FOREWORD **INTRODUCTION**

MENTHOLS

CASN°:2216-51-5, 15356-60-2, 89-78-1, 1490-04-6

SIDS Initial Assessment Report

For

SIAM 16

Paris, 27-30 May 2003

1. Chemical Category: Menthols

2. CAS Number: Menthols Category:

L-Menthol	CAS No: 2216-51-5
D-Menthol	CAS No: 15356-60-2
D/L-Menthol	CAS No: 89-78-1
Menthol	CAS No: 1490-04-6

3. Sponsor Country: Germany
Contact Point:
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4. Shared Partnership with:

5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium: Bayer AG, Germany
  Contact person:
  Dr. Burkhardt Stock
  D-51368 Leverkusen
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- Process used: See next page

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Progran? by ICCA-Initiative

7. Review Process Prior to the SIAM: last literature search (update):

9 June 2002 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms
27 June 2002 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms

8. Quality check process: As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA.

9. Date of Submission: 20 August 2002

10. Date of last Update: August 2003

11. Comments:

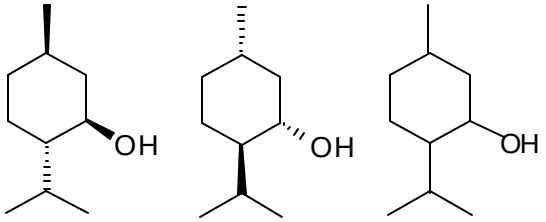
OECD/ICCA - The BUA* Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4), i.e. reliability not assignable)
- Review of validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
- In case of data gaps, review of testing plan or rationale for not testing

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

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.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

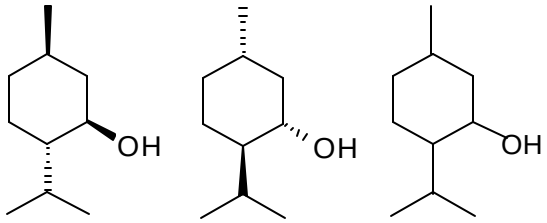
CAS Number:

L-Menthol	CAS No: 2216-51-5
D-Menthol	CAS No: 15356-60-2
D/L-Menthol	CAS No: 89-78-1
Menthol	CAS No: 1490-04-6

IUPAC Name: cyclohexanol, 5-methyl-2-(1-methylethyl)-

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

Structural Formula:



L-Menthol D-Menthol Menthol

Molecular Weight: 156.27 g/mol

The menthol molecule has 3 stereo centers, i.e. there are 8 possible stereoisomers. In nature the compound occurs generally as L-menthol as a component of e.g. peppermint oil, Mentha piperita, Mentha oil etc. Peppermint oil contains about 35 – 60 % menthol (menthone (15 - 30 %), menthylacetate (4 ,-14 %), and small amounts of cineole and other terpenes) (Nair, 2001)

There are 4 menthol products of technical importance:

Substance	Synonyms	CAS-No.	Remark
L-Menthol	(-)-Menthol Menthol, (1R, 3R, 4S)-(-)-	2216-51-5	Natural or synthetic menthol
D-Menthol	(+)-Menthol	15356-60-2	non marketed by-product
D/L-Menthol	Racemate, "D/L-Menthol pure"	89-78-1 former CAS-No.: 15356-70-4	Synthetic product
Menthol	"D/L-Menthol raw"	1490-04-6	Unspecified mixture of isomers

1.2 Physico-Chemical properties

The menthol products are white solids with a minty odour. The physico-chemical properties of the products are (for references cf. IUCLID datasets):

Substance	L-Menthol	D-Menthol	D/L-Menthol	Menthol
CAS-No.	2216-51-5	15356-60-2	89-78-1	1490-04-6
Melting point	Ca. 42 °C	43 °C	30-32 °C	
Boiling point (1013 hPa)	212 °C	216.5°C	216 °C	215.5 °C
Density Vapour pressure	0.89 g/cm^3 (20 °C) 0.085 hPa (25 °C)		0.895 g/cm^3 (20 °C) 1.3 hPa (55 °C)	0.898 g/cm^3 (25 °C) 0.085 hPa (25 °C)
Log Kow	3.4	3.4 (read-across from value for L-menthol and D/L-menthol)	3.4	3.4 (read-across from value for L-menthol and D/L-menthol)
Water solubility	431 mg/l (20 °C)		508 mg/l (20 °C)	420 mg/l (20 °C)

The enantiomeric menthols have identical physical properties (apart from their specific rotation), but the racemates differ from the optically active forms in, for example, their melting points (Ullmann 2002). The slight differences in the cited data are within the range of uncertainty of laboratory tests.

Of particular importance for the environmental behaviour and ecotoxicity are the values for partition coefficient (log Kow), vapour pressure and water solubility. The partition coefficient (log Kow) was measured for L-menthol and D/L-menthol to be 3.40 for both, and thus can be calculated for D-menthol and any mixture of D-menthol and L-menthol. Water solubility was determined for three substances. Due to the similar molecular structures, no significant differences in these parameter can be expected, thus the values are acceptable for D-menthol.

The vapour pressure at environmental relevant temperatures was determined for L-menthol and an unspecified isomer mixture. As well as for the parameters mentioned above, similar values for vapour pressure can be expected for D-menthol and the racemate, thus the values are acceptable as well.

1.3 Category Justification

See Annex 1

2 GENERAL INFORMATION ON EXPOSURE

World-wide production capacity of menthol was estimated to be about 13,600 tonnes in 2001. Menthol is a naturally occurring compound of plant origin, which gives plants of the mentha species (*Mentha piperita*, *Mentha arvensis*) the typical flavour. Two general ways of manufacturing menthol isomers exist: each menthol isomer can be generated synthetically and L-menthol may be produced via plant extraction. 25 % of the yearly menthol output is of synthetic and 75 % of biotic origin (Haarmann and Reimer, 2002). The world-wide production figures can be split up as follows:

Western Europe	1 producer	10 %
USA	1 producer	9 %
Russia		0 %
China	10 - 20 producers	34 %
India	10 big to medium size producers and several dozens small producers	35 %
Japan	3 producers	7 %
Other Asia	approx. 5 producers	3 %
Other World	approx. 5 producers	2 %

In Western Europe, menthol is currently produced only in Germany, realised in a batch process. D/L-menthol is produced via reaction of m-cresol with propene to thymol, and hydrogenation of thymol, resulting in 4 isomers: D/L-neomenthol, D/L-neoisomenthol, D/L-menthol and D/L-isomenthol. D/L-menthol is isolated by fractional distillation and is dispatched to the production site of L-menthol. Neomenthole, isomenthole and neoisomenthole are epimerized and given back to the distillation process.

To produce L-menthol, D/L-menthol is transesterificated with methylbenzoate and further manufactured. Resulting products are L- and D-menthol. The raw L-menthol is filled in barrels or containers. After crystallisation the solid L-menthol is filled in air-tight packages. D-Menthol as a side-product of this process is filled in rail tank cars and transported to the plant, where D/L-menthol is produced. There it is isomerized (Haarmann and Reimer, 2002). All intermediate products arising during the production process of L-menthol are interim stored in tanks. In China, Japan, India and other Asian countries L-menthol is supposed to be mainly produced from cornmint oil (*Mentha arvensis*), which contains 70 - 90 % menthol, via crystallisation. The Mentha oils are extracted from the plants by steam distillation. No exposure information for this production procedure is available.

L-Menthol, D/L-menthol and menthol liquid are widely used as flavoring, disinfectant and cooling compounds in confectionery products, liqueurs, chewing gums, toothpastes, cosmetics and common cold ointments and medications for human purposes (Haarmann and Reimer, 2002, Gestis Stoffdatenbank [Information on hazardous substances of the Berufsgenossenschaften - German Institutions for statutory accident insurance and prevention]). D-Menthol is not commonly distributed and only used for scientific purposes. L-Menthol is marketed in solid form and isomeric mixtures of menthol in liquid form.

The estimated use pattern for L-menthol is as follows (Haarmann and Reimer, 2002):

36 % Oral Care
22 % Pharma
17 % Flavors
12 % Tobacco

7 % Chewing Tobacco
6 % Others

In Canada menthol is registered for control of mites (Acarapis woodi) in apiculture (Westcott and Winston, 1999).

In the Swiss Product register (2002), 68 products, among them 49 consumer products containing D/L-menthol are listed with concentrations up to 10 %. Product types are paints and lacquers, adhesives, metal care products, cleaning products, shoe- and leather-care products, disinfectants, solvents, cosmetics, odor improvers, repellents and animal care products.

In the Danish Product register (2002) menthols are listed in a total of 95 products in amounts up to 50 %. Product types are cosmetics and odor agents with menthol concentrations up to 20 %. The most frequent industry groups are farming of cattle and other animals, manufacture of foodstuffs, manufacture of pharmaceutical and medicinal chemicals and of cleaning products.

The Swedish product register (2002) lists 37 products, 18 of those are consumer products containing menthol up to 5 %. The main uses are in cosmetics, hygienic articles and veterinary medicine.

Uses identified in sources available to the US, include the following (Westat, 1987 a,b,c):

Product (No identified)	Weight fraction
Non-prescription decongestants (1)	0.4
External analgesics and counterirritants (8)	0.018 – 0.165
Pharmaceutical skin preparations (1)	0.1
Aftershave (4)	0.001
Shampoo (2)	0.005
Oral hygiene products (6)	0.001 – 0.013
Cosmetics and toiletries (1)	0.001
Facial scrubs and masks (1)	0.001
Shaving soap and cream (1)	0.001

Release during production

Easily accessible information on exposure from production of the chemical in the sponsor country is available at Bayer AG.

The Bayer menthol synthesis plant continuously produces an isomer mixture of D/L-menthol. The exhausts from menthol production are connected to a thermal exhaust purification (in other menthol plants, exhaust air of the manufacture process is usually collected and purified in a gas washer). Some tanks are equipped with activated carbon filters to enable tank respiration. Thus during normal operation no menthols are emitted.

The production process and the filling of the product are executed in a closed system. In general there is no sewage leaving the menthol production. Extremely low quantities of menthols are released into the wastewater due to maintenance, e.g. from cleaning of changed parts. The wastewater of the menthol production unit is generally checked for TC at the production plant before reaching the industrial wastewater treatment plant.

The comparison of influent and effluent concentrations of the industrial wastewater treatment plant in Uerdingen is not possible due to low influent and effluent concentrations. The effluent

concentrations of menthols were always below the detection limit of 0.01 mg/l. This equals a maximum emission of 80 kg/a, however, the true emission is far below this maximum.

For the receiving water a maximum PEC of 14 x 10^{-3} µg/l is calculated taking in account the 10 percentile of the river flow (1050 m³/s), the dilution factor of 700 (derived from effluent volume of 1.5 m³/s), and the detection limit (10 µg/l; Bayer AG, 2002a)

Releases from products

Consumer use of oral care products, pharmaceuticals and flavours containing menthol also leads to environmental releases, mainly into the hydrosphere. There are no data available on emissions of menthol into the environment from consumer use.

Releases into the environment may also occur from the use in agents that contain menthol in veterinary agents or in the acaricidal treatment of honey bees against parasitic mites. However, a quantification is not possible.

2.1 Environmental Exposure and Fate

Distribution

As the main physico-chemical properties of the menthol isomers are in the same order of magnitude, the environmental distribution behaviour is expected to be similar.

The distribution of menthols in a "unit world" was calculated according to the Mackay fugacity model level I (Mackay, 1991), considering the values for vapour pressure (8.5 Pa), log Kow (3.4) and water solubility (431 mg/l for L-menthol and D-menthol, 508 mg/l for D/L-menthol and 420 mg/l for menthol). The main target compartments were estimated to be air (39.5 – 44.2 %) and water (40.5 – 43.8%), whereas soil (8.0 - 8.7 %) and sediment (7.3 - 8.1 %) are expected to be of minor importance.

The distribution of menthols between aqueous solutions and air can be calculated from water solubility and vapour pressure. Using solubilities of 420 - 508 mg/l and a vapour pressure of 8.5 Pa (25°C), Henry's law constants of 2.61 - 3.16 Pa.m3/mol are obtained, indicating the menthol isomers to be volatile from aqueous solution according to the criteria of Thomas (1990).

Using a fragment constant estimation method (not further specified), a Henry's law constant of 1.5 Pa.m3/mol was calculated for L-menthol, corresponding to volatilization half-lives of 2 days for a model river (1 m deep, flow-rate 1m/s, wind velocity 3 m/s) and 18 days for a model lake (1 m deep, flow-rate 0.05 m/s, wind velocity 0.5 m/s) (HSDB, 2001). Because of the structural similarities these values are expected to be similar for the other menthol isomers.

The distribution between the organic phase of soil or sediment solids and porewater can be calculated from the octanol/water partitioning coefficient. Using a log Kow of 3.4 and the equation log Koc = 0.52 log Kow + 1.02 (EC, 1996) a Koc value of 614 l/kg can be calculated, indicating a moderate sorption potential of the menthol isomers to soil organic matter according to the criteria of Blume (1990).

Degradation

A calculation of the indirect photodegradability of menthols in the atmosphere by hydroxyl radicals according to a structure estimation method revealed a rate constant of 2.4 x 10-11 cm3/molecule/s. Based on an atmospheric concentration of 500,000 OH-radicals/cm3, a half-life of about 16 hours was estimated (SRC-AOPWIN v. 1.90), Based on the chemical structure menthols are not expected to undergo direct photolytical degradation in the hydrosphere because of the lack of a chromophore

group. Furthermore, hydrolytic degradation of menthol is not to be expected based on the chemical structure.

Several studies on the ready biodegradability of menthols are available. In a modified OECD screening test (OECD 301E) using L-menthol as test substance the DOC decrease was determined to be 53% after 7 days, 93% after 14 days and 100 % after 28 days (Bayer AG, 1992a). No information on possible volatilisation and/or adsorption of the test substance is available. Therefore, it cannot be excluded that a significant amount of L-menthol was removed from the test system by this processes and the test is regarded as invalid. No conclusion on the ready biodegradability of this substance can be drawn.

On the other hand, a MITI I test (not specified, whether L- or D/L-menthol was used; in the literature source both CAS-numbers are referred) resulted in 0% oxygen consumption after 28 days of incubation (MITI, 1992). In tests with activated sludge EC50 values in the range of 237 – 306 mg/l have been found for L-menthol and D/L-menthol. Therefore, it cannot be excluded that the inoculum was (partly) inhibited by the employed test concentration of 100 mg/l and also this test is regarded as invalid.

A test on inherent biodegradability was conducted by Pitter (1976). The test design is comparable to the Zahn-Wellens-test. The test substance "menthol" (not further specified) was the sole source of carbon. Based on COD measurement a removal of 95% within 5 days was obtained in an open system after 20 days of adaptation. Again, no information is available about possible volatilisation and/or adsorption.

The positive result of the test conducted by Pitter indicates that an unspecified menthol isomer may be inherently biodegradable. It remains unclear, however, whether menthols are readily biodegradable.

To enable the assessment on the ready biodegradation of menthols, two tests according to OECD 301D (Closed Bottle Tests) were performed with both D-menthol and L-menthol. Two concentrations were tested in each test. For L-menthol a biodegradation of 92 % after 28 d was obtained using a concentration of 0.84 mg/l. With a concentration of 2 mg/l a biodegradation of 79 % after 28 days was found. For both concentrations the 10d window-criterion was fulfilled (TNO, 2003a). For D-menthol nearly the same result was found. At a concentration of 0.84 mg/l a biodegradation of 92 % after 28 days was found and at a concentration of 2 mg/l the biodegradation after 28 days was 76 %. For both concentrations the 10d window-criterion was fulfilled (TNO, 2003b). From these studies it can be concluded that both D-menthol and L-menthol are readily biodegradable.

Bioaccumulation

The bioaccumulation of menthols in fish (Cyprinus carpio) was determined in a test according to OECD guideline 305 C. It is unclear whether D- or L-menthol was used, in the literature source both CAS-numbers are referred. BCFs in the range of <0.5 - 15 l/kg with 0.2 mg menthol/l resp. < 4.6 - 11 l/kg with 0.02 mg menthol/l were reported (MITI, 1992) indicating no significant bioaccumulation potential. The variation of results may be partially explained by the variation of the lipid content in fish (2 - 6 %).

Summary of Environmental Fate

The available data reveal that menthols released into the atmosphere are rapidly degraded by OH-radicals with an estimated half-life of 16 hours. For menthols released into the aquatic environment, the calculated Henry's law constants indicate evaporation from surface waters within 2 - 18 days. Biotic degradation in surface waters is a relevant removal mechanism. From newly performed tests

it can be concluded that menthols are readily biodegradable. The calculated Koc of 614 l/kg indicates a moderate sorption potential of menthols onto sediment or suspended solids.

The results of an available fish test indicate no significant bioaccumulation potential of menthols.

2.2 Human Exposure

The major route of occupational exposure to menthol isomers is the inhalation route. Although dermal exposure may also occur, the volatility of menthol isomers is high enough to limit the extent of absorption through the skin (see Henry´s law constant). The main sources of occupational exposure are menthol manufacture, intertank transfers and cleaning processes. Further sources of occupational exposure in the processing industry are the following: manufacture of cosmetics, medical ointments, toothpastes, manufacture of sweets, liqueurs, and chewing gums (Haarmann and Reimer, 2002).

The Bayer menthol synthesis plant continuously produces an isomer mixture of D/L-menthol from m-cresol and propene via thymol in a closed system. The exhausts from menthol production are connected to a thermal exhaust purification. Some tanks are equipped with activated carbon filters to enable tank respiration.

Although for menthol and thymol there are no occupational exposure limits (OELs) like MAK, to ensure protection of workers at the workplace, thymol was used as an indicator for menthol and other expositions 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/m³ and < 0,8 mg/m³ in the Bayer menthol manufacturing factory (Bayer AG, 2002a).

Since menthol is a food ingredient (FAO/WHO) and generally recognized as safe (US FDA), it was decided not to monitor menthols at the workplace in the Bayer production plant (Bayer AG, 2002a). In the Haarmann and Reimer menthol processing plants e.g. from olfaction and measurements of solvents used in the manufacturing process it is assumed that the menthol concentrations at their workplaces are very low.

The most significant routes of consumer exposure to menthol isomers from the use of mentholated products are likely to be dermal and oral. Consumers may also be exposed to menthol through the inhalational route, e.g. by smoking mentholated cigarettes, or by odour improving agents. Consumer exposure to menthol isomers is possible from a number of different sources including oral care products, pharmaceuticals, food and flavouring products, tobacco, and others.

In a survey of flavoring usage levels, the Flavoring Extract Manufacturing Association has summarized "average maximum use levels" on which an expert panel based its judgements that the substances are generally recognized as safe (Hall and Oser 1965). For menthol these levels are (in ppm):

Beverages	35
Ice cream	68
Candy	400
Baked goods	130
Chewing gums	1100

Recommended levels for the addition of L-menthol to products are e.g. (Hopp 1993)

Oral care products (concentrated mouthwashes)	up to 2 %
Pharmaceuticals (medicated oils)	up to 4 %
Menthol cigarettes	up to 0.45 %
Pipe tobacco	up to 0.3 %
Perfumed products (e.g. refreshing towels, cooling gels)	up to 1 %

Additional information of identified uses from the US are given under section 2, "General Information on Exposure".

Information on consumer products from Product Registers revealed that the highest menthol concentrations are reported for cosmetics (2-20%), and odor agents (2-20%) (Danish Product Register, 2002). Concentrations in the range between 1 and 10% may be found in paints, animal care products, veterinary medicines, repellents, and cleaning products (Danish Product Register, 2002; Swedish Product Register, 2002; Swiss Product Register, 2002). Menthol concentrations of max. 1 % are reported for shoe- and leather care products and disinfectants (Swiss Product Register, 2002).

The Joint FAO/WHO Expert Committee on Food Additives derived in their 51st meeting in 1998 an acceptable daily intake (ADI) for L-menthol and D/L-menthol in the range of 0 - 4 mg/kg bodyweight (FAO/WHO 1999).

Exposure to menthol also occurs through the use of peppermint oil, since menthol is the primary component of peppermint oil (35 - 60 %) (Nair, 2001). Peppermint oil is used in cosmetic formulations, in the manufacture of chewing gum, confectionery, toothpastes and pharmaceutical products.

Potential exposure to menthol isomers from drinking water and ambient air is expected to be negligible (Haarmann and Reimer, 2002).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics

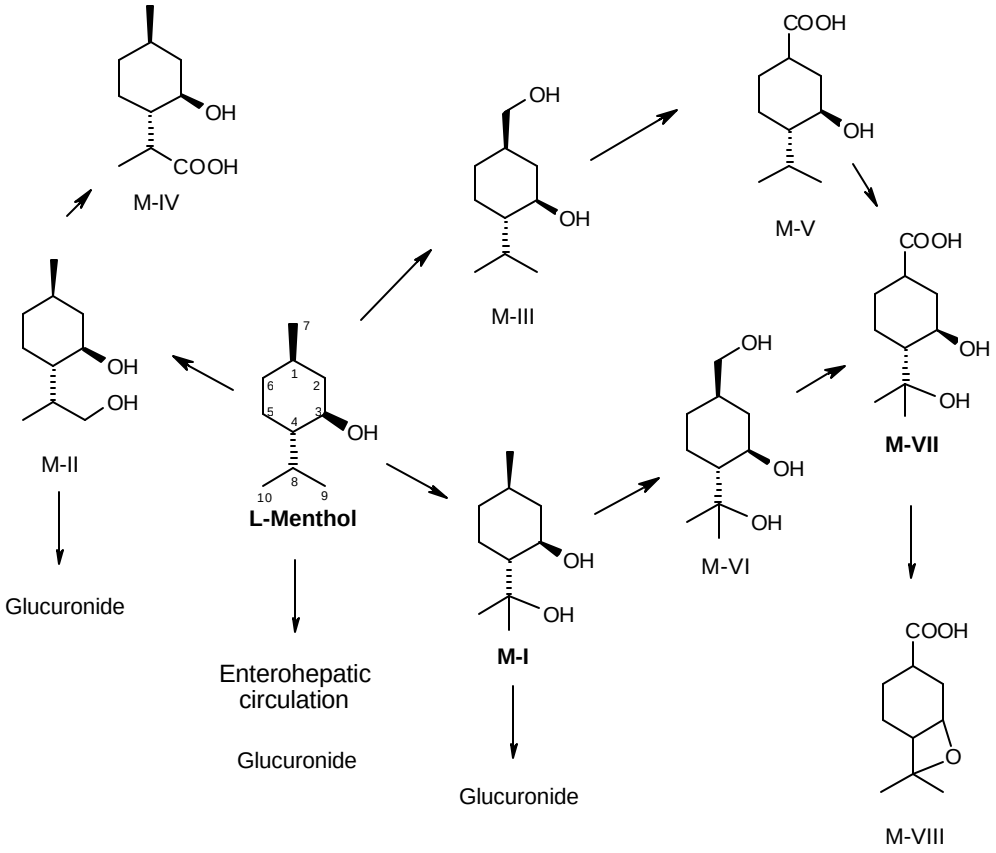
Absorption

From the studies on metabolism with L-, D/L- and the unspecified menthol isomer mixture it can be concluded that menthol is well absorbed by the oral route (Madhava Madyastha and Srivatsan, 1988; Yamaguchi, et al., 1994, Williams, 1938, Atzl et al., 1972). Dermal absorption is slower than oral absorption (Atzl et al., 1972). No quantitative data are available. From case reports it also can be concluded, that absorption by inhalation is very efficient (Atzl et al., 1972).

Metabolic transformation

The metabolic pathways of L-menthol have been studied in detail in two investigations with rats (Madhava Madyastha and Srivatsan, 1988; Yamaguchi, et al., 1994). In the first investigation IISc rats were treated by gavage with 800 mg L-menthol/kg bw/d for 20 days, urine was collected daily and metabolites in urine were analyzed. In the second investigation 3-tritium-L-menthol was administered by gavage to intact and bile duct-cannulated male Fischer 344 rats at a dose level of 500 mg/kg and metabolites in urine, faeces and bile were analyzed up to 48 h after administration. The investigations on intact rats show that menthol is rapidly glucuronidated and excreted in urine and faeces. In the studies with bile duct-cannulated rats it was shown that biliary excretion is rapid and extensive and that menthol undergoes an intensive enterohepatic circulation. After cleavage of the glucuronide and reabsorption in the small intestine it is further metabolized in the liver. It is proposed, that the first step is hydroxylation at the C-8 position, followed by oxidation of the C-1 methyl group (C7) to a carboxylic group. Further it is hydroxylated at the C-9 position. p-Menthane-3,8-diol (M-I) and 3,8-dihydroxy-p-menthane-7-carboxylic acid (M-VII) were identified as major metabolites (not further quantitated) in the urine in both studies. Further (minor urinary) metabolites were p-menthane-3,9-diol (M-II), 3,8-oxy-p-menthane-7-carboxylic acid (M-VIII), 3-hydroxy-p-menthane-9-carboxylic acid (M-IV), 3-hydroxy-p-menthane-7-carboxylic acid (M-V), p-menthane-3,7-diol (M-III) and p-menthane-3,7,8-triol (M-VI) (Madhava Madyastha and Srivatsan, 1988; Yamaguchi, et al., 1994, see Figure 1). Part of these metabolites are excreted as glucuronides.

Fig. 1: Proposed metabolic pathway scheme of L-menthol (Yamaguchi, et al., 1994)



In the investigation of Madhava Madyastha it was further found, that repeated oral administration of L-menthol for 3 days induced cytochrome P450 and the NADPH-cytochrom c reductase activity in the liver of rats by nearly 80%. Further treatment (for 7 days) reduced their levels considerably, although the levels were still higher than the control values. The metabolism of L-menthol was induced in the rat liver by phenobarbital, but not by methylcholanthrene (Madhava Madyastha and Srivatsan, 1988).

In contrast to the results of studies with rats, L-menthyl glucuronide was detected in the urine of sheep fed with L-menthol in major amounts - within 24 hours after application, the excretion being almost complete (Wright, 1945). Similarly also rabbits excreted major amounts of L-menthol in the urine. 48 % conjugated L-menthol was recovered after 2 days as glucuronide in the urine from rabbits fed with 1000 mg/kg bw L-menthol (Williams, 1938).

Also humans excrete considerable amounts of L-menthol as the glucuronide. In an investigation with two human volunteers between 17 and 38 % of menthol was excreted as menthyl glucuronide in urine within 24 hours after 8 daily doses of 750 mg L-menthol (Eisenberg et al., 1955).

In the urine of rabbits fed 1 g/kg bw of D/L-menthol and L-menthol, respectively, D/L-menthol glucuronides were found in similar amounts (59 % of the dose) as L-menthol glucuronides (48 % of the dose) (Williams, 1938).

Glucuronide excretion was investigated in the urine of several persons after oral ingestion of menthol (unspecified isomer) in a variety of studies. In older studies about 70% of the total dose (10

mg to 1560 mg) were found in the urine of humans as glucuronide 6 to 24 hours after ingestion (Quick, 1928; Atzl et al., 1972; Bolund et al., 1967). In a study of Somerville et al. (1984) 35 to 40% menthol was found in the urine of 6 volunteers 24 hours after ingestion of 180 to 190 mg menthol. In another study (Kaffenberger and Doyle, 1990) an average of 40 % menthol was recovered in the urine of 4 volunteers 14 hours after dosing with 72 mg menthol. In summary, the studies show that in humans the unspecified menthol isomer is rapidly glucuronidated and excreted mainly via urine.

Distribution

17 hours after oral administration of 470 mg/kg bw of [3-^{3}H]-menthol (unspecified isomer) to rats 2.1 % of the dose was found in fat, 0.8 % in the liver, 0.2 % in the kidney, 0.3 % in serum and traces (< 0.1 %) in brain, and testes (Clegg et al., 1982).

Excretion

Investigations with male Fischer 344 rats showed that 48 h after administration of 500 mg/kg radiolabelled L-menthol > 70 % of the administered dose was found in urine and faeces (Yamaguchi, et al, 1994).

Rats were administered 470 mg/kg bw of [3-^{3}H]-menthol (unspecified isomer) orally. After 17 hours 52 % of the administered radioactivity was found in the urine, 4.5 % and 3.5 % were found in the faeces and ileum (Clegg et al., 1982).

In humans urinary elimination of menthol after oral application was almost complete within about 12 to 24 hours (Atzl et al., 1972; Bolund et al., 1967; Kaffenberger and Doyle, 1990; Sommerville et al., 1984).

Conclusion: L, D/L, and the unspecified menthol isomers are well absorbed via the oral route of exposure and are mainly excreted as glucuronic acid conjugates. In rats an extensive enterohepatic circulation leads in addition to various hydroxylated degradation products. Glucuronides and degradation products are mainly eliminated via urine, minor quantities via the faeces.

3.1.2 Acute Toxicity

Oral

The studies on acute oral toxicity were not performed according to guideline methods. However, the number of treated animals and the used protocols are scientifically acceptable to evaluate this endpoint sufficiently. All substances demonstrated an acute oral toxicity with LD50 values higher than 2000 mg/kg bw. The menthol isomers tested according to the same protocol (Haarmann and Reimer, 1974) are presented in Table 1. In an orientating study with 2 mice/dose no deaths occurred with doses up to and above 6000 mg/kg bw of the unspecified isomer mixture (Haarmann and Reimer, 1980). For L-menthol a LD50 value of 4380 mg/kg bw was determined in mice (FDA, 1977). Other studies with rats and mice gave similar results, indicating a low acute oral toxicity of the menthol isomers (Herken, 1961 in FAO/WHO, 1999; Mengs and Stotzem, 1989; FDA, 1975). Clinical signs of toxicity observed were a narcotic status and depressed activity (Haarmann and Reimer, 1974, Haarmann and Reimer, 1980, FDA, 1975). No information is given in the study reports at which doses these effects occurred.

A considerably lower LD50 of 940 mg/kg bw was observed in a single study with L-menthol in rats (FDA, 1975). In this study a severe irritation of the mucosal lining of the stomach and intestine was reported. Such effects have not been reported by the other investigators mentioned above.

The human lethal dose is reported to be in the range of 50 – 500 mg/kg bw (FAO/WHO, 1999).

Table 1: Results of studies on acute oral toxicity

Chemical	Species	Protocol	Result (LD_{50})	Reference
L-Menthol	Rat	Other*	2426 – 2615 mg/kg bw	Haarmann and Reimer, 1974
D-Menthol	Rat	Other*	2046 mg/kg bw	Haarmann and Reimer, 1974
D/L-Menthol	Rat	Other*	2602 mg/kg bw	Haarmann and Reimer, 1974

* LD_{50} values were evaluated in the same laboratory, using the same protocol

Conclusion: All menthol isomers show low acute oral toxicity with LD_{50} values normally greater than 2000 mg/kg bw (rats and mice). Clinical symptoms were unspecific, and included apathy and reduced activity. A considerably lower LD_{50} of 940 mg/kg bw was determined in a single study with L-menthol in rats. Severe irritation of the mucosal lining of stomach and intestine was reported in this study. Such effects have not been reported by any other investigators, but may have contributed to the lower LD50 value.

Inhalation

Although no experimental studies are available the low systemic toxicity of menthols (LD_{50} > 2000 mg/kg bw) that is documented for oral application and single dermal contact can be expected also for the inhalation route.

Dermal

Only limited studies are available investigating dermal toxicity (Table 2). In one study the LD_{50} of D/L-menthol in rabbits was above 5000 mg/kg bw. In a second investigation a dermal dose of 34500 mg menthol liquid / kg bw was lethal to a mouse.

Table 2 : Results of studies on acute dermal toxicity

Chemical	Species	Protocol	Result	Reference
D/L-Menthol	rabbit	other	LD50 >5000 mg/kg bw	Levenstein,1973 in Opdyke, 1976
Menthol liquid (unspec. isomer)	mouse	other*	LD = 34500 mg/kg bw	Macht,1939

*orientating study, 1 mouse was treated

Conclusions: It can be assumed that the acute dermal toxicity of the menthol isomers is low, based on old and limited studies for the racemate and the unspecified isomer.

3.1.3 Irritation

Skin Irritation

All compounds were tested for skin irritation in rabbits according to the current OECD-guideline 404. All isomers were tested undiluted and in 50, 25, 5 and 1% concentrations. Diethylphthalate (DEP) was used as diluent. The investigations were performed in the same laboratories, using the same protocol; the results are given in Table 3. The undiluted compounds were irritating to the skin.

Dilution of the compounds led to a pronounced decrease in the irritating properties of the compounds. No skin reaction at all were observed for D-menthol and menthol liquid at 5 % dilution and for L- and D/L-menthol at 1 % dilution.

Table 3: Results of studies on skin irritation

Chemical	Undiluted		50 %		25 %		5 %		1 %		Reference
	Scores		Scores		Scores		Scores		Scores		
	eryt.	oed.	eryt.	oed.	eryt.	oed.	eryt.	oed.	eryt.	oed.	
L-Menthol	3.0	2.9	1.6	2.2	1.0	0.2	0.3	0.1	0.0	0.0	Haarmann and Reimer, 1989, No. 11874
D-Menthol	2.5	2.4	1.9	1.3	0.7	0.0	0.0	0.0	0.0	0.0	Haarmann and Reimer, 1989, No. 11875
D/L-Menthol	3.0	3.0	1.6	1.7	0.8	0.5	0.2	0.0	0.1	0.0	Haarmann and Reimer, 1989, No. 11877
Menthol liquid	2.8	2.4	1.8	1.0	0.8	0.0	0.0	0.0	0.0	0.0	Haarmann and Reimer, 1989, No. 11876

eryt.: erythema, oed.: oedema

Conclusion: All studied isomers of menthol are, if applied undiluted, moderately irritating to skin.

Eye Irritation

All compounds were tested for eye irritation according to the current OECD-guideline 405. All examinations were performed in the same institute according to the same protocol; the results (means of Draize scores after 24, 48, and 72 h) are given in Table 4 in detail. The vehicle diethylphthalate (DEP) alone, tested in the opposite eye of the animals, showed no irritating properties. In all studies with the test compounds only slight reactions of cornea and conjunctiva were observed, depending on the concentration tested. There was no reaction in the iris observed in all cases. After treatment with menthol liquid (100% and 71%) slight redness of conjuctiva 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. Data are summarized in Table 4.

In a study by Carpenter and Smyth (1946) undiluted, 1% and 5% solutions of menthol (unspecified isomer and purity, no definite vehicle mentioned) are reported to affect the eyes of rabbits.. Only the overall result is available in tabulated format and no details are available with regard to the individual experiments, the scores obtained in single animals and the number of animals used in the test with menthol. In summary the injuries were graded 9 on a scale of maximum 10.

In a quantitative structure-activity relationsship (QSAR) analysis eye irritating properties have been predicted for unspecified menthol (Barratt, 1997).

Table 4: Results of studies on eye irritation

Chemical	Conc.	Scores*			Reference
		Cornea opacity	Conjunctivae		
			Redness	Chemosis	
L-Menthol	29 %	0.2	0.6	0.1	Haarmann and Reimer, 1989, No. 11754
L-Menthol	64 %	1.0	2.0	0.6	Haarmann and Reimer, 1989, No. 11870
D-Menthol	29 %	0.4	1.3	0.4	Haarmann and Reimer, 1989, No. 11755
D-Menthol	64 %	0.9	2.1	0.3	Haarmann and Reimer, 1989, No. 11871
D/L-Menthol	40 %	0.8	1.5	0.4	Haarmann and Reimer, 1989, No. 11753
D/L-Menthol	64 %	1.0	2.1	0.3	Haarmann and Reimer, 1989, No. 11873
Menthol liquid	100 %	1.0	2.2	0.7	Haarmann and Reimer, 1989, No. 11872
Menthol liquid	71 %	1.0	2.2	0.7	Haarmann and Reimer, 1989, No. 11756

*scores are based on the results from the 24-, 48- and 72-hours reading 83/467/EEC of July 29, 1983

Conclusion: In studies performed according to OECD TG 405, concentrations of 29 to 64 % of L-, D-, and D/L-menthol in diethylphthalate and undiluted menthol liquid were shown to be slightly irritating to the eye. In another rabbit study instillation of undiluted menthol (of unknown purity) and a 1% and 5% solution in a unknown vehicle were reported to result in eye injury (grade 9 on a scale of maximum 10; no details are available on the number of animals and the nature of the effects seen after menthol treatment). Overall, the menthol isomers are slightly irritating to the eye.

3.1.4 Sensitisation

In non-adjuvant tests for skin sensitization (Buehler Test, Haarmann and Reimer, 1991; local lymph node assay, Haarmann and Reimer, 1995) L-menthol gave no indication of a sensitizing effect in animals. In the induction and the challenge phase of the Buehler test 0.5 ml of a 25 % solution was applied occlusively to the skin of guinea pigs. The test procedure was in accordance with the OECD guideline 406. The local lymph node assay was performed after the protocol of Kimber and Weisenberger, who developed and established the assay. In a modified Draize test, a positive result was only obtained when induction and challenge were followed by a second induction/challenge procedure (Sharp, 1978). The results of the animal studies are shown in Table 5.

In a maximization test with 8 % D/L-menthol in petrolatum performed in 25 volunteers, there was no positive reaction (Kligman, 1975 in Opdyke, 1976).

No valid study is available testing the sensitizing potential of D-menthol.

There are several case reports and clinical studies describing patch-tests with not further specified menthol isomers in patients with dermatological lesions. Of in total 6227 patch-tested patients (out of 9 investigations) about 82 showed positive reactions (0.3 to 6.1 % positive reactions were reported in these studies). The results of the clinical studies are given in detail in Table 6.

The presence of menthol and menthol-containing flavour and fragrance oils in consumer products such as cigarettes, toothpaste, and topical medications can lead to sensitivity reactions in the oral and nasal cavity of susceptible persons (Morton et al. 1995, Camarasa and Alomar 1978, Shah et al., 1996).

Table 5: Results of animal studies on skin sensitization

Chemical	Species	Protocol	Result	Reference
L-Menthol	rabbit	Buehler	not sensitizing	Haarmann and Reimer,1991, No. HR90/000102
	mouse	Local lymph node assay (LLNA)	not sensitizing	Haarmann and Reimer,1995, No.CTL/E/160
	guinea pig	modified Draize	ambiguous (positive only after rechallenge)	Sharp,1978

Table 6: Results of studies on sensitization in humans

Chemical	Number of patients	Complaints	% positive	Reference
D/L-Menthol	25	Volunteers	0	(Kligman, 1975 in Opdyke, 1976
Menthol (D/L-menthol or L-menthol)	228	Dermatoses	1.3	Baer, et al., 1955
	330	Eczematous lesions	6.1	Blondeel, et al., 1978
	1385	Dermatologic complaints	0.4	Jarisch and Sandor, 1978
	1070	Atopic eczema or dermatitis	0.9	Rudzki and Kleniewska, 1971
	1200	Contact dermatitis	1.0	Santucci, et al., 1987
	1077	Crural ulcerations and eczema	1.9	Legiec, et al., 1996
	512	Intraoral complaints	2.1	Morton, et al., 1995
	75	Patients with mucosa/skin reactions caused by dental products	0	Kanerva, et al., 2001
	350	Anal eczema (20.2 % atopic dermatitis)	0.3	Schnuch and Geier, 1995

Conclusion: Standard non-adjuvant animal tests with L-menthol were negative. In humans, a few cases of hypersensitivity reactions, including skin reactions and reactions in the oral and nasal cavity, have been reported. Based on the wide exposure of consumers to these substances and also on the results from clinical studies, which investigated a high number of subjects, the overall sensitizing potential of the menthol isomers is considered to be low.

3.1.5 Repeated Dose Toxicity

Valid studies investigating the repeated dose toxicity of menthol isomers were available for L-menthol and D/L-menthol.

L-Menthol

Oral exposure

Female and male Wistar rats (10/sex/dose) received 200, 400 and 800 mg/kg bw/d L-menthol in soybean oil daily by gavage for 28 days. This study was performed mainly according to OECD TG 407. It is reported that liver weights were significantly increased in male rats at doses of 200, 400 and 800 mg/kg bw/d and also in female rats at doses of 400 and 800 mg/kg bw/d. Additionally, rats of all menthol treatment groups showed vacuolization of hepatocytes (4/20; 5/17, 4/19; no distinction between sexes), which was not seen in the control animals. This effect was not dose related and may reflect an adaptation (Thorup, 1983). 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 cannot be deduced from this study. In a feeding study, groups of 40 male and 40 female rats received 0, 100 or 200 mg/kg bw/d of either L-menthol or D/L-menthol in their diets for 5.5 weeks. There were no adverse effects on weight gain or excretion of glucuronide, water and electrolytes, nor was there any interference with central nervous system reactions to stimulants (Herken, 1961 in: FAO/WHO, 1999). Therefore for L-menthol and the racemate D/L-menthol a NOAEL of 200 mg/kg bw/d can be deduced from this study.

Exposure by inhalation

There is one detailed study from 1954 available with exposure to L-menthol by whole body vapour inhalation for 71 to 79 days with male and female Sherman rats (groups of 12). Although the authors attempted to measure the menthol concentrations in the gas phase, there was no adequate analytic method available. Therefore the exposure concentrations are given as weight of menthol vaporized divided by the volume of air circulated. The exposure concentrations were determined to be 0.087, 0.148 and 0.259 ppm (according to 0.57, 0.96 and 1.68 mg/m³). Besides this shortcoming, the study is of good design with numerous parameters investigated. Histopathological organ examinations showed toxic effects in the lungs only, ranging from tracheitis to severe congestion of the lungs at the highest dose, changes indicative of irritation (Rakieten et al., 1954). As the measurement of the exposure concentration does not seem reliable, this study cannot be used to derive a NOAEL. However, it points to the respiratory system as possible target organ after exposure by inhalation.

