'-Thiobis(6-*tert*-butyl-*m*-cresol) (also known as TBBC) 6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol Bis(2-methyl-5-*tert*-butyl-4-hydroxyphenol) sulfide
Molecular weight (g/mol)	358.54
SMILES (canonical)	OC=1C=C(C(SC2=CC(=C(O)C=C2C)C(C)(C)C)=C C1C(C)(C)C)C
Structural formula	

Relevant physical and chemical properties

Physical form	White to cream coloured crystalline fine powder or pellets with a phenol-like odour.
Melting point	162°C (at 1013.25 hPa)
Boiling point	378°C (at 1013.25 hPa)
Density	1.11 g/cm³ at 20°C
Vapour pressure	< 1.47 x 10^{-3} Pa (< 1.10 x 10^{-5} mm Hg) at 20°C
Water solubility	27.7 mg/L at 20°C
pK_a	10.50 or 10.64 (estimated)

log K_{ow}	5.24 at 25°C (pH: 7)

Sources: CAS n.d.; ECHA n.d.; REACH n.d.; US EPA 2010

Introduction and use

Australia

According to information provided to AICIS as part of this evaluation, the chemical is used in the manufacture of articles for electrical products.

No other publicly reported Australian use, import or manufacturing information has been identified for the chemical.

International

The following international uses have been identified through:

- Galleria Chemica (Chemwatch n.d.)
- Substances in Preparations in Nordic Countries (SPIN) database (SPIN n.d.)
- European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossier
- United States Environmental Protection Agency Chemical Data Reporting (CDR) (US EPA 2020)
- United States Environmental Protection Agency ChemExpo Knowledgebase (US EPA 2025a)
- Draft Assessment – Substituted Phenols Group (Government of Canada 2024).
- Contact Dermatitis Report (Antelmi et al. 2023)
- Health Council of the Netherlands (HCOTN 2005)
- National Toxicology Program (NTP 1994)
- The Food Contact Chemicals database, Food Packaging Forum (2025).

The chemical primarily has functional use as an antioxidant in the manufacture of rubber and plastic products. This includes use in the manufacture of food-contact materials.

It also has reported commercial use in lubricants and additives.

No cosmetic or domestic uses were reported in United States of America (USA), Canada or Europe.

The chemical has also reported non-industrial uses in the manufacture of latex gloves, surgical and wound closing tapes (medicals devices).

Existing Australian regulatory controls

AICIS

No existing controls are currently available for the chemical.

Public

No restrictions are identified for the chemical.

Workers

The chemical is not listed on the Hazardous Chemical Information System (HCIS) for hazard classification under the GHS (SWA n.d.).

The chemical is listed on the HCIS (SWA n.d.) with a Workplace Exposure Standard (WES) of 10 mg/m^3 (8-hour time weighted average (TWA)) (SWA n.d.).

Safe Work Australia has published the *Workplace Exposure Limits for airborne contaminants (WEL list)*. From 1 December 2026 and following implementation into the work health and safety laws of the Commonwealth, states and territories, new Workplace Exposure Limits (WEL) for airborne contaminants (WEL list) have been adopted throughout Australia. The WEL for the chemical is the same as the WES (TWA 10 mg/m^3) (SWA 2024).

International regulatory status

Exposure standards

The following exposure standards were identified (Chemwatch n.d.):

- Time weighted average (TWA): 1–22 mg/m^3 in Argentina, Australia, Belgium, Bulgaria, China, Colombia, Denmark, Estonia, France, Greece, Iceland, Japan, Malaysia, Mexico, New Zealand, Peru, Poland, Singapore, South Africa, South Korea, Sweden, Switzerland, United Kingdom, and the USA.

- The US American Conference of Governmental Industrial Hygienists (ACGIH 2011). ACGIH set a TLV-TWA: 1 mg/m^3 (intended to protect for potential upper respiratory irritation).

- Short term exposure limit (STEL): 20–44 mg/m^3 in Argentina, Austria, Mexico, Croatia, South Africa, Denmark, United Kingdom, and the United States.

The Health Council of the Netherlands (HCOTN) (2005) recommended a conservative occupational exposure limit for the chemical of 5 mg/m^3 as inhalable dust, as an 8 hour TWA derived from a no observed adverse effect level (NOAEL) for systemic toxicity ≥ 20 mg/kg bw/day based on a 2 year chronic oral rat study.

European Union

The chemical is listed in Regulation (European Commission (EC)) Directive 10/2011/EU (effective 14 January 2011) on plastics in contact with food (food packaging products), Annex I – Plastics materials and articles intended to come into contact with food as follows (Chemwatch n.d.):

- Restrictions and/or specifications – specific migration limit (SML) = 0.48 mg/kg.

It is also listed on the European ECHA Plastic additives initiative – antioxidants:

- Typical concentration (Polymer type: Polyolefin-I) – 0.001%.

The chemical is also listed in a 'France Order' (effective 5 August 2020) relating to rubber materials and objects intended to come into contact with foodstuffs and pacifiers for infants and young children, Annex II – Authorised additives and Annex III. Antioxidants (Chemwatch n.d.).

The chemical is listed on the Germany Federal Institute for Risk Assessment (BfR) Database Recommendations on Food-Contact Materials – Commodities based on Natural and Synthetic Rubber (Chemwatch n.d.).

