Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Phenol, 2,4,6-tris(1,1-dimethylethyl)-

Evaluation statement (EVA00174)

31 March 2025

Draft

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AICIS evaluation statement (EVA00174)

Subject of the evaluation

Phenol, 2,4,6-tris(1,1-dimethylethyl)-

Chemical in this evaluation

CAS name	CAS number
Phenol, 2,4,6-tris(1,1-dimethylethyl)-	732-26-3

Reason for the evaluation

New information is available about human health risks.

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 this chemical.

Summary of evaluation

Summary of introduction, use and end use

Based on the international information, the chemical primarily has site-limited functional use conditions as an intermediate. It is also functions as an antioxidant with end use in fuel and related products including fuel additive products and to a lesser extent lubricants and greases. Consumer uses in retail fuel additive products at concentrations up to 3% 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 data, the chemical:

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

Based on the available data, the chemical is expected to have moderate acute oral toxicity (median lethal dose (LD50) between 200 and 2000 mg/kg bw in rats).

The chemical is expected to be a sensitiser with low to moderate potency based on local lymph node assay (LLNA) which reported a 3-fold increase in lymphocyte proliferation (EC3) value of 22.2%.

Based on the available data, the chemical has adverse effects on the liver following repeated exposure. In a combined repeat dose oral toxicity study with reproduction/developmental toxicity screening test in rats, effects on the liver included significant increase in liver weight, hepatocellular hypertrophy and hepatocellular necrosis. Additionally, liver effects were also reported in a chronic oral toxicity study at doses equivalent to 25 mg/kg bw/day after 6 months of exposure. These treatment related effects included significantly higher liver weight, focal necrosis and vacuolisation of hepatocytes in rats.

Based on the available data, the chemical is expected to cause specific adverse effects on development. In a combined repeat dose oral toxicity study with reproduction/developmental toxicity screening test in rats, decreased post-natal viability and decreased body weight of pups were observed at doses ≥10mg/kg bw/day. No adverse effects of the chemical were reported on reproductive parameters relating to sexual function and fertility. Maternal liver toxicity was reported in the absence of severe body weight changes or clinical symptoms in the dams. Therefore, developmental changes are not considered secondary to maternal toxicity. The reported no observed adverse effect level (NOAEL) for developmental toxicity was reported to be 3 mg/kg bw/day.

No inhalation data are available. 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
Acute Toxicity	Acute Tox. 4	H302: Harmful if swallowed
Skin sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction
Specific target organ toxicity (repeated exposure)	STOT RE 2	H372: Causes damage to organs (liver) through prolonged or repeated exposure
Reproductive toxicity	Repr.1B	H360D: May damage the unborn child

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemical at concentrations up to 3 % by incidental skin and eye contact during use of retail fuel additive products. Considering that this type of use would be infrequent, repeated exposure is expected to be limited.

A margin of exposure or MOE methodology was used to characterise the risk to human health associated with developmental toxicity. When used as a fuel additive at concentrations up to 3% and taking into consideration likely limited dermal absorption, an MOE greater than 100 was predicted. In general, an MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. This indicates that the chemical is unlikely to pose a risk to human health if used in fuel additive products at concentrations of 3% or less.

Given the incidental nature of exposure and given the chemical has low to moderate potency, the risk of sensitisation is considered low.

There is potential for secondary exposure through the environment, as the chemical is persistent, bioaccumulative and toxic (PBT) according to domestic PBT environmental hazard thresholds. However, identified international end uses indicate the majority of chemical is expected to be consumed through industrial processes, which will minimise environmental releases. While no environmental monitoring information was identified for the chemical, secondary exposure is anticipated to be low.

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

Workers

During product formulation and packaging, dermal, inhalation (if dusts created) 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.

Worker exposure to this chemical at lower concentrations could also occur while using formulated products containing this chemical. 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 critical systemic long-term effects and skin sensitisation potential, the chemical could pose a risk to workers. Control measures to minimise exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section).

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.

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 oral, dermal and inhalation exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- 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 these chemicals are 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

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.