D/L-Menthol

Oral exposure

D/L-Menthol was applied in the feed at 930 to 15000 ppm in a subchronic dose-finding study (10 animals/sex/dose) for a carcinogenicity assay to F344 rats (Tracor Jitco, 1976, Project-No. 976-243) and to B6C3F1 mice (Tracor Jitco, 1976, Project-No. 976-223).

Duration	Species	Dose (ppm)	Dose (mg/kg bw) for males	Dose (mg/kg bw) for females
13 weeks	Rat	930	59	67
		1870	114	142
		3750	231	285
		7500	472	521
		15000	(NOAEL) **937**	(NOAEL) **998**
13 weeks	Mouse	930	243	290
		1870	488	595
		3750	978	1193
		7500	(NOAEL) **1956**	(NOAEL) **2386**
		15000	3913	4773

In rats the only effect recorded after 13 weeks of D/L-menthol exposure at 15000 ppm (corresponding to 937 mg/kg bw/d in males and 998 mg/kg/d in females) was a minimal increase in the severity of spontaneous interstitial nephritis in males, which was considered by the authors of the study as of questionable significance. Thus the NOAEL for this study is 937 mg/kg bw/d for male rats and 998 mg/kg bw/d for female rats.

In male and female mice a slight decrease in body weight gain was observed at 15000 ppm but not at 7500 ppm (corresponding to 1956 mg/kg bw/d in males and 2386 mg/kg bw/d in females). Histologic examination of tissues at the 7500 and 15000 ppm levels revealed no compound-related tissue alterations in any of the mice. The sections of lung in control and treated mice revealed early spontaneous respiratory disease lesions (peribronchial and perivascular lymphoid hyperplasia) and occasional focal areas of pneumonitis, which were unrelated to the treatment with the test substance. Also minimal focal interstitial nephritis was noted as a spontaneous lesion which was observed in control and treated mice, and not related to the treatment with D/L-menthol. The NOAEL therefore can be considered with 1956 mg/kg bw/d for male mice and 2386 mg/kg bw/d for female mice based on slightly reduced body weight gain.

In carcinogenicity feeding studies (103 weeks; NCI, 1979) F344 rats were administered 3750 and 7500 ppm D/L-menthol (intake calculated for rats with a mean body weight of 400 g and 20 g/day of food consumption: ca. 188 and 375 mg/kg bw/d) and B6C3F1 mice were administered 2000 and 4000 ppm (intake calculated for mice with a mean body weight of 30 g and 5 g/day of food consumption: ca. 334 and 667 mg/kg bw/d). The mean body weights of male and female rats and mice were slightly reduced at all dose levels. No statistical analysis has been performed on body weights. Estimated maximal body weight differences between control and high dose groups were < 10 % in male rats and male and female mice and < 14 % in female rats. In low dosed female rats body weights were reduced by maximal 10 %. In male rats chronic inflammation of the kidney was found with greater frequency in dosed males than in control males (controls: 29/49; low-dose: 41/50; high-dose 41/50). These findings were regarded as of questionable relevance by the authors, since such lesions are often found in aged male Fischer rats. In B6C3F1 mice, no effects were found at the highest dose tested. The NOAELs in these studies can be considered with 375 mg/kg bw/d for male rats and 667 mg/kg bw/d for male and female mice. For female rats the NOAEL is 188 mg/kg based on slightly reduced body weight at 375 mg/kg bw.

Menthol (unspecified isomers)

There are a number of repeat dose studies using menthol (unspecified isomers) as the test substance. However, these studies do not add to the assessment and are therefore not described here.

Conclusion: In rats given = 200 mg/kg bw of L-menthol in soybean oil by gavage, increased liver weights and a non dose-related vacuolization of hepatocytes were reported. The relevance of these findings remain unclear. 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 (up to 15,000 ppm) for 13 weeks to rats and mice 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 (NOAEL, rat: 15,000 ppm, corresponding to 937 mg/kg bw/d for the male and 998 mg/kg bw/d for the female rat; NOAEL, mouse: 7500 ppm, corresponding to 1956 mg/kg bw/d (males) and 2386 mg/kg bw/d (females).

In a 103-week study in rats with D/L menthol (3750 and 7500 ppm in the diet), 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 at the high dose level (NOAEL: 7500 ppm (approx. 375 mg/kg bw/d) for male rats, and 3750 ppm (188 mg/kg bw/d) for female rats). In 103-week studies in mice with D/L menthol (2000 and 4000 ppm in the diet), the NOAEL for both sexes was 4000 ppm (approx. 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-isomer. 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 these menthol isomers induce no specific systemic effects and are well tolerated after repeated oral administration.

3.1.6 Mutagenicity

Genotoxicity in vitro

L-Menthol

L-Menthol was not mutagenic in Ames tests using the tester strains *S. typhimurium* TA 97a, TA 98, TA 100, TA 102, TA 1535, TA 1537, and TA 2637 with and without metabolic activation (Nohmi, et al.,1985, Andersen and Jensen, 1984, Gomes-Carneiro, et al., 1998). The tests were performed also at cytotoxic concentrations (800 µg/plate, Gomes-Carneiro et al., 1998). A reverse mutation assay with *E. coli* WP2 *uvrA* (trp^-) was negative in concentrations up to 0.8 mg/plate; a recombination assay with *Bacillus subtilis* M 45 and H 17 gave positive results in doses up to 10 mg/disk (Yoo, 1986).

In a detailed study of Murthy et al. (1991) peripheral lymphocytes of 24 human donors were treated in vitro with L-menthol in the absence and in the presence of rat S9-mix. The concentration range tested was 0.1 to 10 mM L-menthol. The authors investigated chromosomal aberrations (in at least 100 cells per donor) and sister chromatid exchanges (in at least 25 second division metaphases per donor). In both test systems L-menthol did not induce chromosomal damage. In a further

cytogenetic assay the anaphase chromosome aberrations of human fibroblasts were investigated. The concentration range tested was 0.1 to 10 µg/ml. There was no indication for chromosomal aberrations induced by L-menthol (FDA, 1975).

Chromosomal aberration tests with Chinese hamster cells (CHL) tested in concentrations of 0.1 to 0.3 mg/ml L-menthol (Sofuni et al., 1985; Matsuoka et al., 1998) were negative with and without metabolic activation.

D-Menthol

Alkaline single gel tests (comet assay) were performed using V79 Chinese hamster cells and human lymphocytes respectively. Both assays were performed with and without metabolic activation. D-Menthol did not induce DNA single strand breaks in both cell types (Hartmann and Speit, 1997).

D/L-Menthol

D/L-Menthol was not mutagenic in the Ames test with the standard tester strains *Salmonella typhimurium* TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537, TA 2637 with and without metabolic activation and including cytotoxic concentrations (Nohmi et al., 1985; Ishidate et al., 1984; Zeiger et al., 1988).

A negative result was obtained for D/L-menthol in a mouse lymphoma assay with L5178Y mouse lymphoma cells with and without metabolic activation (Myhr and Caspary, 1991). The concentration range tested was 12.5 to 200 µg/ml; the lethal dose was 200 µg/ml (see Table 8).

An alkaline elution assay to detect DNA damage in primary rat hepatocytes – testing concentrations of 0.1, 0.3, 0.7, 1.0, 1.3 mM up to cytotoxic concentrations - was negative (Storer et al., 1996).

Chromosomal aberration tests performed with D/L-menthol show primarily negative results. Tests conducted with CHO cells in concentrations of 100, 150 and 200 µg/ml without metabolic activation and in concentrations of 50, 124 and 200 µg/ml with metabolic activation by Ivett et al. (1989) were negative. A cytogenetic assay with CHL cells performed by Sofuni et al. (1985) and Ishidate et al. (1984) showed a negative result without metabolic activation. The concentrations tested were 100, 150 and 200 µg/ml. A study of Hilliard et al. (1998) showed ambiguous results. Weak but statistically significant increases in chromosomal aberrations were observed in CHO cells and TK6 human lymphocytes after treatment with D/L-menthol in concentrations of 250 to 281 µg/ml (cell viability 47-33% of controls) and 128 to 187 µg/ml (cell viability at 187 µg/ml 20% of controls), respectively, without metabolic activation. However, in a second experiment this result could only be reproduced for the highest scorable concentration for CHO cells (250 µg/ml). Negative results were obtained in CHO cells with metabolic activation, but due to too high cytotoxicity of D/L-menthol only the concentration of 203 µg/ml could be evaluated. A further chromosome aberration test with CHO cells with limited documentation was positive, showing maximal 7% aberrant metaphases (Galloway et al., 1998). It is not published whether Galloway´s investigations were performed with or without metabolic activation. It can be assumed that the data presented are originally from Hilliard et al. (see above). Test results in detail are given in Table 7.

Table 7: Results of chromosome aberration tests of D/L-menthol

Test system	Protocol	Concentrations		Results*		Reference
		Exp. [µg/ml]	Cytotox. [µg/ml] (% cell viability)	+ MA	- MA	
CHO	Exposure time: 8 hrs (-); 2 hrs (+) Harvest time: 10.50 (-), 12.50 (+) hrs	100, 150, 200 (- MA), 50, 124, 250 (+ MA)	200	-	-	Ivett, et al., 1989
CHL	Exposure time: 24, 48 hrs	100, 150, 200	200 = 50 % cell-growth inhibition	n.d.	-	Sofuni, et al., 1985, Ishidate, et al., 1984
CHO	Exposure time: 3 hrs Harvest time: 20 hrs	203, 219, 234	234 (45 %)	+*[1]		Galloway, et al., 1998
CHO	Exposure time: 3 hrs Harvest time: 20 hrs	46-297	(47%), 266 (39%), 281 (33%)	(+)*[2]	(+)*[2]	Hilliard, et al., 1998
TK6 human lymphocytes	Exposure time: 3 hrs Harvest time: 17-35 hrs	128-187	187 (20%)	n.d.	(+)*[2]	Hilliard, et al., 1998

* summarized Chromosome aberrations are: Chromatid and chromosome breaks, triradials, chromatid and chromosome exchanges. Gaps and endoreduplications are not counted.

*[1] it is not defined, whether the test was performed with or without metabolic activation.

*[2] result positive only at cytotoxic concentration (≥ 250 µg/ml).

A sister chromatid exchange assay with chinese hamster ovary cells was judged negative with and without metabolic activation (Ivett et al., 1989).

Table 8: Results of different tests on *in vitro* genotoxicity of menthol isomers

	L-Menthol		D-Menthol	D/L-Menthol		Reference
Bacteria						
Ames Tests	+ MA: negative	- MA: negative	n.d.	+ MA: negative	- MA: negative	Nohmi et al. 1995, Andersen and Jensen, 1984, Gomes-Carneiro et al., 1998
Reverse mutation assay	E.coli WP2 uvrA (trp-): negative		n.d.	n.d.		Yoo et al., 1986
Recombination assay	*Bacillus subtilis* M45 H 17: positive		n.d.	n.d.		Yoo et al. 1986
Mammalian cells						
Gene mutation	n.d.		n.d.	L5178Y mouse lymphoma cells		Myhr and Caspary, 1991
				+ MA: negative	- MA: negative	
Cytogenetic assay	Human fibroblasts: Negative		n.d.	n.d.		FDA, 1975
Chromosomal aberration	CHL cells and human lymphocytes		n.d.	CHO/CHL: ambiguous (see Table 7)		Sofuni et al., 1985 Matsuoka et al., 1998 Murthy, et al., 1991
	+ MA: negative	– MA: negative				
DNA damage (alkaline elution)	n.d.		n.d.	Rat hepatocytes : negative		Storer, et al. 1996
DNA damage (comet assay)	n.d.		V79 CHL and human lymphocytes: negative	n.d.		Hartmann and Speit, 1997
Sister chromatid exchange	Human peripheral lymphocytes		n.d.	CHO		Murthy, et al., 1991 Ivett et al., 1989
	+ MA: negative	+ MA: negative		+ MA : negative	- MA : negative	

Conclusion: All menthol isomers were consistently tested negative in standard bacterial gene mutation tests, both in the presence and in the absence of metabolic activation and including cytotoxic concentrations. A slightly increased frequency of chromosomal aberrations was found in CHO cells and human lymphocytes at cytotoxic concentrations, but not in CHL cells or in human fibroblasts.

Overall, menthol and its isomers are considered non-genotoxic in *in vitro* bacterial and mammalian test systems.

Genotoxicity in Vivo

L-Menthol

L-menthol did not lead to an increased rate of chromosomal aberrations in the bone marrow of rats at oral doses up to 3000 mg/kg bw (single dose; sacrifice 6, 24 and 48 h after treatment) and 1150 mg/kg bw/d (5 applications; sacrifice 6 h after last dose). Besides the restriction that only 50 metaphases have been investigated per animal, the experiments were performed in accordance with current standards. L-menthol was not mutagenic in a dominant lethal test in rats (FDA, 1975) with doses up to 3000 mg/kg bw (single dose; providing 14 to 20 pregnant females per mating group) and 1150 mg/kg bw/d (5 applications; providing 13 to 19 pregnant females per mating group). The results are summarized in Table 9.

D/L-Menthol

The *in vivo* mutagenicity of D/L-menthol was investigated in two *Drosophila* SLRL tests and in a mouse bone marrow micronucleus assay.

Canton-S males of *Drosophila* were administered D/L-menthol via feed (3 days) or injection in concentrations of 50000 and 10000 ppm respectively. No genotoxicity for a total of 3 broods was observed (Foureman, et al., 1994).

In a micronucleus assay in bone marrow cells of B6C3F1 mice, which received daily intraperitoneal injections of 250, 500 or 1000 mg/kg bw/d D/L-menthol for 3 days, performed in accordance with current guidelines, no increase in micronuclei was observed. The data do not indicate cytotoxic effects on the bone marrow cells. However, at the highest dose level 3 out of 6 mice died prior to sacrifice. This dose was obviously exceeding the reported intraperitoneal LD50 of 750 mg/kg bw for rats (FAO/WHO, 1999).

Table 9: Results of in vivo mutagenicity tests of menthol isomers

Test system species, strain	L-Menthol		D/L-Menthol	Reference
Drosophila SLRL test	n.d.		10000 (injection) and 50000 (feed) ppm: negative	Foureman et al., 1994
Dominant lethal assay - rats	single dose (1.45, 14.5, 145 mg/kg bw and 500, 3000 mg/kg bw): negative	5 applications (1.45, 14.5, 145 mg/kg bw/d and 1150 mg/kg bw/d): negative	n.d	FDA, 1975
Cytogenetic assay – bone marrow albino rats	Single dose (1.45, 14.5, 145 mg/kg bw and 500, 3000 mg/kg bw): negative	5 applications (1.45, 14.5, 145 mg/kg bw/d and 1150 mg/kg bw/d): negative	n.d.	FDA, 1975
Micronucleus assay B6C3F1 (Bone marrow cells) mice	n.d.		3 i.p. injections (250, 500, 1000 mg/kg bw/d): negative	Shelby, et al., 1993

Although the studies mentioned in Table 9 were not fully conducted in accordance with current test guidelines, taken together they allow drawing conclusions as to the mutagenic potential of L- and D/L-menthol in vivo.

Conclusion: 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.

3.1.7 Carcinogenicity

D/L-Menthol was tested in a well performed study for carcinogenicity (103 weeks) in doses of 3750 and 7500 ppm in the feed in F344 rats (intake calculated for rats with a mean body weight of 400 g and 20 g/day of food consumption: about 188 and 375 mg/kg bw/d) and of 2000 and 4000 ppm in the feed in B6C3F1 mice (intake calculated for mice with a mean body weight of 30 g and 5 g/day of food consumption: about 334 and 667 mg/kg bw/d). 50 animals per sex and dose were treated. In male and female rats the survival rate was not affected by treatment and no carcinogenic effects of D/L-menthol were found in any organ. In treated females, the incidences of chromophobe adenomas in the pituitary gland, of mammary gland fibroadenomas and adenocarcinomas were reduced, compared to the controls (NCI, 1979).

In male mice the survival rate was not affected (control 62%, high dose 70%). Female control mice showed a very high survival rate of 90%. However, the survival of high dosed females (72%) was in the range of control male mice and seems not to be affected by the test substance. In male mice the incidence of hepatocellular carcinoma was increased at the highest dose (8/47 controls, 8/49 low-dose, 14/48 high-dose), however, the incidence was not statistically significant and within the range of the laboratory historical-control groups of mice of this age and strain. It was therefore not considered to be relevant by the authors of the study. The incidence of alveolar/bronchial adenoma or carcinoma in female mice was also slightly increased (1/49, 3/47, 5/48), but not statistically significant. This type of neoplasm has been commonly seen at a similar low incidence in historical-control groups.

Conclusion: There was no evidence of carcinogenicity of D/L-menthol in rats and mice in a study performed in accordance with current standards (highest tested dose levels in rats approx. 375 mg/kg bw, in mice approx. 667 mg/kg bw). Since D/L-menthol contains the two relevant isomers in a 50:50 ratio it can be assumed that also L- and D-menthol have no carcinogenic properties.

3.1.8 Toxicity for Reproduction

Toxicity to fertility

There are no fertility studies with menthol or its isomers available. Examinations of reproductive organs in repeated dose studies can however be used to evaluate adverse effects on reproductive organs. These studies are reported in detail in chapters 3.1.6 (repeated dose toxicity) and 3.1.8 (carcinogenicity).

D/L-Menthol was applied in the feed at 930 to 15000 ppm in a subchronic 13 week-study to F344 rats (Tracor Jitco, 1976, Project No. 976-243) and to B6C3F1 mice (Tracor Jitco, 1976, Project No. 976-223). There were no changes observed in the histopathological examination of testes, prostate, uterus, ovaries, mammary glands and adrenals in rats and mice at any of the doses administered (male rats: up to 937 mg/kg bw/d, female rats: up to 998 mg/kg bw/d, male mice: up to 3913 mg/kg bw/d, female mice: up to 4773 mg/kg bw/d).

Also in a feeding carcinogenicity study with D/L-menthol in mice and rats (103 weeks), no changes in reproductive organs (testes, prostate, uterus, ovaries, mammary gland and adrenals) were observed in histopathological examinations at any of the doses administered (up to about 375 mg/kg bw/d in rats and 667 mg/kg bw/d in mice) (NCI, 1979).

Conclusion: There is no evidence indicating a potential of D/L-menthol to interfere adversely with reproduction. 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.

Developmental Toxicity

L-Menthol

Teratogenicity studies with L-menthol were conducted in rats, mice, hamsters and rabbits (FDA,1973). In all four developmental toxicity studies, maternally toxic dose levels were not used. The dose levels were, however, sufficiently high to allow an initial assessment of this endpoint:

2.18, 10.15, 47.05 and 218.0 mg/kg bw/d were administered by gavage to Wistar rats from gestation day 6 to 15. There was no effect on maternal and fetal survival and the number of abnormalities in soft or skeletal tissues observed did not differ from sham treated control. No clinical signs of maternal toxicity were observed. Therefore the NOEL derived for maternal and fetal toxicity and teratogenicity in rats can be determined as 218.0 mg/kg bw/d.

Doses of 1.85, 8.59, 39.9 and 185.0 mg/kg bw/d were administered to CD-1 mice from gestation day 6 to 15. No effect on maternal and fetal survival and no dose-related increase in the number of abnormalities in soft or skeletal tissues was observed. No clinical signs of maternal toxicity were observed. The NOEL derived for maternal and fetal toxicity and teratogenicity was 185.0 mg/kg bw/d.

Rabbits were administered menthol from gestation day 6 to 18 in following doses: 4.25, 19.75, 91.7 and 425.0 mg/kg bw/d. Few of the rabbits died or aborted before day 29 (4.25/2 out of 13 animals, 19.75/3 out of 12 animals, 91.7/1 out of 11 animals, 425.0/4 out of 14 animals), however, these effects were not dose related and are not considered to be a consequence of test substance administration. Also in rabbits no effect on maternal and fetal survival and no dose-related increases in the number of abnormalities in soft or skeletal tissues were observed. No clinical signs of maternal toxicity were observed. The NOEL derived for maternal and fetal toxicity and teratogenicity was therefore 425.0 mg/kg bw/d.

4.05, 21.15, 98.2 and 405.0 mg/kg bw/d were administered to Syrian hamsters during gestation days 6-10. No effect on maternal and fetal survival and no dose-related number of abnormalities in soft or skeletal tissues were observed. The NOEL for maternal and fetal toxicity and teratogenicity was therefore 405.0 mg/kg bw/d.

No experimental data with the other menthol isomers is available with regard to this endpoint. Since there is no indication of a difference between the isomers in their toxicokinetics and metabolism, and since this is further supported by all other available toxicological data, which do not show any evident differences in the individual toxicological profiles, there is no reason to assume that the stereoisomeric properties may affect the toxicological properties of menthol isomers. Hence, a similar result in developmental toxicity studies would reasonably be expected from studies with D-menthol, the racemate or the unspecified menthol isomer.

Conclusion: 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).

3.1.9 Other relevant information

Human experiences

Ingestion of high menthol doses may cause abdominal pain, convulsions, nausea, vomiting, vertigo, ataxia, drowsiness and coma (Dukes, 1980; Gleason et al., 1969) After drinking of about 200 – 250 mg menthol/kg bw a child became drowsy, somnolent, felt pain in the stomach and vomited. The symptoms were fully reversible within 4 days (Leiber, 1967). Oral intake of 8000 to 9000 mg of menthol (unspecified isomer) by three volunteers (corresponding approx. 120 mg menthol/kg bw)

led to a cold burning sensation in mouth, throat and esophagus, a cold sensation on the mucous membranes of the nose, on the skin of the hand and feet, and fatigue (Schwenkenbecher, 1908). About 20 mg menthol/kg bw led only to a mild abdominal discomfort (Bolund, et al.,1967).

Adverse CNS effects are described for a 13-year old boy after inhalation of a menthol containing olbas oil. The estimated inhaled amount of menthol was 200 mg (O´Mullane et al., 1982). Similar symptoms are described after smoking mentholated cigarettes (after smoking 80 mentholated cigarettes for 3 months a woman developed insomnia, unsteady gait, mental confusion, depression, vomiting, and cramp in the legs (Luke, 1962).

In very few cases, all in children younger than 1 year, menthol applied to the nostrils or near the nose caused reflex apnea. Clinical signs were laryngospasm, spasm of the glottis or instant collapse, dyspnea, apnea, unconsciousness, cyanosis and hyperextensive extremities (Champeau, 1935, Kleinschmidt, 1935, Klinke, 1967, Lesoine, 1965, Leiber 1967, Martindale, 1982, Melis, 1989). This effect is assumed not to be a poisoning effect but a reflectory reaction of the nervus trigeminus (Kratschmer reflex) (Leiber, 1967).

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 (Olowe and Ransome-Kuti, 1980).

Menthol has been tested in humans mainly for its pharmaceutical properties, such as enhancement of lung and airway volume (FAO/WHO, 1999).

3.2 Initial Assessment for 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 LD_{50} 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 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-isomer. 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.

Application to nose, nostrils and near to the nose in newborns and children younger than two years of age may cause a severe and dangerous trigeminus reflex (apnea) and should be avoided.

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

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

For the effects assessment of menthols on aquatic organisms the volatility of the isomers from aqueous solutions has to be taken into account, particularly in tests with open systems and longer exposure periods. Toxicity tests with analytical monitoring of the applied menthols reveal that after 4 days the concentrations decreased to about 60 - 80 % of the nominal concentrations.

In most of the studies available on the toxicity of menthols on aquatic species the reported effect values are based on measured (effective) test substance concentrations. However, also the results of the tests with invertebrates and activated sludge (being the only tests without analytical monitoring) should more or less correspond to nominal test substance concentrations due to the short exposure periods (24 h resp. 3 h). Ecotoxicity data available for L-menthol and D/L-menthol are summarized in the following table:

Substance	L-Menthol	D/L-Menthol
CAS-No.	2216-51-5	89-78-1
Fish (*P. promelas*)	EC_{50}(96 h) = 18.4 mg/l (e)	
Fish (*D. rerio*)	LC_{50} (96 h) = 15.6 mg/l (e)	LC_{50} (96 h) = 17.6 mg/l (e)
Fish (*O. latipes*)	LC_{50} (48 h) = 26 mg/l (e)	
Invertebrates (*D. magna*)	EC_{50} (24 h) = 37.7 mg/l (n) EC_{50} (48 h) = 26.6 mg/l (e)	EC_{50} (24h) = 71 mg/l (n)
Algae (*S. subspicatus*)	ErC50 (72h) = 21.4 mg/l (e) NOEC (72h) = 9.65 (e)	ErC_{50} (72 h) = 16.2 mg/l (n) NOEC (72 h) = 5mg/l (n)
Sludge (Respiration inhibition)	EC_{10} = 51 mg/l (n) EC_{50} = 237 mg/l (n)	EC_{10} (3 h) = 117 mg/l (n) EC_{50} (3 h) = 306 mg/l (n)

Values based on effective (e) or nominal (n) TS concentrations

Fish

A flow-through test on the acute toxicity of L-menthol to *Pimephales promelas* was conducted by Geiger et al. (1988). The fish were exposed in Lake Superior water to 5 test substance concentrations in the range of 4.39 to 24.6 mg/l. Analytical measurements revealed that the menthol concentrations were >80 % of the nominal during the test period. Based on measured concentrations a 96h-LC_{50} of 18.9 mg/l was obtained. The affected fish lost schooling behaviour, were hyperactive and underreactive to external stimuli. They had increased respiration, were darkly coloured and lost equilibrium prior to death. Considering these sub-lethal effects, a 96h-EC_{50} of 18.4 mg/l was determined.

A static test on the acute toxicity of L-menthol to *Danio rerio* was conducted according to the OECD guideline 203 (Bayer AG, 1992b). The fish were exposed to 5 nominal test substance concentrations in the range of 7.8 to 31 mg/l. In all test media, undissolved substance particles remained on the water surface. Analytical measurements revealed that the test substance concentrations decreased below 80 % of the nominal within 96 h, probably due to volatilization.

Based on the mean measured concentrations, a LC_{50} of 15.6 mg/l was calculated using adjusted probit analysis. At a nominal concentration of 11 mg/l, all fish had a slow and inactive swimming behaviour even after 2 hours; the behaviour at the lowest concentration is not reported. The same test conducted with D/L-Menthol (Bayer AG, 1990a) resulted in a LC_{50} of 17.6 mg/l based on mean measured concentrations. The same sub-lethal effects as for L-menthol are reported at the nominal concentration of 11 mg/l.

A static or semistatic test on the acute toxicity to *Oryzias latipes* in accordance with the Japanese Industrial Standard resulted in a 48h-LC_{50} of 26 mg/l (MITI, 1992). It remains unclear whether D/L or L-menthol was used, in the literature source both CAS-numbers are referred.

Invertebrates

The acute toxicity of D/L-menthol to *Daphnia magna* was determined in a static test conducted according to a proposal of the German Federal Environmental Agency after an exposure period of 24 h. The organisms were exposed to 8 test substance concentrations between 2.0 and 250 mg/l, analytical control was not performed. The nominal LC_{50} was calculated to be 71 mg/l (Bayer AG, 1990b).

In a recent test the acute toxicity of L-menthol to *Daphnia magna* was studied in a static test conducted according to method 92/69/EEC Annex V C2. The organisms were exposed to 6 test concentrations in the range of 3.2 to 100 mg/l. At start and end of the test the test substance concentration was measured with GC. Measured concentrations ranged from 93.1 to 104 % of nominal values at test begin and from 81.3 to 91.6 % after 48 hours. The test results were expressed in terms of nominal concentrations at 24 hours and in terms of mean measured concentrations at 48 hours. A 24h-EC50 of 37.7 mg/l and a 48h-EC50 of 26.6 mg/l was found (Bayer AG, 2002b).

Algae

The growth inhibition of D/L-menthol to the alga *Scenedesmus subspicatus* was tested by Bayer AG (2000) according to OECD guideline 201. The algae were exposed to 6 nominal concentrations between 1.25 and 40 mg/l. Analytical control (TOC measurements) revealed that the test concentrations have not decreased below 80 % of the nominal. Based on nominal concentrations the 72h-ErC_{50} value was 16.2 mg/l. The NOEC resulting from the Dunnett test was 5mg/l.

In a recent test the acute toxicity of L-menthol to the green algae *Desmodesmus subspicatus* was studied in a static test conducted according to method 92/69/EEC Annex V C3. The algae were exposed to 4 test concentrations in the range of 5 mg/l to 40 mg/l. At start and end of the test the test substance concentration was measured with GC. Measured concentrations ranged from 92 to 102.5 % of nominal values at test begin and from 88 to 105 % after 72 hours. The test results were expressed in terms of mean measured concentrations. A 72h-ErC50 of 21.4 mg/l and a 72h-NOEC of 9.65 mg/l was found (Bayer AG, 2002c).

Summary of aquatic effects

Ecotoxicity data for fish, invertebrates and algae are available for L- and D/L-menthol. The data for the two category members within each trophic level are in the same order of magnitude and are within the uncertainty range of laboratory effect tests. 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.

Determination of PNECaqua

Tests on acute aquatic toxicity for 3 trophic levels are available for L-menthol and D/L-menthol. Most tests were conducted with analytical control. The lowest effect value was found in an algal growth inhibition test (*Scenedesmus subspicatus*) with an ErC_{50} of 16.2 mg/l.

Applying an assessment factor of 1000 to the algae ErC_{50}, a PNECaqua of 16.2 µg/l is calculated. This PNEC is valid for the whole category.

Tests on long-term toxicity are not available.

Microorganisms

A respiration inhibition test on sludge from a laboratory facility was conducted with D/L-menthol according to OECD guideline 209 (Bayer AG, 1989). The nominal 3h-EC_{10} was 117 mg/l and the EC_{50} 306 mg/l.

In a similar test according ISO 8192 with L-menthol, an EC10 of 51 mg/l and an EC_{50} of 237 mg/l was determined (Bayer AG, 1992c).

4.2 Terrestrial Effects

No results from standard soil toxicity tests are available. There are some data e.g. from studies with insects (bees, caterpillars) and from menthol-treated bee-hives, which cannot be related to relevant environmental conditions (Lee at al., 1999; Kevan et al., 1999; Westcott and Winston, 1999).

4.3 Other Environmental Effects

No reliable data available.

4.4 Initial Assessment for the Environment

Environmental behaviour:

According to a Mackay Level I model calculation menthols are mainly distributed to air (39.5 - 44.2 %) and water (40.5 – 43.8 %), followed by soil (8.0 - 8.7%) and sediment (7.3 – 8.1 %). The calculated Henrys' law constant indicates evaporation from surface waters within 2-18 days.

In the atmosphere, indirect photodegradation by hydroxyl radicals is expected with an estimated half-life of 16 hours.

Under environmental conditions, neither hydrolysis nor direct photolysis are to be expected due to the chemical structure. From recently performed tests it can be concluded that menthols are readily biodegradable. The results of one laboratory test indicate no significant bioaccumulation potential of menthols.

Environmental effects:

Ecotoxicity data for fish, invertebrates and algae are available for L-menthol and D/L-menthol. The data for both isomers within each trophic level are in the same order of magnitude and are within the uncertainty range of laboratory effect tests. 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. Tests on acute aquatic toxicity for 3 trophic levels are available for L-menthol and D/L-menthol. For Danio rerio an LC50 (96 h) of 17.6 mg/l was found. For the acute toxicity on Daphnia magna, an EC50 (48 h) of 26.6 mg/l was obtained. The most sensitive organism tested is

the alga Scenedesmus subspicatus with an ErC50 (72 h) of 16.2 mg/l. Using an assessment factor of 1000, a PNECaqua of 16.2 µg/l is derived. This PNEC is valid for the whole category.

Two tests on sludge respiration inhibition are available for L-menthol and D/L-menthol with EC10 values of 51 and 117 mg/l.

Tests on long-term toxicity on aquatic species as well as on terrestrial species are not available.

5 RECOMMENDATIONS

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.

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.

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Annex 1: Menthols Category Justification

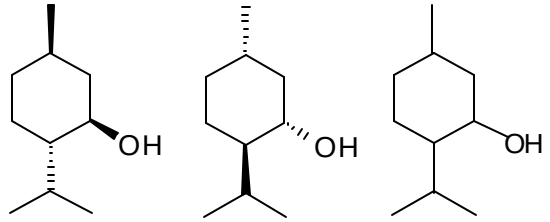
Identity:

Chemical name: cyclohexanol, 5-methyl-2-(1-methylethyl)-

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

Molecular weight: 156.27 g/mol

Structural Formula:



L-Menthol D-Menthol Menthol

The molecule has 3 stereo centers, i.e. there are 8 possible stereoisomers (menthols, neomenthols, isomenthols, neoisomenthols). In nature the compound occurs generally as L- menthol, the main component of e.g. peppermint oil, mentha piperita, mentha oil etc. D/L-menthol, the racemic mixture of the L- and D- isomer, is exclusively of synthetic origin. D-menthol is a non-marketed side-product in the production process of L-menthol. However, as a main component of the widely used D/L-menthol it was included in this Category Approach.

The unspecified mixture of menthol isomers (CAS-No. 1490-04-6; here called menthol or menthol liquid) contains the L- and D- isomer in unspecified relation and can contain additional not specified stereoisomers. This mixture was included in the Menthol Category Approach because of the following reasons:

- The correct assignment of CAS-Nos. and chemical identities is very confusing for the group of menthol-isomers (16 different CAS- and EINECS Nos.). As a consequence, many authors used this CAS-No. in their publications not knowing the correct assignment.
- The data base for the unspecified isomer mixture is very large (see IUCLID). Not to include this mixture would lead to a loss of important knowledge on the physico-chemical, toxicological and environmental properties of the menthols.

L-menthol, D/L-menthol and menthol liquid are widely used as flavourings, disinfectant and cooling compounds.

The other stereoisomers (neomenthols, isomenthols, neoisomenthols) are of minor importance. These isomers are formed in the production of D/L-menthol and are re-introduced into the process after epimerization.

Below see the 4 menthol products of technical importance selected for the category approach:

Substance	Synonyms	CAS-No.	Remark
L-Menthol	(-)-Menthol Menthol, (1R, 3R, 4S)-(-)-	2216-51-5	Natural or synthetic menthol
D-Menthol	(+)-Menthol	15356-60-2	Non marketed by-product
D/L-Menthol	Racemate, "D/L-Menthol pure"	89-78-1	Synthetic product
Menthol or Menthol liquid	"D/L-Menthol raw"	1490-04-6	Unspecified mixture of isomers

In the following data summaries information will be presented that indicate these materials share similar physico-chemical properties, environmental fate characteristics, ecotoxicity, and mammalian toxicity.

Scientific literature was searched and summarized. Each study on category materials was evaluated for adequacy. Robust summaries were developed for each study addressing specific SIDS endpoints. Summaries were also developed for studies either considered not adequate but providing information of relevance for hazard identification and evaluation, or which covered non-SIDS endpoints.

Category Justification

As structural isomers, the members of the menthol category share the same molecular weight. Of particular importance to environmental effects are the values for partition coefficient (log Kow), vapour pressure and water solubility.

Available Physico-Chemical Data for Menthols:

Substance	**L-Menthol**	**D-Menthol**	**D/L-Menthol**	**Menthol**
CAS-No.	**2216-51-5**	**15356-60-2**	**89-78-1**	**1490-04-6**
Vapour Pressure	0.085 hPa (25°C)		1.3 hPa (55°C)	0.085 hPa (25°C)
Log Kow	3.4	3.4 (read-across from value for L-menthol and D/L-menthol)	3.4	3.4 (read-across from value for L-menthol and D/L-menthol)
Water Solubility	431 mg/l (20°C)		508 mg/l (20°C)	420 mg/l (20°C)

The enantiomeric menthols have identical physical properties (apart from their specific rotation), but the racemates differ from the optically active forms in, for example, their melting points (Ullmann 2002). The slight differences in the cited data are within the range of uncertainty range of laboratory tests.

The water solubility was determined for three products. Due to the similar molecular structures, no significant differences in the solubility are expected. The vapour pressure at environmental relevant temperatures was determined for L-menthol and an unspecified isomer mixture. As well as for the parameters above, similar values are expected for D-menthol and the racemate.

Available Data on Ready Biodegradability

Substance	**L-Menthol**	**D-Menthol**	**D/L-Menthol**	**Menthol**
CAS-No.	**2216-51-5**	**15356-60-2**	**89-78-1**	**1490-04-6**
OECD 301E	100 % after 28 d;			
MITI I	0% after 28d		0% after 28d	
OECD 301D	79 – 92 % after 28 d	76 – 92 % after 28 d		

The OECD 301E test using L-menthol as test substance showed a rapid decrease of DOC. However, there is no information about possible volatilisation and /or adsorption. The MITI (I) test (not clearly specified whether L- or D/L-menthol was used, in the literature source both CAS-numbers are referred) resulted in 0% oxygen consumption. It cannot be excluded that the employed substance concentration partly inhibited the inoculum. The two recently performed Closed-Bottle tests with D-menthol and L-menthol show clearly that both isomers are readily biodegradable.

Available Ecotoxicity Data

Substance	**L-Menthol**	**D-Menthol**	**D/L-Menthol**	**Menthol**
CAS-No.	**2216-51-5**	**15356-60-2**	**89-78-1**	**1490-04-6**
Fish (*P. Promelas*)	EC50 = 18.4 mg/l (e)			
Fish (*B. rerio*)	LC50 = 15.6 mg/l (e)		LC50 = 17.2 mg/l (e)	
Fish (*O. latipes)*	LC50 = 26 mg/l (e)			
Invertebrates (D. magna)	EC50 (24 h) = 37.7 mg/l (n) EC50 (48 h) = 26.6 mg/l (e)		EC50 (24 h) = 44.3 mg/l (n)	
Algae (*S. subspicatus*)	ErC50 = 21.4 mg/l (e) NOEC = 9.65 (e)		ErC50 = 16.2 mg/l (n) NOEC = 5 mg/l (n)	
Sludge (Respiration Inhibition)	EC10 = 51 mg/l (n) EC50 = 237 mg/l (n)		EC10 (3 h) = 117 mg/l (n) EC50 (3 h) = 306 mg/l (n)	

(e): effective concentration (n): nominal concentration

For the toxicity of menthols on aquatic species experimental results from tests with fish, daphnis and algae are available for L-menthol and D/L-menthol. The available effect values for the two

category members indicate a similar range of toxicity within each trophic level, thus the available test results can be considered as being representative for all menthol isomers. Results are within the uncertainty range of laboratory effect tests.

Available Toxicity Data (Human Health)

The following data were identified for materials in the category:

Substance	**L-Menthol**	**D-Menthol**	**D/L Menthol**	**Menthol**
CAS-No.	**2216-51-5**	**15356-60-2**	**89-78-1**	**1490-04-6**
Acute toxicity oral dermal	v / + 	v / + 	v / + v / +	v / + v / -
Irritation skin eye	v / + v / +	v / + v / +	v / + v / +	v / + v / +
Sensitization	v / +		v / +	
Repeated dose toxicity	v / +		v / +	
Genetic toxicity in vitro in vivo	v / + v / +	v / -	v / + v / +	
Carcinogenicity			v / +	
Toxicity to fertility Developmental toxicity Toxicity to reproduction	 v / + X*		 X*	

v / + Adequate data available
v / - Data available, but not adequate
X* Data taken from repeated dose toxicity studies

Investigations on toxicokinetics show that L-, D/L- and the unspecified menthol are well absorbed via the oral route. For all of the isomers, elimination is rapid and mainly occurs as glucuronic acid conjugates via urine, minor amounts via faeces. Significant differences in toxicokinetic properties of menthol isomers were not reported.

The available toxicity data indicate very similar toxicity profiles for D-, L-, D/L-menthol and the unspecified menthol isomer mixture. In mammalian species the low toxicity is manifested in LD_{50} values generally greater than 2000 mg/kg bw in acute studies, limited toxicity in repeated dose studies, and no effects in teratology evaluations. Irritation to skin and eyes was slight to moderate. The low hazard potential is not unexpected, since the FDA regulates menthol as a GRAS (generally recognized as safe) component and an acceptable daily intake (ADI) of 0-4 mg/kg bw for L-menthol and D/L-menthol was adopted in 1999 by the Joint FAO/WHO Committee.

All of the products have been tested for acute oral toxicity, skin and eye irritation in rodents, often following identical test protocols.

Data for sensitization, repeated dose toxicity, genetic toxicity, fertility, and carcinogenicity are available for D/L-menthol and mostly for L-menthol as well.

D/L-menthol is a racemic mixture of the D- and L- isomers and contains both isomers in equal proportion. Data gaps for D-menthol and the unspecified isomer mixture can therefore be filled by

the respective results with the racemic mixture and the doses for each isomer might be equivalent to half of the total tested D/L -dose.

L-menthol showed no embryotoxic or teratogenic properties at not maternally toxic dose levels (maternally toxic dose levels were not tested). No experimental data with the other menthol isomers is available with regard to developmental toxicity. Since there is no indication of a relevant difference between the isomers in their toxicokinetics and metabolism, and since this is further supported by all other available toxicological data, which do not show any evident differences in the respective toxicological profiles, there is no reason to assume that the stereoisomeric properties may affect the toxicological properties of the menthol isomers. Hence, a similar result in developmental toxicity studies would reasonably be expected from studies with D-menthol, the racemate or the unspecified menthol isomer.

Because of the low hazard potential of the chemicals in the menthols category, no further toxicity tests are recommended.

Menthol containing mixtures - peppermint oil:

Peppermint oil contains about 35 – 60 % menthol (menthone (15 - 30 %), menthylacetate (4 -14 %), and small amounts of cineole and other terpenes) (Nair, 2001). Hence, adverse effects after administration of peppermint oil cannot be associated with menthol. The peppermint oil studies are therefore considered to be not relevant for the hazard assessment of menthol.

