WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

Menthol(2014)

I. IDENTIFICATION

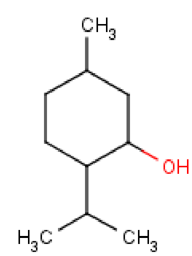
Chemical Name: Menthol

Chemical Name (CAS #)[1]	Synonyms
DL-Menthol Raw (1490-04-6)	2-Isopropyl-5-methylcyclohexanol; 5-Methyl-2-(1-methylethyl)cyclohexanol; Menthol; Menthyl alcohol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-; DL-Menthol; 5-Methyl-2-(1-methylethyl) cyclohexanol;
DL-Menthol Synthetic (89-78-; Former 15356-70-4)	Racementhol; D/L-Menthol Racemate; Menthol; Racemic menthol; (+-)-Menthol; (1R,2S,5R)-Menthol; 5-Methyl-2-(1-methylethyl) cyclohexanol, (1alpha,2beta, 5alpha)-; 2-isopropyl-5-methylcyclohexanol; Hexahydrothymol; Menthacamphor; Menthol natural; Menthol natural, brazilian; Menthol racemic; Menthomenthol; Peppermint camphor; Racementhol; Racementholum; Racementol; p-Menthan-3-ol; rac-Menthol; (+-)-(1R*,3R*,4S*)-Menthol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1R,2S,5R)-rel-; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1alpha, 2beta,5alpha)-; Menthol; Menthol, cis-1,3,trans-1,4-; d,l-Menthol; dl-Menthol
L-Menthol Natural or Synthetic (2216-51-5)	(-)-Menthol; Levomenthol; (l)-Mentho; (-)-Menthyl alcohol; (-)-trans-p-Menthan-cis-ol; (1R)-(-)-Menthol; (1R-(1-alpha,2-beta,5-alpha))-5-Methyl-2-(1-methylethyl) cyclohexanol; D-(-)-Menthol; Levomenthol; Levomentholum; Menthol, (1R,3R,4S)-(-)-; Menthol, l-; U.S.P. Menthol; l-(-)-Menthol; l-Menthol; l-Menthol (natural); (-)-(1R,3R,4S)-Menthol; (-)-Menthol; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1R,2S,5R)-; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1R,3R,4S)-; Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1R-(1alpha,2beta,5alpha))-

Statement on similar isomer activity relationship: The different menthol isomers are considered similar for the purposes of toxicological assessments.[2–4]

Molecular Formula: $C_{10}H_{20}O$

Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[2,4,5–16]

Physical State: Crystals or granules

Molecular Weight: 156.27

Conversion Factors 1 ppm = 6.4 mg/m^3; 1 mg/m^3 = 0.16 ppm

Melting Point: 41-43 ^{o}C (106-109 ^{o}F) Isomer not specified. DL-Menthol exists in two polymorphs melting at 28 ^{o}C and 38 ^{o}C, respectively

Freezing point: 27 to 28 ^{o}C, rising on prolonged stirring to 30 ^{o}C to 32 ^{o}C. Isomer not specified

Boiling Point: 212 ^{o}C (414 ^{o}F) Isomer not specified

Density/Specific Gravity: 0.890 g/cm^3 Isomer not specified; 0.895 g/cm^3 at 20 °C (CAS# 1490-04-6)

Vapor Pressure: 8.5 Pa (0.064 mm Hg) at 25 °C (L-menthol, Isomer not specified); 30 Pa (0.975 mm Hg) at 55 °C D/L menthol

Saturated Vapor Concentration: 84 ppm (538 mg/m^3) at 22-25 °C (calculated; = Vapor Pressure X 1315); 132 ppm (845 mg/m^3) at 55 °C (calculated; = Vapor Pressure X 1315)

Octanol/Water Partition Coefficient: log Kow = 3.2–3.4 CAS-No. 1490-04-6, 2216-51-5, 15356-70-4, Isomer not specified

Solubilities:

Water solubility: 456 mg/l @ 25 °C (Isomer not specified); 431–508 mg/l at 20 - 25°C flask method (CAS# 1490-04-6, 2216-51-5, 15356-70-4, Isomer not specified);
Slightly soluble in water; very soluble in alcohol, chloroform, ether, petroleum ether acetone, benzene,

organic solvents; freely soluble in glacial acetic acid, liquid petrolatum

Odor Description and Threshold: Peppermint odor;

Threshold odor concentration, detection 0.14–0.26 ppm, 0.9 - 1.7 mg/m^3

Threshold odor concentration 0.002–11.6 mg/ m^3

Threshold odor concentration, recognition 0.33 ppm, 2.1 mg/m^3

Taste: Peppermint

Flammability Limits: Not available

Flash Point: > 100°C (closed cup; isomer not specified; purity > 99.7 %)

Autoignition Temperature: Not available

Other Properties:

Specific optical rotation: +49.2 degree/D (alcohol, 5%, D-menthol)

UV: 635 (Sadtler Research Laboratories Spectral Collection)

NMR: 410

Hazardous Reactivities & Incompatibilities:

Incompatible with phenol; beta-naphthol; resorcinol or thymol in trituration; potassium permanganate; chromium trioxide; pyrogallol, butylchloral hydrate, camphor, phenol, chloral hydrate, exalgine

Hazardous Decomposition:

When heated to decomposition it emits acrid smoke and irritating fumes.

III. USES AND VOLUMES

Menthol is an alcohol produced from mint oils or prepared synthetically. Peppermint oil contains about 35–60 % menthol (menthone (15–30 %), menthylacetate (4–14 %), and small amounts of cineole and other terpenes).[17] Menthol is widely used in consumer products as well as other uses. Product types were listed as antipruritics, dermatologic agents, approved as a Group II pesticide, flavoring substance, flavoring agents, denaturants, fragrance ingredients, used in cosmetics as denaturant, masking, refreshing, soothing agents, FDA direct food additive, paints and lacquers, adhesives, metal care products, cleaning products, shoe- and leather-care products, disinfectants, solvents, cosmetics, odor improvers, repellents and animal care products, farming of cattle and other animals, manufacture of foodstuffs, manufacture of pharmaceutical and medicinal chemicals and of cleaning products. Concentrations for oral products range from 0.001–2%; dermal products range from 0.001–6%; and inhaled products from 0.1–0.45%.[4,18–24]

