Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

# Phenol, 4-(1,1-dimethylpropyl)- (4-tert-pentylphenol)

## Evaluation statement

**14 September 2021**

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# AICIS evaluation statement

## Subject of the evaluation

Phenol, 4-(1,1-dimethylpropyl)- (4-tert-pentylphenol).

## Chemical in this evaluation

| Name | CAS registry number |
|---|---|
| Phenol, 4-(1,1-dimethylpropyl)- | 80-46-6 |

## Reason for the evaluation

The Evaluation Selection Analysis (ESA) indicated a potential risk to human health.

## Parameters of evaluation

A human health risk assessment for all identified industrial uses of the chemical.

## Summary of evaluation

### Summary of introduction, use and end use

There is currently no available information on the chemical's use and volume of use in Australia.

Based on international use information, industrial use of the chemical is predominantly as an intermediate for the production of:

- perfumes and fragrances
- phenolic resins
- vulcanising agents for the curing of rubber.

Although some possible domestic use of the chemical in paints and varnishes and as a cleaning agent were identified, this is not expected to be widespread.

### Human health

#### Summary of health hazards

The critical health effects for risk characterisation include local effects (corrosive to skin, severe eye irritation, respiratory tract irritation and skin sensitisation). Adverse systemic long-term effects including reproductive effects and skin depigmentation cannot be ruled out.

Information on toxicokinetics of phenol, 4-(1,1-dimethylpropyl)- (4-*tert*-pentylphenol) is not available. The available information for closely related chemicals, 4-*tert*-butylphenol and 4-*tert*-octylphenol, indicates that 4-*tert*-pentylphenol is likely to be rapidly absorbed from the gastrointestinal tract and excreted mainly via urine and bile.

The chemical 4-*tert*-pentylphenol has low acute oral toxicity, with an oral LD50 of >2000 mg/kg bw derived from a acute oral study in rats. There was insufficient information to draw conclusions regarding acute dermal and inhalation toxicity. However, studies of 4-*tert*-butylphenol indicate that it is likely to have low acute dermal and inhalation toxicity.

The chemical is corrosive to skin, and although eye irritation was not tested, as it was considered scientifically unjustified, studies with 4-*tert*-butylphenol show that it can cause serious eye damage. The chemical, 4-*tert*-pentylphenol is also a skin sensitiser based on the positive results seen in a local lymph node assay (LLNA).

The chemical is not expected to cause serious systemic health effects following repeated oral exposure. Following repeated exposure, mucosal hypertrophy of the glandular stomach was noted in male and female rats at 600 mg/kg bw/day and these findings were considered adverse effects. A No-Observed-Adverse-Effect Level (NOAEL) of 200 mg/kg/day was determined based on the adverse microscopic findings in the stomach at the next higher dose (600 mg/kg bw/day). Repeated dose dermal studies did not show any effect through this route. No data are available on the repeated dose inhalation effects.

Negative results were reported for 4-*tert*-butylphenol in the in vitro bacterial reverse mutation assay and in vivo bone marrow micronucleus assay.

The carcinogenic potential of 4-*tert*-pentylphenol has not been investigated in standard studies, but on the basis of the negative findings in the mutagenicity tests, it is not expected to cause cancer by a genotoxic mechanism.

There are no reproductive toxicity data available for the chemical. Based on a 2 generation study conducted with a closely related chemical (4-*tert*-butylphenol), 4-*tert*-pentylphenol has potential to have reproductive toxicity. However, the information is insufficient to classify 4-*tert*-pentylphenol for reproductive toxicity. In a standard prenatal developmental toxicity study, there was some evidence of effects on the offspring, increased incidence of bent ribs and reduced foetal body weight (6% lower). However, these effects were considered to be secondary to the observed maternal toxicity.

The oestrogenic and androgenic activities of 4-*tert*-pentylphenol have been investigated in a series of screening studies with mammals. No potential for androgenic effects was identified in a Hershberger assay.The chemical has been shown to have weak oestrogenic activity, but there are currently no established adverse outcome pathways for weak oestrogenic activity.