SPECIES		PROTOCOL	RESULTS			
			L-Menthol	**D-Menthol**	**D,L-Menthol**	**Unspecified mixture of Menthol isomers**
CAS NO:			**2216-51-5**	**15356-60-2**	**89-78-1** **former CAS-No.:** **15356-70-4**	**1490-04-6**
PHYSICAL-CHEMICAL						
2.1	Melting Point		Ca. 42 °C	43 °C	30-32 °C	
2.2	Boiling Point (1013 hPa)		212°C	216.5 °C	216 °C	215.5 °C
2.3	Density		0.89 g/cm³ (20°C)		0.895 g/cm³ (20°C)	0.898 g/cm³ (25°C)
2.4	Vapour Pressure		0.085 hPa (25°C)		1.3 hPa (55°C)	0.085 hPa (25°C)
2.5	Partition Coefficient (Log Kow)		3.4	3.4	3.4	3.4
2.6 A.	Water Solubility		431 mg/l (20°C)		508 mg/l (20°C)	420 mg/l (20°C)
B.	pH					
	pKa					
2.12	Oxidation: Reduction potential					

	SPECIES		PROTOCOL	RESULTS			
CAS NO:				**2216-51-5**	**15356-60-2**	**89-78-1**	**1490-04-6**
ENVIRONMENTAL FATE AND PATHWAY							
3.1.1	Photodegradation		Calculated	In air $T_{1/2}$ = 16 h (0.5 * 10^6 OH/cm^3)			
3.1.2	Stability in Water			Neither hydrolytic nor photolytic degradation expected			
3.1.3	Stability in Soil						
3.2	Monitoring Data						0.0093 - 0.139 µg/l
3.3	Transport and Distribution		Henry-constant (calculated) Calculated distribution (Fugacity Level I acc. to Mackay) Koc (calculated)	3.08 (Pa x m^3/mol) In Air: 43.2 % In Water: 40.6 % In Soil: 8.0 % In Sediment: 8.1 % In Biota: <0.1 % 614 l/kg	3.08 (Pa x m^3/mol) In Air: 43.2 % In Water: 40.6 % In Soil: 8.0 % In Sediment: 8.1 % In Biota: <0.1 % 614 l/kg	2.62 (Pa x m^3/mol) In Air: 39.5 % In Water: 43.8 % In Soil: 8.7 % In Sediment: 7.9 % In Biota: <0.1 % 614 l/kg	3.16 (Pa x m^3/mol) In Air: 44.2 % In Water: 40.4 % In Soil: 8.0 % In Sediment: 7.3 % In Biota: <0.1 % 614 l/kg
3.5	Biodegradation	Mixed activated sludge, non-adapted Mixed activated sludge, non-adapted activated sludge, adapted	OECD 301 E OECD 301C (MITI I) Comparable to OECD 302 B OECD 301 D (Closed Bottle Test)	53% after 7 days 93% after 14 days 100 % after 28 days 0% after 28 days 79 – 92 % after 28 days	76 – 92 % after 28 days	0% after 28 days	95.1% after 5 days
3.7	Bioaccumulation	*Cyprinus carpio*	OECD 305 C	BCF < 0.5 - 15 after 6-8 weeks			

		SPECIES	PROTOCOL	RESULTS			
CAS NO:				**2216-51-5**	**15356-60-2**	**89-78-1**	**1490-04-6**
ECOTOXICOLOGY							
4.1	Acute/Prolonged Toxicity to Fish	*Pimephales promelas* *Brachydanio rerio* *Oryzias latipes*	flow-through OECD 203 JIS K 0102-1986-71 (Japan)	EC50 (96 h) = 18.4 mg/l (effective) LC50 (96 h) = 15.6 mg/l (effective) LC50 (48 h) = 26 mg/l (effective)		LC50 (96 h)= 17.6 mg/l (effective)	
4.2	Acute Toxicity to Aquatic Invertebrates	*Daphnia magna*	Static	EC50 (24 h) = 37.7 mg/l (nominal) EC50 (48 h) = 26.6 mg/l (effective)		EC50 (24 h) = 71 mg/l (nominal)	
4.3	Toxicity to Aquatic Plants e.g. Algae	*Scenedesmus subspicatus*	OECD 201	ErC50 (72h) = 21.4 mg/l (effective) NOEC (72h) = 9.65 (effective)		ErC50 (72 h) = 16.2 mg/l (nominal) NOEC (72 h) = 5 mg/l (nominal) (Concentrations were measured but did not fall < 80 % of the nominal concentration)	
4.4	Toxicity to Microorganisms e.g. Bacteria	activated sludge	OECD 209	EC10 (3 h)= 51 mg/l (nominal) EC50 (3 h)= 237 mg/l (nominal)		EC10 = 117 mg/l (nominal) EC50 = 306 mg/l (nominal)	

		SPECIES	PROTOCOL	RESULTS			
CAS NO:				2216-51-5 - L-Menthol	15356-60-2 - D-Menthol	89-78-1 - D/L-Menthol	1490-04-6 - Menthol, unspecified isomer
TOXICOLOGY							
5.1	Acute Oral Toxicity	Rat (f) Mouse (m)	Mainly according to OECD 401	LD50 = 940 - 2615 mg/kg bw	LD50 = 2046 mg/kg bw	LD50 = 2602 mg/kg bw	No data LD50 >> 2000 mg/kg bw
5.1.2	Acute Inhalation Toxicity			No data	No data	No data	No data
5.1.3	Acute Dermal Toxicity	Rabbit Mouse	No data orientating study (only 1 animal treated)	No data	No data	LD50 > 5000 mg/kg bw	No data LD = 34 500 mg/kg bw
5.2	Corrosiveness and Irritation						
5.2.1	Skin Irritation	Rabbit	OECD 404	Moderately irritating	Moderately irritating	Moderately irritating	Moderately irritating
5.2.2	Eye Irritation	Rabbit	OECD 405 (vehicle: DEP) 1%, 5%,undiluted (vehicle: no data)	Slightly irritating	Slightly irritating	Slightly irritating	Slightly irritating irritating
5.3	Sensitization	Rabbit Mouse Guinea pig Human	Buehler LLNA Modified Draize Patch Case reports	Not sensitizing Not sensitizing Ambiguous (positive after rechallenge) No data Sensitizing	No data No data No data No data	No data No data No data Not sensitizing Sensitizing	No data No data No data No data Sensitizing

		SPECIES	PROTOCOL	RESULTS			
CAS NO:				2216-51-5 - L-Menthol	15356-60-2 - D-Menthol	89-78-1 - D/L-Menthol	1490-04-6 - Menthol, unspecified isomer
5.4	Repeated Dose Toxicity	Rat (m/f)	Gavage, 4 w	NOAEL/LOAEL not assignable	No data	No data	No data
		Rat (m/f)	Feed, 5.5 w	NOAEL: 200 mg/kg bw/d (highest tested dose)	No data	NOAEL: 200 mg/kg bw d (highest tested dose)	No data
		Rat (m/f)	Feed, 13 w	No data	No data	NOAEL m = 937 mg/kg bw/d; f = 998 mg/kg bw/d	No data
		Mouse (m/f)	Feed, 13 w	No data	No data	NOAEL m = 1956 mg/kg bw/d, f = 2386 mg/kg bw/d	No data
		Rat (m/f)	Feed, 103 w	No data	No data	NOAEL m = 375 mg/kg bw/d; f = 188 mg/kg bw/d	No data
		Mouse (m/f)	Feed, 103 wk	No data	No data	NOAEL m/f = 667 mg/kg bw/d	No data
		Rat (m/f)	Vapour Inhalation, 71-79 days	Irritation (lung, trachea)	No data	No data	No data
5.6	Genetic Toxicity in Vitro						
Bacteria							
	Bacterial (Gene mutation)	*Salmonella typhi-murium* TA 92, 94, 97a, 98, 100, 102, 1535, 1537, 2637	Ames Test	TA 97a, 98, 100, 102, 1535, 1537, 2637: negative (+/- MA)	No data	TA 92, 94, 98, 100, 1535, 1537, 2637: negative (+/- MA)	No data
	Bacterial (Reverse Mutation)	*E. coli* WP2 *uvrA* (trp^-)	Ames Test	Negative	No data	No data	No data
	Bacterial (Recom-bination assay)	M45 and H17	Recombination assay	Positive	No data	No data	No data

		SPECIES	PROTOCOL	RESULTS			
CAS NO:				2216-51-5 - L-Menthol	15356-60-2 - D-Menthol	89-78-1 - D/L-Menthol	1490-04-6 - Menthol, unspecified isomer
Mammalian cells							
	Gene mutation	L5178Y mouse lymphoma cells	Mouse lymphoma assay	No data	No data	Negative (+/- MA)	No data
	Cytogenetic Assay	Human Tissue cells	Chromosomal aberration test	Negative	No data	No data	No data
	Cytogenetic Assay	CHO TK6 human lymphoblasts CHL Human lymphocytes	Chromosomal aberration test	No data No data Negative (+/- MA)	No data	Negative (+/- MA); Positive (+ MA) Negative (- MA) No data	No data
	DNA-damage	Primary rat hepatocytes	Alkaline elution assay	No data	No data	Negative	No data
	DNA-damage	V79 CHL Human lymphocytes	Comet assay	No data	Negative (+/- MA) Negative (+/- MA)	No data	No data
	DNA-damage	CHO Human lymphocytes	Sister chromatid exchange assay	No data Negative (+/- MA)	No data	Negative (+/- MA) No data	No data
5.6	Genetic Toxicity in Vivo						
	SLRL Assay	*Drosophila melanogaster*	Feed Injection	No data	No data	Negative Negative	No data
	Dominant lethal Assay	Rat	Single dose (gavage) 5 applications (gavage)	Negative Negative	No data	No data	No data

		SPECIES	PROTOCOL	RESULTS			
CAS NO:				2216-51-5 - L-Menthol	15356-60-2 - D-Menthol	89-78-1 - D/L-Menthol	1490-04-6 - Menthol, unspecified isomer
	Cytogenetic Assay	Bone marrow albino rats	Single dose (gavage) 5 applications (gavage)	Negative Negative	No data	No data	No data
	Micronucleus assay	Bone marrow B6C3F1 mice	3 applications (injection)	No data	No data	Negative	No data
5.7	Carcinogenicity	Rat (m/f)	Feed, 103 w	No data	No data	No evidence of carcinogenicity	No data
		Mouse (m/f)	Feed, 103 w			No evidence of carcinogenicity	
5.8.1	Toxicity to Fertility	Rat	Feed, 13 w Feed, 103 w	No data	No data	No evidence of adverse effects on reproduction organs	No data
		Mouse	Feed, 13 w Feed, 103 w	No data	No data	No evidence of adverse effects on reproduction organs	No data
5.8.2	Developmental Toxicity/Teratogenicity	Rats	Gavage, gd 6-15	NOEL (maternal and foetal) = 218 mg/kg bw/d	No data	No data	No data
		Mouse	Gavage, gd 6-15	NOEL (maternal and foetal) = 185 mg/kg bw/d			
		Rabbits	Gavage, gd 6-18	NOEL (maternal and foetal) = 425 mg/kg bw/d			
		Syrian hamster	Gavage, gd 6-10	NOEL (maternal and foetal) = 405 mg/kg bw/d			

		SPECIES	PROTOCOL	RESULTS			
CAS NO:				2216-51-5 - L-Menthol	15356-60-2 - D-Menthol	89-78-1 - D/L-Menthol	1490-04-6 - Menthol, unspecified isomer
5.9	Specific Investigations						
5.10	Exposure Experience	Humans	Pharmaceutical properties				enhancement of lung and airway volume
		children under 1 year					Menthol applied to the nostrils or near the nose in few cases caused reflex apnea

I U C L I D Data Set

Existing Chemical	:	ID: 2216-51-5
CAS No.	:	2216-51-5
EINECS Name	:	L-Menthol
EC No.	:	218-690-9
TSCA Name	:	Cyclohexanol, 5-methyl-2-(1-methylethyl)-
Molecular Formula	:	C10H20O

Producer related part

Company	:	Bayer AG
Creation date	:	17.10.2001

Substance related part

Company	:	Bayer AG
Creation date	:	17.10.2001
Status	:	
Memo	:	ICCA Bayer AG
Printing date	:	10.06.2003
Revision date	:	
Date of last update	:	18.03.2003
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (pr ofile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1. General Information Id 2216-51-5
Date 10.06.2003

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : solid
Purity : >= 99.7
Colour : white
Odour : minty

Remark : maximum of 0.3 %: other menthol isomers
Flag : Critical study for SIDS endpoint
07.08.2002

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

(-)-Menthol

Flag : Critical study for SIDS endpoint
17.10.2001

1-Menthol (natural)

Flag : Critical study for SIDS endpoint
17.10.2001

5-METHYL-2-(1-ETHYLETHYL)-CYCLOHEXANOL

Flag : Critical study for SIDS endpoint
03.06.2002

Cyclohexanol, 5-methyl-2-(1-methylethyl)-

Flag : Critical study for SIDS endpoint
17.10.2001

Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1R- (1alpha, 2beta, 5alpha)

Flag : Critical study for SIDS endpoint
03.06.2002 (1)

L-MENTHOL

Flag : Critical study for SIDS endpoint
03.06.2002

Levomenthol

Flag : Critical study for SIDS endpoint
17.10.2001

MENTHOL L

Flag : Critical study for SIDS endpoint
03.06.2002

Menthol, (1R, 3R, 4S)-(-)-

Flag : Critical study for SIDS endpoint
17.10.2001

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Labelling : provisionally by manufacturer/importer
Specific limits :
Symbols : Xi, , ,
Nota : , ,
R-Phrases : (38) Irritating to skin
S-Phrases : (25) Avoid contact with eyes

Flag : Critical study for SIDS endpoint
17.07.2002

1.6.2 CLASSIFICATION

Classified : provisionally by manufacturer/importer
Class of danger : irritating
R-Phrases : (38) Irritating to skin
Specific limits :
Flag : Critical study for SIDS endpoint

03.06.2002

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Wide dispersive use

Remark : L-Menthol, D/L-menthol and menthol liquid are widely used as flavoring, disinfectant and cooling compounds in confectionery products, liqueurs, chewing gums, toothpastes, cosmetics and common cold ointments and medications and veterinary activities
Flag : Critical study for SIDS endpoint
23.07.2002

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Remark : L-Menthol is produced via reaction of m-cresol with propen to thymol, and hydrogenation of thymol, resulting in 4 isomers: D/L-neomenthol, D/L-neoisomenthol, D/L-menthol and D/L-isomenthol. D/L-menthol is isolated by fractional distillation. To produce L-menthol, D/L-menthol is transesterificated with methylbenzoate and further manufactured.
03.06.2002

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : other: Registry of Toxic Effects of Chemical Substances, NIOSH, USA
Additional information :

03.06.2002 (2)

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 5
Date of search : 01.09.2001

Remark : Human Health: last literature search September 2001: CAS number search in external and internal databases, e.g. Biosis, Embase, Toxline, Scisearch
Flag : Critical study for SIDS endpoint
10.07.2002

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 14.01.2002

Remark : Physico-chemical properties / Environment / Ecotoxicology : last literature search January 2002: CAS number search in external and internal databases, e.g. HSDB, Aquire.
Flag : Critical study for SIDS endpoint
29.07.2002

1.13 REVIEWS

Memo : Menthol: Its Origins, Chemistry, Physiology and Toxicological Properties

Flag : Critical study for SIDS endpoint
03.06.2002 (1)

2.1 MELTING POINT

Value : ca. 42 °C
Sublimation :
Method : other: PIQ-Method DS061 modified
Year : 2000
GLP :
Test substance : other TS: purity > 99.7 %

Flag : Critical study for SIDS endpoint
18.03.2003 (2) (3)

Value : 41 - 43 °C
Sublimation :
Method :
Year :
GLP : no data
Test substance : other TS: no data

14.03.2003 (4) (5)

Value : 43 °C
Sublimation :
Method :
Year : 1993
GLP : no data
Test substance :

14.03.2003 (1)

Value : 35 - 36 °C
Sublimation :
Method :
Year : 1992
GLP : no data
Test substance : other TS: not clearly identified, cf. Remark

Remark : The reference notes both CAS-No. 2216-51-5 and 15356-70-4 (former CAS number for 89-78-1)
14.03.2003 (6)

2.2 BOILING POINT

Value : 212 °C at
Decomposition :
Method :
Year : 1954
GLP : no
Test substance : no data

Flag : Critical study for SIDS endpoint
14.03.2003 (4) (7) (5)

Value : ca. 216 °C at 1013 hPa
Decomposition :
Method :

Year : 2002
GLP :
Test substance : other TS: purity > 99.7 %

18.03.2003 (2)

Value : 103 - 105 °C at 21.3 hPa
Decomposition :
Method :
Year : 1992
GLP :
Test substance : other TS: see Remark

Remark : The reference notes both CAS-No. 2216-51-5 and 15356-70-4 (former CAS number for 89-78-1)
18.03.2003 (6)

2.3 DENSITY

Type : density
Value : .89 g/cm³ at 20 °C

Flag : Critical study for SIDS endpoint
14.03.2003 (2) (4) (5)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .085 hPa at 25 °C
Decomposition :
Method :
Year : 1954
GLP : no
Test substance : no data

Remark : extrapolated to 25 °C
Flag : Critical study for SIDS endpoint
14.03.2003 (4) (7) (8)

Value : < .1 hPa at 20 °C
Decomposition :
Method :
Year : 2002
GLP : no data
Test substance : other TS: purity > 99.7 %

18.03.2003 (2)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water

Log pow : 3.4 at °C
pH value :
Method : other (measured)
Year : 1999
GLP : no data
Test substance : other TS: purity not reported but HPLC applied

Method : Reversed-phase high-performance liquid chromatography
Flag : Critical study for SIDS endpoint
14.03.2003 (9)

Partition coefficient : octanol-water
Log pow : 3.3 at °C
pH value :
Method : other (measured)
Year :
GLP :
Test substance :

Remark : The reference "MITI (1992)" notes both CAS-No. 2216-51-5 and 15356-70-4 (former CAS-No. for 89-78-1).
The Chemical Safety Data Sheet "Menthol L H&R Cryst", Haarmann & Reimer GmbH gives no information on the method. The HSDB is secondary literature.
18.03.2003 (2) (4) (6)

Partition coefficient : octanol-water
Log pow : 3.38 at °C
pH value :
Method : other (calculated): SRC-KOWWIN v. 1.66
Year : 2002
GLP :
Test substance :

18.03.2003 (10)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 431 mg/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: flask method
Year : 1992
GLP :
Test substance :

Flag : Critical study for SIDS endpoint
06.03.2003 (11) (2)

Solubility in : Water

Value	:	456 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	1992
GLP	:	no data
Test substance	:	no data

18.03.2003 (12)

Solubility in	:	Water
Value	:	490 mg/l at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	1992
GLP	:	
Test substance	:	other TS: see Remark

Remark : The reference notes both CAS-No. 2216-51-5 and 15356-70-4 (former CAS number for 89-78-1)

18.03.2003 (6)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	> 100 °C
Type	:	closed cup
Method	:	
Year	:	
GLP	:	no data
Test substance	:	other TS: purity > 99.7 %

18.03.2003 (2)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Refraction index (nD): 1.458 at 25 °C

03.06.2002 (5)

Memo : alpha D18 = - 50 degree (10 % alc. solution)

03.06.2002 (5)

Memo : alpha D20 = - 50.2 degree

03.06.2002 (1)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Method	:	structure estimation method
Result	:	Rate constant: k = 2.4 E -11 cm3/molecule/sec at 25 degrees C; considering an atmospheric OH-radical concentration of 5 E5 OH-radicals/cm3, the half-life is about 16 h
Reliability	:	(2) valid with restrictions accepted calculation procedure
Flag	:	Critical study for SIDS endpoint

29.07.2002 (13) (4)

3.1.2 STABILITY IN WATER

Deg. product	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	
Result	:	volatilization half-lives for a model river (1 m deep, flow-rate 1 m/sec, wind velocity 3 m/sec) and a model lake (1 m deep, flow-rate 0.05 m/sec, wind velocity 0.5 m/sec) are estimated to be 2 and 18 days
Reliability	:	(2) valid with restrictions accepted calculation procedure
Flag	:	Critical study for SIDS endpoint

29.07.2002 (4)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	volatility
Media	:	water - air
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	
Year	:	2003

Result : Based on a water solubility of 431 mg/l and a vapour pressure of 8.5 Pa (see chapter 2), the Henry's law constant is calculated to be 3.08 Pa x m3/mol
Reliability : (2) valid with restrictions
Generally accepted calculation method
Flag : Critical study for SIDS endpoint
14.03.2003 (14)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2003

Result : Air: 43.2 %
Water: 40.6 %
Soil: 8.0 %
Sediment: 8.1 %
Biota: 0.005 %
Test condition : Base data for calculation:
temperature: 20 °C
molar mass: 156.27 g/mol
vapour pressure: 8.5 Pa
water solubility: 431 g/m3
log Kow: 3.4
environmental compartments:
- air: 6*10^9 m³, 1.2 kg/m³
- water: 7*10^6 m³, 1000 kg/m³
- soil: 4.5 *10^4 m³, 1500 kg/m³, 2 % org. C
- sediment: 2.1*10^4 m³, 1300 kg/m², 5 % org. C
- susp. sediment: 35 m³, 1500 kg/m³, 16.7 % org. C
- aerosol: 0.12 m³, 1500 kg/m³
- aquatic biota: 7 m³, 1000 kg/m³, 5 % fat
Reliability : (2) valid with restrictions
Generally accepted calculation method
Flag : Critical study for SIDS endpoint
14.03.2003 (14)

Media : water - soil
Method : other (calculation)
Year :

Result : Using the equation log Koc = 0.52 log Kow + 1.02 and based on a log Kow of 3.40 (see chapter 2) a Koc value of 614 can be calculated for the distribution between the organic phase of soil and pore water
Reliability : (2) valid with restrictions
Generally accepted calculation method
Flag : Critical study for SIDS endpoint
07.03.2003 (15)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic

Inoculum	:	activated sludge, domestic
Concentration	:	.84 mg/l related to Test substance related to
Contact time	:	28 day(s)
Degradation	:	93 (±) % after 21 day(s)
Result	:	readily biodegradable
Kinetic of testsubst.	:	0 day(s) 0 % 7 day(s) 64 % 14 day(s) 90 % 21 day(s) 93 % 28 day(s) 92 %
Control substance	:	Acetic acid, sodium salt
Kinetic	:	7 day(s) 86 % 14 day(s) 100 %
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	2003
GLP	:	yes
Test substance	:	other TS: purity 99.963 %
Remark	:	Measured degradation of acetic acid was 103 % after 14 d
Result	:	The biodegradation in the toxic controls exceeded 25 %. According to the guideline, the test substance is not toxic to the medium
Test condition	:	Two concentrations of the test substance (0.84 mg/l, 2 mg/l) a control (blank medium), an inoculum activity control (sodium acetate) and a toxicity control (sodium acetate and L-menthol) were prepared with mineral medium, saturated with oxygen, placed in approximately 300 ml BOD bottles, and incubated for 28 d in the dark at about 20 °C, except for the activity control and the toxicity control which were incubated for 14 d. To prevent leakage of gases out of the BOD bottles the bottles were incubated upside down. The O2 concentration was determined with an oxygen electrode after 0, 7, 14, 21, and 28 d of incubation
Reliability	:	(1) valid without restriction Guideline study in accordance with the OECD principles of GLP
Flag	:	Critical study for SIDS endpoint

05.03.2003 (16)

Type	:	aerobic
Inoculum	:	activated sludge, domestic
Concentration	:	2 mg/l related to Test substance related to
Contact time	:	28 day(s)
Degradation	:	79 (±) % after 28 day(s)
Result	:	readily biodegradable
Kinetic of testsubst.	:	0 day(s) 0 % 7 day(s) 64 % 14 day(s) 76 % 21 day(s) 77 % 28 day(s) 79 %
Control substance	:	Acetic acid, sodium salt
Kinetic	:	7 day(s) 86 % 14 day(s) 100 %
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	2003
GLP	:	yes
Test substance	:	other TS: purity 99.963 %
Remark	:	Measured degradation of acetic acid was 103 % after 14 d

Result	:	The biodegradation in the toxic controls exceeded 25 %. According to the guideline, the test substance is not toxic to the medium
Test condition	:	Two concentrations of the test substance (0.84 mg/l, 2 mg/l) a control (blank medium), an inoculum activity control (sodium acetate) and a toxicity control (sodium acetate and L-menthol) were prepared with mineral medium, saturated with oxygen, placed in approximately 300 ml BOD bottles, and incubated for 28 d in the dark at about 20 °C, except for the activity control and the toxicity control which were incubated for 14 d. To prevent leakage of gases out of the BOD bottles the bottles were incubated upside down. The O2 concentration was determined with an oxygen electrode after 0, 7, 14, 21, and 28 d of incubation
Reliability	:	(1) valid without restriction Guideline study in accordance with the OECD principles of GLP
Flag	:	Critical study for SIDS endpoint

05.03.2003 (16)

Type	:	anaerobic
Inoculum	:	activated sludge
Deg. product	:	
Method	:	
Year	:	1995
GLP	:	no
Test substance	:	other TS: (-)-menthol, analytical grade

Method	:	Determination of microbial growth under nitrate-reducing conditions
Result	:	Microbial growth was observed within 10 days to 3 weeks; no quantification of growth or degree of degradation
Test condition	:	Enrichment cultures were prepared using 2 ml sewage sludge, 400 ml mineral salt medium, and 200 mg TS with 4 ml HMN as carrier, atmosphere N2/CO2. Incubation at 28 degrees C in the dark.
Reliability	:	(2) valid with restrictions No standard test procedure, but in accordance with generally accepted scientific standards

05.03.2003 (17)

Type	:	aerobic
Inoculum	:	other: Rhizoctonia solani
Contact time	:	
Degradation	:	(±) % after
Result	:	other: Biotransformation
Deg. product	:	yes
Method	:	other: Growth medium
Year	:	2001
GLP	:	no
Test substance	:	no data

Result	:	Almost all of the substrate was consumed in 3 days incubation. The major metabolite was determined to be 6-Hydroxymenthol.
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles.

05.03.2003 (18)

Type	:	aerobic
Inoculum	:	other: activated sludge, inoculum from effluent of a laboratory facility run with municipal sewage
Concentration	:	20 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	28 day(s)
Degradation	:	100 (±) % after 21 day(s)

Result	:	readily biodegradable
Kinetic of testsubst.	:	0 hour(s) 0 % 7 day(s) 53 % 14 day(s) 93 % 21 day(s) 100 % 28 day(s) 100 %
Control substance	:	Aniline
Kinetic	:	28 day(s) 100 % %
Deg. product	:	
Method	:	OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year	:	1992
GLP	:	yes
Test substance	:	other TS: 99.9%
Remark	:	Method according to guideline: 79/831 EWG. Annex V, Part C (updated: July 1990), Method C.4-B: modified OECD Screening-Test
Test condition	:	mineral salt medium; 20-24 degrees C
Reliability	:	(3) invalid Possible loss of test substance by volatilisation

05.03.2003 (19)

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100 mg/l related to Test substance related to
Contact time	:	28 day(s)
Degradation	:	0 (±) % after
Result	:	
Deg. product	:	
Method	:	other: corresponding to OECD 301C
Year	:	1992
GLP	:	
Test substance	:	
Remark	:	The reference notes both CAS-No. 2216-51-5 and 15356-70-4 (former Cas-No for 89-78-1)
Test condition	:	sludge concentration 30 mg/l
Reliability	:	(3) invalid Biodegradation possibly affected by toxicity of the substance at the concentration tested

05.03.2003 (6)

Deg. product	:	
Method	:	
Year	:	1999
GLP	:	
Test substance	:	other TS: (-)-menthol
Remark	:	Based on the previous literature it can be stated that the bacteria species: Thauera terpenica, strain 21Mol may degrade L-menthol.
Reliability	:	(4) not assignable Review. No experimental data is given

05.03.2003 (20)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	at °C
Concentration	:	
Elimination	:	
Method	:	other: corresponding to OECD guideline 305C
Year	:	1992
GLP	:	
Test substance	:	no data
Remark	:	The reference notes both CAS-No. 2216-51-5 and 15356-70-4 (former CAS-No. for 89-78-1)
Result	:	BCF: <0.5 - 15 l/kg at 0.2 mg/l BCF: <4.6 - 11 l/kg at 0.02 mg/l
Test condition	:	flow-through system; 25 degrees C; O2 6-8 mg/l; 15-20 fish/level; exposure period 6-8 weeks
Reliability	:	(2) valid with restrictions Test procedure according to guideline without detailed documentation
Flag	:	Critical study for SIDS endpoint

05.03.2003 (6)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	18.9
EC50	:	18.4
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other
Year	:	1985
GLP	:	no
Test substance	:	other TS: purity 99%
Method	:	Fish (30 d old; mean length 17.6 mm; mean weight 0.079 g) exposed in Lake Superior water; 5 TS concentrations in the range of 4.39 to 24.6 mg/l tested (plus control); number of dead fish recorded every 24 h; observations of fish behaviour and body morphology at regular intervals; TS analysis by GLC
Result	:	Affected fish lost schooling behaviour, were hyperactive and underreactive to external stimuli. They had increased respiration, were darkly colored and lost equilibrium prior to death. The 96-h samples were omitted due to unrealistic analytical results.
Test condition	:	24.4 degrees C; dissolved oxygen 6.8 mg/l; hardness 44.5 mg CaCO3/l; alkalinity 44.5 mg CaCO3/l; pH 7.7
Reliability	:	(1) valid without restriction Test procedure comparable to standard method and in accordance with general accepted scientific standards; detailed documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

21.12.2001 (21)

Type	:	Static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	13.2
LC50	:	15.6
LC100	:	18.4
Limit test	:	no
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1992
GLP	:	yes
Test substance	:	other TS: 99.9 %
Remark	:	LC50-value: geom. mean of LC0 and L C100. LC50 can be calculated with probit analysis. In this test the LC50 obtained with probit analysis is identical to the geometric mean. All LC values are based on measured concentrations
Result	:	RESULTS: EXPOSED - Nominal/measured concentrations: nominal (mg/l) 7.8 11 16 22 31 measured (mg/l) (0 h) 6.6 9.5 13.8 19.8 27.5 (mg/l) (24 h) 6.7 8.9 13.5 18.6 25.9 (mg/l) (48 h) 6.0 8.7 13.3 18.2 (mg/l) (72 h) 5.5 8.4 12.9 17.1

(mg/l) (96 h) 5.2 8.0 12.5
- Effect data (Mortality):
Mortality, visible abnormities of fishes
- Concentration / response curve:
There were no dead fishes in tanks with concentration: 7.8, 11 and 16 mg/l.
22 mg/l
hours (h) 0 2 24 48 72 96
Mortality (%) 0 0 50 50 100
31 mg/l
Mortality (%) 0 100
- Effect concentration vs. test substance solubility:
Undissolved substance particles remained on the water surface of all test media.
- Other effects:
Temperature degradation during testing process was higher than 1 °C.
RESULTS: CONTROL: No dead fish
- Number/percentage of animals showing adverse effects:
7.8 mg/l
hours (h) 2 24 48 72 96
7.8 mg/l - - - - -
11 mg/l 100%A 100%A 100%A 100%A 100%A
16 mg/l 100%A 100%A 80%A 80%A 100%A
20%B 20%B
22 mg/l 100%A 50%B 50%B 10%B 10%B
- Nature of adverse effects:
A: slow and inactive swimming behaviour
B: loss of equilibrium (uncontrolled movements)

Reliability : (2) valid with restrictions
Guideline Study; effective concentrations decreased below 80% of the nominal during the test period

Flag : Critical study for SIDS endpoint

05.03.2003 (22)

Type : other: Static or semi-static
Species : Oryzias latipes (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : 26
Method : other: according to JIS K 0102-1986-71 (Japanese Industrial Standard)
Year : 1992
GLP :
Test substance : no data

Remark : TS unclear. The reference notes both CAS -No. 2216-51-5 and 15356-70-4
Test condition : 25 +- 2 degrees C; 10 fish/level
Reliability : (2) valid with restrictions
Test procedure according to guideline without detailed documentation

Flag : Critical study for SIDS endpoint

07.03.2002 (6)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC0 : 11.35
EC50 : 26.6

EC100	:	92.35
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.2
Year	:	2002
GLP	:	yes
Test substance	:	other TS: purity 99.985 % according to H & R GmbH
Method	:	Method for chemical analysis: GC analysis Limit of quantitation: 0.5 mg/l Recovery rate: 102% ± 5% Sampling schedule of chemical analysis Stock solution: at 0 h Control: at 0 and 48 h Test concentrations: at 0, 24 and 48 h
Result	:	The results are expressed in terms of nominal concentrations (at 24 h), and in terms of mean measured concentrations (at 48 h). Measured concentrations ranged from 93.1 - 104 % of nominal values at 0 h, and from 81.3 - 91.6 % of nominal values at 48 h, respectively. After 24 h EC0 was 25 mg/l, EC50 37.7 (lower/upper 95% confidence limit: 18.8/75.6) mg/l and EC100 100 mg/l After 48 h EC0 was 11.35 mg/l, EC50 26.6 (14.7/48.2) mg/l and EC100 92.35 mg/l Highest test concentration resulting in 0 % immobilisation (EC0 48 h): 11.35 mg/l Lowest test substance concentration resulting in 100 % immobilisation (EC100 48 h): 92.35 mg/l
Test condition	:	Test species: - A population of parthenogenetic females of synchronized age structure is maintained since more than 15 years in the test facility under constant temperature conditions (20 +/- 1 °C) at a 16/8 h light-dark photoperiod (illumination: < 1000 lux) - The culture water (so-called 'M4 medium') is partly renewed once a week. The Daphnia are exclusively fed with unicellular green algae (Desmodesmus subspicatus) ad libitum - Mortalities of parent Daphnia during the culture period are recorded daily in a semi-quantitative way. The neonates are separated from their parent Daphnia by filtration prior to the acute test Culture and dilution water: - Reconstituted water (so-called 'M4 medium', originally described in Water Research 24 (9): 1157 - 1167), prepared according to the recommendations of Bundesgesundheitsamt Berlin. This standard dilution water is used for both, the maintenance of the test animals and the preparation of stock and test solutions of the test substance - The total hardness of the dilution water, measured at test start, was 13.8°dH (= 246.3 mg/l CaCO3) Test substance: - The test substance was pulverized. - A stock solution was prepared to give the desired series of test concentrations. To achieve this 119.9 mg of the test substance were added to 1 litre of dilution water and treated for 1 hour in an ultrasonic bath and afterwards stirred for 24 hours on a magnetic stirrer. - Finally undissolved particles of the test substance were removed by filtration using a folded filter of pore size 7 - 12 µm. Exposure conditions: - Test vessels: holding 10 neonates in 20 ml of test medium - Experimental design: 6 test concentrations plus 1 control 10 neonates per vessel, 2 replicates per concentration/control, no feeding during the exposure period, static system - Method of initiation: neonates were placed in prepared media

- Photoperiod: 16 h light/8 h dark
- Temperature: 20 +/- 1 °C
- Aeration: none
- Test concentration/s (nominal): 3.2, 6.3, 12.5, 25, 50 and 100 mg/l
- Method of administration: stock solution
- Medium renewal: none
- Duration of exposure: 48 h
- Criteria of effects: The criterion of adverse effects used in this study was the substance-induced alteration of the normal mobility behaviour and the loss of locomotory actions of the neonates, observed at 24 and 48 h

Reliability : (1) valid without restriction
Guideline study in accordance with the OECD principles of GLP

Flag : Critical study for SIDS endpoint
21.02.2003 (23)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	9.65
LOEC	:	18.75
EC50	:	21.4
Limit test	:	
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.3
Year	:	2002
GLP	:	yes
Test substance	:	other TS: purity 99.985 % according to H & R GmbH

Method : Chemical analysis method: GC analysis
Limit of quantitation: 0.5 mg/l
Recovery rate: 105 % ± 5 %
Sampling schedule of chemical analysis
- Stock solution: at 0 h
- Control: at 0 and 72 h
- Test concentrations: at 0 and 72 h

Expression of results
· Cell density measurements in the test and control cultures are tabulated according to the concentration of test substance and the time of measurement
· Growth curves are plotted for each test concentration and control
· The area under the growth curve [b] is calculated for each test culture
· The growth rate [r] is calculated for each test culture
· The percentage inhibition of both, growth [b] and growth rate [r], is calculated for each test concentration
· If possible, EC 50 values for both, growth [b] and growth rate [r], are calculated by probit analysis
· If possible, NOEC and LOEC of both, growth [b] and growth rate [r], are determined by a multisample comparison (according to DUNNETT 1955, 1964)

Result : b: growth
r: growth rate
Results (72 h)[mg/l]:
EbC50: 20
ErC50: 21.4
NOEC [b]: 9.65

LOEC [b]: 18.75
NOEC [r]: 9.65
LOEC [r]: 18.75
All results are expressed in terms of mean measured concentrations. Measured concetrations ranged from 92.0 - 102.5 % of nominal values at 0 h, and from 88.0 - 105 % of nominal values at 72 h, respectively.

Test condition : Test species:
- Name: Desmodesmus subspicatus; former name: Scenedesmus subspicatus
- Source: Non-axenic strain of the test species obtained from 'The Collection of Algal Cultures' of the Institute of Plant Physiology at the University of Göttingen (Germany)
- Maintenance of stock cultures: Exponentially-growing stock cultures are maintained in the test facility under constant temperature conditions (23 +/- 2°C) at a light intensity in the range 60 - 120 µE m-2 s-1 (measured in the range 400 to 700 nm using a spherical quantum flux meter). The nutrient medium (according to BRINGMANN & KÜHN 1977) is renewed once a week. Cell density measurements are made using a microcell counter
- Preparation of pre-cultures: Pre-cultures are set up three days before the start of a test. They are grown under identical exposure conditions as the stock cultures, except from the use of a different nutrient medium (annex 1)
- Test cultures: The algal inocula for a test are taken from an exponentially-growing pre-culture and are mixed with the nutrient medium (annex 1) to make up to a final cell density of about 10000 cells/ml in the test medium.
Pretreatment of the test substance
- The test substance was pulverized
- A stock solution was prepared to give the desired series of test concentrations. To achieve this 124.9 mg of the test substance were added to 1 litre of dilution water and treated for 1 h in an ultrasonic bath and afterwards stirred for 24 h on a magnetic stirrer
Exposure conditions
- Test vessels: 300 ml Erlenmeyer flasks with stoppers
- Culturing apparatus: light chamber in which a temperature in the range 21 °C to 25 °C can be maintained at +/- 2 °C, and continuous uniform illumination is provided in the spectral range 400 to 700 nm
- Light intensity: at the average of the test solutions, a light intensity in the range 60 to 120 µE m-2 s-1
- Cell density measurements: microcell counter
Experimental design:
- 4 Test concentrations plus 1 control, 3 replicates per concentration, 6 replicates per control, initial cell density in the test cultures approximately 10000 cells/ml additionally highest test concentration without algae
- Test concentration/s (nominal): 5.0, 10, 20 and 40 mg/l
- Method of administration: stock solution
- Duration of exposure: 72 h
- Criteria of effects: The criteria of adverse effects used in this study were the substance-induced inhibition of growth [b] and growth rate [r], respectively, of the algal population.

Reliability : (1) valid without restriction
Guideline study in accordance with the OECD principles of GLP

Flag : Critical study for SIDS endpoint
21.02.2003 (24)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : activated sludge
Exposure period :

Unit	:	mg/l
EC10	:	51
EC50	:	237
Analytical monitoring	:	no
Method	:	ISO 8192 "Test for inhibition of oxygen consumption by activated sludge"
Year	:	1992
GLP	:	yes
Test substance	:	other TS: 99.9 %
Remark	:	direct weight
Reliability	:	(2) valid with restrictions Guideline Study, incubation period not reported
Flag	:	Critical study for SIDS endpoint

07.03.2002 (25)

Type	:	
Species	:	aerobic microorganisms
Exposure period	:	48 hour(s)
Unit	:	
Method	:	Test of antimicrobial activity of the essential oil of Calamintha nepeta and its main constituents against bacteria and funghi (Listeria momocytogenes, Bacillus cereus, Salmonella veneziana, Salmonella paratyphi B, Salmonella typhimulium, Fusarium monoliforme, Bortrytis cinera, Aspergillus niger, Pyricularia oryzae). Bacteria and funghi cultures were placed on the surface of a culture medium. 20 µl menthol solution (dissolved 1:1 in Tween 80) were placed on paper disks which were placed in the petri dishes and incubated at 37 degrees C.
Result	:	Menthol showed no activity against any of the tested microorganisms.
Reliability	:	(3) invalid Unsuitable test system. Tween 80 was present at a high concentration.

26.07.2002 (26)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Species	:	other: larvae of Ostrinia nubilalis (Lepidoptera: Pyralidae; European corn borer)
Endpoint	:	other: survival and growth
Exposure period	:	6 day(s)

Unit	:	
Method	:	
Year	:	1999
GLP	:	no
Test substance	:	other TS: l-Menthol, laboratory chemical
Method	:	Two different chemical application m ethods conducted: dripping the solution onto the solidified artificial diet (on-diet test) or mixing the solution in the diet before it solidified (in-diet test). In each test cup 1 neonate larva was placed on the diet. On-diet test: 199 larvae tested at 6 doses In-diet test: 160 larvae tested at 5 doses
Result	:	On-diet test: LC50 = 2.35 mg per cup (1st-instar) In-diet test: LC50 = 17.4 mg per cup (2nd-instar)
Test condition	:	25 +- 2 degrees C; photoperiod 14:10 (light:dark) hours
Reliability	:	(3) invalid No conclusion from environmental concentrations to effects possible

22.12.2001 (27)

Species	:	other: Aspergillus flavus
Endpoint	:	
Exposure period	:	5 day(s)
Unit	:	
Method	:	
Year	:	1998
GLP	:	no
Test substance	:	other TS: menthol from Mentha piperita
Method	:	Maize grain protection assay against A. flavus
Result	:	Total inhibition of A. flavus
Test condition	:	Maize grains immersed in essential oil, dried, and sprayed with fungal spore suspension
Reliability	:	(3) invalid No conclusion from environmental concentrations to effects possible

22.12.2001 (28)

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males :
Females :
Doses
Males : 800 mg/kg bw
Females :
Vehicle : other: 1% methyl cellulose solution
Route of administration : gavage
Exposure time : 20 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product : yes
Method : other: analysis of metabolites in urine
Year : 1988
GLP : no data
Test substance : other TS: L-menthol, purity not

Result : Metabolites in urine (not further quantified)
p-menthane-3,8-diol (major),
p-menthane-3,9-diol,
3,8-oxy-p-menthane-7-carboxylic acid
3,8-dihydroxy-p-menthane-7-carboxylic acid (major).