IV. TOXICOLOGY DATA

A. Acute Toxicity and Irritancy

1. Lethality Data

Menthol Isomer	Species	Route	LD50 or LC50
D-	Rat	Oral	2046[4]
DL-	Rat	Oral	940[3]
DL-	Rat	Oral	2602[4]
			2900[3]
			3180[4]
		Inhalation	5289 mg/m^3 [29] (4h, aerosol)
		IM	10,000[16]
		IP	750[3]
	Mouse	Oral	3100[25]
		SubQ	14000-16000[3]
	Rabbit	IP	2000[3]
	Cat	Oral	1500 – 1600[3]
		IP	1500 – 1600[3]
L-	Rat	Oral	2426 – 2615*[4]
			3300[3]
			3400[25]
		IP	710[3]
		SubQ	1000 – 2500[3]
	Mouse	Oral	4380[3]
			2600[3]
		IP	2000[3]
		SubQ	5000-6000[3]
	Guinea Pig	IP	4000[3]
	Cat	IP	800 – 1000[3]
		Oral	800 – 1000[4]
L-/DL-	Rabbit	Dermal	≥ 5000[4]
INS	Rat	Oral	3180[16]
	Mouse	Oral	> 6000[4]
		Dermal	34500[28]

*Females; h – hours; INS – isomer not specified; SubQ – Subcutaneous; IP – Intraperitoneal; IM – Intramuscular

Death occurred 1-3 days after dosing. Clinical signs were reported as narcotic status and depressed activity but no data were available on exposure level at which the effects were observed.[3,4] At sublethal doses of L-menthol in mice, lethargy was reported.[25] In one study with L- menthol, a lower LD_{50} of 940 mg/kg was observed.[4] In this study, a severe irritation of the mucosal lining of the stomach and intestine was reported. Other investigators have not reported such effects.

2. Eye Irritation

Concentrations of 29 to 64% of L-, D- or DL-menthol in diethylphthalate, undiluted or 71% menthol liquid were tested for eye irritation in the same institute and by the same OECD Guideline 405 protocol. The vehicle was tested in the opposite eye of the animals, and showed no irritating properties. Mean scores 24, 48, and 72 h after the various menthol isomer treatments indicated concentration dependent reactions of cornea and conjunctiva. In all cases, there was no reaction observed in the iris. After treatment with menthol liquid (100% and 71%), slight redness of the conjunctiva was seen on day 7 in 1/4 and 2/4 animals, respectively. For the undiluted menthol liquid it was shown that these effects were completely reversible within 14 days.(4) In another rabbit study, instillation of 1% or 5% solution in an unknown vehicle or undiluted menthol (of unknown purity), were reported to result in eye injury (grade 9 on a scale of maximum 10). No details were available on the number of animals or the nature of the effects seen after menthol treatment.(26) Additionally in a Draize test, concentrations of 10% to 60% DL-menthol were applied to the eyes of eight animals with four eyes rinsed after one minute and four without rinsing. In this test, menthol was not considered irritating.(4)

3. Skin Absorption

No data other than lethality are available.

4. Skin Irritation

Concentrations ranging from 1% to undiluted L-, D-, DL-menthol or menthol liquid in diethylphthalate were tested for skin irritation in the same institute and by the same OECD Guideline 404 protocol. All undiluted isomers were irritating to the skin. No skin reactions were observed for D-menthol and menthol liquid at the 5% dilution, and for L- and DL-menthol at the 1% dilution.(4)

5. Sensitization

Sensitization studies were conducted on L-menthol. In an OECD 406 Buehler test, 0.5 ml of a 25 % solution was applied in an occlusive dressing to guinea pig skin for both the induction and the challenge phases.(4) A local lymph node assay was performed according to the protocol of Kimber and Weisenberger.(4) In both studies, L-menthol was negative. In a modified Draize test, a positive result was only obtained when four 0.1 ml induction injections of 0.1% L-menthol and two challenge periods consisting of a 0.1 ml intradermal injection of the 0.1% solution and a topical application of a 10% solution were used.(4) A local lymph node assay was performed with concentrations up to 50% DL-menthol and was negative.(27)

6. Inhalation Toxicity

In one study, bradypnea, labored breathing pattern, dyspnea, motility reduced, atony, tremor, high-legged gait, staggering gait, movements uncoordinated, piloerection, ungroom hair coat, nasal discharge (serous, red), stridor, breathing sounds, apathy, narcosis, prostration, miosis, hypothermia, decreased reflexes, and transient decrease in body weights were observed. The authors stated that the effects were suggestive of a narcotic condition associated with increased airway secretions/mucous membrane irritation. CNS-related effects were rapidly reversible. Bradypnea and labored breathing patterns were observed through post exposure day 10. The respirability of the aerosol was adequate to achieve the objective of study, *i.e.*, the average mass median aerodynamic diameter was 3.1μm ± 1.8 (geometric standard deviation).(29)

Several acute irritation studies were available. In mice, 16 ppm for 15 min caused mild irritation in the upper respiratory tract as determined by changes in respiratory function.(28) Sprague-Dawley rats were exposed to 0.13 mg/m^3 (0.02 ppm) menthol as part of a cold preparation vapor for 4 or 8 hours in a whole body chamber. No differences in bacterial clearance were observed between control and treated rats.(29) The sensory irritation potential of menthol was evaluated in 30-minute exposures of Swiss-Webster mice to seven menthol concentrations ranging from 18 to 31 ppm (115 to 198 mg/m^3). Periocular wetness was observed in several animals 24 hours following exposure to concentrations of 22 ppm (140 mg/m^3) and above, and mortalities were recorded among the 20 and 30 ppm (140 and 191 mg/m^3) exposure groups. The airborne concentration resulting in a 50% decrease in respiratory rate (RD_{50}) in anesthetized mice was determined to be 45 ppm (288 mg/m^3).(30,31)

B. Subacute Toxicity

Groups of six male mice were dosed with 2000, 2500, 3200, 4000, or 5000 mg/kg L-menthol by gavage for five days and monitored for 14 days. The LD_{50} was 2600 mg/kg.(3)

Ten male and 10 female Wistar rats per group were gavaged for 28 days with 200, 400 or 800 mg/kg/day L-menthol. The study was conducted mainly according to OECD guideline 407. Animals were checked for clinical signs and mortality twice daily. Body weight, food and water consumption were recorded weekly. At necropsy, kidneys, adrenals, heart, brain, liver and the stomach (with contents) weights were taken. Hematology consisting of hemoglobin, PCV, total erythrocyte count, total white blood cells, white blood cell differential count, and reticulocyte counts; biochemistry consisting of glucose, creatinine, urea, and liver enzyme activities; and urine for presence of blood, ketones, glucose and proteins were examined. The organs were prepared for histological examination as described in OECD guideline 407 with the exception of the full histopathology examinations of urinary bladder and prostate. There was no effect of treatment on body weight gain, food consumption or clinical chemistry. There was significantly increased water consumption and an increased number of neutrophilic granulocytes at the highest dose level; however, for both effects, neither the magnitude nor the sex was reported. In males at all doses and females at ≥ 400 mg/kg/day, absolute and relative liver weights were significantly increased (no information on magnitude and incidence of this findings is given in the publication). In all treated males and females, histopathological examination revealed vacuolization of hepatocytes (male and female combined totals were as follows. Controls, 0/20; 200 mg/kg, 4/20; 400 mg/kg, 5/17; 800 mg/kg, 4/19). The liver effects were not dose-related and were interpreted by the authors as a possible adaptation process. Since no information is available as to the magnitude and the incidence of increased liver weights in the various exposure groups, the relevance of this finding is questionable and a NOAEL or a LOAEL could not be deduced from this study.(4)