## Health Hazard Classification

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 does not consider classification of physical hazards and environmental hazards.

| Health Hazards | Hazard Category | Hazard Statement |
|---|---|---|
| Skin corrosion / irritation | Category 1C | H314: Causes severe skin burns and eye damage |
| Skin sensitisation | Category 1 | H317: May cause an allergic skin reaction |

### Summary of health risk

**Public**

Based on its international use patterns, limited consumer use of the chemical is expected in Australia. Therefore, there are no identified risks to the public that require management.

However, risk management may be required if consumer uses occur in Australia given that the chemical is a corrosive, a skin sensitiser and there are uncertainties relating to its effects on fertility.

**Workers**

During product formulation and packaging, dermal, ocular and inhalation 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 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 acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented (see **Recommendations** section).

## Conclusions

The conclusions of this evaluation are based on the information described in the statement. Obligations to report additional information about hazards under section 100 of the Industrial Chemicals Act 2019 apply.

The Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks provided all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory. The proposed means of managing the risks identified during this evaluation are set out in the Recommendations section.

# Recommendations

## 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.

### Advice to Industry

The information in this report including recommended hazard classifications should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls.

Recommended control measures that could be implemented to manage the risk arising from dermal, ocular exposure and inhalation to the chemical 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
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills
- regularly cleaning equipment and work areas
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

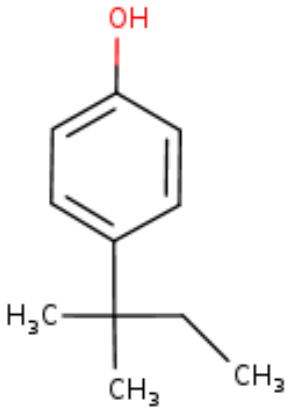
Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used.

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.

# Supporting information

## Chemical identity

| | |
|---|---|
| Synonyms | 4-*tert*-pentylphenol<br>1-hydroxy-4-(1,1-dimethylpropyl)benzene<br>2-methyl-2-*p*-hydroxyphenylbutane<br>4-*tert*-amylphenol<br>para- (or *p*-) *tert*-amylphenol<br>para- (or *p*-) *tert*-pentylphenol<br>ucar amyl phenol 4T<br>*p*-(alpha,alpha-dimethylpropyl)phenol<br>pentaphen |
| Structural formula |  |
| Molecular formula | C11H16O |
| Molecular weight (g/mol) | 164.2 |
| SMILES | CCC(C)(C)c1ccc(O)cc1- |

# Relevant physical and chemical properties

| | |
|---|---|
| Physical form | Solid, usually marketed in the form of a powder, flakes, or briquettes. Also available in molten form. |
| Melting point | 95 ºC |
| Boiling point | 262 ºC |
| Vapour pressure | 0.27 Pa at 25 °C |
| Water solubility | 168 mg/L |
| pKa | 10.4 |
| log $K_{ow}$ | 4.0 |

# Introduction and use

## Australia

No information is available on the use of this chemical in Australia.

## International

The following international uses have been identified through Galleria Chemica; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the Environment Agency (UK), European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers and the Substances and Preparations in Nordic countries (SPIN) database.

The predominant uses of the chemical are site-limited uses including:

- as an intermediate in the production of perfumes and fragrances
- as synthetic intermediate for phenolic resins (novolaks and resoles)
- in petroleum industry
- as an intermediate in vulcanising agent for the curing of rubber.

The chemical also has reported commercial uses including:

- in plastic and polymer products
- in printing ink.

The chemical has the following reported domestic uses in the SPIN database:

- as a cleaning and washing agent

- in paints and coating products.

However, it should be noted that SPIN does not distinguish between direct use of the chemical, or use of the materials that are produced from chemical reactions involving the chemical.

