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

Propyl and butyl phenols

Evaluation statement

26 June 2023

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

Propyl and butyl phenols

Chemicals in this evaluation

Name	CAS registry number
Phenol, 2-propyl-	644-35-9
Phenol, 4-propyl-	645-56-7
Phenol, 2-(1-methylethyl)-	88-69-7
Phenol, 3-(1-methylethyl)-	618-45-1
Phenol, 4-(1-methylethyl)-	99-89-8
Phenol, 4-butyl-	1638-22-8
Phenol, (2-methylpropyl)-	31195-95-6
Phenol, 2-(1-methylpropyl)-	89-72-5
Phenol, 4-(1-methylpropyl)-	99-71-8
Phenol, 2-(1,1-dimethylethyl)-	88-18-6
Phenol, 3-(1,1-dimethylethyl)-	585-34-2

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

Chemicals in this group are propyl and butyl phenols listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of chemicals itemised in this group. These chemicals have been assessed as a group as they are expected to have similar toxicity and end uses.

In the absence of toxicological data, endpoint information for identified structurally related chemicals are used to predict the toxicity of chemicals in this evaluation where appropriate.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of these chemicals in Australia.

Internationally these chemicals are reported to have a number of commercial and site-limited uses, such as in fuel additives corrosion inhibitors and chemical intermediates.

Limited data are available about the presence of these chemicals in consumer products. Chemicals in this group, except CAS No. 618-45-1, are included in the list of fragrance ingredients published by the International Fragrance Association (IFRA) indicating potential domestic and cosmetic use. There is limited evidence of use in cosmetic products. Information from a previously assessed structurally related chemical indicate use of the chemical in consumer products is likely, although at low concentrations.

Human health

Summary of health hazards

The critical health effect for risk characterisation is corrosivity. These chemicals are also expected to have low to moderate acute toxicity.

Based on the available data chemicals in this group are considered to be corrosive. In a dermal irritation study in rabbits, 2-*tert*-butylphenol (CAS No. 88-18-6) and 2-*sec*-butylphenol (CAS No. 89-72-5) caused corrosive effects following exposures at ≥3 minutes.

Chemicals in this group are expected to have moderate acute oral toxicity. The reported median lethal dose (LD50) values were mostly in the range 300–2000 mg/kg body weight (bw)/day. Reported sublethal signs of toxicity included increased salivation and ptosis. Limited data are available for dermal toxicity. In a single guideline study with 2-*tert*-butylphenol (CAS No. 88-18-6) the LD50 was reported to be 1373 mg/kg bw and 705 mg/kg bw in males and females, respectively. In guideline studies with the structurally related chemicals p-*tert*-butylphenol and 3-propylphenol LD50 values were >2000 mg/kg bw/day. It is not possible to draw conclusions on the classification of this group as a whole. Limited data are available for inhalation toxicity. Based on an LC50 value (aerosol) of between 1.08–4.98 mg/L for the structurally related chemical 3-propylphenol, the chemicals are expected to have moderate acute inhalation toxicity.

Data on the reproductive toxicity of these chemicals is limited. There were no effects on reproductive parameters in a single guideline study (OECD TG 422) with 2-*sec*-butylphenol. Tissue alterations in reproductive organs were not observed in repeated dose toxicity studies. Based on a 2 generation study conducted with the structurally related chemical, 4-*tert*-butylphenol, the potential for these chemicals to cause reproductive toxicity at high doses cannot be ruled out. However, observed effects occurred only at the high dose and there was not an obvious severe alteration of reproductive performance.

Although some evidence indicates that chemicals in this group may have weak oestrogenic activity, there are currently no established adverse outcome pathways for weak oestrogenic activity.

. Based on the available data these chemicals are not expected:

- to cause serious systemic health effects following repeated exposure
- to have genotoxic potential.

Hazard classifications relevant for worker health and safety

These chemicals satisfy 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.

The classification for acute dermal toxicity applies only to 2-*tert*-butylphenol (CAS No. 88-18-6)

Health hazards	Hazard category	Hazard statement
Acute toxicity - oral	Acute Tox. 4	H302 (Harmful if swallowed)
Acute toxicity - dermal	Acute Tox. 4	H312 (Harmful in contact with skin)
Acute toxicity - inhalation	Acute Tox. 4	H332 (Harmful if inhaled)
Corrosion/skin irritation	Skin Corr. 1A	H314 (Causes severe skin burns and eye damage)
Serious damage to eyes/eye irritation	Eye Damage 1	H318: Causes serious eye damage

Summary of health risk

Public

Based on the available use information, the public may be exposed to these chemicals:

- by direct skin contact during use of cosmetic and domestic products
- by incidental skin and eye contact during use of domestic products
- by inhaling vapours when applying spray application products.

Given the low chemical concentrations expected to be in use in personal care and domestic products (<1%), there are no identified risks to the public from these uses that require risk management.

Workers

During product formulation, 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of preparation and work practices employed.

Given the critical local health effects, these chemicals 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**). Control measures implemented due to the corrosivity classification are expected to be sufficient to protect workers from any potential reproductive health effects.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the 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 at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from ocular, dermal or inhalation exposure to these chemicals 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
- 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 these hazardous chemicals depend on the physical form and how these chemicals are 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.

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 conclusions of this evaluation are based on the information described in this statement.

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

Note: Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.

Supporting information

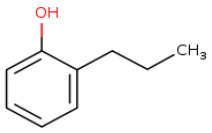
Grouping rationale

Chemicals in this group are propyl and butyl phenols. They are similar in structure, molecular weight, and physicochemical properties. Structurally they differ only by the position of propyl and butyl groups on the phenolic ring and the degree of branching of the alkyl chain. While the substitution patterns on benzene rings can lead to major differences in toxicological properties, chemicals in this group and other previously assessed short chain alkylphenols NICNAS 2014; 2020) show a similar hazard profile. They are expected to have similar physico-chemical properties and toxicity. All chemicals in this group have similar end uses, typically as fragrances in domestic and commercial cleaning products and as intermediates.

The evaluation does not cover propyl and butyl phenols previously assessed under NICNAS, 3-propylphenol (CAS No. 621-27-2), 4-*tert*-butylphenol (CAS No. 98-54-4) and 4-*tert*-pentylphenol (CAS No. 80-46-6). However, data on these chemicals have been included for read across purposes.