C. Subchronic Toxicity

Male and female B6C3F1 mice were treated with DL-menthol in the diet for 13 weeks with a post exposure period of one week. The dose groups of 10 males and 10 females each included the vehicle, 930, 1870, 3750, 7500 or 15000 ppm (male mice: 0, 243, 488, 978, 1956 or 3913 mg/kg/day; female mice: 290, 595, 1193, 2386 or 4773 mg/kg/day, respectively). Mortality was examined daily. Clinical signs including appearance and behavior, body weight and food consumption were recorded weekly. At the end of the exposure period, organs were examined according to OECD guideline 408 except the aorta, peripheral nerve and spinal cord were not examined. Histopathology was conducted for the controls, 7500 and 15000 ppm concentration groups. No differences were found between treated and controls with respect to clinical signs, mortality, time to death, food consumption, gross pathology or histopathology. For males and females, treatment at the highest dose of 15000 ppm, 3913 mg/kg/day and 4773 mg/kg/day, respectively, decreased body weight gain by 5 -10 % compared to controls. Findings described as spontaneous lesions included kidney (interstitial nephritis, nonsuppurative pyelitis) and early spontaneous respiratory disease lesions (peribronchial or perivascular lymphoid hyperplasia, lung congestion). The NOAELs for male and female mice were 7500 ppm, corresponding to 1956 mg/kg/day and 2386 mg/kg/day, respectively, based on reduced body weight gain.(4)

Male and female Fischer 344 rats were treated with DL-menthol in the diet for 13 weeks with a post exposure period of one week. The dose groups of 10 males and 10 females each included vehicle, 930, 1870, 3750, 7500 or 15000 ppm (males: 0, 59, 114, 231, 472 or 937 mg/kg/day; females: 0, 67, 142, 285, 521 or 998 mg/kg/day, respectively). Mortality was examined daily. Clinical signs, including appearance and behavior, body weight and food consumption, were recorded weekly. At the end of the exposure period, organs were examined according to OECD guideline 408 except that the aorta, peripheral nerve and spinal cord were not examined. Histopathology was conducted for the control, 7500 and 15000 ppm concentration groups. No differences were found between treated and controls with respect to clinical signs, mortality, time to death, food consumption, gross pathology or histopathology. Findings of questionable relevance at the high dose included minimal increase in the severity of spontaneous interstitial nephritis. The NOAEL for male and female rats was 15000 ppm, corresponding to 937 mg/kg/day and 998 mg/kg/day, respectively, the highest dose tested.(4)

In a dietary study in male and female rats exposed to 0, 100 or 200 mg/kg/day L-menthol or DL-menthol for 5.5 weeks, with limited end points examined, no adverse effects on weight gain, excretion of glucuronides, water, or electrolytes, or interference with central nervous system reactions to stimulants were observed. The NOAEL was considered 200 mg/kg/day.(3)

Menthol solutions of 1% and 5% were applied daily to the nasal mucous membrane of a rabbit for nine months. Animals were examined daily for amount and type of nasal discharge, general state of activity and body weight. The histopathology of the nasal mucosa was examined from the posterior or ethmoturbinate. Degenerative changes were observed with destructive changes throughout all layers of the nasal membrane after treatment with 5% menthol solution.(4)

Twelve male and female Sherman Rats per group were exposed for 6.75 hours daily to 0.087, 0.148 or 0.259 ppm (according to 0.57, 0.96 or 1.68 mg/m³, respectively) L-menthol in whole body inhalation chambers for 71–79 days. Two control groups of 12 animals were utilized; one under identical conditions except without menthol exposure and the other group remained in their cages throughout the study. Although the authors attempted to measure the menthol concentrations in the gas phase, there was no adequate analytical method available. Therefore the exposure concentrations are given as weight of menthol vaporized divided by the volume of air circulated. Clinical signs, mortality, food consumption and water consumption were examined daily. Body weights were examined twice a week. Organ weights, hematology, and microscopic examinations of the eye, turbinates, nasopharynx, trachea, lungs, and skin, sections of liver, spleen, kidney, heart, testes, ovaries, intestine and skeletal muscle were conducted. Mortality and time to death, body weight gain, food and water consumption, hematology, organ weights, and gross pathology were not different from controls. During daily clinical sign examinations, transient erythema of the conjunctiva was observed, which then disappeared shortly after the animals were returned to their cages. Upon histopathological examination of the lung in the highest dose group, respiratory tract effects were observed that included tracheitis, pneumonitis, pulmonary congestion and severe congestion to pneumonitis, which was suggestive of irritation. A NOAEL or LOAEL could not be assigned due to invalid analytical methods for measurement of the menthol air concentrations.(4)

A 13-week rat inhalation study comparing 200, 600 or 1200 mg/m^3 smoke particulates of which 2% was L-menthol (4, 12 or 24 mg/m^3; 0.6, 1.9 or 3.8 ppm, respectively) to non-menthol containing cigarette smoke, demonstrated that menthol did not increase the respiratory tract histopathological lesions observed after inhalation of cigarette smoke alone. No further conclusions could be drawn on the toxicity of menthol since a menthol-only treatment group was not included in the study.(32)

D. Chronic Toxicity/Carcinogenicity

B6C3F1 mice were treated with 0, 2000 or 4000 ppm (approximately 334 or 667 mg/kg/day) DL-menthol in the feed for 103 weeks. Clinical signs and mortality were checked twice daily. Body weights and food consumption was determined every two weeks. At the end of the one-week post-exposure period, organs were preserved and examined according to OECD Guideline 451. There were no treatment related effects on survival, clinical signs of toxicity, food consumption or gross pathology. A slight decrease in body weight gain estimated at less than 10% was observed in treated groups. There was a slight increase in the incidence of hepatocellular carcinomas in males. However, it was not statistically significant and was within the range of historical controls. Overall, the conclusion was that there was no increased incidence of neoplasms compared to controls. The NOAEL for males and females was 667 mg/kg/day.[33]