There is no evidence from available databases for use of this chemical in consumer industrial products, indicating that it is not likely to be widely available for domestic use. Uses identified in the Consumer Product Information Database were limited to disinfectants which have non-industrial uses in Australia.

The chemical has reported non-industrial uses including, as a germicide and fumigant.

# Existing Australian Regulatory controls

## AICIS

No specific controls are currently applicable to the chemical.

## Public

No specific controls are currently applicable to 4-*tert*-pentylphenol. Phenol and homologues with boiling point below 220 °C are listed in schedules in 2, 4, 5, 6 of the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2021). However, this chemical is not captured as its boiling point is 262 °C.

## Workers

The chemical is not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (Safe Work Australia).

# International regulatory status

## European Union

The chemical is listed on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2017). The reason for inclusion is 'Endocrine disrupting properties (Article 57(f) - environment)'. In the European Union (EU), companies could have legal obligations if the chemical that they produce, supply, or use is included on the candidate list whether on its own, in mixtures, or present in articles.

## Exposure standards

No specific exposure standards are available.

# Human exposure

## Workers

Internationally when used as an intermediate, the chemical is reported to be used either as flakes or in a molten form at elevated temperatures covered by a nitrogen blanket (ECHA, 2016). Therefore, inhalation exposure to dusts or fumes could occur. Based on the physicochemical properties, and urine monitoring data for workers handling *tert*-butyl phenols, skin contact is also expected to be a significant potential route of exposure.

# Health hazard information

Toxicological information for 4-*tert*-pentylphenol is limited. Toxicological data are available for its closest analogue, 4-*tert*-butylphenol (CAS No. 98-54-4). Both chemicals are branched alkyl phenols, substituted at the 4 position. They have similar molecular weights (*tert*-butyl phenol contains one less carbon atom in its alkyl chain) and physicochemical properties. As a result, 4-*tert*-butylphenol is presented as an analogue of 4-*tert*-pentylphenol for certain toxicological endpoints.

## Toxicokinetics

There are no data available for 4-*tert*-pentylphenol from toxicokinetic studies conducted in accordance with Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 417. Toxicokinetics of 2 closely related chemicals that differ in the chain length, 4-*tert*-butylphenol and 4-*tert*-octylphenol, have been studied in rats. These data will be used to predict the toxicokinetic behaviour of 4-*tert*-pentylphenol.

In a study reported by Freitag et al., (1982), radiolabelled 4-*tert*-butylphenol (147 µg/kg bw/day) was given to 3 male Wistar rats by gavage on three successive days. Mass balance measurements showed that 26.7% and 72.9% of the administered radioactivity was excreted in the faeces and urine, respectively. The proportion of the administered radioactivity remaining in the body 7 days after dosing was negligible (0.1%).

In another study, male Wistar rats (4 animals/dose) were given a single intravenous dose of 1.2–10.3 mg/kg bw radiolabelled 4-*tert*-butylphenol (Koster et al., 1981). Between 91% and 93% of the radioactivity was recovered from the urine and bile within 4 hours of dosing. Most of the applied radioactivity was excreted as glucuronide (65–71%) and sulfate (17–21%) conjugates of the chemical. The total recovery of radioactivity was 91–93%.

In vitro studies investigating the enzyme activity of the chemical and similar phenolic compounds in rat hepatocytes and the human liver supported the results showing conjugation in the in vivo rat study with intravenously injected p-*tert*-butylphenol.

Studies with 4-*tert*-octylphenol showed that after oral dosing to rats the chemical was rapidly absorbed from the gastrointestinal tract. Bioavailability was reported to vary between strains. In an oral study in Sprague Dawley (SD) rats, there were no significant differences in tissue concentrations following single and repeated treatment indicating no bioaccumulation of 4-*tert*-octylphenol (NICNAS, 2020).

