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

Extracts and essential oils primarily composed of methyl salicylate

Evaluation statement (EVA00153)

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AICIS evaluation statement (EVA00153)

Subject of the evaluation

Extracts and essential oils primarily composed of methyl salicylate

Chemicals in this evaluation

Name	CAS registry number
Oils, sweet birch	68917-50-0
Oils, wintergreen	68917-75-9
Birch, *betulalenta*, ext.	85251-66-7
Gaultheria procumbens, ext.	90045-28-6

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

These chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory).

Chemicals in this evaluation are essential oils and extracts of *Gaultheria procumbens* and *Betula lenta* plants. These unknown or variable composition, complex reaction products or biological materials (UVCB) have been assessed as a group as they typically contain methyl salicylate at concentrations greater than 90%. This evaluation is a human health risk assessment of all identified industrial uses of these chemicals.

With limited toxicological data, methyl salicylate is a suitable read across analogue for all chemicals in this evaluation. The AICIS report on methyl salicylate should be read in conjunction with this evaluation (AICIS 2024a).

This evaluation does not consider crude extracts that are obtained by pyrolysis. Sweet birch oil (CAS no. 68917-50-0) and birch, *betulalenta*, ext. (CAS no. 85251-66-7) have been linked by the International Fragrance Association (IFRA) with “birch wood pyrolysate” and may be “subject to a ban in fragrance products” (IFRA n.d.-a). The ban is specifically for birch extracts (crude oils) obtained by pyrolysis or destructive distillation of the bark due to presence of polyaromatic hydrocarbons (IFRA n.d.). Essential oils of birch oil (rectified oils) that predominantly contain methyl salicylate are typically produced by steam distillation, hydro-distillation or solvent extraction of the plant material and are not subject to the IFRA Standard.

Summary of evaluation

Summary of introduction, use and end use

Based on the limited available Australian use information, chemicals in this group are available as “essential oils” at concentrations up to 100%. Essential oils are commonly used in aromatherapy including as massage oils and in aroma diffusers. Reported concentrations of wintergreen oil in massage oil products internationally were up to 10%.

Based on international and Australian use information, chemicals in this group are used in personal care products (cosmetics) including products applied to skin, hair care products, perfumes and body sprays and oral care products. The concentrations in these products are expected to be up to 2.5%.

These chemicals may also be used in domestic settings in cleaning and furniture care products and air care products.

These chemicals also have reported non-industrial uses in therapeutic products, food flavouring, pet care products and insect repellents.

Human health

Summary of health hazards

There are limited data about the health hazards of chemicals in this group. As these chemicals typically contain greater than 90% methyl salicylate, hazard data for methyl salicylate and its metabolite salicylic acid have been used to support the hazard conclusions. The contributions of other minor components of these chemicals were not considered for hazard characterisation.

Based on available data chemicals in this group are expected:

- to have low acute dermal and inhalation toxicity
- to be at most slightly irritating to skin
- not to be respiratory sensitisers
- not to have genotoxic potential
- not to be carcinogenic
- not to cause specific adverse effects on fertility.

Based on available data for methyl salicylate (median lethal dose in rats of 887 mg/kg/bw/day) and evidence of human acute poisoning following oral exposure to wintergreen oil, these chemicals are expected to have moderate acute oral toxicity.

Based on available in vitro (OECD TG 491) and in vivo data for methyl salicylate, including observations of corneal necrosis in rabbit eyes, these chemicals are expected to cause serious eye damage.

Chemicals in this group are expected to be weak skin sensitisers based on animal and human data for methyl salicylate. Reported concentrations producing a three fold increase in lymphocyte proliferation (EC3) values ranged from 15–65% in various local lymph node assays (LLNAs) on methyl salicylate. Guinea pig maximisation tests (GPMT) were mostly negative for sensitisation. In human patch testing with methyl salicylate applied to dermatitis

patients, there was a 1–2% positive reaction rate, indicating that the chemical can cause skin sensitisation.

Based on the data for methyl salicylate, chemicals in this group are expected to cause specific adverse effects on development warranting hazard classification. Increased incidences of neural tube defects in pups born from rats or hamsters exposed during gestation, increased incidences of skeletal variations in the pups and lower pup body weight were reported in a 3 generation study. The no observed adverse effect level (NOAEL) for development is 75 mg/kg bw/day based on a 3 generation study in rats. In addition, the metabolite salicylic acid is reported to cause adverse effects on development in rats and monkeys including increased foetal mortality, increased incidences of neural tube defects and foetal growth retardation. There is also reported extensive human use of acetylsalicylic acid as aspirin which shares a metabolite with the chemical. There is a lack of evidence to support an increased risk of birth defects following exposure to aspirin.