Fischer 344 rats were treated with 0, 3750 or 7500 ppm (approximately 188 or 375 mg/kg/day) DL-menthol in the feed for 103 weeks. Clinical signs and mortality were checked twice daily. Body weights and food consumption was determined every two weeks. At the end of the one-week post-exposure period, organs were preserved and examined according to OECD Guideline 451. There were no treatment related effects on survival, clinical signs of toxicity, food consumption or gross pathology. However, there was a slight decrease in body weight gain estimated at less than 10% for the low and high dosed males and the low dose females and approximately 14% for the high dose females. A common finding in aged rats, increased chronic renal inflammation was found in treated male rats compared to controls (29/49, 41/50 and 41/50, respectively). Treated female rats showed a decrease in mammary gland fibroadenomas compared to controls (20/50, 20/49 and 7/43, respectively). Overall, the conclusion was that there was no increased incidence of neoplasms compared to controls. The overall NOAEL was 188 mg/kg/day, which was based on females showing decreased body weight gain with a difference greater than 10% compared to control rats.[33]

E. Developmental / Reproductive Toxicity

Four oral developmental toxicity studies were conducted to examine the effect of oral DL-menthol exposure during gestation in the mouse, rat, hamster, or rabbit. Mouse, rat, hamster and rabbit maternal and fetal NOELs were 185, 218, 405 and 425 mg/kg, respectively, the highest doses tested. No effects on survival of dams, body weight of dams or average fetal weight were observed. No fetotoxicity, abnormalities/ malformations, or skeletal findings or soft tissue abnormalities compared to control group were observed.[4] But the positive control fetuses did experience altered vertebrae.

F. Genotoxicity/Mutagenicity

Multiple *in vitro* and *in vivo* studies were conducted on the isomers/racemates of menthol. In the Ames study with L or DL-isomers using bacterial strains of *Salmonella typhimurium* (TA92, TA94, TA97, TA97a, TA98, TA100, TA102, TA1530, TA1535, TA1537, TA2637 and G-46), and *Escherichia coli* (WP2 *uvr*A) with and without metabolic activation at up to cytotoxic concentrations, which ranged from of 500 to 1000 μg/plate depending on the strain; menthol was negative.[34–41] In a mouse lymphoma mutation assay in L5178Y mouse lymphoma cells, DL-menthol was negative.[42] L- and/or DL-menthol with and without metabolic activation was examined for chromosomal aberrations or sister chromatid exchanges in Chinese hamster fibroblast cells, Chinese hamster ovarian cells, human embryonic lung cells, human peripheral lymphocytes or human TK6 cells blood lymphocytes. There were no significant increases in polyploidy or number of aberrations.[37,43–48] Several comet assays were conducted in Chinese hamster ovary K5 cells.[49] Other systems were used to examine menthol mutagenicity: *Bacillus subtilis* (L-menthol), *E. coli* WP2 uvrA(trp-), anaphase chromosome aberrations test in human tissue culture cells (fibroblasts), carcinoma prediction assay in C3H/10T1/2 cells carrying bovine papilloma virus DNA (DL-menthol), umu DC-lacZ genes in *S. typhimurium* strain TA1535/pSK1002 (DL-menthol). The results were negative.[3,41,50–52] D-Menthol was negative in the comet assay using either V79 hamster cells or human lymphocytes at concentration up to 2 mM with and without activation.[4] In an alkaline elution assay to detect DNA damage in primary rat hepatocytes from 0.1 mM up to cytotoxic concentrations of 1.3 mM, D-menthol was negative.[53] Only in a DNA repair test in *bacillus subtilis* M 45 (rec-) and H17 (rec+) at up to 10 mg/disk was menthol considered positive.[41] At cytotoxic concentration in an *in vitro* alkaline elution/rat hepatocyte assay, DL-menthol was positive; however, when tested at non cytotoxic concentrations of 0.1–1.3 mM, DL-menthol was not considered genotoxic.[53]

Several *in vivo* tests were conducted with DL-menthol. Two oral cytogenetic assays in male rats were conducted using a single dose of 1.45, 14.5, 145, 500 or 3000 mg/kg; or 5 daily doses of 1.45, 14.5, 145 or 1150 mg/kg. Five animals per dose and time point were injected with colcemid 2 hours prior to termination at 6 hours (all animals in 5 day study), 24 hours or 48 hours. Bone marrow analysis for chromosome aberrations did not show a difference between vehicle and treated animals.[3] Two dominant lethal assays in male rats were conducted in which ten animals were either given a single dose of 1.45, 14.5, 145, 500 or 3000 mg/kg; or 5 daily doses of 1.45, 14.5, 145 or 1150 mg/kg followed by mating with 2 females per week for eight or seven weeks, respectively. Fertility index, preimplantation loss and lethal effects on the embryos were examined. There were no significant differences between treated and control animals.[3] In a host mediated assay, in which mice were treated with either a single dose of 1.45, 14.5, 145, 500 or 3000 mg/kg; or 5 daily doses of 1.45, 14.5, 145 or 1150 mg/kg menthol and using the indicator organisms *Salmonella typhimurium* (his TA 1530 or G-46) or *Saccharomyces cerevisiae* (D-3), three hours after injection with the indicator organism, animals were killed and yeast or bacterial species were collected and recombinants were counted. In three of the assays, the results were negative. In one assay after 5 daily doses, there was a slightly enhanced recombinant frequency at all doses. In a second test, at the highest dose of 1150 mg/kg using *Saccharomyces cerevisiae* (D-3), the result was negative.[3] *In vivo* mouse micronucleus after three intraperitoneal doses of 250, 500 or 1000 mg/kg DL-menthol; or an *in vivo* comet assay (alkaline single cell gel electrophoresis) in ddy mice after oral gavage administration of 2000 mg/kg in olive oil, DL-menthol was negative.[54–57] A replicative DNA synthesis test was conducted in mouse or rat hepatocytes from male B6C3F1 mice or F344 rats, respectively, that had received a single oral dose at 1000 or 2000 mg/kg, the maximum tolerated dose (MTD) in corn oil. After 24, 39 or 48 hours, hepatocytes were prepared and radiolabelled thymidine incorporation was measured *in vitro*. DL-menthol was positive in mice at both the dose levels at 24 hours. In the high dose group, there was also a significant increase in cell viability at 24 hours. In rats, DL-menthol was positive at 24 hours in the low dose group and at 39 hours in the high dose group.(55,56)

Although 3 studies indicated a positive result with respect to inducing chromosomal aberrations, these positive responses appear to be due to cytotoxic concentrations of menthol. The weight of evidence indicates that menthol is not genotoxic.(4)

G. Metabolism and Pharmacokinetics

1. Absorption

The isomers L-, DL- and the unspecified menthol isomer mixture appear to be well absorbed orally in rats with reports of ≥ 63% to ≥ 74%(58–60) and in rabbits with reports of ≥ 86% to 90%.(61–63)

Dermal absorption is lower than oral absorption.(63) To assess *in vitro* skin penetration, radiolabeled, neat L-menthol was applied to rat skin using flow-through diffusion cells under either occluded or unoccluded conditions. The receptor fluid was collected at 48 hours and analyzed, demonstrating that 3% and 1% was absorbed under occluded conditions compared to unoccluded skin, respectively.(64)

