Xylenols: Human health tier II assessment

28 June 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phenol, 3,4-dimethyl-	95-65-8
Phenol, 2,5-dimethyl-	95-87-4
Phenol, 2,3-dimethyl-	526-75-0
Phenol, 2,4-dimethyl-	105-67-9
Phenol, 3,5-dimethyl-	108-68-9
Phenol, 2,6-dimethyl-	576-26-1
Phenol, dimethyl-	1300-71-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This assessment relates to xylenols, which are dimethyl phenols. The following six members of the group are chemical isomers differing only in the position of the methyl groups relative to the hydroxyl group on the phenol ring:

- 2,3-xylenol (CAS No. 526-75-0);
- 2,4-xylenol (CAS No. 105-67-9);
- 2,5-xylenol (CAS No. 95-87-4);
- 2,6-xylenol (CAS No. 576-26-1);
- 3,4-xylenol (CAS No. 95-65-8); and
- 3,5-xylenol (CAS No. 108-68-9).

The seventh member, xylenol (CAS No. 1300-71-6), referred to as 'mixed xylenol', is a mixture of these isomers. There is no set definition for this substance; and it is reported that no single product or mixture is understood by industry as representative of mixed xylenols (USEPA, 2010). One report lists cresols and phenols as constituents of the mixed xylenol (REACHa), while another report describes one commercial "mixed xylenols" mixture containing, at most, 22.5 % xylenol, with the remainder being

'a combination of phenols, cresols, xylenols, ethylphenols and higher boiling alkyl phenols' (USEPA, 2010). For the purposes of this report, only the xylenols are being assessed as part of this group. Note that cresols and phenol have been assessed by NICNAS and published reports are available for these (NICNASa; NICNASb).

The seven members of this group have the same molecular weight (or average molecular weight, in respect to the mixed xylenol), and while variations in substitution patterns on benzene rings can lead to differences in toxicological properties, the chemicals in this group show a generally similar hazard profile and share the same existing health hazard classification. The members of the group also have similar reported uses and are grouped together for regulatory control purposes.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The six "unique" isomers (i.e. members apart from mixed xylenol) are all reported to have been used in fragrance compounds in 2015, according to the International Fragrance Associaction (IFRA) Volume of Use Survey 2016: Transparency List (IFRA, 2016).

The following chemicals are listed in the European Commission Cosmetic Ingredients and Substances (CosIng) database as being available for cosmetic use in fragrances:

- 2,3-xylenol;
- 2,5-xylenol;
- 2,6-xylenol; and
- 2,4-xylenol.

It is noted that none of the chemicals in this group assessment are listed in the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

Internationally, domestic uses have been identified for 2,3-xylenol through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers, where it is reported to be used in washing and cleaning products (REACHb).

Mixed xylenol (CAS No. 1300-71-6) is reported to be used in a household liquid disinfectant product, as listed in the US National Library of Medicine's Household Product Database, it is also reported to have been used in an auto liquid disinfectant product at a concentration of 1.0–2.5 %; however, this is listed as an 'old product' (US HPD).

Mixed xylenol and 3,4-xylenol are reported to have commercial use in the manufacture of bulk, large scale chemicals (REACHa; REACHc), including:

- coatings and paints;
- thinners and paint removers; and
- petroleum products.

The chemicals have reported site-limited uses, as identified through REACH, the US National Library of Medicine's Hazardous Substances Data Bank (HSDB), Galleria Chemica, and the Substances and Preparations in Nordic countries (SPIN) database, including:

- as intermediates in manufacturing fine chemicals; and

- in manufacturing plastics products, including compounding and conversion, such as polymer preparations and compounds.

The chemicals are also reported to have non-industrial use as food additives (Galleria Chemica; HSDB).

Restrictions

Australian

The chemicals in this group (xylenols) are included in the listing for 'phenol' in the Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in Schedule 6 as follows (SUSMP, 2018):

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

(a) when separately specified in the Schedules; or

(b) in preparations containing 1 per cent or less of phenols, and in preparations containing 3 per cent or less of cresols and xylenols and other homologues of phenol.

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2018).'

The chemicals are also listed in Schedules 2, 4 and 5 for non-industrial uses; the Schedule 5 entry relates to use in animal feed (SUSMP, 2018).

International

No relevant international restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group are classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity – Category 3; H301 (Toxic if swallowed)
- Acute toxicity – Category 3; H311 (Toxic in contact with skin)
- Skin corrosion – Category 1B; H314 (Causes severe skin burns and eye damage)

Exposure Standards

Australian

No specific exposure standards are available.

International

A short-term exposure limit (STEL) of 2 mg/m^3 in Vietnam (limit value for airborne chemicals in the workspace) is reported for 'dimethyl phenol' (Galleria Chemica). No other specific international exposure standards have been identified.