Proposed major transformation:
hydroxylation at the C-8 position followed by oxidation of C-1 methyl group to a carboxylic group; the secondary carbon atoms of the ring seem to be resistant to hydroxylation.

Test condition : ANIMALS:
rat strain: IISc
No. of animals not specified.
Control rats were given the vehicle only.

Urine was collected daily from control and treated rats and maintained at 0-4 °C.
Urine was acidified (pH 3-4) before analysis.
Substances were isolated by silica gel chromatography with hexane/ethyl acetate as solvent system. Analysis of metabolites were done by gas chromatographic measurments and protone NMR spectra.

Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
25.02.2003 (29)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males : 12

Females :
Doses
Males : 800 mg/kg bw/d
Females :
Vehicle : other: 1 % methyl cellulose solution
Route of administration : gavage
Exposure time : 7 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method : other: hepatic drug metabolism study
Year : 1988
GLP : no data
Test substance : other TS: L-menthol, purity not

Result : Results in detail (% of control):
days of treatment/cyt. P-450/cyt. b5/ NADPH-cyt. c reductase;
1/44%+/9%+/69%+
3/82%+/14%+/80%+
5/49%+/5%+/50%+
7/17%+/12%-/35%+

Repeated oral administration of 800 mg/kg/day of L-menthol to rats for 3 days resulted in the increase of both liver microsomal cytochrome P-450 content and NADPH-cytochrome c reductase activity by nearly 80 %. Further treatment (for 7 days total) reduced their levels considerably, although the levels were still higher than the control values. Both cytochrome b5 and NADH-cytochrome c reductase levels were not significantly changed during the 7 days of treatment.

Test condition : rat strain: IISc
No. of animals: 12 per group
Exposure: 1, 3, 5 or 7 days

Liver was removed, perfused and minced 24 hours after administration of the final dose. Cytochrome P-450 and b5 contents were determined by the method of Omura and Sato (J. Biol. Chem. 239, 1964). The NADPH-cytochrome c reductase activity was measured at 550 nm. In NADH-cytochrome c reductase assays, NADH was substituted for NADPH.

Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
25.02.2003 (29)

In Vitro/in vivo :
Type : Metabolism
Species : other: rat liver microsomes
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other

Year : 1988
GLP : no data
Test substance : other TS: L-menthol, purity not

Result : Rat liver microsomes readily converted L-menthol to p-menthane-3,8-diol (II) in the presence of NADPH and O2 (reaction is NADPH dependent; NADH showed no synergistic effect and could not support the reaction alone). This activity was significantly higher in microsomes obtained from PB-induced rats than from control microsomal preparations, whereas 3-MC-induced microsomes failed to convert L-menthol to compound II in the presence of NADPH and O2. PB-induced microsomal hydroxylation of L-menthol was inhibited to a significant extent by CO, SKF 525-A, metyrapone, cytochrome c, and p-chloromercuribenzoate, indicating the possible involvement of the cytochrome P-450 system in the hydroxylation reaction.

Test condition : Rats (strain: IISc, 4-6 animals per group) were treated with phenobarbital (PB, 80 mg/kg bw) or 3-methylcholanthrene (3-MC, 25 mg/kg bw). Investigations on the hydroxylation activity of L-menthol were perfomed with the isolated liver microsomes.

Examinations:
- Co-factor specificity of L-menthol hydroxylase activity;
- Effect of PB- and 3-MC treatment on the L-menthol hydroxylase activity;
- Effect of inhibitors (CO, SKF 525-A, Metyrapone, Cytochrome c, p-Chloromercuribenzoate, sodium azide) on hydroxylation of L-menthol;

Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
25.02.2003 (29)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males : 3
Females :
Doses
Males : 500 mg/kg bw
Females :
Vehicle : other: trioctanoin
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method : other
Year : 1994
GLP : no data
Test substance : other TS: [3-3H]-L-Menthol, puri

Result : In intact rats, some 71% of the dose was recovered in 48 hours with approximately equal amounts in urine and feces. 74 % of the dose was recovered from bile duct-cannulated rats, with 67% in the bile and 7% in

the urine.

Excretion of radioactivity after oral dosing of 500 mg/kg of [3H]-Thymidin:
% [3H] dose excreted in intact rats:
Time period/Urine (%)/Feces (%)/Total (%)
0-24 hr/18.8/26.6/45.5
24-48 hr/19.0/7.3/26.3
Total/37.8/33.9/71.8
% [3H] dose excreted in bile duct-cannulated rats:
Time period/Bile (%)/Urine (%)/Total (%)
0-24 hr/66.9/7.3/74.2

Degradation products are mono- and di-hydroxymenthols and carboxylic acids, excreted in part as glucuroic acid conjugates

Metabolites:
Urine: p-menthane-3,8-diol (major), p-menthane-3,9-diol (minor), 3,8-dihydroxy-p-menthane-7-carboxylic acid (major urinary), mentholglucuronide (minor)

Bile: Mentholglucuronide (major),

Following structures of supposed metabolites are principally based on GC-MS measurements:
3-hydroxy-p-menthane-9-carboxylic acid (stereoisomers at C-8 - minor - very minor urinary),
3-hydroxy-p-menthane-7-carboxylic acid (isomers – major urinary metabolites), p-menthane-3,7,8-triol (minor urinary).

Test condition : Animals: intact and bile duct-cannulated Fischer 344 rats (3 per group)

Excreta collection: intact rats: urine and feces 24 and 48 hrs after dosage bile duct-cannulated rats: bile samples were collected on ice (0-2, 2-4, 4-6 and 6-24 hrs) urine samples: 0-24 hrs).

Administration: 500 mg/kg 3-Tritium-L-Menthol (128 µCi/kg) were administered as a single dose.

Metabolites in urine and bile were analyzed by TLC, solid phase extraction, GLC, and GC-MS.

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

25.02.2003 (30)

In Vitro/in vivo : In vivo
Type : Excretion
Species : Rabbit
Number of animals
Males :
Females : 4
Doses
Males :
Females : 1000 mg/kg bw
Vehicle : other: warm water emulsion
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:

2nd.:
3rd.:

Toxic behaviour :
Deg. product :
Method :
Year : 1938
GLP :
Test substance : other TS: L-Menthol, no further

Result : After a single oral administration of 1000 mg/kg bw, 48% of the dose were excreted as L-menthol glucuronides
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
25.02.2003 (31)

In Vitro/in vivo : In vivo
Type : Distribution
Species : human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 2001
GLP :
Test substance : other TS: peppermint oil

Result : Mean maximum plasma concentration of menthol were 1.2 and 1.5 mg/ml at 1.7 or 3 hours after oral administration of a immediate release formulation or an enteric coated formulation.
Test condition : 16 healthy male volunteers received 180 mg peppermint oil after a 10 hours fast. Menthol content was about 44 %.
Plasma levels were measured by GC/MS.
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. However, test substance was peppermint oil with only 44 % menthol content.
25.02.2003 (32)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : Human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :

Result : After a daily dose of 750 mg l-menthol for a total of 8 days to two human volunteers 17-38% menthol was recoverd as urinary menthyl glucuronide within 24 hours. Urine was first collected 3 days after dosage with l-menthol started.
Reliability : (2) valid with restrictions

limited documenta tion

Flag : Critical study for SIDS endpoint
05.03.2003 (33)

In Vitro/in vivo :
Type :
Species : other: for further data see chapter 5.11
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :

Reliability : (2) valid with restrictions
05.03.2003

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 2615 mg/kg bw
Species : rat
Strain : Wistar
Sex : female
Number of animals : 10
Vehicle : peanut oil
Doses : 1000, 2000, 2500, 3000, 3500 and 4000 mg/kg bw
Method : other: see test conditions
Year : 1974
GLP : no
Test substance : other TS: l-menthol H&R

Result : MOR TALITY:
- Time of death: 1-3 days after application
- Number of deaths at each dose:
dose (mg/kg)/number of deaths
1000/0/10
2000/3/10
2500/4/10
3000/6/10
3500/7/10
4000/10/10
CLINICAL SIGNS: narcotic status (no data available on exposure level at which the clinical signs were observed)

Test condition : ADMINISTRATION:
- Volume administered or concentration: 10-20 ml/kg
- Post dose observation period: 14 days
EXAMINATIONS:
deaths, clinical signs
No information on statistical methods and confidence limts.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: No information on statistical methods and confidence limits.

Flag : Critical study for SIDS endpoint
06.08.2002 (34)

Type : LD50
Value : = 2426 mg/kg bw
Species : rat
Strain : Wistar
Sex : female
Number of animals : 10
Vehicle : peanut oil
Doses : 1000, 2000, 2400, 2700, 3000 mg/kg bw
Method : other
Year : 1974
GLP : no
Test substance : other TS: menthol brazilian

Result : MORTALITY:
- Time of death: 1-3 days after application
- Number of deaths at each dose:
dose (mg/kg)/number of deaths
1000/0/10
2000/2/10
2400/4/10
2700/7/10
3000/9/10
CLINICAL SIGNS: narcotic status (no data available on exposure level at which the clinical signs were observed)

Test condition : ADMINISTRATION:
- Volume administered or concentration: 10-20 ml/kg
- Post dose observation period: 14 days
EXAMINATIONS:
deaths, clinical signs
No information on statistical methods and confidence limits.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: no inform ation on statistical methods and confidence limits.

Flag : Critical study for SIDS endpoint
01.07.2002 (34)

Type : LD50
Value : = 3300 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other
Year : 1961
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Secondary literature
24.05.2002 (35) (36)

Type : LD50
Value : = 940 mg/kg bw
Species : rat
Strain : no data
Sex : male

Number of animals	:	5
Vehicle	:	other: 0.85 % saline
Doses	:	100, 250, 500, 1000, 2000, 3000 mg/kg bw
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	other TS: menthol brazilian
Remark	:	The lower LD50 (compared to other LD50 values) may be attributed to irritant effects after bolus administration in saline.
Result	:	MORTALITY: - Time of death: dose (mg/kg)/time of deaths 500/day 6 1000/day 4 (2) day 5 (1) 2000/day 2 3000/day 1 (1) day 2 (3), day 4 (1) - Number of deaths at each dose: dose (mg/kg)/deaths 100/0 250/0 500/1/5 1000/3/5 2000/4/5 3000/5/5 NECROPSY FINDINGS: severe irritation of mucosal lining of the stomach and intestine. Observation period: 10 days
Test condition	:	TEST ORGANISMS: - Source: no data - Age: no data - Weight at study initiation: 250 g - Controls: no data ADMINISTRATION: - Volume administered or concentration: no data - Post dose observation period: 10 days EXAMINATIONS: deaths, necropsy
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: number of animals: 5 (Mutagenic evaluation study)
Flag	:	Critical study for SIDS endpoint

10.07.2002 (37)

Type	:	LD50
Value	:	= 3400 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	10
Vehicle	:	other: olive oil
Doses	:	2000, 4000 mg/kg bw
Method	:	other
Year	:	1932
GLP	:	no
Test substance	:	other TS: not further specified
Reliability	:	(4) not assignable

Documentation insufficient.

17.07.2002 (38)

Type	:	LD50
Value	:	= 4380 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	male
Number of animals	:	6
Vehicle	:	other: 0.85 % saline
Doses	:	2000, 2500, 3200, 4000, 5000 mg/kg bw
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	other TS: menthol brazilian
Result	:	MORTALITY: - Time of death: dose (mg/kg)/time 4000/day 4 5000/day 2 - Number of deaths at each dose: dose (mg/kg)/number of deaths 2000/0/6 2500/0/6 3200/0/6 4000/2/6 5000/6/6 CLINICAL SIGNS: depressed activity at day 1 (no data available on exposure levels at which the clinical signs were observed) NECROPSY FINDINGS: no gross abnormalities
Test condition	:	TEST ORGANISMS: - Source: no data - Age: no data - Weight at study initiation: 35 g - Controls: no data ADMINISTRATION: - Volume administered or concentration: no data - Post dose observation period: 8 days EXAMINATIONS: deaths, necropsy, clinical signs
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: number of animals: 6 (Mutagenic evaluation study)
Flag	:	Critical study for SIDS endpoint

17.07.2002 (39)

Type	:	other: lethal dose
Value	:	800 - 1000 mg/kg bw
Species	:	cat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other
Year	:	1926
GLP	:	no

Test substance : other TS: natural menthol, not further specified

Reliability : (4) not assignable
Documentation insufficient.

25.02.2003 (40)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Value : = 780 mg/kg bw
Species : rat
Strain : other: white rats
Sex : no data
Number of animals : 10
Vehicle : other: olive oil
Doses : 500, 600, 700, 800, 900, 1000, 1100, 1200 mg/kg bw
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1952
GLP : no
Test substance : other TS: natural menthol

Result : MORTALITY:
- Time to death: within 12 hours after application
- Number of deaths at each dose:
dose (mg/kg bw)/number of deaths
500/1/10
600/2/10
700/5/10
800/7/10
900/6/10
1000/7/10
1100/9/10
1200/10/10
CLINICAL SIGNS: imbalance, paralysis, partial to total relaxation, deep sleep with abolition of reflexes.

Test condition : TEST ORGANISMS:
- Source: no data
- Age: no data
- Weight at study initiation: 90-120 g
- Controls: no data
ADMINISTRATION:
- Volume administered or concentration: no data
- Post dose observation period: The animals were observed until deaths or until return to normal behaviour.
EXAMINATIONS:
deaths, clinical signs

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (41)

Type : LD50
Value : = 710 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1961
GLP : no
Test substance : other TS: not further specified

Remark : no data on Test conditions or further results
Reliability : (4) not assignable
Secondary literature
24.05.2002 (36)

Type : LD50
Value : = 6600 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1962
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient for assessment of reliability
25.02.2003 (42)

Type : LD50
Value : ca. 2000 mg/kg bw
Species : rabbit
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1961
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Secondary literature
17.12.2001 (36)

Type	:	LD50
Value	:	= 860 mg/kg bw
Species	:	guinea pig
Strain	:	no data
Sex	:	no data
Number of animals	:	10
Vehicle	:	other: olive oil
Doses	:	500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400 mg/kg bw
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1952
GLP	:	no
Test substance	:	other TS: natural menthol
Result	:	MORTALITY: - Time of death: 12 hours after application - Number of deaths at each dose: dose (mg/kg bw)/number of deaths 500/2/10 600/3/10 700/3/10 800/6/10 900/7/10 1000/8/10 1100/7/10 1200/6/10 1300/8/10 1400/10/10 CLINICAL SIGNS: imbalance, faccid paralysis of the back, partial to total relaxation, deep sleep with abolition of reflexes.
Test condition	:	TEST ORGANISMS: - Source: no data - Age: no data - Weight at study initiation: 280-360 g - Controls: no data ADMINISTRATION: - Volume administered or concentration: no data - Post dose observation period: the animals were observed until deaths or until normal behaviour EXAMINATIONS: deaths, clinical signs
Reliability	:	(2) valid with restrictions Limited documentation

25.02.2003 (41)

Type	:	other: LD
Value	:	= 1500 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: olive oil
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1939
GLP	:	no

Test substance : other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient for assessment
25.02.2003 (43)

Type : other: LD
Value : = 2000 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: olive oil
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1939
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient for assessment
25.02.2003 (43)

Type : other: LD
Value : > 800 mg/kg bw
Species : cat
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: not specified oil
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1926
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient.
25.02.2003 (40)

Type : other: LD
Value : = 4000 mg/kg bw
Species : guinea pig
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: olive oil
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1939
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient for assessment
25.02.2003 (43)

Type : other: LD
Value : 1000 - 2500 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: not specified oil
Doses :
Route of admin. : s.c.
Exposure time :
Method : other
Year : 1926
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient.
25.02.2003 (40)

Type : other: LD
Value : 5000 - 6000 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: not specified oil
Doses :
Route of admin. : s.c.
Exposure time :
Method : other
Year : 1926
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient.
25.02.2003 (40)

Type : other: LD
Value : = 34 mg/kg bw
Species : cat
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: alcohol with physiological saline
Doses :
Route of admin. : i.v.
Exposure time :
Method : other
Year : 1939
GLP : no
Test substance : other TS: not further specified

Test condition : Solution or suspensions, 1:1000, were prepared by diluting 2 per cent solutions of menthol in alcohol with physiological saline and were injected

at one-minute intervals into the femoral vein while blood pressure was recorded from the carotid artery.

Reliability : (4) not assignable
Documentation insufficient for assessment.

25.02.2003 (43)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	100 %
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	4
Vehicle	:	other: diethylphthalate (DEP)
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1989
GLP	:	yes
Test substance	:	other TS: menthol l H&R, HR 89/620001, purity: no data

Result :
AVERAGE SCORE
100%/50%/25%/5%/1%/Vehicle
3.0/1.6/1.0/0.3/0.0/0.0 (erythema)
2.9/2.2/0.2/0.1/0.0/0.0 (oedema)
REVERSIBILITY: yes
Day 7: 100%: 4/4 - treated sites were covered with a layer of white to white-brown scales
50%: 4/4 - thin layer of white scales
Day 14: 100%: 4/4 - treated sites were covered with white to white-brown scales, underlaying skin was intact
50%: 2/4 - treated sites showed scattered scale formation on intact skin.

Test condition :
TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer/Biberach
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss
- Age: no data
- Weight at study initiation: 2400-3000 g
- Number of animals: 4
- Controls: internal control (one part of skin)

ADMINISTRATION/EXPOSURE
- Preparation of test substance: dilutions of substance with DEP, concentrated test substance was moistened with DEP in the ratio 6:1
- Area of exposure: six different fields on back (two anterior, two centrally located and two posterior treatment sites)
- Occlusion: substance is covered with gauze packs, gauze packs were secured with a cross of 1 cm wide adhesive tape and fixed with Scanpor tape.
- Concentration in vehicle: 100, 50, 25, 5 and 1 %, Vehicle
- Total volume applied: 0.5 ml
- Postexposure period: up to 14 days
- Removal of test substance: skin was washed with luke warm water and soap

Reliability : (2) valid with restrictions
Guideline study. Purity of TS not stated

Flag : Critical study for SIDS endpoint

25.02.2003 (44)

Species	:	guinea pig
Concentration	:	other
Exposure	:	Open
Exposure time	:	14 day(s)
Number of animals	:	20
Vehicle	:	no data
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	other TS: l-menthol H&R
Test condition	:	Substance was rubbed into the skin for 30 s once daily. Substance was applied 2 x 5 days, results were taken after 14 days.
Reliability	:	(3) invalid Significant methodological deficiencies. e.g. concentration and amount of substance is unclear; lack of control experiment.

17.12.2001 (45)

Species	:	guinea pig
Concentration	:	no data
Exposure	:	Open
Exposure time	:	14 day(s)
Number of animals	:	20
Vehicle	:	no data
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	other TS: menthol brazilian
Test condition	:	Substance was rubbed into the skin for 30 s once daily. Substance was applied 2 x 5 days, results were taken after 14 days.
Reliability	:	(3) invalid Significant methodological deficiencies. e.g. concentration and amount of substance is unclear; lack of control experiment.

17.12.2001 (45)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	29 %
Dose	:	.1 ml
Exposure time	:	24 hour(s)
Comment	:	rinsed after (see exposure time)
Number of animals	:	4
Vehicle	:	other: diethylphthalate (DEP)
Result	:	slightly irritating
Classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1989
GLP	:	yes
Test substance	:	other TS: menthol l H&R, HR 89/620001 DEP, purity: no data

Result : AVERAGE SCORE
- Cornea: 0.2
- Iris: 0.0
- Conjunctivae (Redness): 0.6
- Conjunctivae (Chemosis): 0.1

REVERSIBILITY: yes, only slight redness of conjunctiva observed in one rabbit after 72 hours.

Test condition : TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer, Biberach: Himalaya)
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss
- Age: no data
- Weight at study initiation: 2400-2800 g
- Number of animals: 4
- Controls: internal control (right eye)

EXAMINATIONS
according guideline

Reliability : (2) valid with restrictions
Purity of TS not stated, unusual vehicle

Flag : Critical study for SIDS endpoint

25.02.2003 (46)

Species : rabbit
Concentration : 64 %
Dose : .1 ml
Exposure time : 24 hour(s)
Comment : rinsed after (see exposure time)
Number of animals : 4
Vehicle : other: 29 % solution of l-menthol in DEP (HR 89/620001 DEP)
Result : slightly irritating
Classification :
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1989
GLP : yes
Test substance : other TS: menthol l H&R, HR 89/620001, purity: no data

Result : AVERAGE SCORE
HR 89/620001 64%/Vehicle (29% l-menthol in DEP)
1.0/0.8 (cornea)
0.0/0.0 (iris)
2.0/1.2 (redness of conjunctivae)
0.6/0.3 (chemosis, conjunctivae)
REVERSIBILITY: yes, no reactions observed after 7 days
The test article formulation was slightly more eye-irritating compared to the vehicle control.

Test condition : TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer, Biberach: Himalaya)
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss
- Age: no data
- Weight at study initiation: 2600-2800 g
- Number of animals: 4
- Controls: internal control with vehicle (right eye)

ADMINISTRATION/EXPOSURE
- Preparation of test substance: Test article was pulverized in a mortar and then diluted with vehicle (absolute concentration of substance in diethyl - phthalate (DEP) is 64%)
- Vehicle: 29% l-menthol in DEP (HR 89/620001 DEP, previously tested by

Scantox, lab.no.: 11754)
Reliability : (2) valid with restrictions
Purity of TS not stated, unusual vehicle
Flag : Critical study for SIDS endpoint
25.02.2003 (47)

Species : rabbit
Concentration : 60 %
Dose : .1 ml
Exposure time : 1 minute(s)
Comment : other: see test conditions
Number of animals : 8
Vehicle : other: olive oil
Result : not irritating
Classification :
Method : Draize Test
Year : 1974
GLP : no
Test substance : other TS: l-Menthol H&R, purity not stated

Test condition : Substance was initially applied in 10, 20 and 30 % solution.
The eyes of 4 animals were rinsed 1 minute after application with physiological saline, substance remained in the eyes of 4 animals. In a second step animals were treated with concentration of 40, 50 and 60 %.
Reliability : (2) valid with restrictions
Limited documentation
25.02.2003 (45)

Species : rabbit
Concentration : 60 %
Dose : .1 ml
Exposure time : 1 minute(s)
Comment : other: see test conditions
Number of animals : 8
Vehicle : other: olive oil
Result : not irritating
Classification :
Method : Draize Test
Year : 1974
GLP : no
Test substance : other TS: menthol brazilian, no further data

Test condition : Substance was initially applied in 10, 20 and 30 % solution.
The eyes of 4 animals were rinsed 1 minute after application with physiologically saline, substance remained in the eyes of 4 animals. In a second step animals were treated with concentration of 40, 50 and 60 %.
Reliability : (2) valid with restrictions
Limited documentation
25.02.2003 (45)

5.3 SENSITIZATION

Type : Buehler Test
Species : guinea pig
Concentration : 1st.: Induction 25 % occlusive epicutaneous
2nd.: Challenge 25 % occlusive epicutaneous
3rd.:
Number of animals : 20

Vehicle : other: ethanol:diethylphthalate (1:1)
Result : not sensitizing
Classification :
Method : other: comparable to OECD-guideline 406, see test conditions
Year : 1991
GLP : yes
Test substance : other TS: menthol-l H&R, HR 90/000102

Result : - Sensitization reaction: No irritation was noted after induction and there were no positve responses in any of the animals after challenge
- Clinical signs: No clinical signs, other than skin reactions induced by treatment, were noted during study.

Test condition : Negative control: vehicle
Day 1-3: induction, 6 hrs
Day 8-10: induction, 6 hrs
Day 15-17: induction, 6 hrs
Day 28: challenge, 6 hrs
TEST ANIMALS:
- Strain: Dunkin-Hartley
- Sex: female
- Source: David Hall Limited, Darley Oaks, Newchurch, Burton-on-Trend, Staffordshire
- Age: less than one year
- Weight at study initiation: 422-509 g
- Number of animals: 44 (20 control, 20 test, 4 dose ranging)
ADMINISTRATION/EXPOSURE
- 0.5 ml were applied for induction
EXAMINATIONS
- Grading system: see guideline
- Pilot study: 25, 10, 5 and 2 % w/v in ethanol:diethylphthalate (DEP) were investigated for 24 hrs.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: Concentration used for induction exposure did not cause mild irritation.

Flag : Critical study for SIDS endpoint
10.07.2002 (48)

Type : Mouse local lymphnode assay
Species : mouse
Number of animals : 4
Vehicle : other: acetone
Result : not sensitizing
Classification :
Method : other: Kimber, I, Hilton, J., Weisenberger, C., The murine local lymph node assay for identification of contact allergens: A preliminary evaluation of in situ measurement of lymphocyte proliferation. Contact Dermatitis, 21, 215-220, 19
Year : 1995
GLP : yes
Test substance : other TS: menthol l H&R, 99.9 %

Result : Conc.Menthol (%w/v) | no of lymph nodes assayed | counts per minute(cpm) | cpm/lymph node | test: ratio control

0 (vehicle)	8	1236	1.55	N/A
1	6	1212	2.02	1.30
10	8	2234	2.79	1.80
30	8	1131	1.41	0.91

Hexylcinnam-aldehyde						
0 (vehicle)	8	672	0.84	N/A		
1	8	1874	2.34		2.79	
10	8	5322	6.65	7.92		
30	8	6711	8.39		9.99	

The increase in isotope incorporation was less than 3 -fold at all concentrations. Also the response was not consistent with a biological dose-response. Test substance has not fulfilled the criteria for a potential sensitiser under the conditions of the tests. Hexylcinnamaldehyde as control has fulfilled the criteria for a potential sensitiser.

Test condition : TEST ANIMALS:
- Strain: CBA/Ca/01a/Hsd strain
- Sex and number: 4 males per dose
- Source: Harlan Olac Limited, Blackthorne, Bicester, Oxon, UK
- Age: young adults
- Weight at study initiation: no data
- Controls: yes, with acetone

ADMINISTRATION/EXPOSURE
- Concentrations used were: 0 (vehicle), 1 %, 10 %, 30 %
- Positive control: Positive control study with hexylcinnamaldehyde (3 and 10% in acetone)

Reliability : (1) valid without restriction
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail.

Flag : Critical study for SIDS endpoint
10.07.2002 (49)

Type : other: Modified Draize procedure
Species : guinea pig
Concentration : 1st: Induction .25 % other: intradermal
2nd: Challenge 10 % other: intradermal in one flank and topical in the other flank
3rd:
Number of animals : 10
Vehicle : no data
Result : ambiguous
Classification :
Method : other: modified Draize: Draize, J.H. Dermal Toxicity, Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, Ass. Food and Drug Officials of the U.S., 1959, 46-59
Year : 1978
GLP : no
Test substance : other TS: L-menthol, not further specified, no data on purity

Remark : The study included 69 perfume ingredients. 9 of these were tested positive (7 of these 9 after a second induction treatment only)
Result : A positive reaction was obtained after a second induction treatment.
Test condition : TEST ANIMALS:
- Strain: Hartley strain albino
- Sex: 4 males, 6 females o r vice versa / test substance
- Source: Unilever Research Laboratory, Colworth House, Sharnbrook, Beds., UK
- Age: no data
- Weight at study initiation: about 350 g
- Controls: 4 previously untreated animals of same sex

ADMINISTRATION/EXPOSURE

Day 0: Induction (4x0.25 %) Day 14: Challenge (intradermal and topical 0.25 %), day 21: Rechallenge. In case a negative result was obtained at the first challenge, a second induction treatment was performed on day 21 (4x0.25 %) with a second challenge (intradermal and topical 2,5 or 10 % on day 35 and a re-challenge on day 42 including controls.
- Positive control: see remark
EXAMINATIONS
- Grading system: 0 - +++ - System, compared to positive control reaction
- Pilot study: 4 animals were injected intradermally 0.1 ml aliquots of a range of concentrations of test material. The concentration giving slight but perceptible irritation with no oedema was selcted as the injection challenge.

Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
25.02.2003 (50) (51)

Type : other: open repetitive dermal test
Species : guinea pig
Number of animals : 20
Vehicle : no data
Result : not sensitizing
Classification : not sensitizing
Method : other
Year : 1974
GLP : no
Test substance : other TS: l-menthol H&R

Test condition : Substance was rubbed into shaved skin for 30 sec once daily for 3x5 days. After 5 days without application the test substance was rubbed into an untreated part of the skin.
Results were taken after 24 h, 2 and 3 days.
Reliability : (3) invalid
Significant methodological deficiencies. e.g. concentration and amount of substance is unclear; lack of control experiment.
25.02.2003 (45)

Type : other: open repetitive dermal test
Species : guinea pig
Number of animals : 20
Vehicle : no data
Result : not sensitizing
Classification : not sensitizing
Method : other
Year : 1974
GLP : no
Test substance : other TS: menthol brazilian

Test condition : Substance was rubbed into shaved skin for 30 sec once daily for 3x5 days. After 5 days without application the the test substance was rubbed into an untreated part of the skin.
Results were taken after 24 h, 2 and 3 days.
Reliability : (3) invalid
Significant methodological deficiencies. e.g. concentration and amount of substance is unclear; lack of control experiment.
25.02.2003 (45)

Type : Patch-Test
Species : human
Number of animals :

Vehicle	:	
Result	:	
Classification	:	
Method	:	other
Year	:	1990
GLP	:	no data
Test substance	:	other TS: not further specified

Result	:	Identified allergens were: menthol, piperitone or pulegone.
Test condition	:	Three patients with allergic contact dermatitis were patch-tested against individual components of peppermint oil.
Reliability	:	(4) not assignable Secondary literature

10.07.2002 (52)

Type	:	Patch-Test
Species	:	human
Number of animals	:	
Vehicle	:	petrolatum
Result	:	
Classification	:	
Method	:	other
Year	:	1992
GLP	:	no data
Test substance	:	other TS: not further specified

Result	:	Case 1: positive reactions to clove oil, cinnamon oil and l-menthol Case 2: positive reactions to clove oil and cinnamon oil.
Test condition	:	Case 1: dermatitis caused by Tiger Balm made in Taiwan Case 2: dermatitis caused from two Essential balms made in China
Reliability	:	(4) not assignable Documentation insufficient for assessment.

25.02.2003 (53)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	3 m
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	50, 150, 450 mg/kg bw/d
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	other TS: Menthol-JPT, melting point: 42.8-42.9°C, aD = - 49.0°

Result	:	NOAEL (NOEL), LOAEL (LOEL): not assignable because effects may have been caused by infection TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Mortality and time to death: 1 animal of control group and 1 animal of 50 mg/kg bw died in month 3 due to pneumonia. - Clinical signs: no effect

- Body weight gain: no significant effect
- Food/water consumption: 450 mg/kg bw.: Feed efficiency: 0.6 % decreased.
- Clinical chemistry: no compound related effect
- Haematology: no compound related effect
- Urinalysis: no effect
- Organ weights:
>= 150 mg/kg bw: absolute and relative thyroid and kidney weight increased
= 450 mg/kg bw: absolute and relative liver weight increased
Testes weights showed some variations, but no dose-dependent effects: mean abs. testes weights in control animals (1.77 g right and 1.67 g left) and in high dosed animals (1.70 g and 1.73 g)
no statistical analysis performed
- Gross pathology: no effect
- Histopathology:
no clear substance related effects, discussed to be due to temporary infection and healing:
>= 150 mg/kg bw: Kupffer cells in liver increased only 150 mg/kg bw: renal casts in the kidney increased

Test condition : TEST ORGANISMS
Age: six weeks
- Weight at study initiation: no data
- Number of animals/dose group: 12
ADMINISTRATION / EXPOSURE
- dosing frequency: daily except on "off days", not further specified
- Vehicle: 10% aquous solution of gum arabic
- Preparation: Test substance is suspended in Vehicle
EXAMINATIONS
- Clinical signs: yes
- Mortality: yes
- Body weight: yes
- Organ weight: yes
- Food consumption: yes
- Water consumption: yes
- Feed efficiency: yes
- Ophthalmoscopic examination: no
- Haematology: yes
- Biochemistry: s-GOT, s-GPT, s-AIP, glucose, protein
- Urinalysis: yes
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
liver, kidneys, heart, lungs, spleen, suprarenal glands, thymus gland, thyroid gland, testicles, pancreas, small intestine, large intestine, stomach, thighbones

Reliability : (3) invalid
Due to infection of the test animals with pneumonia, effects cannot be related to TS administration.

01.08.2002 (54)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : gavage
Exposure period : 28 days
Frequency of treatm. : daily
Post exposure period : no
Doses : 200, 400, 800 mg/kg bw/d
Control group : other: Yes, not specified

Method : other: mainly according to OECD TG 407
Year : 1983
GLP : no data
Test substance : other TS: L-menthol, purity: 99%

Remark : NOAEL and LOAEL: cannot be determined from the study results
Result : TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: no data
- Body weight gain: no effect
- Food/water consumption: significantly increased water consumption at the highest dose level (magnitude not reported, not reported in which sex)
- Clinical chemistry: no effect
- Haematology: Increased number of neutrophile granulocytes at the highest dose level (magnitude not reported, not reported in which sex)
- Organ weights:
m >= 200, f >=400 mg/kg bw: absolute and relative liver weight significantly increased (no information on magnitude and incidence of this findings is given in the publication).
- Histopathology:
m and f >= 200 mg/kg bw: vacuolization of hepatocytes (controls: 0/20, 200 mg/kg: 4/20; 400 mg/kg: 5/17; 800 mg/kg: 4/19, no distinction between sexes); not dose-related; is interpreted as a possible adaptation process
- Other: no changes in cerebellum

Test condition : TEST ORGANISMS
- Age: 4 weeks
- Weight at study initiation: no data
- Number of animals/dose group: 10 males and 10 females
ADMINISTRATION / EXPOSURE
- Vehicle: soybean oil (food grade quality)
- Total volume applied: 5 ml/kg/bw
- control group: yes, not stated whether untreated or treated with vehicle
EXAMINATIONS:
- Clinical signs: yes (inspection twice daily)
- Mortality: yes (inspection twice daily)
- Body weight: yes (weekly recorded)
- Organ weight: yes (kidneys, adrenals, heart, brain, liver and stomach with content)
- Food consumption: yes (weekly recorded)
- Water consumption: yes (weekly recorded)
- Ophthalmoscopic examination: no
- Haematology: yes (Hemoglobin, PCV, total erythrocyte count, total WBC, white blood cell differential count, reticulocytes, glucose)
- Biochemistry: yes (creatinine, urea, activities of ASAT)
- Urinalysis: urine examined for presence of blood, ketones, glucose and proteins
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined as described in OECD guideline 407 with the exception of the full histopathology examinations of urinary bladder and prostate.
OTHER EXAMINATIONS: special examination of the brain: frozen sections were prepared on selected specimens and stained with Luxol fast blue. For the light microscopic examination of organs/tissues the following staining was performed in addition to Haematoxylin-Eosin (HE) staining: Oil Red O (liver), Perl (liver and spleen), and PAS (liver).
STATISTICAL METHODS: Student's t-test was performed on all parameters for males and females separately and analyses of variance were applied to organ weights. P<0.01 was regarded as significant.

Reliability : (2) valid with restrictions
Study design mainly in accordance with OECD TG 407; generally sufficient

documentation of study results, but no information was provided on the magnitude/incidence of the increase in liver weights. Therefore, and because no clearly pathological microscopic and enzymatic changes indicating an adverse effect on the liver have been reported, the relevance of this finding is questionable and a NO(A)EL cannot be deduced from this study

Flag : Critical study for SIDS endpoint
25.02.2003 (55)

Type	:	Sub-chronic
Species	:	Rat
Sex	:	male/female
Strain	:	Sherman
Route of admin.	:	Inhalation
Exposure period	:	71, 74, 75, 79 days
Frequency of treatm.	:	6.75 h daily
Post exposure period	:	no data
Doses	:	0.087, 0.148, 0.259 ppm (according to 0.57, 0.96 and 1.68 mg/m³)
Control group	:	Yes
Method	:	other
Year	:	1954
GLP	:	No
Test substance	:	other TS: not further specified

Remark : VARIABILITY of EXPOSURE CONCENTRATIONS: 0.087 ± 0.021 ppm; 0.148 ± 0.031 ppm; 0.259 ± 0.166 ppm
The VAPOUR INHALATION was performed as whole body inhalation

Result : NOAEL, LOAEL: not assignable due to invalid analytical methods
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: no effect
- Clinical signs: transient erythema of the conjunctiva; disappeared shortly after they were returned to their cages
- Body weight gain: no effect
- Food/water consumption: no effect
- Haematology: no effect
- Organ weights: no effect
- Gross pathology: no effect
- Histopathology:
Lung, respiratory tract (tracheitis, pneumonitis, pulmonary congestion) 3/9 (2/9 evidence of pneumonitis), 1/8, 4/8, 9/11 (severe congestion to pneumonitis)

Test condition : TEST ORGANISMS
- Age: young
- Weight at study initiation: 125-185
- Number of animals/dose group: 12
- Control groups: 12 animals - 4 m, 8 f (identical conditions except menthol); one additional control group: 8 (4 m, 4 f) remained in their cages throughout the study.
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (daily observation)
- Mortality: yes (daily)
- Body weight: yes (twice weekly)
- Organ weight: yes
- Food consumption: yes (estimated daily)
- Water consumption: yes (estimated daily)
- Ophthalmoscopic examination: no
- Haematology: yes
- Biochemistry: no

- Urinalysis: no
- Histophathology: yes
ORGANS EXAMINED AT NECROPSY (MICROSCOPIC):
- Microscopic: eye, turbinates, nasopharynx, trachea, lungs, and skin, sections of liver, spleen, kidney, heart, testes, ovaries, intestine and skeletal muscle.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: no valid analytical method to observe concentration of menthol in exposure chamber.

Flag : Critical study for SIDS endpoint
19.08.2002 (56)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 13 w
Frequency of treatm. : 1hr/d, 5d/w
Post exposure period : 6 w
Doses : smoke particulate concentration: 200, 600, 1200 mg total particle matter/m3
Control group : other: see test conditions
Method : other
Year : 1997
GLP : no data
Test substance : other TS: synthetic l-menthol, not further specified

Result : NOAEL (NOEL), LOAEL (LOEL): not assignable
ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX
- Time of death: no
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: no effect
- Clinical signs:
clear nasal discharge in reference nicotin and menthol smokers (higher incidence in rats exposed to reference smoke)
- Body weight gain: 200, 600, 1200 mg/m3: decreased body weight (reference and menthol)
- Food/water consumption: no effect
- Clinical chemistry: 1200 mg/m3: decrease in glucose levels (reference and menthol)
- Haematology: Dose-dependant increase in carboxyhaemoglobin level, m and f (reference and menthol) – significantly smaller in menthol- smokers
- Urinalysis: no effect
- Organ weights: Dose-dependent increase of lung to body weight ratio, m and f (Reference and menthol);
dose-dependent heart to body weight ratio, m and f - slightly greater effect in m (Reference and menthol).
- Histopathology: Dose-dependant increase in incidence of histopathological changes in respiratory tract, m and f
(Reference and menthol) changes were slightly more severe in mentholated smoke females than in reference smoke females.
CONCLUSION: Rats exposed to menthol cigarette smoke showed the same changes in clinical signs, clinical chemistry, organ weights and histopathology than the rats exposed to nicotine reference smoke, despite:
- the cotinine level in the 200 mg total particle matter/m3 menthol group was lower than in reference groups
- carboxyhemoglobin levels in rats exposed to menthol smoke were lower

compared to reference smokers (observation is consistent with the reduced smoke carbon monoxide concentration for menthol smoke exposures)
- dose-related increase in nasal discharge was not observed in menthol cigarette smokers

Test condition : TEST ORGANISMS
- Age: 6 weeks
- Weight at study initiation: male: 200-220 g, female: 140-150 g (both estimated from graphic)
- Number of animals/dose group: 15 per sex, 21 per sex (reference)

ADMINISTRATION / EXPOSURE
- Examined groups: Menthol: 3 dosed groups (mentholated cigarette smoke), Reference: 3 reference dosed group (non-mentholated cigarette smoke), Control: 1 control group (no smoke)
- Duration of test/exposure: 30 min smoke, 15 min filtered air, 30 min smoke
- Post exposure period: a portion of each group was autopsied immediately, remaining rats: 6 wk non-exposure recovery period
- Vehicle: nicotin smoke
- Concentration in vehicle: 5000 ppm menthol
- Particle size: 0.47-0.90 µm
- Type or preparation of particles: 30-port AMESA Mark IIIA smoking machine (individual nose-only) using machine vacuum to puff the cigarettes according to Federal Trade Commission standards of a 35 ml, 2-sec puff taken once per minute.