Chemical identity

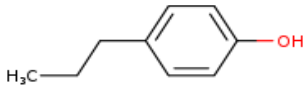
Chemical name	Phenol, 2-propyl-
CAS No.	644-35-9
Synonyms	1-(2-hydroxyphenyl)propane
Molecular formula	C9H12O
Molecular weight (g/mol)	136.19
SMILES	CCCc1ccccc1O
Structural formula	



Chemical name	Phenol, 4-propyl-
CAS No.	645-56-7
Synonyms	4-n-propylphenol

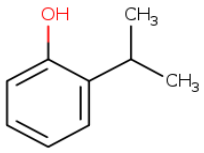
Molecular formula	C9H12O
Molecular weight (g/mol)	136.19
SMILES	CCCc1ccc(O)cc1

Structural formula:



Chemical name	Phenol, 2-(1-methylethyl)-
CAS No.	88-69-7
Synonyms	o-isopropyl phenol
	2-isopropylphenol
Molecular formula	C9H12O
Molecular weight (g/mol)	136.19
SMILES	CC(C)c1ccccc1O

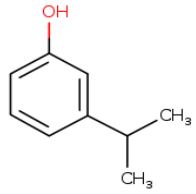
Structural formula:



Chemical name	Phenol, 3-(1-methylethyl)-
CAS No.	618-45-1
Synonyms	3-isopropylphenol

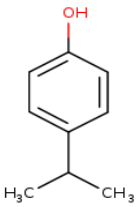
Molecular formula	C9H12O
Molecular weight	136.19
SMILES	CC(C)c1cccc(O)c1

Structural formula:



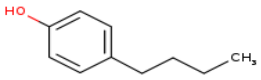
Chemical name	Phenol, 4-(1-methyethyl)-
CAS No.	99-89-8
Synonyms	p-isopropylphenol
	p-cumenol
	p-hydroxycumene
Molecular formula	C9H12O
Molecular weight (g/mol)	136.19
SMILES	CC(C)c1ccc(O)cc1

Structural formula

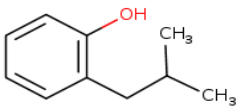


Chemical name	Phenol, 4-butyl-
CAS No.	1638-22-8

Synonyms	4-n-butylphenol
	p-butylphenol
Molecular formula	C10H14O
Molecular weight (g/mol)	150.22
SMILES	CCCCc1ccc(O)cc1
Structural formula	

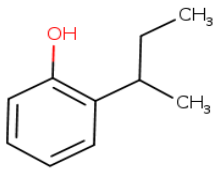


Chemical name	Phenol, (2-methylpropyl)-
CAS No.	31195-95-6
Synonyms	Isobutylphenol
Molecular formula	C10H14O
Molecular weight (g/mol)	150.22
SMILES	CC(C)Cc1ccccc1O
Structural formula	

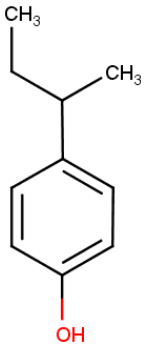


Chemical name	Phenol, 2-(1-methylpropyl)-
CAS No.	89-72-5

Synonyms	2-*sec*-butylphenol
Molecular formula	C10H14O
Molecular weight (g/mol)	150.22
SMILES	CCC(C)c1ccccc1O
Structural formula	

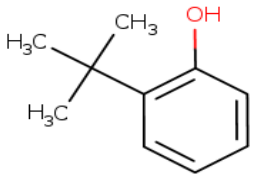


Chemical name	Phenol, 4-(1-methylpropyl)-
CAS No.	99-71-8
Synonyms	4-*sec*-butylphenol
Molecular formula	C10H14O
Molecular weight (g/mol)	150.22
SMILES	CCC(C)c1ccc(O)cc1
Structural formula	

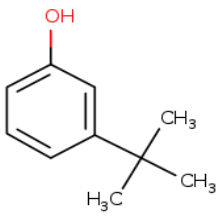


Chemical name	Phenol, 2-(1,1-dimethylethyl)-
CAS No.	88-18-6

Synonyms	2-*tert*-butylphenol
	phenol, o-*tert*-butyl-
Molecular formula	C10H14O
Molecular weight (g/mol)	150.22
SMILES	CC(C)(C)c1ccccc1O
Structural formula	



Chemical name	Phenol, 3-(1,1-dimethylethyl)-
CAS No.	585-34-2
Synonyms	3-*tert*-butylphenol
	phenol, 3-(1-dimethylethyl)-
Molecular formula	C10H14O
Molecular weight (g/mol)	150.22
SMILES	CC(C)(C)c1cccc(O)c1
Structural formula	



Relevant physical and chemical properties

Chemicals in this group are mostly liquids at ambient temperatures, except 3 chemicals, which have melting points above 40ºC. They have boiling points between 213ºC and 240ºC and are moderately soluble in water. Most of the alkylphenols in this group have dissociation constants >10. Based on the calculated vapour pressures of some of these chemicals (0.05 mm Hg at 25ºC), chemicals in this group are expected to have low volatility. All chemicals in this group have log K_{OW} = 2.1 – 3.46 at 20°C

Introduction and use

Australia

There is currently no specific information about the introduction, use and end use of these chemicals in Australia.

The structurally related chemical 3-propylphenol was previously assessed for the following proposed usage concentrations:

- leave on cosmetic products (≤0.1%),
- air fresheners and rinse-off cosmetic products (≤0.4%)
- other household products (≤0.7%).

International

The following international uses have been identified through:

- European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers
- the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR)
- Galleria Chemica
- Substances and Preparations in the Nordic countries (SPIN)
- the European Commission Cosmetic Ingredients and Substances (CosIng) database
- IFRA Transparency List and OECD High Production Volume chemical program (OECD HPV).

All chemicals in this group, except CAS No. 618-45-1, are included in the list of fragrance ingredients used in consumer goods published by the IFRA (The IFRA transparency list (IFRA 2022b). Therefore, these chemicals are considered to have potential use in cosmetic and domestic products. Only 4-isopropylphenol (CAS No. 99-89-8) is listed in the (CosIng) database. These chemicals are not listed in the ‘Compilation of Ingredients Used in Cosmetics in the United States’, although individual chemicals used at low concentrations in compound fragrances are not reported in this compilation (Personal Care Products Council).