The above studies indicate that 4-*tert*-pentylphenol is likely to be rapidly absorbed from the gastrointestinal tract and excreted mainly via urine and bile. Similar to other alkyl phenols, the chemical is expected to undergo rapid first pass metabolism by phase I and phase II

enzymes in the liver. Detoxification pathways include hydroxylation, glucuronidation and sulfation.

Based on the water solubility, the partition coefficient of 4 and the molecular weight of 168 g/mol, high dermal bioavailability can be assumed. There is evidence of dermal absorption from urine monitoring data for workers handling 4-*tert*-butyl phenol (NICNAS 2016).

## Acute toxicity

### Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure.

In an oral acute toxicity study performed according to the OECD TG 401 and good laboratory practice (GLP), five SD rats (5 animals/sex) received 2000 mg/kg bw of 4-*tert*-pentylphenol suspended in arachis oil and administered by gavage. No mortality and no signs of systemic toxicity were noted during the observation period (REACH). Based on the available data, the chemical has low acute oral toxicity.

Similarly, the oral mean lethal dose (LD50) values are reported for 4-*tert*-butylphenol (>2000 mg/kg bw) in rats (NICNAS, 2016).

### Dermal

No information is available on the acute dermal toxicity of 4-*tert*-pentylphenol.

Based on the reported LD50 value of >2000 mg/kg from a study similar to the OECD TG 402 for 4-*tert*-butyl phenol (NICNAS, 2016), the dermal toxicity of 4-*tert*-pentylphenol is expected to be low.

### Inhalation

No information is available on the acute inhalation toxicity of 4-*tert*-pentylphenol. A limit test (OPPTS 870.1300, Acute Inhalation Toxicity) was performed with 4-*tert*-butylphenol. Rats ((SD) five/sex) were exposed whole body for 4 h to the chemical as a dust aerosol of 5,600 mg/m$^3$ (median particle diameter of 3.6 micrometres) with an additional vapour component of 30 mg/m$^3$. Clinical signs observed on the day of exposure and up to 7 days after exposure included mucosal irritation (perinasal, perioral, and periocular encrustation) and signs of respiratory distress (audible respiration, gasping, and decreased respiration rate).

Within 1 to 2 days following exposure of the rats to the chemical resulted in a mortality rate of 20%. The necropsied animals showed dark red or purple discolouration of the lungs and/or kidneys. No macroscopic lesions were observed in the surviving animals (EU RAR, 2008). Based on these observations,the acute systemic inhalation toxicity of 4-*tert*-pentylphenol is expected to be low.

## Corrosion/Irritation

### Skin irritation

Based on the available data, the chemical is corrosive to skin and warrants hazard classification (see **Recommendations** section).

In an acute dermal irritation study conducted according to OECD TG 404, 4-*tert*-pentylphenol was applied 0.5 g in a 0.5 mL water suspension to the dorsal skin (2.5 cm x 2.5 cm) of New Zealand White rabbits (2 males; 1 female) for 4 hours. Green-coloured necrosis and severe oedema were noted at 1 treated skin site, 1 and 24 hours after treatment. Moderate erythema surrounded the other skin reactions at the 24 hour observation. Adverse reactions prevented accurate evaluation of erythema and oedema at this treated skin site at the 48 and 72 hour and 7 day observations.

The reactions included a hardened dark brown/black coloured scab surrounded by moderate erythema, dried blood, scar tissue, thickening of the skin, glossy skin and reduced re-growth of fur. After the 14 days s of treatment scarred tissue, glossy skin and reduced regrowth of fur were observed at these treated skin sites. Scar tissue is indicative of full thickness destruction and is; therefore, a sign of corrosion (REACH).

There is also evidence of irritation at low doses from the 90-day repeat dose dermal toxicity study, and a no oberseved effect level (NOEL) of 2.5 mg/kg bw/day was derived for local effects (see **Repeat Dose Dermal toxicity**).