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

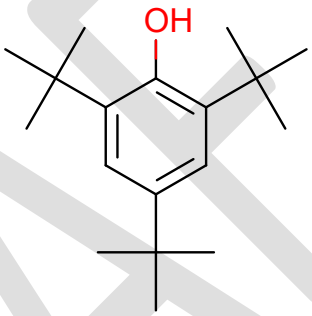
The Executive Director proposes to be satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory

Supporting information

Chemical identity

CAS number	732-26-3
CAS name	Phenol, 2,4,6-tris(1,1-dimethylethyl)-
Molecular formula	$C_{18}H_{30}O$
Associated names	2,4,6-Tri-*tert*-butylphenol (also known as 2,4,6-TTBP)
Molecular weight (g/mol)	262.43
SMILES (canonical)	OC=1C(=CC(=CC1C(C)(C)C)C(C)(C)C)C(C)(C)C
Structural formula	

Additional chemical identity information

The chemical is a member of the hydrocarbylphenol group (phenols with any kind of saturated or unsaturated hydrocarbon substituent).

Relevant physical and chemical properties

Physical form	Yellow solid
Melting point	131°C
Boiling point	278°C
Density	0.977 g/cm³ at 20°C
Vapour pressure	3.5 x 10-2 Pa (2.6 x 10-4 mm Hg) at 20°C
	7.3 x 10-2 Pa (5.5 x 10-4 mm Hg) at 25°C
Water solubility	0.063 mg/L at 20°C
pK_a	12.62

log K_{ow}	7.1 at 35°C

Source: ECHA 2019

Introduction and use

Australia

No specific Australian use, import, or manufacturing information has been identified. Australian safety datasheets (SDS) indicate use in consumer fuel additive products up to concentrations of 3%.

International

The chemical is primarily used as chemical intermediate but also as antioxidant in the formulation of fuels and lubricants. Four main use categories have been identified (US EPA 2021):

- Site-limited use as intermediate/reactant in processing at chemical facilities; 94% of the US production was reportedly for the manufacture of alkylphenols
- Site-limited use for fuel treatment in refineries and fuel facilities
- Commercial and consumer use in formulations intended for the maintenance or repair of motor vehicles and machinery
- Commercial and consumer use in lubricants and oils.

The US EPA noted the availability of fuel stabiliser products and fuel injector cleaners at retail locations and online (US EPA 2021). The US EPA did not identify users of the chemical in liquid lubricant and grease additives/antioxidants but found some indications of current use. In North American Product databases, the chemical was identified in one fuel additive product (concentration up to 0.14%) and one fuel injector cleaner (concentration up to 3%).

In Canada, the only reported use was as a fuel additive. Use as a lubricant additive was not identified (Government of Canada 2008).

In the 2000s, a total production volume up to 50 million pounds (approximately 22680 tonnes) per year was reported in the US (US EPA 2021). Canada imported volumes of the chemical were reported between 10–100 tonnes in the year 2000, decreasing to a maximum of 10 tonnes in 2006. In the European Union (EU), the chemical was registered between 100–1000 tonnes/year under the REACH regulation (REACH n.d.).

Existing Australian regulatory controls

AICIS

No existing controls are currently available for the chemical.

Public

No existing controls are currently available for the chemical.

Workers

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia, SWA).

No exposure standards are available for the chemical in Australia (SWA n.d.)

Environment

No existing controls are currently in place for the chemical.

International regulatory status

Exposure standards

No specific exposure standards have been identified for the chemical.

OECD

The chemical is on the OECD List of High Production Volume (HPV) Chemicals (Chemwatch n.d.).

Canada

The chemical is on the Canadian Domestic Substances List (DSL). Significant new activity (SNAc) provisions of the Canadian Environmental Protection Act, 1999 (CEPA) apply to the chemical, which trigger an obligation for a person to provide the Government of Canada with information about the chemical when proposing to use, import or manufacture for a significant new activity' (Government of Canada 2008).

European Union

The chemical is listed in Regulation (European Commission (EC)) 1223/2009 on cosmetic products, Annex II – List of substances prohibited in cosmetic products (Chemwatch n.d.).

The chemical is listed on the Candidate List of Substances of Very High Concern (SVHC) for eventual inclusion in Annex XIV of REACH (ECHA 2023). The reasons for inclusion are:

- Toxic for reproduction (Article 57c)
- PBT (Article 57d).

In the European Union (EU), the inclusion in the Candidate List brings immediate obligations for suppliers of the substance, such as:

- supplying a safety data sheet
- communicating on safe use
- responding to consumer requests within 45 days
- notifying ECHA if the article they produce contains an SVHC in quantities above one tonne per producer/importer per year and if the substance is present in those articles above a concentration of 0.1% (w/w).