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

Hazard classifications relevant for worker health and safety

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

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Serious eye damage/eye irritation	Eye Damage 1	H318: Causes serious eye damage
Skin sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction
Reproductive toxicity	Repr. 2	H361d: Suspected of damaging the unborn child

Summary of health risk

Public

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

- by direct skin contact during use of personal care products (applied to skin, hair, and lips) and massage oils (applied to the skin)
- by the oral route, when using oral care products
- by incidental skin and eye contact with these chemicals during use of domestic products
- by inhalation of aerosols or vapours from aroma diffuser products.

The critical health effect for risk characterisation is developmental toxicity. These chemicals are also acutely toxic by the oral route, can cause serious eye damage and are weak sensitisers.

Based on quantitative risk assessment conclusions for methyl salicylate (conservative aggregate margins of exposure (MOE) greater than 100) and given that the use patterns of chemicals in this group for the majority of cosmetic and household uses are expected to be similar to methyl salicylate, these chemicals are unlikely to pose a risk when used at low concentrations.

Additional uses of these chemicals as essential oils have been identified. Essential oils are commonly used in aromatherapy including as massage oils and in aroma diffusers and are available to the public as pure oils (concentrations of 100%). Based on the high concentrations, the risk of skin sensitisation and damage to the eyes cannot be ruled out. The MOEs for developmental effects from the use of these chemicals in massage oils at concentrations of 10% (1:10 dilution) were estimated to be 11. Hence, these chemicals pose a potential risk to the public which requires management (see **Proposed means of managing risk**). The risk could be managed by listing these chemicals in the *Poison Standard – Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Workers

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

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

Given the critical systemic long-term and local health effects, these chemicals could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (refer to **Proposed means of managing risk**).

Proposed means for managing risk

Public

Recommendation to Department of Health and Aged Care

It is recommended that the delegate list these chemicals in the *Poisons Standard* (the SUSMP) **(See Summary of Health Risk Section)**.

It is recommended that the management of the potential risk associated with the use of these chemicals:

- results in labelling requirements that provide warning labels relating to the use of these chemicals by pregnant women or women likely to become pregnant, and for skin sensitisation.

Consideration should be given to the following:

- the primary component of the oils, methyl salicylate, is listed in the SUSMP (an amendment to this entry may be needed to align risk management measures)

- these chemicals are expected to have similar toxicity based on the levels of their primary component, methyl salicylate
- these chemicals are unlikely to pose a potential risk when used at low concentrations
- these chemicals are available to consumers as pure oils (100% concentration)
- adverse effects on the development of the unborn child can occur from acute exposures
- several cases of salicylate toxicity from the ingestion of wintergreen oil have been reported.

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.

Control measures that could be implemented to manage the risk arising from oral, dermal and inhalation exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

Measures required to eliminate, or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

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

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

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

contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemicals 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

Grouping rationale

These chemicals have been assessed as a group as they have similar uses and compositions and are expected to have similar critical health effects. As the reported compositions of these chemicals are typically greater than 90% methyl salicylate (CAS no. 119-36-8), chemicals in this group are expected to have similar critical health effects that are driven by the presence of methyl salicylate.

Chemical identity

The chemicals are UVCB oils and extracts derived from plants of *Gaultheria procumbens* and *Betula lenta*. They can be produced by steam distillation, hydro-distillation, or solvent extraction of the plant material.

The exact chemical composition may vary depending on the part of the plant (e.g. stem, leaves, flowers or bark), methods of extraction (mechanical or distillation), duration of extraction and climatic and geographical conditions in which the plant is grown (Michel and Olszewska 2024; Ohja et al. 2022). The exact concentrations of methyl salicylate (CAS no. 119-36-8) in these oils and extracts may vary but is expected to be typically greater than 90%. In analyses of the compositions of wintergreen and sweet birch oils, it was found that:

- 34 authentic wintergreen essential oils contained on average 99.77% methyl salicylate (range 99.47–100%)
- 21 authentic birch essential oils (derived from *Betula lenta*) contained on average 98.54% methyl salicylate (range 93.24–99.84%)
- 27 commercial sweet birch “100% pure essential oils” (mostly identified as *Betula lenta*) from the US market contained on average 97% methyl salicylate (range 56.71–99.9%). There were more than 100 unique chemicals identified in the commercial samples and the concentrations of these varied significantly between samples
- the range of methyl salicylate concentrations in wintergreen oils (derived from *Gaultheria*) on the Nepalese and Chinese markets were 99.54–99.86% and 99.42–99.91%, respectively
- commercially available wintergreen oils (derived from *Gaultheria procumbens*) had methyl salicylate content in the range 96.9–100% (Dosoky et al. 2022; Michel and Olszewska 2024; Ohja et al. 2022).