### Eye irritation

In the acute dermal irritation study described above, 4-*tert*-pentylphenol was found to be corrosive to skin. As such, an eye irritation study was considered scientifically unjustified.

A closely related chemical, 4-*tert*-butylphenol, was corrosive to eyes. In a study similar to the OECD TG 404, 4-*tert*-butylphenol produced severe corneal injury, iritis and severe conjunctival irritation. The corneal opacity did not reverse within 21 days (NICNAS, 2016).

### Respiratory tract irritation

Although not directly studied in animals, on the basis of the results from the skin irritation studies it can be anticipated that 4-*tert*-pentylphenol has the potential to cause respiratory tract irritation. There is some information on the potential of 4-*tert*-butylphenol to cause irritation of the respiratory tract from the acute inhalation toxicity study.

### Observation in humans

There are some reported incidents associated with exposure to end-use products containing 4-*tert*-pentylphenol. Dermal, ocular, and inhalation are the primary routes of exposure. Dermal exposure is considered a very important route of exposure. Most of the incidents are related to irritation. The most common symptoms reported for cases of inhalation exposure were respiratory irritation/burning, irritation to mouth/throat/nose, coughing/choking, shortness of breath, dizziness, flu-like symptoms, and headache. Eye pain, burning of eyes, conjunctivitis, blurring vision, and acute inflammation have been reported in ocular exposure incidents. Neurological effects, such as dizziness, headache and blurred vision have also been reported (HSDB).

## Sensitisation

### Skin sensitisation

The chemical was found to be sensitising in a LLNA conducted in accordance with OECD TG 429. CBA female mice (n = 5/group) received daily topical applications of 25 µL of 100, 50 or 25% of the chemical in dimethyl sulfoxide (maximum soluble concentration, 3.41 g/mL) for 3 consecutive days. Hexyl cinnamaldehyde (CAS No 101-86-0) was used as the positve control. At all test concentrations of 4-*tert*-pentylphenol, the stimulation index (SI) was 3 times (or more) higher than the negative control (dimethyl sulfoxide) (REACH).

## Repeat dose toxicity

### Oral

In a study similar to OECD TG 408, 3 treatment groups of 20 male and 20 female CD® [Crl:CD®(SD)] rats were administered 4-*tert*-pentylphenol by gavage, at dose levels of 50, 200, or 600 mg/kg bw/day for 13 weeks. One additional group of 20 animals/sex served as the control and received the vehicle, 0.5% methylcellulose in deionized water. The vehicle or test article was administered to the appropriate groups once daily in a dose volume of 10 mL/kg.

There was no chemical treatment related mortality, adverse clinical findings, or ophthalmologic findings. Male body weight at 600 mg/kg/day group was lower for the entire treatment period and females at this dose were affected during weeks 11 to 13. Food consumption was only transiently lower at this dose level during week 1. No test chemical-related effects were noted in the functional observational battery (FOB) or motor activity evaluations.

Minor clinical pathology changes in males and/or females at 600 mg/kg/day groups included: minimal prolongations in prothrombin time at termination; slight reductions in glucose on days 7 and 45; slight decreases in albumin at all intervals; and moderate increases in urine volume with a corresponding decrease in specific gravity. These changes were not considered adverse as they were not biologically relevant based on their sporadic nature, small magnitude and lack of correlative findings.

In male rats, dosed at 200 and 600 mg/kg bw/day, decreased thymus weights were noted but there were no microscopic correlates for these weight changes. There were no effects on indirect tests (red cell mass, cholesterol) or direct tests of thyroid function (T3, T4 or TSH levels) or histopathology to indicate any effect on the thyroid.Test substance treatment related macroscopic findings were limited to the nonglandular stomach and included swelling/thickening, nodule, and red to tan foci. These observations correlated with epithelial hyperplasia of the nonglandular stomach in males at ≥50 mg/kg/day and in females at ≥200 mg/kg bw/day. The hyperplasia of the nonglandular stomach was characterised by the thickening of the epithelium with hyperkeratosis and was associated with minimal to mild nonglandular erosion/ulceration within the limiting ridge in a male and female dosed at 600 mg/kg/day.

