



Australian Government

Department of Health, Disability and Ageing

Australian Industrial Chemicals Introduction Scheme

Phenol, 5-methyl-2-(1-methylethyl)- (Thymol)

Evaluation statement (EVA00190)

30 September 2026

Draft



Table of contents

Contents

AICIS evaluation statement (EVA00190).....	4
Subject of the evaluation.....	4
Chemical in this evaluation	4
Reason for the evaluation	4
Parameters of evaluation	4
Summary of evaluation	4
Summary of introduction, use and end use.....	4
Human health.....	5
Proposed means for managing risk.....	7
Workers.....	7
Conclusions	8
Supporting information	9
Chemical identity	9
Relevant physical and chemical properties	9
Introduction and use	9
Australia.....	10
International	10
Existing Australian regulatory controls	11
Public	11
Workers.....	11
International regulatory status.....	12
Exposure standards	12
United States of America.....	12
Asia	12

Human exposure	12
Public	12
Health hazard information	16
Toxicokinetics.....	16
Acute toxicity.....	17
Corrosion/Irritation.....	20
Sensitisation.....	22
Repeat dose toxicity	27
Genotoxicity	29
Carcinogenicity.....	31
Reproductive and development toxicity	31
Neurotoxicity	33
Human health risk characterisation.....	33
Critical health effects.....	33
Public risk.....	34
References	36

AICIS evaluation statement (EVA00190)

Subject of the evaluation

Phenol, 5-methyl-2-(1-methylethyl)- (Thymol)

Chemical in this evaluation

CAS name	CAS number
Phenol, 5-methyl-2-(1-methylethyl)-	89-83-8

Reason for the evaluation

New information is available about human health risks.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). The evaluation statement includes a human health risk assessment for all identified industrial uses of the chemical in Australia. The use of thymol in food, therapeutic and agricultural products and veterinary products is not assessed in this evaluation as these are not industrial uses. The chemical is a major component of some essential oils and plant extracts in Australia. This evaluation does not cover these essential oils and extracts.

The chemical was previously assessed under the former scheme, National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (AICIS n.d.). The chemical was published as a Tier I assessment (determined not to pose an unreasonable risk to workers and public health at the time of publication) based on available data. New information has become available including for skin sensitisation and neurotoxicity. Therefore, this evaluation will:

1. Review the weight of evidence including new toxicity and use information.
2. Undertake a quantitative risk assessment to estimate potential public risks related to the chemical being used in consumer products.
3. Consider whether any means for managing risks are required based on the new information.

Summary of evaluation

Summary of introduction, use and end use

Thymol occurs naturally in thyme, savoury, marjoram, oregano and cumin and can be synthetically produced from m-cresol. Thymol is used in a variety of personal care products (cosmetics) and domestic products. Several personal care (cosmetic) and domestic products containing thymol have been identified in Australian commercial outlets and on websites

Based on available Australian and international information, the chemical is used in:

- Personal care products (cosmetics) at concentrations up to 0.06% in leave on products and 0.35% in rinse off products with identified functional uses as a denaturant, preservative and fragrance ingredient.
- Oral care products up to 0.25%.
- Domestic products including laundry and dishwashing products, cleaning and furniture care products and air care products, at concentrations up to 0.2%.

Online product information indicates that the chemical is mostly used in oral care products, skin care products applied to the face, body washes and soaps. The Australian use volume of thymol as a fragrance in 2023 was estimated to be 4,500 kg/year based on data collected in the Asia-Pacific region by the International Fragrance Association (IFRA).

The chemical is used in non-industrial applications including therapeutic goods, agricultural products, veterinary chemicals products, food and feed in Australia.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical. Based on physicochemical properties, the chemical is expected to be readily absorbed following oral, dermal and inhalation exposure.

The chemical is expected to have moderate acute oral toxicity. The majority of the available animal data support the existing GHS classification for this endpoint. The chemical has low acute dermal toxicity.

The available data indicate the chemical has potential to cause neurotoxic effects following single and repeated exposure. Reported effects following a single exposure to the chemical include depression, ataxia, coma, hypoactivity, drowsiness, paralysis, slight agitations, tremors, muscle twitching and loss of locomotor activity. The majority of these effects were reversible and occurred at sub-lethal doses from 500 mg/kg bw in acute toxicity studies and from 200 mg/kg bw/day in a repeat dose toxicity study. In a non-guideline study in Swiss mice, neurotoxic effects including memory impairment (reduced latency), compromised blood brain barrier (BBB) integrity, biochemical disruptions in the brain and elevated oxidative stress were observed. Based on these findings, a NOAEL of 10 mg/kg bw/day for neurotoxicity was determined.

Based on the available data, the chemical is considered to be corrosive to the skin, eyes and respiratory tract. In rabbits, skin necrosis and irreversible effects in the eyes were reported. Although no reliable inhalation data are available, based on the site of contact the chemical is also expected to be corrosive to the respiratory tract.

Based on the weight of evidence from animal and human studies, the chemical is considered as a weak skin sensitiser. Negative results were reported in two out of three animal studies. A positive result was observed at 20% concentration in the third study. Several human studies and case reports have shown mixed results with majority of positive cases observed at concentration of $\geq 1\%$.

Some evidence of chromosomal damage has been reported for thymol in both *in vitro* studies and *in silico* predictions. However, most guideline compliant *in vitro* and *in vivo* studies showed negative results. Overall, based on the weight of evidence, thymol does not present clear evidence of genotoxicity.

Based on the limited available data, there is no evidence the chemical causes specific adverse effects on sexual function, fertility and development. No reliable data are available to evaluate carcinogenicity for the chemical.

For further details of the health hazard information see **Supporting information**.

Hazard classifications relevant for worker health and safety

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

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Skin corrosion/irritation	Skin Corr. 1	H314: Causes severe skin burns and eye damage
Serious eye damage/eye irritation	Eye Dam. 1	H318: Causes serious eye damage
Skin sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Specific target organ toxicity (single exposure)	STOT Single Exp. 1	H370: Causes damage to organs – nervous system
Specific target organ toxicity (repeated exposure)	STOT Rep. Exp. 1	H372: Causes damage to the nervous system through prolonged or repeated exposure

In addition, the chemical satisfies the criteria for the following non-GHS hazard statements:

- AUH071: Corrosive to the respiratory tract.

Summary of health risk

Public

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

- at concentrations up to 0.35% in personal care products and up to 0.2% in domestic products
- by direct application of the chemical to the skin/hair/lips/oral cavity
- by direct skin contact during use of domestic products
- by incidental skin and eye contact with the chemical during use of domestic products
- by inhaling aerosols/vapours from air care and cosmetic products.

This chemical is acutely toxic by the oral route, corrosive to the skin, eyes and respiratory tract and is a weak skin sensitiser. At the low concentrations in use, the risk of corrosive and

sensitisation effects is expected to be low. The critical health effect for risk characterisation is neurotoxicity with a NOAEL of 10 mg/kg bw/day.

A margin of exposure (MOE) methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. Based on a quantitative risk assessment (QRA), using the worst-case exposure scenario, an MOE of 111 was calculated. For this risk characterisation, an MOE is considered protective when it is >100, to account for intra- and inter-species differences. Although the public may be exposed to the chemical from non-industrial uses, the worst-case exposure estimate assumes simultaneous use of all products containing the chemical at the highest concentration identified. International estimates of exposure based on probabilistic modelling indicate that the MOE would likely be significantly higher.

The risk estimates indicate that thymol is unlikely pose a risk to human health if used in cosmetic and domestic products at the low concentrations reported to be currently in use. Therefore, the chemical is not considered to pose a potential risk to the public which requires management.

Workers

During product formulation and packaging, oral, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment.

Worker exposure to the chemical at a lower concentration could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical local and systemic acute and long-term health effects, the chemical could pose a risk to workers. Control measures to minimise oral, dermal, ocular and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

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

Information relating to safe introduction and use

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

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

- using closed systems or isolating operations
- using local exhaust ventilation to prevent the 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.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

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

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

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

Conclusions

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

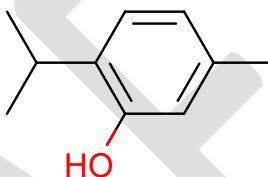
Note:

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

Supporting information

Chemical identity

CAS number	89-83-8
CAS name	Phenol, 5-methyl-2-(1-methylethyl)-
Molecular formula	C ₁₀ H ₁₄ O
Associated name	Thymol
Molecular weight (g/mol)	150.22
SMILES (canonical)	OC1=CC(=CC=C1C(C)C)C
Structural formula	



Relevant physical and chemical properties

Experimental (exp.) values are taken from the registration dossier for thymol submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the European Union (EU) (ECHA CHEM n.d.-a; ECH CHEM n.d.-b).

Physical form	White or colourless crystalline powder (exp)
Melting point	49.2 °C (exp.)
Boiling point	231.8 °C (exp.)
Vapour pressure	2.2 Pa at 25 °C (exp.)
Water solubility	980 mg/L at 20 °C (exp.)
pK_a	10.62 at 20°C (exp.)
log K_{ow}	3.3 at 20°C (exp.)

Introduction and use

Thymol is a naturally derived phenolic monoterpene compound mainly present in thyme, savoury, marjoram, oregano and cumin. It can also be produced synthetically from *m*-cresol (CIR 2006).

Australia

Limited specific Australian import, or manufacturing information for thymol has been identified. The Australian reported use volume of thymol in 2023 was estimated to be 4,500 kg/year based on data collected in the Asia-Pacific region by IFRA (IFRA).

Thymol is used in a variety of personal care products (cosmetics) and domestic products as identified in Australian commercial retail outlets and on websites, including:

- Skin care products [serum, mask, mist, hydrating gel, foam, cream (including eye cream), lip balm, face wash, soap] and hand clean products.
- Oral care products (toothpaste and mouthwash).

The chemical has reported domestic use in cleaning, furniture care and air care products. The chemical is also available neat for formulation of personal care products (soap) and domestic products (surface cleaning and air care products) by the public.

Thymol has reported non-industrial uses including in food flavouring agents and adjuvants, agricultural products, veterinary products and therapeutic goods (APVMA 2024; TGA n.d.). Thymol is listed in the [Australian Register of Therapeutic goods \(ARTG\)](#) as both an excipient and active ingredient in topical and oral products (TGA n.d.; TGA 2026a).

In Australia, chemicals in anti-dandruff hair care products and oral care products such as toothpaste and mouthwash may be regulated as cosmetic ingredients if they are excluded from TGA regulation under the [Therapeutic Goods \(Excluded Goods\) Determination 2018](#) (TGA 2024).

International

The chemical is listed in the International Nomenclature of Cosmetic Ingredients (INCI) database (Personal Care Products Council n.d.). The chemical has reported use in personal care products (cosmetics) with function as denaturant, preservative, fragrance ingredient or skin conditioning agent (CIR 2006; INCI beauty n.d.; Personal Care Products Council n.d.; ECHA CHEM n.d.-a). The chemical is listed on the IFRA transparency list (IFRA n.d.). Online product searches indicate that the chemical is mostly used in oral care products, skin care products applied to the face, body washes and soaps. There were no identified uses in leave on products applied to whole of body (INCI beauty n.d., INKEEDecoder n.d.). The chemical may be found at the following concentrations in personal care products (cosmetics) (Api et al., 2024; CIR 2006; DeLima Associates n.d.):

- 0.004% in hair care products (hair colorant/dye and shampoo)
- 0.06% in skin care products that include hand cream, face creams and serums
- 0.13% in lip balm
- 0.35% in facial cleansers
- 0.25% in toothpaste and 0.064% in mouthwashes.