In oils derived from *Gaultheria Procumbens* L., the methyl salicylate content of leaf and fruit extracts ranged from 91.1–100%, while extracts from other aerial parts of the plant contained only 61.14% methyl salicylate (Michel and Olszewska 2024).

The minor components of these chemicals may comprise over 100 compounds including phenolic acids, chlorogenic acid isomers, glycosides, flavonoids and proanthocyanidins, triterpene acids and sterols (Liu et al. 2013; Michel and Olszewska 2024). No polyaromatic hydrocarbons were detected in the above samples.

As the chemical compositions are dominated by a single chemical component, methyl salicylate, names of these oils and extracts are often used interchangeably.

CAS number	68917-50-0
CAS name	Oils, sweet birch
Molecular formula	Unspecified
Associated names	Birch wood pyrolysate
	Betula lenta, Betulaceae
Molecular weight (g/mol)	-
SMILES (canonical)	-

Additional chemical identity information

The chemical is a UVCB and is primarily comprised of methyl salicylate (CAS number 119-36-8) at concentrations up to 100%. CAS notes describe this chemical as "Extractives and their physically modified derivatives. *Betula lenta*, *Betulaceae*" (CAS n.d.).

CAS number	68917-75-9
CAS name	Oils, wintergreen
Molecular formula	Unspecified
Associated names	Betula lenta, Betulaceae
	Gaultheria procumbens, Ericacenae
Molecular weight (g/mol)	-
SMILES (canonical)	-

Additional chemical identity information

The chemical is a UVCB and is primarily comprised of methyl salicylate (CAS number 119-36-8) at concentrations up to 100%. CAS notes describe this chemical as "Extractives and their physically modified derivatives. *Gaultheria procumbens*, *Ericacenae* or *Betula lenta*, *Betulaceae*" (CAS n.d.).

CAS number	85251-66-7
CAS name	Birch, *Betulalenta*, ext.
Molecular formula	Unspecified
Associated names	Betula lenta bark oil Sweet birch extract
Molecular weight (g/mol)	-
SMILES (canonical)	-

Additional chemical identity information

The chemical is a UVCB and is primarily comprised of methyl salicylate (CAS number 119-36-8) at concentrations up to 100%. CAS notes describe this chemical as "Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from *Betula lenta*, *Betulaceae*." (CAS n.d.).

CAS number	90045-28-6
CAS name	Gaultheria procumbens, ext.
Molecular formula	Unspecified
Associated names	Gaultheria procumbens flower/leaf/stem oil (INCI)
Molecular weight (g/mol)	-
SMILES (canonical)	-

Additional chemical identity information

The chemical is a UVCB and is primarily comprised of methyl salicylate (CAS number 119-36-8) at concentrations up to 100%. CAS notes describe this chemical as "Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues etc., obtained from *Gaultheria procumbens*, *Ericaceae*." (CAS n.d.).

Relevant physical and chemical properties

The exact chemical composition of these chemicals may vary (see **Chemical identity**), although all are expected to be liquids with volatile components. Methyl salicylate, the predominant component, has a vapour pressure of 13 Pa at 20°C, a reported log Kow of 2.55 and reported water solubility of 6.25 mg/L at 30°C (AICIS 2024a).

Introduction and use

Australia

There is limited specific information about the introduction, use and end use of these chemicals in Australia. Information reported to AICIS indicated use in toothpastes and skin or hair products at low concentrations (<1%).

Wintergreen and sweet birch essential oils are also available as pure oils (with concentrations up to 100%) in Australian markets.

Chemicals in this group have non-industrial uses in therapeutics (as analgesics in topical pain relief ointments and creams at up to 50%).