United States of America

Under its Toxic Substances Control Act (TSCA), the US Environmental Protection Agency (EPA) has prohibited '*distribution in commerce of 2,4,6-TTBP and products containing 2,4,6-TTBP at concentrations above 0.3% in any container with a volume of less than 35 gallons for any use, in order to effectively prevent the use of 2,4,6-TTBP as an antioxidant in fuel additives or fuel injector cleaners by consumers and small commercial operations (e.g., automotive repair shops, marinas). This final rule also prohibits the processing and distribution in commerce of 2,4,6-TTBP, and products containing 2,4,6-TTBP at concentrations above 0.3 percent by weight, for use as an oil or lubricant additive, regardless of container size.*' (US EPA 2021).

Asia

The chemical is listed as Class I Specified Chemical Substances on Japan Chemical substances control law (CSCL). Class I Specified Chemical Substances are substances that are persistent, are highly bioaccummulative, and have a risk of long-term toxicity to humans or predator animals at higher trophic level (Chemwatch n.d.).

Human exposure

Public

Based on the available use information, the public may be exposed to the chemical by incidental skin and eye contact during use of retail fuel additive products. Exposure is expected to be intermittent and at low frequency.

The following assumptions are used to estimate consumer exposure during do-it-yourself (DIY) use of a fuel additive:

- Weight Fraction (WF): 3% (see **Introduction and use** section)
- Surface area exposed (SA): 12 cm^2 (Government of Canada 2024)
- Density (DSY) = 0.853 g/cm^3
- Film thickness (T) retained on skin: 15.88 × 10^{-3} cm (Government of Canada 2024)
- Body weight: 60 kg
- Estimated exposure = (WF × SA × T × DSY) / Body weight.

The estimated exposure, assuming 100% dermal absorption, is 0.08 mg/kg bw/day. This is expected to be a significant overestimate as dermal absorption is considered limited, based on:

- K_{ow} value (>6) indicating transfer rate between the stratum corneum and deeper layers of the epidermis will be slow and will limit absorption across the skin
- lower acute dermal toxicity in comparison to oral (see **Acute toxicity** section)
- read across from a structurally related chemical (dermal absorption <1%) (see **Toxicokinetics** section).

There is potential for secondary exposure through the environment as the chemical is persistent, bioaccumulative and toxic (PBT) according to domestic PBT environmental hazard thresholds. However, identified international end uses indicate the majority of chemical is expected to be consumed through industrial processes, which will minimise

environmental releases. While no environmental monitoring information was identified for the chemical, secondary exposure is anticipated to be low.

Health hazard information

Toxicokinetics

Limited data are available. Based on the molecular weight (<500 g/mol) and partition coefficient (log K_{ow} >6) the chemical is expected to be readily available following oral exposure, and to a lesser extent following dermal exposure. The transfer rate between the stratum corneum and deeper layers of the epidermis will be slow and will limit absorption across the skin. However, the skin sensitisation study indicates some potential for dermal absorption (see **Skin sensitisation** section). A structurally related chemical, 2,6-bis(1,1-dimethylethyl)-4-methyl-phenol (CAS No. 128-37-0) has an estimated dermal absorption of 0.41% based on in vitro experiments using pig skin (Government of Canada 2024).

In a toxicokinetic study, Sprague Dawley (SD) rats were orally administered a single dose of 260 mg/kg bw of the chemical. Peak blood concentrations were measured 15 to 60 min after dosing, indicating rapid absorption of the chemical through the gut. The chemical half-life (time required for concentration in plasma to decrease by 50%) was 18 min for the alpha phase (describing the rapidity of the distribution phase following administration) and 11.8 hours for the beta phase (describing the rapidity of the elimination phase occurring after drug distribution equilibrium). Maximum tissue concentrations were reached after 2 to 3 hours in the liver, 2 to 6 hours in the kidneys, 1.5 to 2.5 hours in the spleen and >24 hours in epididymal adipose tissues. The chemical was not detected in the urine or faeces. Only one metabolite, a 2,4,6-tri-tbutylphenoxy radical, was detected in the faeces and bile (Takahashi & Hiraga 1983).

Acute toxicity

Based on the available data, the chemical is expected to have moderate acute toxicity via oral route warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section).