Health Hazard Information

Toxicokinetics

In an in vivo oral metabolism study, the six xylenol isomers (i.e. 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-xylenol) were individually administered by gavage to female rabbits weighing 2–3 kg (administered dose of 1000 mg for all except 2,4-xylenol, for which 850 mg was administered). The metabolism of xylenols was reported to be similar to that of cresols, with little difference observed in metabolism across the six isomers (Bray et al., 1950; REACHb). The chemicals reported to have low bioaccumulation potential with majority of the administered dose (77–93 %) excreted as O-conjugates (Bray et al., 1950; REACHb) and small amounts excreted either unchanged, oxidised or hydroxylated. Ether-soluble acid, ether glucuronide, sulfate, ester glucuronide and free non-acidic phenol were reported metabolites detected in excreted urine. Crystalline glucuronides were also reported to have been isolated as metabolites of all six isomers. Paper chromatography of ether extracts of all urine samples identified phenolic compounds (no further details available) in xylenol-treated rabbits that were not detected in untreated rabbits. Additionally, 2,5-dihydroxy-1,3-dimethylbenzene (also known as 2,6-dimethylhydroquinone) was reported as an identified metabolite of both 2,6-xylenol and 3,5-xylenol (Bray et al., 1950).

In a study with limited detail, 3,5-xylenol was applied to the skin of two rabbits at 2000 mg/kg bw (as a 5 mL solution in water) under semi-occlusive conditions for a period of 24 hours. No indication of dermal absorption was reported (REACHd).

One report on 2,6-xylenol, based on physico-chemical properties alone, states that the chemical is expected to be well absorbed by the oral, dermal and inhalation routes of exposure, and 'is anticipated to be widely distributed through the body, metabolised and excreted mainly in the urine' (REACHe).

Acute Toxicity

Oral

The chemicals in this group are classified as hazardous with hazard category ‘Acute Toxicity Category 3’ and hazard statement ‘Toxic if swallowed’ (H301) in the HCIS (Safe Work Australia). The only available data to support this classification is a rat oral median lethal dose (LD50) value of 296 mg/kg bw reported for 2,6-xylenol; however, no information on the study method or further details are available (REACHe; USEPA, 2003). The remainder of the available data for these chemicals do not support this classification; the following rat oral LD50 values are reported for the six isomers of xylenol (REACHb-g; USEPA, 2003; USEPA, 2010):

- 562–790 mg/kg bw for 2,3-xylenol;
- 2300–3200 mg/kg bw for 2,4-xylenol;
- 444–708 mg/kg bw for 2,5-xylenol;
- 1470–1790 mg/kg bw for 2,6-xylenol;
- 727–1600 mg/kg bw for 3,4-xylenol; and
- 608–3620 mg/kg bw for 3,5-xylenol.

Reported sublethal signs of toxicity included dyspnoea (shortness of breath), loss of motor coordination and spasms. In the absence of more comprehensive information, the available data are not sufficient to recommend amendment to the current HCIS classifications.

Dermal

The chemicals in this group are classified as hazardous with hazard category ‘Acute Toxicity Category 3’ and hazard statement ‘Toxic in contact with skin’ (H311) in the HCIS (Safe Work Australia). While the available data do not consistently support this classification (dermal LD50 values reported between 987–2400 mg/kg bw) (REACHb-g; USEPA, 2002; USEPA, 2010), in the absence of more comprehensive information, the available data are not sufficient to warrant amendment of the current HCIS classification.

Inhalation

There are insufficient data to determine whether the chemicals cause acute toxicity following inhalation exposure.

The reported median lethal concentration (LC50) values available are:

- >85.5 mg/m^3 for 2,3-xylenol (vapour) following whole body exposure for four hours (REACHb);
- >270 mg/m^3 for 2,6-xylenol (no further details available) (REACHe);
- and >0.7 mg/L for 3,5-xylenol (gas) following whole body exposure for seven hours (REACHg).

Corrosion / Irritation

Corrosivity

The chemicals are classified as hazardous with hazard category ‘Skin corrosion Category 1B’ and hazard statement ‘Causes severe skin burns and eye damage’ (H314) in the HCIS (Safe Work Australia). The available data support this classification. The chemicals applied to intact rabbit skin or eyes produced adverse effects that were not reversible.

Severe burns to the intact or abraded skin of rabbits (three animals/group) were reported to be observed 72 hours after application of 0.5 g of 2,6-xylenol under non-occlusive conditions (REACHe; USEPA, 2003). Moderate burns to the skin were reported in rabbits after 5–10 minutes of exposure to 3,5-xylenol (concentration not specified) skin, in addition to hyperaemia and oedema with moderate necrosis (REACHg). A study in guinea pigs (n=3) reported 3,4-xylenol, at doses of 0.25– 1.0 mg/kg bw, to be severely irritating to the skin, with moderate oedema developing within 24 hours, in addition to necrosis and eschar formation (USEPA, 2010).

Eye irritation studies in rabbits available for 2,6-xylenol, 3,4-xylenol and 3,5-xylenol, all report permanent eye damage following administration of the chemical. 2,3-Xylenol was also reported to be potentially corrosive to the skin and eyes of rabbits, as determined by Quantitative Structure-Activity Relationship (QSAR) predictive calculations (REACHb).