International

Based on international data, chemicals in this group are used for their wintergreen aroma in a wide range of personal care (cosmetics) and domestic products:

- Wintergreen oil is listed on the IFRA Transparency List (IFRA n.d.-b).
- Birch, *Betulalenta*, ext. and *Gaultheria Procumbens* ext. are listed in the CosIng database with the reported functions of skin conditioning, fragrance and perfuming (EC n.d.).
- Gaultheria Procumbens (Wintergreen) Flower/Leaf/Stem Oil (CAS no. 90045-28-6) has reported functions as a fragrance ingredient and skin conditioning agents on the International Nomenclature of Cosmetic Ingredients (INCI) database. These names 'wintergreen oil' and 'sweet birch oil' are linked to multiple entries in INCI, including methyl salicylate (Personal Care Products Council n.d.).
- The Environmental Working Group (EWG) Skin Deep Database shows that Gaultheria Procumbens (Wintergreen) Flower/Leaf/Stem Oil (CAS no. 90045-28-6) is used in personal care products, including oral care products (EWG n.d.).

Personal care products containing these chemicals may include bath products, toothpastes, cleansers, fragrances, and moisturisers. As these names are often used interchangeably in these products and chemicals in this group have similar chemical components, typical uses and concentrations of these chemicals in cosmetic products are expected to be similar to those reported for methyl salicylate. Methyl salicylate was used in these types of products at concentrations up to 2.5%, with typical concentrations of use below 0.1% (AICIS 2024a).

Based on the available use information for methyl salicylate, chemicals in this group may have domestic use as a fragrance ingredient in air freshener, cleaning and washing products (AICIS 2024a).

Additional uses of these chemicals as essential oils have been identified. Pure oil (with expected concentrations up to 100%) is available to consumers. Essential oils are commonly used in aromatherapy including as massage oils and in aroma diffusers. Reported concentrations of wintergreen oil in massage oil products in Canada were up to 10% (Government of Canada 2020)

Wintergreen oil is widely used in non-medicinal topical, oral and nasal natural health products including analgesic creams, ointments, and antacid tablets at concentrations up to 20% (Government of Canada 2020; SCCS 2021).

Other non-industrial uses include food flavouring, pet care, insect repellents, pesticides and aromatherapy.

Existing Australian regulatory controls

Public

These chemicals are not individually listed in the *Poisons Standard*— (SUSMP).
Methyl salicylate is listed in the SUSMP as follows (TGA 2024).

Schedule 5:

"METHYL SALICYLATE in preparations containing 25% or less of methyl salicylate **except**:

a) in preparations for therapeutic use; or
b) in preparations containing 5% or less of methyl salicylate."

Schedule 6:

"METHYL SALICYLATE **except**:

a) when included in Schedule 5; or
b) in preparations for therapeutic use; or
c) in preparations containing 5% or less of methyl salicylate."

Schedule 5 chemicals are labelled with 'Caution' and are described as: "Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label."

Schedule 6 chemicals are labelled with 'Poison' and are described as: "Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label." (TGA 2024).

Workers

These chemicals are not listed on the Hazardous Chemical Information (HCIS) and no specific exposure standards are available for these chemicals in Australia (SWA n.d.).

International regulatory status

No specific regulatory action has been identified for chemicals in this evaluation with the exception of: under the US Food and Drug Administration (FDA) Federal Food, Drug, and Cosmetic Act Code of Federal Regulations (21CFR201.303) "any drug containing more than 5 percent methyl salicylate (wintergreen oil)" must be labelled "to warn that use otherwise than as directed therein may be dangerous and that the article should be kept out of reach of children to prevent accidental poisoning" (FDA n.d.).

Several restrictions relating to allowable concentrations of methyl salicylate in cosmetics apply in several countries (AICIS 2024a).

Human exposure

Public

As these chemicals are used in a wide range of cosmetic and household products (see **Introduction and use**), there is expected to be significant public exposure to these chemicals.

Chemicals listed in this evaluation are expected to be used at similar concentrations to methyl salicylate in personal care products (cosmetics). Exposure estimates considered indicative of likely exposures to methyl salicylate in personal care products (cosmetics) in Australia have previously been calculated. The calculated aggregate daily systemic exposure to methyl salicylate in personal care products (cosmetics) was 0.52 mg/kg bw/day. This included an estimate of oral, dermal and inhalation exposure to all product types with maximum concentrations permitted in the EU (AICIS 2024a). An aggregate daily systemic exposure dose in children aged 0.5–1, 1–3 and 3–6 years was also estimated as 0.035, 0.463 and 0.454 mg/kg bw/day respectively.