The chemical is listed on the Switzerland Annex 10 (effective 1 December 2020) of the Ordinance of the FDHA (Federal Department of Home Affairs) on materials and articles intended to come into contact with foodstuffs – List of permitted substances for the production of packaging inks, and related requirements – Table 1: List of substances (Chemwatch n.d.).

United States of America

The chemical is listed in the US Code of Federal Regulations, Title 21 – Food and Drugs:

- 175.105 Adhesives: for uses as preservative only
- 177.2600 Rubber articles intended for repeated use: Antioxidants and antiozonants (total not to exceed 5 percent by weight of rubber product)
- 178.2010 Antioxidants and/or stabilizers for polymers: At levels not to exceed 0.25 percent by weight of polyethylene (with restrictions on food types).

Asia

The chemical is listed in China's GB 9685-2016 National Food Safety Standard: Standard for the Use of Additives in Food-Contact Materials and Articles (A) – SML = 0.48 mg/kg as follows (Chemwatch n.d.):

- A1: permitted additives for plastic food-contact materials and articles
- A3: permitted additives for rubber food-contact materials and articles
- A5: permitted additives for adhesives for food-contact use.

Human exposure

Public

If the chemical is used in the manufacture of plastics intended for food contact, there is potential for public exposure through migration into food. Limited data are available regarding use in and exposure from food-contact materials. Food contact use is permitted in several countries (see **International regulatory status** section). In a study in China, the chemical was detected in 8% of materials tested (n=118) with a geometric mean concentration of 0.01 µg/kg (Han et al. 2024). This study also investigated migration into 5 food simulants (distilled water, acetic acid 3% (v/v), ethanol 10% (v/v), ethanol 50% (v/v), and ethanol 95% (v/v)). The chemical was only detected in the ethanol 95% simulant (maximum concentration 0.03 µg/kg). In another migration study investigating migration from food-contact plastics materials (n=257), the chemical was not detected (limit of detection 0.1 ng/mL). Food simulants used in this study were 95% (v/v) ethanol, water, and 4% (v/v) acetic acid (Liu et al. 2023). Government of Canada considered the probable daily intake of the chemical from use in food-contact materials was negligible (Government of Canada 2024).

Health hazard information

Toxicokinetics

Based on the available data, the chemical is rapidly absorbed following oral exposure but has lower bioavailability following dermal exposure. The chemical is predominantly excreted in the faeces.

In a non-guideline study that was also not compliant with good laboratory practice (GLP), the radiolabelled chemical was administered to male F344/N rats by gavage at doses of 5, 50 or 500 mg/kg bw or through a single intravenous (i.v.) injection at 5 mg/kg bw. After oral and i.v. administration of the chemical, it was reported to be rapidly distributed throughout the body, with the highest concentrations found in the liver. It was also detected in the blood, muscle, skin, and adipose tissue. Three days after administration, less than 4% of the administered dose was detected in the tissues. The chemical was predominantly excreted via the faeces, with a half-life of 20 hours. Metabolites (mainly glucuronides) of the chemical accounted for the total amount of radioactivity in bile but only accounted 80% in the faeces. Less than 2% of the administered dose was excreted in the urine as total metabolites (mainly glucuronides) within the first day, with a half-life of 9 hours (HCOTN 2005).

In a follow up study, the radiolabelled chemical was administered in ethanol/acetone vehicle at single oral, dermal or i.v. doses of 5 mg/kg bw to female Sencar mice and male Fischer rats. In addition, male Fischer rats were administered the chemical dermally at doses of 50 or 200 mg/kg bw. After dermal application of 5 mg/kg bw, around 24% of the dose was absorbed by the mouse skin whereas only up to 2% of the dose was absorbed by the rat skin indicating mouse skin was more permeable to the chemical than rat skin. Absorption did not increase linearly as the dose increased. Results from both studies showed a similar pattern of excretion between rats and mice, with faecal excretion as the major route of elimination (HCOTN 2005; REACH n.d.).

In another non-GLP compliant, non-guideline toxicokinetics study, the radiolabelled chemical was administered as a single i.v. injection of 5 mg/kg bw in emulphor:ethanol:water to male Fischer 344 rats (5/dose; ages 2.5, 16, and 26 months old). It was reported that the chemical was mainly excreted through faeces (60–80% of the applied dose) during the first 72 hours. There was a decreased ability for older animals in the group to excrete the chemical through bile, faeces, and urine and an overall decrease in the percentage of the dose eliminated in bile as glucuronide for all animals (REACH n.d.).

Acute toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity with reported median lethal dose (LD50) values above 2000 mg/kg bw/day.

In a non-GLP compliant, non-guideline acute oral toxicity study (similar to OECD Test Guideline (TG) 401), Sprague Dawley (SD) rats (5/sex/dose) were given a single dose of the chemical by gavage at 1580, 2000, 2510 or 3160 mg/kg bw. The experiment was repeated. The LD50 was reported to be greater than 2000 mg/kg bw in the 2 separate experiments (2315 mg/kg bw and 2420 mg/kg bw). Reported clinical signs of toxicity included severe diarrhoea, marked weight loss, increasing weakness, and collapse in animals. However, no detailed information on mortality was reported. Reported treatment-related effects from

pathology investigations included gastroenteritis, liver discolouration, and severe renal hyperaemia in animals upon necroscopy (REACH n.d.).