Mucosal hypertrophy of the glandular stomach was noted in males and females at 600 mg/kg bw/day. Parietal cells within the adjacent glandular mucosa were minimally enlarged in 2 males and one female at 600 mg/kg bw/day. These findings at 600 mg/kg bw/day were considered adverse effects. All other microscopic observations were considered to be incidental. There was no evidence of neurotoxicity or reproductive effects in any of the parameters examined.

A no observed adverse effect level (NOAEL) of 200 mg/kg/day was determined based on progressively lower body weight among males throughout the study and the adverse microscopic findings in the stomach in both sexes at 600 mg/kg/day (HSDB; REACH).

### Dermal

In a subchronic dermal study, conducted according to EPA guidelines (EPA OPP 82-3; Subchronic Dermal Toxicity 90 Days), SD rats (10 rats/sex/dose) were exposed to 0, 2.5, 10, or 25 mg/kg bw/day of 4-*tert*-pentylphenol in ethanol (6 mL of 0, 0.42, 1.67 and 4.17 mg/mL 4-*tert*-pentylphenol, respectively), for 6 hours a day, 5 days a week for 13 weeks. The dose was held in contact with the skin using a porous 2 x 3 inch 12-ply gauze dressing which was secured in place using a self-adherent wrap. Control animals were treated with the vehicle under the same experimental conditions and at an equivalent dose volume.

No treatment related mortality or clinical signs of toxicity were observed during the study. Substantial dose dependent dermal irritation was produced by the test chemical in the 10 and 25 mg/kg bw/day groups (scores not provided). The dermal findings in these groups included erythema and desquamation, which progressed to eschar formation with subsequent eschar exfoliation. The incidence and severity of the dermal irritation were increased in the 25 mg/kg bw/day group where the eschar formation progressed to cover >50% but <75% of the application site in 2 males and 5 females. Ulcerations were also observed within exposure sites of 3 males and 5 females in the 25 mg/kg bw/day group. Eschar formation in the 10 mg/kg bw/day group progressed to cover >10%, whereas eschar formation progressed to cover <25% of the application site in 1 male and 3 females. No signs of dermal irritation were observed for males or females in the control or 2.5 mg/kg bw/day group.

There were no apparent chemical related changes noted among the groups with respect to body weight, food consumption, ophthalmology, clinical pathology, necropsy or organ weight data. Similarly, no treatment related histopathological changes were noted in any of the study animals beyond the dermal changes noted above.

A dermal NOAEL for systemic effects of 25 mg/kg bw/day was established for 4-*tert*-pentylphenol in this study based on the absence of any systemic toxicity up to the highest dose tested.

A NOAEL of 2.5 mg/kg bw/day was established for skin irritation effects of 4-*tert*-pentylphenol in rats (REACH, HSDB).

### Inhalation

No data are available on the chemical.

### Observation in humans

The occurrence of vitiligo, a depigmentation of the skin has been associated with exposure to phenolic and catecholic compounds including 4-*tert*-butlyphenol. Limited data are available for 4-*tert*-pentylphenol. No cases of depigmentation were reported in a study of 129 men exposed to the chemical during manufacture (O'Sullivan and Stevenson, 1981). However, several workers using detergents containing the chemical developed depigmentation. Studies of induction of the condition in black guinea pigs and mice of both sexes are described. Depigmentation of certain sites is reported with 4-*tert*-pentylphenol (Hazardous Substances Data Bank (HSDB).

## Genotoxicity

### In vitro

Negative results were reported for 4-*tert*-butylphenol in a bacterial reverse mutation assay using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537, at concentrations up to 5000 µg/plate. All 4 bacterial strains exhibited mutagenic responses to the appropriate positive control substances (REACH).