In a mouse model using racemic menthol, the menthol upper respiratory tract uptake efficiency into the systemic circulation was measured to be 90.3% ± 1.1 and 66.3% ± 2.8 at the inspired concentration of 1.3 ppm and 18.3 ppm menthol for 15 minutes, respectively.(28)

2. Distribution

A single oral dose of 470 mg/kg [3-^{3}H]-menthol (unspecified isomer) was administered to rats and after 17 hours, 52% of radioactivity was found in urine, 4.5% in feces, 3.5% in ileum, 2.1% in fat, 0.8% in liver, 0.31% in serum, 0.2% in kidney, and < 0.1% in brain and testes.(58)

3. Metabolism

Yamaguchi and colleagues have investigated the metabolism of menthol and menthol glucuronide in rats.(59) Menthol glucuronide is formed in the liver and passes into the bile, where the molecule is eliminated or enters the enterohepatic circulation. Various oxidation reactions may occur upon subsequent passages through the liver. The oxidation products of menthol include *para*-menthane-3,8-diol, *para*-menthane-3,9-diol, and 3,8-dihydroxy- *para*-menthane-7-carboxylic acid.(59,60) The oxidation metabolites, a primary alcohol, a triol, and hydroxy acids have also been identified.(59) *In situ* nasal metabolism of menthol occurs, as evidenced by the decreased absorption efficiency in CYP450 inhibitor metyrapone-pretreated mice.(28)

4. Excretion

In rats, menthol is primarily metabolized to the glucuronide conjugate and eliminated in the urine or feces.(58–60) In one study in rats, 470 mg/kg of [3-^{3}H]-menthol (unspecified isomer) was administered orally, 52% of the radioactivity was found in the urine, 4.5% and 3.5% were found in the feces and ileum 17 hours after dosing.(58) After a single dose of 500 mg/kg of radiolabeled L-menthol to male uncannulated Fischer 344 rats, 71% of the dose was found in urine and feces 48 hours later. After the first 24 hours, 45% of the dose was recovered with 18% and 27% of the total radiolabel in the urine and feces, respectively. At 48 hours, a similar percentage of the total dose was recovered in the urine and a lower concentration of 7.3% in the feces. The same treatment was given to bile duct-cannulated rats where the total recovery of radiolabeled material in the urine and bile was 74%, the majority (67%) being recovered in the bile. The major metabolite found in the bile was menthol glucuronide and various oxidation products were found in the urine.(59)

Other species have been examined for elimination of menthol. In sheep fed with L-menthol, L-menthyl glucuronide was detected in the urine and within 24 hours after consumption the excretion was considered almost complete.(65) In the urine of rabbits fed 1 g/kg of DL-menthol or L-menthol, DL-menthol and L-menthol glucuronides were found in similar amounts of 59% and 48% of the dose, respectively.(62,66) In rabbits fed 3 g of menthol, 86% was eliminated by glucuronidation, even when this maximum toxic dose was given.(61) The last of 24 daily doses of 2 g menthol, 90% was excreted as menthol glucuronide within 6 hours. The glucuronide was a minor urinary excretion product in dogs, suggesting that other metabolic routes would be more important in this species.(62) (Williams, 1938). In the dog, 5% of a 5 g oral dose of menthol was excreted in the urine as the glucuronide conjugate.(61)

H. Other

Three Wistar rats were exposed to L-menthol for 4 weeks by whole body inhalation at a concentration of 1.6×10^{-13} M (0.000025 mg/m^3; 3.9×10^{-6} ppm) continuously. Control animals were exposed to filtered fresh air only. The rats were sacrificed after 4 weeks of exposure and the mitral cells of olfactory bulbs were examined. L-Menthol exposure produced selective degeneration of the mitral cells in various sections of the olfactory bulb.(67) The authors state that “degeneration in this context in no way implies cell death” and the cells in the heavily degenerated zones behave normally.

Menthol has pharmacological activity with the effect being considered a chemesthesis effect, which is defined as “sensations that arise when chemical compounds activate receptor mechanisms for other senses, usually those involved in pain, touch, and thermal perception in the eye, nose, mouth and throat.”(68) Cooling of the upper airway, which stimulates specific cold receptors and inhibits laryngeal mechanoreceptors, reduces respiratory activity in un-anesthetized humans and anesthetized animals. More recent investigations have provided evidence for menthol to increase cough thresholds(69,70) but only when it is administered as vapor to the upper airway.[71] Menthol is an agonist of transient receptor potential melastatin-8 (TRPM8) receptor, which is a cationic ion channel rat dorsal root ganglion[72] involved in detection of normal cooling-sensation in mammals.[73] In studies, cold air or warm air and L-menthol in anesthetized new born dogs or guinea pigs (390 ng L-menthol/ml for 10 seconds duration with an airflow of 30 ml/s) greatly reduced ventilation.[74,75] In an investigation of neurophysiological responses in individual fibers of the lingual and chorda tympani nerves and in single cortical neurons, in the rat, lingual fibers and a different category of cortical units (Type II) were extremely sensitive to menthol exposure.[76]

An analgesic effect as determined by a significant reduction in pain during functional tasks was observed after application of a 3.5% gel to osteoarthritic individuals.[77] Also in animals, an analgesic effect was observed when application of 40% menthol to the contralateral rat hind paw tended to reduce responses to cooling and noxious heat.[78] In patch clamp and tetrodotoxin mediated Na^+ channel blockade *in vitro* and in mice, the role for Na^+ channel blockade in DRG neurons was demonstrated in the efficacy of menthol as topical analgesic compound.[79]

A study demonstrated the roll of TRPM8 lacrimation after low concentration instillations to the cornea. Tear measurements were made using a cotton thread in TRPM8 wild type and knockout mice after application of menthol (0.05-50 mM) to the cornea. In additional studies, nocifensive responses (eye swiping and lid closure) were quantified following cornea menthol application. Trigeminal ganglion electrophysiologic single unit recordings were performed in rats to determine the effect of low and high concentrations of menthol on corneal cool cells. At low concentrations, menthol increased tear production in TRPM8 wild type and heterozygous animals, but had no effect in TRPM8 knockout mice, while nocifensive responses remained unaffected. At the highest concentration, menthol (50 mM) increased tearing and nocifensive responses in TRPM8 wild type and knockout animals. This study indicates low concentrations of menthol (0.1 mM) responses were via the TRPM8, yet a high concentration of menthol increased tearing and nocifensive responses were via a separate mechanism.[80]