There were no identified uses in personal care products applied to whole of body.

Thymol has reported domestic uses in washing and cleaning products (including surface cleaners, polishes and waxes), laundry and dishwashing products and air care products (ECHA CHEM n.d.-a). Limited information on product types and concentrations is available. An online product database identified use of the chemical in the following products (DeLima Associates n.d.):

- domestic cleaning products (0.05%)

- as a fragrance in an air freshener spray and car air freshener (concentration not specified).

Average use in perfumery applications has been reported as 0.2% (PerfumersWorld n.d.).

Thymol has also reported non-industrial uses:

- as FDA approved food ingredients (USFDA n.d.-a; USFDA n.d.-b)
- as an ingredient in various therapeutic products for its antifungal and antibacterial activity, including nail conditioners, oral care products, hair and scalp treatment
- in pet care products and insect repellent sprays
- in biocide products to control varroa mite in honeybee colonies (USEPA 2019)
- as antimicrobial and disinfectant products (USEPA 2019).

Globally, 100–1,000 metric tonnes of thymol have been reported to be used by the fragrance industry (Api et al., 2024). The Asia-Pacific use volume of thymol in 2023 was estimated to be 90,000 kg/year based on data collected by IFRA. Approximately 1,000–10,000 tonnes of thymol are introduced (manufactured or imported) annually into the European Union (ECHA Chem n.d.-a).

Existing Australian regulatory controls

Public

There are no identified controls for industrial uses of the chemical.

Thymol is listed in the Poisons Standard – [*The Standard for the Uniform Scheduling of Medicines and Poisons \(SUSMP\)*](#) in Schedule 6 as follows: THYMOL when packed and labelled for use as a pesticide. Schedule 6 chemicals are labelled with 'Poisons'. These are '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' (TGA 2026b). All other preparations of thymol are currently unscheduled.

Thymol is listed in Therapeutic Goods (Permissible ingredients) Determination as a [Schedule 1- Specified permissible ingredients and requirements applying to these ingredients when contained in a medicine](#) as follows: 'When used as an active ingredient, the medicine must be medicated space spray or medicated throat lozenges. When used as an excipient, only for use in medicated throat lozenges or topical medicines for dermal applications' (TGA 2026a).

Workers

The chemical is listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia, SWA) with the following hazard category and statements for human health (SWA n.d.):

Health hazards	Hazard category	Hazard statement
Acute Toxicity	Acute toxicity – Category 4	H302: Harmful if swallowed
Skin corrosion / irritation	Skin corrosion – Category 1B	H314: Causes severe skin burns and eye damage

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

International regulatory status

Exposure standards

The following Protective Action Criteria (PAC) (formerly known as temporary emergency exposure limits (TEELs) have been recommended by the [United States Department of Energy for thymol](#) (Chemwatch n.d.):

- 2.9 mg/m³ (PAC-1)
- 32 mg/m³ (PAC-2)
- 190 mg/m³ (PAC-3).

United States of America

The Cosmetic Ingredients Review (CIR) Expert Panel has concluded that thymol was safe at a concentration up to 0.5% when used in cosmetic and personal care products (CIR 2006).

Asia

In Japan, the chemical is restricted when used as preservative in cosmetic products at a maximum of 0.05 g per 100 g for rinse-off or leave-on products. The chemical is permitted to be used in cosmetic products intended for mucous membranes only for oral cavity (MHLW n.d.).

In Thailand, the chemical is permitted to be used as preservative in cosmetic products at up to [0.1%](#) (ASEAN n.d.).

Human exposure

Public

Cosmetic products

As thymol is used in a wide range of personal care and domestic products (see **Introduction and use**), public exposure to the chemical is expected to be significant. Oral, dermal, ocular and inhalation exposure is expected, depending on the type of product. The duration of exposure for various products is expected to differ significantly as the chemical is used in both rinse-off and leave-on products. For rinse-off products such as soaps or shampoos, exposure might only be for a few minutes, although some residual product can remain.

Whereas for leave-on products, the period of exposure could last for several hours. Australian use patterns for the various product categories are assumed to be similar to those internationally.

Cosmetics

Adult dermal exposure to the chemical in cosmetic products (see **Table 1** for details) was calculated as an internal dose (systemic exposure dose) which is proportional to the:

- use volumes (product amounts)
- product retention factors (reflecting proportions of product remaining on the skin during normal use)
- dermal absorption of the chemical.

For the exposure assessment, the product amounts and product retention factors were determined using values previously established by the SCCS (SCCS 2023) and RIVM (RIVM 2025). Given the chemical is also present in foot cream products, and in the absence of product-specific estimated daily use data, the default daily amount for hand cream was applied as a surrogate value to represent use in the foot creams. Oral exposure from oral hygiene products is considered incidental. The daily systemic exposure dose was calculated based on the amount that may remain on the oral mucosa during normal use (see **Table 2**). Product categories were chosen based on typical identified uses and reported concentrations for the chemical (see **Introduction and use** section). In the absence of product specific information, the concentration for skin care products was chosen (0.06%). A dermal absorption (DA) rate of 100% is assumed and a default body weight of 60 kg is used for calculation purposes.

Table 1 – Daily dermal systemic exposure to thymol through relevant cosmetic products based on the typical concentrations of thymol

Product type	Amount (mg/day)	C (%)	Retention Factor (RF) (unitless)	Daily systemic exposure (mg/kg bw/day)
Face cream	1540	0.060	1.000	0.0154
Hand/foot cream	2160	0.060	1.000	0.0216
Shampoo/conditioner	14380	0.004	0.010	0.0001
Shower gel (body soap)	18670	0.060	0.010	0.0019
Hand wash soap	20000	0.060	0.010	0.0020
Lip balm	57	0.13	1.000	0.0012
Facial cleanser	4800	0.35	0.01	0.0028
Hair styling products	4000	0.004	0.100	0.0003
Hair dye	11600	0.004	0.100	0.0008
Total	—	—	—	0.0461

Daily systemic exposure = (amount x C x RF x A)/BW
(C= Chemical concentration; RF= retention factor; A= absorption; BW=body weight). Note - conversion factor of 0.0001 to account for C/DA as a % (1/100 x 1/100)

Table 2 – Daily oral systemic exposure to thymol through relevant oral hygiene products based on typical concentrations of thymol

Product type	Amount (mg/day)	C (%)	Retention Factor (RF) (unitless)	Daily systemic exposure (mg/kg bw/day)
Toothpaste (adult)	2750	0.250	0.050	0.0057
Mouthwash	21620	0.064	0.100	0.0231
Total	–	–	–	0.0288

Daily systemic exposure = (amount x C x RF x A)/BW

(C= Chemical concentration; RF= retention factor; A= absorption; BW=body weight). Note - conversion factor of 0.0001 to account for C/A as a % (1/100 x 1/100)

The chemical may also be used in cosmetic products that could lead to inhalation exposure. Based on probabilistic modelling, RIFM estimated inhalation exposure and total systemic exposure to the chemical to be 0.000063 and 0.0012 mg/kg/day, respectively (Api et al. 2024). These exposure estimates assume 100% absorption via dermal, oral and inhalation routes and consider 25 product categories, including personal care products and air care products. Inhalation contributes approximately 5%, indicating that non-inhalation routes account for ~95% of exposure. The calculated total systemic exposure (0.0749 mg/kg bw) (see **Table 1** and **Table 2**) covers the worst-case scenario when thymol is used daily in all products at maximum identified concentration levels. Therefore, the estimated total systemic exposure from dermal exposures and use of oral hygiene products is considered conservative enough to cover both dermal and inhalation exposures.

Domestic products

The public may also be exposed to the chemical through its identified uses as a fragrance in domestic products (see **Introduction and use** section), including various cleaning, laundry and dishwashing products. Data on typical use patterns of cosmetic and domestic product categories in which thymol may be used are shown in the following tables (See **Table 3** and **Table 4**) (Cadby et al., 2002; ACI 2010; Loretz et al., 2006). The concentration is based on reported concentrations for household cleaning products. Although these concentrations were reported for disinfectant use, they are considered reasonable worst-case concentrations.

Table 3 – Daily indirect dermal exposure to thymol from household products (from wearing clothes) based on the typical concentrations of thymol

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.05	0.95	10	0.0018
Fabric softener	90	0.05	0.95	10	0.0007
Total	–	–	–	–	0.0025

Daily systemic exposure = (Amount x C x PR x PT x A)/BW

(C = chemical concentration; PR = product retained; PT = product transferred; A = dermal absorption; BW = body weight). Note - conversion factor of 0.00001 to account for C/PR/PT/A as a % and unit conversion (g to mg) ((1/100 x 1/100 x 1/100 x 1/100) x 1000)

Table 4 – Direct dermal exposure to thymol from household products based on the typical concentrations of thymol

Product type	Frequency (use/day)	C (%)	Contact Area (cm ²)	Product Use C (g/cm ³)	Film Thick ness (cm)	Time Scale Factor (unitless)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.05	1980	0.01	0.01	0.007	0.00002
Dishwashing liquid	3	0.05	1980	0.009	0.01	0.03	0.00013
All-purpose cleaner	1	0.05	1980	1	0.01	0.007	0.00116
Total	–	–	–	–	–	–	0.00131

Daily systemic exposure = (frequency x C x contact area x product use concentration x film thickness on skin x time scale factor x A)/body weight. Note - conversion factor of 0.1 to account for C/A as a % and unit conversion (g to mg) ((1/100 x 1/100) x 1000).

Inhalation exposure from the use of air care products was estimated using the ConsExpo web tool v1.2.1 (RIVM 2026). The assessment applied standard assumptions and exposure parameters as outlined in the RIVM Air Fresheners Fact Sheet (RIVM 2021), with the exception of adult body weight, which was set at 60 kg.

Based on the limited information available the following product scenarios and associated inhalation exposure models were selected within the relevant product categories:

1. Instant action air fresheners – volatile substances
Scenario: Spraying volatile substances by adult users
Product: Instant air refreshment sprays (aerosol can)
Category: Home air fresheners.
2. Car air fresheners
Scenario: Inhalation from fragrance infused items by adult users
Product: Fragrance infused items
Category: Car air fresheners.

These scenarios were selected to represent typical consumer use patterns and product types within the air care category. The concentration value of 0.2% was chosen based on average concentration in perfumery products. The estimated daily systemic exposure based on these assumptions are:

- 0.0111 mg/kg bw/day for instant action air fresheners
- 0.0000059 mg/kg bw/day for car air fresheners.

Health hazard information

Toxicokinetics

Several animal and human toxicokinetic studies are available for thymol. Overall, the data indicates that the chemical is likely to be rapidly absorbed, widely distributed and rapidly eliminated mostly as metabolites.

Absorption

Limited absorption data are available. Based on physicochemical properties of thymol (log Kow value of 3.3 low molecular weight (< 200 g/mol) and relatively high-water solubility (980 mg/L)) the chemical is expected to be well absorbed via all routes of exposure.

In a non-guideline study, thymol was detected in the stomach, intestine, and urine following oral administration of thymol in sesame oil to rats (500 mg) and rabbits (1–3 g).