Oral

In a GLP compliant acute oral toxicity study conducted in accordance with OECD Test Guideline (TG) 401, SD rats (n= 5/sex/dose) were given a single dose of the chemical by gavage at 200 or 2000 mg/kg bw. The median lethal dose (LD50) was <2000 mg/kg bw, based on 2/5 female rats that died 24 hours after ingestion. Additionally, 3/5 female rats and 1/5 male rats died a few days after ingestion. Reported sublethal signs of toxicity included ataxia, hunched posture, lethargy, decreased respiratory rate, laboured respiration, ptosis and loss of righting reflex. Treatment-related effects post pathology included ‘haemorrhagic lungs, dark or pale liver, patchy pallor of the liver or red coloured possible necrosis of the liver and haemorrhagic or pale gastric mucosa’. Surviving animals were reported to recover 3–10 days post-treatment. There was no mortality or observed adverse effects at the 200 mg/kg bw dose (ECHA 2020).

Dermal

Based on the available data, the chemical is expected to have low acute toxicity via dermal route.

In a GLP-compliant acute dermal toxicity study conducted in accordance with OECD TG 402, Wistar rats (n = 5/sex/dose) were treated with the chemical, applied under occlusive patch for 24 hours at 2000 mg/kg bw. No mortality and no clinical signs of toxicity were reported, except for a general erythema observed in 1/5 female rats 2 days post-exposure. The LD50 was reported to be greater than 2000 mg/kg bw (ECHA 2020).

Inhalation

No data are available for the chemical.

Corrosion/Irritation

Skin irritation

In a GLP-compliant skin irritation study conducted in accordance with OECD TG 404, 3 male New Zealand White (NZW) rabbits were treated with 0.5 g of the chemical in distilled water for 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours after patch removal. The following mean scores were reported based on observations at 24, 48 and 72 hours: 0.67 for erythema in one animal (effects were fully reversible within 72 hours), 0 for erythema in 2 animals and 0 for oedema in all animals (out of a maximum score of 4) (ECHA 2019, ECHA 2020). The chemical is considered at most slightly irritating to skin.

Eye irritation

In a GLP-compliant eye irritation study conducted in accordance with OECD TG 405, 0.1 mL of the chemical was instilled into 1 eye each of 2 males and 1 female, New Zealand White (NZW) rabbits. Observations were recorded at 1, 24, 48 and 72 hours after exposure. The maximum mean scores in any of the animals based on observations at 24, 48 and 72 hours: corneal opacity 0/4, iritis 0/2, conjunctival redness 0.33/3, chemosis 0/4. All reported effects were fully reversible within 72 hours (ECHA 2020). The chemical is considered at most slightly irritating to eyes.

Observation in humans

No data are available for the chemical.

Sensitisation

Based on the available data, the chemical is expected to be a skin sensitiser with low to moderate potency, which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section).

Skin sensitisation

In a GLP-compliant local lymph node assay (LLNA) conducted in accordance with OECD TG 429, groups of 5 female CBA/J mice received topical applications of the chemical at

0, 10, 25 or 50% in N, N-dimethylformamide. The reported stimulation indices (SI) were 1.7, 3.3 and 4.6 for concentrations of 10, 25 and 50%, respectively. The EC3 value was reported to be 22%, indicating moderate sensitisation potential (ECHA 2020).

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 QSAR Application Toolbox (OECD QSAR Toolbox v4.5).

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 was utilised 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 2018).

Observation in humans

No data are available for the chemical.

Repeat dose toxicity

Based on the available data, the chemical is expected to cause serious systemic health effects following repeated oral exposure, which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section). The liver was reported to be the main target organ. Significant increase in liver weight and histopathological changes in hepatocytes were reported in both the chronic oral toxicity study and combined 28-day repeat dose oral toxicity study with the reproduction/developmental toxicity screening. The necrotic effects observed after 6 months of exposure in a chronic toxicity study at approximately 25 mg/kg bw/day and totality of liver effects observed in females at 30 mg/kg bw/day are considered relevant for classification (ECHA 2020). Based on extrapolated equivalent guidance values considering the duration of exposure, classification in Category 2 is considered appropriate.