Willis and colleagues examined the interaction of menthol and cigarette smoke in the lung conducted studies. Menthol acts as a broad-spectrum counterirritant, diminishing the chemosensory responses to inhaled irritants. In a mouse model using racemic or L-menthol, the effect of menthol pre-treatment on acrolein irritation was investigated. It was shown that 16 ppm menthol attenuated a 2 ppm acrolein induced breathing pattern change; however, 4 ppm menthol did not diminish the effect. This attenuation effect of menthol was significantly diminished in animals treated with AMTB, a TRPM8 antagonist. The counterirritant properties of menthol appear to be due to parent menthol itself rather than a CYP450 metabolite, as counter irritation was fully apparent in P450 inhibitor, metyrapone-pretreated mice. Conversely, the CYP450 metabolite of menthol appears to be responsible for sensory irritation as evidenced by inhibition of menthol sensory irritation by metyrapone and the absence of sensory irritation in transient receptor potential ankyrin 1 (TRPA1) -/- mice. This suggests that the metabolite likely acts through TRPA1. Thus, the direct stimulation of sensory nerves (*e.g.*, the sensory irritant response) and the counter irritation are likely due to differing molecules (*e.g.*, metabolite *vs.* parent menthol).[28]

The subcutaneous administration of menthol produced ambulation in mice. From experiments conducted with dopamine agonists and a monoamine-depleting compound, the authors suggested that dopamine is involved in the abilities of menthol to promote ambulation in mice.[81]

Several studies have shown that menthol-containing formulations function to enhance dermal penetration.[82,83] Synchrotron X-ray diffraction was employed to evaluate the effect of ethanol and L-menthol on lipid arrangements in the stratum corneum of hairless rats. It was shown that L-menthol was dispersed through the stratum corneum, intruded mainly into hexagonal hydrocarbon chain packing, and disrupted the regular organization of these structures.[84]

Some studies have investigated the involvement of menthol in metabolic processes. A single oral dose of 470 mg/kg [3-^{3}H]-menthol (unspecified isomer) administered to rats resulted in 70% inhibition of HMG-CoA reductase activity 17 hours after treatment, which returned to normal activity by 41 hours.[60] Male Wistar rats exposed for two weeks to dietary 0.5% or 1% menthol caused an increase in serum cholesterol and serum triglycerides levels in the high-dose group, but no effect on apo A-1 lipids, an indicator of high-density lipoprotein status or body weights. Liver weight was slightly increased.[85]

MacDougall reported that that L-menthol and synthetic congeners inhibit the microsomal oxidation of nicotine to cotinine and the P450 2A6-mediated 7-hydroxylation of coumarin *in vitro*.[86]

V. HUMAN USE AND EXPERIENCE

The pharmacokinetics of menthol has been described in humans. The oral absorption of menthol ranged between 10 and 90%. Menthol is primarily metabolized to the glucuronide conjugate and excreted almost completely in the urine within 12 to 24 hours.[61,87–92] In a crossover placebo-controlled study, twelve subjects received three 100 mg L-menthol capsules, a placebo capsule, and 10 mg menthol in mint candy or mint tea. Plasma and urine levels of menthol and conjugated menthol (glucuronide), cardiovascular measurements, and subjective effects were measured. Only the menthol glucuronide could be measured in plasma or urine. The plasma half-life of menthol glucuronide averaged 56.2 minutes and 42.6 minutes under the menthol capsule and mint candy/mint tea conditions, respectively. Urinary recovery of menthol as the glucuronide averaged 45.6 and 56.6% for menthol capsule and mint candy/tea, respectively.[93] In patients with liver disease, alcohol-induced cirrhosis or steatosis, doses of 2 g menthol were given and menthol glucuronide was determined. The mean excretion of menthol glucuronide was slightly lower than healthy subjects and the authors conclude that patients with liver disease retain a significant capacity to metabolize menthol.[3] Glucose-6-phosphate-dehydrogenase-deficiency in newborn babies may result in development of severe jaundice after menthol administration due to the inability of the neonates to conjugate menthol.[94]

When considering pharmacokinetics after dermal applications, an unspecified amount of menthol containing ointment was applied to the skin and urine samples were collected. The excretion of menthol was stated to be slower after dermal absorption than after oral administration. Additionally, the urine of an untreated person living in the same room as a patient rubbed with a menthol-containing ointment was analyzed and menthol was detected. The authors concluded that a large percentage of menthol absorbed after dermal application was inhaled.[63] In another study, a number of commercial patches (2, 4 or 8) containing 37.44 mg menthol (isomer not specified) were applied to the skin of 8 subjects (4 male, 4 female) for 8 hours. For the 4 and 8-patch groups, the average maximum plasma concentrations (Cmax +/- SD) were 19.0 +/- 5.4 and 31.9 +/- 8.8 ng/mL, respectively. The 2-patch group had measurable but low plasma concentrations. The harmonic mean terminal half-live was 4.7 +/- 1.6 hours. The absolute dermal bioavailability could not be determined in this study; however, the authors concluded that there appears to be relatively low systemic exposure even when an unrealistically large number of patches were applied for an extended period.[95]

In the literature, there have been a number of studies and case reports that provided a summary of the potential adverse effects after menthol exposure by various routes. The usual human oral dose is 60-120 mg menthol per person.[3] The maximum doses tested in humans in pharmacokinetic studies were 180 mg[87] and 1000 mg.[61] It is reported that about 20 mg/kg led to a mild abdominal discomfort.[91] Three volunteers were exposed orally with 8000 to 9000 mg (approximately 120 mg/kg) of an unspecified isomer of menthol which resulted in cold burning sensation in mouth, throat and esophagus, a cold sensation on the mucous membranes of the nose, on the skin of the hands and feet, and fatigue.[96] Abdominal pain, convulsions, nausea, vomiting, vertigo, ataxia, drowsiness and coma have been reported after ingestion of high doses of menthol.[97,98] Over-dosage with menthol (isomer not specified) over an extended period of time has resulted in gastrointestinal distress, ataxia, stupor, convulsions and blood dyscrasias.[4] The WHO estimates the human oral lethal dose to be approximately 50–500 mg/kg.[3]

In a crossover placebo-controlled study, twelve subjects received 3 exposures of 100 mg L-menthol capsule, or a placebo capsule and evaluated for cardiovascular and subjective effects. Following menthol capsule ingestion, the decrease in heart rate was less than the decrease after placebo administration.[93]

In another study examining sensory irritation, subjects received ten menthol solutions at one of two concentrations. After the subject rinsed three times with distilled water, 10-ml samples were presented at 1-min intervals. Subjects sipped the sample, tilted the head forward to hold the solution in the anterior of the oral cavity, and then agitated it gently with the tongue. They were prompted to expectorate at 10 seconds, then instructed to keep the mouth closed to prevent evaporative cooling. At 15 seconds (5 seconds after expectoration) and at 45 seconds, subjects were asked to rate the intensity of irritation and coolness in the mouth. Mean ratings of sensations of irritation produced by a high concentration of racemic menthol (0.3% w/v) decreased significantly over repeated exposures, even when the time between stimuli was as long as 5 minutes. This shows menthol is capable of producing desensitization to sensory irritation in the oral cavity.[99]

Dermal sensitization of menthol has been investigated in controlled studies and described in case reports. In a maximization test with 8% DL-menthol in petrolatum (5520 $\mu g/cm^2$) performed with 25 volunteers, there were no positive reactions[100]. In 9 human patch tests using DL- or L- menthol with 6227 patients with dermatological disease, a low incidence of positive responses, 0.3 to 6.1% positive reactions, were demonstrated.[4,101–109] Based on the negative results obtained in several animal and human studies with L- and DL-menthol, the widespread use of menthol in consumer dermal contact products and the low number of skin reactions reported in dermal compromised patients or case reports, dermal sensitization is of low concern for menthol.