The public may also be exposed to these chemicals due to their presence in household products. In general, exposure from cleaning products with low concentrations of these chemicals (typically less than 1%) would be incidental.

The group of chemicals listed in this evaluation are also sold as pure oils (concentrations up to 100%) for use in aromatherapy including as massage oils and in room diffusers. Worst case daily systemic exposures to these chemicals from these uses were estimated using ConsExpo Web (RIVM n.d.). A default adult body weight of 60 kg was assumed for both scenarios.

The daily systemic exposure dose to these chemicals in massage oil is estimated to be 6.7 mg/kg bw/day, based on the following parameters and assumptions (RIVM 2006):

- Exposure model: Direct product contact – instant application
- Dermal absorption: 50% (fixed fraction)
- Use scenario: 8.0 g of massage oil containing 10% of these chemicals (see **Introduction and Use**), applied once daily
- Retention factor: 1.

The daily systemic exposure dose to these chemicals used in room diffusers is estimated to be 0.27 mg/kg bw/day, based on the following parameters and assumptions (RIVM 2006):

- Exposure model: Exposure to vapour – constant rate
- Assumed inhalation absorption: 100% (fixed fraction)
- Use scenario: 1.08 g (24 drops) of the oil (100% chemical concentration) are added to a living room, 168 times a year (or 14 times per month) on average
- Exposure duration: 4 hours
- Room volume: 58 m^3
- Ventilation rate: 0.5 per hour
- Inhalation rate: 23.11 L/min
- Emission duration: 180 minutes.

Health hazard information

Limited hazard data are available for wintergreen and sweet birch oil. No hazard data are available for *Gaultheria procumbens*, ext. or birch, *Betulalenta*, ext. Clinical reports often use these names ‘methyl salicylate’, ‘oil of wintergreen’ and ‘wintergreen oil’ interchangeably. For this evaluation, only data linked to these names ‘oil of wintergreen’ or ‘wintergreen oil’ have been reported.

The specific composition of these chemicals may vary (see **Chemical identity**); however, the toxicity is expected to be driven by the major component, methyl salicylate. As these oils typically contain greater than 90% methyl salicylate, the available hazard data on methyl salicylate is suitable to be used as read across for all health endpoints.

The AICIS evaluations for methyl salicylate (AICIS 2024a) and its metabolite salicylic acid (AICIS 2024b) should be read in conjunction with this report.

Toxicokinetics

There is limited information on the toxicokinetics of these chemicals.

Chemicals in this group are expected to be absorbed following oral, dermal and inhalation exposure based on the available information for methyl salicylate.

The absorption of these chemicals by the oral route is expected to be 100% as methyl salicylate is readily absorbed orally. The dermal absorption is dependent on vehicle composition, pH, application site, structure of the skin, conditions of application in the skin and frequency of applications. However, a default value for dermal absorption of methyl salicylate is 50% which is considered a conservative estimate and applies to these chemicals in this evaluation. Although no data are available on absorption of these chemicals via inhalation, based on the physicochemical properties of methyl salicylate, absorption via inhalation route is expected (AICIS 2024a; AICIS 2024b).

After absorption, the methyl salicylate component of these chemicals is expected to be widely distributed and hydrolyse into the metabolite, salicylic acid. A significant amount of methyl salicylate is hydrolysed to salicylic acid 90 minutes after exposure. Concentrations of salicylic acid in the blood are higher from oral exposures compared to dermal exposures. Therefore, the developing foetus could be exposed to salicylic acid metabolite. Excretion is mainly via urine (AICIS 2024a; AICIS 2024b).

Acute toxicity

Oral

No animal data are available for these chemicals. Based on the available data for methyl salicylate and evidence of human acute poisoning following oral exposure to wintergreen oil (see **Observation in humans)**, chemicals in this group are expected to have moderate acute oral toxicity, warranting classification.

In acute toxicity studies conducted similarly to the Organisation for Economic Cooperation and Development Test Guideline (OECD TG) 401, the reported median lethal values (LD50) for methyl salicylate were 887 mg/kg bw and 1060 mg/kg bw in rats and guinea pigs, respectively. The clinical signs of toxicity in rats included piloerection, shaggy coat, hunched

posture, lethargy, oscillated movements, difficulty breathing, convulsions and mydriasis (dilated pupils) (AICIS 2024a).