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (weekly examination)
- Mortality: yes (twice daily)
- Body weight: yes (weekly)
- Organ weight: Adrenal glands, heart, right kidney, lungs, liver, spleen, and right testis were recorded on animials terminated after 13 wk exposure. Lungs and heart weights were recorded at autopsy of all recovery group animals.
- Food consumption: yes
- Water consumption: yes
- Ophthalmoscopic examination: no
- Haematology: yes (hemoglobin, hematocrit, leucocyte count and differentials, erythrocyte count and indices)
- Clinical chemistry: yes (aspartate and alanine aminotransferase, blood urea, nitrogen, alkaline phosphatase, bilirubin, cholesterol, creatinine, glucose, g-glutamyltransferase, total protein, albumin, blobulin, sodium, potassium, calcium and chloride)

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined as described in OECD guideline 408.
STATISTICAL METHODS: One-way analysis of variance (ANOVA) followed by a Tukey's HSD test for body weights, organ weights, calculated organ weight/body weight ratios, quantitative clinical pathology data.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles. However, since the study compares toxic effects of cigarette smoke with those of mentholated cigarette smoke no assessment can be made for the effects of menthol alone.

12.11.2002 (57)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : i.p.

Exposure period	:	3 d
Frequency of treatm.	:	daily
Post exposure period	:	no
Doses	:	40 mg/kg bw/d in 10 % ethanol and 90 % corn oil
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1988
GLP	:	no data
Test substance	:	other TS: 97-99 %
Result	:	No significant change in the total cytochrome P-450 content of liver microsomal membranes, no visible change in the pattern of liver microsomal membrane proteins, no effect on the amount of hepatic cytochrome b5, small but significant inductions of PB P-450 in liver microsomal membrane vesicles.
Test condition	:	Rats were given three consecutive daily intraperitoneal injections of menthol. Test was conducted to study the effect of terpenoid compounds on cytochrome P-450 Levels in rat liver.
Reliability	:	(3) invalid Unsuitable test system (see test conditions).

18.01.2002 (58)

Type	:	Sub-acute
Species	:	rat
Sex	:	no data
Strain	:	no data
Route of admin.	:	other: oral by stomach tube
Exposure period	:	7 d
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	800 mg/kg bw/d
Control group	:	no data specified
Method	:	other
Year	:	1988
GLP	:	no data
Test substance	:	other TS: not further specified
Result	:	Biochemical changes in the liver.
Reliability	:	(4) not assignable Secondary literature

17.12.2001 (59)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	other: diet
Exposure period	:	5.5 weeks
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	0, 100 or 200 mg/kg bw/d
Control group	:	other: Yes, not specified
NOAEL	:	200 mg/kg bw
Method	:	other: no data
Year	:	1961
GLP	:	no
Test substance	:	other TS: L-menthol, purity not stated
Remark	:	Type: other: Repeated dose study with L-menthol and D/L-menthol

Result : No adverse effects on weight gain, excretion of glucuronides, water, or electrolytes, or interference with central nervous system reactions to stimulants were observed
Test condition : NUMBER OF ANIMALS: 40 rats of each sex/dose
Reliability : (4) not assignable
secondary citation from peer-reviewed document (FAO/WHO report 1999)
Flag : Critical study for SIDS endpoint
25.02.2003 (60)

Type : Sub-chronic
Species : mouse
Sex : male
Strain : other: white mice
Route of admin. : inhalation
Exposure period : 3 m
Frequency of treatm. : 5h/d
Post exposure period : no data
Doses : 50, 100 mg/m3
Control group : yes
NOAEL : 5 ppm
Method : other
Year : 1962
GLP : no
Test substance : other TS: menthol oil vapors, not further specified

Result : NOAEL (NOEL), LOAEL (LOEL): Concentration of 5 ppm is assumed by the authors as safe from the toxicological point of view. No further data.
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- clinical sings: fatigue, lower mobility
- histopathology: regressive changes in the liver and kidney (no detailed data given)

Test condition : TEST ORGANISMS:
- weight at study initiation: ca. 20g
- number of animals: 10

SATELLITE GROUPS AND REASONS THEY WERE ADDED:
A group of 10 mice was exposed to menthol oil vapors in the production site for 76 days. No data on exposure concentrations are given.
CLINICAL OBSERVATIONS AND FREQUENCY:
- clinical signs: yes, no data on frequency
- mortality: no data
- body weight: no data
- organ weight: no data
- food consumption: no data
- water consumption: no data
- ophthalmoscopic examination: no data
- haematology: no data
- biochemistry: no data
- urinanalysis: no data

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC)
No detailed data on macroscopic or microscopic examinations are given.
STATISTICAL METHODS: no data

Reliability : (3) invalid
Significant methodological deficiencies: no detailed data on observed changes. No correlation to doses. The method of menthol concentration measurement is doubtful (colour reaction with vaniline).
10.07.2002 (61)

Type : Sub-acute

Species	:	mouse
Sex	:	male
Strain	:	other: white mice
Route of admin.	:	inhalation
Exposure period	:	6 days
Frequency of treatm.	:	6h/day
Post exposure period	:	21 days
Doses	:	1 mg/l
Control group	:	
Method	:	other
Year	:	1962
GLP	:	no
Test substance	:	other TS: menthol oil vapors, not further specified
Result	:	NOAEL (NOEL), LOAEL (LOEL): No NOAEL assigned. TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - clinical sings: no signs of intoxication - histopathology: erythraemia, small hematoma in brain, heart, lungs, kidneys and regressive changes in the liver and kidney
Test condition	:	TEST ORGANISMS: - weight at study initiation: ca. 20g - number of animals: 10 CLINICAL OBSERVATIONS AND FREQUENCY: - clinical signs: yes, no data on frequency - mortality: no data - body weight: no data - organ weight: no data - food consumtion: no data - water consumption: no data - ophthalmoscopic examination: no data - haematology: no data - biochemistry: no data - urinanalysis: no data ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC) No detailed data on macroscopic or microscopic examinations are given. STATISTICAL METHODS: no data
Reliability	:	(3) invalid Significant methodological deficiencies: no detailed data on observed changes. No correlation to doses. The method of menthol concentration measurement is doubtful (colour reaction with vaniline).

10.07.2002 (61)

Type	:	Sub-acute
Species	:	mouse
Sex	:	male
Strain	:	ICR
Route of admin.	:	oral unspecified
Exposure period	:	5 d
Frequency of treatm.	:	daily
Post exposure period	:	9 d
Doses	:	2000, 2500, 3200, 4000 and 5000 mg/kg bw/d
Control group	:	no
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	other TS: menthol, natural, brazilian
Result	:	ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX

MORTALITY:
- Time and number of deaths at each dose:
dose (mg/kg)/deaths/time of deaths
2000/2(6)/day 2 (2)
2500/2(6)/day 1 (1), day 2 (2)
3200/3(6)/day 1 (1), day 2 (1)
4000/6(6)/day 2 (6)
5000/6(6)/day 2 (6)
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: 14-day subacute oral LD50 in male mice is 2652 mg/kg with 95% conficence limits of 1951 to 3218 mg/kg
- Clinical signs: Signs of toxicity and abnormal behavior included depression, excitability, rapid respiration and unthrifty appearance
- Histopathology: No abnormal gross findings in gross necropsy were observed.

Test condition : TEST ORGANISMS
- Age: no data
- Weight at study initiation: average bw. 35 g
- Number of animals/dose group: 6
ADMINISTRATION / EXPOSURE
- Vehicle: 0.85% saline
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes
- Mortality: yes
- Body weight: no
- Organ weight: no
- Food consumption: no
- Water consumption: no
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Animals were subjected to gross necropsy; no further data.

Reliability : (3) invalid
Significant methodological deficiencies: e.g. no control group, relevant parameters were not studies (Mutagenic evaluation study)

17.12.2001 (39)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : S. typhimurium (TA 98, 100, 2637)
Test concentration : 0.02, 0.05, 0.1, 0.2, 0.5 mg/plate
Cycotoxic concentr. : 0.1 mg/plate (lethal dose in TA 100; 0.5 mg/plate lethal for TA 98 and 2637)
Metabolic activation : with and without
Result : negative
Method : other: according to Ames et al. (1975)
Year : 1985
GLP : no data
Test substance : other TS: purity not stated

Result : No increases in mutant frequency were seen in any strain both in the absence and in the presence of metabolic activation. The positive control compounds induced strongly enhanced number of revertants in all strains.
Test condition : Metabolic activation system: S9-mix from PCB induced BALB/c mice

Vehicle: DMSO
Negative control: DMSO
Positive controls: AF-2 0.02 µg/plate (for TA 100 and TA 98 without S9-mix), 2-aminoacridine 0.2 mg/plate (for TA 1537 without S9-mix), 2-aminoanthracene 0.05 mg/plate (for all used strains with S9-mix)

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

25.02.2003 (62)

Type : Ames test
System of testing : S. typhimurium TA 1537, TA 1535, TA 100, TA 98
Test concentration : 6.4, 32, 160, 800 µg/plate
Cycotoxic concentr. : 800 µg/plate (lethal dose)
Metabolic activation : with and without
Result : negative
Method : other: according to Ames et al. (1975)
Year : 1984
GLP : no data
Test substance : other TS: menthol, purity: 99%

Result : No increases in mutant frequency were seen in any strain both in the absence and in the presence of metabolic activation. At a concentration of 800 µg/plate strong cytotoxicity was induced. The positive control compounds induced strongly enhanced number of revertants in all strains.

Test condition : Metabolic activation system: S9-mix from Aroclor-1254 induced male Wistar rats
Vehicle: DMSO
Negative control: DMSO
Positive controls: sodium azide (for TA 1535 and TA 100 without S9-mix), 2-nitrofluorene (for TA 1537 and TA 98 without S9-mix), 2-anthramine (for all used strains with S9-mix)

Reliability : (2) valid with restrictions
Only 3 concentrations evaluated for mutagenicity

Flag : Critical study for SIDS endpoint

25.02.2003 (63)

Type : Ames test
System of testing : S. typhimurium TA100, TA98, TA97a and TA102
Test concentration : 5 - 800 µg/plate
Cycotoxic concentr. : Tested up to and including cytotoxic concentration
Metabolic activation : with and without
Result : negative
Method : other: according to Maron and Ames, Mutat. Res. 113 (1983) 173-215
Year : 1997
GLP : no data
Test substance : other TS: commercial grade

Result : No increases in mutant frequency were seen in any strain both in the absence and in the presence of metabolic activation. The positive control compounds induced strongly enhanced numbers of revertants in all strains.

Test condition : Metabolic activation system: S9-mix from Aroclor-1254 induced rats
Vehicle: ethanol
Negative control: ethanol
Positive controls: sodium azide, nitro-o-phenylene-diamine, 4-nitroquinolineoxid, 2-aminoanthracene, mitomycin C, 2-aminofluorene, benzo-a-pyrene
Tested concentrations:
TA 100: 100 - 700 µg/plate

TA 98: 100 - 800 µg/plate (cytotoxic at 800 µg)
TA 97a: 100 - 800 µg/plate (cytotoxic at 800 µg)
TA 102: 5 - 500 µg/plate (cytotoxic at 500 µg)

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
25.02.2003 (64) (65)

Type : Bacterial gene mutation assay
System of testing : Bacillus subtilis
Test concentration : up to 20 mg/plate
Cycotoxic concentr. :
Metabolic activation :
Result : negative
Method : other
Year : 1978
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Secondary literature.
14.02.2002 (66)

Type : other: Antimutagenicity
System of testing : E. coli WP2 uvrA (trp-), pre-treated with AF-2
Test concentration : 0.5 - 2 mg/ml
Cycotoxic concentr. :
Metabolic activation :
Result : negative
Method : other
Year : 1986
GLP : no data
Test substance : other TS: analytical grade

Result : In the present study an antimutation test in E.coli WP2 uvrA (trp-) was performed. Bacteria were pretreated with AF-2 and MNNG and the mutation of AF-2 and MNNG induced trp+ revertants was investigated. L-Menthol had no antimutagenic effect.
Test condition : Ratio (maximal revertants/spontanous revertants x 100) >> 2.0 is regarded as a positive result.
Reliability : (2) valid with restrictions
Limited documentation
25.02.2003 (67)

Type : Escherichia coli reverse mutation assay
System of testing : E.coli WP 2 uvrA
Test concentration : 0.1 0.8 mg/plate
Cycotoxic concentr. :
Metabolic activation :
Result : negative
Method : other
Year : 1986
GLP : no data
Test substance : other TS: analytical grade

Remark : The positive control AF-2 exhibited clear mutagenic activity in this test
Test condition : Ratio (minimal revertants/AF-2-induced revertants x 100) less than 50 % is regarded as a positive result.
Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (67)

Type	:	other: DNA repair assay
System of testing	:	Bacillus subtilis M 45 (rec-) and H 17 (rec+)
Test concentration	:	up to 10 mg/disk
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	positive
Method	:	other: rec-assay
Year	:	1986
GLP	:	no data
Test substance	:	other TS: analytical grade
Remark	:	The DNA damaging activity was measured by the difference in growth inhibition zones between strains M45 and H17; a test substance was considered negative if the difference was < 4 mm.
Result	:	Inhibition zones: M45: 42 cm H17: 23 cm Difference: 19 cm
Reliability	:	(2) valid with restrictions Limited documentation; no information on dose response.
Flag	:	Critical study for SIDS endpoint

25.02.2003 (67)

Type	:	Chromosomal aberration test
System of testing	:	Human peripheral blood lymphocytes
Test concentration	:	0.1, 1, 10 mM
Cycotoxic concentr.	:	> 10mM
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1991
GLP	:	no data
Test substance	:	other TS: purity: > 98 %
Result	:	Combined percentage structural aberration rate for males and female) Results/without S-9/with S-9 Solvent controls: 1.76/2.00 10mM menthol: 2.11/2.25 MMC -positive control: 9.13 Results with the test material were not statistically significantly different from the solvent controls. No changes in polyploid cells.
Test condition	:	SYSTEM OF TESTING - Species/cell type: 12 male and 12 female donors - Culturing: RPME 1640 medium, 2mM-L-glutamine, 100 U penicillin/ml, 100 µg streptomycin/ml, 10% foetal calf serum, 1% phytohaemagglutinin, test substance (from beginning of incubation) - Metabolic activation system: S9 - No. of metaphases analyzed: 100 ADMINISTRATION: - Positive and negative control groups and treatment: negative control: solvent DMSO positive Control: 5 male donors with mitomycin C in distilled water (1 x 10E -7 M)
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint

25.02.2003 (68)

Type : Sister chromatid exchange assay
System of testing : Human peripheral blood lymphocytes
Test concentration : 0.1, 1, 10 mM
Cycotoxic concentr. : > 10mM
Metabolic activation : with and without
Result : negative
Method : other
Year : 1991
GLP : no data
Test substance : other TS: purity: > 98 %

Test condition : SYSTEM OF TESTING
- Species/cell type: 12 male and 12 female donors
- Culturing: RPME 1640 medium, 2mM-L-glutamine, 100 U penicillin/ml, 100 µg streptomycin/ml, 10% foetal calf serum, 1% phytohaemagglutinin, 10 µM 5-bromodeoxyuridine, test substance (from beginning of incubation)
- Metabolic activation system: S9
- No. of metaphases analyzed: >= 25 second-division cells/each culture
- No. of cells in which chromosomal aberrations were investigated: >= 100
ADMINISTRATION:
- Positive and negative control groups and treatment:
negative control: solvent DMSO
positive Control: 5 male donors with mitomycin C in distilled water (1 x 10E -8 M)

Reliability : (2) valid with restrictions
Limitd documentation
Flag : Critical study for SIDS endpoint
25.02.2003 (68)

Type : Chromosomal aberration test
System of testing : Chinese hamster lung cells
Test concentration : 0.0313, 0.0625, 0.125 mg/ml
Cycotoxic concentr. : no data
Metabolic activation : without
Result : negative
Method : other
Year : 1982
GLP : no data
Test substance : other TS: not further specified

Result : Test was negative after 24 / 48 hours of treatment (- S9):
- Vehicle control: 1 / 0 % aberrations
- 0.0313 mg/ml: 1 / 1 % aberrations
- 0.0625 mg/ml: 3 / 1 % aberrations
- 0.125 mg/ml: 3 / 0 % aberrations

Test condition : Solvent: DMSO
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
25.02.2003 (69)

Type : Chromosomal aberration test
System of testing : Chinese hamster cells (direct method)
Test concentration : 0.1 - 0.3 mg/ml
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative

Method : other
Year : 1982
GLP : no data
Test substance : other TS: not further specified

Result : No TS related effects on polyploidy.
Gaps were included in the frequency of aberrations.
Test was negative (- / + S9):
- Vehicle control: 1 / 1 % aberrations
- 0.1 mg/ml: 0 / 0 % aberrations
- 0.2 mg/ml: 0 / 1 % aberrations
- 0.3 mg/ml: - / 1 % aberrations
Overall conclusion: negative

Test condition : Method: Direct method
Solvent: DMSO
Application: 24 and 48 hours.
chromosomal effects evaluated: chromatid and isochromatid gaps, chromatid breaks, chromatid exchanges, chromosome breaks, chromosome exchanges including dicentric and ring chromosomes.
Duration of treatment: 24 and 48 hours
In this study 25 chemicals nave been tested. Acrylamide and acrylonitrile gave positive results (up to 15% and 25% aberrations, respectively9. No further positve controls tested.
Statistics: not performed

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint
25.02.2003 (69)

Type : other: Anaphase chromosome aberration
System of testing : Human tissue culture cells (fibroblasts)
Test concentration : 0.1, 1.0, 10.0 µg/ml
Cycotoxic concentr. :
Metabolic activation :
Result : negative
Method : other
Year : 1975
GLP : no
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : negative control: two cells with bridges
positive control: within normal limits
1.0 and 10 µg/ml: each a cell with an acentric fragment % cells with aberrations (0.1, 1.0, 10.0 %, negative control, positive control): 0, 1, 1, 2, 30

Test condition : Negative control: saline
Pos itive control: Triethylene Melamine (TEM)
No. of cells: 100

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint
25.02.2003 (39)

Type : Chromosomal aberration test
System of testing : Chinese hamster cells
Test concentration : 0.1, 0.2, 0.3 mg/ml
Cycotoxic concentr. : up to cytotoxic concentrations
Metabolic activation : with and without
Result : negative

Method	:	other
Year	:	1998
GLP	:	no data
Test substance	:	other TS: 99.9% purity
Test condition	:	Metabolic activation with mouse liver S9 mix No. of cells with chromosomal aberrations was counted on 100 well-spread metaphases. Judgement of clastogenicity (based on historical database): - less than 4%: negative - between 5.0 and 9.9%: equivocal - more than 10.0%: positive
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint

25.02.2003 (70)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Cytogenetic assay
Species	:	rat
Sex	:	male
Strain	:	other: albino rats
Route of admin.	:	gavage
Exposure period	:	acute
Doses	:	1.45, 14.5, 145.0 mg/kg and 500, 3000 mg/kg (second test)
Result	:	negative
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	other TS: Menthol natural brazilian, FDA 71-57
Result	:	Treated animals showed no increased number of aberrations (max. 0.8 %) compared to control animals (max. 0.66 %). Positive control animals showed 22.8 - 37 % aberrant metaphases.
Test condition	:	Analysis of chromosome aberrations in bone marrow Age: 10-12 weeks Groups: Animals were killed 6 hours, 24 hours and 48 hours after treatment respectively Number of animals/group: 5 number of negative control animals/group: 3 Number of positive control animals: 5 animals killed after 48 hours No. of metaphases investigated/animal: 50 Negative control: Vehicle (saline) Positive control: 0.30 mg/kg Triethylene melamine injected intraperitoneally Colcemid injection: 4 mg/kg administered 2 hrs prior killing
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restriction: only 50 metaphases per animal investigated.
Flag	:	Critical study for SIDS endpoint

10.07.2002 (39)

Type	:	Cytogenetic assay
Species	:	Rat
Sex	:	Male
Strain	:	other: albino rats
Route of admin.	:	Gavage

Exposure period	:	5 days
Doses	:	1.45, 14.5, 145.0 mg/kg and 1150 mg/kg (second test)
Result	:	Negative
Method	:	other
Year	:	1975
GLP	:	No
Test substance	:	other TS: Menthol natural brazilian, FDA 71-57
Result	:	Treated animals showed a comparable number of aberrations (max. 0.8 %) to that of control animals (0 %).
Test condition	:	Analysis of chromosome aberrations in bone marrow Age: 10-12 weeks Number of animals/dose group: 5 Number of negative control animals: 3 No. of metaphases investigated/animal: 50 Negative control: vehicle (saline) Exposure: Five doses 24 hours apart, animals killed 6 hours after last dose Colcemid injection: 4 mg/kg administered 2 hrs prior killing No positive control animals.
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restriction: only 50 metaphases per animal investigated.
Flag	:	Critical study for SIDS endpoint

10.07.2002 (39)

Type	:	Dominant lethal assay
Species	:	rat
Sex	:	male
Strain	:	no data
Route of admin.	:	gavage
Exposure period	:	acute
Doses	:	1.45, 14.5, 145.0 mg/kg and 500, 3000 mg/kg (second test)
Result	:	negative
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	other TS: Menthol natural brazilian, FDA 71-57
Result	:	Positive control showed strong effects on implantation, fertility, number of dead implants etc. The values calculated for menthol did not significantly vary from those of the negative control.
Test condition	:	Following treatment 10 males/dose were mated with 2 females/week for 8 weeks - resulting in 14 to 20 pregnant females per dose, negative and positive control per mating interval. females were killed 14 days after separation from males Positive control: triethylene melamine (TEM 0.3 mg/kg, i.p.) Negative control: saline Fertility index, preimplantation loss and lethal effects on the embryos were determined and compared to those calculated from negative (saline dosed) and positive (TEM-dosed) control animals. Statistics: fertility index: chi-square test number of implants: t-test number of corpora lutea: t-test preimplantation lossess: Freeman-Tukey transformation and t-test
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint

25.02.2003 (39)

Type : Dominant lethal assay
Species : rat
Sex : male
Strain : no data
Route of admin. : gavage
Exposure period : 5 days
Doses : 1.45, 14.5, 145.0 mg/kg and 1150 mg/kg (second test)
Result : negative
Method : other
Year : 1975
GLP : no
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : The values calculated for menthol did not significantly vary from those of the negative control.
Test condition : Subacute study
Following treatment 10 males/dose were mated with 2 females/week for 7 weeks - resulting in 13 to 19 pregnant females per dose, negative and positive control per mating interval.
females were killed 14 days after separation from males
Positive control: triethylene melamine (TEM 0.3 mg/kg, i.p.)
Negative control: saline
Fertility index, preimplantation loss and lethal effects on the embryos were determined and compared to those calculated from negative (saline dosed) and positive (TEM-dosed) control animals.
Statistics:
fertility index: chi-square test
number of implants: t-test
number of corpora lutea: t-test
preimplantation lossess: Freeman-Tukey transformation and t-test
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint

25.02.2003 (39)

Type : other: Host mediated Assay
Species : other: mouse (indicator organism: Salmonella typhimurium G-46)
Sex : male
Strain : ICR
Route of admin. : gavage
Exposure period : acute
Doses : 1.45, 14.5, 145.0 (first test) and 500, 5000 mg/kg bw (second test)
Result : negative
Method : other
Year : 1975
GLP : no
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : The corresponding in vitro tests gave negative results.
Test condition : Acute Ex-vivo study:
Number of animals/dose level: 10
Indicator Organisms (reverse mutation): Salmonella typhimurium (his G-46)
Negative control: solvent
Positive control: dimethyl nitrosamine (only at 100 mg/kg)
Injection of indicator organisms in mice: 2.0 ml (each ml contained 3.0 x 10E8 cells) intraperitoneally
Three hours later mice were killed, Salmonella species were collected and

the number of mutants was counted.
Mutation frequency (MF): MF of experimental sample/MF of control sample

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (39)

Type : other: Host mediated assay
Species : other: mouse (indicator organism: Salmonella typhimurium TA 1530)
Sex : Male
Strain : ICR
Route of admin. : Gavage
Exposure period : Acute
Doses : 1.45, 14.5, 145.0 (first test) and 500, 5000 mg/kg bw (second test)
Result : Ambiguous
Method : other
Year : 1975
GLP : No
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : Positive effects occurred only at intermediate dose levels with no dose response (significant increased mutant frequency at 145.0 mg/kg bw; 500 and 5000 mg/kg were negative). Effects can therefore be considered as non-relevant.
The corresponding in vitro test gave negative results.

Test condition : Acute Ex-vivo study:
Number of animals/dose level: 10
Indicator Organisms (reverse mutation): Salmonella typhimurium (TA-1530)
Negative control: solvent
Positive control: dimethyl nitrosamine (only at 100 mg/kg)
Injection of indicator organisms in mice: 2.0 ml (each ml contained 3.0 x 10E8 cells) intraperitoneally
Three hours later mice were killed, Salmonella species were collected and the number of mutants was counted.
Mutation frequency (MF): MF of experimental sample/MF of control sample

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (39)

Type : other: Host mediated assay
Species : other: mouse (indicator organism: Salmonella typhimurium G-46)
Sex : Male
Strain : ICR
Route of admin. : Gavage
Exposure period : 5 days
Doses : 1.45, 14.5, 145.0, mg/kg (first test) and 1150 mg/kg (second test)
Result : Negative
Method : other
Year : 1975
GLP : No
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : The in vitro test results were negative as well.
Test condition : Subacute Ex-vivo study:
Number of animals/dose level: 10
Dosages: Aute dosage was given once a day.
Indicator Organisms (reverse mutation): Salmonella typhimurium (his G-46)
Negative control: solvent
Positive control: dimethyl nitrosamine (only at 100 mg/kg)
Injection of indicator organisms in mice: Within 30 minutes after the last

dosage each animal was given 2.0 ml (each ml contained 3.0 x 10E8 cells) intraperitoneally
Three hours later mice were killed, Salmonella species were collected and the number of mutants was counted.
Mutation frequency (MF): MF of experimental sample/MF of control sample

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (39)

Type : other: Host mediated assay
Species : other: mouse (indicator organism: Saccharomyces cerevisiae (D-3))
Sex : Male
Strain : ICR
Route of admin. : Gavage
Exposure period : Acute
Doses : 1.45, 14.5, 145.0 mg/kg (first test) 500, 5000 mg/kg (second test)
Result : Negative
Method : other
Year : 1975
GLP : No
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : The recombinant frequency in the in vitro test with D3 was slightly elevated.
Test condition : Acute Ex-vivo study:
Number of animals/dose level: 10
Indicator Organisms (mitotic recombination): Saccharomyces cerevisiae (D-3)
Negative control: solvent
Positive control: ethyl methane sulfonate (intramusculary injected at a dose of 350 mg/kg)
Injection of indicator organisms in mice: 2.0 ml (each ml contained 5.0 x 10E8 cells) intraperitoneally
Three hours later mice were killed, Yeast species were collected and the number of recombinants was counted.
Recombinant frequency (RF): total recombinants counted/total number colonies screened

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (39)

Type : other: Host mediated assay
Species : other: mouse (indicator organism: Saccharomyces cerevisiae (D-3))
Sex : Male
Strain : ICR
Route of admin. : Gavage
Exposure period : 5 days
Doses : 1.45, 14.5, 145 (first test), 1150 mg/kg (second test)
Result : Ambiguous
Method : other
Year : 1975
GLP : No
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : Slightly enhanced recombinant frequecies in all subacute dose levels.
In a second test with a single subacute dose level of 1150 mg/kg the test result was negative.
The recombinant frequency in the in vitro test with D3 was slightly elevated too.

Test condition : Subacute Ex-vivo study:

Number of animals/dose level: 10
Indicator Organisms (mitotic recombination): Saccharomyces cerevisiae (D-3)
Negative control: solvent
Positive control: ethyl methane sulfonate (intramusculary injected at a dose of 350 mg/kg)
Injection of indicator organisms in mice: Within 30 minutes after last dosage mice were given 2.0 ml (each ml contained 5.0 x 10E8 cells) intraperitoneally
Three hours later mice were killed, Yeast species were collected and the number of recombinants was counted.
Recombinant frequency (RF): total recombinants counted/total number colonies screened

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (39)

Type : other: Host mediated assay
Species : other: mouse (indicator organism: Salmonella typhimurium TA 1530)
Sex : Male
Strain : ICR
Route of admin. : Gavage
Exposure period : 5 days
Doses : 1.45, 14.5, 145.0, mg/kg (first test) and 1150 mg/kg (second test)
Result : Negative
Method : other
Year : 1975
GLP : No
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : The in vitro test results were negative as well.
Test condition : Subacute Ex-vivo study:
Number of animals/dose level: 10
Dosages: Aute dosage was given once a day.
Indicator Organisms (reverse mutation): Salmonella typhimurium (TA 1530)
Negative control: solvent
Positive control: dimethyl nitrosamine (only at 100 mg/kg)
Injection of indicator organisms in mice: Within 30 minutes after the last dosage each animal was given 2.0 ml (each ml contained 3.0 x 10E8 cells) intraperitoneally
Three hours later mice were killed, Salmonella species were collected and the number of mutants was counted.
Mutation frequency (MF): MF of experimental sample/MF of control sample

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (39)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type : other: Sub-chronic
Species : Rat
Sex :
Strain : Wistar
Route of admin. : Gavage
Exposure period : 3 m

Frequency of treatm.	:	Daily
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	
Doses	:	50, 150, 450 mg/kg bw/d
Control group	:	yes, concurrent vehicle
Result	:	150 mg/kg bw/d: decrease of absolute testis weight, no changes in histopathological examinations of testes
Method	:	other
Year	:	1974
GLP	:	No
Test substance	:	other TS: menthol-JPT
Remark	:	There are discrepancies between the full text of the present study and the attached table concerning testes weights. Given information are obtained from table analysis.
Test condition	:	The testis were weighed and histopathologically examined. Details of the study design see chapter 5.4 Repeated dose toxicity.
Reliability	:	(3) invalid Significant methodological deficiencies, see remark.

12.11.2002 (71)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Wistar
Route of admin.	:	Gavage
Exposure period	:	gestation day 6-15
Frequency of treatm.	:	Daily
Duration of test	:	10 consecutive days
Doses	:	2.18, 10.15, 47.05 or 218.0 mg/kg bw/d
Control group	:	other: sham treated with corn oil
other: NOEL Maternal Toxicity	:	= 218 mg/kg bw
other: NOEL Teratogenicity	:	= 218 mg/kg bw
Result	:	Negative
Method	:	other
Year	:	1973
GLP	:	No
Test substance	:	other TS: white needle-like crystalline material
Result	:	Survival of dams: no deaths Body weight of dams: no compound-related changes compared to control (only positive control treated mice showed decreased body weight gain) Fetotoxicity: no dead fetuses in dosage groups (3 deaths in positive control) Average fetus weight: no change in treated groups compared to controls Abnormalities/malfunctions (no. of fetuses affected/no. of litters affected) (sham control, pos.control, 2.18, 10.15, 47.05, 218 mg/kg bw) Skeletal findings: sternebrae (incomplete oss.): 80/22, 94/18, 92/20, 93/22, 101/19, 92/19 sternebrae (missing): 14/6, 11/19, 11/8, 17/5, 11/4, 0/22

skull (incomplete closure): 41/16, 114/19, 46/15, 63/16, 67/20, 49/17
Soft tissue abnormalities:
- pos. control: 7 pups with meningoencephalocele and spina bifida
- 10.15 mg/kg: 1 pup: petechiae, 1 pup: anophthalmia
- 47.05 mg/kg: 2 pups anophthalmia, 2 pups: gastroschisis 1 pup hydrocephalus
All other findings were completely in the range of spontaneous abnormalities found in negative controls.

Test condition : TEST ORGANISMS
No of animals/dose group: 25
No of pregnant animals (2.18, 10.15, 47.05, 218 mg/kg bw): 22, 23, 23, 22
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
- sacrifice: Day 20
NEGATIVE CONTROL: 25 pregnant
POSITIVE CONTROL: aspirin - 250 mg/kg (23 pregnant), no data on expected historical range
MATING PROCEDURES: Virgin adult were mated with young adult males (observation of the vaginal sperm plug was considered Day 0 of gestation)
PARAMETERS ASSESSED DURING STUDY P AND F1:
- Clinical observations : appearance (daily), food consumption (daily), body weight (day 0, 6, 11, 15, 20)
- Estrous cycle: no data
- Other: number of live and dead fetuses, body weights of live pups
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Organ weights P and F1: no
- Histopathology P and F1:
P: urogenital tract, number of implantation and resorption sites
F1: All fetuses were examined grossly, one-third of fetuses of each litter underwent detailed visceral examinations employing 10x magnification, two-third were examined for skeletal defects.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restriction: no full macroscopic examination of dams; no data on statistical evaluation, not tested at maternally toxic doses.

Flag : Critical study for SIDS endpoint

25.02.2003 (72)

Species	:	mouse
Sex	:	female
Strain	:	CD-1
Route of admin.	:	gavage
Exposure period	:	gestation days 6-15
Frequency of treatm.	:	daily
Duration of test	:	10 consecutive days
Doses	:	1.85, 8.59, 39.9 or 185.0 mg/kg bw/d
Control group	:	other: sham treated with corn oil
other: NOEL Maternal Toxicity	:	= 185 mg/kg bw
other: NOEL Teratogenicity	:	= 185 mg/kg bw
Result	:	negative
Method	:	other
Year	:	1973
GLP	:	no

Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : Survival of dams: no deaths
Body weight of dams: no compound-related changes compared to control (only positive control treated mice showed decreased body weight gain)
Fetotoxicity:
dead fetuses (sham control/pos. control/1.85/8.59/39.9/185.5 mg/kg bw): 3/0/0/5/1/3
Average fetus weight: no change in treated groups compared to controls (pos. control: fetus weight reduced)
Abnormalities/malfunctions (no. of fetuses affected/no. of litters affected) (sham control, pos. control, 1.85, 8.59, 39.9, 185.5 mg/kg bw)
Skeletal findings:
sternebrae (incomplete oss.): 53/16, 101/21, 55/15, 69/17, 58/15, 50/17
extremities (incomplete oss.): 1/1, 12/5, 7/5, 8/4, 6/3, 4/2
miscellaneous (hyoid missing): 24/11, 60/13, 31/12, 43/15, 31/13, 45/15
Soft tissue abnormalities: no compound related changes
All other findings were completely in the range of spontaneous abnormalities found in negative controls.

Test condition : TEST ORGANISMS
No of animals/dose group: 25
No of pregnant animals (1.85, 8.59, 39.9, 185.0 mg/kg bw):
19 (28 animals were mated), 22, 22 (2 animals were not mated), 22
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
- Total volume applied: 10 ml/kg bw
- sacrifice: Day 17
NEGATIVE CONTROL: 23 pregnant
POSITIVE CONTROL: aspirin - 150 mg/kg (23 pregnant), no data on expected historical range
MATING PROCEDURES: Virgin adult were mated with young adult males (observation of the vaginal sperm plug was considered Day 0 of gestation)
PARAMETERS ASSESSED DURING STUDY P AND F1:
- Clinical observations: appearance (daily), food consumption (daily), body weight (day 0, 6, 11, 15, 17)
- Estrous cycle: no data
- Other: number of live and dead fetuses, body weights of live pups
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Organ weights P and F1: no
- Histopathology P and F1:
P: urogenital tract, number of implantation and resorption sites
F1: All fetuses were examined grossly, one-third of fetuses of each litter underwent detailed visceral examinations employing 10x magnification, two-third were examined for skeletal defects.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restriction: no full macroscopic examination of dams; no data on statistical evaluation, not tested at maternally toxic doses.

Flag : Critical study for SIDS endpoint
25.02.2003 (72)

Species : rabbit
Sex : female
Strain : no data

Route of admin.	:	gavage
Exposure period	:	gestation days 6-18
Frequency of treatm.	:	daily
Duration of test	:	13 consecutive days
Doses	:	4.25, 19.75, 91.7 or 425.0 mg/kg bw/d
Control group	:	other: sham treated with corn oil
other: NOEL Maternal Toxicity	:	= 425 mg/kg bw
other: NOEL Teratogenicity	:	= 425 mg/kg bw
Result	:	negative
Method	:	other
Year	:	1973
GLP	:	no
Test substance	:	other TS: Menthol natural brazilian, FDA 71-57

Result :
Survival of dams:
Died or aborted before day 29 (sham control/pos. control/4.25/19.75/91.7/425 mg/kg bw): 1, 1, 2, 3, 1, 4
Body weight of dams: no compound-related changes compared to control
Fetotoxicity:
dead fetuses (sham control/pos. control/4.25/19.75/91.7/425 mg/kg bw): 0, 2, 2, 0, 0, 0
Average fetus weight: weight of fetuses from treated groups (19.75, 91.7 and 425 mg/kg) is slightly higher compared to controls
Abnormalities/malfunctions
Skeletal findings and soft tissue abnormalities: All findings were completely in the range of spontaneous abnormalities found in negative controls.
Pos. controls: scrambled vertebrae in 23, Scoliosis in 14, tail defects in 41 fetuses (in neg. controls and treated animals max. seen in 2 fetuses); enhanced numbers of anopia

Test condition :
TEST ORGANISMS
No of mated animals/dose group: 17/4.25 mg/kg bw, 19/19.75 mg/kg bw, 15/91.7 mg/kg bw, 19/425 mg/kg bw
No of pregnant animals (4,25, 19.75, 91.7, 425.0 mg/kg bw): 13, 12, 11, 14
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
- Time of death: Day 29
NEGATIVE CONTROL: 16 mated, 12 pregnant animals
POSITIVE CONTROL: 6-aminonicotinamide dosed on day 9 - 2,5 mg/kg (17 mated, 12 pregnant animals), no data on expecte historical range
MATING PROCEDURES: Day 0 each virgin adult - 0.4 ml human chorionic gonadotropin (injection via ear vein); three hours later - insemination with 0.3 ml of diluted semen with appr. 20 x 10E6 motile sperm (Vogin et al.: Pharmacologist 11, 282, 1969)
PARAMETERS ASSESSED DURING STUDY P AND F1:
- Clinical observations: appearance (daily), food consumption (daily), body weight (day 0, 6, 12, 18, 29)
- Estrous cycle: no data
- Other: number of live and dead fetuses, body weights of live pups
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Organ weights P and F1: no
- Histopathology P and F1:
P: urogenital tract, numbers of corpora lutea, number of implantation and resorption sites
F1: All fetuses - detailed gross examination, neonatal survival of live

fetuses of each litter was observed (incubator for 24 hrs), all surviving pups were sacrificed and all pups examined for visceral abnormalities (dissection); all fetuses were examined for skeletal defects.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: no full macroscopic examination of dams; no data on statistical evaluation, not tested at maternally toxic doses.

Flag : Critical study for SIDS endpoint
25.02.2003 (72)

Species : Syrian hamster
Sex : female
Strain : no data
Route of admin. : gavage
Exposure period : gestation days 6-10
Frequency of treatm. : daily
Duration of test : 5 consecutive days
Doses : 4.05, 21.15, 98.2 or 405.0 mg/kg bw/d
Control group : other: sham treated with corn oil
other: NOEL Maternal Toxicity : = 405 mg/kg bw
other: NOEL Teratogenicity : = 405 mg/kg bw
Result : negative
Method : other
Year : 1973
GLP : no
Test substance : other TS: Menthol natural brazilian, FDA 71-57

Result : Survival of dams: no deaths
Died or abortedbefore day 14 (sham, pos. control, 4.05, 21.15, 98.2, 405.0 mg/kg bw) 0, 0, 2, 1, 1, 1,
Body weight of dams: average body weights of all treated groups is increased compared to control
Fetotoxicity: dead fetuses (sham, pos. control, 4.05, 21.15, 98.2, 405.0 mg/kg bw) 1, 18, 1, 1, 0, 0
Average fetus weight: no change in treated groups compared to controls
Abnormalities/malfunctions (no. of fetuses affected/no. of litters affected)(sham, pos. control, 4.05, 21.15, 98.2, 405.0 mg/kg bw)
- Skeletal findings:
- sternebrae (incomplete oss.): 84/21, 79/21, 56/18, 112/21, 74/18, 62/18
- ribs (more that 13): 40/18, 62/18, 74/17, 56/16, 38/13, 44/15
- vertebrae (incomplete oss.): 1/1, 0, 0, 7/5, 5/5, 0
- extremities (incomplete oss.): 0, 0, 2/2, 5/3, 3/3, 1/1
- miscellaneous (hyoid reduced): 3/1, 1/1, 2/2, 8/6, 9/5, 2/2
Soft tissue abnormalities:
- sham: 1 pup: cardiomegaly, apulmonism
- pos. control: 1 pups: moderate hydrocephalus
- 4.05 mg/kg bw: 1 pup: abdominal hernia, 1 pup: gastroschisis
- 21.15 mg/kg bw: 2 pups: cardiomegaly, apulmonism, 2 pups atelocardia
All other findings were completely in the range of spontaneous abnormalities found in negative controls.
Positive control enhanced letality of fetuses but did not induce teratogenic effects.

Test condition : TEST ORGANISMS
No of animals/dose group: 25

No of pregnant animals (4.05, 21.15, 98.2, 405.0 mg/kg bw):
22 (one animal was not mated), 23, 21, 21
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
- Time of death: Day 14
NEGATIVE CONTROL: 22 pregnant
POSITIVE CONTROL: aspirin - 250 mg/kg (22 pregnant), no data on expected historical range
MATING PROCEDURES: Virgin adult were mated (1:1) with mature males (appearance of motile sperm in the vaginal smear was considered as Day 0 of gestation)
PARAMETERS ASSESSED DURING STUDY P AND F1:
- Clinical observations: appearance (daily), food consumption (daily), body weight (day 0, 8, 10, 14)
- Estrous cycle: no data
- Other: number of live and dead fetuses, body weights of live pups
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Organ weights P and F1: no
- Histopathology P and F1:
P: genital tract, number of implantation and resorption sites
F1: All fetuses were examined grossly, one-third of fetuses of each litter underwent detailed visceral examinations employing 10x magnification, two-third were examined for skeletal defects.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: no full macroscopic examination of dams; no data on statistical evaluation, not tested at maternally toxic doses.