Limited data are available for chemical concentrations used in consumer products.

Chemicals in this group have reported commercial uses, including as:

- viscosity adjustors
- fuel additives

- process regulators.

Chemicals in this group have reported site limited uses, including as:

- intermediates in the manufacture of resins, plasticisers, surface-active agents and fragrances
- stabilisers
- vulcanising agents
- polymer component of a formulation.

Some chemicals in this group have reported non-industrial uses including, as pesticides and germicides.

Existing Australian regulatory controls

AICIS

No specific controls are currently applicable to these chemicals.

Public

No specific controls are currently applicable to most chemicals in this group. Phenol and homologues with boiling points below 220ºC are listed in schedules in 2, 4, 5 and 6 of the *Poisons Standard — the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) (TGA 2022).

Only one chemical in this group (CAS No. 88-69-7) has a boiling point <220°C (BP: 213°C) and is; therefore, covered under the broad entries for 'PHENOL' in the *SUSMP* (TGA 2022) as follows:

Schedule 2
'PHENOL, or any homologue boiling below 220°C, for human therapeutic use **except**: when included in Schedule 4; or

a) in preparations for external use containing 1 per cent or less of phenol

b) preparations for external use containing 3 per cent or less of cresols and xylenols and other homologues of phenol.

Schedule 4

PHENOL in preparations for injection.

Schedule 5

PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, when in animal feed additives containing 15 per cent or less of such substances, **except** in preparations containing 1 per cent or less of phenol and in preparations containing 3 per cent or less of cresols and xylenols and other homologues of phenol.

Schedule 6

PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, **except**:

when separately specified in these Schedules; or

a) in preparations containing 1 per cent or less of phenols, and in preparations

b) containing 3 per cent or less of cresols and xylenols and other homologues of phenol.'

Workers

Chemicals in this group are not listed as hazardous on the Safe Work Australia (SWA n.d.) Hazardous Chemicals Information System (HCIS).

Only one chemical in this group has an exposure standard in Australia (SWA n.d.). 2-*sec*-butylphenol (CAS No. 89-72-5): time weighted average (TWA) of 5 ppm (31 mg/m^3).

International regulatory status

Exposure standards

The following exposure standards were identified for 2-sec-butylphenol (CAS No. 89-72-5) (Chemwatch n.d.):

Time weighted average (TWA): 30–31 mg/m^3 (5 ppm)—New Zealand, United States of America, Canada, South Korea, Singapore, Belgium, and Denmark.

STEL (Short-term Exposure Limit): 60 mg/m^3 (7–10 ppm)— United States of America, Canada, and Austria.

No international exposure standards were identified for the other chemicals in this group.

Other

No specific restrictions regarding their use as fragrance ingredients have been identified in the IFRA Standard (IFRA 2022b).

Health hazard information

There are limited toxicological data available for chemicals in this group. Data from suitable structurally related chemicals will be used to read-across and inform the human health assessment. Structurally related chemicals were selected based on their structural and functional similarity to the members of this group and based on the availability of toxicological data. Toxicology data are available for 3 such structurally related chemicals, 3-propylphenol (CAS No. 621-27-2), 4-*tert*-butylphenol (CAS No. 98-54-4) and 4-*tert*-pentylphenol (CAS No. 80-46-6). These chemicals differ from the chemicals being assessed by either the positions of the alkyl groups on the phenolic ring, or by the degree of branching of the alkyl chain. The structurally related chemicals selected have similar molecular weights and physicochemical properties to the chemicals in this group.

Toxicokinetics

No toxicokinetic data are available for the chemicals in this group. Some toxicokinetic data for the structurally related chemical, 3-propylphenol and 4-*tert*-butylphenol, have been generated from studies in rats and will be used to infer toxicokinetic information for the propyl- and butyl phenols in the group.

Based on the water solubility, partition coefficient (log Kow = 2.1–3.46 at 20°C) and the low molecular weights of propyl and butyl phenols, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are possible. Some absorption across the respiratory tract may also occur.

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 oral gavage on 3 successive days. Mass balance measurements showed that 26.7% and 72.9% of the administered radiolabelled dose was excreted in the faeces and urine respectively. The proportion of the administered dose remaining in the body 7 days after dosing was negligible (0.1%).

The role of sulfonation and glucuronidation in the biotransformation of p-*tert*-butylphenol was assessed in rats. Male Wistar rats were given a single intravenous dose of the radiolabelled chemical at 1.2–10.3 mg/kg bw. Between 91% and 93% of the radioactivity was recovered from the urine and bile within 4 hours of dosing. Most of the applied dose was excreted as glucuronide (65–71%) and sulfate conjugates (17–21%) of the chemical. The total recovery of radioactivity was 91–93% (Koster et al. 1981).

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 aforementioned rat study with intravenously injected p-*tert*-butylphenol. Retention of the chemical after 7 days in rat studies was negligible (0.1%) and the likelihood for bioaccumulation is low.

The urinary metabolite levels in workers handling p-*tert*-butylphenol were also measured. The levels of metabolites in the urine increased along with increasing exposure to the parent compound. Most of the p-*tert*-butylphenol was shown to be excreted within 24 hours (EU RAR 2008).

From the above studies it can be deduced that the short chain alkyl phenols are likely to be rapidly absorbed via the gastrointestinal tract and excreted mainly via urine and bile. These chemicals are expected to undergo rapid first pass metabolism by phase I and phase II enzymes in the liver. Detoxification pathways include hydroxylation, glucuronidation and sulfation.

Acute toxicity

Oral

Based on the available animal data, chemicals in this group are expected to have moderate acute oral toxicity, warranting classification. The reported LD50 values were mostly in the range of 300–2000 mg/kg bw/day.

In a good laboratory practice (GLP) compliant acute oral toxicity study conducted according to OECD TG 401, Fischer 344 rats (5/sex/dose) were administered single doses of 2-*tert*-butylphenol (CAS No. 88-18-6) by gavage. The LD50 was 789 mg/kg bw. Reported sublethal signs of toxicity included lachrymation (tearing), ataxia (impaired balance and coordination), prostration (lying down), hunched posture and lethargy (REACHa n.d.). A similar LD50 of 868 mg/kg bw for 2-*tert*-butylphenol was reported in an acute oral toxicity study (conducted according to US guidelines) in Sprague Dawley (SD) rats (REACHa n.d.).