The LD50s reported in other species were 580–1440 mg/kg bw in mice, 1300–2800 mg/kg bw in rabbits and 2100 mg/kg bw in dogs (AICIS 2024a).

Dermal

No data are available for these chemicals. Based on the available data for methyl salicylate, chemicals are not expected to be acutely toxic via the dermal route.

This group of chemicals are expected to have low acute dermal toxicity. The reported LD50 values are greater than 2500 mg/kg bw in rats and rabbits (AICIS 2024a; Lapczynski et al. 2007).

Inhalation

No data are available for these chemicals. Based on information on a sub-chronic inhalation toxicity study for methyl salicylate, these chemicals are not expected to be acutely toxic via the inhalation route.

In studies with limited details, median lethal concentrations (LC50) greater than 114 mg/m^3 in rats and greater than 400 mg/m^3 in mice have been reported (AICIS 2024a).

Observation in humans

Several cases of salicylate toxicity from the ingestion of wintergreen oil have been reported.

In a retrospective review of mortalities unintentionally caused by salicylates that were recorded in the American Association of Poison Control Centres' Toxic Exposure Surveillance System (TESS) between 1985 and 2003, 6 mortalities were reported after ingestion of 4–120 mL wintergreen oil were reported. In children under the age of 6, 9 cases of acute poisoning were attributed to the ingestion of 4–60 mL wintergreen oil. Toxicity was reported as moderate to severe in most cases with doses approximately equivalent to 378–1,842 mg/kg bw. Poisoning was confirmed by presence of the salicylate ion in serum for most cases. Mortality was observed in 2 cases. In patients over 6 years of age, the lowest fatal dose reported in TESS was 5–15 mL wintergreen oil. Reported symptoms included: haematemesis, tachypnoea, hyperpnoea, dyspnoea, tinnitus, deafness, lethargy, seizures, unexplained lethargy and confusion (Chyka et al. 2007).

Acute methyl salicylate poisoning in humans causes fever, nausea, vomiting, CNS excitation, tachycardia, rapid breathing, high blood pressure, respiratory failure, pneumonia, pulmonary oedema, convulsions and coma (Chyka et al. 2007).

Corrosion/Irritation

Skin irritation

Limited data are available for wintergreen oil. Based on the available animal data on wintergreen oil and methyl salicylate, chemicals in this group are at most, slightly irritating to skin. Human studies indicate that methyl salicylate is not a skin irritant.

To determine the skin irritation potential of wintergreen oil for phototoxicity studies, neat wintergreen oil was applied to the skin of 2 miniature swine and 6 hairless mice. Flaking of the skin, hyperkeratosis and dry desquamation were observed in both animals (Lapczynski et al. 2007).

The extent of skin irritation caused by methyl salicylate in animals is highly dependent on the vehicle and concentration (SCCS 2021). In an OECD TG 404 skin irritation study, methyl salicylate caused mild, reversible irritation to the skin of rabbits at concentrations of 20% and 100%. The erythema and oedema scores were not sufficient to warrant classification. Mild to moderate skin irritation in rabbits, guinea pigs and mice were observed in other non-guideline studies (AICIS 2024a).

Eye irritation

Based on the available data for methyl salicylate, chemicals in this group are considered to cause serious eye damage, warranting hazard classification.

Methyl salicylate was recommended for classification in Australia with hazard category "Serious eye damage – Category 1" and hazard statement "H318: Causes serious eye damage". The conclusion was based on a positive result in a GLP compliant in vitro guideline eye corrosion study (OECD TG 491) and observations of corneal necrosis in rabbit eyes after application of neat methyl salicylate in a non-guideline eye irritation study (AICIS 2024a).

Observation in humans

In a human patch test, 12% wintergreen oil (containing 80–99% methyl salicylate) in petrolatum was applied to 25 subjects for 48 hours under occlusion. No signs of irritation were observed in this study (Lapczynski et al. 2007).

Based on skin studies in over 900 human subjects, salicylate esters (including methyl salicylate) are not considered skin irritants (Belsito et al. 2007).

In human patch test studies, methyl salicylate did not cause skin irritation at concentrations up to 12% (SCCS 2021). Irritation was observed at higher concentrations but information on severity and reversibility is limited or not available.

Sensitisation

Skin sensitisation

Limited human data are available for wintergreen oil. Based on the available data for methyl salicylate, chemicals in this group are considered to be weak skin sensitisers, warranting classification.