In 2 non-GLP compliant, non-guideline acute oral toxicity studies (similar to OECD TG 401) in SD rats, LD50 values greater than 2000 mg/kg bw were reported. However, details of both the studies were limited. In the first study (5/sex/dose; at doses of 2510, 3160, 3980 or 5010 mg/kg bw), clinical signs of toxicity reported included reduced appetite, decreased activity, progressive weakness, collapse and mortality. Mortality was reported in females at all doses and high dose male rats (number of deaths unspecified). Treatment-related effects at necropsy included lung and liver hyperaemia and inflammation of the gastrointestinal mucosa (US EPA 2010). An LD50 value of 4150 mg/kg bw/day was reported. In the second study (5/sex/dose; at doses of 1580, 2000, 2510 or 3160 mg/kg bw) clinical signs of toxicity included severe diarrhoea, loss of appetite, tremors, and collapse in animals. Renal (kidney) and liver congestion and inflammation of the gastrointestinal mucosa in animals were also reported upon gross pathology. No detailed information on mortality was reported. An LD50 value of 2345 mg/kg bw/day was reported (HCOTN 2005; REACH n.d.).

Dermal

Based on the available data, the chemical has low acute dermal toxicity.

In a non-GLP compliant, non-guideline acute dermal toxicity study (similar to OECD TG 402), New Zealand White (NZW) rabbits (1 male at low and high doses; 1/sex for mid-dose; 4 in total) were treated with the chemical (> 96% purity; 40% suspension solution in corn oil), applied as a single dermal patch under occlusive conditions for 24 hours at doses of 3160, 5010 or 7940 mg/kg bw. The reported median LD50 was between 5010 and 7940 mg/kg bw. Mortality was reported at the highest dose. Clinical signs of toxicity included reduced appetite and activity in the surviving animals over 3–7 days and at the highest dose progressive weakness and collapse. Treatment-related effects in surviving animals post-pathology (after 14 days) included lung hyperaemia, liver and kidney discolouration, enlarged gall bladder, and gastrointestinal inflammation (REACH n.d.; US EPA 2010).

A dermal LD50 value of > 1260 mg/kg bw was reported in rabbits (HCOTN 2005). No further study details are available including doses tested limiting its value.

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is likely to be, at most, slightly irritating to skin.

In a non-GLP compliant *in vivo* skin irritation study similar to OECD TG 404, 3 NZW rabbits (unspecified sex) were treated with 0.5 g of the chemical (99.93% purity; in physiological saline) for 4 hours under semi-occlusive conditions. Observations were recorded at 30 minutes, 4.5, 24, 48, 72 hours and 7 days after patch removal. The following mean scores for all animals were reported based on observations at 24, 48 and 72 hours for intact skin:

- erythema 1.87
- oedema 1.06.

Individual animal scores were not reported. The erythema and oedema signs were reversible in all animals within 7 days (REACH n.d.).

In a non-GLP compliant non-guideline *in vivo* skin irritation study, 6 NZW rabbits (unspecified sex) were treated with 0.5 g of the chemical (moistened with water) for 4 hours under unspecified conditions. Observations were recorded at 4, 24, 48, 72 hours and 7 days after patch removal. The mean erythema score for all animals of 0.94 was reported based on observations at 24, 48 and 72 hours, respectively. No oedema was observed in treated animals (mean score = 0). Individual animal scores were not reported. Skin irritation effects were reversible in all animals within 7 days (REACH n.d.; US EPA 2010).

Eye irritation

Based on the available data, the chemical may be irritating to eyes. The available scoring information are not able to be directly compared to the GHS classification criteria. However, as effects were reversible within 7 days the chemical would be considered at most slightly irritating (UNECE 2017).

In a non-GLP compliant *in vivo* eye irritation study similar to OECD TG 405, 0.1 g of the chemical (finely ground powder) was instilled into one eye each of 6 female NZW rabbits. The eyes of 3 animals were washed out after 30 seconds (for 1 minute), where the remaining 3 animals were left unwashed as a comparison group. Observations were recorded at 10 minutes, 1, 24, 48, 72, 96 hours and 7 days. Conjunctival redness, corneal opacity and iritis were reported in all animals in the unwashed group, whereas only conjunctival redness was reported in the washed group. No chemosis was reported for both the unwashed and washed groups. The irritation effects were fully reversible within 7 days for both groups (REACH n.d.; US EPA 2010). The scoring method used in the study was not compatible with the criteria required for GHS classification.

In a non-GLP compliant non-guideline *in vivo* eye irritation study, 0.1 g of the chemical was instilled into one eye each of 6 female NZW rabbits. Observations were recorded at 24, 48, 72 and 7 days. Conjunctival redness was reported in all animals but resolved within 72 hours. No corneal opacity, iritis and chemosis were reported. All treatment-related effects were fully reversible within 7 days (REACH n.d.). The scoring method used in the study was not comparable with the criteria required for GHS classification.

Sensitisation

Skin sensitisation

Based on the available data, the chemical is a skin sensitiser, warranting GHS hazard classification (see **Hazard classifications relevant for worker health and safety**).

Based on an EC3 (concentration required to produce a 3-fold increase in lymph node cell proliferation value) of 0.23% in a LLNA study and a sensitisation rate in a GPMT of ≥ 60% following intradermal induction at > 0.1% but ≤ 1% (see **In vivo** section below), the chemical is likely to have strong potency (ECETOC 2003, ECHA 2024). Overall, the available data support GHS classification with sub-categorisation proposed as skin sensitisation category 1A (UNECE 2017). There is limited evidence of sensitisation in humans, with some identified case studies supporting the potential for sensitisation.