In a GLP compliant acute oral toxicity study conducted according to OECD TG 401, SD rats (5/sex/dose) were treated with single doses of 2-*sec*-butylphenol (CAS No. 89-72-5). The median lethal dose was >200 – <2000 mg/kg bw. Reported sublethal signs of toxicity included increased salivation and ptosis (droopy eyelids) (REACHb n.d.).

A number of other reported LD50 values have been reported in rats:

- >200 – <2000 mg/kg bw for 2-*tert*-butylphenol (CAS No. 88-18-6) (OECD TG 401) (REACHa n.d.)
- 1231 mg/kg bw (males) and 1414 mg/kg bw (females) for 2-*tert*-butylphenol (REACHa n.d.)
- >500 – <1000 mg/kg bw for 2-*sec*-butylphenol (CAS No. 89-72-5) (OECD TG 401) (OECD 2012)
- 340 mg/kg bw for 2-*sec*-butylphenol (CAS No. 89-72-5) (OECD TG 401) (OECD 2012)
- 2450 mg/kg bw for 4-*sec*-butylphenol (CAS No. 99-71-8) (NLM n.d.)
- 1630 mg/kg bw for 3-isopropylphenol (CAS No. 618-45-1) (NLM n.d.)
- 500 mg/kg bw for 2-propylphenol (CAS No. 644-35-9) (NLM n.d.)
- 500 mg/kg bw for 4-propylphenol (CAS No. 645-56-7) (NLM n.d.).

Reported LD50 values in mice include:

- 875 mg/kg bw for 4-isopropylphenol (CAS No. 99-89-8) (NLM n.d.)
- 348 mg/kg bw for 4-propylphenol (CAS No. 645-56-7) (NLM n.d.).

No data were available for CAS Nos. 88-69-7, 585-34-2, 1638-22-8 and 31195-95-6.

Dermal

Based on the limited available data, chemicals in this group are expected to have low to moderate acute dermal toxicity. In a single guideline study with 2-*tert*-butylphenol (CAS No. 88-18-6) the LD50 was reported to be 1373 mg/kg bw and 705 mg/kg bw in males and females, respectively. In guideline studies with the structurally related chemicals p-tertbutyl phenol and 2-propylphenol LD50 values were >2000 mg/kg bw/day. It is not possible to draw conclusions on the classification of this group as a whole.

In a study conducted according to OECD TG 402, 2-*tert*-butylphenol (CAS No. 88-18-6) was applied to the clipped skin of Fischer 344 rats (5/sex/dose) as single doses at 0, 1020, 1420, or 2000 mg/kg bw (males), and 500, 729, 1020 or 2000 mg/kg (females). The chemical remained in contact with the skin for 24 hours under occlusive conditions. Mortalities occurred on days 2 to 5 (no details on the number of deaths provided). There was a range of adverse clinical signs observed and gross pathology, inflammation of the stomach and abnormalities in liver, gut and kidney. The LD50 was reported to be 1373 mg/kg bw and 705 mg/kg bw in males and females, respectively (REACHa n.d.).

In a study conducted similarly to OECD TG 402, an LD50 of >2000 mg/kg bw was reported for the structurally related chemical, p-*tert*-butylphenol (NICNAS 2016). The chemical was moistened with distilled water and applied to the clipped skin of New Zealand White (NZW) rabbits (5/sex/dose) in 2000, 8000 or 16000 mg/kg bw. The chemical remained in contact with the skin for 24 hours under occlusive conditions. Signs of toxicity included reduced body weight in the mid and high dose groups and skin irritation. No animals died in this study. Severe skin irritation was observed in both sexes at all doses.

A dermal LD50 of >2000 mg/kg bw was reported for the structurally related chemical, 3-propylphenol (CAS No. 621-27-2) in RccHanTM:WIST rats in a study conducted similar to OECD TG 402. No signs of systemic toxicity were observed. One female animal was found deceased 5 days after dosing. Abnormalities noted in the deceased rats included dark liver, dark kidneys and epithelial sloughing of the gastric epithelium and mucosa (NICNAS 2015).

Inhalation

Information on acute inhalation toxicity is very limited. Based on the available data, the chemicals in this group may have moderate acute inhalation toxicity warranting hazard classification.

A median lethal concentration (LC50) of >1.78 mg/L for a 4 hour exposure (vapour) was reported for 2-*sec*-butylphenol (CAS No. 89-72-5) in rats (OECD 2012). Details of the study were not provided.

In an acute inhalation toxicity study conducted according to OECD TG 436, RccHanTM:WIST rats (3/sex/dose) were exposed (nose only) to 2 concentrations of the structurally related chemical 3-propylphenol as an aerosol (0, 1.08 or 4.98 mg/mL). They were tested at the high concentration, 3 animals (1 male and 2 female) died, and one was euthanised. At the low concentration, 2 animals were euthanised as they showed similar signs of toxicity as the rats subject to high concentration of the chemical. Therefore, the LC50 was considered to be between 1.08–4.98 mg/L (4 hours exposure) (NICNAS 2015).

Corrosion/Irritation

Skin irritation

Based on the available data, chemicals in this group are considered to be corrosive, warranting hazard classification

In the group treated for 3 minutes, well defined moderate to severe erythema was observed at all treated sites, 1 and 24 hours after patch removal, and at 2 treated skin sites at 48 hours. Well defined erythema and oedema marked by the presence of adverse brown/black coloured scabs and thickening of the skin extended up to areas surrounding the application sites. Other effects included hardened light, brown coloured scabs, reduced regrowth of fur, glossy skin, desquamation (skin peeling) and small superficial scattered scabs. In the group treated for 4 hours, severe erythema, haemorrhage of the dermal capillaries and oedema were noted at all treated skin sites one hour after patch removal. Evaluation of the erythema and oedema was not possible at other observation times due to corrosion marked by severe adverse dermal reactions and scabs. Well defined erythema surrounded the scabs, with erythema extending up to 8 cm beyond the sites of application during the study (REACHa n.d.). On the basis of these effects, the test chemical was considered to be severely irritating to corrosive.