Methyl salicylate is classified as hazardous in the HCIS with hazard category "Skin sensitisation – Category 1B" and hazard statement "H317: May cause an allergic skin reaction" (SWA n.d.).

Methyl salicylate showed a low to moderate frequency of reactions in humans and a low to moderate sensitisation potency in animals. In several local lymph node assays (LLNA) conducted in accordance with OECD TG 429, positive skin sensitisation results for mice were reported at concentrations greater than 25%, with reported concentrations producing a three fold increase in the lymphocyte proliferation (EC3) ranging from 15–65%. In several

guinea pig maximisation tests (GPMT) conducted similarly to OECD TG 406, negative skin sensitisation results were reported at induction concentrations ranging from 2.5–5%, and challenge concentrations up to 100%. Positive skin sensitisation results were reported in 2 non-guideline maximisation tests applied to guinea pigs with 2/8 (25%) and 2/20 (10%) of the animals responding after challenge. Other non-guideline maximisation tests were negative for skin sensitisation (AICIS 2024a).

Respiratory sensitisation

Chemicals in this group are not expected to be respiratory sensitisers based on the limited data available. There are no reports of respiratory sensitisation from the use or manufacture of methyl salicylate in the EU. Methyl salicylate was not found to be a respiratory sensitiser in a respiratory sensitisation LLNA in mice (AICIS 2024a).

Observation in humans

In a human volunteer induction study, 12% wintergreen oil in petrolatum was applied topically on 25 subjects under occlusion for 5 alternate day 48 hour periods. After topical challenge with methyl salicylate, no reactions were reported (Lapczynski et al. 2007).

In 8 out of 9 reported diagnostic human patch testing studies with up to 2% methyl salicylate, there were positive skin sensitisation incidences of 0.13–2.0% in selected subjects. No reactions were reported in 2 human-repeat insult patch tests in subjects exposed to 1.25% or 8% methyl salicylate. In addition, there were 2 isolated human case reports that showed positive sensitisation reactions to methyl salicylate exposure (AICIS 2024a).

Repeat dose toxicity

Limited data are available for sweet birch oil. Based on the available data for these chemicals and methyl salicylate, chemicals in this group are expected to cause adverse effects on foetal development if pregnant dams are exposed to these chemicals (see **Reproductive and development toxicity**). Other adverse effects caused by methyl salicylate reported in repeat dose studies only occurred at very high doses.

Oral

Limited data are available for these chemicals.

In a limited detailed 2 year study, 25/sex/group experimental animals (unknown strain) were administered sweet birch oil in the diet at 700 and 2100 ppm. No significant adverse effects on growth, survival, food consumption, physical condition of the animals, blood and clinical chemistry or gross and histopathological findings were observed (SCCS 2021). In a chronic study in weanling albino rats, no treatment-related adverse effects were seen with methyl salicylate derived from sweet birch oil (90.4% of the extract) (SCCS 2021). No further details are available.

Several repeated oral exposure studies are available, with the lowest observed adverse effect level (LOAEL) in rats reported to be 50 mg/kg bw/day, based on reduced body weight and effects on liver following exposure to methyl salicylate (AICIS 2024a).

In two different chronic studies in Osborne-Mendel rats and Beagle dogs, methyl salicylate was administered via oral route at doses of 50–1000 mg/kg bw/day or 0–350 mg/kg bw/day. respectively. Observed effects included significantly reduced body weight gains, retarded

growth, significantly increased heart and kidney weights in rats and enlarged livers in dogs. These adverse effects were reported at and above 120 mg/kg bw/day in rats and 150 mg/kg bw/day in dogs. A no observed adverse effect level (NOAEL) of 50 mg/kg bw/day was reported for both the studies (Government of Canada 2020).

Dermal

No data are available for these chemicals.

A LOAEL of 585 mg/kg bw/day for dermal exposure based on reduced weight gains, nephritis and mild hepatitis was determined for rabbits exposed to topical methyl salicylate at 585–4720 mg/kg bw/day for 96 days (AICIS 2024a; SCCS 2021).

Inhalation

No data are available for these chemicals.

No adverse effects were observed in a sub-chronic inhalation study in female Alderley Park rats exposed to methyl salicylate vapours with saturated concentration of 700 mg/m^3 for 7 hours/day for 5 days/week for 4 weeks (SCCS 2021).

Genotoxicity

Limited data are available for these chemicals. Based on available data for these chemicals and methyl salicylate, chemicals in this group are not expected to have genotoxic potential.