Severe erythema, severe oedema and eschar formation were reported in male New Zealand White (NZW) rabbits (n=2) following dermal application of an 'undescribed xylenol mixture' at 5000 mg/kg bw to shaved skin for a 24-hour exposure period under occluded conditions (REACHa). An eye irritation study of an 'undescribed xylenol mixture' is also available, in which moderate conjunctival injury was reported in male NZW rabbits following administration of the substance (REACHa). No details on xylenol composition or percentage are available for either of the studies.

Sensitisation

Skin Sensitisation

The available data do not provide a clear picture as to the skin sensitisation potential of this group of chemicals. There is insufficient data to warrant recommending hazard classification for any or all of these chemicals.

The chemical 2,4-xylenol was reported to cause skin sensitisation in a guinea pig maximisation test (GPMT) conducted similar to OECD TG 406 (REACHf). Necrotic skin changes and swelling was reported following intradermal induction with a 0.5 % preparation of the chemical. Necrotic skin changes and swelling was also reported following the subsequent percutaneous induction with a 25 % preparation of the chemical. The two challenges were performed using a 5 % preparation of the chemical. Although a positive result was reported by following the evaluation criteria, based on the effects observed, it cannot be ruled out that this result is an artefact resulting from reactions to the excessive concentrations used in the induction phases.

The chemical 3,5-xylenol was reported to not cause skin sensitisation in a GPMT conducted according to OECD TG 406 (REACHc). A 1 % test substance preparation was used for the intradermal induction, followed by a 5 % preparation for the percutaneous induction. Necrotic skin changes and swelling were reported at both of these phases. A 0.5 % preparation was used for the challenge phases.

The chemical 2,6-xylenol was concluded to not cause skin sensitisation in a GPMT (REACHc). Necrotic skin changes and swelling were reported at the induction phases. A positive result obtained following the first challenge phase could not be confirmed by the second challenge phase. It is also reported that some animals that showed skin reactions at the first challenge also reacted to the vehicle itself.

A paper by Yamano et al. (2007) reported on a local lymph node assay (LLNA) conducted in mice using all the members in this group of chemicals except for the mixed xylenol. Following exposure to 25 µL of a 1M solution of each of the chemicals, positive skin sensitisation results were obtained for 2,4-, 2,5- and 3,4-xylenol, with resulting Stimulation Index (SI) values of 3.7, 8.9 and 10.1, respectively. The SI value for the remainder of the chemicals was reported to be <3. The pattern of results found in this study is unexpected, as chemical differences between the isomers found to give positive results and those giving negative results, cannot explain the responses. In addition, quantitative structure-activity relationship (QSAR) results do not distinguish any relevant chemical differences (OECD QSAR Toolbox v.4.2; Derek Nexus v.6.0.0; OASIS-TIMES v.2.28.1; VEGA CEASAR v.2.1.6). It is unclear whether any false positives or false negatives are responsible for the mix of positive and negative LLNA results within this group of chemicals.

Repeated Dose Toxicity

Oral

Several repeated oral dose toxicity studies are available for this group of chemicals. Based on the treatment-related effects reported, and considering the lowest concentration level at which they were observed, repeated oral exposure to the chemicals in this group is not considered to cause serious damage to health.

Two 90-day repeated dose toxicity studies (no test guidelines cited) are available for 2,4-xylenol; one in rats and one in mice (USEPA 2010). In the study in rats (SD; 10 animals/sex/dose), the chemical was administered by oral gavage at 60, 180 or 540 mg/kg bw/day. Mortalities were observed in the high dose group (540 mg/kg bw/day) and reported to be due to the corrosive effect of the chemical on the oesophagus and stomach. A lowest observed adverse effect level (LOAEL) of 180 mg/kg bw/day was reported based on the following effects including decreased body weight and histopathology (epithelial hyperplasia of the forestomach). The no observed adverse effect level (NOAEL) was reported to be 60 mg/kg bw/day.

In the 90-day study in mice (albino; 30 animals/sex/dose), 2,4-xylenol was administered by oral gavage at 5, 50 or 250 mg/kg bw/day. A NOAEL of 50 mg/kg bw/day was reported, while a LOAEL of 250 mg/kg bw/day was reported based on haematological effects (statistically significant decrease in mean corpuscular volume and mean corpuscular haemoglobin concentration in females); clinical signs of toxicity (squinting, lethargy and ataxia) were also observed in males and females at this dose.

The available repeated oral dose toxicity studies for 2,6-xylenol range in duration from 28 days to 8 months. In a 28-day study (non-guideline) in Wistar rats (5 animals/sex/dose), 2,6-xylenol was administered by oral gavage at 20, 100, 400 or 800 mg/kg bw/day, daily, 5 days/week (USEPA 2010). A NOAEL of 100 mg/kg bw/day was reported, with effects observed at higher doses (LOAEL of 400 mg/kg bw/day) including signs of toxicity (salivation and ataxia), haematological changes (decreased red blood cells, haemoglobin and haematocrit in females) and significantly increased absolute and relative liver weights.