A human study was conducted to determine systemic availability and pharmacokinetics of thymol (Kohlert et al. 2002). Healthy volunteers (n=12) were administered with a single oral dose of Bronchipret® TP tablet, (equivalent to 1.08 mg thymol). Thymol was found to be rapidly absorbed from the upper part of gastrointestinal tract (within 20 min detected as thymol sulphate) and the maximum peak plasma concentration (93.1 ± 24.5 ng/mL) was reached at 1.97 ± 0.77 h.

Distribution

Free thymol is typically undetectable in plasma and mainly found as a sulphate form rather than glucuronide. Following oral administration in humans, thymol exhibited a large volume distribution ($V_{dss/f}$) of 14.7 L, indicating extensive distribution throughout the body (Kohlert et al. 2002).

In a non-guideline study, rabbits were fed with thymol for 21 days at 250 mg/kg feed (Bacova et al. 2020). On day 21, thymol was detected in the intestinal wall, plasma and faeces at concentrations of 0.04 ± 0.03 µg/L, 0.05 ± 0.02 µg/L and 0.89 ± 0.45 µg/L, respectively. However, 7 days following the end of administration, thymol was no longer detected in the plasma or intestinal wall though it remained in the faeces at a much lower concentration (0.08 µg/L).

Metabolism

Human metabolic studies demonstrate that thymol undergoes phase I and phase II metabolic transformation following oral administration. In a human study (n=2), administration of thymol at 0.6 g oral dose showed that majority of thymol is metabolised, and only a minor amount of unmetabolised thymol is excreted in the urine after 24 hrs. Metabolites detected included thymol glucuronide, thymol sulphate and small amounts of thymolhydroquinone sulphate (Takada et al. 1979). In a study of human volunteers (n=6), participants received an oral dose of thymol at 50 mg (dissolved in 1 ml ethanol and 200 ml water). Urine analysis revealed phase I metabolites of thymol, including p-cymene-3,8-diol and its dehydration product, p-cymene-3-ol-8-ene, and p-cymene-2,5-diol, the corresponding oxidation product p-cymene-2,5-dione and p-cymene-2,3-diol (Thalhamer et al. 2011). In other human studies thymol was shown to primarily metabolise to phase II metabolites mainly thymol sulphate, thymol glucuronide and with a smaller amount to thymolhydroquinone sulfate (Kohlert et al.

2002; Takada et al. 1979). Both sulphate and glucuronide metabolites were detected in the urine while only the sulphate metabolite was identified in plasma (Kohlert et al. 2002).

Elimination

In humans, approximately 16% of the administered dose was excreted via kidney with a renal clearance rate of 0.271 ± 0.7 L/h (Kohlert et al. 2002). Urinary thymol was measured as the sum of its glucuronide and sulphate conjugates. Thymol showed a mean terminal elimination half-life of 10.2 h and was detectable in plasma as thymol sulphate for up to 41 h post-administration (Kohlert et al. 2002).

In male albino rats, thymol and its metabolites were rapidly excreted within 24 hrs following oral administration of approximately 150 mg/kg body weight in 1-2 mL propylene glycol (Austgulen et al. 1987). In this study, a significant portion of either unchanged thymol or glucuronide or sulphate conjugates were eliminated via urine. Substantial oxidation of methyl and isopropyl side chains resulted in the formation of benzyl alcohol and 2-phenylpropanol, along with their corresponding carboxylic acids. In contrast, a ring hydroxylation of two phenols was considered as a minor reaction.

Acute toxicity

Oral

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Acute toxicity – Category 4; H302 (Harmful if swallowed)' (SWA n.d.). The majority of the available animal data support the existing classification. Some more recent studies reported to be conducted according to OECD test guidelines (TG) indicate that the chemical has low acute oral toxicity. However, given the limitations in either the study methodology or study details there is not sufficient evidence to remove the current classification.

Several non-guideline studies on animals and a poisoning case study in humans are available for evaluating the acute oral toxicity of thymol. There is limited information on the studies performed and most of these studies are either not conducted according to OECD test guidelines (TG) or not specified as being compliant with good laboratory practice (GLP). The two available studies reported to be in accordance with OECD TG reported a median lethal dose (LD₅₀) value of > 2000 mg/kg bw, while majority of the non-guideline studies reported LD₅₀s between 300 and 2000 mg/kg bw in a range of animal species.

In an acute oral toxicity study (GLP compliance-not specified) reported to be conducted in accordance with OECD TG 423, female Sprague-Dawley (SD) rats (3 /dose) were treated with a single oral dose of the chemical at 5, 50, 300 or 2000 mg/ kg in 20% w/v in methyl cellulose. No mortality was observed in the 4 days post-administration. The LD₅₀ value of > 2000 mg/kg bw was reported. Reported sublethal signs of toxicity included decreased locomotor activity, recumbent (lying down), walking abnormality, muscle relaxation and deep breathing at 2000 mg/kg bw. At 300 mg/kg there were no clinical signs of toxicity. Some macroscopic changes in internal organs were observed during necropsy at both 300 mg/kg and 2000 mg/kg bw (ECHA CHEM n.d.-b). This study was assigned a reliability score of 4 (not assignable) by ECHA due to insufficient experimental details (ECHA 2024b).

In an acute oral toxicity study (GLP compliance-not specified) conducted in accordance with OECD TG 401, male albino rats (5/dose) were treated with a single oral dose of the chemical at 500, 1000, 2000, or 4000 mg/kg bw (prepared as 10% oil-in-water emulsion). Rats were

subjected to 14 days observation period. Limited details on study design were available. Rat mortality was observed at 2000 mg/kg bw (1/5 rats) and 4000 mg/kg bw (5/5 rats). The LD50 value of 2462 mg/kg bw was reported. No changes to the body weights, skin, eyes, respiratory systems and behavioural patterns were observed. No other clinical observations were reported (Gad et al. 2013).

In a non-guideline rat study, male and female rats (n=5/sex/dose) received thymol as a 20% solution in propylene glycol per by gavage. Animals were observed for up to 2 weeks. Clinical signs of toxicity reported included depression, ataxia in most groups and coma at high doses. The LD50 value of 980 mg/kg bw was reported (Jenner et al. 1964; ECHA CHEM n.d.-a).

In non-guideline mouse studies, the following LD50s and clinical signs were reported:

- 1050 mg/kg bw in female and 1200 mg/kg bw in male mice (hypoactivity, ataxic gait and small intestinal congestion) (ECHA CHEM n.d.-a).
- 640 mg/kg bw [no further details on clinical signs were available (ECHA CHEM n.d.-a)].
- 1210 mg/kg bw (no further details on clinical signs were available) (ECHA CHEM n.d.-a)
- 650 mg/kg bw (10% emulsion in water) and 1300 mg/kg bw (10% solution in peanut oil) (drowsiness, paralysis, muscle twitching, spasm and slight agitations) (ECHA CHEM n.d.-a)
- 640 mg/kg bw (alcohol/propylene glycol/water) in male mice (decrease in spontaneous movements, piloerection and paralysis of anterior limbs) (ECHA 2024a).
- 1800 mg/kg bw (depression to the point of prostration at a higher dose and only depression at lower dose; pathological examination showed gastrointestinal irritation (haemorrhages in the region of small intestine), severe oedema and congestion of lungs observed acute and delayed deaths (McOMIE et al. 1949).

In other non-guideline studies, the following LD50 and sublethal effects were reported:

- 750 mg/kg bw in rabbits (no further details are available (ECHA CHEM n.d.-a)
- 880 mg/kg bw in guinea pigs [irritated gastro-intestinal tract, tremors, coma and respiratory failure (Jenner et al. 1964)].

Dermal

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

In a GLP compliant acute dermal toxicity study conducted in accordance with Directive 84/449/EWG, Wistar rats (n = 5/sex) were treated with a single dose of 2000 mg/kg bw of the chemical (purity: 99.5-99.6%) in Cremophor for 24 hours. Animals were observed for clinical signs for 14 days. No mortality was observed. The LD₅₀ was > 2000 mg/kg bw. Reported signs of toxicity included brownish discolouration in their skin in 3/5 male and 2/5 female rats which lasted up to 4 days (ECHA CHEM n.d.-a).

In an acute dermal toxicity study (GLP compliance-not specified), New Zealand rabbits (n = 10 /sex) were treated with a single dose of the chemical at 2000 mg/kg bw. No mortality was observed. The LD50 was >2000 mg/kg bw. Reported signs of local toxicity included moderate erythema (10/10 rabbits), moderate oedema (8/10 rabbits) and slight oedema (2/10 rabbits) at 24 hrs and slight erythema (4/10 rabbit) on day 7 (ECHA CHEM n.d.-b; ECHA 2024b).

Inhalation

No reliable data are available.

Observation in humans

There are reports in humans that involve accidental or incidental poisoning from products containing thymol. An accidental aerosol spraying of volatile oil (that includes thymol at an unknown concentration) which led to a fast breathing and pneumonitis in a 6 week-old infant was reported (Krueger, 1967). In addition, a fatal poisoning case involving the ingestion of approximately 3 L of mouthwash containing a mixture of ingredients, including an estimated 1.92 g of thymol (5.94 g total phenolic compounds), has been reported (Soo Hoo et al. 2003). However, because thymol was not the sole or primary ingredient involved in these incidences, the contribution of thymol to the reported clinical symptoms and fatal outcomes cannot be determined with certainty.

Specific target organ toxicity – single exposure (STOT SE)

Based on the available acute and subchronic toxicity studies, the chemical has potential to cause neurotoxic effects following a single oral exposure, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section).

Clinical signs of toxicity included in rats included depression, ataxia, coma, hypoactivity, drowsiness, paralysis, slight agitations, tremors, muscle twitching and loss of locomotor activity (see **Acute toxicity- Oral**). The majority of these effects were reversible and occurred at sub-lethal doses from 500 mg/kg bw in acute toxicity studies. While the observed effects may be indicative of central nervous system depression, some effects e.g. tremors, spasms and agitations suggest neurotoxicity. This is also supported by the neurotoxicity effect such as ataxic gait observed from day 0-1 in a repeated dose toxicity study in female rats at 200 mg/kg bw/day, after the first exposure (see **Neurotoxicity** section).

The following sub-lethal clinical effects were reported:

- Decreased and increased activity, piloerection, ataxia, slow breathing, hunched posture, lethargy and drooping eyelids at 1000 mg/kg bw. These effects were reversible within 2 days (ECHA 2024a; ECHA 2024b).
- Dose-dependent increase of the severity of effects including decreased activity at 500 mg/kg bw, ataxia at 1000 mg/kg, ptosis and lethargy at 2000 mg/kg bw. These effects were reversible within 2–3 days (ECHA 2024a; ECHA 2024b).
- Reduced locomotor activity, lying down, walking abnormality, muscle relaxation and deep breathing occurred at 2000 mg/kg bw (no mortality reported) (ECHA CHEM n.d.-b).
- Decrease in spontaneous motor activity and ataxic gait were observed in some females in a repeat dose and reproductive/development study from day 0-1 at 200 mg/kg bw/day of administration. Locomotor effects were reversible within 10 days while ataxic gait was observed throughout the treatment period. No clear exacerbation of the symptoms was described after repeated exposure pointing to an acute effect (ECHA 2024a; ECHA 2024b).

A number of studies with limited information available had similar clinical observations as above. However, the doses for which sub-lethal effects occurred were not specified and there was no information of incidence and reversibility for these studies.