In a mouse lymphoma gene mutation assay conducted to US EPA guidelines, 4-*tert*-pentylphenol was tested without activation at concentrations up to 40 µg/mL and with activation at concentrations up to 10 µg/mL (Lloyd, 1990). Although in some individual cell cultures treated with 4-*tert*-pentylphenol there was a higher incidence of mutant colonies than in controls, there was no relationship with dose and this was considered to be a chance finding related to biological variation in the control cultures.

### In vivo

In a bone marrow micronucleus assay, 4-*tert*-pentylphenol was administered orally to CD1 strain mice (5/sex/dose level) at dose levels of 0, 62.5, 250, 1000, 4000 mg/kg in maize oil. No signs of toxicity in the bone marrow cells were observed. There were no treatment related effects on the frequency of chromosomal aberrations. The chemical was not mutagenic under the conditions of this study (REACH).

## Carcinogenicity

No data are available on the chemical.

## Reproductive and development toxicity

Limited data are available for the chemical. The related chemical p-*tert*-butylphenol is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Reproductive toxicity - Category 2' with the hazard statement 'H361f (Suspected of damaging fertility)'. The chemical caused effects on ovarian weight, the incidence of vaginal atrophy and of primordial follicles, the number of implantation sites and litter size. It is uncertain whether effects related to reproductive organs in females are substance-specific or due to weight reduction and pregnancy. No effects on female bodyweight or effects in the ovaries were observed in the repeated dose toxicity study with p-*tert*-pentylphenol.

For both the chemical and related chemical p-*tert*-butylphenol, developmental effects were only observed secondary to maternal toxicity.

Overall, based on the weight of evidence, classification of the chemical is not considered warranted.

#### ***Reproductive Toxicity***

No specific reproductive toxicity studies were identified for the chemical. A 90 day oral repeated dose toxicity study (see **Repeated dose toxicity: oral**) found no evidence of tissue alterations in the testes and ovaries. Gonad weight for rats of both sexes treated with the

chemical at doses up to 600 mg/kg bw/day were not affected. No effects were noted in oestrous cycle or sperm evaluations (REACH).

In a 2 generation reproduction study performed according to OECD TG 416, SD rats were exposed to 4-*tert*-butylphenol (REACH). The chemical was given orally in the diet at 0, 800, 2500 and 7500 mg/kg, corresponding approximately to 0, 70, 200 and 600 mg/kg bw/day. In the parental (F0) generation, 28 rats/sex/group were mated to produce the first group of offspring (F1). Animals from the F1 generation (24/sex/group) were subsequently mated to produce the second generation of pups (F2).

The following results were reported: at 2500 ppm. Statistically significant decreases in weight gain were reported in F0 and F1 animals prior to mating. During gestation and lactation, statistically significant reductions in body weight gain were reported at 7500 ppm. Statistically significant reductions in food consumption were reported from 2500 ppm in F0 and F1 animals prior to mating. No effects on mating performance, fertility or duration of gestation were reported at concentrations up to 7500 ppm. Slight decreases in the number of implantation sites, live pups born and viability of the pups were reported at 7500 ppm.

Decreases in pup body weights and litter weights in the F1 and F2 generation from 2500 ppm were reported on lactation day 14, as well as a smaller litter size. Pup survival was reduced, particularly over days 1–4 of lactation when six different litters had more than 3 pup mortalities, and in 2 of these litters mortality occurred in all pups. Delays in vaginal opening and preputial separation in the F1 generation were reported at 7500 ppm. In the F0 and F1 female generations, marked increases in atrophy of the vaginal epithelium were reported from 2500 ppm. The severity in the vaginal epithelial atrophy in the F1 generation was greater compared to the F0 generation. Increases in the incidence of primordial follicles with concurrent decreases in the incidence of growing follicles were reported in the F0 and F1 females at 7500 ppm. This effect was also more pronounced in the F1 generation. From 2500 ppm, statistically significant decreases in the weight of the ovaries were reported in the F0 generation but this was only seen at 7500 ppm in the F1 generation. A NOAEL at 800 ppm (corresponding to 70 mg/kg bw/day) was derived for effects on reproduction and development from the 2-generation study.