In vivo

In a non-GLP compliant non-guideline LLNA (similar to OECD TG 429), female BALB/c mice (5/dose) received topical applications at 0.1, 0.5, 1, 5 or 10% (w/v) of the chemical in acetone for 3 consecutive days. The reported stimulation indices (SI) were 1.13, 6.89, 14.28, 20.19

and 15.3 for concentrations of 0.1, 0.5, 1, 5 and 10%, respectively. The reported concentration producing a 3-fold increase in lymphocyte proliferation (EC3) was 0.23% (Myers et al. 2007; US EPA 2010).

In another *in vivo* skin sensitisation study (GLP compliance unspecified) conducted in accordance with OECD TG 406 (GPMT), female Dunkin Hartley guinea pigs (10/dose; 5 controls/group) received intradermal injection of 0.5% of the chemical in olive oil and topical application of 25% chemical under occlusive conditions. The animals were challenged with topical application of the chemical at 5% in olive oil and dermal reactions were observed at 48 and 72 hours after removal of the patch. Clinical signs of moderate irritation (erythema and oedema) at the challenge sites were reported during the induction phase and alleviated using 10% sodium lauryl sulfate (SLS) in Vaseline ointment. Positive reactions were reported in 70% (7/10) of the animals challenged with 5% of the chemical at both 48 and 72 hours (REACH n.d.).

In silico

The *in silico* data was negative for skin sensitisation.

The chemical has no structural alerts for protein binding based on the mechanistic profiling functionality of the OECD Quantitative Structure Activity Relationship (QSAR) Application Toolbox (OECD QSAR Toolbox v4.5) when modelled both with and without skin metabolism (OECD 2025).

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 was used to estimate the skin sensitisation potential of the chemical. The chemical did not match any structural alerts or examples for skin sensitisation in DEREK. Additionally, the query structure did not contain any unclassified or misclassified features and was consequently predicted to be a non-sensitiser (Lhasa Limited n.d.).

Observation in humans

In a patch test study with 50 healthy human volunteers, it was reported that the chemical did not elicit positive skin sensitisation reactions after challenge at unspecified doses. The authors concluded that the chemical was not considered a primary irritant nor a fatiguing agent. However, further study details including the reliability of the study are not available (REACH n.d.).

Two cases of allergic contact dermatitis were reported in patients who developed lesions on their hands and/or face after exposure to ‘latex examination gloves’ (for which the chemical is used as an antioxidant in the manufacture of latex gloves). Both patients had reacted positively to a separate human patch test study when dermally applied with a 1% solution of the chemical in petrolatum (Rich et al. 1991).

Human patch tests conducted between 1986 and 1987 in 65 patients (37 females and 28 males), in which a 2% solution of the chemical in petrolatum was applied to the skin, did not result in positive allergic reactions. No further details are available (HCOTN 2005; Rich et al. 1991).

A case study in Sweden included patients who had experienced eczematous reactions after application of different types of medical devices such as surgical tape and different wound dressings (n=6). These patients were patch tested with the chemical at 1% in petrolatum. The patients were also patch tested with different tapes or wound dressings (containing the chemical) and acetone extracts from these medical devices. The occlusion time for all patch

tests was 48 hours and test readings were performed on day 3 and 7. All patients reported had a positive reaction to the chemical (1% in petrolatum) and to at least one product containing the chemical as is or as an acetone extract (Antelmi et al. 2023).

The chemical was added to a baseline series for testing in Sweden in 2021 (Antelmi et al. 2023). Overall, 722 patients were patch tested. No positive reactions were observed. One patient had an uncertain skin sensitisation reaction at the first test reading, but this was concluded as negative at the second test reading. (Antelmi et al. 2023; HCOTN 2005).

Repeat dose toxicity

Oral repeat dose toxicity studies indicate that the chemical can cause adverse health effects following repeated exposure. However, the effects occurred mainly at high doses and were not severe enough to warrant hazard classification. The main reported effects were in the liver, kidney and haemopoietic system in both mice and rats. A non-guideline 2 week study in mice indicated that the chemical may have effects on the immune system (see **Immunotoxicity** section).

Oral

Sub-chronic studies

In a 13 week GLP compliant study conducted in accordance with NTP guidelines, F344/N rats (10/sex/dose) were administered the chemical (99% purity) in feed at concentrations of 0, 250, 500, 1000, 2500 or 5000 ppm once daily for 13 weeks. This was equivalent to doses of approximately 0, 15, 30, 60, 165 and 315 mg/kg bw/day for males; and 0, 15, 35, 70, 170 and 325 mg/kg bw/day for females. No mortalities occurred in the study. Body weight was significantly reduced in both males (40%) and females (27%) at the highest dose. The reduced body weights were associated with reduced food intake. Since reduction in feed consumption was apparent from the beginning of the study, the reduction was likely to have been caused by decreased feed palatability rather than due to toxicity. (ECHA 2019; NTP 1994).

The main target organs were the liver, kidneys and the haematopoietic system.