Flag : Critical study for SIDS endpoint
25.02.2003 (72)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human - Medical Data

Result : Concentration of menthol oil vapor in the production site ranged within limits of 0.005 to 0.378 mg/l. Reported complaints were: pain in the area around the liver and kidney. Signs of intoxication: Enlargement of the liver, protein in urine (50 % of subjects), dysfunction in the detoxification capacity of the liver (14 % of subjects).

Test condition : In order to determine the value of the maximum allowable concentration of vapors of menthol medical examinations (twice in a period of six months) of employers working in the essential oil manufacturing plant were carried out. 104 subjects were examined (30 % females). 25 subjects were aged between 36-46 years, 12 subjects were older than 56 years. Duration of employment was 3-12 years with an average value of 6 years. Environmental investigations were done as well: Method of determination of menthol vapor was based on the colour reaction with vaniline.

Reliability : (4) not assignable

Documentation insufficient for assessment. No detailed data on study population. Nodata on dose relation. The method of menthol concentration measurement is doubtful.

25.02.2003 (61)

Type of experience : Human

Result : Results:
Self-desensitiza tion for both chemicals
Cross-desensitization of menthol by capsaicin
Revealed cross-sensitization of capsaicin by menthol
Test condition : 15 persons (9f, 6m, aged 24-34 years)
3.5 ppm capsaicin and 0.30% l-menthol was given to the tongue tip.
Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (73) (74)

Type of experience : Direct observation, poisoning incidents

Result : Ingestion causes severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma.
Test substance : obtained principally from peppermint oil
Reliability : (4) not assignable
Data from handbook or collection of data.

25.02.2003 (75)

5.11 ADDITIONAL REMARKS

Type : Biochemical or cellular interactions

Result : L-Menthol enhances transdermal drug penetration.
Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (76) (77)

Type : Excretion

Result : In the urine of sheep fed with l-menthol, the glucuronide and the ammonium salt of l-menthol was obtai ned in nearly quantititative recovery.
Test condition : The detoxification mechanism of sheep was examined.
Reliability : (4) not assignable
Documentation insufficient for assessment.

03.05.2002 (78)

Type : Metabolism

Result : L-Menthol was not a potent in vitro inhibitor of MROD (CYP1A2) activity (IC50:>300 µM) and of EROD (CYP1A1) activity (IC50 µM:>400 µM); it did inhibit PROD (CYP2B1) activity (IC50: 10.6 µM), but was much less potent than beta-ionon which had an IC50 of 0.03 µM.
Test condition : The inhibitory effects of (-)-menthol on liver microsomal enzymes involved in biotransformation of xenobiotic substances were studied in vitro.
Reliability : (2) valid with restrictions
non-standard in vitro test system

18.01.2002 (79)

Type : Metabolism

Result : (-)-/(+)-menthol glucuronidation ratio: 2.6/1
Vmax (-)/(+)-menthol glucuronidation ratio: 2.8/1
Data suggest, that monkey UGT2B9 and human UGT2B7 are functionally similar (89 % identity in cDNA library).
Test condition : Enantioselective glucuronidation for (+)- and (-)-menthol was studied using expressed monkey UGT2B9 (UDP-glucuronosyltransferase)
Reliability : (2) valid with restrictions
non-standard in vitro test system
22.01.2002 (80)

Type : Metabolism

Result : Addition of 1% l-menthol increased the total skin permeability coefficient (cm/h) to about 2.5 times. The metabolic index was decreased, compared to the controls.
Test condition : The effect of l-menthol as an enhancer on the simultaneous transport and metabolism of ehtyl nicotinate through excised hairless rat skin were measured.
Reliability : (2) valid with restrictions
non-standard in vitro test system
22.01.2002 (81)

Type : Metabolism

Result : After a daily dose of 750 mg l-menthol for a total of 8 days to two human volunteers 17-38% menthol was recovered as urinary menthyl glucuronide within 24 hours. Urine was first collected 3 days after dosage with l-menthol started.
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
03.05.2002 (33)

Type : other: carcinogenicity inhibition

Result : Dietary additions of (-)-menthol resulted in a significant inhibition of mammary carcinogenesis.
Test condition : Rats administered 7,12-dimethylbenz[a]anthracene were given (-)-menthol in diet and the inhibition effect of mammary carcinogenesis was observed.
Reliability : (4) not assignable
Documentation insufficient
05.03.2003 (82)

Type : other: typical flavor

Result : Only l-menthol shows the peppermint typical flavor and odour, associated with the cooling effect.
22.05.2002 (83)

Type : other: ventilation depression

Result : The addition of l-menthol to a warm airflow depresses ventilation to a similar extent as compared to cold airflows.
Menthol influences the activity of the sensory and cold receptors of the larynx.
Test condition : The respiration rate of 8 anesthetized 7-14-days old dogs was investigated. Constant flows of warm air (37 °C) with and without addition of l-menthol

and cold air (25 °C) were delivered through the upper airway.

Reliability : (2) valid with restrictions
limited documentation

05.03.2003 (84)

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

I U C L I D Data Set

Existing Chemical	:	ID: 1490-04-6
CAS No.	:	1490-04-6
EINECS Name	:	Menthol
EC No.	:	216-074-4
TSCA Name	:	Cyclohexanol, 5-methyl-2-(1-methylethyl)-
Molecular Formula	:	C10H20O

Producer related part

Company	:	Bayer AG
Creation date	:	09.11.2001

Substance related part

Company	:	Bayer AG
Creation date	:	09.11.2001
Status	:	
Memo	:	ICCA - Category Menthole
Printing date	:	18.03.2003
Revision date	:	
Date of last update	:	18.03.2003
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status :
Purity : >= 99 % w/w
Colour : colourless to white
Odour : minty

Remark : "Unspecified mixture of menthol isomers".
The CAS-No. 1490-04-6 is correctly assigned to "5-Methyl-2-(1-methylethyl)cyclohexane" in the English EINECS. In the German EINECS it is incorrectly assigned to "DL-Menthol" (GESTIS). Thus the English EINECS does not exclude the neo-, iso- and neoisomenthols from the mixture!
Flag : Critical study for SIDS endpoint
07.08.2002 (1)

Purity type :
Substance type : organic
Physical status :
Purity :
Colour : colourless
Odour : like peppermint smelling

Flag : Critical study for SIDS endpoint
14.03.2003 (2)

Purity type :
Substance type : organic
Physical status : solid
Purity :
Colour : white
Odour :

Remark : White crystals (cf. 2.1 Melting Point)
Flag : Critical study for SIDS endpoint
14.03.2003 (3)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

5-METYL-2-(1-METHYLETHYL)-CYCLOHEXANOL

Flag : Critical study for SIDS endpoint
29.05.2002

5-METYL-2-(1-METHYLETHYL)-CYCLOHEXANOL ISOMERS

Flag : Critical study for SIDS endpoint
03.06.2002

CYCLOHEXANOL, 5-METYL-2-(1-METHYLETHYL)-

Flag : Critical study for SIDS endpoint
29.05.2002

MENTHOL, UNSPECIFIED MIXTURE OF MENTHOL ISOMERS

Flag : Critical study for SIDS endpoint
29.05.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Labelling : provisionally by manufacturer/importer
Specific limits :
Symbols : Xi, , ,
Nota : , ,
R-Phrases : (38) Irritating to skin
S-Phrases : (25) Avoid contact with eyes

Flag : Critical study for SIDS endpoint
29.05.2002

1.6.2 CLASSIFICATION

Classified : provisionally by manufacturer/importer
Class of danger : irritating
R-Phrases : (38) Irritating to skin
Specific limits :

Flag : Critical study for SIDS endpoint
29.05.2002

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Use in closed system

Remark : used in chemical industry as an intermediate in synthesis
Flag : Critical study for SIDS endpoint
18.03.2003

Type of use : type
Category : Wide dispersive use

Remark : use in veterinary activities and pharmaceutical industry for production of pharmaceuticals
Flag : Critical study for SIDS endpoint
25.07.2002

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Remark : Menthol is produced via reaction of m -cresol with propen to thymol, and hydrogenation of thymol, resulting in 4 isomers: D/L-neomenthol, D/L-neoisomenthol, D/L-menthol and D/L-isomenthol. D/L-menthol is isolated by fractional distillation. To produce L-menthol, D/L-menthol is transesterificated with methylbenzoate and further manufactured. Resulting products are L- and D-menthol. Plant materials from some Mentha and other species also contain various menthols in the essential oils. These oils may vary in composition.
03.06.2002 (4)

Origin of substance : Natural origin
Type : Plant extract

03.06.2002 (4)

Origin of substance : Synthesis
Type : Plant extract

Remark : Various synthetic methods start from plant extracts
30.07.2002 (4)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by :
Labelled by :
Class of danger : 1 (weakly water polluting)

29.05.2002 (1)

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : no
No. in Seveso directive :

29.05.2002 (1)

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

Type : EINECS
Additional information :

29.05.2002

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 5
Date of search : 01.09.2001

Remark : Human Health: last literature search September 2001: CAS number search in external and internal databases, e.g. Biosis, Embase, Toxline, Scisearch
Flag : Critical study for SIDS endpoint
10.07.2002

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 14.01.2002

Remark : Physico-chemical properties / Environment / Ecotoxicology : last literature search January 2002: CAS number search in external and internal databases, e.g. HSDB, Aquire.
Flag : Critical study for SIDS endpoint
29.07.2002

1.13 REVIEWS

Memo : Menthol: Its Origins, Chemistry, Physiology and Toxicological Properties

Flag : Critical study for SIDS endpoint
03.06.2002 (4)

2.1 MELTING POINT

Value : 5 °C
Sublimation :
Method : other: no data
Year : 1996
GLP : no data
Test substance : no data

Reliability : (3) invalid
The melting point of 5 °C is in contrast to the reported "white crystals". The vapour pressure is reported twice (with small diffences) in mm Hg and hPa. The solubility is reported to be "508,000 mg/l" (= 508 g/l) which is interpreted to be a typographical error. A wrong structural formula and a low boiling point are also reported in the reference.

11.03.2003 (3)

2.2 BOILING POINT

Value : ca. 215.5 °C at 1013 hPa
Decomposition :
Method :
Year : 2002
GLP : no data
Test substance : no data

Flag : Critical study for SIDS endpoint
18.03.2003 (2)

Value : 212 °C at
Decomposition :
Method : other: no data
Year :
GLP : no data
Test substance : no data

18.03.2003 (5)

Value : 175 °C at
Decomposition :
Method : other: no data
Year : 1996
GLP : no data
Test substance : no data

Reliability : (3) invalid
The boiling point reported by Verschueren is very low compared to other sources. This is in line with other information on this substance: Verschueren reports the solubility to be "508,000 mg/l" (= 508 g/l) which was interpreted to be a typographical error. Verschueren also reports a wrong structural formula. The melting point of 5 °C is in contrast to the reported "white crystals" (expected: colourless liquid when melting point is correct). The vapour pressure is reported twice (with small diffences) in mm Hg and hPa.

11.03.2003 (3)

2.3 DENSITY

Type : density
Value : .898 g/cm³ at 25 °C
Method :
Year : 2002
GLP : no data
Test substance : no data

Flag : Critical study for SIDS endpoint
18.03.2003 (2)

Type : density
Value : .89 at °C
Method :
Year : 1996
GLP : no data
Test substance : no data

18.03.2003 (5)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .085 hPa at 25 °C
Decomposition :
Method :
Year : 1996
GLP : no data
Test substance : no data

Remark : Extrapolated to 25 °C. The vapour pressure is reported twice (with small diffences) in mm Hg and hPa. The mm Hg data are identical with data of Jordan (1954) reported for L-menthol. These data were extrapolated to 25 °C.
The handbook also contains a wrong structural formula and a wrong solubility. Both were assumed to be typographical errors. The melting point of 5 °C is in contrast to the reported "white crystals". The boiling point is lower than reported by others.
Flag : Critical study for SIDS endpoint
14.03.2003 (3)

Value : 1.3 hPa at 55 °C
Decomposition :
Method :
Year : 1996
GLP : no data
Test substance : no data

Remark : The vapour pressure is reported twice (with small diffences) in mm Hg and hPa. The mm Hg data are identical with data of Jordan (1954) reported for L-menthol.
The handbook also contains a wrong structural formula and a wrong solubility. Both were assumed to be typographical errors. The melting point

of 5 °C is in contrast to the reported "white crystals". The boiling point is lower than reported by others.

14.03.2003 (3)

Value : 13 hPa at 95 °C
Decomposition :
Method :
Year : 1996
GLP : no data
Test substance : no data

Remark : The vapour pressure is reported twice (with small diffences) in mm Hg and hPa. The mm Hg data are identical with data of Jordan (1954) reported for L-menthol.
The handbook also contains a wrong structural formula and a wrong solubility. Both were assumed to be typographical errors. The melting point of 5 °C is in contrast to the reported "white crystals". The boiling point is lower than reported by others.

14.03.2003 (3)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : 3.4 at °C
pH value :
Method : other (calculated)
Year : 1999
GLP : no data
Test substance : other TS: L-menthol and D/L-menthol

Method : The log kow was determined for L-menthol and D/L-menthol by reversed-phase high-performance liquid chromatography. The log kow was 3.40 for both L-menthol and D/L-menthol and is thus valid for any mixture of D-menthol and L-menthol
Flag : Critical study for SIDS endpoint
14.03.2003 (6)

Partition coefficient : octanol-water
Log pow : 3.38 at °C
pH value :
Method : other (calculated): SRC-KOWWIN v. 1.66
Year : 2002
GLP :
Test substance :

Flag : Critical study for SIDS endpoint
14.03.2003 (7)

Partition coefficient : octanol-water
Log pow : 3.25 at °C
pH value :
Method : other (calculated)
Year : 1996
GLP :
Test substance :

Remark : The vapour pressure is reported twice (with small diffences) in mm Hg and

hPa. The mm Hg data are identical with data of Jordan (1954) reported for L-menthol.
The handbook also contains a wrong structural formula and a wrong solubility. Both were assumed to be typographical errors. The melting point of 5 °C is in contrast to the reported "white crystals". The boiling point is lower than reported by others.

18.03.2003 (3)

Partition coefficient : octanol-water
Log pow : 3.3 at °C
pH value :
Method :
Year : 2002
GLP : no data
Test substance : no data

18.03.2003 (8)

Partition coefficient : octanol-water
Log pow : 3.23 at °C
pH value :
Method : other (calculated)
Year : 1991
GLP :
Test substance :

18.03.2003 (9)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 420 mg/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: stalogmometric method
Year : 1922
GLP : no
Test substance : no data

Remark : Seidell refers to a report of Rhode (1922) and briefly describes method. Measuring temperature is room temperature.
Wakita K, Yoshimoto M, Miyamoto S, Watanabe H (1986) [Chem Pharm Bull 34: 4663 - 4681] cite Yalkowsky and Morzowich [(1980) in Drug Design Vol 9, ed. by Ariens EJ, Academic Press New York, p. 121] as log 1/S (S = solubility, mol/l) = 2.57, which equals to 420 mg/l.
Flag : Critical study for SIDS endpoint
14.03.2003 (10)

Solubility in : Water
Value : 431 mg/l at 20 °C
pH value :

concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	2002
GLP	:	no data
Test substance	:	no data

18.03.2003 (2)

Solubility in	:	Water
Value	:	456 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	2002
GLP	:	
Test substance	:	

18.03.2003 (8)

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	

Remark : "slightly soluble"
25.01.2002 (5)

Solubility in	:	Water
Value	:	508 mg/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	

The handbook reports the solubility to be "508,000 mg/l" (= 508 g/l) which was interpreted to be a typographical error.
The handbook also contains a wrong structural formula and reports low melting and boiling points. The melting point of 5 °C is in contrast to the reported "white crystals" (expected: colourless liquid when melting point is

correct). The vapour pressure is reported twice (with small diffences) in mm Hg and hPa.

10.03.2003 (3)

Solubility in	:	Water
Value	:	593 mg/l at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: calculated with fragment solubility constants
Year	:	1986
GLP	:	
Test substance	:	other TS: not indicated which menthol was used for calculation, but method is applicable for all menthol isomers

Remark : Wakita et al. (1986) cite Yalkowsky and Morzowich [(1980) in Drug Design Vol 9, ed. by Ariens EJ, Academic Press New York, p. 121] as log 1/S (S = solubility, mol/l) = 2.57, which equals to 420 mg/l.
Their calculated solubility is log 1/S (S = solubility, mol/l) = 2.42, which equals to 593 mg/l.

14.03.2003 (11)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	100 °C
Type	:	closed cup
Method	:	
Year	:	2002
GLP	:	no data
Test substance	:	no data

18.03.2003 (2)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Threshold odour concentration

Result : Threshold odour concentration, detection 0.9 mg/m3
Threshold odour concentration, recognition 2.1 mg/m3

11.03.2003 (3)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Method	:	structure estimation method
Result	:	Rate constant: k = 2.4 E -11 cm3/molecule/sec at 25 degrees C; considering an atmospheric OH-radical concentration of 5 E5 OH-radicals/cm3, the half-life is about 16 h
Reliability	:	(2) valid with restrictions accepted calculation procedure
Flag	:	Critical study for SIDS endpoint

29.07.2002 (12)

3.1.2 STABILITY IN WATER

Deg. product	:	
Method	:	other: calculated
Year	:	2001
GLP	:	
Test substance	:	
Result	:	volatilization half-lives for a model river (1 m deep, flow-rate 1 m/sec, wind velocity 3 m/sec) and a model lake (1 m deep, flow-rate 0.05 m/sec, wind velocity 0.5 m/sec) are estimated to be 2 and 18 days
Reliability	:	(2) valid with restrictions accepted calculation procedure derived from L-Menthol cause of structural similarities
Flag	:	Critical study for SIDS endpoint

18.03.2003 (13)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Type of measurement	:	background concentration
Media	:	surface water
Concentration	:	
Method	:	GC/MS
Remark	:	Measurements in the rive Neckar (Germany) at various seasons gave menthol concentrations between 0.0093 and 0.139 ug/l.
Reliability	:	(2) valid with restrictions Acceptable procedure and publication.

26.07.2002 (14)

Result	:	In an investigation of eight small rivers and brooks which flow into Lake Constance (SW Germany) menthol was detected qualitatively.
Reliability	:	(2) valid with restrictions Acceptable procedure and publication.

30.07.2002 (15)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	volatility
Media	:	water - air
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: estimation method
Year	:	2003
Result	:	Based on a water solubility of 420 mg/l and a vapour pressure of 8.5 Pa (see chapter 2), the Henry's law constant is calculated to be 3.16 Pa x m3/mol
Reliability	:	(2) valid with restrictions Generally accepted calculation method
Flag	:	Critical study for SIDS endpoint

14.03.2003 (16)

3.3.2 DISTRIBUTION

Media	:	air - biota - sediment(s) - soil - water
Method	:	Calculation according Mackay, Level I
Year	:	2003
Result	:	Distribution air: 44.2 % water: 40.4 % soil: 8.0 % sediment: 7.3 % biota: 0.005 %
Test condition	:	Base data for calculation: temperature: 20 °C molar mass: 156.27 g/mol vapour pressure: 8.5 Pa water solubility: 420 g/m3 log Kow: 3.4 environmental compartments: - air: 6*10^9 m³, 1.2 kg/m³ - water: 7*10^6 m³, 1000 kg/m³ - soil: 4.5 *10^4 m³, 1500 kg/m³, 2 % org. C - sediment: 2.1*10^4 m³, 1300 kg/m², 5 % org. C - susp. sediment: 35 m³, 1500 kg/m³, 16.7 % org. C - aerosol: 0.12 m³, 1500 kg/m³ - aquatic biota: 7 m³, 1000 kg/m³, 5 % fat
Reliability	:	(2) valid with restrictions Generally accepted calculation method
Flag	:	Critical study for SIDS endpoint

14.03.2003 (16)

Media : water - soil
Method : other (calculation)
Year :

Result : Using the equation log Koc = 0.52 log Kow + 1.02 and based on a log Kow of 3.4 a Koc value of 614 can be calculated for the distribution between the organic phase of soil and pore water
Reliability : (2) valid with restrictions
Generally accepted calculation method
Flag : Critical study for SIDS endpoint
11.03.2003 (17)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, adapted
Concentration : 200 mg/l related to COD (Chemical Oxygen Demand)
related to
Contact time :
Degradation : 95.1 (±) % after 5 day(s)
Result : inherently biodegradable
Deg. product :
Method : other: batch system (comparable to Zahn-Wellens Test)
Year : 1976
GLP : no
Test substance : other TS: menthol, not further specified

Method : Test compound as sole source of carbon; inoculum density:
100 mg dry matter/l; gradual increase of TS concentration during 20 days adaptation period; losses due to volatilization were monitored
Result : Pitter reported the biodegradation rate (for menthol 17.7 mg COD/g/h) and the total removal after 5 days (for menthol 95.1 %).
The total removal is due to biodegradation and other removal mechanisms e.g. volatilization. When testing volatile substances he incubated blanks (test assay without inoculum) and measured removals after short periods to distinguish between volatilization and biodegradation, and to derive a kinetic for biodegradation. Using this normalized biodegradation rate (in mg COD/g/h) he considered substances with a biodegradation rate larger than 15 mg COD/g/h "to be biologically readily decomposable".
Test condition : 20 +/- 3 °C; pH 7.2; mineral salts medium; dark; continuously stirred
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
12.03.2003 (18)

Contact time :
Degradation : (±) % after
Result : other: Readily degradable
Deg. product :
Method :
Year : 1985
GLP : no data
Test substance : no data

Method : Method not described but reported to be recommended by the Department of Environment, Standing Committee of Analysts (1981) and by King (1981)

Reliability : (4) not assignable
Documentation insufficient for assessment. Missing details.

11.03.2003 (19)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	other: QSAR estimation
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	
Unit	:	mg/l
LC50	:	19
Method	:	
Year	:	1999
GLP	:	
Test substance	:	
Method	:	QSAR estimation for non-polar narcotics
Reliability	:	(3) invalid QSAR not usable for risk assessment

18.03.2003 (20)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	other: Hydractinia echinata
Exposure period	:	3 hour(s)
Unit	:	mg/l
EC50	:	78.3
Limit Test	:	no
Analytical monitoring	:	no data
Method	:	other: as summarised
Year	:	2000
GLP	:	no
Test substance	:	other TS: 1-Isopropyl-5-methylcyclohexanol CAS Nr. 1490-04-6
Remark	:	Missing information, namely, details of the method, whether or not an analytical monitoring was performed and tested concentrations.
Result	:	Result is given as log (1/EC50)=3.3 where EC50 is the concentration in mol/l at which the frequency of induction (methamorphosis) was reduced by 50 % with respect to a control.
Test condition	:	The culture medium was artificial seawater (980 mosmol, pH 8.2, 18 degree C). Observed was the percentage of animals that underwent methamorphosis (development into polyps). For 3 hours the larvae were exposed to seawater containing 20 mM CsCl and simultaneously the test substance. On the day after the effect (metamorphosis) was measured. Experiments were performed in triplicate for each concentration and were repeated at least twice.
Reliability	:	(2) valid with restrictions

18.03.2003 (21)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	other: potato-dextrose-agar

Species	:	other fungi: Colletotrichum gloeosporioides
Exposure period	:	
Unit	:	mg/l
EC50	:	452
Analytical monitoring	:	no data
Method	:	other: as described
Year	:	1998
GLP	:	no data
Test substance	:	other TS: Several monoterpenoids, including menthol
Remark	:	Assessment of the effect under real environmental conditions not possible
Result	:	EC50 for the mycelial growth inhibition of C. gloeospordioides on potato-dextrose-agar medium was determined by the poisoned food technique. The percentages of inhibition observed at the tested concentrations (250, 400, 500, 600 and 700 mg/l) were converted to probits and EC50 was computed from a linear relationship between logarithms of concentrations and probits.
Test condition	:	The oils of peppermint were obtained by hydrodistillation of the leaves. Appropriate quantity of test substance was dissolved in 0.25 ml acetone and were added to 30 ml of sterilized medium to get the medium of required concentration, the same amount of acetone being added in the control also. Mycelial discs of C. gloeosporioides were transferred asceptically to the Petri dishes and these were incubated at 27 +/- 2 degrees C for 5 days.
Reliability	:	(2) valid with restrictions Unsuitable test system namely the tested medium, not relevant for environmental hazard assessement

07.08.2002 (22)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Species	:	other: Apis mellifera (honey bee)
Endpoint	:	other: colony population, growth, foraging activity, honey production
Exposure period	:	
Unit	:	
Method	:	
Year	:	1999
GLP	:	no
Test substance	:	no data

Method	:	Corrugated cardboard dipped in a menthol - vegetable oil mixture placed in bee colony. Board replaced after 8 days.
Result	:	Brood survival, adult population, foraging acitity, and honey production did not differ from control. Brood area was lower than in control colonies.
Reliability	:	(3) invalid No conclusion from environmental concentrations to effects possible, not relevant for environmental hazard assessement

07.08.2002 (23)

Species	:	other: Apis mellifera
Endpoint	:	mortality
Exposure period	:	48 hour(s)
Unit	:	other: microg/Bee
LC6	:	100
Method	:	other: as summarised
Year	:	1999
GLP	:	no data
Test substance	:	other TS: no purity given
Method	:	Bees were fed with liquid sandwiches with syrup drawn into micropipette, followed by menthol in ethanol followed again by syrup.
Remark	:	No mortality in honeybees attributable to menthol.
Reliability	:	(2) valid with restrictions No conclusion from environmental concentrations to effects possible. The same effect was observed in the control sample. Not relevant for environmental hazard assessment.

07.08.2002 (24)

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type : Distribution
Species : rat
Number of animals
Males :
Females :
Doses
Males : 470 mg/kg bw
Females :
Vehicle : other: olive oil
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st.:
2nd.:
3rd.:
Toxic behaviour :
Deg. product :
Method :
Year : 1982
GLP : no
Test substance : other TS: [3-3H]-Menthol, analyt

Result : Tissue or fluid distribution of menthol after 17 hours (in % of administered radioactivity):
Urine: 52 %
Feces: 4.5 %
Ileum: 3.5 %
Liver: 0.8 %
Fat: 2.1 %
Kidney: 0.2 %
Brain and Testes: < 0.1 %-
Serum: 0.31 %
After 17 hours after treatment HMG-CoA reductase activity was inhibited by up to 70%. The transient nature of this effect (no inhibition 41 h after dosing) was compatible with the rapid metabolism and excretion of menthol.

Test condition : 3.0 mmol/kg (470 mg/kg bw) menthol were administered to 3 male rats (strain: Wistar) in a single dose. Controls were given olive oil alone. After 17 hours the animals were killed. Urine and faeces were collected over the 17 h period. After killing, samples of a variety of tissues were removed, digested with tissue solubilizer, and counted for radioactivity. Body fluids were counted directly without prior solubilization.

Liver 3-hydroxy-3-methylglutaryl coenzyme A reductase activity (HMG-CoA) inhibition was measured.

Reliability : (2) valid with restrictions
menthol isomer not specified, short samping period

Flag : Critical study for SIDS endpoint
24.02.2003 (25)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human

Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method : other
Year : 1972
GLP :
Test substance :

Result : Individual data is shown for only one volunteer. In this person 77.5 % of the dose could be recovered in the urine within 11 hours.

The excretion of menthol after dermal application was slower than after oral administration. No data on the applied amount of menthol are given.

Menthol was found in the urine of an untreated person, who was living in the same room as a patient rubbed with a menthol-containing unguent. It is concluded that a great amount of menthol (among other etheral oils) even after dermal application is inhaled.

Test condition : 10-20 mg menthol was administered orally to humans (number not specified) and urine samples were collected after 3, 6, 9, 12, 24 and 36 hours.

Additionally urine-samples of persons were analyzed after dermal application of a menthol containing unguent.

Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (26)

In Vitro/in vivo : In vivo
Type : Excretion
Species : other: human and dog
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1928
GLP :
Test substance :

Result : Human:
79 % of a 1 g oral dose of menthol is excreted in the urine via glucuronide conjugate within 6 h after administration.
Number of persons not given

Dog:
5 % of a 5 g oral dose of menthol is excreted in the urine via glucuronide conjugate. Sampling time is not given.

Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint

24.02.2003 (27)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :

Result : 35-40 % of menthol was recovered in the urine in 24 hours.
Test condition : Pharmacokinetic studies were performed in six volunteers (four m, two f, 17-37 years). Peppermint oil was ingested in two soft gelatine capsules. Each capsule contained 91-97 mg m enthol (total dose: 180-190 mg). Urine was collected for 24 hours (2 hours aliquots up to 14 h).
Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (28)

In Vitro/in vivo : In vivo
Type : Excretion
Species : Human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1990
GLP :
Test substance : other TS: commercial grade

Result : Human investigation with 4 male volunteers: An average of 40 % of menthol was recovered in urine after ingestion of 180 mg of peppermint oil (= 72 mg menthol) in an enteric-coated capsule following a 16 h fast. Total urine output was collected every 2 hours for up to 14 hours after dosing.
Reliability : (2) valid with restrictions
limited documentation; isomer not specified
Flag : Critical study for SIDS endpoint
24.02.2003 (29)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : Human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1967

GLP	:	
Test substance	:	other TS: unspecified isomer
Result	:	Between 40.1 % and 98.7 % of the oral dose of menthol was excreted as glucuronide in urine in 24 hours. Most individuals (11/19) excreted between 70 and 89% of the administered dose. Within the first few hours after the intake of menthol (dose was approx. 20 mg menthol/kg bw) a mild abdominal discomfort was nearly always felt, sometimes with nausea.
Test condition	:	In 19 healthy men, aged between 19 and 24 years, urine was collected up to 24 hours after ingestion of a 1.59 g oral dose of menthol, administered as an oil-in-water emulsion.
Reliability	:	(2) valid with restrictions limited documentation; isomer not specified
Flag	:	Critical study for SIDS endpoint
24.02.2003		(30)
In Vitro/in vivo	:	
Type	:	
Species	:	other: further data see chapter 5.11
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint
04.03.2003		

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 8100 mg/kg bw
Species	:	mouse
Strain	:	NMRI
Sex	:	male
Number of animals	:	2
Vehicle	:	physiol. saline
Doses	:	4.64, 6.81, 8.25, 10.00, 12.10 ml/kg
Method	:	other: orientating study
Year	:	1980
GLP	:	no data
Test substance	:	other TS: menthol liquid
Remark	:	LD50 value is calculated,given value is LD 50: ca. 9 ml/kg bw., estimated density factor: 0.9 g/ml
Reliability	:	(2) valid with restrictions With regard to the screening purposes of this study the restrictions e.g. number of animals/per dose do not affect the suitability for assessment in principle.
Flag	:	Critical study for SIDS endpoint
21.08.2002		(31)

Type	:	LD50
Value	:	= 3180 mg/kg bw
Species	:	rat
Strain	:	Osborne-Mendel
Sex	:	no data
Number of animals	:	
Vehicle	:	other: corn oil
Doses	:	no data
Method	:	other
Year	:	1964
GLP	:	no
Test substance	:	other TS: not specified isomer
Result	:	MORTALITY: - Time of death: 4 hrs to 3 days after application CLINICAL SIGNS: ataxia, scrawny appearance
Test condition	:	- Post dose observation period: 14 days EXAMINATIONS: time of deaths, clinical signs
Reliability	:	(4) not assignable Documentation insufficient.

17.07.2002 (32)

Type	:	other: LD
Value	:	= 2000 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other
Year	:	1883
GLP	:	no
Test substance	:	other TS: not specified isomer
Remark	:	Weight of rabbit is supposed to be 2.0 kg ("4 g of menthol were lethal to a rabbit")
Reliability	:	(4) not assignable Documentation insufficient.

24.02.2003 (33)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	other: LD
Value	:	= 34500 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	1
Vehicle	:	other: no
Doses	:	
Method	:	other
Year	:	1939

GLP : no
Test substance : other TS: pure menthol liquid (density 0.897)

Result : The mouse showed depression 15 min after administration, unconsciousness after 20 min and died 105 min after administration.
Test condition : one mouse of 26 g bw
1 ccm of the TS was applied to skin of back and abdomen.
Reliability : (2) valid with restrictions
With regard to the screening purposes of this study the restrictions (e.g. number of animals) do not affect the suitability for assessment in principle.
Flag : Critical study for SIDS endpoint
24.02.2003 (34)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Value : = 700 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: 50/50 v/v
Doses : no data
Route of admin. : i.p.
Exposure time : unspecified
Method : other
Year : 1982
GLP : no data
Test substance : other TS: not further specified

Reliability : (4) not assignable
Insufficient documentation
24.02.2003 (35)

Type : other: LD
Value : = 1500 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: olive oil
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1939
GLP : no
Test substance : other TS: menthol liquid

Reliability : (4) not assignable
Documentation insufficient for assessment
24.02.2003 (34)

Type : other: LD
Value : = 1800 mg/kg bw
Species : mouse
Strain : no data

Sex : no data
Number of animals :
Vehicle : other: olive oil
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1939
GLP : no
Test substance : other TS: menthol liquid

Reliability : (4) not assignable
Documentation insufficient for assessment
24.02.2003 (34)

Type : other: LD
Value : = 4000 mg/kg bw
Species : guinea pig
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: no
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1939
GLP : no
Test substance : other TS: menthol liquid

Reliability : (4) not assignable
Documentation insufficient for assessment
24.02.2003 (34)

Type : LDLo
Value : = 2600 mg/kg bw
Species : rabbit
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: olive oil
Doses :
Route of admin. : s.c.
Exposure time :
Method : other
Year : 1922
GLP : no
Test substance : other TS: not specified isomer

Result : Immediate cause of death was paralysis of the respiratory center.
Reliability : (4) not assignable
Documentation insufficient for assessment
24.02.2003 (36)

Type : LD50
Value : = 10000 mg/kg bw
Species : rat
Strain : no data
Sex : no data

Number of animals	:	
Vehicle	:	no data
Doses	:	
Route of admin.	:	i.m.
Exposure time	:	
Method	:	other
Year	:	1954
GLP	:	no
Test substance	:	other TS: not specified isomer
Reliability	:	(4) not assignable Documentation insufficient for assessment

24.02.2003 (37)

Type	:	other: LD
Value	:	= 37 mg/kg bw
Species	:	cat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: alcohol with physiological saline
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	
Method	:	other
Year	:	1939
GLP	:	no
Test substance	:	other TS: menthol liquid
Test condition	:	Solution or suspensions, 1:1000, were prepared by diluting 2 per cent solutions of menthol in alcohol with physiological saline and were injected at one-minute intervals into the femoral vein while blood pressure was recorded from the carotid artery.
Reliability	:	(4) not assignable Documentation insufficient for assessment.

24.02.2003 (34)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	
Exposure time	:	4 hour(s)
Number of animals	:	4
Vehicle	:	other: 100% was applied pure, other concentrations in diethylphthalate (DEP)
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1989
GLP	:	yes
Test substance	:	other TS: menthol fl, HR 89/620006, purity: no data
Result	:	AVERAGE SCORE 100%/50%/25%/5%/1%/Vehicle 2.8/1.8/0.8/0.0/0.0/0.0 (erythema)

2.4/1.0/0.0/0.0/0.0/0.0 (oedema)
REVERSIBILITY: yes
Day 7: 100%: 4/4 - treated sites were covered with a massive layer of white scales
50%: 4/4 - thin layer of white scales
25%: 2/4 - very thin layer of white scales
Day 14: 100%: 4/4 - treated sites were covered with white to white-brown scales, underlaying skin was intact
50%: 3/4 - treated sites showed scattered scale formation on intact skin.

Test condition : TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer/Biberach
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss
- Age: no data
- Weight at study initiation: 2400-2700 g
- Number of animals: 4
- Controls: internal control (one part of skin)

ADMINISTRATION/EXPOSURE
- Area of exposure: six different fields on back (two anterior, two centrally located and two posterior treatment sites)
- Total volume applied: 0.5 ml
- Postexposure period: up to 14 days
- Removal of test substance: skin was washed with luke warm water and soap

Reliability : (2) valid with restrictions
purity of TS not stated

Flag : Critical study for SIDS endpoint

24.02.2003 (38)

Species : guinea pig
Concentration : undiluted
Exposure : Open
Exposure time : 7 day(s)
Number of animals : 12
Vehicle : other: no
PDII :
Result : not irritating
Classification : not irritating
Method : other
Year : 1980
GLP : no data
Test substance : other TS: menthol fluid, 620006

Test condition : Guinea pig (6 female, 6 male), Pirlbright white, weight: 400-700 g
The test substance was rubbed into the animals` skin (flank) for ca. 30 sec./d, the exposure (open) being repeated once daily on 7 days. Results were taken immediately

Reliability : (3) invalid
Significant methodological deficiences. e.g. no standardized amount of applied substance.

17.12.2001 (39)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : .1 ml

Exposure time : 24 hour(s)
Comment : rinsed after (see exposure time)
Number of animals : 4
Vehicle : none
Result : slightly irritating
Classification :
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1989
GLP : yes
Test substance : other TS: menthol fl, HR 89/620006, purity: no data

Result : AVERAGE SCORE
- Cornea: 1.0
- Iris: 0.0
- Conjuntivae (Redness): 2.2
- Conjuntivae (Chemosis): 0.7

REVERSIBILITY: yes, slight reactions of cornea and conjunctiva were seen in one rabbit on day 7, no reactions were seen on day 14.

Test condition : TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer, Biberach: Himalaya)
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss
- Age: no data
- Weight at study initiation: 2300-2900 g
- Number of animals: 4
- Controls: internal control (right eye)

Reliability : (2) valid with restrictions
purity of TS not stated
Flag : Critical study for SIDS endpoint
24.02.2003 (40)

Species : rabbit
Concentration : 71 %
Dose : .1 ml
Exposure time : 24 hour(s)
Comment : rinsed after (see exposure time)
Number of animals : 4
Vehicle : other: diethylphthalate (DEP)
Result : slightly irritating
Classification :
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1989
GLP : yes
Test substance : other TS: menthol fl, HR 89/620006 DEP, purity: no data

Result : AVERAGE SCORE
- Cornea: 1.0
- Iris: 0.0
- Conjunctivae (Redness): 2.2
- Conjunctivae (Chemosis): 0.7

REVERSIBILITY: slight reactions of conjunctiva were seen in two rabbits on day 7.

Test condition : TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer, Biberach: Himalaya)
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss
- Age: no data
- Weight at study initiation: 2600-2800
- Number of animals: 4

- Controls: internal control (right eye)

Reliability : (2) valid with restrictions
purity of TS not stated, short duration of test (not up to reversibility of effects)

Flag : Critical study for SIDS endpoint

24.02.2003 (41)

Species : rabbit
Concentration : 25 %
Dose : .1 ml
Exposure time : unspecified
Comment : other: see test conditions
Number of animals : 8
Vehicle : other: olive oil
Result : not irritating
Classification : not irritating
Method : Draize Test
Year : 1980
GLP : no data
Test substance : other TS: menthol fluid, 620006

Test condition : After application of 25 % test substance in one eye and closing of lids for 1 minute, the eyes of four rabbits were rinsed with physiologically sodium salt solution for one minute. Substance remained in the eyes of the other 4 rabbits.

Reliability : (2) valid with restrictions
limited documentation

24.02.2003 (39)

Species : rabbit
Concentration :
Dose :
Exposure time :
Comment : not rinsed
Number of animals :
Vehicle :
Result : irritating
Classification :
Method : other
Year : 1946
GLP : no
Test substance : other TS: not specified isomer, purity: no data

Result : 0.005 ml undiluted testmaterial and 5 % solution yield scores of over 5.0, 1 % solution not over 5.0. (A level of 5.0 is representative of severe injury, corresponding to necrosis, visible only after staining and covering about three fourths of the surface of the cornea,or a more severe necrosis covering a smaller area.)

Test condition : Exposure time: 18 to 24 hours.
No. of animals: no data
Concentration of TS: undiluted, 5 and 1 %
0.005 ml of the undiluted TS was applied to the center of the cornea of normal albino rabbit eyes while the lids were retracted. About one minute later, the lids were released. 18 to 24 h later, the eye was examined in strong diffuse daylight, stained with fluorescein, and the injury scored. The individual numerical scores of each eye (total of 20 at maximum) treated with a given volume or concentration of a TS are added together and then divided by the number of eyes (usually 5) to obtain the score of the injury caused by the treatment. Where dilution of a TS was necessary, the

preferred solvent was propylene glycol. Preference is next given to water, and in some cases a deordorized kerosene has been used. The applied volume for the solutions is not mentioned The observation period is not known.

Reliability : (2) valid with restrictions
Restrictions: no precise information on: e.g. number of animals; reading time; scores for each individual animal; observation period, reversibility of lesions, purity of test substance not stated

Flag : Critical study for SIDS endpoint

24.02.2003 (42)

Species : other: in vitro
Concentration : 100 %
Dose :
Exposure time : 24 hour(s)
Comment :
Number of animals :
Vehicle : none
Result : irritating
Classification :
Method : other: EYETEX in vitro test
Year : 1992
GLP : no data
Test substance : other TS: menthol, not specified isomer

Result : Result of the biomacromolecular test method (EYETEX): mild/moderate irritation

Test condition : Study was conducted to investigate a target biomacromolecular test method, in order to predict in vivo ocular irritancy potentials of chemicals and formulations. The test results were compared with data from in vivo tests (Draize test).