In a pharmacokinetic study, CD1 mice (n =15-19/sex/dose) were given single oral doses of 1000 or 1250 mg/kg bw and blood samples were taken at 1, 2, 4, 8, 12 and 24 h post dosing. In two preliminary tests (single oral doses of 1000 and 1250 mg/kg bw, respectively), the following effects were observed in all mice: ataxia, bradypnoea, prone posture, piloerection, decreased activity and ptosis. One male in the preliminary study at 1000 mg/kg bw dose also displayed loss of righting reflex and ptosis from 2 to 4 hrs after dosing and one female displayed prone and pallor extremities from 15 min to 4hrs after dosing. Treated mice appeared normal on day 2 post-dosing. In the main test (single oral 1000 mg/kg bw dose), similar clinical signs of toxicity were reported: increased activity, piloerection, ataxia and decreased activity ranging from 1 to 8 hrs post-dose in both male and female mice. Additional symptoms included bradypnea (1 male at 8 h), ataxia (4 males up to 2 hrs post dose and 6 females up to 4 h post dose) and both hunched posture and lethargy (1 male at 2 h post dose, 1 female at 4 h post dose). These observations indicate transient toxic effects to the nervous system at doses of 1000 and 1250 mg/kg bw (ECHA 2024a; ECHA 2024b).

In two *in vivo* genotoxicity studies, transient effects to the nervous system were observed after single oral administration by gavage. This included a GLP compliant chromosome aberration study performed in accordance with OECD TG 475, CrI:CD-SD rats (ataxia and decreased activity from 1000 mg/kg bw/day) and an *in vivo* micronucleus test (ataxia, decreased activity and respiratory stress from 500 mg/kg bw/day) (ECHA 2024a; ECHA 2024b).

Corrosion/Irritation

Skin irritation

The chemical is currently classified as Skin Corr 1B. in the HCIS (SWA n.d.). The observation of necrosis in animal studies support classification as a corrosive. However, as the chemical has not been tested for exposure durations of less than 4 hrs, the available data were not sufficient to support the current subcategorisation. Therefore, a minor amendment to the current classification is warranted (see **Hazard classifications relevant for worker health and safety** section).

In a skin irritation study (GLP compliance-not specified) conducted in accordance with OECD TG 404, 6 New Zealand White rabbits (4 males and 2 females), were treated with 500 mg of the chemical (99.5% pure as paste in water) for 4 hrs under semi-occlusive conditions. Observations were recorded at 24, 48, 72 hrs, 7 days and 14 days after patch removal. The following mean scores for all animals were reported based on observations at 24, 48 and 72 hrs: 2.1 for erythema and 2.1 for oedema, respectively (maximum score of 4). Signs of irritation include necrosis at application site within 1 h (1 animal), hardened application site within 1h (2 animals) and necrosis in 1 rabbit within 1 day and in 2 rabbits within 2 days. The erythema and oedema were not fully reversible within 14 days in 4/6 animals and 2/6 animals, respectively (ECHA CHEM n.d.-a; ECHA 2024a).

In a non-guideline skin irritation study (GLP compliance- not specified), rabbits (number, sex, strain not specified) were treated with the chemical prepared in ether for 24 hrs at a dose of 420 mg/kg bw under occluded conditions on the shaved back skin. Observations were recorded at 24 hrs and 10 days after patch removal. Signs of irritation include skin turning (parchment-like) within 24 hrs and complete necrosis of superficial layer was observed after 10 days (McOMIE et al. 1949).

In a non-guideline skin irritation study (GLP compliance- not specified), Himalayan white-spotted guinea pigs (n = 6-8 animals/group) were treated with the 0.025 mL of chemical (purity unspecified) (undiluted and progressively diluted solution). The chemical

was applied to a 2 cm² area under non-occlusive conditions to establish a dose-response curve for minimal irritating concentration. Observations were recorded 24 hrs after application. The minimum irritating concentration was reported as 3% after single application. Signs of irritation at 3% concentration include mild erythema in 25% of tested animals. The erythema reversibility was not specified (Klecak et al. 1977).

Eye irritation

Based on the available data, the chemical causes irreversible effects on the eye, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section).

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, the chemical (0.1 mL) was instilled into 1 eye each of 3 New Zealand White rabbits. The eyes were washed out after 24 hrs and observed at 1, 24, 48, 72 hrs as well as 7, 14 and 21 days. The following mean scores for individual animals were reported at 24, 48 and 72 hrs:

- Corneal opacity – 2.7, 2, 1.3
- Iritis – 1, 1, 1
- Conjunctival redness – 2.3, 2.3, 2.3
- Chemosis – 2, 2, 2.3.

On day 14, 2 out of 3 rabbits developed pannus and eyeball swelling was observed in one of the rabbits. All rabbits showed a corneal lesion (as determined by fluorescein test) at the end of observation period (day 21). The observed effects were not reversible in 2 animals within 21 days. (ECHA CHEM n.d.-a).

In a non-guideline eye irritation study (GLP compliance-not specified), the chemical (0.03 mL thymol prepared in 40% ethylene glycol) was instilled into the cornea of rabbit for 72 hrs. The extent of cornea damage was observed and scored according to the Draize score at 1, 24, 48, and 72 hrs. The Draize scores were 32, 80 and 80 out of maximum score of 110 after exposure for 1, 24 and 72 hrs, respectively. At 24 hrs exposure, an entire corneal epithelium surface was damaged as observed from fluorescein test. After 24 hrs of exposure, the treated eyes were completely closed, and the extent of injury could not be evaluated by the scoring method. Thus, these scores were estimated for 24 and 72 hrs (McOMIE et al. 1949).

Respiratory corrosion

The chemical is corrosive as observed in skin and eye exposure studies. Therefore, inhalation of thymol is expected to cause corrosion of the mucous membrane of the respiratory tract. From animal studies, clinical signs such as gastrointestinal irritation, stomach erosion, glandular stomach changes, thickening of forestomach wall, mucosal hyperplasia, infiltration of inflammatory cells and oedema were observed (Jenner et al. 1964; ECHA CHEM n.d.-a) (See **Acute and Repeat dose toxicity** section). This indicates that the mechanism of toxicity is irritation/corrosivity (see **Hazard classifications relevant for worker health and safety** section). Although no reliable inhalation data are available, the available evidence of site of contact corrosive effects and the decision by ECHA (ECHA 2024a), support classification with the following non-GHS hazard statements:

- AUH071: Corrosive to the respiratory tract.

Sensitisation

Skin sensitisation

No guideline studies are available. Based on the weight of evidence from animal and human data, the chemical is expected to be a weak skin sensitiser, which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section). Due to limitations in the quality of the data sub-categorisation according to the GHS criteria is not supported.

In 2 out of 3 animal studies (including one incorporating 4 tests) no skin sensitisation reactions were reported (Klecak et al. 1977; Van der Walle et al. 1982). However, a weak sensitisation reaction was reported at 20% thymol concentration in a third animal study (ECHA 2024a, ECHA 2024b).

Thymol has been evaluated in multiple skin sensitisation studies in humans, with both positive and negative results reported (see **Table 5a** and **5b**). Some studies have reported skin sensitisation responses at concentrations $\geq 1\%$. In positive studies, the frequency identified has been graded as both high and low/moderate (ECHA 2024a). The available studies do not allow characterisation of the incidence of exposure.

Animal studies

Thymol (purity unspecified) was assessed for skin sensitisation in four non-guideline tests by Klecak et al. 1977; Draize test, Maximisation test (GPMT), Freund's Complete Adjuvant (FCA) test and an Open Epicutaneous test (OET). Concentrations above 10% were not tested due to systemic toxicity concerns.

In a GPMT study (guideline not stated), 20 female guinea pigs were treated with 10% thymol in FCA and distilled water intradermally followed by topical induction 7 days later. The animals were challenged two weeks after topical induction with 5%, 10%, and 20% thymol in acetone. A weak sensitisation effect was observed at the 20% challenge concentration (mean response score 0.4). The chemical was considered negative at 10% concentration (mean response 0.2) (ECHA 2024b).

In the non-guideline Draize test, guinea pigs (Himalayan white-spotted, 6-8 animals, male and female) were treated intradermally with 0.05 mL of a 0.1% solution of the chemical in an isotonic saline on day 0 and further doses of 0.1 mL each on 9 alternate days. The treated animals did not elicit any response during the induction or upon challenge treatment with 0.05 mL of 0.1% solution on days 35 and 49. The chemical was reported to be non-sensitising in this study (Klecak et al. 1977). No other details were provided.

In the non-guideline maximisation test, guinea pigs (Himalayan White-spotted, 6-8 animals, male and female) were induced by intradermal injection with 0.1 mL of 5% emulsion of the chemical, 0.1 mL of a 5% emulsion of the same chemical in FCA, and 0.1 mL of FCA alone. Each injection was given twice. On day 8, 250 mg of the chemical dissolved in petrolatum at 25% was applied to a clipped skin area on the neck of the animals under occlusion for 2 days. The animals were challenged with the application of sub irritant concentration of the chemical in petrolatum in flank for 24 hrs on day 21. None of the treated animals showed skin reactions until 48 hrs of observation period. The chemical was reported to be non-sensitising in this study (Klecak et al. 1977). No other details were provided.

In the non-guideline sensitisation FCA test, guinea pigs (Himalayan White-spotted, 6-8 animals, male and female) were treated intradermally into the neck with 0.05 mL of the undiluted chemical mixed with the same volume of FCA on day 0, 2, 4, 7, and 9 (total dose- 250 mg. The control animals were treated with 5 × 0.05 mL of FCA alone. The animals were challenged with the application of sub-irritant concentration of the chemical in petrolatum in flank for 24 hrs on day 21. None of the treated animals showed skin reactions until 48 hrs during the observation period. The chemical was reported to be non-sensitising in this study (Klecak et al. 1977). No other details were provided.

In the non-guideline OET, guinea pigs (Himalayan White-spotted, 6-8 animals, male and female) were treated with the 0.1 mL of 3% chemical in a vehicle to an area of 8 cm² of the clipped flank skin. The 3% concentration was selected based on preliminary OET results which identified 3% as a threshold concentration suitable for evaluating early skin sensitisation potential. The application was repeated daily for 21 days at same site. The application site was left uncovered and monitored for reaction for 24 hrs after each treatment. The animals were challenged with 0.025 mL of 3% chemical to a skin measuring area of 2 cm². The animals were monitored for 24, 48 and 72 hrs. None of the treated animals showed skin reactions. The chemical was reported to be non-sensitising in this study (Klecak et al. 1977). No other details were provided.

In a non-guideline sensitisation test, guinea pigs sensitised to p-methoxyphenol were tested for cross-reactivity to thymol (in methyl ethyl ketone and arachis oil). No sensitisation to thymol was reported (Van der Walle et al. 1982).

In silico

The chemical has no structural alerts for protein binding based on the mechanistic profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox v 4.5 (OECD 2025).

The QSAR modelling using OASIS-TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator) version 2.31.2.82 (GHS model version 02.04) (OASIS LMC 2025) predicted that the chemical is a non-sensitiser.