Effects related to the liver included:

- Significantly greater relative liver weights of female rats at the 5000 ppm dose and male rats fed the 2500 ppm and 5000 ppm doses. Absolute liver weights were significantly greater in female rats at 5000 ppm but not in males at any dose.
- Significantly higher serum alkaline phosphatase (ALP) levels in males fed doses of 2500 and 5000 ppm as compared to slightly higher ALP levels in females fed 5000 ppm.
- Significantly higher serum alanine aminotransferase levels in males and females in the 2500 and 5000 ppm dose groups.
- Increased incidence of lesions in the liver of males and females in the 2500 and 5000 ppm dose groups based histopathologic findings (hypertrophy of Kupffer cells, hyperplasia in the bile duct, and individual cell necrosis of hepatocytes).
- Centrilobular hepatocyte hypertrophy in males and females in the 5000 ppm group.

Effects in the haematopoietic system included:

- Significantly lower haematocrit and haemoglobin concentrations (2–5%) at 1000, 2500, and 5000 ppm in males (suggestive of mild anaemia).
- Lower mean erythrocyte volume (MCV) values at 1000, 2500, and 5000 ppm in males and at 5000 ppm in females.
- Increases in total leukocyte counts in females and segmented neutrophil counts in males and females consistent with an inflammatory response at 5000 ppm.
- Macrophages were increased in size and number in the mesenteric lymph nodes of both sexes fed at 5000 ppm (and to a lesser extent at 2500 ppm).

Effects related to the kidney included:

- Pigmentation and degeneration of the renal cortical tubule epithelial cells in both sexes were fed the chemical at 2500 and 5000 ppm, noting cortical tubule necrosis in both sexes fed at 5000 ppm.
- No urinalysis was undertaken to further assess potential renal effects.

The NOAEL was 1000 ppm (equivalent to 60 or 70 mg/kg bw in male and female rats, respectively) based on liver and kidney effects from 2500 ppm (NTP 1994).

In a 13 week GLP compliant study conducted in accordance with NTP guidelines, B6C3F1 mice (10/sex/dose) were administered the chemical (99% purity) in feed at concentrations of 0, 100, 250, 500, 1000 or 2500 ppm once daily for 13 weeks. This was equivalent to doses of approximately 0, 15, 30, 65, 145 and 345 mg/kg bw/day for males; and 0, 10, 35, 60, 165 and 340 mg/kg bw/day for females, respectively. No mortalities occurred in the study. No treatment-related clinical signs were reported in mice. Body weight changes included significantly decreased final mean body weight of males at 2500 ppm and females at 500 ppm and above. The reduced body weights were associated with reduced food intake likely due to decreased food palatability (ECHA 2019; NTP 1994).

Effects related to the liver included:

- Slightly but significantly greater absolute and relative liver weights in both sexes at 2500 ppm.
- Increased incidences of hypertrophy of Kupffer cells and hyperplasia in the bile duct at 2500 ppm.

Effects in the haematopoietic system included:

- Significantly lower haematocrit and erythrocyte (at 1000 and 2500 ppm) and haemoglobin concentrations (7−8%) and MCV values (at 2500 ppm) in both sexes (suggestive of mild anaemia).
- Macrophages were increased in size and number in the mesenteric lymph nodes in both sexes fed at 2500 ppm.
- Significantly increased absolute and relative spleen weights in males fed at ≥ 500 ppm (and females at 2500 ppm), relative spleen weight was also significantly increased in females at 1000 ppm. There were no accompanying histopathological findings. A

Effects related to the kidney included:

- Pigmentation and degeneration of the renal cortical tubule epithelial cells in both sexes at 2500 and 5000 ppm, and cortical tubule necrosis in both sexes fed at 5000 ppm.

The NOAEL was 1000 ppm (equivalent to 145 or 165 mg/kg bw in male and female mice, respectively) based on liver and kidney effects at 2500 ppm. The increased spleen weight reported in mice may be an indicator for immunotoxicity. However, they could also be a result of 'mild anaemic effects or a response to stress' (NTP 1994).

In a 28 day toxicity study (similar to OECD TG 407; GLP compliance unspecified), Crj:CD SD rats (6/sex/dose), were administered the chemical (98% purity) by gavage at doses of 0, 15, 60 or 250 mg/kg bw/day (vehicle: 0.5% Arabic gum solution). No mortality occurred in the study. The chemical did not affect body weight and there were no clinical signs of toxicity during the study. Haematological effects included an increase in platelets in both sexes in the highest dose group, an increase in segmented neutrophil ratio and a decrease in neutrophile-to-lymphocyte ratio in females at the highest dose. A significant increase in relative liver weight and hypertrophy of centrilobular hepatocytes were observed in both sexes in the 250 mg/kg bw group. Changes in the intestines at the highest dose included wall thickening and hyperplasia of intestinal villi in the small intestine and dilation of the large intestine. Most the effects were reversible after the 14 day recovery period. The NOAEL was 60 mg/kg bw for both sexes for the chemical, based on effects at the 250 mg/kg bw (REACH n.d).