Reliability : (4) not assignable
non-validated test system

24.02.2003 (43)

5.3 SENSITIZATION

Type : other: open repetitive dermal test
Species : guinea pig
Number of animals : 12
Vehicle : other: no
Result : not sensitizing
Classification :
Method : other
Year : 1980
GLP : no data
Test substance : other TS: menthol liquid

Test condition : Guinea pig (6 female, 6 male), Pirlbright white, weight: 400-700 g.
The test substance was rubbed into the animals` skin (flank) for ca. 30 sec./d, the exposure (open) being repeated once daily on 7 days. Results were taken immediately.
After 5 days without treating, test substance was applied and rubbed into not-pretreated part of shaved skin for 3 days once daily.
Skin was observed 24 hours, 2 days and 3 days after termination of challenge.

Reliability : (3) invalid
Significant methodological deficiences. e.g. no standardized amount of

applied substance and procedure of application.
18.01.2002 (39)

Type : Patch-Test
Species : Human
Number of animals :
Vehicle : Petrolatum
Result :
Classification :
Method : other
Year : 1955
GLP : No
Test substance : other TS: not specified isomer, 1 %

Result : Incidence of pronounced sensitization: 1.3 % (reaction 2+ or stronger)
Test condition : Allergic hypersensitivity was investigated in a group of 228 selected patients with dermatoses.
Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (44)

Type : Patch-Test
Species : Human
Number of animals :
Vehicle : other: white petrolatum
Result :
Classification :
Method : other: Fregert et al, Epidemiology of contact dermatitis. Transactions of the St. John´s Hospital Dermatological Society 55, 17-35, 1969.
Year : 1978
GLP : No
Test substance : other TS: not specified isomer, 1 %

Result : The percentage of allergic reactions (positive patch tests) was 6.1 %.
Test condition : 330 patients with eczematous lesions (88 patients (57 female and 31 male) with leg ulcers and 242 patients (141 female and 101 male) with eczematous dermatitis) were tested with menthol 1 % in white petrolatum. Patch tests are placed on the back and removed after 48 hours. Results were read at 48 and 72 (or 96) h after application.
Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (45)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other
Year : 1978
GLP : no
Test substance : other TS: not specified isomer, 1 %

Result : 6/1385 (= ca. 0.4 %) reacted positive, the incidences of sensitization were as follows: 2/131 in 1972; 0/205 in 1973;

2/252 in 1974; 0/408 in 1975 and 2/389 in 1976.

Test condition : 1385 patients (824 female, 561 male, average age: 34.1 and 41.1) with varying dermatologic complaints were tes ted against menthol in the years 1972-1976.

Reliability : (2) valid with restrictions
limited documentation

Flag : Critical study for SIDS endpoint

24.02.2003 (46)

Type : Patch-Test
Species : Human
Number of animals :
Vehicle : other: Vaseline flav.
Result :
Classification :
Method : other: Magnusson, B. et al.: Routine patch testing IV, Acta derm.-vener. 48: 110-114 1968
Year : 1971
GLP : No
Test substance : other TS: not specified isomer

Result : 0.9 % were positive with 0 % strong positive reactions.

Test condition : 1070 patients with atopic eczema or dermatitis were patch tested against menthol.

Reliability : (2) valid with restrictions
limited documentation

Flag : Critical study for SIDS endpoint

24.02.2003 (47)

Type : Patch-Test
Species : Human
Number of animals :
Vehicle : Petrolatum
Result :
Classification :
Method : other
Year : 1987
GLP : no data
Test substance : other TS: not specified isomer, 5 %

Result : 1 % reacted positive.

Test condition : 1200 persons (750 female, 450 male, average age 40.7 years) with contact dermatitis were patch tested against menthol.
Patch tests were performed on 2 sides of the upper back using Finn Chambers on Scanpor. Tests were read at 48, 72, 96 hours according to the ICDRG scale; the last reading was taken as definitive.

Reliability : (2) valid with restrictions
limited documentation

Flag : Critical study for SIDS endpoint

24.02.2003 (48)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : other: yellow paraffin
Result :
Classification :
Method : other
Year : 1970

GLP : no
Test substance : other TS: not specified isomer, 5 %

Remark : These patients are presumably included in the study reported by Rudzki (1971)
Result : 1% (0.9 % male and 1.1 % female) reacted positive.
Test condition : 877 persons with primary contact, atopic, nummular and stasis dermatitis, and unclassified eczema were patch-tested against menthol (among other substances).
Reliability : (2) valid with restrictions
limited documentation
04.03.2003 (49)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other
Year : 1996
GLP : no data
Test substance : other TS: not specified isomer, 1 %

Result : Number of patients with positive reaction to menthol:
21/1077 (1.9 %).
Test condition : Among 1077 patients with crural ulceration and eczema contact allergy to externally applied drugs and its basic vehicles was confirmed in 491 persons (45.6 %) using the method of patch tests.
Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (50)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other: Andersen, K.G., Contact Dermatitis 4, 195-198 (1978)
Year : 1995
GLP : no data
Test substance : other TS: not specified isomer, 5 %

Method : Standard protocol: Patches are applied to the patient´s back and removed after 2 days. Readings were made 15 min after patch removal and again 2 days later. Reactions were graded according to the International Contact Dermatitis Research Group protocol.
(Andersen, K.G., Contact Dermatitis 4, 195-198 (1978)).
Result : 4/5 patients with burning mouth syndrome reacted positive to menthol.
4/4 patients with recurrent intra-oral ulceration were sensitive to menthol.
3/3 patients with an oral lichenoid reaction were positive to menthol.
After a mean follow-up of 32.7 months (range 9-48 months), of the 9 patients that could be contacted, 6 patients described clearance or improvement of their symptoms as a consequence of avoidance of menthol/peppermint. 7/11 menthol-positive patients also reacted positively with peppermint oil.
Test condition : 512 patients with intraoral complaints (burning mouth syndrome, recurrent

oral ulceration, lichenoid reaction) were tested to menthol over a 4-year period for assessment of the possible contribution of contact sensitivity to their complaints.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
24.02.2003 (51)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : other: vaseline
Result :
Classification :
Method : other
Year : 1995
GLP : no data
Test substance : other TS: not specified isomer, 1%

Result : 1/350 patients (0.3%) reacted positive.
Test condition : From 1990 to 1993 351 patients (188 m, 163 f, 28.5% younger than 40 years, 38.5% between 40 and 60 years and 33.0% older than 60 years; 20.2% suffered from atopic dermatitis actually or historically) were patch tested with the test series for anal eczema; among them menthol (350 patients).
Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (52)

Type : Patch-Test
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year : 2001
GLP : no data
Test substance : other TS: not specified isomer

Result : Menthol provoked neither allergic nor irritant patch test reactions.
Test condition : Retrospective study: patch test data were collected from 7 patch test clinics in Finland. Patch tests were performed between 1994 and 1998. A total of 75 patients were tested against menthol.
Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (53)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other
Year : 1978
GLP : no
Test substance : other TS: not specified isomer, 1 %

Result : A woman showed a positive result. Since she stopped smoking mentholated cigarettes, the patient is totally free of symptoms.
Test condition : A female patient who was suffering from a mild scaly erythema with irregular edges was tested with menthol. She regularly smoked menthol cigarettes.
Reliability : (2) valid with restrictions
case-report
Flag : Critical study for SIDS endpoint
24.02.2003 (54)

Type : Patch-Test
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year : 1963
GLP : no
Test substance : other TS: not specified isomer

Result : Both patients reacted positive to menthol.
Test condition : Case reports:
After using "la pommade Vick", a 69 years old man suffered from an eczema on the nose and the upper lip. Patient was patch-tested against menthol.
A 43 years old man suffered from an contact eczema on his hands. After treating his hands with "Baume tranquille" his eczema got worse and reached up to the arms. He was patch-tested against menthol.
Reliability : (4) not assignable
Documentation insufficient for assessment.
24.02.2003 (55)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other
Year : 1977
GLP : no
Test substance : other TS: not specified isomer, 1 %

Result : No sensitization reaction to menthol observed. Hypersensitivity to peppermint oil was observed and referred to the sensitizig properties of the three ingredients alpha-pinene, limonene, and phellandrene.
Test condition : Case report: a patient suffering from swelling of the tongue, lips and gingival mucosa was tested against menthol.
Reliability : (2) valid with restrictions
case-report
Flag : Critical study for SIDS endpoint
24.02.2003 (56)

Type : Patch-Test
Species : Human
Number of animals :
Vehicle : other: glycerine

Result :
Classification :
Method : other
Year : 1939
GLP : No
Test substance : other TS: not specified isomer, 1%, 2% and 5%

Result : Positive result with all concentrations; symptoms of sensitization: erythema and pruritus.
Test condition : Case report: a patient who was suffering from an anal eczema was tested with mentholated glycerin ointments containing 1%, 2 % or 5 % menthol.
Reliability : (4) not assignable
Case report. Documentation insufficient for assessment.
24.02.2003 (57)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : other: as recommended in literature
Result :
Classification :
Method : other
Year : 1991
GLP : no data
Test substance : other TS: not specified isomer

Result : There was no positive allergic skin reaction found.
Test condition : 31 males, average age 30.8 years, range 20 to 49 years, were patch tested. None had any history of allergy, including to dental materials. Finn Chambers on Scanpor tape were used, following ICDRG guidelines. Test results were read at 2 and 3 days and scored according to the Japanese standard method.
Reliability : (4) not assignable
Documentation insufficient for assessment.
02.05.2002 (58)

Type : Patch-Test
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year : 1984
GLP : no data
Test substance : other TS: not specified isomer, not further specified

Result : One of them showed sensitization (menthol, among other substances, used in production).
Test condition : 11 industrial workers suffering from disorders with a probable immune pathogenesis were tested against menthol.
Reliability : (4) not assignable
Documentation insufficient for assessment
24.02.2003 (59)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum

Result :
Classification :
Method : other
Year : 1996
GLP : no data
Test substance : other TS: not specified isomer 1 %

Result : No reaction.
Test condition : Case report: A 46-year-old man with an acute eczema of the genitals due to benzyl alcohol was patch-tested.
Reliability : (4) not assignable
Documentation insufficient for assessment.
24.02.2003 (60)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other
Year : 1995
GLP : no data
Test substance : other TS: not specified isomer, 2 %

Result : A woman had a positive reaction to menthol on patch testing. On appropriate avoidance her symptoms resolved rapidly.

A man was allergic to menthol on patch te sting. When excluding these substances from the diet definite reduction in lip swelling was noted. On re-exposure to menthol, further episodes of lip swelling occurred.
Test condition : Case Reports:
A 26-year-old woman presented with a 12-month history of recurrent oral ulceration. This occurred weekly and had not responded to corticosteroid mouthwashes.

A 43-year-old man with Down's syndrome had histologically proven orofacial granulomatosis mainly affecting the lower lips.

Patch tests were performed on both persons.
Reliability : (4) not assignable
Documentation insufficient for assessment.
24.02.2003 (61)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : other: vaseline
Result :
Classification :
Method : other
Year : 1974
GLP : no data
Test substance : other TS: not specified isomer, 2 %

Result : There were no reactions observed
Test condition : 3/4 patients with allergic reaction to toothpastes were tested epicutaneously against 2 % menthol in vaseline
Reliability : (4) not assignable

Insufficient documentation for assessment
24.02.2003 (62)

Type : Patch-Test
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year : 1962
GLP : no
Test substance : other TS: not specified isomer

Result : An allergy to oil of turpentine can cause a group sensitization to some related substances, among them menthol.
Reliability : (4) not assignable
Insufficient documentation for assessment
24.02.2003 (63)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other
Year : 1998
GLP : no data
Test substance : other TS: not specified isomer, 5%

Result : Positive reaction.
Test condition : One patient suffering from oral and lip dermatitis was patch tested against menthol (5% in pet.).
Reliability : (4) not assignable
Case report. Insufficient documentation for assessment.
24.02.2003 (64)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other
Year : 1998
GLP : no data
Test substance : other TS: not specified isomer, 5%

Result : Day 5: itch, erythema and swelling at sites of application of menthol
Day 7: ++ reaction

Earlier readings were negative.

Prick tests were negative.
Test condition : Case report: 34 year old woman, 9-year history of oral burning and discomfort.
Reliability : (4) not assignable
Case report. Insufficient documentation for assessment.

24.02.2003 (65)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other
Year : 2000
GLP : no data
Test substance : other TS: not specified isomer, 1%

Result : 13/54 patients reacted positive with TCS. 1/13 patients reacted positive with menthol
Test condition : 54 patients (33f, 21 m, aged 15-74 years) with exzematous lesions on the lips were tested (among other substances) against specially-targeted toothpaste cheilitis series (TCS) containing menthol.
The persons reacting positive against the TCS were patch tested against the single allergens.
Reliability : (2) valid with restrictions
limited documentation

24.02.2003 (66)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : no data
Result :
Classification :
Method : other
Year : 1991
GLP : no data
Test substance : other TS: not specified isomer

Result : positive reaction
Test condition : Case report: 66 year old man with chronic eczematous eruption 3 years ago and actual contact dermatitis was patch-tested against menthol (among other substances).
Reliability : (4) not assignable
Insufficient documentation for assessment.

24.02.2003 (67)

Type : Patch-Test
Species : Human
Number of animals :
Vehicle : Petrolatum
Result :
Classification :
Method : other
Year : 1996
GLP : no data
Test substance : other TS: not further specified

Result : In 13 patients showing mouth or lip swelling 5 patients were considered to have positive relevant allergic reactions on patch testing. 3 patients were allergic to food additives or flavourings (butylhydroxyanisole, dodecyl gallate, peppermint oil, and menthol). All 3 patients were put on an appropriate exclusion diet, resulting in rapid improvement or clearing of

symptoms.

Test condition : Patches were removed after 2 days, and readings were taken at 2 and 4 days according to standard practice.
Menthol concentration tested: 2%

Reliability : (2) valid with restrictions
Limited documentation.

Flag : Critical study for SIDS endpoint

24.02.2003 (68)

Type : other: Provocative systemic test/provocative skin test
Species : Human
Number of animals :
Vehicle : other: ethanol
Result :
Classification :
Method : other
Year : 1964
GLP : No
Test substance : other TS: not specified isomer

Result : Oral provocation: after 30 minutes a flushing reaction evolved and at 40 minutes she complained of a headache; there was a marked decrease in circulating basophils.
Skin provocation: within 20 minutes the patient experienced a severe burning sensation and there was a fiery erythematous reaction about the treated area.
Basophil degranulation tests were negative to menthol.

Test condition : The case of a woman suffering from generalized urticaria is reported: she had been exposed to menthol in various forms (peppermint-flavored toothpaste, peppermint candies, mentholated cigarettes, mentholated facial cream) partly for years.
Oral provocative test: the patient ingested 10 mg of menthol in 5 cc of 50 % ethanol.
Skin provocative test: one-tenth of a milliliter of 75 % menthol in ethanol was applied to the forearm.
Additional provocative tests with thymol and terpin hydrate were performed.

Reliability : (4) not assignable
Case report. Insufficient documentation for assessment.

24.02.2003 (69)

Type : other: challenge test
Species : Human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year : 1978
GLP : No
Test substance : other TS: not specified isomer

Result : Immediately after challenge the dermatitis recurred. Since discontinuing the offending cigarettes again, her condition has remained completely clear.

Test condition : Case report: A 25-year-old woman suffered from a chronic dermatitis of the upper lip. When she discontinued her menthol cigarettes temporarily, her dermatitis immediately cleared. After several weeks, she performed a challenge test by resuming the menthol cigarettes.

Reliability : (4) not assignable
Case report. Insufficient documentation for assessment.

24.02.2003 (70)

Type : other: challenge test
Species : Human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year : 1992
GLP : no data
Test substance : other TS: not further specified

Result : Menthol contained in toothpastes may act as asthma-inducing agents.
Test condition : Case reports are given on aspirin-sensitive patients and patients with aspirin-induced asthma, whose asthma was exacerbated by the mint flavour contained in their toothpaste. Challenge tests were performed with menthol.
Reliability : (4) not assignable
Case report. Insufficient documentation for assessment.

24.02.2003 (71) (72)

Type : other: challenge test
Species : Human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year : 2001
GLP : no data
Test substance : other TS: not further specified

Result : She showed positive patch test reaction and was positive after challenge (FEV1 decreased).
Test condition : Case-report: 40 year old nonsmoking woman experienced attacks of sneezing, nasal obstruction, rhinorrhea, dyspnea, and wheezing whenever she brushed her teeth and/or ingested mint candies. Patch test was performed and a challenge test: the patient rinsed her mouth with a 0.02 % menthol solution.
Reliability : (4) not assignable
Case report. Insufficient documentation for assessment.

24.02.2003 (73)

Type : other: provocative test by oral challenge
Species : Human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year : 1966
GLP : No
Test substance : other TS: not specified isomer

Result : An urticarial reaction and a fall in the total number of circulating basophils following menthol challenge were observed.
Epicutan and Scratch Tests with menthol were negative.
Test condition : The case of a young girl suffering from generalized urticaria is reported:

she had been exposed to menthol in various forms for many years, the initial episode of urticaria came coincidentally with an increased exposure to cough drops, aerosol room spray and a medicated petrolatum.
Provocative test by oral challenge: menthol was administered to the patient at a dose of 10 mg menthol in 5 cc of 50 % ethanol.

Reliability : (4) not assignable
Case report. Insufficient documentation for assessment.

24.02.2003 (74)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	Rat
Sex	:	Male
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	2 w
Frequency of treatm.	:	Continously
Post exposure period	:	no data
Doses	:	0.5%, 1 %
Control group	:	Yes
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	other TS: not specified isomer

Result : Increased serum cholesterol and serum triglycerides were observed in the high-dose group, no effect on apo A-1 lipids, an indicator of high-density lipoprotein status.
Body weight was unaffected. Liver weight was slighthly increased

Test condition : Rats weight: 240-300 g

Reliability : (4) not assignable
Documentation insufficient for assessment.

02.08.2002 (75)

Type	:	Sub-acute
Species	:	Rat
Sex	:	Male
Strain	:	other: FDA-Osborne Mendel or Rockland Wistar
Route of admin.	:	Gavage
Exposure period	:	3 d
Frequency of treatm.	:	Daily
Post exposure period	:	No
Doses	:	20 mg/kg bw/d
Control group	:	Yes
Method	:	other
Year	:	1972
GLP	:	No
Test substance	:	other TS: not specified isomer

Result : Decrease in hepatic aminopyrine demethylation and in aniline hydroxylation, increase in hepatic hexobarbital hydroxylation.

Test condition : Menthol was melted and suspended in either water or 0.5% methylcellulose, each warmed to 50 °C;
doses administered was equivalent to 1ml/100 g bw;
6 rats were treated with menthol,
no further examinations.
Test was conducted to identify whether menthol changes parathion toxicity.

Reliability : (3) invalid
Unsuitable test system (see test conditions)
30.11.2001 (76)

Type : Sub-acute
Species : Mouse
Sex : male/female
Strain : no data
Route of admin. : oral unspecified
Exposure period : 5 d
Frequency of treatm. : see test conditions
Post exposure period : No
Doses : 40 or 60 mg/animal/d (= ca. 2000 or 3000 mg/kg bw/d)
Control group : Yes
Method : other
Year : 1940
GLP : No
Test substance : other TS: not specified isomer

Result : increased activity of beta-glucuronidase in the liver, kidney and spleen, no increase in enzymic activity in the testis, ovary, uterus and vagina
Test condition : Experimental design: the animals received 20 mg of menthol, 3 doses/d, for 4 d and 2 doses of 20 mg of menthol on the 5th d.
Study was conducted to investigate the increase in ß-Glucoronidase activity of mammalian tissues induced by feeding glucuronidogenic substances.
Reliability : (3) invalid
Unsuitable test system (see test condition)
17.12.2001 (77)

Type : Chronic
Species : Rabbit
Sex : no data
Strain : no data
Route of admin. : Inhalation
Exposure period : 9 m
Frequency of treatm. : Daily
Post exposure period : No
Doses : 1% and 5 % in liquid petrolatum
Control group : yes, concurrent vehicle
NOAEL : < 1 %
Method : other
Year : 1929
GLP : No
Test substance : other TS: not specified isomer

Result : When applied to the nasal mucous membrane of a rabbit for nine months, menthol (1% solution) cause some degenerative changes, menthol (5 % solution) cause definite destructive changes throughout all layers of the nasal membrane.
Test condition : Rabbits used were healthy and about 1 year old. Daily history was kept of each animal, with observations as to the amount and type of nasal discharge, general state of activitiy of the animal and the animal´s weight. Paraffin sections of the nasal mucosa was performed. The tissues selected were usually from the posterior or ethmoturbinate of the animal.
Reliability : (3) invalid
Unsuitable test system: is only regarding a specific topic.
17.12.2001 (78)

Type	:	Sub-acute
Species	:	Monkey
Sex	:	no data
Strain	:	no data
Route of admin.	:	Inhalation
Exposure period	:	14 d
Frequency of treatm.	:	8 h, daily
Post exposure period	:	no data
Doses	:	40 mg/kg bw/d
Control group	:	no data specified
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	other TS: not specified isomer
Result	:	no overt toxicity
Reliability	:	(4) not assignable Secondary literature

17.12.2001 (79)

5.5 GENETIC TOXICITY 'IN VITRO'

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

Species	:	Mouse
Sex	:	Female
Strain	:	Strain A
Route of admin.	:	i.p.
Exposure period	:	7 w
Frequency of treatm.	:	3 doses/w
Post exposure period	:	17 w
Doses	:	25 or 100 mg/kg bw (= single dose)
Result	:	Negative
Control group	:	other: two series of base-line controls were maintaining during the experimental period, one consisting of untreated mice killed along with the treated animals and the other control receiving injections of tricaprylin (vehicle)
Method	:	other
Year	:	1973
GLP	:	No
Test substance	:	other TS: not specified isomer
Remark	:	It became apparent, that the used tricaprylin 2097 was an unsuitable vehicle (mice lost weight after a single injection of tricaprylin, appr. 20 % of the animals died after 12 injections of the vehicle, mean tumor value of 0.59/mouse was considerably higher than expected from earlier reports)
Result	:	Both dose groups: no increase in incidence of lung tumors compared to the controls.
Test condition	:	Total number of i.p. injections: 20 the animals were killed at 24 w after the first injection.
Reliability	:	(3) invalid Unsuitable test system.

30.11.2001 (80)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human - Medical Data

Result : In vivo:
The methaemoglobin concentration of the erythrocytes was raised (within physiological limits).
In vitro:
Methemoglobin reductase and glucose-6-phosphate-dehydrogenase activity were reduced.

Test condition : Clinical tests: mentholated ointments were applied to 2 groups of 4 patients (2-11 months old) and the methaemoglobin values obtained, before treatment and 24 h afterwards respectively, were compared. The haemoglobin-reductase-activity and the glucose-6-phosphate-dehydrogenase-activity were measured.

In vitro investigations in human erythrocyte homogenisates were performed:
methemoglobin reductase and
glucose-6-phosphate -dehydrogenase were analyzed.

Test substance : unspecified isomer

Reliability : (2) valid with restrictions
Limited documentation.

24.02.2003 (81)

Type of experience : Human - Medical Data

Result : In young children (younger than 1 year), application of menthol to the nostrils can result in reflex apnoea (reflectory reaction of the nervus trigeminus – Kratschmer reflex), laryngospasm, spasm of the glottis or in instant collapse (even reported after local application).
Further clinical signs are: dyspnea, unconsciousness, irregular and decreased respiration rate, apnea, bradycardia, cyanosis, hyperextensive extremities.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

24.02.2003 (82) (83) (84) (85) (86) (87) (88) (89) (90) (91)

Type of experience : Human - Medical Data

Result : The consumption of menthol lozenges or the smoke of mentholated cigarettes may have played role in acquired essential cold urticaria.

Test condition : A few cases of acquired essential cold urticaria (a kind of cold dermatological hypersensitivity) are reported.
Reliability : (4) not assignable
Documentation insufficient for assessment.
04.03.2003 (92)

Type of experience : Human - Medical Data

Result : 1. The laryngeal examination itself has no mechanical pathological effect on the laryngeal mucosa. 2. The laryngoscopic results showed no difference between the group of ill children and the group who had received additional menthol rub treatment. 3. The menthol contained in the ointment had no adverse effect on the laryngeal mucous membrane.
Test condition : A controlled clinical study on a mentholated preparation (Vicks VapoRub) which is mostly employed at home in the United States was carried out in order to determine whether rubbing with mentholated ointments in normal dosages can provoke toxic symptoms.

3 groups of patients:
- Healthy children who had not been treated (control group),
- Children with acute respiratory affections receiving standard treatment
- Children with acute respiratory affections being treated with mentholated ointment.

Laryngoscopy took place within 48 hours after hospitalization, during treatment 48 hours later and also 96 hours after the treatment with mentholated rub.
Dosage: 1 teaspoon ful of ointment per 10 kg of body weight twice a day).
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
Limited documentation
24.02.2003 (93)

Type of experience : Human - Medical Data

Result : After drinking 2500-3500 mg menthol (corresponding 200-250 mg/kg bw) a 3 year old child became drowsy, somnolent, felt pain in the stomach and vomited. The symptoms were fully reversible within 4 days.
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (94)

Type of experience : Direct observation, clinical cases

Result : Ingestion of menthol causes severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma.
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (95)

Type of experience : Direct observation, clinical cases

Remark : Chronic inhalation of menthol in cigarettes can cause ataxia.
Result : Case report: 13 year old boy with history of bronchial asthma had nasal catarrh for which he started to use olbas oil by inhalation. Examination: weakness of the left arm and leg and ataxia; he was euphoric.

Content of olbas oil: 4.1 % menthol, 18.5 % oil of cajuput, 0.1 % clove 35.5 % eucalyptus, 2.7 % juniper berry, 35.5 % peppermint, 3.7 % wintergreen oil (methyl salicylate). The amount of menthol inhaled was approximately 200 mg.

Patient fully recovered 12 h later.

Reliability : (2) valid with restrictions
Limited documentation

24.02.2003 (96)

Type of experience : Direct observation, clinical cases

Result : An allergic reaction to menthol may be exhibited in active patients who use topical analgesics. The major symptom is slight redness the day after exposure.

Test condition : The occurrence of allergic contact dermatitis in active patients after exposure to certain types of sports equipment and topical analgesics is studied.

Reliability : (4) not assignable
Documentation insufficient for assessment.

24.02.2003 (97)

Type of experience : Direct observation, clinical cases

Result : Topical menthol is a rare sensitizer, but such reactions have occured, including allergic contact cheilitis, contact urticaria, and shaking chills when used over a wide area of the body, especially in elderly persons.

Test substance : unspecified isomer

Reliability : (4) not assignable
Documentation insufficient.

23.05.2002 (98) (99) (100)

Type of experience : Direct observation, clinical cases

Result : A case of non-thrombocytopenic purpura caused by mentholated cigarettes was described.

Test substance : unspecified isomer

Reliability : (4) not assignable
Documentation insufficient for assessment

24.02.2003 (101)

Type of experience : Direct observation, clinical cases

Result : Case reports:
A woman became addicted to mentholated cigarettes and developed toxic exhaustive pyschosis.

A woman who smoked 80 mentholated cigarettes daily for 3 months developed insomnia, unsteady and ataxic gait, thick speech, tremor of the hands, vomiting, and cramp in the legs. Her heart-rate was 44 per minute. Mentally she became oversensitive, irritable, confused, depressed and quarrelsome.

The latter woman was given 1 g menthol three times daily for one week. On the third day she was apathetic and tired; and on the seventh day she complained of nausea, anorexia, and exhaustion and had difficulty in concentrating. She looked pale and drawn. The pulse-rate slowed down (from 76 at the beginning of the menthol application to 60 at the seventh day).

Symptoms disappeared when menthol was withheld.

Test substance : unspecified isomer
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (102)

Type of experience : Direct observation, clinical cases

Result : Both patients got complaint-free.
Test condition : Two patients suffering from palindromic rheumatism were put on a menthol-free (among other substances) diet.
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient
24.02.2003 (103)

Type of experience : Direct observation, clinical cases

Result : Case report: methaemoglobinaemia (31% free hemoglobine) was diagnosed in a 15 w old baby who had been treated topically with a menthol containing cough balm (other ingredients of the preparation: camphor, ol. eucal., ol. pinix., other essential oils). It was assumed, that menthol was dermally absorbed.

Menthol as an oxidizing agent is associated with methemoglobinemia.
Test substance : not specified isomer
Reliability : (4) not assignable
Documentation insufficient for assessment
24.02.2003 (86) (104) (105)

Type of experience : Direct observation, clinical cases

Result : Experience with human exposure: overdosage with menthol, particularly if it is continued over a long period can result in gastrointestinal distress, ataxia, stupor and convulsions; blood dyscrasias have been reported.
(no details)
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (82)

Type of experience : Direct observation, poisoning incidents

Result : Human:
Oral intake of 8 or 9 g menthol were not lethal. The symptoms observed were a cold burning sensation in mouth, throat and esophagus, a cold sensation on the mucous membranes of the nose, on the skin of the hand and feet, and fatigue.
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient
23.05.2002 (106) (107) (108)

Type of experience : Direct observation, poisoning incidents

Result : One hour later she had the following symptoms: fatigue, pallor, cold limbs, cyanotic face, irregular and spasmodic respiration, irregular and rapid

pulse, vomiting. The pulse interrupted completely for some seconds, while the diaphragm contracted convulsively.

Test condition : Case report: A 4 1/2-year old girl ingested 3 bonbons, each containing 2 mg menthol (unspec. isomer).
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag : Critical study for SIDS endpoint
24.02.2003 (109)

Type of experience : Direct observation, poisoning incidents

Result : Case report: Sucking of eucalyptol and menthol bonbons caused abundant formation of aphthae on the mouth mucosa.
Clearance of the symptoms was observed on avoidance of the bonbons for some time.
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient
24.02.2003 (110)

Type of experience : Direct observation, poisoning incidents

Result : An acute intoxication was observed in an infant after cutanous application of menthol-containing medications. No further information from abstract available.
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient for assessment
24.02.2003 (111)

Type of experience : Direct observation, poisoning incidents

Result : Baby was somnolent and hypotonic and had cornea erosions.

Menthol may give rise to hypersensitivity reactions including contact dermatits, apnea, and instant collaps, but no ocular side effects were reported before this clinical case.

Conclusion: It is not clear, if the symptoms resulted from inhalation of fumes.
Test condition : Rhino-Caps are used in an inhalation therapy for relief of nasal congestion. One Rhino-Caps capsule contains 25 mg Camphor, 125 mg eucalyptol, 55 mg menthol 120 mg terpineol and 5 mg chlorothymol.

Case-report: a 4 month old baby was exposed by inhalation to Rhino-Cap among other medications (after emptying the content of the capsule on a pillow).
Reliability : (4) not assignable
Insufficient documentation for assessment
24.02.2003 (112)

Type of experience : Direct observation, poisoning incidents

Result : Case report: 62-year old man experienced full-thickness skin and muscle necrosis and persistent interstitial nephritis, due to excessive percutaneous absorption of a topical ointment, containing 18.3% methyl salicylate and 16 % menthol.

The barrier function of the skin has possibly been destroyed by menthol and methyl salicylate was systemically absorped through the damaged skin.

Reliability : (4) not assignable
Insufficient documentation for assessment.

24.02.2003 (113)

Type of experience : Human – Epidemiology

Result : 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.

Test condition : The effect of smoking mentholated cigarettes on lung cancer risk is studied. Investigated were current cigarette smokers: 588 male lung cancer cases, 914 male controls 456 female lunge cancer cases and 410 female controls The prevalence of menthol usage did not differ between cases and controls of either sex.

Reliability : (2) valid with restrictions
co-exposure to cigarette smoke

24.02.2003 (114)

Type of experience : Human – Epidemiology

Result : Menthol was not a risk factor for cancer. The use of mentholated cigarettes is unlikely to be an important independent factor in oropharyngeal cancer.

Test condition : The following hypothesis was tested:
Smoking mentholated cigarettes increases the risk of cancer of the oral cavity and pharynx, a cancer with a 50% higher incidence in black Americans compared with whites.

194 male and 82 female persons as test subjects and 845 male and 411 female controls were part of the study.

Reliability : (2) valid with restrictions
co-exposure to cigarette smoke

24.02.2003 (115)

Type of experience : Human – Epidemiology

Result : No change in risk for males ever-smoking menthol versus those never smoking menthol cigarettes could be observed.
For women, however, there was an increased risk.

Because of the limitations of the study the issue of menthol cigarette smoking and oesophageal cancer is not resolved.

Test condition : The present study test whether menthol cigarette smoking is related to oesophageal cancer. Data from a large hospital-based case-control study are used.

Reliability : (2) valid with restrictions
co-exposure to cigarette smoke

24.02.2003 (116)

Type of experience : Human – Epidemiology

Result : The relative risk of lung cancer associated with mentholation compared with nonmentholated cigarettes was 1.45 in men and 0.75 in women.
Conclusion: There is an increased risk of lung cancer associated with mentholated cigarette use in male smokers but not in female smokers.

Test condition : The association of mentholated cigarette use with lung cancer in men and

women was examined in a cohort study. The study population consisted of 11761 members (5771 men, 3990 women).

Reliability : (2) valid with restrictions
co-exposure to cigarette smoke

24.02.2003 (117)

Type of experience : Human – Epidemiology

Result : Menthol (n=49) smokers had larger puff volumes, higher cotinine levels and shorter time to first cigarette compared to non-menthol smokers*.

* statistically significant

Test condition : 95 women (48 Black, 47 White)
menthol-cigarette smokers (n=27 in Blacks, n=22 in Whites)
Investigated was:
smokin topography, plasma continine, plasma nicotine,
expired carbon monoxide, time to first cigarette, smoking history

Test substance : unspecified isomer

Reliability : (2) valid with restrictions
co-exposure to cigarette smoke

24.02.2003 (118)

Type of experience : Human - Epidemiology

Result : Lung-cancer risk from smoking mentholated cigarettes resembles the risk from smoking non-mentholated cigarettes.

Test condition : Association between menthol cigarette smoking and lung-cancer risk among smokers was studied.
Population: 337 incident lung cancer
Controls: 478

Test substance : unspecified isomer

Reliability : (2) valid with restrictions
co-exposure to cigarette smoke

24.02.2003 (119)

Type of experience : Human – Epidemiology

Result : Menthol smokers may be chronically less aroused and more sensitive to the effects of nicotine than non-menthol smokers.

Test condition : The psychophysiological and subjective effect of smoking menthol versus non-menthol cigarettes was investigated using mentholated and not-mentholated denicotinized cigarettes.
Parameters:
EEG
Heart rate (HR)
mental alertness
muscular relaxation
anxiety/nervousness
desire to smoke usual brand

22 participants (27,4 years, SD 4.1, range 21-35), 12 menthol smokers and 10 non-menthol smokers.

Reliability : (2) valid with restrictions
co-exposure to cigarette smoke

24.02.2003 (120)

Type of experience : other: hyposmia

Result : The examination showed evidently a diminution of the smell acuity.

Test condition : 25 employees exposed to menthol are olfactometrically examined.
Control group: 25 employees working in the same plant, but are not exposed to menthol
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient
02.05.2002 (121)

Type of experience : other: influence on taste receptors

Result : 0.4-4 ug per ml: decreased the taste threshold up to 60%;
larger amounts increased the threshold up to 60 %;
With 40-400 ug a decrease in threshold was found in 1/4 individuals only and it is always preceded by an increase.
Test condition : Test subjects: two female and two male students (24-28 years).
Investigation of the influence of menthol on the sensitivity of taste receptors in man by dropping solutions of menthol on the tip of the tongue
Reliability : (3) invalid
Invalid test system.
17.01.2002 (122)

Type of experience : other: specific investigations

Result : Menthol given by steam inhalation to urethanized rabbits augmented the soluble mucus content and lowered the specific gravity of respiratory tract fluid (less than 20 micrograms/kg bw).
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient for assessment
24.02.2003 (123)

Type of experience : other: Animals - Taste and Thermoreceptors

Result : Menthol elicited a slowly increasing activity in all gustatory fibres of the chorda tympani nerve; adding menthol changed the gustatory response of the sapid solutions.
Thermoreceptors are influenced (the threshold of the menthol effect lies between a concentration 1:1,000,000 and 1:500,000).
Test condition : Study on the effect of menthol on the excitability of the gustatory receptors and on thermoreceptors in cats.
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
Limited documentation
24.02.2003 (124) (125)

Type of experience : Other

Result : Menthol as a flavoring content in toothpaste, cigarettes and hard candy may cause oral sensitivities or mucosal contact sensitization reactions.
Details under 5.3 Sensitization.
Reliability : (2) valid with restrictions
limited documentation
24.02.2003 (126)

Type of experience : other: Food intolerance

Result : 73 subjects reported food allergy or intolerance reactions and 16 % (12 of 73) of the self-reported reactions could be objectively confirmed.
Only one person, a 58 year old woman reported food intolerance reactions

caused by menthol. This could be confirmed by a menthol challenge. The subject reported aggravation of aphthae 1 h after administration.

Test condition : The prevalence of food allergy and intolerance was studied in a random sample of the Dutch adult population (n=1484). First the self-reported reactions were investigated by questionnaire. In a clinical follow-up study, it was determined in how many cases this self-reported food allergy or intolerance reactions could be objectively confirmed by double-blind placebo-controlled food challenge.

Reliability : (1) valid without restriction
24.02.2003 (127)

Type of experience : other: ADI

Result : Menthol´s ADI increased from 0,2 mg/kg bw up to 4 mg/kg bw.
Reliability : (1) valid without restriction
Expert Committee report
Flag : Critical study for SIDS endpoint
24.02.2003 (128) (129)

Type of experience : other: fatal dose

Result : the fatal dose of menthol in man has been estimated to be about 2 g.
Reliability : (4) not assignable
Documentation insufficient.
13.11.2002 (88)

Type of experience : other: fatal dose

Result : The probable letal dose for man is 50-500 mg/kg bw.
Reliability : (4) not assignable
Documentation insufficient.
13.11.2002 (95)

Type of experience : other: fatal dose

Result : The fatal dose of menthol is approximately 1 g/kg bw.
Reliability : (4) not assignable
Documentation insufficient.
13.11.2002 (130)

Type of experience : other: glucose-6-phosphate dehydrogenase deficiency

Result : Treated babies developed significantly more often severe jaundice.

Conclusions:
- Neonates were unable to conjugate menthol.
- Use of menthol-containing products on neonates should be discontinued (especially in communities where the incidence of glucose-6-phosphate dehydrogenase deficiency is high).

Test condition : 60 glucose-6-phosphate dehydrogenase-deficient babies were studied:
in 30 babies the umbilical cord was dressed daily for 5 days after birth with "mentholated" powder
30 babies were not treated with the powder and served as controls.

Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
24.02.2003 (131)

Type of experience : other: risk group

Result : All incidents reported in connection with the use of menthol ointments are examined and analysed in detail. Serious clinical cases are often combined with a very high amount of applied menthol and the application to the nostrils.

Symptoms are:
Laryngospasms, dyspnoe, hyperactivity, tremor, spasm of the glottis, hypersensitivity, drowsiness, cyanosis.

The author assumes, that laryngospasms, spasm of the glottis, dyspnoe, cyanosis are not a poisoning effect of menthol but a reflectory reaction of the nervus trigeminus (Kratschmer reflex).

A special risk group are newborn babies:
- high resorption capacity
- detoxification mechanism (glucuronidation) is not fully developed.

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint
24.02.2003 (94)

Type of experience : other: ADI

Result : Estimate of acceptable daily intake (ADI) for man in 1976 by WHO: 0 - 0.2 mg/kg bw.

Reliability : (1) valid without restriction
Expert Committee report

Flag : Critical study for SIDS endpoint
04.03.2003 (132)

5.11 ADDITIONAL REMARKS

Type : Behaviour

Result : After a single i.m. or oral administration of menthol to rats, a choleretic effect was noted.

Test substance : unspecified isomer

Reliability : (4) not assignable
Documentation insufficient.
25.02.2003 (37)

Type : Behaviour

Result : ED 50 rats: 35 mg/kg bw.

Test condition : ED 50 for shaking after i.p. injection in rats was determined.
Effect: more than 10 times shaking in the 10 min interval after injection.
Vehicle: 50/50 v/v ethanol water.

Reliability : (2) valid with restrictions
Limited documentation.
25.02.2003 (35)

Type : Biochemical or cellular interactions

Result : In an in vitro study with human liver samples menthol (isomer unspec.) inhibited the glucuronidation of 7-hydroxy-4-methylcoumarin (45 % inhibition).

