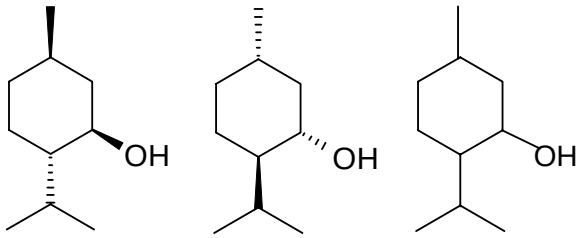
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2216-51-5	15356-60-2	89-78-1 (former CAS No. 15356-70-4)	1490-04-6
Chemical Name	L-Menthol	D-Menthol	D/L-Menthol	Menthol
Structural Formula	 L-Menthol D-Menthol Menthol			

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

The menthols category is comprised of the isomers L-menthol, D-menthol, the racemate and menthol (unspecified isomers). The menthols can be considered as a category because of their similarity in physico-chemical, toxicological, ecotoxicological and environmental fate properties.

Human Health

L-, D/L- and the unspecified menthol isomer are well absorbed by the oral route of exposure and are mainly excreted as glucuronides. In rats an extensive enterohepatic circulation additionally leads to various hydroxylated degradation products. Glucuronides and degradation products are eliminated mainly via urine, minor quantities via the faeces.

All menthol isomers are of very low acute oral toxicity with LD50 values normally greater than 2000 mg/kg bw. Clinical signs of intoxication are unspecific, and included apathy and reduced activity. Based on old and limited studies for the racemate and the unspecified isomer, it can be assumed that the acute dermal toxicity of the menthol isomers is low.

All studied isomers of menthol are moderately irritating to the skin and slightly irritating to the eye. The skin sensitization potency of menthol isomers in animals and humans is low.

In rats given ≥ 200 mg/kg bw/d of L-menthol in soybean oil by gavage for 28 days, increased liver weights and a non dose-related vacuolization of hepatocytes were reported. The relevance of these findings remains unclear and a NOAEL could not be derived from this study. No toxicity was observed in rats receiving diets providing up to 200 mg/kg bw/d of either L- or D/L menthol for 5.5 weeks. Therefore for L-menthol and the racemate D/L-menthol a NOAEL of 200 mg/kg bw/d can be deduced from this study. Irritant effects on lungs and trachea, but no systemic effects were found in rats that were whole body exposed to L-menthol vapour for 71-79 days.

D/L-menthol administered with the diet for 13 weeks to rats (up to 937/998 mg/kg bw/d for males/females) and mice

(up to 3913/4773 mg/kg bw/d for males/females) did not induce any effects on organ weights. Microscopic examination of a comprehensive range of tissues revealed a slight increase in the severity of spontaneous interstitial nephritis in the male rats at the highest dose level. The only effect seen in mice of both sexes was a reduction in body weight gain in the highest dose group. The NOAELs derived from these studies were 937 mg/kg bw/d for the male rat, 998 mg/kg bw/d for the female rat and 1956 mg/kg bw/d for the male mouse and 2386 mg/kg bw/d for the female mouse.

In a 103-week feeding study in rats with D/L menthol (about 188 and 375 mg/kg bw/d), the only effect was a slight increase in spontaneous, chronic inflammation of the kidney in male rats of both dose groups, and a slightly reduced body weight in female rats. The NOAELs in this study were 375 mg/kg bw/d for male rats, and 188 mg/kg bw/d for female rats. In a 103-week feeding study in mice with D/L menthol (about 334 and 667 mg/kg bw/d), the NOAEL for both sexes was 667 mg/kg bw/d.

Because the racemate D/L-menthol contains the D- and L-isomers in equal proportions, the study results with the racemate are considered adequate for the evaluation of the D-isomer and of the L-isomers This view is further supported by the FAO/WHO 1999 safety evaluation on menthol, where the FAO/WHO expert committee had concluded that “the limited data that allow comparisons of metabolism and toxicity provide no indication of a difference in the toxicity of L-menthol and D/L-menthol”. Overall it can therefore be concluded that the D-, L- and D/L- menthol isomers induce no specific systemic effects and are well tolerated after repeated oral administration.