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.3.0 (Lhasa Limited) was utilised to estimate the skin sensitisation potential of the chemical. The chemical is predicted to be positive with an alert for skin sensitisation by substituted phenols. Substituted phenols may interact with proteins via formation of free radicals, electrophilic ortho- or para-quinones, or ortho- or para-quinone methides. The predicted effective concentration for a 3-fold increase in lymphocyte proliferation (EC3) for the chemical was 3.4% based on local lymph node assay (LLNA) EC3 values available for other substituted phenols. The DEREK reasoning level was equivocal indicating there is an equal weight of evidence for and against the proposition.

Observation in humans

Human skin sensitisation data for dermal exposure to thymol are summarised below in **Table 5a** and **Table 5b**:

Table 5a – Summary of human case studies evaluating skin sensitisation potential of thymol

Source	Population and study information	Thymol concentration and Vehicle	Findings/observation	Conclusion
Fisher 1989	A 43-year-old patient with chronic paronychia was applied with Listerine for 3 weeks under occlusion. A spreading of pruritic dermatitis after 3-weeks exposure was observed. Further 48h patch tests with ingredients of Listerine were conducted. Listerine had following active ingredients; thymol 0.6%, eucalyptus oil 0.9%, methyl salicylate 0.6%, menthol 0.4% and traces of benzoic acid. It also contained water, alcohol 26.9% and poloxamer 407 and caramel.	Patch tests were conducted with following ingredients: 1% thymol in petrolatum; Eucalyptus oil in 1% alcohol; methyl salicylate in 2% in olive oil; menthol in 1% petrolatum and benzoic acid in 5% petrolatum.	A positive reaction was observed with 1% thymol in petrolatum: None in three controls.	Weak sensitiser requiring prolonged contact with occluded and inflamed skin.
Lorenzi et al., 1995	Patch test in 70 years old woman with chronic paronychia and control group (20 volunteers).	4% thymol in chloroform (in 70 years old woman) and 1% thymol in pet. (control group).	Positive reaction at 4% thymol in chloroform and negative reaction in control group.	Positive
Papa and Shelley 1964	Skin test in women aged 31 years with methanol hypersensitivity.	0.1 cc of 75% thymol in alcohol.	Local irritation only, negative reaction.	Negative
Bleumink et al. 1973	A patch test in a wood worker for 2 years who developed allergic contact dermatitis in face, hands and arms.	0.1 and 1% thymol in ethanol.	Negative reaction.	Negative

Table 5b – Summary of human patch test studies evaluating skin sensitisation potential of thymol

Source	Population and study information	Thymol concentration and Vehicle	Findings/observation	Conclusion
Berova et al., 1990	Patch test in 84 dental professionals with contact dermatitis .	1% thymol in petrolatum.	One positive reaction (1.2%).	low/moderate frequency of sensitisation
Menenghini et al., 1971	Study 1. Patch test in 290 patients with eczematous dermatitis. Study 2. Patch test on the intact skin of the back of 50 healthy volunteers.	Study 1. 1% thymol in petrolatum. Study 2. Concentration not specified.	1. None of them showed positive reactions. 2. Highest non-irritant thymol concentration is 5% thymol (typical concentration in topical preparation is 0.4%).	Negative
Nethercott et al., 1989	Patch test in 19 patients with eyelid dermatitis out of 70 patients.	1% thymol in petrolatum.	No positive reactions.	Negative
Dohn 1980	Patch test in 221 city resident patients in whom allergy was suspected because of contact dermatitis or as a complication of other dermatological disease. Considered by ECHA RAC a general population study (ECHA 2024a).	1% thymol in spir.dilut.	1 positive reaction (0.45%).	High frequency of sensitisation
ECHA CHEM n.d.-a.	Patch test in 300 persons working in stomatologists consulting room.	5% thymol in glycerol.	39 positive reactions (13%).	High frequency of sensitisation
ECHA CHEM n.d.-a.	Patch test in 100 eczematous patients.	1% thymol in petrolatum.	No positive reaction.	Negative
Reichert-Penetrat et al. 2001	Patch test in 2 volunteers who showed acute dermatitis after operation.	1% thymol in petrolatum and 1% thymol in alcohol.	Negative reactions.	Negative

Source	Population and study information	Thymol concentration and Vehicle	Findings/observation	Conclusion
Francalanci et al. 2000	Patch test in 13 out of 54 patients who developed allergic contact cheilitis were tested with thymol and other substances.	1% thymol in petrolatum.	Negative reactions.	Negative
ECHA CHEM n.d.-a.	Patch test in 131 persons with eczema and dermatitis and a control group of 21 persons.	1% thymol (Vehicles: not specified).	Negative reactions.	Negative
ECHA CHEM n.d.-a.	Patch tested in 365 patients in eczema and dermatitis patients.	1% thymol (Vehicles: not specified).	2 positive reaction (0.5%).	Low/Moderate frequency
Larsen 1977	Patch test on 20 perfume sensitive patients.	1% thymol in petrolatum.	1 positive reaction (5%).	High frequency of sensitisation
Smeenk et al. 1987	Patch test in 23 patients with an allergic contact dermatitis due to Hirudoid cream that contained 0.1% thymol by weight.	Tested at 1% thymol in petrolatum with Hirudoid cream components either singly or in various combinations, degradation and reaction products.	Negative reactions (thymol).	Negative
Santucci et al. 1987	Patch test in 1200 patients with contact dermatitis (450 male and 750 female).	1% thymol in petrolatum.	Negative reaction.	Negative
Nardelli et al. 2009	Data from 18,960 patients retrieved and investigated for contact allergy between 1978 and 2008. Out of 3378 patients developing iatrogenic allergic contact dermatitis, 127 were found to react with 48 specific products.	n/a	1 out of 127 patients tested positive (0.8%).	Low/Moderate frequency

Repeat dose toxicity

Oral

Based on the available data in mice, the chemical may damage the central nervous system following repeated oral exposure warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section).

There are no 90 day toxicity studies available. A GLP-compliant study in rats (similar to OECD TG 422 but with deviation) showed transient central nervous system effects (up to 10 days). Sensory reactivity to stimuli and functional observations tests were not performed. A non-guideline study in mice (Baldissera et al., 2018) indicate that the chemical may impair memory, affect the integrity of the blood brain barrier, increase in cerebral acetyl choline esterase (AChE) activity, reduce acetylcholine (ACh) levels and Na⁺, K⁺-ATPase activity and increase in oxidative stress in the brain. Reversibility of these effects were not studied. ECHA RAC considered these effects to be clear neurotoxic effects and suggested that the changes observed [AChE and reactive oxygen species (ROS) increase, ACh and Na⁺, K⁺-ATPase decrease] were indicative of a potential mechanism of action. Disruption of the blood brain barrier (BBB) is a significant adverse effect that may be part of the pathogenesis for neurodegenerative diseases. In addition, reduced Na⁺, K⁺-ATPase activity and ACh have been associated with neurodegenerative diseases. The observed decrease of latency time was dose-dependent and statistically significant from a very low dose (20 mg/kg bw/day). Therefore, hazard classification is warranted.

In a GLP-compliant dose range finding study described below, SD rats (10/sex/dose) were administered the chemical via gavage at 30, 100 or 300 mg/kg bw/day for 13 days prior to mating and up to 4 days after mating for males (total 17 days) for males and up to 7–9 days after mating for females (total: 20–22 days). Clinical signs of toxicity included reduced locomotor activity, impaired movement, belly crawling, slowed breathing, ptosis, salivation and reduced bodyweight at 300 mg/kg bw/day. Salivation was reported in the 100 mg/kg treated group. No other effects were reported at doses below 300 mg/kg bw/day (ECHA 2024a; ECHA 2024b; ECHA CHEM n.d.-a).

In a GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test similar to OECD TG 422 but with deviation, SD rats (10/sex/dose) were administered the chemical via gavage at 0, 8, 40 or 200 mg/kg bw/day for 43 days in males and for 14 days prior to mating, mating, gestation and up to day 3 of lactation in females.

Mortality occurred at the highest dose only and included 1 male (unknown cause) and 1 female (administration error). Body weight gain was reduced in males administered the chemical at 200 mg/kg bw/day. Clinical signs of toxicity included, decreased locomotor activity (9/10 females) and ataxic gait (6/10 females) in the 200 mg/kg bw/day groups. Decrease in locomotor activity was observed from day 0–1 and lasted up to 10 days while ataxic gait was observed from day 1 throughout the treatment. Transient salivation in all males and 5/10 females was considered related to the irritant effect of thymol in the upper gastrointestinal tract. There was no statistically significant difference for either absolute or relative organ weights. However, there was a trend of increased thymus weight in males receiving 200 mg/kg bw/day. Other thymus related changes included reduced thymus size in one female rat given 40 mg/kg bw/day and one female rat given 200 mg/kg bw/day, confirmed by histopathological examination (slight thymus involution). Other observations included whitening of the adrenals in 2 females of the 200 mg/kg bw/day group, confirmed by an increase in fatty droplets in the fascicular zone. Thickening of the forestomach wall was attributed to local irritation. There were no significant changes in haematology or clinical

chemistry (ECHA 2024a; ECHA 2024b). Brain weights were not measured. At necropsy dilatation of cerebral ventricle as observed in one high dose male. The significance of this observation is uncertain. Sensory reactivity to stimuli and functional observations tests were not performed. The NOAEL for systemic effects was 40 mg/kg bw based on reduced body weight and motor activity, and increased thymus weight at 200 mg/kg bw/day (ECHA 2024a; ECHA 2024b; ECHA CHEM n.d.-a).

In a non-guideline neurotoxicity study, Swiss male mice (n = 6 /dose) were administered the chemical ($\geq 98.5\%$ purity) via gavage at 0, 10, 20 or 40 mg/kg bw/day for 30 days. Brain thymol concentrations increased with the dose of the chemical (up to $2.66 \pm 0.31 \mu\text{g/mg}$ at the highest dose). The chemical did not affect locomotor activity or exploratory behaviour. There was significant reduction in latency time in the mid- and high-dose groups, by approximately 50% and 90%, respectively, which indicates impaired memory function. In these dose groups there was also a significant increase in BBB permeability (to Evan's blue dye). The high-dose group exhibited significantly increased AChE activity, associated with reduced ACh levels. Na^+ , K^+ -ATPase activity was reduced in the mid- and high-dose groups, which may be related to impaired neuronal excitability and synaptic transmission. The chemical significantly increased brain ROS and xanthine oxidase (XO) at the 2 highest doses. Based on these findings, a NOAEL of 10 mg/kg bw/day for neurotoxicity was determined (ECHA 2024a; Baldissera et al. 2018).

In a non-GLP compliant 28 day study similar to OECD TG 407, Wistar rats (12 male/dose) were administered the chemical via oral gavage at 0, 15.39, 30.78 or 61.55 mg/kg bw/day for 28 days. The study deviated from the test protocol by including only male test animals, limiting histopathological examination to the liver and kidneys, and omitting motor activity assessment. All animals survived the study. Body weights were not affected. No changes attributed to the chemical were observed from haematological, biochemical and histopathological (kidney and liver) analysis. The reported NOAEL from the study was 61.55 mg/kg bw/day based on the absence of systemic toxicity at the highest dose (Gad et al. 2013).

In a non-guideline dose-range finding study for prenatal developmental toxicity study (see **Reproductive toxicity** section) in pregnant Wistar Han rats, 600 mg/kg bw/day was considered the maximum tolerated dose due to severe signs of toxicity. At 400 mg/kg bw/day observations included, slight to moderate uncoordinated movements, incidentally erected fur, slight salivation, lower body weight gain, and low food intake, and erosion of the glandular stomach. At 200 mg/kg, a slightly lower body weight gain was observed. (ECHA CHEM n.d.-a).