The chemical, 2-*sec*-butylphenol (CAS No. 89-72-5) was also corrosive to rabbit skin. A dermal irritation study similar to that described above was conducted with 2-*sec*-butylphenol. A single 3 minute, semi-occluded application of the test material to dorsal skin of 3 rabbits produced well defined to severe erythema and very slight to severe oedema. Other adverse reactions noted were haemorrhage of the dermal capillaries, light brown discolouration of the epidermis, loss of skin elasticity, thickening of the skin, scabbing, reduced re-growth of fur and desquamation. A single 4 hour, semi-occluded application of the test material to the intact skin of rabbits produced reactions indicative of corrosion (REACHb n.d.).

In another dermal irritation study, conducted similarly to OECD TG 404, 6 male NZW rabbits were exposed to 0.5 ml of 2-*tert*-butylphenol (CAS No. 88-18-6) for 24 hours under semi-occlusive conditions. Observations were recorded at 24 and 72 hours (REACHa n.d.). All 6 animals showed severe erythema (Draize score 4/4). The test material caused eschar formation in all animals and in addition, 2 animals showed abnormal wrinkled skin at the treated areas. All effects were irreversible.

The two structurally related chemicals, phenol, 3-propyl and 4-*tert*-butylphenol, were also severe reported as skin irritants or as corrosive in animal tests (NICNAS 2015; NICNAS 2016).

Eye irritation

Corrosive chemicals are also considered to cause irreversible effects in the eyes.

In an acute eye irritation study, conducted according to USA Interagency Regulatory Liaison Group Guideline, 0.1 mL of 2-*tert*-butylphenol was instilled into the left eye of 6 male NZW rabbits. Eyes were not washed afterwards. Animals were observed after 2 hours as well on days 1, 2, 3, 4, and 7. All animals showed cornea pannus (growth of small blood vessels in the cornea) after 7 days, additionally, 2 animals showed damage of the corneal epithelium (REACHa n.d.).

The chemical 2-*sec*-butylphenol was tested for eye irritation using the in vitro isolated chicken eye test method study conducted according to OECD TG 438. The study was performed to evaluate the possible corrosivity or severe irritancy potential of the test item. 0.03 mL of the test item was applied onto the cornea of each of 3 enucleated eyes. Appropriate controls were also included. Cornea opacity score, corneal swelling score and fluorescein scores were all high for the test chemical and positive control. Following assessment of the data for all endpoints, the test item was considered to have the potential to cause ocular corrosivity/severe irritancy in vivo (REACHb n.d.).

The structurally related chemical, 4-*tert*-butylphenol, was also found to be corrosive to the 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).

Sensitisation

Skin sensitisation

Based on the available data, the chemicals are not considered to be skin sensitisers.

In a guinea pig maximisation test (GPMT) conducted according to OECD TG 406, intradermal induction was performed on 10 male Dunkin Hartley guinea pigs using 2-*tert*-butylphenol (CAS No. 88-18-6) at 0.2% in corn oil, followed by topical induction with

the chemical at 10%. The animals were then challenged with the chemical at 0.5%. No skin reactions were reported after the challenge (REACHa n.d.).

In a non-GLP compliant GPMT conducted similarly to OECD TG 406, intradermal induction was performed on 10 female Pirbright-White guinea pigs using 2-*tert*-butylphenol at 0.5% in paraffin oil, followed by topical induction with the chemical at 20%. The animals were then challenged with the chemical at 1%. No skin reactions were reported after the challenge (REACHa n.d.).

There was no evidence of sensitisation in a local lymph node assay (LLNA) study with the structurally related chemical 3-propylphenol (NICNAS 2015)

The QSAR application toolbox showed no positive alerts for skin sensitisation by profiling analysis (protein binding by OASIS, protein binding by OECD, protein binding potency), that predict the potential of a chemical to bind to protein (OECD 2012).

Repeat dose toxicity

Oral

Based on the available data, chemicals in this group are not expected to cause serious systemic health effects following repeated oral exposure.

In a 28 day sub-chronic oral toxicity study, conducted similarly to OECD TG 407, Crj:CD(SD)IGS rats were administered 2-*tert* butylphenol in olive oil, at 0, 4, 20, 100 or 500 mg/kg bw/day by oral gavage (n = 6/sex/dose). Ataxic gait was observed in 9 males from all treatment groups and all females in the 500 mg/kg bw group sporadically during the administration period. These changes were observed from day 1. They occurred after dosing but disappeared within 5 hours of dosing. Higher relative weight of the liver was observed in males and females in the 500 mg/kg bw/day group at the end of the administration period. However, there were no statistically significant changes in the absolute weight of the liver. Histopathological examination showed no changes that were related to the change in the relative weight. A no observed adverse effect level (NOAEL) of 100 mg/kg bw/day was established for 2-*tert*-butylphenol by the study authors (REACHa n.d.).

In a GLP compliant oral repeat dose study, SD rats (10/sex/dose) were administered 0, 20, 100 or 500 mg/kg bw/day 2-*tert*-butylphenol in the diet for 13 consecutive weeks. No mortality occurred and no treatment related clinical signs were observed during the study. No signs of toxic or neurotoxic effects were seen during the study. A slight increase in the number of white blood cells was recorded at the end of treatment in some males dosed at 100 mg/kg bw/day and in a number of animals of both sexes receiving 500 mg/kg bw/day. Statistically significant fluctuations of some clinical chemistry parameters were recorded in treated animals, but these changes were no longer observed at the end of recovery. Due to the low severity, the complete reversibility, and the absence of a dose-relationship, all the above changes were not considered adverse. The absolute and relative weights of the liver and kidneys showed slight increases which, due to the low magnitude, complete reversibility, and the absence of a support from the histopathological examination, were not considered adverse. No treatment related findings were reported at post-mortem macroscopic and histopathological examination. An NOAEL of 500 mg/kg bw/day was established in this study (REACHa n.d.).