Chronic studies

In a 2 year GLP compliant study conducted in accordance with NTP guidelines, F344/N rats (115 males/75 females) were administered the chemical (99% purity) in feed at concentrations of 0, 500, 1000, or 2500 ppm once daily for 2 years. This was equivalent to doses of approximately 0, 20, 40 and 100 mg/kg bw/day for males; and 0, 20, 45 and 120 mg/kg bw/day for females, respectively. Survival rates were not significantly affected. The mean body weights of male rats fed 2500 ppm were slightly lower than those of the controls throughout the study. There were no effects on feed consumption, behaviour, and general health and appearance any dose. The only observed kidney effects was an increase in severity of nephropathy in 2500 ppm females in comparison to controls. The severity of nephropathy was similar among all groups of male rats. The authors of the study concluded nephropathy was a common occurrence in aging F344/N rats and was found in nearly all males and majority of females in the study. Haematological effects were limited to slight inconsistent decreases in haematocrit, haemoglobin, erythrocyte counts and increases in platelets at some timepoints. There were no significant effects on nerve conduction, neuromuscular transmission, muscle contractility, or neuropathology.

Liver related effects included:

- Increased liver weights in 2500 ppm females.
- Kupffer cell hypertrophy at 2500 ppm in both sexes.
- Cytoplasmic vacuolisation was slightly increased in 1000 and 2500 ppm males and significantly increased in 1000 and 2500 ppm females.
- Fatty change was increased in 2500 ppm females.
- Mixed cell foci were increased in 1000 and 2500 ppm males and females, respectively.
- Increases in serum liver enzymes (ALP, ALT, SDH) in 2500 ppm males and females at 15 months.

The NOAEL for systemic toxicity in rats was 500 ppm (20 mg/kg bw) based on liver effects at a 1000 ppm (40 mg/kg bw) (ECHA 2019; NTP 1994).

In a 2 year GLP compliant study conducted in accordance with NTP guidelines, B6C3F1 mice (80/sex) were administered the chemical (99% purity) in feed at concentrations of

0, 250, 500, or 1000 ppm once daily for 2 years. This was equivalent to doses of approximately 0, 30, 60 and 145 mg/kg bw/day for males; and 0, 45, 110 and 255 mg/kg bw/day for females, respectively. Survival rates were not significantly affected. The final mean body weights of male and female mice exposed to 1000 ppm were 8% and 18% lower than those of the controls, respectively. Feed consumption was not affected. There were no marked signs of liver or kidney toxicity. The main findings were mild anaemia in males and myelofibrosis in females. Myelofibrosis was seen in all treated females including controls, but the incidence was significant by comparison at 1000 ppm as compared to controls and the lower doses.

The NOAEL for systemic toxicity in mice was 60 and 110 mg/kg bw/day for males and females, respectively based on effects at 1000 ppm (equivalent to 60 or 110 mg/kg bw in males and females respectively) (ECHA 2019; NTP 1994).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Genotoxicity

Based on the available data, the chemical is not likely to be genotoxic. The chemical was reported as mostly negative in available *in vitro* assays, and no genotoxic effects were observed *in vivo*.

In vitro

The following results were reported (Chemwatch n.d.; HCOTN 2005; NTP 1994; REACH n.d.; US EPA 2010):

- Negative in GLP compliant bacterial reverse mutation assays (OECD TG 471) in *Salmonella typhimurium (S. typhimurium)* TA97, TA98, TA100, TA102, TA1535 and TA1537 strains; and *Escherichia coli* WP2 uvrA with and without S9 metabolic activation at concentrations up to 5000–10000 µg/plate.
- Negative in GLP compliant bacterial reverse mutation assays (OECD TG 471) in *S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 strains with and without S9 metabolic activation at concentrations up to 500 µg/plate.
- Negative in a GLP compliant mammalian chromosome aberration assay (OECD TG 473) in cultured Chinese hamster lung cells (CHL/IU) with and without S9 metabolic activation at concentrations up to 20–5000 µg/mL.
- Negative in a mammalian chromosome aberration assay (GLP compliance unspecified; similar to OECD TG 473) in cultured Chinese hamster ovary (CHO) cells with and without S9 metabolic activation at concentrations of 3–12.5 µg/mL.
- Positive in a sister chromatid exchange (SCE) assay (GLP compliance unspecified; similar to OECD TG 479) in cultured CHO cells with and without S9 metabolic activation at concentrations of 1.5–12.5 µg/mL.

In vivo

Negative results were reported in a GLP compliant mammalian bone marrow chromosomal aberration test conducted in accordance with OECD TG 475. Fischer 344 (F344) rats (5/sex/dose) were administered a single dose of the chemical (99% purity) by oral gavage at doses of 0, 700, or 1400 mg/kg bw/day (in corn oil). The incidence of chromosome aberrations in bone marrow did not increase at any dose of the treated groups or testing interval (6, 18, or 30 hours) when sampled at 6, 24, or 48 hours after dosing, indicating a lack of clastogenicity in the hemopoietic cells of the bone marrow of rats (HCOTN 2005; REACH n.d.; US EPA 2010).

In silico

The *in silico* data was negative for genotoxicity.

The chemical has no structural alerts for DNA binding based on the mechanistic profiling functionality of the QSAR Application Toolbox (OECD QSAR Toolbox v4.5) (OECD 2025).

The knowledge based expert system DEREK Nexus version 6.0.1 was utilised to estimate the genotoxic potential of the chemical. The chemical did not match any structural alerts or examples for bacterial *in vitro* mutagenicity in DEREK. Additionally, the query structure did not contain any unclassified or misclassified features and was consequently predicted to be inactive in the bacterial *in vitro* Ames mutagenicity test (Lhasa Limited n.d.).