In a non-guideline 19 week feeding study, rats (n = 5/sex/dose) were administered thymol (purity unknown as commercially available material used) in the diet at 1000 or 10000 ppm. The NOAEL was determined to be >10000 ppm (ca. 667 mg/kg bw/day) as no effects were observed up to the highest dose (Hagan et al. 1967).

Inhalation

Limited data are available.

In a non-guideline study (GLP compliant), CD-1 mice (n = 8/sex/dose) were exposed to thymol at concentrations of 0 (air), 0 (vehicle control), 0.1% (0.009 mg/L) or 0.5% (0.069 mg/L) for 10 min three times a week for a total of 26 consecutive weeks. There was no mortality throughout the 26 week treatment period. No effects were observed in body weight, weight changes and behaviour. Histopathological examination of lungs, bronchial lymph nodes, nasal passages/nasopharynx and trachea showed no significant differences between

treated and control groups. A benign bronchiole-alveolar adenoma was observed in control female mouse (air) and minimal to mild bronchioloalveolar hyperplasia was observed in two males (one each from vehicle group and 0.1% thymol group). In the lung of high dose group females (0.5%), minimum alveolar macrophage accumulation was observed. At 0.5%, reduced neutrophil count in the bronchial lymph node was reported without concurrent infection in one male and a prominent high endothelial venule in the cortex of the bronchial lymph was observed in two females. In nasal turbinates, minimal to mild eosinophil globules were observed in one animal at low dose and two animals at high dose. Based on low toxicity in mice, the NOAEL (NOAEC) for 26 week exposure was considered as 1.26 mg/kg bw/week (0.069 mg/L) (Xie et al. 2019). However, this study has several limitations, including the use of only two dose levels at low concentrations, short treatment duration (30 min a week) and infrequent dosing resulting in minimal overall exposure. Therefore, the absence of toxicity from the study cannot be considered conclusive.

Observation in humans

A clinical case of thyroid intoxication was reported in three patients following chronic, intentional use of thymol-containing mouthwashes over a period ranging from six months to three years. Two out of three patients exhibited tremors, restlessness, sleeplessness, languidness, palpitations, perspirations and diarrhoea. All patients showed recovery and notable weight gains after discontinuing the use of the mouthwash. No further details are available (ECHA CHEM n.d.-a).

Genotoxicity

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

Some evidence of chromosomal damage has been reported for thymol in both *in vitro* studies and *in silico* predictions. However, most guideline compliant *in vitro* and *in vivo* studies showed negative results. Overall, based on the weight of evidence, thymol does not present clear evidence of genotoxicity.

In Vitro

Negative results were reported in following *in vitro* studies (ECHA CHEM n.d.-a, ECHA 2024a; ECHA 2024b):

- A bacterial reverse mutation assay (similar to OECD TG 471) in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 uvrA) with and without metabolic activations at concentrations up to 5000 µg/plate.
- A mammalian cell gene mutation assay (OECD TG 476) in hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene in Chinese hamster V79 cells with or without metabolic activation at concentrations up to 10 mM.
- A mammalian cell gene mutation assay (OECD TG 476) in HPRT gene in mouse lymphoma L5178Y tk^{+/−} cells with or without metabolic activation at concentrations up to 140 µg/mL and 200 µg/mL, respectively.

Negative results were also reported in several supportive non-guideline *in vitro* studies or guideline studies with variations (ECHA 2024a; ECHA 2024b). These include:

- 3 bacterial reverse mutation assays (OECD TG 471 with deviations).
- A mammalian cell gene mutation assay (OECD TG 490 with deviations) in thymidine kinase gene.

- A mammalian cell micronucleus (MN) test (OECD 487 with deviations) in mouse lymphoma L5178Y tk⁺ cells.
- A DNA comet assay in Caco-2 cells at concentrations up to 250 µM.

Furthermore, results from a chromosome aberration (CA) study (OECD TG 473 with deviations) in CHL/IU cells were mainly negative with a positive response observed only at a cytotoxic dose (80 µg/mL) in presence of metabolic activation. The ECHA RAC considered this to be mainly a negative case (ECHA 2024a; ECHA 2024b).

Positive results were reported in a mammalian cell CA test and MN test (IPCS guidelines) in human peripheral lymphocytes (whole blood cells) at concentrations up to 100 µg/mL. No metabolic activation systems were used in both tests (Buyukleyla and Rencuzogullari 2009). These studies were considered as acceptable studies by ECHA RAC. In the CA test, a dose dependent increase in the percentage of structural CA was reported after 48 hrs exposure that was statistically significant from 50 µg/mL. In the MN study, an increase of MN (but not dose dependent) was seen at 24 and 48 hrs. This increase was statistically significant from 25 µg/mL (ECHA 2024a; ECHA 2024b).

Positive results were also reported. Several supportive studies included a:

- Mammalian cells CA assay in Syrian Hamster Embryo (SHE) cells at concentration from 130 µM with metabolic activation.
- Sister chromatid exchange assay in human peripheral lymphocytes (whole blood cells) at concentration from 25 µg/mL.
- DNA comet assay in human lymphocytes at concentration from 0.2 mM (ECHA 2024a; ECHA 2024b).

In vivo

Negative results were reported in following *in vivo* studies (ECHA 2024a; ECHA 2024b; ECHA CHEM n.d.-a):

- A mammalian bone marrow chromosome aberration test (OECD TG 475, GLP), CrI:CD-SD rats (6/sex/group) were administered thymol as a single oral gavage at doses of 500, 1000, or 2000 mg/kg bw. The incidence of chromosome aberrations in bone marrow did not increase in any of the treated groups, indicating a lack of clastogenicity. Thymol was detected in the plasma providing an indication of bone marrow exposure.
- A mammalian erythrocyte micronucleus Test (non-guideline, GLP not specified), Crj: BDF1 mice (5 animal/sex/dose) were administered thymol as a single oral gavage at doses of 0, 312.5, 625, or 1250 mg/kg bw. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity. Despite limitations in the study including use of only a single treatment and sampling, the ECHA RAC considered this study as acceptable.
- A mammalian erythrocyte micronucleus Test [similar OECD TG 474 with deviation (single treatment), GLP], ICR mice (5 animal/sex/dose) were administered thymol as a single oral gavage at a dose of 0, 275, 550, or 1100 mg/kg bw. The incidence of micronuclei in bone marrow polychromatic erythrocytes (PCE) did not increase in any of the treated groups, indicating a lack of clastogenicity. Slight reductions in the ratio of PCE to total erythrocytes were observed relative to the vehicle control in high dose animals indicating bioavailability of the test article to the bone marrow target.

A supportive non-guideline sex-linked recessive lethal (SLRL) test in *Drosophila melanogaster* were administered with a dose of 3 mM thymol solution (1:100 ethanol in water containing 5% sucrose). The results showed two lethal mutations among 742 examined chromosomes (0.27%) indicating no significant mutagenic effects (ECHA CHEM n.d.-a).

A positive result was reported in a mammalian CA test in SD rats (2/sex/dose). This study had a number of deviations from OECD TG 475 including administration by intraperitoneal injection (i.p.), small group sizes and the pooling of individual animal data. In this study rats were exposed by i.p. to a single treatment of the chemical in DMSO at 0,40, 60, 80 and 100 mg/kg bw. Sampling was undertaken at 6,12 and 24 hrs. A dose dependent increase in structural aberrations was observed at each sampling time (ECHA 2024a; ECHA 2024b).

In a GLP compliant chromosome aberration study performed in accordance with OECD TG 475, Crl:CD rats (n = 3-6/sex/dose) were given a single oral dose of 1000, 1400 or 2000 mg/kg bw (preliminary test) or 500, 1000 or 2000 mg/kg bw (main test). A decreased activity at 1000 mg/kg bw and a dose-dependent increase of the severity of the effects were reported. Mortalities were reported at the highest dose (ECHA 2024b).

In silico

The knowledge-based expert system DEREK and SARAH Nexus version 6.3.0 (Lhasa Limited) was utilised to predict the genotoxic potential of the chemical. The chemical did not match any structural alerts or examples for (bacterial *in vitro*) mutagenicity in the DEREK model. The chemical was predicted to be negative for mutagenicity *in vitro* based on Sarah Model-2023.1 (thymol is included the training set) (Lhasa Limited). The chemical was predicted positive for chromosome damage (probable) in the DEREK model. However, thymol is included in the model training set, and this prediction was partly based on supportive *in vitro* study Syrian Hamster Embryo (SHE) cells at concentration from 130 µM with metabolic activation (see **In vitro data**).

The QSAR predictions using OASIS TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.31.2.82) indicates that the chemical or its metabolites are positive for *in vitro* chromosomal aberration based on alerts from hydroxylated or substituted phenols. The chemical or its metabolites were predicted negative for Ames mutagenicity. The predictions were within the applicability domain of 100% of the genotoxicity models. Genotoxicity predictions were outside the applicability domain for all OASIS TIMES *in vivo* genotoxicity models.

Carcinogenicity

No data were available for the chemical.

Reproductive and development toxicity

Based on the limited available data, there is no evidence the chemical causes cause specific adverse effects on sexual function, fertility and development.

Two guideline studies (OECD TG 422 with deviation and OECD TG 414) on reproductive and development toxicity after thymol exposure are available.

In the first study (OECD TG 422 with deviation), a dose-dependent increase in pre-coital time and reduced pup body weights at birth and postnatal day 4 were observed at the highest

tested dose of 200 mg/kg bw/day. The increase in pre-coital time was attributed to reduced activity (narcotic effects). No other adverse effects in sexual functions, fertility and development or lactation were identified. RAC considered this study as supportive only, due to several methodological limitations including:

- lack of male fertility assessments (sperm effects)
- females dosed until day 3 of lactation instead of 13
- absence of anogenital distance measurement
- incomplete organ weights and histopathological evaluations
- omission of the sensory reactivity to stimuli/functional
- lack of the historical control data (ECHA 2024a; ECHA 2024b).

In the second study (OECD TG 414), reduced foetal body weight was also observed at the high dose and was considered secondary to the maternal toxicity (ECHA CHEM n.d.-a).

Sexual function and fertility

In a GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted similar to OECD TG 422 with deviations, Crj:CD SD rats (10/sex/dose) were administered the chemical by gavage once daily at 0, 8, 40 or 200 mg/kg bw/day for a total of 43 days [males (premating period not stated)] or from 14 days before mating to day 3 of lactation (females), (see **Repeat dose toxicity – oral** section). Clinical signs of toxicity included a dose-dependent increase in pre-coital times (2.3, 2.7, 3.0 and 3.6 days at 0, 8, 40 and 200 mg/kg bw/day, respectively), but without statistical significance. The increase in pre-coital time was correlated to narcotic effect of thymol. Vaginal discharge was observed on gestation day 24 in one high dose female. This female had only 3 implantation sites and subsequently failed to deliver pups. The number of implantations (15.6 vs 15.9 in controls) and implantation rate (86.9% vs 92.9% in controls) were slightly lower in a high dose group.

There were no effects on reproductive parameters including the oestrous cycle, mating index, fertility index, gestation length, number of corpora lutea or implantation sites, parturition or maternal behaviour. Sperm parameters were not evaluated. The NOAEL for sexual function and fertility toxicity was 200 mg/kg bw/day (ECHA CHEM n.d.-a; ECHA 2024a; ECHA 2024b).