In a 90-day dietary study (non-guideline), 2,6-xylenol was incorporated into the feed of Charles River rats (10–16 animals/sex/dose) resulting in a dietary intake concentration of 5.99 mg/kg bw/day for males and 6.95 mg/kg bw/day for females

(REACHe). No adverse effect on growth, food intake, haematological and clinical chemistry parameters, organ weights or organ pathology were seen, with the administered concentrations reported as the no observed effect level (NOEL) values for this study.

In an eight-month repeated dose toxicity study (non-guideline) with limited reported information, 2,6-xylenol was administered orally (unspecified) to rats (number of animals not reported) at 0.6 or 6 mg/kg bw/day (REACHe). In the reported study methodology, it states that blood pressures were measured before and after adrenalin injection. While a lowest observed effect level (LOEL) of 6 mg/kg bw/day was reported in this study based on significant changes (not specified) in body weight, groups of blood serum (not specified) and pathomorpological changes of internal organs (not specified), it is unclear as to the reliability of these results in comparison with the other available studies of the xylenols.

Two sub-chronic studies are available for the mixed xylenol (REACHg). In one study following OECD TG 422 (combined repeated dose and reproductive toxicity), mixed xylenol was administered to SD rats (10 animals/sex/dose) by oral gavage at 30, 100 or 245 mg/kg bw/day for a period of 28 days for males and 54 days for females. The NOAEL for this study was reported to be 100 mg/kg bw/day based on urine-stained fur, and increased kidney, liver and ovarian relative weight at the higher dose (245 mg/kg bw/day).

In the other sub-chronic study (following OECD TG 407), mixed xylenol was administered by oral gavage to SD rats (7 animals/sex/dose) at 100, 300 or 1000 mg/kg bw/day for 28 days followed by a 14-day recovery period. A NOEL of 100 mg/kg bw/day was reported for females based on increased relative liver weights at higher doses (≥300 mg/kg bw/day), while for males, a NOEL of 300 mg/kg bw/day was reported based on histopathological changes in the liver seen at higher doses (1000 mg/kg bw/day). In the executive summary of this study, these values are reported as NOAELs; however, it is noted that the changes seen in the liver (hypertrophy of centrilobular hepatocytes) of males at the 1000 mg/kg bw/day dose were only observed in 1/7 animals and were not observed in any animals at the end of the 14-day recovery period. Additionally, no significant difference in relative liver weights was observed in females at the end of the recovery phase.

One sub-chronic study following OECD TG 407 using 3,5-xylenol is available, in which the chemical was administered to SD rats (5 animals/sex/group) at 30, 100 or 300 mg/kg bw/day for 28 days (REACHg). A NOAEL was established at 300 mg/kg bw/day in this study, and a NOEL of 30 mg/kg bw/day was reported based on effects including increased salivation, slightly lower bodyweight gain and food consumption, observed at higher doses. No treatment-related effects on organ weight, haematology or clinical chemistry were reported.

No studies are available for 2,3- or 2,5-xylenol.

Dermal

No data are available.

Inhalation

Only limited repeat-inhalation dose toxicity study information is available for 2,6-xylenol; no information is available for the other xylenol isomers.

In a non-guideline study, 2,6-xylenol was administered to Fischer 344 rats (10 animals/sex/dose) by whole-body aerosol exposure at concentrations of 67, 200 or 670 mg/m^3 in air (nominal dose), for six hours/day, five days/week, over a 14-day period (i.e. a total of 10 exposures) (REACHe). Red nasal discharge in all animals from the high dose group, which subsided overnight following each exposure, was the only clinical sign of toxicity reported. Significantly decreased body weights of mid and high dose males, and high dose females, compared to control group animals was reported, with significantly increased absolute kidney weights and relative liver weights only reported in high dose group animals. Treatment-related non-neoplastic (non cancerous) lesions were reported to be detected in the same anatomical location of the nasal cavity, and to the same degree of severity in high dose males and females. A no observed effect concentration (NOAEC) of 200 mg/m^3 and lowest observed effect concentration (LOEC) of 670 mg/m^3 were reported for 2,6-xylenol in this study.

One other study using 2,6-xylenol is available for which, apart from slight differences in the details on duration of exposure provided, appears to be very similar to the study described above. In this study, Fischer rats (10 animals/sex/dose) were also

administered 2,6-xylenol by whole-body aerosol exposure at 67, 200 or 670 mg/m^3 in air. In addition to the same dose-group effects reported in the above study, haemoglobin and platelets were reported to be significantly decreased in males from the high dose group, and increased organ-to-body-weight ratios for heart, lung and liver were reported in females from the high dose group. Effect levels were reported as above.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemicals are not considered to be genotoxic. Some in vitro genotoxicity tests gave positive or weakly positive results, but all in vivo tests were negative.