In a 13 week oral repeat dose study (OECD TG 408), the structurally related chemical 4-*tert*-pentylphenol, was administered to CD® [Crl:CD®(SD)] rats (n= 20/sex/dose) at 0, 50, 200, or 600 mg/kg bw/day by oral gavage. There were no chemical related mortalities,

adverse clinical findings, or ophthalmologic findings. At higher doses (200 and 600 mg/kg bw/day), decreased thymus weights were noted, but there were no microscopic correlates for these weight changes. 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. There was no evidence of neurotoxicity or reproductive effects in any of the parameters examined. An NOAEL of 200 mg/kg bw/day was determined based on progressively lower body weight among males throughout the study and adverse microscopic findings in the stomach in both sexes at 600 mg/kg/day (AICIS 2021).

Dermal

Dermal repeat dose toxicity studies are not available for chemicals in this group. Based on information available for the structurally related chemicals, these chemicals are not expected to have dermal repeat dose toxicity.

In a subchronic dermal toxicity study, conducted according to EPA guidelines (EPA OPP 82-3), SD rats (10 rats/sex/dose) were exposed to 0, 2.5, 10 or 25 mg/kg bw/day of the structurally related chemical 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 thirteen weeks. The dose was held in contact with the skin using a porous 2 × 3 inch 12-ply gauze dressing. 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 further progressed. Ulcerations were also observed in this dose group. 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 (AICIS 2021).

Inhalation

No data are available on the repeat inhalation toxicity of the chemicals.

Genotoxicity

Based on available data, the chemicals in this group are not considered to have genotoxic potential. Additionally, due to the lack of structural alerts for genotoxicity.

In vitro

In vitro studies with 2-*tert*-butylphenol and 2-*sec*-butylphenol reported mostly negative results:

- Negative results were reported in a bacterial reverse mutation assay (Ames test) in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation system (Arochlor 1254 induced liver S9 mix). 2-*tert*-butylphenol was tested up to cytotoxic concentrations and the limit concentration (5000 µg/plate).

- Negative results were reported with 2-*tert*-butylphenol in a bacterial reverse mutation assay (Ames test) in *S. typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2*uvrA* as index bacterial strains. with and without metabolic activation system (phenobarbital and 5,6-benzoflavone induced rat liver S9). 2-*tert*-butylphenol was tested up to cytotoxic concentrations and the limit concentration (6.25 to 200 µg/plate).

- The chemical 2-*tert*-butylphenol did not induce any chromosome aberrations in Chinese hamster lung fibroblasts (V79) in the absence of metabolic activation, but induced chromosome aberrations and polyploidy in the presence of metabolic activation at concentrations up to 60 µg/mL (a chromosomal aberration test conducted according to OECD TG 473).

- The chemical 2- *tert*- butylphenol gave negative results in a bacterial reverse mutation assay using *S. typhimurium* and chromosomal aberration test using Chinese hamster lung fibroblasts (V79) and human lymphocytes with or without activation (REACHb n.d.).

In vivo

In vivo studies with 2-*tert*-butylphenol and 2-*sec*-butylphenol were reported as negative:

- In a mammalian erythrocyte micronucleus test (OECD TG 474), male and female CD-1 mice (n=5/sex/dose) were administered 2-*tert*-butylphenol by oral gavage at 0, 250, 500 or 1000 mg/kg bw. The incidence of micronuclei in bone marrow polychromatic erythrocytes (PCEs) did not increase in any of the treated groups, indicating a lack of clastogenicity (REACHa n.d.).

- 2-*sec*-butylphenol was administered twice at 24 hour intervals by oral gavage to male and female Crj:CD(SD) rats (n=5/sex/dose) at doses of 0, 75, 150, 300 or 600 mg/kg bw/day. The frequency of micronucleated immature erythrocytes (MNPCE) increased significantly in male rats at 600 mg/kg bw/day but this increase was within the range of vehicle control background data in the testing facility. In female rats, there was no significant increase in the number of micronucleated cells at any dose. The proportion of PCE among the total erythrocyte populations was unchanged. It was concluded that 2-*sec*-butylphenol did not induce chromosomal aberrations in bone marrow cells in rats (REACHb n.d.).

Carcinogenicity

The carcinogenic potential of the alkylphenols has not been investigated in guideline studies, but on the basis of the mostly reported negative findings in the genotoxicity tests (see **Genotoxicity**) they are not expected to cause cancer by a genotoxic mechanism. There is also no evidence to suggest these chemicals are carcinogenic via non-genotoxic mechanisms.

In a high dose dietary study with the structurally related chemical 4-*tert*-butylphenol (CAS No. 98-54-4), the only relevant effects in male rats and Syrian Golden hamsters were observations of hyperplasia in the forestomach of both species. Papillomatous lesions were also induced in the stomach of hamsters. In addition, the chemical induced forestomach tumours in an initiation-promotion study in rats following initiation with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). On the basis of these findings, it was not possible to draw any absolute conclusions in relation to carcinogenic potential of the chemical alone. The chemical may act as a promoter in the induction of rodent forestomach tumours. The evidence

pertaining to the location of the tumours (the rodent forestomach) and the fact that the mechanism is likely to involve *p-tert*-butylphenol acting as a promoter does not support classification as a carcinogen (NICNAS 2016).

The findings of forestomach hyperplasia and papillomas in two 4-*tert*-butylphenol rodent studies suggest that long-term exposure to high doses of alkylphenols might cause an increase in tumour incidence at the site of contact as a consequence of long term local irritation (EA 2008). Also, due to their corrosive nature, repeated exposure to high doses of alkylphenols could conceivably cause an increase in tumour incidence at the site of contact as a consequence of long term local irritation (EA 2008).

Reproductive and development toxicity

Data on the reproductive toxicity of these chemicals is limited. There were no effects on fertility or developmental parameters in a single guideline study (OECD TG 422) with 2-*sec*-butylphenol. Tissue alterations in reproductive organs were not observed in repeated dose toxicity studies.

The structurally related chemical, p-*tert*-butylphenol, is classified as hazardous in the Hazardous Chemical Information System (HCIS) (SWA n.d.) as 'Reproductive toxicity - Category 2' with the hazard statement 'H361f (Suspected of damaging fertility)'. The classification is based on the evidence of potential effects in fertility in experimental animals in a two generation reproduction toxicity study. The chemical caused effects on ovarian weight, the incidence of vaginal atrophy and of primordial follicles, the number of implantation sites and litter size. Observed effects occur only at the high dose and there was not an obvious severe alteration of reproductive performance. It is uncertain whether effects related to reproductive organs in females are substance specific or due to weight reduction and pregnancy.