Developmental toxicity

In a GLP compliant prenatal development toxicity study conducted in accordance with OECD TG 414, pregnant Wistar Han rats (n = 22 females/dose) were administered the chemical in corn oil by oral gavage once daily at 0, 40, 150 or 400 mg/kg bw/day on gestational days (GD) 6 to 20. Dams were sacrificed on GD 21, and the foetuses were examined.

Clinical signs of toxicity included uncoordinated movements in all dams and salivation in most dams receiving 400 mg/kg bw/day. There was no treatment related clinical signs of toxicity in dams receiving 150 or 40 mg/kg bw/day. Body weight gain (GD6-21) and gravid uterus adjusted body weight gain (GD21) were lower in dams of the highest dose group. Food consumption was reduced at doses ≥ 150 mg/kg bw/day. No adverse effects were observed in macroscopic and histopathological examinations. There were no treatment related effects on thyroid parameters. The reported NOAEL for maternal toxicity was 150 mg/kg bw/day based on uncoordinated movements in all dams at 400 mg/kg bw/day.

The only sign of developmental toxicity was reduced foetal body weight in the highest dose group, which can be secondary effect to maternal toxicity as this effect was observed at only 400 mg/kg bw/day.

There were some occurrences of skeletal malformations; however, they were considered incidental. The reported NOAEL for developmental toxicity was 150 mg/kg (ECHA CHEM n.d.-a).

In a GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted similar to OECD TG 422 with deviation (see **sexual function and fertility**), there were no significant differences in the gestation index, number of offspring, number of live births, sex ratio, live birth index or viability index among the groups. There were no abnormal findings during external examination, clinical observations and necropsy of fetuses. A lower delivery index (by 12%) was reported at the high dose as a result of the dam that failed to deliver. Mortality was observed in 5 out of 17 pups from one dam at a high dose. However, this effect was considered a secondary to the emaciation showed by dam around the time of delivery rather than thymol effects. Lower pup body weights compared to controls (10.3% and 9.4% in males and females, respectively at birth and 10.2 and 8.8% in males and females, respectively at PND 4) and lower body weight gains (14.6% and 10.5% in males and females, respectively) were reported at the high dose but without statistical significances. There were no treatment related effects at lower doses 0, 8 and 40 mg/kg bw/day. There were some occurrences of skeletal malformations; however, they were considered incidental. The reported NOAEL for developmental toxicity was 40 mg/kg bw/day based on reduction in pup weight and weight gain at 200 mg/kg bw/day (ECHA CHEM n.d.-a; ECHA 2024a; ECHA 2024b).

Neurotoxicity

Based on the weight of evidence from available studies, thymol is expected to cause toxic effects following single and repeated exposures to the chemical.

Reported acute effects (single exposure) indicative of neurotoxicity include depression, ataxia, coma, hypoactivity, drowsiness, paralysis, slight agitations, tremors, muscle twitching and loss of locomotor activity. The majority of these effects occurred at sub-lethal doses from 500 mg/kg bw in acute toxicity studies and from day 0–1 at 200 mg/kg bw/day in a repeat dose toxicity study. While the observed effects may be indicative of central nervous system depression, some effects e.g. tremors, spasms and agitations suggest neurotoxicity (see **Acute toxicity section**).

Reported effects indicative of neurotoxicity after repeated exposures included: reduced locomotor activity, impaired movement, belly crawling, slowed breathing, ptosis, salivation at 300 mg/kg bw/day (OECD TG 422); and memory impairment (reduced latency), compromised BBB integrity, biochemical disruptions in the brain and elevated oxidative stress at 20 mg/kg bw/day (non-guideline study). Based on these findings, a NOAEL of 10 mg/kg bw/day for neurotoxicity was determined (see **Repeat dose toxicity section**).

Human health risk characterisation

Critical health effects

The critical health effects for risk characterisation are acute and subchronic neurotoxicity. Sub-lethal effects indicative of acute neurotoxicity included ataxia, tremors, paralysis, coma,

depression, and hypoactivity following single oral sublethal doses of 500–2000 mg/kg bw. Effects observed in repeated dose studies included motor dysfunction (ataxia and reduced locomotor activity), memory impairment (reduced latency time), biochemical changes in the brain, elevated oxidative stress, and compromised BBB integrity. These effects varied across species and occurred at doses of ≥ 20 mg/kg bw/day in mice and 200 mg/kg bw/day in rats (see **Repeat dose toxicity**). The lowest NOAEL for the chemical is 10 mg/kg bw/day based on a non-guideline study in mice (see **Repeat dose toxicity**) (Baldissera 2019; ECHA 2024a).

Public risk

An MOE methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals. The MOE approach compares estimated human exposure with a toxicological point of departure (POD), to determine whether a sufficient margin exists to protect against a particular adverse health effect. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, an MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

There is potentially widespread public exposure to thymol as it is present in various types of cosmetic and domestic products (see **Human exposure section**). The calculated MOE values for use of cosmetic and domestic products in adults are provided in **Table 6** and **Table 7**, respectively.

Table 6 – MOE values for thymol in cosmetic products

Product type	POD (mg/kg bw/day)	Daily systemic exposure (mg/kg bw/day)	MOE
Face cream	10	0.0154	649
Hand/foot cream	10	0.0216	463
Shampoo/conditioner	10	0.0001	100000
Shower gel (body soap)	10	0.0019	5263
Hand wash soap	10	0.0020	5000
Lip balm	10	0.0012	8333
Facial cleanser	10	0.0028	3571
Hair styling products	10	0.0003	33333
Hair dye	10	0.0008	12500
Toothpaste	10	0.0057	1754
Mouthwash	10	0.0231	433
Total	10	0.0749	134

Table 7 – MOE values for thymol in domestic products

Product type	POD (mg/kg bw/day)	Daily systemic exposure (mg/kg bw/day)	MOE
Laundry products*	10	0.00252	3968
Dishwashing products	10	0.00013	76923
Cleaning products	10	0.0012	8333
Instant air refreshment sprays (aerosol can)	10	0.0111	901
Car air freshener - Fragrance infused items	10	0.0000059	1694915
Total	10	0.0149559	669

*Includes indirect and direct exposure

MOE values for use of individual products containing the chemical are all ≥ 400 . The worst-case scenario when thymol is used daily in all products (both domestic and cosmetic) results in a combined daily systemic exposure of 0.08983 mg/kg bw/day for the chemical, accounting for both dermal and inhalation routes. This is a conservative estimate since in the absence of dermal absorption data 100% dermal absorption is assumed. The MOE based on the POD of 10 mg/kg bw/day is 111. Although the public may be exposed to the chemical from non-industrial uses the worst-case exposure estimate assumes simultaneous use of all products containing the chemical at the highest concentration identified. International estimates of exposure based on probabilistic modelling (Api et al. 2024) indicate that the MOE would likely be significantly higher. This risk estimate indicates that thymol is unlikely pose a risk to human health if used in cosmetic and domestic products at the low concentrations reported to be in use.

References

ACI (2010) *Consumer Product Ingredient Safety, Exposure and risk screening methods for consumer product ingredients, 2nd Edition*, American Cleaning Institute, Washington DC.

AICIS (Australian Industrial Chemicals Introduction Scheme) (AICIS) (n.d.) [Thymol](#), AICIS website, accessed 16 February 2026.

Api AM, Bartlett A, Belsito D, Botelho D, Bruze M, Bryant-Freidrich A, Burton GA Jr, Cancellieri MA, Chon H, Dagli ML, Dekant W, Deodhar C, Farrell K, Fryer AD, Jones L, Joshi K, Lapczynski A, Lavelle M, Lee I, Moustakas H, Muldoon J, Penning TM, Ritacco G, Sadekar N, Schember I, Schultz TW, Siddiqi F, Sipes IG, Sullivan G, Thakkar Y and Tokura Y (2024) 'RIFM fragrance ingredient safety assessment, thymol, CAS Registry Number 89-83-8', *Food and Chemical Toxicology*, 189 (Suppl 1): 114739, doi:10.1016/j.fct.2024.114739.

APVMA (Australian Pesticides and Veterinary Medicines Authority) (2024) [Acceptable daily intakes \(ADI\) for agricultural and veterinary chemicals used in food producing crops or animals Edition 4/2024](#), APVMA, accessed 6 January 2026.

ASEAN (Association of Southeast Asian Nations) (n.d.) [List of substances which must not form part of the composition of cosmetic products: Part IV- List of Preservatives Allowed](#), ASEAN, accessed 14 October 2025.

Austgulen LT and Solheim E and Scheline RR (1987) 'Metabolism in rats of p-cymene derivatives: carvacrol and thymol', *Pharmacology & toxicology*, 61(2):98-102, doi: 10.1111/j.1600-0773.1987.tb01783.x.

Bacova K, Zitterl-Eglseer K, Chrastinova L, Laukova A, Madarova M, Gancarcikova S, Sopkova D, Andrejckova Z and Placha I (2020) 'Effect of Thymol Addition and Withdrawal on Some Blood Parameters, Antioxidative Defence System and Fatty Acid Profile in Rabbit Muscle' *Animals (Basel)*, 10(8):1248, doi: 10.3390/ani10081248.

Baldissera MD, Souza CF, De Matos AFIM, Doleski PH, Baldisserotto B, Da Silva AS and Monteiro SG (2018) 'Blood-brain barrier breakdown, memory impairment and neurotoxicity caused in mice submitted to orally treatment with thymol' *Environmental Toxicology and Pharmacology*, 62:114-119, doi: 10.1016/j.etap.2018.06.012.

Berova N, Stransky L and Krasteva M (1990) 'Studies on contact dermatitis in stomatological staff', *Dermatologische Monatsschrift*, 176(1),15-8.

Bleumink E, Mitchell JC and Nater JP (1973) 'Allergic contact dermatitis from cedar wood (*Thuja plicata*)', *British Journal of Dermatology*, 88(5):499-504, doi: 10.1111/j.1365-2133.1973.tb15458.x.

Buyukleyla M and Rencuzogullari E (2009) 'The effects of thymol on sister chromatid exchange, chromosome aberration and micronucleus in human lymphocytes', *Ecotoxicology and Environmental Safety*, 72(3):943-7, doi: 10.1016/j.ecoenv.2008.10.005.

Cadby PA, Troy WR and Vey MG (2002) 'Consumer Exposure to Fragrance Ingredients: Providing Estimates for Safety Evaluation', *Regulatory Toxicology and Pharmacology*, 36(3):246-252, doi.org/10.1006/rtp.2002.1581.

Chemwatch (n.d.) [Galleria Chemica](#), Chemwatch website, accessed 28 May 2025.

CIR (Cosmetic Ingredient Review) (2006), [Final report on the safety assessment of sodium p-chloro-m-cresol, p-chloro-m-cresol, chlorothymol, mixed cresols, m-cresol, o-cresol, p-cresol, isopropyl cresols, thymol, o-cymen-5-ol, and carvacrol](#), CIR, accessed 01 September 2026.

DeLima Associates (n.d.) [Consumer Product Information Database](#), DeLima Associates website, accessed 26 May 2025.

Dohn W (1980) 'Dermatological patients not employed in handicraft or factories', *Contact Dermatitis*, 6(2):148-50. doi: 10.1111/j.1600-0536.1980.tb03937.x.