A solution of 0.5% or 0.2% L-menthol in petrolatum or 0.1% L-menthol in saline was applied to the nasal passages of 16 subjects three times per day at 2 day intervals. The 0.5% concentration was considered irritating, the 0.2% concentration was considered almost non-irritating to non-irritating and the 0.1% concentration was considered non-irritating to the nasal and mucous membranes.[110]

Menthol provides a cooling sensation to the skin and respiratory tract that appears to be pharmacologically mediated. Menthol is an agonist of transient receptor potential melastatin-8 (TRPM8), a cationic ion channel that is involved in detection of normal cooling-sensation in mammals.[73] The psychophysical effects of TRPM8 activation in humans by application of 40% menthol solution for 20 minutes on the forearm was examined in 10 volunteers. All subjects experienced pain from the 40% menthol application described as burning, pulling, freezing, cutting, tingling; hot, cold, spreading, dull or taut. Quantitative sensory testing and laser Doppler imaging was performed before and after exposure. Menthol produced no axon reflex reaction and resulted in cold hyperalgesia.[111]

Another study investigated the ability to perceive gradual increases in skin temperature on the vermilion border of the lip after application of 0.2 or 2.0% L-menthol in mineral oil. Supra-threshold sensations of warmth could be significantly attenuated and the threshold for warmth was increased significantly whereas the threshold for heat pain was unchanged by exposure to menthol.[112] In a sensory perception test, 0.5% menthol in ultrapure water was applied to the nasolabial fold of 58 adult (19 male and 39 female) volunteers for 2.5, 5 or 8 minutes. The volunteers completed a questionnaire during the treatment to provide information on the type and intensity of any sensory effect. Menthol at 0.5% elicited stinging and cooling sensations. A significant response (sensory score of 3 or more) after exposure to 0.5% menthol was observed in 22/58 subjects. However, after screening these 22 volunteers for cooling sensation only 9 were classified as being sensitive to 0.5% menthol.[113]

Menthol was demonstrated to affect ventilation in humans in several studies as was shown in animals. Total nasal resistance to airflow was measured in 31 subjects before and after a five-minute exposure to 0.2 mg/L (200 mg/m^3; 31 ppm) menthol vapor. Menthol inhalation had no consistent effect on nasal resistance but the majority of subjects reported an increased sensation of nasal airflow and a cooling effect of menthol. The results indicate that menthol stimulates cold receptors in the nasal mucosa to create an increased sensation of airflow.[114,115]

In young (18 to 26 years) or elderly (over 65 years) healthy volunteers, 9–10 per group; 0.21, 0.42, 0.85, 1.70, 3.39, 6.78 or 13.56 ppm (1.3, 2.7, 5.4, 11, 22, 43 or 87 mg/m^3) menthol was inhaled through the nostrils by a Dravniecks Dynamic Dilution Binary Scale Olfactometer. An odor threshold was measured using the up-down staircase method. Intensity and pleasantness were measured by magnitude estimation. The average threshold for the elderly participants (approximately 0.7 ppm) was significantly higher than for young participants (0.26 ppm). The median slope of the intensity function was steeper by a factor of two for younger adults. A 10-fold increase in menthol concentration produced a four-fold increase in perceived intensity for young adults and a two-fold increase in perceived intensity for elderly persons. The younger persons had a steeper average pleasantness function and found menthol less pleasant with repeated exposure; however, menthol concentrations corresponding to perceived unpleasantness were not provided.[12]

A study was conducted to examine olfactory and chemosensory threshold. It was found that the absolute odor threshold was lower than the chemosensory threshold. Absolute detection in both the nasal and oral cavities was based on olfaction and not stinging, cooling or taste. The individual threshold concentration was 5.00 x 10^{-5} M to 5.10 x 10^{-2} M (three orders of magnitude variation) in PEG200 (relative headspace concentration ranging from 0.002 µg/L to 11.600 µg/L), with an exception of two data points (3.00 x 10^{-3} M, 1.20 x 10^{-2} M), and with an overall geometric mean threshold concentration of 3.42 mM.[13]

Twenty-five employees exposed to an unspecified menthol isomer (concentration not specified) were examined olfactometrically. A control group was also examined which consisted of 25 employees working in the same plant, but not exposed to menthol. The examination showed a general diminution of smell acuity on an odor identification task.[116] The airway hyper-responsiveness of 23 human subjects with chronic mild asthma was tested by use of a nebulizer containing 10 mg menthol twice a day for four weeks. An estimate of the air concentration was 32 mg/m^3 (5 ppm) assuming a nebulizer treatment time of 15 minutes. Two patients in the menthol group withdrew from the study because of an uncomfortable sensation in the upper airway. As measured by expiratory flow rates, vital capacity, and forced expiratory volume, menthol improved airway hyper-responsiveness at doses as low as 20 mg per day.[117]