In a combined repeat dose and reproductive screening study, similar to the principles of OECD TG 422, Crj:CD(SD) rats (n=13/sex/dose) were given 2-*sec*-butylphenol in corn oil by oral gavage at doses of 0, 12, 60 and 300 mg/kg bw/day for 42 days (males) and 28 days plus gestation period and up to 3 days of lactation in females. There were no changes in body weights, food consumption, haematological parameters, blood chemistry, urinalysis, necropsy or histopathological examination. Clinical observations that were thought to be caused by administration of the chemical were decreased locomotor activity and (in females) staggering gait at 300 mg/kg bw/day. Some clinical signs of transient salivation and decreased activity were observed in some males in the 60 mg/kg bw/day group.

No adverse clinical effects were seen at the 12 mg/kg dose. No adverse effects were observed on copulation, fertility, maintenance of pregnancy, delivery, and lactation. In addition, 2-*sec*-butylphenol had no effect on the viability of neonates, sex ratio, body weight changes, and morphological appearance of pups. No observed effect levels (NOELs) for reproductive and developmental toxicity were considered to be 300 mg/kg/day in males, females and pups (REACHb n.d.).

In a 2-generation reproductive toxicity study conducted according to OECD TG 416 in SD rats with the structurally related chemical, 4-*tert*-butylphenol, no effects on reproductive organs, mating performance, fertility, or duration of gestation were reported in parental animals at concentrations up to 7500 ppm (highest dose tested; approximately 600 mg/kg bw/day). Slight decreases in the number of implantation sites, live pups born, and viability of the pups were reported at 7500 ppm. In the F1 and F2 generations, decreases in pup body weights and litter weights were reported on lactation day 14, as well as a smaller litter size. Pup survival was reduced, particularly over days 1–4 of lactation. Delays in vaginal opening and preputial separation in the F1 generation were reported at the highest dose tested (7500

ppm or 600 mg/kg bw/day). In the F0 and F1 female generations, marked increases in atrophy of the vaginal epithelium were reported from 2500 ppm (approximately 200 mg/kg bw/day). The severity of 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 (approximately 600 mg/kg bw/day). This effect was also more pronounced in the F1 generation (NICNAS 2016).

In a standard pre-natal developmental toxicity study, the structurally related chemical, 4-*tert*-pentylphenol, was administered by oral gavage to pregnant SD rats (25/dose) from gestation days 6 to 15. Doses were 0, 50, 200 or 500 mg/kg/day and dams and litters were sacrificed and examined 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 were 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 for developmental toxicity based on the presence of bent ribs at the top dose. Developmental effects were only observed secondary to maternal toxicity (AICIS 2021.).

Endocrine effects

Some alkylphenols are known to have endocrine effects.

When added to culture medium, some alkylphenols stimulate in vitro proliferation of the MCF-7 breast cancer cell line (a human breast cancer cell line with oestrogen, progesterone and glucocorticoid receptors). They bind to the oestrogen receptor and elicit transcription-stimulating activity (Kayama et al. 2003).

In a comprehensive study of a number of alkylphenols, the binding affinity to the oestrogen receptor was found to increase as the alkyl chain was lengthened from C4 to C9 (nonylphenol > octylphenol > heptyloxyphenol > amylphenol > butylphenol > ethylphenol). Although, it was noted that the affinity of all was at least 3 orders of magnitude less than that of 17β-oestradiol. A smaller number of alkylphenols has also been assayed for oestrogenic activity in vivo in the uterotrophic assay. This assay found evidence that oestrogenic potency also increases as the degree of branching increases.

In summary, in vitro and in vivo screening assays have shown longer or branched chain alkylphenols to possess weak oestrogenic activity but lack androgenic activity (EA 2008).

The binding affinity of 2-*sec*-butylphenol and 4-*sec*-butylphenol (chemicals in this group being evaluated) to the oestrogen receptor was very low compared to that of nonylphenol (relative binding affinity: 0.00029% and 0.00043%, respectively) (Blair et al. 2000). In vitro studies suggest that the chemicals have weak endocrine activity by binding to steroid hormone receptors. These activities indicate possible mechanisms for causing endocrine related adverse effects. At this stage there is no evidence of these weak endocrine activities causing adverse effects in animals or humans.

The structurally related chemical, 4-*tert*-pentylphenol (CAS No. 80-46-6), was screened for oestrogenic activity with in vitro assay and in vivo assays. In both these assays, 4-*tert*-pentylphenol did not exhibit oestrogenic activity (Yamasaki et al. 2002; Yamasaki et al. 2003).

Another structurally related chemical, 4-*tert*-butylphenol, was shown to bind to the human breast cancer cell line MCF-7 eostrogen receptor with approximately 10000-fold less affinity than 17β-oestradiol (the binding affinity was 0.01–0.03% compared to 100% for 17β-oestradiol). In this study 4-*tert*-butylphenol also stimulated cell growth, but the highest stimulation of cell growth (7 %) was observed at 10 µM of 4-*tert*-butylphenol, compared to 30 pM for 17β-oestradiol inducing a 100% cell growth (Olsen et al. 2002).

The mechanistic profiling functionality of the OECD QSAR Application Toolbox did not reveal any specific endocrine activity structural alerts for any of the chemicals in this group (OECD 2018).

References

AICIS (Australian Industrial Chemicals Introduction Scheme) (2021). *Public Report: 4-tert-pentylphenol (CAS No. 98-54-4)*. Accessed November 2022.

BKH, 2002. Endocrine Disrupters: Study on Gathering Information on 435 Substances with Insufficient Data. B4-3040/201/325850/MAR/02. Final report for the European Commission. BKH Consulting Engineers, Delft, The Netherlands (as cited in Environmental Agency 2008).

Blair RM, Fang H, Branham WS, Hass BS, Dial SL, Moland CL, Tong W, Shi L, Perkins R & Sheehan DM (2000). The estrogen receptor relative binding affinities of 188 natural and xenochemicals: structural diversity of ligands. *Toxicological Sciences*, 54: 138–153.

Chemwatch (n.d.) *Galleria Chemica*, Chemwatch website, accessed December 2022.