ECHA (European Chemicals Agency) CHEM (n.d.-a) REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) registered dossier for Thymol, CAS No. 89-83-8 , dossier registration date: 18 October 2010, [European Chemicals Agency website](#), accessed 01 September 2026.

ECHA (European Chemicals Agency) CHEM (n.d.-b) REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) registered dossier for Thymol, CAS No. 89-83-8 , dossier registration date: 25 May 2018, [European Chemicals Agency website](#), accessed 01 September 2026.

ECHA (European Chemicals Agency) (2024a) Committee for Risk Assessment RAC [Opinion proposing harmonised classification and labelling at EU level of thymol; 5-methyl-2-\(propan-2-yl\)phenol \(EC Number: 201-944-8\) \(CAS Number: 89-83-8\) \(CLH-O-0000007441-79-01/F\)](#), ECHA website, Accessed 26 August 2025.

ECHA (European Chemicals Agency) (2024b) Committee for Risk Assessment RAC [Annex 1 Background document to the Opinion proposing harmonised classification and labelling at EU level of thymol; 5-methyl-2-\(propan-2-yl\)phenol EC Number: 201-944-8 CAS Number: 89-83-8 CLH-O-0000007441-79-01/F](#), ECHA website, Accessed 21 October 2025.

Fisher AA (1989) 'Allergic contact dermatitis due to thymol in Listerine for treatment of paronychia', *Cutis*, 43(6):531-2.

Francalanci S, Sertoli A, Giorgini S, Pigatto P, Santucci B and Valsecchi R (2000) 'Multicentre study of allergic contact cheilitis from toothpastes', *Contact Dermatitis*, 43(4):216-22. doi: 10.1034/j.1600-0536.2000.043004216.x.

Gad, MME-S, Mohammad YS and Mohammad TGM (2013) 'Acute and repeated-doses (28 days) toxicity of thymol formulation in male albino rats', *Australian Journal of Basic and Applied Sciences*, 7(10): 594–601.

Hagan EC, Hansen WH, Fitzhugh OG, Jenner PM, Jones WI, Taylor JM, Long EL, Nelson AA and Brouwer JB (1967) 'Food flavourings and compounds of related structure. II. Subacute and chronic toxicity', *Food and Cosmetics Toxicology*, 5(2):141-57. doi: 10.1016/s0015-6264(67)82961-4.

IFRA (International Fragrance Association) (n.d.) [Transparency List](#), IFRA website, accessed 26 May 2025.

INCI beauty (International Nomenclature Cosmetic Ingredient) (n.d.) [Thymol](#), INCI beauty website, accessed 16 February 2026.

INKEEDecoder (n.d.) [Products with Thymol](#), INKEEDecoder website, accessed 01 September 2026.

Jenner PM, Hagan EC, Taylor JM, Cook EL and Fitzhugh OG (1964) 'Food flavourings and compounds of related structure I. Acute oral toxicity', *Food and Cosmetics Toxicology*, 2:327-343. doi.org/10.1016/S0015-6264(64)80192-9

Klecak G, Geleick H and Frey JR (1977) 'Screening of fragrance materials for allergenicity in the guinea pig I. Comparison of four testing methods', *Journal of Cosmetic Science*. 28 (2): 53-64.

Kohlert C, Schindler G, März RW, Abel G, Brinkhaus B, Derendorf H, Gräfe EU and Veit M (2002) 'Systemic availability and pharmacokinetics of thymol in humans', *Journal of Clinical Pharmacology*, 42(7):731-7, doi:10.1177/009127002401102678.

Krueger RP (1967) 'Chemical Pneumonitis from Medicated Vapor Aerosol Spraying', *Clinical Pediatrics*, 6(8):465-467. doi:10.1177/000992286700600809.

Larsen WG (1977) 'Perfume dermatitis a study of 20 patients', *Archives of Dermatology*, 113(5):623-6, doi:10.1001/archderm.113.5.623.

Lhasa Limited Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (Version 6.3.0), [Computer software], Lhasa Limited, accessed 01 September 2025.

Lorenzi S, Placucci F, Vincenzi C, Bardazzi F and Tosti A (1995) 'Allergic contact dermatitis due to thymol', *Contact Dermatitis*, 33(6):439-40, doi:10.1111/j.1600-0536.1995.tb02092.x.

Loretz L, Api AM, Barra J, Burdick J, Davis DA, Dressler W, Gilberti E, Jarrett G, Mann S, Pan YHL, Re T, Renskers K, Scrafford C and Vater S (2006) 'Exposure data for personal care products: Hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant', *Food and Chemical Toxicology*, 44(12):2008-2018, Doi: 10.1016/j.fct.2006.06.029.

McOmie WA, Anderson HH and Estess FM (1949) 'Comparative toxicity of certain t-butyl substituted cresols and xylenols', *Journal of the American Pharmaceutical Association (Scientific ed.)*, 38(7):366-9, doi: 10.1002/jps.3030380704.

Menenghini CL, Rantuccio F and Lomuto M (1971) 'Additives, vehicles and active drugs of topical medicaments as causes of delayed-type allergic dermatitis', *Dermatologica*, 143(3):137-47, doi: 10.1159/000252183.

MHLW (Ministry of Health, Labour and Welfare (MHLW) (n.d.). [Standards for Cosmetic Products \(Notification no. 331 of 2000\)](#). Accessed 13 October 2025.

Nardelli A, Carbonez A, Ottoy W, Drieghe J and Goossens A (2008) 'Frequency of and trends in fragrance allergy over a 15-year period' *Contact Dermatitis*, 58(3):134-41, doi: 10.1111/j.1600-0536.2007.01287.x.

Nethercott JR, Nield G and Holness DL (1989) 'A review of 79 cases of eyelid dermatitis', *Journal of the American Academy of Dermatology*, 21(2 Pt 1):223-30, doi: 10.1016/s0190-9622(89)70165-1.

OASIS LMC (Laboratory of Mathematical Chemistry) Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator (OASIS–TIMES) (2025) (Version 2.31.2.82), [Computer software], LMC, accessed 02 September 2025.

OECD (Organisation for Economic Co-operation and Development) (2025) *Quantitative Structure-Activity Relationship Toolbox* (Version 4.5) [Computer software], OECD website, accessed 02 September 2025.

Papa CM and Shelley WB (1964) 'Menthol Hypersensitivity: Diagnostic Basophil Response in a Patient with Chronic Urticaria, Flushing, and Headaches', *The Journal of the American Medical Association*, 189(7):546–548, doi:10.1001/jama.1964.03070070018004.

PerfumersWorld n.d. [Thymol](#), PerfumersWorld website, accessed 07 September 2026

Personal Care Products Council (n.d.) [Cosmetic Ingredient Identification Database](#), Personal Care Products Council website, accessed 31 August 2026.

Reichert-Pénétrat S, Barbaud A, Pénétrat E, Granel F and Schmutz JL (2001) 'Allergic contact dermatitis from surgical paints', *Contact Dermatitis*, 45(2):116-7, doi:10.1034/j.1600-0536.2001.045002116.x.

RIVM (2021). [Air Fresheners Fact Sheet Default parameters for estimating consumer exposure – Version 2021 RIVM report 2021-0233](#). National Institute for Public Health and the Environment (RIVM). RIVM website, accessed 27 January 2026.

RIVM (2025). [Factsheet Cosmetics. Standard parameters to estimate consumer exposure - revised version 2025. National Institute for Public Health and the Environment \(RIVM\)](#). RIVM website, accessed 08 September 2026.

RIVM (2026). [ConsExpo web: Consumer exposure models-model documentation](#). National Institute for Public Health and the Environment (RIVM). RIVM website, accessed 27 January 2026.

Santucci B, Cristaudo A, Cannistraci C and Picardo M (1987) 'Contact dermatitis to fragrances', *Contact Dermatitis*, 16(2): 93-95, <https://doi.org/10.1111/j.1600-0536.1987.tb01386.x>.

SCCS (2023) [The SCCS's notes of guidance for the testing of cosmetic substances and their safety evaluation \(12th revision\)](#), European Commission - Scientific Committee on Consumer Safety, European Commission website, assessed 17 February 2026.

Smeenk G, Kerckhoffs HP and Schreurs PH (1987) 'Contact allergy to a reaction product in Hirudoid cream: an example of compound allergy', *British Journal of Dermatology*, 116(2):223-31, doi: 10.1111/j.1365-2133.1987.tb05816.x.

Soo Hoo GW, Hinds RL, Dinovo E and Renner SW (2003) 'Fatal large-volume mouthwash ingestion in an adult: a review and the possible role of phenolic compound toxicity', *Journal of Intensive Care Medicine*, 18(3):150-155, doi:10.1177/0885066602250783

SWA (Safe Work Australia) (n.d.) [Hazardous Chemical Information System](#), SWA website, accessed 07 September 2026.

Takada M, Agata I, Sakamoto M, Yagi N and Hayashi N (1979) 'On the metabolic detoxication of thymol in rabbit and man', *The Journal of toxicological sciences*, 4(4):341-350, doi:10.2131/jts.4.341.

TGA (Therapeutic Goods Administration) (n.d.). [Australian Register of Therapeutic Goods \(ARTG\)](#), accessed 07 September 2026

TGA (Therapeutic Goods Administration) (2024). [Therapeutic Goods \(Excluded Goods\) Determination 2018, F2024C00750 C11](#), TGA, accessed 07 September 2026.

TGA (Therapeutic Goods Administration) (2026a). [Therapeutic Goods \(Permissible Ingredients\) Determination \(No. 1\) 2026, F2026L00162](#), TGA, accessed 07 September 2026.

TGA (Therapeutic Goods Administration) (2026b) [Standard for the Uniform Scheduling of Medicines and Poisons No. F2026L00060 \(Poisons Standard January 2026\)](#), TGA, accessed 07 September 2026.

Thalhamer B, Buchberger W and Waser M (2011) 'Identification of thymol phase I metabolites in human urine by headspace sorptive extraction combined with thermal desorption and gas chromatography mass spectrometry', *Journal of Pharmaceutical and Biomedical Analysis*, 56(1):64-69, doi:10.1016/j.jpba.2011.04.014.

UNECE (United Nations Commission for Europe) (2017), [GHS](#), UNECE website, accessed 07 September 2026

USEPA (United States Environmental Protection Agency) (2019). [Registration review draft risk assessment for Thymol](#). EPA-HQ-OPP-2010-0002. Accessed 20 January 2026

USFDA (United States Food and Drug Administration) (n.d.-a). [Drug Approval and Databases](#). FDA Website. Accessed 13 October 2025.

USFDA (United States Food and Drug Administration) (n.d.-b). [§ 172.515 Synthetic flavoring substances and adjuvants](#). Electronic Code of Federal regulations Website. Accessed 13 October 2025.

Van der Walle HB, Delbressine LP and Seutter E (1982) 'Concomitant sensitization to hydroquinone and P-methoxyphenol in the guinea pig; inhibitors in acrylic monomers'. *Contact Dermatitis*, 8(3):147-54, doi: 10.1111/j.1600-0536.1982.tb04173.x.

Xie K, Tashkin DP, Luo MZ and Zhang JY (2019) 'Chronic toxicity of inhaled thymol in lungs and respiratory tracts in mouse model' *Pharmacology Research and Perspective*, 7(5):e00516, doi:10.1002/prp2.516.