In vitro bacterial assays

In one in vitro bacterial reversion assay (Ames test; no guideline specified), *Salmonella typhimurium* strains TA98, TA100 and TA1535 were exposed to 2,4-xylenol at concentrations of 3.3-500 µg/plate, with or without metabolic activation (USEPA, 2010). A weakly positive result was reported for strain TA100 in the presence of metabolic activation; negative results were obtained in TA100 without metabolic activation, and in the other strains tested with or without metabolic activation.

Negative results for this chemical group were observed in several other in vitro bacterial assays using the chemicals (REACH; USEPA 2010):

- 2,3-xylenol in *S. typhimurium* strains TA 98 and TA100 at concentrations of 10000-20000 µg/mL, or strains TA98, TA100, TA1535 and TA1537 at a concentration of 3 µmole/plate, either with or without metabolic activation;
- 2,4-xylenol in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 at concentrations of 10-30 µg/plate, either with or without metabolic activation;
- 2,5-xylenol in *S. typhimurium* strains TA98 and TA100 over a 1000-fold concentration range (not specified), either with or without metabolic activation (similar to OECD TG 471);
- 2,6-xylenol in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 at concentrations of 10-5000 µg/plate, either with or without metabolic activation (following OECD TG 471);
- 3,4-xylenol in *S. typhimurium* strains TA98 and TA100 (test concentration not specified), either with or without metabolic activation; and
- mixed xylenol in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537, and *Escherichia coli* strain WP2 uvrA at a concentrations of 6.7-50000 µg/plate, either with or without metabolic activation (following OECD TG 471).

In vitro mammalian cell assays

In an in vitro mammalian chromosomal aberration test (following OECD TG 473), Chinese hamster lung fibroblasts (V79) were exposed to 2,6-xylenol at concentrations of 10-600 µg/mL, with or without metabolic activation (REACHe). Positive results were reported at ≥300 µg/mL in the presence of metabolic activation; no mutagenic potential was reported at <300 µg/mL, or at any test concentration in the absence of metabolic activation.

In another in vitro mammalian chromosomal aberration test (following OECD TG 473), mixed xylenol was reported to show mutagenic potential in Chinese hamster ovary (CHO) cells at concentrations of 300-550 µg/mL, both with and without metabolic activation (REACHa).

Negative results were reported in several other in vitro mammalian cell assays on the chemicals (REACH):

- 2,3-xylenol did not induce sister chromatid exchange in human lymphocytes at concentrations up to 0.5 mM;
- 2,6-xylenol did not induce gene mutations in Chinese hamster lung fibroblasts (V79) at concentrations of 10-600 µg/mL, either with or without metabolic activation (following OECD TG 476); and
- mixed xylenol did not induce gene mutations in Chinese hamster lung fibroblasts (V79) at concentrations of 6.25-800 µg/mL, either with or without metabolic activation (following OECD TG 476).

In vivo studies

No genotoxic potential was reported for these chemicals in the available in vivo studies:

- 2,4-xylenol did not induce chromosome-damaging (clastogenic) effects in mice (NRMI) in a mammalian erythrocyte micronucleus test (following OECD TG 474), at oral dose concentrations ranging from 250-1000 mg/kg bw (REACHf). No indications of any impairment of chromosome distribution during the course of mitosis was reported;
- 2,6-xylenol did not induce an increase in structural chromosomal aberrations in SD rats in a mammalian bone marrow chromosome aberration test (following OECD TG 475), at oral dose concentrations ranging from 300-1200 mg/kg bw for females, and 350-1400 mg/kg bw/kg for males (REACHe); and
- 3,5-xylenol did not induce clastogenic effects in NMRI mice in a mammalian erythrocyte micronucleus test (following OECD TG 474) at concentrations ranging from 375-1500 mg/kg bw (REACHg). 1500 mg/kg bw was reported to be the maximum tolerated dose in this study.

Carcinogenicity

There are no available high quality, or reliable, carcinogenicity studies conducted in animals using the chemicals in this group. However, based on the available, well-conducted, genotoxicity studies (see **Genotoxicity** section), the chemicals are not expected to be genotoxic carcinogens.

Reproductive and Developmental Toxicity

Based on the limited data available, the chemicals in this group do not cause specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In the only available reproductive toxicity study (conducted according to OECD TG 422), mixed xylenol was administered to SD rats (10 animals/sex/dose) by oral gavage at 30, 100 or 245 mg/kg bw/day, daily, for a period of 28 days for males and 54 days for females; this included 14 days of dosing prior to cohabitation, with a maximum cohabitation period of 14 days (REACHa). The NOAEL for general toxicity was reported to be 100 mg/kg bw/day (refer to **Repeated Dose Toxicity** section). While a reduced mating frequency was observed at the highest dose (245 mg/kg bw/day), this was not considered to be treatment-related as it was not statistically significant in comparison with the control group, and was also within the historical control range. Offspring produced (F1) were reported to not show any clinical signs of toxicity or treatment-related effects at necropsy. Haematology, clinical pathology and neurobehavioral parameters were also reported to be unaffected; no further details are provided. A reproductive NOAEL of ≥245 mg/kg bw/day is reported.