DeLima Associated (n.d) Consumer Product Information Database. Accessed May 2021.

ECHA (European Chemicals Agency) (2017) Inclusion of substances of very high concern in the Candidate List for eventual inclusion in Annex XIV. Accessed November 2022.

EA (Environment Agency) (2008). Environmental Risk Evaluation Report: 4-tert-pentylphenol (CAS No. 80-46-6). Environment Agency, Bristol, UK. Product Code: SCHO0208BNQR-E-P.

EU RAR (European Union Risk Assessment Report) (2008). p-Tert-butylphenol (CAS No. 98-54-4). Accessed December 2022.

Freitag D, Geyer H, Kraus A, Viswanathan R, Kotzias D, Attar A, Klein W & Korte F (1982). Ecotoxicological profile analysis. *Ecotoxicol Environ Safety*, **6**, 60–81. Information on study obtained from draft ESR Risk Assessment Report for para-tert-butylphenol.

Hazardous Substances Data Bank (HSDB). PubChem Compound summary for 4-*tert*-pentylphenol. National Library of Medicine. Accessed December 2022.

IFRA (2022a). (International Fragrance Association) (2022) *'International Fragrance Association (IFRA) Standards Library*', IFRA website, accessed August 2022.

IFRA (2022b). (International Fragrance Association) (n.d.) *IFRATransparency List*, https://ifrafragrance.org/priorities/ingredients/ifra-transparency-list, accessed December, 2022.

EC JRC (European Commission Joint Research Centre) (2013). Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances. Report of the Endocrine Disrupters Expert Advisory Group.

Kayama F, Horiguchi H and Hamamatsu A (2003). Potential Health Effects of Alkylphenols in Japan JMAJ 46: 108–114.

Koster H, Halsema I, Scholtens E, Knippers M & Mulder GJ (1981). Dose-dependent shifts in the sulfation and glucoronidation of phenolic compounds in the rat in vivo and in isolated hepatocytes. *Biochem Pharmacol*, 30: 2569–2575. (As cited in Environmental Agency, 2008).

NLM (National Library of Medicine) (n.d.) *ChemIDplus Advanced Database*, NLM website, accessed December 2022.

NTP (National Toxicology Program) (2018) Chemical Effects in Biological Systems, NTP, accessed December 2022.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2015). Public Report: Phenol, 3-propyl (CAS No. 621-27-2). Accessed December 2022.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2016). IMAP Assessment Report - 4-tert-butylphenol (CAS No. 98-54-4): Human health Tier II assessment report. NICAS accessed December 2022.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2020). IMAP Assessment Report - 4-tert-octylphenol (CAS No. 140-66-9): Human health Tier II assessment report. NICNAS accessed December 2022.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2014). IMAP Assessment Report - Ethylphenols (CAS No. 90-00-6, 123-07-9, 620-17-7): Human health Tier II assessment report. NICNAS accessed December 2022.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2020). IMAP Assessment Report – Methylphenols (Cresols) (CAS No. 95-48-7, 106-44-5, 108-39-4, 1319-77-3): Human health Tier II assessment report. NICNAS accessed December 2022.

Olsen et al (Olsen CM, Meussen-Elholm ETM, Holme JA and Honglso JK) (2002).Brominated phenols: Characterisation of estrogen-like activity in the human breast cancer cell-line MCF-7. Toxicology Letter: 129: 55-63 (as cited in EURAR, 2008).

OECD (Organisation for Economic Co-operation and Development) (2012). SIDS Initial Assessment Profile (SIAP) on 2-*sec*-Butylphenol. Accessed December 2022.

OECD (Organisation for Economic Co-operation and Development) (2018) *Quantitative Structure-Activity Relationship (QSAR) Toolbox (Version 4.4.1)* [Computer software], OECD, accessed December 2022.

Personal Care Products Council (n.d.) *Cosmetic Ingredient Identification Database*, Personal Care Products Council. Personalcarecouncil.org, accessed December 2022.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d) (REACHa) Registered dossier for CAS No. 88-18-6 (2-tert-butylphenol). European Chemicals Agency website, accessed December 2022.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d) (REACHb) Registered dossier for CAS No. 89-72-5 (2-sec-butylphenol). European Chemicals Agency website accessed September 2022.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals)(n.d) (REACHc) Registered dossier for CAS No. 80-46-6 (P-(1,1-dimethylpropyl)phenol). European Chemicals Agency website accessed December 2022.

Siglin JC (1991) Nipacide PTAP: *Teratology study in rats*. Springborn Labs. Inc. Study No. 3227.3. Unpublished study. (As cited in Environmental Risk Evaluation Report: 4-tert-pentylphenol *(CAS No. 80-46-6)*. (See reference Environmental Agency, 2008).

SPIN (Substances in Preparation in Nordic Countries) (n.d.) SPIN Database, SPIN website accessed December 2022.

SWA (Safe Work Australia) (n.d.) *Hazardous Chemical Information System*, SWA website, accessed September 2022.

TGA (Therapeutic Goods Administration) (2022) *Standard for the Uniform Scheduling of Medicines and Poisons No.36 (Poisons Standard June 2022)*, TGA, accessed November 2022.

UNECE (United Nations Economic Commission for Europe), (2017). Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Seventh Revised Edition, UNECE, accessed December 2022.

Webster F, Gagné M, Patlewicz G, Pradeep P, Trefiak N, Judson RS and Barton-Maclaren TS (2019). Predicting estrogen receptor activation by a group of substituted phenols: An integrated approach to testing and assessment case study. Regul Toxicol. Pharmacol. 106: 278–291.

Yadav GD (2002). Stereoselective hydrogenation of p-tert-butylphenol over supported rhodium catalyst. Molecular catalyst. Vol: 184, 281-288.

Yamasaki K, Takeyoshi M, Yakabe Y, Sawaki M, Imatanaka N & Takatsuki M (2002). Comparison of reporter gene assay and immature rat uterotrophic assay of twenty-three chemicals. *Toxicol*, 170: 21–30.

Yamasaki K, Takeyoshi M, Sawaki M, Imatanaka N, Shinoda K & Takatsuki M, 2003. Immature rat uterotrophic assay of 18 chemicals and Hershberger assay of 30 chemicals. *Toxicol*, 183: 93–115.