***Developmental Toxicity***

In a standard prenatal developmental toxicity study, 4-*tert*-pentylphenol was administered by gavage to pregnant SD rats (25 per dose) from gestation day 6 to 15 (Siglin, 1991). Doses were 0, 50, 200 and 500 mg/kg/day and dams and litters were sacrificed and examined after termination of the study on gestation day 20. There was evidence of maternal toxicity at the top 2 doses; the incidence of hair loss, urine stains, abnormal respiratory sounds and mucoid/soft stools were increased and body weight gain and food consumption were decreased by 10–50%, compared with controls. At the top dose of 500 mg/kg bw/day there was evidence of effects on offspring; the incidence of bent ribs was increased and foetal body weight was decreased by 6%. However, these effects are considered secondary to the significant maternal toxicity seen. The NOAEL was 50 mg/kg bw/day for maternal toxicity and 200 mg/kg bw/day based on the presence of bent ribs at the top dose. Developmental effects were only observed secondary to maternal toxicity (REACH).

## Endocrine effects

The chemical 4-*tert*-pentylphenol was screened for oestrogenic activity with an in vitro assay and an in vivo uterotrophic assay. In addition, the androgenic activity of 4-*tert*-pentylphenol was investigated in vivo in castrated rats in a Hershberger assay. The uterotrophic and

Hershberger assays have been used for a number of years in several laboratories worldwide to screen for endocrine activity. The in vitro assay measured the binding of alkylphenols to the oestrogen receptor in rat uterine tissue (Blair et al., 2000). In this assay the oestrogenic activity of 4-*tert*-pentylphenol was found to be five orders of magnitude lower than that of 17ß-oestradiol, but was of a similar order of magnitude as that of 4-*tert*-butylphenol and 4-*tert*-octylphenol.

In the in vivo uterotrophic assay, 4-*tert*-pentylphenol was administered to 20-day old female rats (Crj: CD strain; 6 per dose) by subcutaneous injection (0, 8, 200 and 600 mg/kg bw/day) for 3 days, and uteri were weighed 24 hours after the final dose (Yamasaki et al., 2003). At 8, 40 and 200 mg/kg bw/day, uterine weights were 94.5, 14.9 and 246% of negative control values respectively, indicative of oestrogenic activity. By comparison, in positive control animals given 17ß-oestradiol at 2, 20 or 200 mg/kg bw/day, uterine weights were 221, 409 and 409% of negative control values, respectively (Yamasaki et al., 2002).

In the Hershberger assay, 4-*tert*-pentylphenol (0, 50, 200 or 600 mg/kg bw/day) was administered to 8-week old Crj: CD rats (6 per dose) by gavage for 10 days (Yamasaki et al., 2003). Positive control animals were injected with testosterone propionate (0.2 mg/kg bw/day) subcutaneously on the same days. The study was terminated 24 hours after the final dose and the organs of the male reproductive tract (glans penis, Cowper's gland, prostate, seminal vesicles) and bulbocavernosus/levator ani muscle were weighed. None of these parameters were affected in animals given 4-*tert*-pentylphenol alone, but in positive control animals the weights of these organs were increased.

Oestrogenic activity of 4-*tert*-pentylphenol was also demonstrated using an oestrogen inducible strain of yeast (*Saccharomyces cerevisiae*) that expresses the human oestrogen receptor. Using the natural oestrogen 17ß-oestradiol for comparison, the data indicated that both the position (para > meta > ortho) and branching (*tert*iary > secondary = normal) of the alkyl group on phenols affect oestrogenicity. In this assay 4-*tert*-pentylphenol, was found to be 100,000-fold less potent than the natural oestrogen, 17ß-oestradiol (HSDB).

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