The QSAR predictions using OASIS TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.31.2.82) indicate that the chemical was negative for *in vitro* mutagenicity Ames and chromosomal aberration. The predictions were within the applicability domain of the genotoxicity models (OASIS LMC).

Carcinogenicity

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

In the 2 year oral toxicity studies conducted by the NTP (GLP compliance unspecified) (see **Repeat Dose Toxicity** section), no carcinogenic activity was reported in:

- Male or female F344/N rats fed the chemical at 0, 500, 1000, or 2500 ppm (equivalent to 0, 20, 40, or 100 mg/kg bw for males; and 0, 20, 45, or 120 mg/kg bw for females).
- Male or female B6C3F1 mice fed the chemical at 0, 250, 500, or 1000 ppm (equivalent to 0, 30, 60, or 145 mg/kg bw for males; and 0, 45, 110, or 255 mg/kg bw for females) (Government of Canada 2024; ECHA 2013; ECHA 2019; NTP 1994; REACH n.d.; US EPA 2010).

Although some neoplastic lesions were reported to be observed by the authors of the studies, these were considered not related to treatment as within the historical control range. The following results reported included:

- **In rats:**
  - A slightly increased incidence of hepatocellular adenoma or carcinoma (combined) in exposed male rats. This was not statistically significant and did not exceed historical controls.

- In the thyroid gland, there was a significant positive trend in the incidence of C-cell adenoma or carcinoma (combined) in female rats that was slightly, but not significantly, increased in the 1000 and 2500 ppm groups at the end of the 2 year study. However, this was not considered treatment-related (NTP 1994) as incidence did not exceed historical controls.
- In the uterus, stromal polyps occurred with a significant positive trend (0 ppm, 2/50; ppm, 500 5/50; 1000 ppm, 9/50; 2500 ppm, 9/50) in female rats. Increased incidences of stromal polyps in females exposed to 1000 or 2500 ppm were significant but did not exceed historical controls (NTP 1994).
- In the mammary gland, the incidence of fibroadenoma occurred with a statistically significant negative trend in female rats (29/50, 24/50, 11/50, 16/50). The decreases were significant in the 1000 and 2500 ppm groups. There was also a significant negative trend in the incidence of mammary gland fibroadenoma, adenoma, or carcinoma (combined) in females (32/50, 24/50, 11/50, 16/50).

- **In mice:**
  - A significantly lower incidence of hepatocellular adenoma or carcinoma (combined) in males fed 1000 ppm compared with controls.

Reproductive and development toxicity

The available data are not sufficient to draw conclusions of effects on fertility or developmental toxicity. There are limitations in the data due to study design or availability of detailed study results. In a non-guideline study, effects on male reproductive organs were reported. Effects on sperm and epididymis were noted in a summary by ECHA of an OECD guideline screening test for reproduction and development (OECD TG 421). There were no changes to fertility parameters in this study. However, it is noted that sperm parameters in the rat have to be affected considerably in order to adversely affect fertility, with humans having a lower sperm reserve. It is also noted that the premating dosing period in OECD TG 421 does not cover an entire spermatogenic cycle. The OECD TG 421 study is not publicly available.

Due to excess observed maternal toxicity it is not possible to conclude on developmental effects observed in available studies.

Due to the uncertainty in effects on reproductive and developmental toxicity ECHA requested an OECD TG 443 to be conducted (ECHA 2016; ECHA 2019). This study is not publicly available.

Sexual function and fertility

In a non-guideline male reproductive toxicity study (GLP compliance unspecified), male Crj:CD-1(ICR) mice and male F344/DuCrj(Fischer) rats (8/species/dose) were fed a diet containing 0.06–0.25% of the chemical (~ 81.6–495 mg/kg bw/day for mice and ~ 41–230 mg/kg bw/day for rats) for 2 months. In mice, there was a decrease in the weight of sex accessory organs (epididymides, seminal vesicles, prostate glands, and preputial glands). although testicular weight was not significantly reduced at the highest dose. Observed testicular pathological effects at this dose, included exfoliation of seminiferous tubules (in 62.5% of mice), and sloughing (in 75%), as well as vacuolisation and proliferation of Leydig cells and dilated seminiferous tubule lumens (in 50%). Daily sperm production was dose dependently reduced. In rats, a decrease in sex accessory organ weight and daily sperm production was reported while relative testicular weight was significantly increased at the highest dose. Similar spermatogenesis effects (exfoliation and sloughing of seminiferous tubules) were observed at the highest dose, and to a lesser extent at the lower doses. The

study author concluded that the chemical is weakly toxic to male reproductive organs in mice and rats (Takahashi & Oishi, 2006; US EPA 2010).

In an OECD TG 421 study (GLP compliance unspecified) in rats (strain not specified) summarised in an ECHA 2019 report, a significantly lowered sperm forward motility index was reported in the high dose parent males (500 mg/kg bw/day). Some effects of sperm and epididymis (reduced forward motility and cell debris in the lumen of the epididymis) were reported at lower doses in individual animals. There was no effect on fertility parameters. In females there were no reported effects on reproductive organs, oestrus cycles, mating ability, gestation periods, birth index, number of corpora lutea, implantations, delivery, and lactation. In this study animals were dosed up to day 4 after delivery and were sacrificed on day 5. Therefore, dosing was only approximately for 54 days (in contrast to the standard 63 day study duration according to OECD TG 421). While detailed study information, including the doses tested, was unavailable, the study was reported to have been conducted in accordance with OECD TG 421. As the study was conducted in 2010 this was prior to the update of the test guideline in 2016, where several parameters suitable to assess endocrine disruption potential were included.