Oral

In a GLP-compliant combined 28-day repeat dose oral toxicity study with the reproduction/developmental toxicity screening conducted in accordance with OECD TG 422, Wistar rats (n = 10/sex/dose) were given the chemical by gavage at doses of 0, 3, 10 or 30 mg/kg bw/day. Male rats were exposed for 29 days, starting 2 weeks before mating and female rats were exposed 2 weeks prior mating and until lactation day 4 (41–56 days in total). The NOAEL was reported to be 3 mg/kg bw/day based on liver toxicity. No treatment-related mortality was reported. Statistically significant changes in haematological parameters (mainly in females at doses ≥10 mg/kg body weight/day) and biochemical parameters (in both sexes) were observed. However, these changes were not associated with any organ weight changes or organ dysfunction. For histopathological examination (5 animals/sex/dose), all collected tissues were microscopically examined in the control and high dose groups. In the low and mid-dose groups, it was reported that only the liver and caecum were examined in males, and the liver and spleen in females. The reported treatment-related effects included:

- enlargement of the liver at doses of 30 mg/kg bw/day in both sexes

- significantly increased liver weight (females at doses of ≥10 mg/kg bw/day; and males at ≥30 mg/kg bw/day)
- hepatocellular hypertrophy (females at doses of ≥10 mg/kg bw (slight at 10 mg/kg bw/day to moderate (30 mg/kg bw/day); males ≥30 mg/kg bw/day (minimal)
- hepatocellular necrosis at doses of 30 mg/kg bw/day in one male and one female
- mucosal hypertrophy in caecum in males at doses of ≥10 mg/kg bw/day
- lower haematopoiesis in spleen in females at doses of ≥10 mg/kg bw/day.

Based on the above effects a NOAEL of 3 mg/kg bw/day was reported (ECHA 2018; ECHA 2020).

In a range-finding study for the combined repeated dose oral toxicity study with reproduction/developmental toxicity screening test (ECHA 2020) female Wistar rats (n = 3/dose) were administered the chemical at doses of 50, 100 or 250 mg/kg bw/day for 10 days by oral gavage. Clinical signs of toxicity included: hunched posture, lethargy, piloerection, uncoordinated movements, abnormal gait, laboured breath. The study reported a decrease in body weight at doses of ≥100 mg/kg bw/day. Mortality was reported in 1/3 animals at the highest dose of 250 mg/kg bw/day, and on day 9, 2/3 animals were sacrificed before necroscopy. An increase in liver weight was reported at doses of 50 and 100 mg/kg bw/day. Changes in liver weight at the highest dose could not be determined as all animals were reported to be euthanised or died prior to necropsy. Histopathological examinations were not performed.

In a chronic oral toxicity study conducted in accordance with OECD TG 452, Wistar rats (n = 40/sex/dose) were fed the chemical at concentrations of 0, 30, 100, 300 or 1000 ppm (equivalent to 0, 2.51, 8.35, 25.05 and 83.5 mg/kg bw/day) in diet for 24 months. No treatment-related mortality or clinical signs were reported. A no-observed effect level (NOEL) of 30 ppm (2.51 mg/kg bw/day) was reported (Matsumoto et al. 1991). After 24 months treatment, notable effects included:

- focal necrosis, swelling and vacuolisation of liver cells at concentrations of ≥300 ppm after 6 months of exposure
- significantly increased liver weight (males at concentrations of ≥300 ppm; and females ≥100 ppm)
- significantly increased kidney weight (males at concentrations of ≥1000 ppm; and females ≥100 ppm)
- significantly increased adrenal weight at concentrations of 1000 ppm in both sexes
- microcytic anaemia (smaller than normal red blood cells) characterised by significant decrease in mean corpuscular volume (MCV) in males at concentrations of 1000 ppm; and females ≥ 300 ppm
- significantly higher levels of serum phospholipids and total cholesterol in males at concentrations of ≥100 ppm, and females ≥30 ppm.

Based on the histopathological effects reported at ≥300 ppm (equivalent to 25.05 mg/kg bw/day) in the liver (swelling, focal necrosis and vacuolisation of liver cells) from 6 months exposure, the chemical was considered toxic to the liver in this study (ECHA 2020; Matsumoto et al. 1991).

In a non-guideline sub-acute oral toxicity study, 10 male Wistar rats were orally administered the chemical at a dose of 1.98 mmol/kg bw/d (equivalent to 519.6 mg/kg bw/day) for up to 3 weeks. It was reported that all rats died between day 5 and 11 post-exposure. The reported signs of toxicity in the animals included haemothorax, haematocele, intracranial haematoma, intranasal haemorrhage, intramuscular haematoma, intratesticular and intra-epididymis haematoma (ECHA 2020; REACH n.d).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Genotoxicity

Based on the available in vitro data, the chemical is not expected to be genotoxic. No in vivo data was available.