In a prenatal developmental toxicity study (following OECD TG 414), 2,6-xylenol was administered to mated female SD rats (24/dose) by oral gavage at 60, 180 or 540 mg/kg bw/day, daily, on gestation days (GD) 6–15 (REACHe; USEPA 2010). It is noted that GD 0 is defined in this study as the day on which evidence of mating was observed. Significantly reduced maternal body weight gain and absolute and relative liver weights were reported in females at ≥180 mg/kg bw/day, with maternal mortality (2/24 animals) reported at the highest dose. Females were euthanised on GD 20 and maternal toxicity and developmental toxicity of the foetuses was evaluated. Significantly (statistically) decreased mean foetal weights were reported in the high dose group (245 mg/kg bw/day maternal dose), which was considered in the study to be treatment-related. A slight increase in the frequency of foetal skeletal abnormalities (reduced ossification of the cervical vertebral transverse processes and metatarsals) at the highest dose in comparison with the control group was also observed; the statistical significance of this observation is not reported. For maternal toxicity, a NOEL of 60 mg/kg bw/day and a LOEL of 180 mg/kg bw/day were reported, while for developmental toxicity, a NOEL of 180 mg/kg bw/day and a LOEL of 540 mg/kg bw/day were reported in this study.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the systemic acute effects of acute toxicity from oral or dermal exposure, and the local effect of corrosivity.

Public Risk Characterisation

The chemicals are currently listed on Schedule 6 of the *Poisons Standard*—the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2018) for preparations containing xylenol. At concentrations greater than 3 %, a number of warning statements, first aid instructions and safety directions relating to the chemicals apply.

Although use in cosmetic or domestic products in Australia is not known, the chemicals are reported to be used in cosmetic products overseas (concentrations not specified) and domestic products overseas at concentrations up to 2.5 %.

Provided that normal precautions are taken to avoid prolonged skin and eye contact, the risk to public health posed by cosmetic or domestic products containing the chemicals at concentrations of less than 3 % is not considered to be unreasonable. At higher concentrations, potential harm is reduced by using strong warnings and safety directions on the label.

Occupational Risk Characterisation

During product formulation, dermal, ocular, oral 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. 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 chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular, oral and inhalation exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Based on the available data, the hazard classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2018).

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Toxic if swallowed - Cat. 3 (H301)* Toxic in contact with skin - Cat. 3 (H311)*
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1B (H314)*

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular, inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

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

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

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

Obligations under workplace health and safety legislation

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

- ensuring that hazardous chemicals are correctly classified and labelled;

- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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Last Update 28 June 2019

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phenol, 3,4-dimethyl-** 3,4-xylenol 3,4-dimethylphenol
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	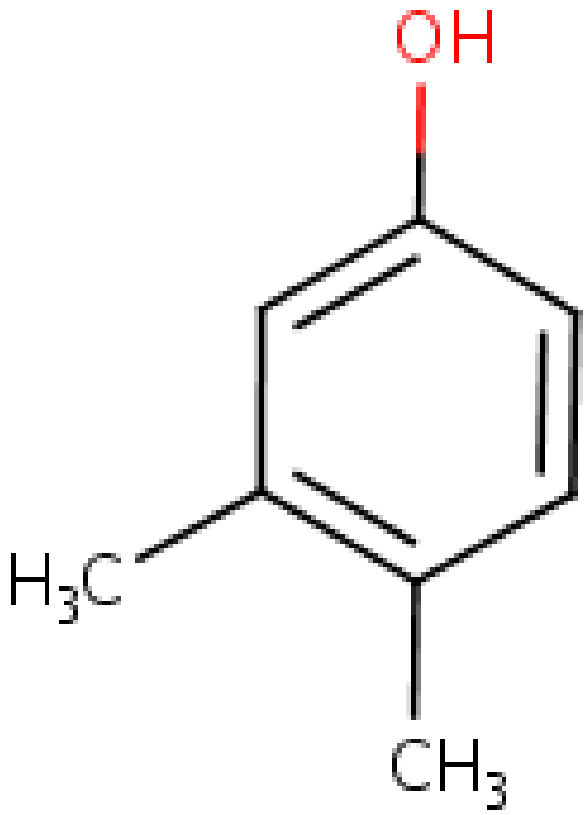
Molecular Formula	C8H10O
Molecular Weight	122.17