Developmental toxicity

In a non-GLP compliant, non-guideline pre-natal developmental toxicity study, pregnant CD-1 mice (50/dose) were administered the chemical once daily by gavage (vehicle: corn oil) at 485 mg/kg bw/day (LD10 value derived from 2 screening studies) on GD 6–15. Increased maternal mortality was reported in treated animals (22/50). A decreased rate of pup survival was observed. However, there were no effect on the number of viable litters, litter size, birth weight and weight gain of the pups. As considerable maternal effects was reported the relevance of findings cannot be assessed (ECHA 2019; HCOTN 2005; NTP 1994; REACH n.d.).

In a non-GLP compliant, non-guideline prenatal developmental toxicity study, pregnant NZW rabbits (13/dose) were administered the chemical by gavage (vehicle: 0.5% gum tragacanth) at 0, 0.2, 2 or 20 mg/kg bw/day on GD 6–18. Dams were sacrificed on GD 29, and the developmental parameters were examined. Treatment-related effects at the highest dose included anorexia and subsequent abortion (4/13 animals), decreased litter size and increased incidences of embryo death. Among rabbits with viable litters, there were no conclusive effects on litter size, foetal loss or litter weight. No significant treatment-related effects on incidences of visceral and skeletal anomalies and skeletal variants were reported. Lower mean pup weight compared to controls was reported at 2 mg/kg bw/day but not at the highest dose. This lack of a dose response relation could be caused by the reduced numbers of pups at the high dose. Overall, the study is considered not sufficient to conclude on teratogenicity and development, but it raises concern of potential adverse effects on development (ECHA 2019; Government of Canada 2024; REACH n.d.; US EPA 2010).

Endocrine effects

Limited data, particularly from *in vivo* studies are available on the endocrine effects of the chemical. Although some endocrine activity has been observed *in vitro*, the potency the chemical was much lower than endogenous ligands. Overall, the available data does not provide sufficient evidence of an adverse effect from an endocrine mode of action.

Endocrine activity

In a study using an ‘Estrogen Receptor’ (ER) alpha competitor screening kit, the 50% inhibitory concentration (IC50) of 6,6'-ditert-butyl-4,4'-thiodi-m-cresol was 1.8×10^{-5} M. The

positive control Bisphenol A had an IC50 of $1.4x10^{-5}$ M. The endogenous ER alpha ligand 17β-estradiol and the therapeutic ligand tamoxifen have IC50s in the nanomolar range (10^{-9}). These results indicate that the chemical has weak oestrogenic activity. Positive results were observed in an Androgen Receptor (AR) Binding Assay. However, the chemical was negative in a human AR reporter gene assay measuring both agonistic and antagonistic activity (no further details are available) (ECHA 2019; ECHA 2021).

ECHA (2019) and the United States Environmental Protection Agencies' Toxicity Forecaster (ToxCast) reported positive results for estrogenic/anti-estrogenic and androgenic/anti-androgenic activities. Antagonistic activity for the thyroid hormone receptor (beta) and agonistic activity for the glucocorticoid receptor and Peroxisome Proliferator Activated Receptor (PPAR) was also reported (ECHA 2019; US EPA 2025b).

In a non-GLP compliant non-guideline uterotrophic assay, ovariectomised mice were administered the chemical (subcutaneously) at doses of 60 and 300 mg/kg/day for 4 days. The chemical increased uterine weight at both doses in mice. This indicated that when the endogenous ligand oestrogen is reduced in the body (via ovariectomy) the chemical can increase uterine weight suggestive of weak oestrogenic activity (ECHA 2019; Takahashi & Oishi, 2006).

Adverse effects

In reproductive toxicity studies, effects on male reproductive organs were reported but no effects on female reproductive organs or fertility parameters were observed (see **Reproductive and development toxicity** section). The available studies did not include several parameters suitable to assess endocrine disruption potential.

Immunotoxicity

Based on the limited available data, the chemical may have effects on the immune system.

In a non-GLP compliant non-guideline oral study, female B6C3F1 mice (n = 5–8 animals/sex/dose) received radiolabelled chemical in corn oil via gavage at doses of 0, 10, 100 or 200 mg/kg bw, once daily for 14 consecutive days. The animals were observed for 24 hours after the last chemical exposure. There were no treatment-related mortalities or clinical signs of toxicity observed during the study. As with previous studies (see **Repeat dose toxicity section**), some signs of liver toxicity were observed. The spleen was enlarged but histopathology was unchanged.

The chemical affected macrophage function, and host resistance capabilities in a complex manner from 10 mg/kg bw. The most prominent effects were reduced antibody responses, an increase in splenic cells and enlarged spleen and a reduced T-cell percentage (differential leukocyte count). Functional effects included suppressed mitogen and mixed lymphocyte response, increased natural killer cell activity and enhanced phagocytic activity of macrophages. There were also signs of increased resistance to *Streptococcus pneumoniae* but not to other tested pathogens. There were increases in resistance to B16F10 melanoma but decreased resistance to PYB6 fibrosarcoma (ECHA 2019; Holsapple et al. 1988; Munson et al. 1988), potentially indicating a selective, not uniform, pattern of immunomodulation.

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