Negative results were reported in the following genotoxicity studies (ECHA 2020; REACH nd):

- in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 and *Escherichia coli* WP2 uvrA with and without metabolic activation at concentrations up to 5000 µg/plate
- in a mammalian gene mutation assay (OECD TG 476) using mouse lymphoma cells L5178Y with and without metabolic activation at concentrations up to 60 µg/plate
- in a mammalian gene mutation assay (OECD TG 476) using Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 0.15 mg/mL.

Carcinogenicity

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

In a chronic oral toxicity study following OECD TG 452 groups of Wistar rats (n = 40/sex/dose) were fed the chemical at concentrations of 0, 30, 100, 300 or 1000 ppm in diet for 24 months (equivalent to 0, 2.51, 8.35, 25.05 and 83.5 mg/kg bw/day). No treatment-related mortality or clinical signs were reported (see **Repeat dose Toxicity – Oral** section). There was no significant increase in tumour incidence in treated groups compared with controls (Matsumoto et al. 1991). However histopathological examinations were only done for 3 organs: liver, kidney and adrenals (ECHA 2020).

Reproductive and development toxicity

Based on the available data, the chemical is expected to cause specific adverse effects on development, which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section). No adverse effects were reported on reproductive function. However, developmental effects including higher post-natal loss, decreased viability index and lower body weight of the pups were reported but were considered independent of maternal toxicity.

In a GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422, Wistar rats (n = 10/sex/dose) were administered the chemical by gavage at doses of 0, 3, 10 or 30 mg/kg bw/day from 14 days before mating for a total of 28 days for males and from 14 days before mating to day 4 of lactation for females for a total of 41–56 days.

There was no effect on the fertility index (reported to be 90, 100, 100 and 100% respectively at doses of 0, 3, 10 and 30 mg/kg bw/day). There were no changes observed in fertility functions (no dose-related changes in corpora lutea, implantation and duration of gestation). No further details on the oestrus cycle, resorptions, pre- and post-implantation loss were available (ECHA 2019; ECHA 2020).

The developmental NOAEL was reported to be 3 mg/kg bw/day based on the following effects observed at doses ≥10 mg/kg bw/day:

- significantly lower viability index of the pups (93.4% and 87.2% respectively, as compared with 100% in the control group)
- significant decrease in pup body weight on day 1 and day 4 of lactation. Clinical signs of toxicity in surviving pups included pallor, absence of milk in the stomach, missing tail and dehydrated appearance (ECHA 2018; ECHA 2020).

In this study, dams experienced moderate liver toxicity (see **Repeat Dose Toxicity** section) at doses ≥10mg/kg bw/day. However, no other clinical signs of maternal toxicity or severe changes in maternal bodyweight were reported. It was reported that maternal liver toxicity did not affect maternal care of the progeny. Reported effects on development were therefore not considered secondary to maternal toxicity.

Human health risk characterisation

Critical health effects

Adverse effects on the development of the unborn child can occur from acute exposures and therefore are relevant to the exposure scenario. Therefore, the critical health effects for risk characterisation for this chemical are potential developmental effects with a NOAEL of 3 mg/kg bw/day.

Public risk

A quantitative risk assessment to estimate a margin of exposure (MOE) is commonly used to characterise risks to human health associated with exposure to chemicals (ECB 2003). The MOE risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, an MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

Based on the estimated daily systemic exposure of 0.08 mg/kg bw/day (see **Human Exposure** section), the calculated MOE is 37. However, this estimate assumes a dermal absorption (DA) value of 100%, and based on the available information, it is expected that the dermal absorption would be well below 36% (DA value resulting in MOE of 100); therefore, an MOE >100 is predicted for infrequent DIY use.

Given the incidental nature of exposure and given the chemical has low to moderate potency, the risk of sensitisation is considered to be low.

References

Chemwatch (n.d.) *Galleria Chemica*, Chemwatch website, accessed January 2025.

ECHA (European Chemicals Agency) (2018) *Substance Evaluation Conclusion as required by REACH Article 48 and Evaluation Report for 2,4,6-tri-tert-butylphenol EC No 211-989-5 CAS No 732-26-3.* Accessed January 2025

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