Wintergreen oil did not induce DNA damage in an in vitro comet assay in either primary rat neurons or in N2a rat brain neuroblastoma cells at concentrations up to 400 mg/L. Based on this result, wintergreen oil was presumed to be non-genotoxic (Celik and Turkez 2016).

Negative results were reported in various in vitro studies with methyl salicylate and no in vivo data are available (AICIS 2024a). The metabolite salicylic acid is not expected to have genotoxic potential based on in vitro and in vivo data (NICNAS 2013).

Carcinogenicity

Limited data are available. Based on methyl salicylate and non-guideline studies with wintergreen oil, chemicals in this group are not expected to have carcinogenic potential. The potential of wintergreen oil to affect tumour growth in mice has been tested in several non-guideline chronic studies. No significant changes in tumour growth were reported, and it was concluded that wintergreen oil is not likely to be carcinogenic (Government of Canada 2020; SCCS 2021).

Methyl salicylate and its metabolite, salicylic acid are not expected to be carcinogenic (AICIS 2024a; AICIS 2024b).

Reproductive and development toxicity

No data are available.

Methyl salicylate is classified as hazardous in the HCIS with hazard category “Reproductive Toxicity – Category 2” and hazard statement “H361d: Suspected of damaging the unborn child” (SWA n.d.).

Based on the available information for methyl salicylate, these chemicals in this group may cause adverse effects on development, warranting hazard classification. In several animal studies, methyl salicylate was able to reach the developing foetus and caused adverse effects which included reduced litter sizes, decreased pup survival and increased incidences of neural tube defects and skeletal abnormalities. These effects were observed when methyl salicylate was administered to the animals orally, dermally or by subcutaneous injection (AICIS 2024a). The same adverse effects were seen in multiple studies in rats and monkeys, using the metabolite salicylic acid, providing further evidence of developmental toxicity (AICIS 2024b).

Based on the available information, chemicals in this group are not expected to have adverse effects on sexual function and fertility. No statistically significant adverse effects on fertility or sexual function were reported in 1, 2 and 3 generation studies at doses up to 648 mg/kg bw/day in rats and 450 mg/kg bw/day in mice (AICIS 2024a; AICIS 2024b).

In a 3 generation oral reproductive toxicity study methyl salicylate was administered to Osborne-Mendel rats, a NOAEL of 250 mg/kg bw/day for fertility and a NOAEL of 75 mg/kg bw/day for development based were determined on decreased pup survival and decreased pup body weight at the highest dose were established (AICIS 2024a).

Observation in humans

No human data are available for these chemicals.

Extensive data are available for acetylsalicylic acid as aspirin which shares a metabolite with methyl salicylate. Aspirin is a widely used medicine and has been used for a long time. Most data indicate that low doses of aspirin do not increase risk of adverse effects on pregnancy. Although some adverse effects such as maternal bleeding and changes in pregnancy duration and labour have been reported, no malformations were identified at any dose. The difference in the dose range between the animal studies and the human epidemiology studies is very high (AICIS 2024a).

Endocrine effects

No data are available for these chemicals.

Based on available information, methyl salicylate does not show oestrogenicity or cause specific adverse effects on uterine weights. However, indications from the literature suggest that salicylates may have endocrine modulating properties. The available data on methyl salicylate and salicylic acid do not provide sufficient evidence of adverse effects from endocrine modes of action (AICIS 2024a; AICIS 2024b).

Human health risk characterisation

Critical health effects

The critical health effects for risk characterisation are systemic effects (developmental toxicity). While the NOAEL for developmental toxicity varies significantly in the experimental

data, an NOAEL of 75 mg/kg bw/day was selected for risk characterisation for methyl salicylate based on both the 3 generation study with methyl salicylate and the prenatal studies with salicylic acid (AICIS 2024a). This NOAEL is appropriate for the risk characterisation of these chemicals in this evaluation.

Public risk

The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB 2003).

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

The risks from the use of methyl salicylate in personal care products and household products at low concentrations has previously been established. MOEs greater than 100 were calculated for adults and children (AICIS 2024a).

However, chemicals in this evaluation are also sold as pure oils (concentrations up to 100%) for use in aromatherapy including as massage oils and in room diffusers.

Based on the conservative daily systemic exposure estimates for use in room diffusers (see **Human Exposure – Public**), the MOE is 278.

Based on the conservative daily systemic exposure estimates for massage oil (see **Human Exposure – Public**), the MOE is 11.

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