The literature is sparse with respect to air concentrations of menthol in the workplace and how these relate to adverse effects. Thymol was used as an indicator for menthol in the Bayer menthol manufacturing plant in 1990-91. Thymol has chemical properties similar to menthol, *e.g.*, a melting point of about 50 °C and a boiling point of 233 °C. The results of the thymol measurements were < 0.5 mg/m^3 and < 0.8 mg/m^3 in the Bayer menthol manufacturing factory.[4] An investigation of occupational exposures to menthol vapors during the manufacture of mentholated Sucret’s throat lozenges was conducted in response to employee complaints of respiratory and ocular irritation. Effects described by production workers included local irritation of the eyes, nasal passages, throat and larynx. Non-smokers complained of runny nose, redness and watering of the eyes and physical exams found inflammatory changes in the nasal mucosa, vocal cords and throats. Seven participants with suspected nasal polyps may represent an excess over the expected occurrence in the normal population. Pre and post exposure pulmonary function testing showed significant decreases in forced vital capacity (FVC) and 1-second forced expiratory volume (FEV1) for non-smoking individuals. The total population showed a decrease in FVC and increases in FEF 25–75%, FEF 75–85% and MEF 75%. Air sampling indicated that menthol was present in the air of packaging and wrapping areas, which ranged from non-detectable to 2.3 mg/m^3 (0.4 ppm). Although exposure concentration comparisons were not evaluated, it was reported that the menthol in the air in the cooling and candy rooms was noticeably higher and more irritating. Air concentrations in these rooms ranged from 1.9 to 39.4 mg/m^3 (0.8 to 6.2 ppm) with a mean and median of 12.7 and 11.8 mg/m^3 (2.0 and 1.8 ppm), respectively. Typical symptoms described while working in these areas included immediate stinging, watering and tearing of the eyes upon entering the room followed by moderate irritation of the nasal passages and throat. One 15 minute air sample in the breathing zone of a NIOSH industrial hygienist by the candy machine was 39.4 mg/m^3 (6.2 ppm) and the symptoms described by this individual during that period were immediate stinging and tearing of the eyes, soreness and dryness in the tonsil area of the throat, a cooling irritation of the nose, watery nasal discharge, periodic (non-productive) coughing, and tingling sensation in the face and arms. Cold sweating occurred for about five minutes after leaving the candy room.[118]

Several incident reports and case reports were identified. Inhalation of high doses of menthol was reported to cause adverse CNS effects. A woman developed insomnia, unsteady gait, mental confusion, depression, vomiting, and cramp in the legs after smoking 80 mentholated cigarettes per day for 3 months.[119] In another report, a 13-year old boy inhaled an estimated 200 mg menthol in a menthol and olbas oil mixture and experienced similar symptoms.[120]

A case of asthma due to menthol exposure was reported in a 40-year-old woman with no history of asthma or any other allergy, presenting with dyspnea, wheezing and nasal symptoms after using menthol containing toothpaste and candies. Menthol was confirmed as the causative agent by positive skin tests and bronchial challenge.[121]

In several epidemiology studies, the effect of smoking mentholated cigarettes as a risk factor in various cancers was investigated. Current cases of cigarette smokers with 588 male lung cancer cases and 914 male controls, and 456 female lung cancer cases and 410 female controls were investigated. The prevalence of menthol usage did not differ between cases and controls of either sex. For specific histological types of lung cancer (squamous cell carcinoma, small cell carcinoma, large cell carcinoma and adenocarcinoma) there was no indication of an association with menthol usage.[122] Carpenter and colleagues concluded that lung-cancer risk from smoking mentholated cigarettes resembled the risk from smoking non-mentholated cigarettes from examining a population of 337 incidents of lung cancer compared to 478 controls.[123] An additional cohort study investigating the use of mentholated cigarettes and lung cancer in men and women was conducted. The study population consisted of 11761 members (5771 men, 3990 women). The relative risk of lung cancer associated with mentholation compared with non-mentholated cigarettes was 1.45 in men and 0.75 in women. The authors' conclusion was that there was an increased risk of lung cancer associated with mentholated cigarette use in male smokers but not in female smokers.[124] In another study, it was investigated whether smoking mentholated cigarettes increased the risk of cancer of the oral cavity and pharynx. One hundred and ninety-four males and 82 females were test subjects and 845 male and 411 female controls were part of the study. From this analysis, menthol was not a risk factor for cancer and it was concluded that the use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer.[125] Next, the relationship of menthol cigarette smoking and esophageal cancer was investigated. Data from a large hospital-based case-control study was used. There was no change in the cancer risk for males ever-smoking menthol versus those never smoking menthol cigarettes. For women, however, there was an increased risk. The authors stated that because of the limitations of the study the issue of menthol cigarette smoking and esophageal cancer could not be resolved.[126] The epidemiology data overall suggest that smoking mentholated cigarettes does not increase cancer or other disease risk above that already present from smoking non-mentholated cigarettes.[127]

VI. RATIONALE

Menthol is a liquid with a high vapor pressure and a minty odor with a low threshold. This chemical is used widely in the consumer products and food industries where low concentrations are added to products with direct oral and dermal exposure. It was found that D- and L-isomers or a mixture of the two are considered to have same toxicity. Menthol has low acute and chronic toxicity potential in mammals. The chemical is neither genotoxic, carcinogenic nor a reproductive or developmental toxicant. It is not a dermal sensitizer, and is not absorbed through the skin in toxicologically significant quantities. However, menthol was irritating to the eyes, skin and respiratory tract.

Using the NOAEL (188 mg/kg, females) from a chronic oral rat study with the lowest effect being decreased weight gain and applying uncertainty factors for intra and interspecies variability would result in a WEEL greater than that proposed below. The most sensitive effect considered as the point of departure for the WEEL was on the lung, including irritancy, lacrimation, and receptor mediated cooling pharmacological responses.

The derivation of the WEEL considered the weight of evidence regarding the dose-response from several human and animal studies, as there was no clear NOEL in a standard toxicity study by the inhalation route. It is acknowledged that an acclimation to the irritation and lacrimation occurs in the workplace and that there is a lack of chronic inhalation dose response data. In a subchronic inhalation study in rats,[128] there was a clear NOEL for respiratory histopathological effects with no systemic effects observed. Even though the air concentration could not be verified, the NOEL indicates that this effect is a dose-dependent, threshold-type irritant effect reasonably expected after repeated exposure. Three reports indicate a WEEL of 1 ppm would prevent respiratory irritation. Application of modest uncertainty factors to either 1) the acute mouse pharmacology study, which identified a 4-ppm no effect level for a counter-irritancy effect[30]; or 2) the mouse RD_{50} of 45 ppm multiplied by 0.03,[30,31,129] both support a WEEL of 1 ppm (6.4 mg/m^3). In addition, 3) the NIOSH report[118] described menthol air concentrations in the workplace areas associated with some complaints of irritation as 0.8 to 6.2 ppm with a median range of 1.8 and 2.0 ppm. This indicates a WEEL of 1 ppm would be appropriate. It is reasonable to consider that shorter exposures to higher concentrations of 3 ppm (19.2 mg/m^3) would not cause noticeable irritation. However, this STEL may not protect all naive individuals of severe lacrimation upon entering an area containing this air concentration of menthol. Based on the weight of evidence, a Workplace Environmental Exposure Level of 1 ppm (6.4 mg/m^3) and a 15 minute Short Term Exposure Limit of 3 ppm (19.2 mg/m^3) are assigned for menthol.

VII. RECOMMENDED WEEL

8-hr Time-Weighted Average (TWA): 1 ppm (6.4 mg/m^3)

15 min Short Term Exposure Limit (STEL): 3 ppm (19.2 mg/m^3)

No additional hazard notations are assigned.

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