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	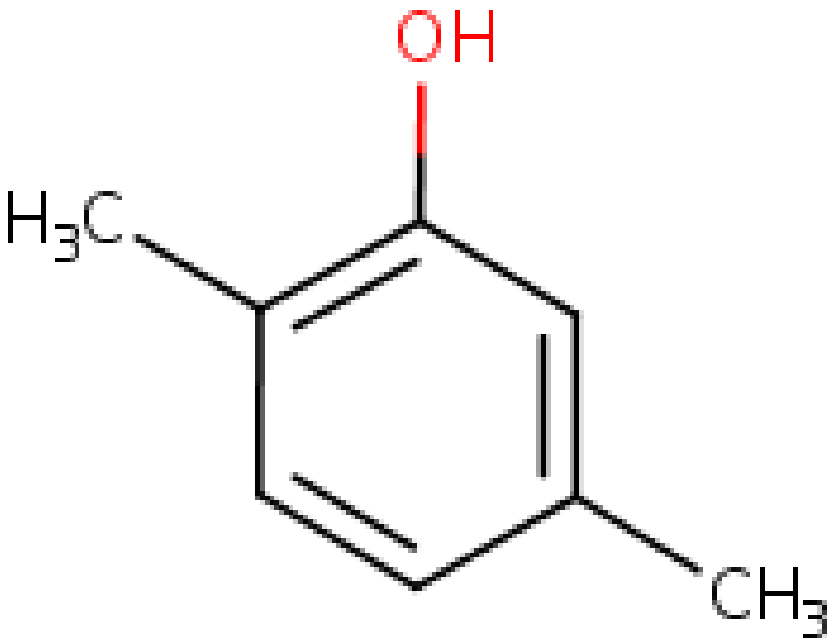
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Molecular Weight	122.17

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	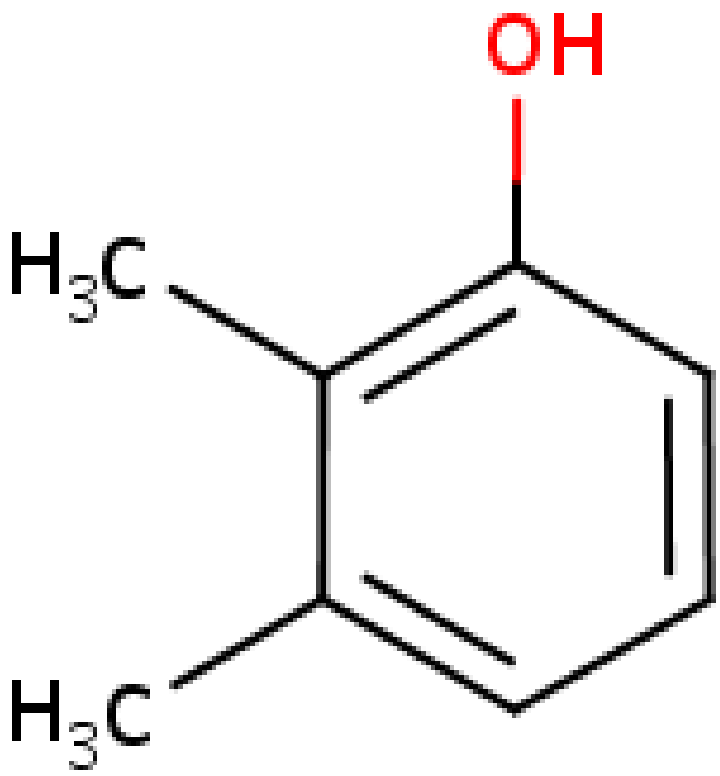
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	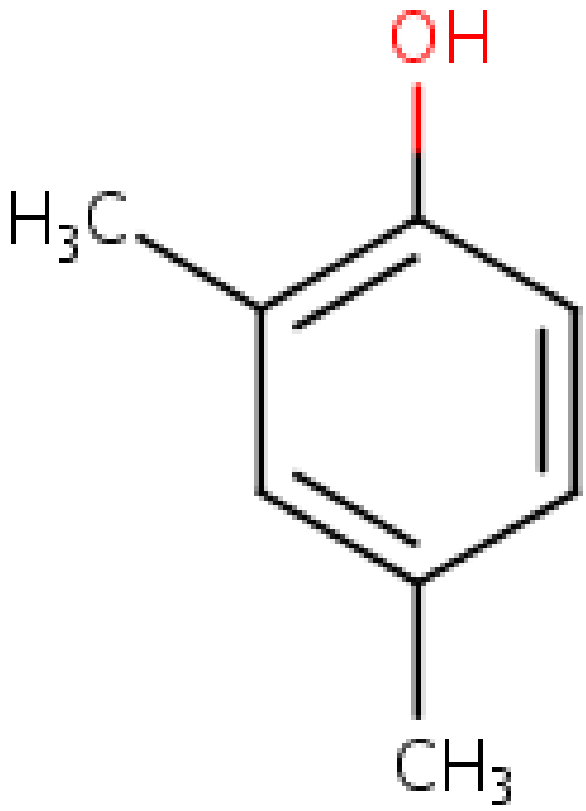
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	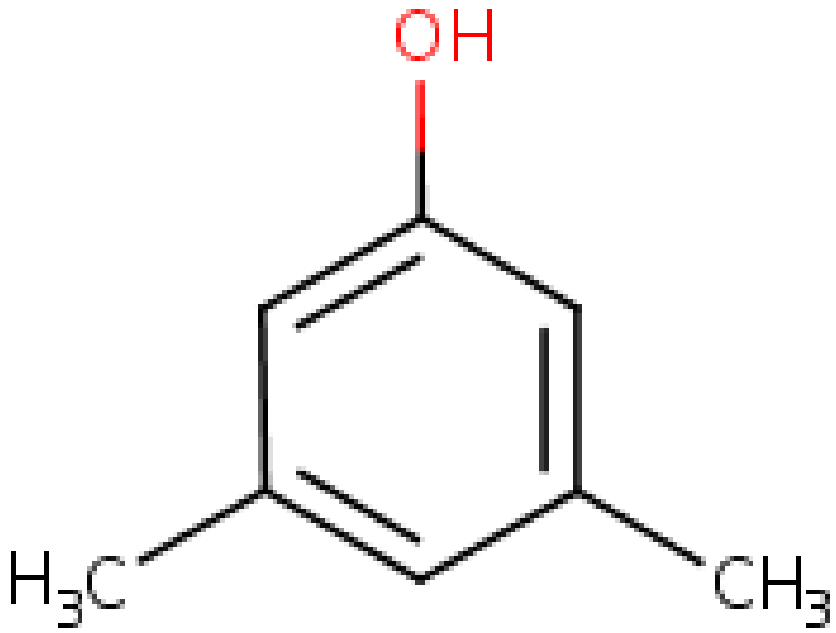
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	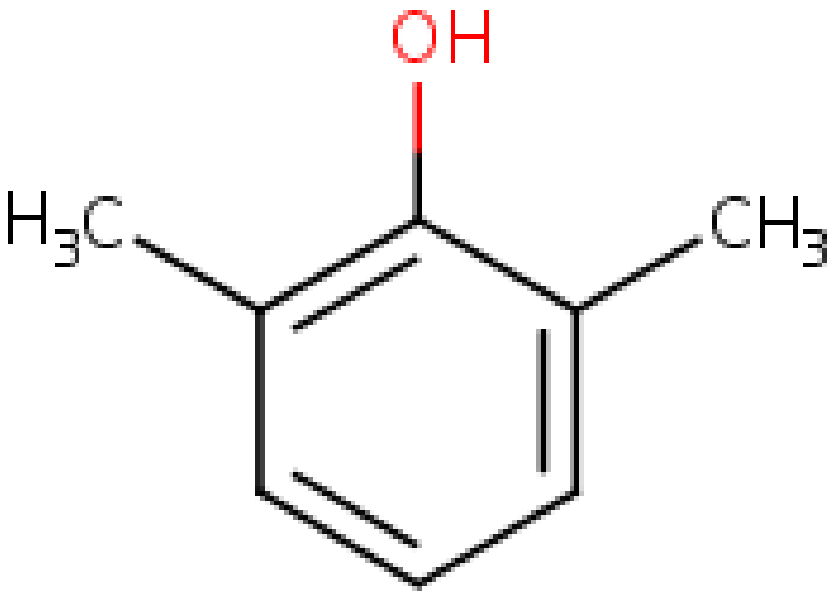
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Molecular Weight	122.17