The menthol isomers are considered non-genotoxic in *in vitro* bacterial and mammalian test systems. *In vivo*, L- and D/L-menthol have demonstrated no mutagenic potential in adequately performed dominant lethal and cytogenetic tests and in a bone marrow micronucleus test in mice.

D/L-Menthol showed no evidence of carcinogenic activity in 2-year studies performed in accordance with current standards in rats and mice (highest tested dose levels in rats approx. 375 mg/kg bw/d, in mice approx. 667 mg/kg bw/d).

There is no fertility study available. Histopathological examinations of the reproduction organs of rats and mice showed no changes in repeated dose toxicity studies with D/L-menthol and also in carcinogenicity studies with D/L-menthol. Hence there is no indication of a potential of D/L-menthol to interfere adversely with reproduction.

L-Menthol was not embryo- or fetotoxic and had no teratogenic properties in well performed gavage studies in various species (rat, mouse, rabbit, hamster) at not maternally toxic doses (185-425 mg/kg bw/d). No maternally toxic dose levels were used in these studies.

In summary, the available toxicity data indicate very similar toxicity profiles for all of the menthol isomers investigated.

Environment

Menthols have a melting point of ca. 40 °C, a density of about 0.9 g/cm³ (20 - 25 °C). A vapor pressure of 8.5 Pa (25 °C) was measured for L-menthol and an unspecified isomer mixture. This value was also used for the other two category members. The measured water solubilities were in the range of 420 - 500 mg/l (20 °C), The log Kow is measured to 3.4 for L-menthol and D/L-menthol. This value can be read-across to the other two category members.

According to a Mackay Level I model calculation, the main target compartments for menthols are air (39.5 - 44.2%) and water (40.5 – 43.8 %). In the atmosphere menthols are indirectly photodegradable by hydroxyl radicals with $t_{1/2}$ = 16 hours. The calculated Henrys’ law constant of 2.6 - 3.2 Pa·m³/mol indicates the menthol isomers to be volatile from aqueous solution. Under environmental conditions, neither hydrolysis nor direct photolysis of menthols is to be expected. The ready biodegradability of menthols was shown in two recently performed Closed Bottle Tests for L- and D-menthol (L-menthol: 79-92 % after 28 d, D-menthol: 76-92 % after 28 d, 10d-window for both isomers was fulfilled). Experimentally determined BCF values in the range of <0.5-15 l/kg indicate no significant bioaccumulation potential of menthols.

For the toxicity of menthols on aquatic species experimental results from tests with fish, daphnids and algae are available for L-menthol and D/L-menthol. The data for the two category members within each trophic level are in the same order of magnitude. D/L-menthol contains the D- and L- isomers, thus effect values obtained with this mixture should cover the toxicity of D-menthol and the unspecific isomer mixture. Therefore, all available effect values can be regarded together for the assessment of this category. In acute toxicity tests the following results were obtained:

fish (3 species): 48- 96h LC50 = 15.6 – 26 mg/l;
invertebrates (*Daphnia magna*): 24h LC50 =37.7 - 71 mg/l; 48h LC50 = 26.6 mg/l
algae (*Scenedesmus subspicatus*): 72h ErC50 = 16.2 – 21.4 mg/l, 72h NOEC = 5 - 9.65 mg/l.

Applying an assessment factor of 1000 to the lowest ErC50for algae, a PNECaqua of 16.2 µg/l is calculated. This PNEC is valid for the whole category. Tests on long-term toxicity on aquatic species as well as on terrestrial species are not available. Two tests on sludge respiration are available with EC10 values of 117 and 51 mg/l.

Exposure

About 13,600 tonnes of menthols were produced worldwide in 2001. About 75 % of the menthol output is of biotic and 25 % of synthetic origin L-Menthol, D/L-menthol and menthol liquid are widely used in oral care products, pharmaceuticals, flavors, tobacco and others. D-menthol is not commonly distributed and only used for scientific purposes. The major route of occupational exposure to menthol isomers is supposed to be inhalation. The most significant routes of consumer exposure are likely to be dermal and oral.

RECOMMENDATION

The chemicals in the Menthols category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals in the menthols category are currently of low priority for further work because of their low hazard potential. However, skin and eye irritation is noted.

Environment: The chemicals in the menthols category are currently of low priority for further work. The chemicals possess properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure levels, they should nevertheless be noted by chemical safety professionals and users.