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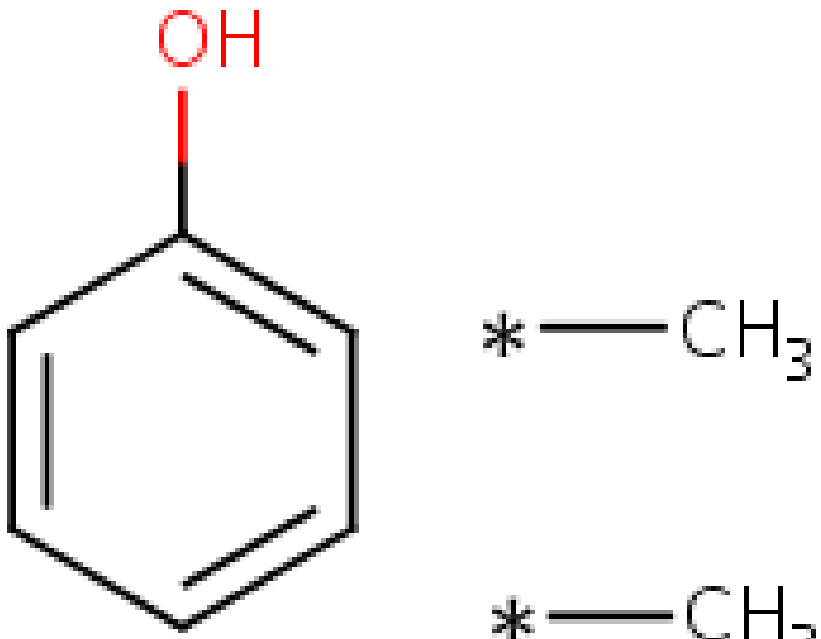
Structural Formula	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Molecular Weight	122.17

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