Test substance : unspecified isomer
Reliability : (2) valid with restrictions
non-standard in vitro system
25.02.2003 (133)

Type : Biochemical or cellular interactions

Result : Menthol depressed the isolate d heart of both the frog and the rabbit directly and dilated the coronary vessles.
The frequency of beat was diminished, the power was increased.
Ultimately the heart stopped in diastole.
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient
25.02.2003 (36) (134) (135)

Type : Biochemical or cellular interactions

Result : Menthol, a specific substrate for GT2a isoform of UDP-glucuronosyltransferase, competitively inhibited glucuronidation of 2,2-di(isopropoxycarbonyl)ethylene-1,1-dithiol.
Test condition : Investigations were performed in rats and rabbits hepatic microsomes.
Test substance : Unspecified isomer
Reliability : (2) valid with restrictions
Limited documentation
25.02.2003 (136)

Type : Biochemical or cellular interactions

Result : Menthol possesses potent Ca2+ channel-modulating properties.
Menthol blocks dihydropyridine insensitive Ca2+ channels in neuronal cells of chick, rat and human origin (this is supposed to be the reason for the cooling feeling).
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
Limited documentation
25.02.2003 (137) (138)

Type : Biochemical or cellular interactions

Result : Menthol down-regulated IL-6 receptors on AF 10 cells at concentrations that inhibited the growth of the cells.
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
non-standard test system
25.02.2003 (139)

Type : Biochemical or cellular interactions

Result : Thiobarbiturate acid reactive substances were increased.
Test condition : In vitro addition of menthol on hepatic lipid peroxidation was studied.
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient.
25.02.2003 (140)

Type : Biochemical or cellular interactions

Result : Menthol has a high choleretic effect.
Test condition : Wistar rats; 260mMol/kg bw in olive oil, gavage.
Menthol was tested among other terpenes.
Reliability : (2) valid with restrictions
Limited documentation
25.02.2003 (141)

Type : Biochemical or cellular interactions

Result : Findings suggest, that menthol acts on two types of Ca channels coexisting on the membrane of cultured sensory neurons:
- blocks currents through low voltage- activated Ca channel
- facilitates inactivation gating of the classical high voltage- activated Ca channel.
Test condition : Cultured dorsal root ganglion cells from chick and rat embryos are used.
Reliability : (2) valid with restrictions
non-standard test system
25.02.2003 (138)

Type : Biochemical or cellular interactions

Result : In the micromolar range, menthol (unspecified isomer) exerts a depressive action on the low-threshold channel (LVA) and shows a modulatory effect on the high-threshold channel (HVA), in that it speeds up its inactivation.
Test condition : In vitro study of block and modulation of neuronal Ca channels performed on primary cultures of chick dorsal root ganglia.
Reliability : (2) valid with restrictions
non-standard test system
25.02.2003 (142)

Type : Cytotoxicity

Result : The 50 % inhibitory concentration (IC50) for the cellular and subcellular systems ranged from 0.32 mM to 0.76 mM
- trachea from chicken embryos:
5 mM menthol completely stopped the ciliary activity within 7 min, while it took 38 min to reach ciliostasis in a 1 mM solution of menthol.
- isolated hamster brown adipocytes:
At a concentration of 0.5 mM menthol the receptor mediated respiratory stimulation was markedly inhibited while the intracellular mitochondrial functions were still unaffected.
- rat liver mitochondria:
Increase in the "state 4" respiratory rate (at 1.0 mM) and osmotic swelling (at 0.5 mM).
Test condition : The toxicity of menthol (unspecified isomer) in concentrations varying from 0.1 mM to 5 mM was tested in 4 different in vitro test systems:
-trachea from chicken embryos
-Ascites sarcoma BP 8 cells
-isolated hamster brown adipocytes
-rat liver mitochondria
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
non validated test systems
25.02.2003 (143) (144)

Type : Metabolism

Result : Menthol is coupled with glucuronic acid (phase-II hepatic detoxication

mechanism).

Test condition : In vitro metabolic studies with liver microsomal fractions of several mammalian species (pig, rat, guinea pig).
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (145) (146)

Type : Metabolism

Result : 2 g:
< 1 hr after administration in urine
6 h: 90 % recovery
3.5 g:
24 h: > 90 % recovery
Test condition : 2 and 3.5 g of menthol were given to rabbits by stomach tube. Menthol glucuronides are determined.
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (147)

Type : Metabolism

Test condition : In patients having drug-induced liver damages, a menthol loading-test (single oral administration of 2 g menthol) can be used for investigating the biotransforming ability of the liver: the excretion of menthol glucuronide with urine is determined as a control parameter and compared to the corresponding values of healthy normal and pathological control groups.
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (148) (149)

Type : Metabolism

Result : Control: 100 %
PB-induced: 110 %
b-NF-induced: 130 %
Test condition : The activity of hepatic UDP-Glucuronosyltransferase from control and (Phenobarbital PB and b-Naphthoflavone b-NF) induced pigs towards menthol was studied.
Test substance : unspecified isomer
Reliability : (4) not assignable
Documentation insufficient

25.02.2003 (145)

Type : Metabolism

Result : Menthol was a potent inhibitor.
Test condition : The inhibition of glucuronidation of 7-hydroxy-4-methylcoumarin by human liver microsomes was studied.
Test substance : not specified isomer
Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (133)

Type : Metabolism

Result : In inhibitory studies menthol - as a specific substrate for GT2a isoform - competitively inhibited glucuronidation of the dithiol.
Test condition : The kinetic activity of UDP-glucuronosyltransferases (UDPGT) toward a dithiol metabolite of malotilate, 2,2.di(isopropoxycarbonyl)ethylene-1,1-dithiol was investigated using rat and rabbit hepatic microsomes.

Phenobarbital, an inducer of the GT2 isoform of UDPGT, increased rat microsomal UDPGT activity towards the dithiol.
Reliability : (2) valid with restrictions
Limited documentation
25.02.2003 (136)

Type : other: QSAR

Result : Menthol is classified as a reactive chemical.
Test condition : Structure-activity relationships of volatile organic chemicals as sensory irritants are studied using the database of Schaper, M., Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am Ind Hyg Assoc J 54, 488-544, 1993 (database in based on the sensory irritating potency obtained in mice (RD50))
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
non-validated SAR
25.02.2003 (150)

Type : other: QSAR

Remark : Basis was data set from Carpenter, C.P. and Smyth, H.F., Chemicalburns of the rabbit cornea, American Journal of Ophthomology 49, 1363-1372, 1946
Result : Quantitative structure-activity relationships (QSARs) for the eye irritation potential was done. Predicted value of eye score from neutral network analysis: 7 (irritating)
Test substance : unspecified isomer
Reliability : (2) valid with restrictions
non-validated SAR
Flag : Critical study for SIDS endpoint
25.02.2003 (151)

Type : other: cooling function of menthol

Result : Menthol is an efficient cooling ingredient with a rapid effect but it has 3 major inconveniences:
- irritant in higher concentrations; it is not recommended to use in products which come into contact with mucous membranes (eye)
- very strong characteristic odour which is not easy to mask
- effect is only of relatively short duration

Conclusions: Menthol derivatives are more effective cooling ingredients
Reliability : (2) valid with restrictions
äLimited documentation
25.02.2003 (152)

Type : other: pharmacology of menthol

Result : Among other contents this review is concerned with the pharmacology of menthol regarding the respiratory system and the skin. Important facts are:
- General conclusion of a symposium - debating the safety of menthol

medication - was that commonly used vaporub remecies were safe to use in infants but that they should not be applied directly to the nostrils.

Reliability : (4) not assignable
Secondary literature

25.02.2003 (153)

Type : other: pharmacology of menthol

Result : Traditional therapy of atopic dermatitis, ie, use of menthol (among others) is often very effective.

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (154)

Type : other: pharmacology of menthol

Result : Menthol acts as a local anaestheticum and it reduces inflammation, when added to an existing medication.

Test condition : Pharmacological effect of 4-chlorophenol-campher-menthol (medicamentation) is described.

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (155)

Type : other: pharmacology of menthol

Result : It is believed that menthol negatively influences the mucociliary clearance, which means that the removal of the mucus is slowed.

Reliability : (4) not assignable
No further reference.

25.02.2003 (156)

Type : other: skin penetration

Result : In vitro: Menthol showed the most potent enhancing effect.
In vivo: formulation containing 0.05% nonivantide, 5% menthol, 20% ethanol showed higher penetration rate and an acceptable degree of skin irritation.

Test condition : Influences of penetration enhancers (azone, cinnamic acid, cinnamyl alcohol, menthol, nonivamide, menthol&nonivamide) regarding the percutaneous absorption and skin irritation of ketoprofen formulations through rat skin is studied in vitro and in vivo.

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (157)

Type : other: smoking

Result : Menthol and other additives that produce a sensation of coolness but without a mint flavour have also been used in cigarettes. There is no evidence that these additives result in a higher risk.

Reliability : (2) valid with restrictions
co-exposure to cigarette smoke

25.02.2003 (158)

Result : The percentage of the administered dose excreted with the urine was between 10 and 90 %

depending on individuum and environmental influences.

Test condition : 0.2-40 mg menthol was orally administered to 3 volunteers once and the 12 h urine was collected. The menthol content in the urine was gas-chromatographically analyzed.

Reliability : (2) valid with restrictions
Limited documentation

25.02.2003 (159)

6. Analyt. Meth. for Detection and Identification Id 1490-04-6
Date 18.03.2003

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8. Meas. Nec. to Prot. Man, Animals, Environment Id 1490-04-6
Date 18.03.2003

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

9. References Id 1490-04-6
Date 18.03.2003

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(158) WHO, IPCS (1999) EHC No. 211, Health Effects of Interactions between Tobacco use and exposure to other agents, p. 15

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10. Summary and Evaluation Id 1490-04-6
Date 18.03.2003

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

I U C L I D Data Set

Existing Chemical	:	ID: 89-78-1
CAS No.	:	89-78-1
EINECS Name	:	DL-menthol
EC No.	:	201-939-0
Molecular Formula	:	C10H20O

Producer related part

Company	:	Bayer AG
Creation date	:	06.08.1992

Substance related part

Company	:	Bayer AG
Creation date	:	06.08.1992
Status	:	
Memo	:	X AKTUELL EG/ICCA
Printing date	:	18.03.2003
Revision date	:	02.06.1994
Date of last update	:	18.03.2003
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

23.10.2001

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : solid
Purity :
Colour : white
Odour : minty

Flag : Critical study for SIDS endpoint
03.06.2002

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

5-METHYL-2-(1-METHYLETHYL)-CYCLOHEXANOL, RACEMATE

Flag : Critical study for SIDS endpoint
03.06.2002

CYCLOHEXANOL; 5-METHYL-2-(1-METHYLETHYL)-

Flag : Critical study for SIDS endpoint
10.10.2001

DL-MENTHOL

Flag : Critical study for SIDS endpoint

MENTHOL

Flag : Critical study for SIDS endpoint

03.06.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Labelling	:	provisionally by manufacturer/importer
Specific limits	:	
Symbols	:	Xi, , ,
Nota	:	, ,
R-Phrases	:	(38) Irritating to skin
S-Phrases	:	(25) Avoid contact with eyes
Flag	:	Critical study for SIDS endpoint

1.6.2 CLASSIFICATION

Classified	:	provisionally by manufacturer/importer
Class of danger	:	irritating
R-Phrases	:	(38) Irritating to skin
Specific limits	:	
Flag	:	Critical study for SIDS endpoint

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use	:	type
Category	:	Wide dispersive use
Remark	:	L-Menthol, D/L-menthol and menthol liquid are widely used as flavoring, disinfectant and cooling compounds in confecti onery products, liqueurs, chewing gums, toothpastes, cosmetics and common cold ointments and medications and cleaning/washing agents and in veterinary activities.
Flag	:	Critical study for SIDS endpoint

24.07.2002

Type of use	:	industrial
Category	:	Chemical industry: used in synthesis
Remark	:	To produce L -menthol, D/L-menthol is transesterificated with

methylbenzoate and further manufactured. Resulting products are L- and D-menthol.

Flag : Critical study for SIDS endpoint
03.06.2002

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Remark : D/L-menthol is produced via reaction of m-cresol with propen to thymol, and hydrogenation of thymol, resulting in 4 isomers: D/L-neomenthol, D/L-neoisomenthol, D/L-menthol and D/L-isomenthol. D/L-menthol is isolated by fractional distillation.
03.06.2002

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: Bayer AG
Labelled by : other: Bayer AG
Class of danger : 1 (weakly water polluting)

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : no
No. in Seveso directive :

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 5
Date of search : 01.09.2001

Remark : Human Health: last literature search September 2001: CAS number search in external and internal databases, e.g. Biosis, Embase, Toxline, Scisearch
Flag : Critical study for SIDS endpoint
03.07.2002

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 14.01.2002

Remark : Physico-chemical properties / Environment / Ecotoxicology :
last literature search January 2002: CAS number search in external and internal databases, e.g. HSDB, Aquire.
Flag : Critical study for SIDS endpoint
29.07.2002

1.13 REVIEWS

Memo : Menthol: Its Origins, Chemistry, Physiology and Toxicological Properties

03.06.2002 (1)

2.1 MELTING POINT

Value : ca. 30 - 32 °C
Sublimation :
Method :
Year : 2002
GLP : no data
Test substance : other TS: typical for technical intermediate

Flag : Critical study for SIDS endpoint
18.03.2003 (2) (3)

Value : 38 °C
Sublimation :
Method :
Year : 1996
GLP : no data
Test substance : no data

18.03.2003 (4)

Sublimation :
Method : other: DIN 51556
Year :
GLP :
Test substance :

Remark : Freezing temperature ca. 27 °C
03.06.2002 (2)

Sublimation :
Method :
Year : 1972
GLP : no data
Test substance : no data

Remark : Freezing point of (+/-) menthol: 27 - 28 °C, rising on prolonged stirring to 30 - 32 °C
18.03.2003 (5)

2.2 BOILING POINT

Value : 216 °C at

Flag : Critical study for SIDS endpoint
24.07.2002 (2) (4)

2.3 DENSITY

Type : density
Value : .903 g/cm³ at 15 °C

18.07.2002 (4)

Type : density
Value : .895 g/cm³ at 20 °C
Method : other: DIN 51757
Year :
GLP :
Test substance :

Flag : Critical study for SIDS endpoint
05.02.2002 (2)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : 1.3 hPa at 55 °C
Decomposition :
Method :
Year : 1977
GLP : no
Test substance : no data

18.03.2003 (6) (2)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : 3.4 at °C
pH value :
Method : other (measured)
Year : 1999
GLP : no data
Test substance : other TS: purity not reported but HPLC applied

Method : Reversed-phase high-performance liquid chromatography
Flag : Critical study for SIDS endpoint
14.03.2003 (7)

Partition coefficient : octanol-water
Log pow : 3.38 at °C
pH value :
Method : other (calculated): SRC-KOWWIN v. 1.66
Year : 2002
GLP :
Test substance :

18.03.2003 (8)

Partition coefficient : octanol-water
Log pow : 3.2 at °C
pH value :
Method : other (calculated): Leo, A. CLOGP-3.54 MedChem Software 1989. Daylight, Chemical Information Systems, Claremont, CA 91711, USA
Year : 1991
GLP :

Test substance :

06.03.2003 (9)

Method :
Year : 1979
GLP : no data
Test substance : no data

Result : log partition oils/water 2.27 resp. 2.40 according to 2 cited references
18.03.2003 (10)

Partition coefficient : octanol-water
Log pow : 3.3 at °C
pH value :

Remark : The reference notes both Cas-No. 2216-51-5 and 15356-70-4 (former CAS -No. for 89-78-1)
06.03.2003 (11)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 508 mg/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: flask method
Year : 1990
GLP :
Test substance : other TS: HR product 131136, d,l-Menthol, purity 99.4 %

Flag : Critical study for SIDS endpoint
07.03.2003 (12)

Solubility in : Water
Value : 456 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

06.03.2003 (13) (14)

Solubility in : Water
Value : 431 mg/l at 20 °C
pH value :
concentration : at °C
Temperature effects :

Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 2002
GLP : no data
Test substance : no data

18.03.2003 (2)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : 92 °C
Type : closed cup

05.02.2002 (2)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Result : other: lower limit 0.80 Vol%, upper limit 7.00 Vol%

06.05.2002 (2)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Value : 6 - mm2/s (static) at 50 °C
Result :

05.02.2002 (2)

2.14 ADDITIONAL REMARKS

Memo : Ignition temperature ca. 405 °C

Method : DIN 51794
03.06.2002 (2)

Memo : Refractive index nD20 = 1.4615

Flag : Critical study for SIDS endpoint
03.06.2002 (4)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Method	:	structure estimation method
Result	:	Rate constant: k = 2.4 E -11 cm3/molecule/sec at 25 degrees C; considering an atmospheric OH-radical concentration of 5 E5 OH-radicals/cm3, the half-life is about 16 h
Reliability	:	(2) valid with restrictions accepted calculation procedure
Flag	:	Critical study for SIDS endpoint

29.07.2002 (15)

3.1.2 STABILITY IN WATER

Deg. product	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	
Result	:	volatilization half-lives for a model river (1 m deep, flow-rate 1 m/sec, wind velocity 3 m/sec) and a model lake (1 m deep, flow-rate 0.05 m/sec, wind velocity 0.5 m/sec) are estimated to be 2 and 18 days
Reliability	:	(2) valid with restrictions accepted calculation procedure derived from L-menthol cause of structural similarities
Flag	:	Critical study for SIDS endpoint

30.07.2002 (16)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	volatility
Media	:	water - air
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	
Year	:	2003

Result : Based on a water solubility of 508 mg/l and a vapour pressure of 8.5 Pa (see chapter 2), the Henry's law constant is calculated to be 2.62 Pa x m3/mol at 25°C
Reliability : (2) valid with restrictions
Generally accepted calculation method
Flag : Critical study for SIDS endpoint
14.03.2003 (17)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2003

Result : air: 39.5 %
water: 43.8 %
soil: 8.7 %
sediment: 7.9 %
biota: 0.0055 %
Test condition : Base data for calculation:
temperature: 20 °C
molar mass: 156.27 g/mol
vapour pressure: 8.5 Pa
water solubility: 508 g/m3
log Kow: 3.4
environmental compartments:
- air: 6*10^9 m³, 1.2 kg/m³
- water: 7*10^6 m³, 1000 kg/m³
- soil: 4.5 *10^4 m³, 1500 kg/m³, 2 % org. C
- sediment: 2.1*10^4 m³, 1300 kg/m², 5 % org. C
- susp. sediment: 35 m³, 1500 kg/m³, 16.7 % org. C
- aerosol: 0.12 m³, 1500 kg/m³
- aquatic biota: 7 m³, 1000 kg/m³, 5 % fat
Reliability : (2) valid with restrictions
Generally accepted calculation method
Flag : Critical study for SIDS endpoint
14.03.2003 (17)

Media : water - soil
Method : other (calculation)
Year :

Result : Using the equation log Koc = 0.52 log Kow + 1.02 and based on a log Kow of 3.40 (see chapter 2) a Koc value of 614 can be calculated for the distribution between the organic phase of soil and pore water
Reliability : (2) valid with restrictions
Generally accepted calculation method
Flag : Critical study for SIDS endpoint
07.03.2003 (18)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic

Inoculum	:	activated sludge
Concentration	:	100 mg/l related to Test substance related to
Contact time	:	28 day(s)
Degradation	:	0 (±) % after 28 day(s)
Result	:	
Deg. product	:	
Method	:	other: corresponding to OECD 301C
Year	:	1992
GLP	:	
Test substance	:	other TS: not clear
Remark	:	TS not clear. The reference notes two CAS -No.: 2216-51-5 and 15356-70-4 (= 89-78-1)
Test condition	:	sludge concentration 30 mg/l
Reliability	:	(3) invalid Biodegradation possibly affected by toxicity of the substance at the concentration teste d
Flag	:	Critical study for SIDS endpoint

05.03.2003 (11)

3.6 BOD5, COD OR BOD5/COD RATIO

COD		
Method	:	
Year	:	
COD	:	2767 mg/g substance
GLP	:	
Remark	:	ThOD: 2970 mg/g
Reliability	:	(4) not assignable Original reference in Czech

30.07.2002 (19)

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	11.3
LC50	:	17.6
LC100	:	26.2
Limit test	:	no
Analytical monitoring	:	yes
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1990
GLP	:	yes
Test substance	:	other TS: HR product 131136, d,l-Menthol, purity 99.4 %

Remark : analyt. monitoring: GC
D,L-menthol (rac., solid)
LC50: 17.2 mg/l (geom. mean between LC0 and LC100)
LC50: 17.6 mg/l (calculated with probit analysis). This value is not reported in the original study.
All effect values reported in the study based on nominal concentrations. However it can be derived the effective values. The results here given based on real concentrations (LC0=11.3 mg/l, LC100=26.2 mg/l).

Result : RESULTS: EXPOSED
- Nominal/measured concentrations:

m.(mg/l)	7.8	11	16	22	31
c. (mg/l) (0 h)	7.2	9.9	11.5	17.1	26.5
c. (mg/l) (24 h)	6.7	9.7	13.2	19.5	25.8
c. (mg/l) (48 h)	6.3	9.2	12.3	18.9	
c. (mg/l) (72 h)	6.1	9.1	10.8	19.1	
c. (mg/l) (96 h)	5.9	8.7	8.9	18.8	

- Effect data (Mortality):
Mortality, visible abnormities of fishes
- Concentration / response curve:
There were no dead fishes in tanks with concentration: 7.8, 11 and 16 mg/l.
22 mg/l

hours (h)	0	24	48	72	96
Mortality (%)	0	80	90	90	90

31 mg/l
Mortality (%) 0 100
- Effect concentration vs. test substance solubility:
Despite bad solubility and high volatility of substance the required concentration was not reached during testing procedure.
Undissolved substance particles remained on the water surface at the start of the test: After 2 hours there were no particles visible at concentration 7.8 mg/l, after 6 hours the particles in tanks with concentration 11 mg/l and 16 mg/l disappeared and after 24 hours there were no undissolved particles in any fish tank visible.
- Other effects:
RESULTS: CONTROL: No dead fish
- Number/percentage of animals showing adverse effects:
7.8 mg/l

hours (h)	2	24	48	72	96
7.8 mg/l	-	-	-	-	-
11 mg/l	-	-	100%A 10%B	90%A	10%B
16 mg/l	-	80%A	80%A	90%A	90%A

20%B 20%B 10%B 10%B
22 mg/l 90%B 20%B 10%B 10%B 10%B
10%A
31 mg/l 100%B
- Nature of adverse effects:
A: slow and inactive swimming behaviour
B: loss of equilibrium (uncontrolled movements)

Reliability : (2) valid with restrictions
Guideline study; effective concentrations decreased below 80% of the nominal during the test period

Flag : Critical study for SIDS endpoint

07.03.2003 (20)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC0 : 15.7
EC50 : 71
EC100 : 125
Limit Test : no
Analytical monitoring : no
Method : other: Daphnien-Schwimmunfaehigkeits-Test, UBA-Verfahrensvorschlag Mai 1984, Bestimmung der Schwimmunfaehigkeit beim Wasserfloh Daphnia magna, EC0, EC50, EC100, 24h, static
Year : 1990
GLP : yes
Test substance : other TS: HR product 131136, d,l-Menthol, purity 99.4 %

Remark : D/L-menthol (rac., solid)
EC50 = 44.3 mg/l (geom. mean between LC0 and LC100)
EC50 = 71 mg/l (calculated with probit analysis). This value was not reported in the original study.
To produce the stock solution, 300 mg/l was weighed into water and after treatment with an Ultra-Turrax for 60 sec., stirred on a magnetic stirrer for two hours. In order to avoid uneven distribution of undissolved particles, the solution was kept in movement when preparing the test concentrations.

Result : RESULTS: EXPOSED
- Nominal concentrations:
250 mg/l, 125 mg/l, 63 mg/l, 31 mg/l, 15.7 mg/l, 7.8 mg/l, 4.0 mg/l, 2.0 mg/l, no analytical monitoring
- Effect data (Immobilisation):
Immobilisation of Daphnia magna
- Concentration / response curve:
- Cumulative immobilisation:
after 24 hours, 2 replicates:

conc. (mg/l)	250	125	63	31	15.7	7.8	4.0	2.0
immobile Daphnia (%)	100	100	35	25	0	0	0	0

- Effect concentration vs. test substance solubility:
The water solubility of test substance is low. To produce the stock solution, 300 mg/l was weighed into water and after treatment with an Ultra-Turrax for 60 sec., stirred on a magnetic stirrer for two hours. In order to avoid uneven distribution of undissolved particles, the solution was kept in movement when preparing the test concentrations.
- Other effects:

RESULTS CONTROL: no immobile Daphnia
RESULTS: TEST WITH REFERENCE SUBSTANCE
Reference substance: Potassium dichromate
- Results:

conc. (mg/l)	0.5	1.0	1.5	2.0	3.0	4.0	5.0
immobile Daphnia (%)	0	0	15	30	30	45	65

Test condition : TEST ORGANISMS: Daphnia magna Straus, parthenogenetic female
- Strain: clone, Bundesgesundheitsamt Berlin
- Source/supplier: Lab breeding, Bayer AG Leverkusen
- Age: 6-24 h
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Vehicle, solvent: Filtered surface water, Monheimer Kiesgrube
DILUTION WATER: Filtered surface water
- Source: Monheimer Kiesgrube
TEST SYSTEM
- Test type: static
- Concentrations: see results
- Renewal of test solution: no
- Exposure vessel type: cylindric vessels, diameter: 4.0 cm, height: 6.5 cm
- Number of replicates, individuals per replicate: 2 replicates with test substance, and 2 replicates with reference substance, 10 individuals in each test
- Test temperature: between 19.9 and 20.0 °C
- Dissolved oxygen: between 8.1 and 8.2 mg/l
- pH: between 8.3 and 8.4
- Adjustment of pH: no
DURATION OF THE TEST: 24 hours
TEST PARAMETER: Oxygen (mg/l), pH, Temperature (°C), Number of immobile Daphnia
MONITORING OF TEST SUBSTANCE CONCENTRATION: no

Reliability : (2) valid with restrictions
Test procedure comparable to standard method and in accordance with general accepted scientific standards; detailed documentation of test procedure and test conditions but not analytical monitoring was conducted

Flag : Critical study for SIDS endpoint
05.03.2003 (21)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	5
LOEC	:	10
ErC50	:	16.2
Limit test	:	no
Analytical monitoring	:	yes
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	2000
GLP	:	yes
Test substance	:	other TS: HR product 131136, d,l-Menthol, purity 99 %

Remark : The NOEC, LOEC and Erc50 values are given as nominal concentrations as the analytical control (TOC mesurements) revealed that the test concentrations have not decreased below 80 % of the nominal.
The test concentrations 1.25 and 2.5 mg/l were not analytically determined

as the measured concentrations to be expected were below the detection limit of the TOC determination method (2 mg/l) d,l-menthol (rac., solid)

Result : RESULTS: EXPOSED
- Nominal concentrations:

nominal concentration (mg/l)	analytically determined conc.
test substance (mg/l)	0 hours 72 hours
control	< 2 3
w. algae*	5 5 3
1.25	- -
2.5	- -
5	4 3
10	8 7
20	15 13
40	29 26
w. algae*	40 27 27

* w. algae: without algal inoculum

All values refer to TOC determination. According to the relevant product information 1 mg/l TOC equals to 1.3 mg/l of the test substance (empirical formula: C10 H20 O; molecular weight: 156.3 mg/l).
- Effect data/Element values:
- Cell density data:

Nominal concentr. test substance (mg/l)	Number of cells/ml mean values (3 replicates) 24 hours	48 hours	72 hours
control*	45600	188000	527000
1.25	41100	174000	541000
2.5	47800	180000	548000
5	44400	161000	452000
10	40000	118000	287000
20	32200	60000	50000
40	18900	15500	10000

*control - 6 replicates
- Growth curves:

Nominal concentr. test substance (mg/l)	Growth (b)	Growth rate (r)
control	472000 (0.0)	1.3 (0.0)
1.25	461000 (2.3)	1.3 (0.0)
2.5	477000 (-1.1)	1.3 (0.0)
5	406000 (14.0)	1.3 (0.0)
10	277000 (41.3)	1.1 (15.4)
20	92200 (80.5)	0.5 (61.5)
40	14400 (96.9)	0.0 (100.0)

Values in brackets indicate % inhibition [+] or % increase [-]

RESULTS CONTROL: see above

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

07.08.2002 (22)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : activated sludge
Exposure period : 3 hour(s)
Unit : mg/l

EC10	:	117
EC50	:	306
EC5	:	89
EC90	:	800
Analytical monitoring	:	no
Method	:	OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year	:	1989
GLP	:	yes
Test substance	:	other TS: HR product 131136, d,l-Menthol, purity 99.4 %
Remark	:	Direct weight
Reliability	:	(1) valid without restriction Guideline Study; deta iled documentation of test procedure and test conditions
Flag	:	Critical study for SIDS endpoint

29.07.2002 (23)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	
Type	:	Metabolism
Species	:	rabbit
Number of animals		
Males	:	
Females	:	4
Doses		
Males	:	1 g/kg
Females	:	
Vehicle	:	
Method	:	
Year	:	1938
GLP	:	no
Test substance	:	other TS: D-, L- and D/L-menthol
Remark	:	The main objects of this study were to find out whether the optical and geometrical isomerism of the menthols influenced their conjugation with glucuronic acid in the body and whether the feeding of a D/L -menthol resulted in the excretion of a conjugated glucuronide containing more of one antipode than the other.
Result	:	After a single oral administration of 1 g/kg bw of menthol racemic to rabbits, 59 % of the applied test substance was excreted as glucuronide with the urine within 2 d.
Test condition	:	Urine was collected for 2 days and analysed for conjugated glucuronic acid by ether extraction.
Reliability	:	(2) valid with restrictions limited documenta tion
Flag	:	Critical study for SIDS endpoint

19.02.2003 (24)

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 2602 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	female
Number of animals	:	10
Vehicle	:	peanut oil
Doses	:	2000, 2500, 3000, 3500 mg/kg bw
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	other TS: menthol racemic 100
Result	:	MORTALITY: - Time of death: 1-3 days after application - Number of deaths at each dose: dose (mg/kg bw): number of deaths 2000 1/10 2500 4/10 3000 7/10 3500 10/10 CLINICAL SIGNS: narcotic status (no data available on exposure level at

which the clinical signs were observed)
NECROPSY FINDINGS: no data

Test condition : ADMINISTRATION:
- Volume administered or concentration: 10-20 ml/kg
- Post dose observation period: 14 days
EXAMINATIONS:
deaths, clinical signs
No further information given on statistical methods and confidence limits.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: no information on statistical methods and confidence limits.

Flag : Critical study for SIDS endpoint

19.02.2003 (25)

Type : LD50
Value : = 2900 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other
Year : 1961
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Secondary literature

19.02.2003 (26) (27)

Type : LD50
Value : = 3100 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals : 10
Vehicle : other: olive oil
Doses : 2000, 4000 mg/kg bw
Method : other
Year : 1932
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient.

19.02.2003 (28)

Type : other: lethal dose
Value : 1500 - 1600 mg/kg bw
Species : cat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other
Year : 1926

GLP : no
Test substance : other TS: synthetic menthol (inactive, Fp.: 35-38 °C)

Reliability : (4) not assignable
Documentation insufficient.
19.02.2003 (29)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value : > 5000 mg/kg bw
Species : rabbit
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other
Year : 1973
GLP : no
Test substance : other TS: not further specified

Reliability : (2) valid with restrictions
Secondary literature from peer-reviewed journal
Flag : Critical study for SIDS endpoint
19.02.2003 (30)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Value : = 750 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1961
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Secondary literature
19.02.2003 (27)

Type : LD50
Value : = 670 mg/kg bw
Species : rat
Strain : other: white rats

Sex	:	no data
Number of animals	:	10
Vehicle	:	other: olive oil
Doses	:	500, 600, 700, 800, 900, 1000, 1100 mg/kg bw
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1952
GLP	:	no
Test substance	:	other TS: not further specified

Result : MORTALITY:
- Time of death: 12 hours after application
- Number of deaths at each dose:
dose (mg/kg bw)/deaths
500/2/10
600/4/10
700/7/10
800/9/10
900/8/10
1000/9/10
1100/10/10
CLINICAL SIGNS: loss of equilibrity, partial to total relaxation, deep sleep with abolition of reflexes

Test condition : TEST ORGANISMS:
- Source: no data
- Age: no data
- Weight at study initiation: 90-120 g
- Controls: no data
ADMINISTRATION:
- Post dose observation period: the animals were observed until deaths or until return to normal behaviour
EXAMINATIONS:
deaths, clinical signs

Reliability : (2) valid with restrictions
limited documentation

04.03.2003 (31)

Type	:	LD50
Value	:	ca. 2000 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1961
GLP	:	no
Test substance	:	other TS: not further specified

Reliability : (4) not assignable
Secondary literature

19.02.2003 (27)

Type	:	LD50
Value	:	= 865 mg/kg bw

Species	:	guinea pig
Strain	:	no data
Sex	:	no data
Number of animals	:	10
Vehicle	:	other: olive oil
Doses	:	500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400 mg/kg bw
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1952
GLP	:	no
Test substance	:	other TS: not further specified

Result :
MORTALITY:
- Time of death: 12 hours after application
- Number of deaths at each dose:
dose (mg/kg bw)/deaths
500/1/10
600/4/10
700/4/10
800/6/10
900/6/10
1000/7/10
1100/6/10
1200/7/10
1300/8/10
1400/10/10
CLINICAL SIGNS: loss of equilibrity, partial to total relaxation, deep sleep with abolition of reflexes

Test condition :
TEST ORGANISMS:
- Source: no data
- Age: no data
- Weight at study initiation: 280-360 g
- Controls: no data
ADMINISTRATION:
- Post dose observation period: the animals were observed until deaths or until return to normal behaviour
EXAMINATIONS:
deaths, clinical signs

Reliability : (2) valid with restrictions
limited documentation

04.03.2003 (31)

Type	:	other: LD
Value	:	> 1500 mg/kg bw
Species	:	cat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: not specified oil
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1926
GLP	:	no
Test substance	:	other TS: not further specified

Reliability : (4) not assignable

Documentation insufficient.
19.02.2003 (29)

Type	:	other: LD
Value	:	> 1000 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: not specified oil
Doses	:	
Route of admin.	:	s.c.
Exposure time	:	
Method	:	other
Year	:	1926
GLP	:	no
Test substance	:	other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient.
19.02.2003 (29)

Type	:	other: LD
Value	:	> 14000 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: not specified oil
Doses	:	
Route of admin.	:	s.c.
Exposure time	:	
Method	:	other
Year	:	1926
GLP	:	no
Test substance	:	other TS: not further specified

Reliability : (4) not assignable
Documentation insufficient.
19.02.2003 (29)

Type	:	LD50
Value	:	= 14200 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Route of admin.	:	other: not specified
Exposure time	:	
Method	:	other
Year	:	1962
GLP	:	no
Test substance	:	other TS: not further specified

Reliability : (4) not assignable
Insufficient documentation for assessment.
04.03.2003 (32)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	100 %
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	4
Vehicle	:	other: diethylphthalate (DEP)
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1989
GLP	:	yes
Test substance	:	other TS: HR 89/131136, purity: no data
Result	:	AVERAGE SCORE 100%/50%/25%/5%/1%/Vehicle 3.0/1.6/0.8/0.2/0.1/0.1 (erythema) 3.0/1.7/0.5/0.0/0.0/0.0 (oedema) REVERSIBILITY: Yes Day 7: 100%: in 3/4 - treated sites were covered with a layer of white-brown scales, 1/4 - thin layer of white scales 50%: 4/4 - white scales 25%: 1/4 - scattered white scales Day 14: 100%: 4/4 - treated sites were covered with white to white-brown scales, underlaying skin was intact 50%: 3/4 - treated sites showed scattered scale formation on intact skin.
Test condition	:	TEST ANIMALS: - Strain: Chbb:HM (C.H.Boehringer/Biberach - Sex: female - Source: Dr. Karl Thomae GmbH, Biberach an der Riss - Age: no data - Weight at study initiation: 2400-2700 g - Number of animals: 4 - Controls: internal control (one part of skin) ADMINISTRATION/EXPOSURE - Preparation of test substance: dilutions of substance with DEP, concentrated test substance was moistened with DEP in the ratio 6:1 - Area of exposure: six different fields on back (two anterior, two centrally located and two posterior treatment sites) - Concentration in vehicle: 100, 50, 25, 5 and 1 %, Vehicle - Total volume applied: 0.5 ml - Postexposure period: up to 14 days - Removal of test substance: skin was washed with luke warm water and soap
Reliability	:	(2) valid with restrictions purity of TS not stated
Flag	:	Critical study for SIDS endpoint

19.02.2003 (33)

Species	:	guinea pig
Concentration	:	no data
Exposure	:	Open
Exposure time	:	14 day(s)
Number of animals	:	20
Vehicle	:	no data
PDII	:	

Result : not irritating
Classification : not irritating
Method : other
Year : 1974
GLP : no data
Test substance : other TS: menthol racemic 100

Test condition : Substance was rubbed into the skin for 30 s once daily.
Substance was applied 2 x 5 days, results were taken after 14 days.
Reliability : (3) invalid
Significant methodological deficiencies. e.g. concentration and amount of substance is unclear; lack of control experiment.
17.12.2001 (34)

Species : human
Concentration : 8 %
Exposure : Occlusive
Exposure time : 48 hour(s)
Number of animals :
Vehicle : petrolatum
PDII :
Result : not irritating
Classification :
Method : other: closed patch-test
Year : 1973
GLP : no
Test substance : other TS: not further specified

Reliability : (4) not assignable
Secondary literature
05.12.2001 (35)

Species : rabbit
Concentration : no data
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals :
Vehicle : no data
PDII :
Result : slightly irritating
Classification :
Method : other
Year : 1973
GLP : no
Test substance : other TS: not further specified

Test condition : Substance applied full strength to intact or abraded skin
(no further data)
Reliability : (4) not assignable
Secondary literature
17.12.2001 (30)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : 40 %
Dose : .1 ml

Exposure time : 24 hour(s)
Comment : rinsed after (see exposure time)
Number of animals : 4
Vehicle : other: diethylphthalate (DEP)
Result : slightly irritating
Classification :
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1989
GLP : yes
Test substance : other TS: menthol rac. HR 89/131136 DEP, purity: no data

Result : AVERAGE SCORE:
- Cornea opacity: 0.8
- Iris lesion: 0.0
- Conjunctivae (Redness): 1.5
- Conjunctivae (Chemosis): 0.4

REVERSIBILITY: a slight reaction of conjunctiva was seen in one rabbit on day 7

Test condition : TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer, Biberach: Himalaya)
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss
- Age: no data
- Weight at study initiation: 2400-2800 g
- Number of animals: 4
- Controls: internal control (right eye)

Reliability : (2) valid with restrictions
purity of TS not stated, short duration of experiment
Flag : Critical study for SIDS endpoint
19.02.2003 (36)

Species : rabbit
Concentration : 64 %
Dose : .1 ml
Exposure time : 24 hour(s)
Comment : rinsed after (see exposure time)
Number of animals : 4
Vehicle : other: 40 % solution of d,l-menthol in DEP (HR 89/131136 DEP)
Result : slightly irritating
Classification :
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1989
GLP : yes
Test substance : other TS: menthol rac, HR 89/131136

Result : AVERAGE SCORE
HR 89/131136 64 %/Vehicle
1.0/1.0 (cornea)
0.0/0.0 (iris)
2.1/1.9 (redness of conjunctivae)
0.3/0.3 (chemosis, conjunctivae)
The right eyes were treated with the vehicle (40% d/l-menthol in DEP) and the left eyes with the test article solution. Both articles had almost the same eye-irritating potential.
REVERSIBILITY: yes, no reactions observed at day 7

Test condition : TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer, Biberach: Himalaya)
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss

- Age: no data
- Weight at study initiation: 2600-2800 g
- Number of animals: 4
- Controls: internal control with vehicle (right eye)
ADMINISTRATION/EXPOSURE
- Preparation of test substance: Test article was pulverized in a mortar and then diluted with vehicle (absolute concentration of substance in DEP is 64%).
- Vehicle: 40% d/l-menthol in DEP (HR 89/131136 DEP, previously tested by Scantox, lab.no.: 11753)

Reliability : (2) valid with restrictions
purity of TS not stated, no untreated controls
Flag : Critical study for SIDS endpoint
19.02.2003 (37)

Species : rabbit
Concentration : 60 %
Dose : .1 ml
Exposure time : 1 minute(s)
Comment : other
Number of animals : 8
Vehicle : other: olive oil
Result : not irritating
Classification : not irritating
Method : Draize Test
Year : 1974
GLP : no data
Test substance : other TS: menthol racemic 100

Test condition : Substance was initially applied in 10, 20 and 30 % solution.
The eyes of 4 animals were rinsed 1 minute after application with physiological saline, substance remained in the eyes of 4 animals. In a second step animals were treated with concentration of 40, 50 and 60 %.
Reliability : (2) valid with restrictions
limited documentation
04.03.2003 (34)

5.3 SENSITIZATION

Type : other: open repetitive dermal test
Species : guinea pig
Number of animals : 20
Vehicle : no data
Result : not sensitizing
Classification : not sensitizing
Method : other
Year : 1974
GLP : no data
Test substance : other TS: menthol racemic 100

Test condition : Substance was rubbed into shaved skin for 30 sec once daily for 3x5 days.
After 5 days without application the test substance was rubbed into an untreated part of the skin.
Results were taken after 24 h, 2 and 3 days.
Reliability : (3) invalid
Significant methodological deficiencies. e.g. concentration and amount of substance is unclear; lack of control experiment.
17.12.2001 (34)

Type	:	other: Maximization test
Species	:	human
Number of animals	:	
Vehicle	:	petrolatum
Result	:	
Classification	:	
Method	:	other
Year	:	1973
GLP	:	no
Test substance	:	other TS: dl-menthol, 8%
Result	:	The material produced no sensitization reactions.
Test condition	:	Number of volunteers: 25
Reliability	:	(2) valid with restrictions Data cited by a peer-reviewed standard reference journal
Flag	:	Critical study for SIDS endpoint

19.02.2003 (35)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	13 w
Frequency of treatm.	:	continuously
Post exposure period	:	1 w
Doses	:	930, 1870, 3750, 7500, 15000 ppm
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	other TS: USP grade was used
Result	:	ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX calculated relation of % in diet to mg/kg bw/d (data obtained from detailed food consumption table given in the study): 930, 1870, 3750, 7500 or 15000 ppm = for male mice: 243, 488, 978, 1956, 3913 mg/kg bw/d for female mice: 290, 595, 1193, 2386, 4773 mg/kg bw/d NOAEL for male mice: 1956 mg/kg bw/d, based on reduced body weight gain NOAEL for female mice: 2386 mg/kg bw/d, based on reduced body weight gain - Time of death: male: control (1/week 12), 3750 ppm (1/week 13), 7500 ppm (1/week 7), 15000 ppm (1/week 1 and 1/week 2) female: control (1/week 5 and 1/week 6), 15000 ppm (1/week 11) - Number of deaths at each dose: control (1 male/2 female), 3750 ppm (1 male), 7500 ppm (1 male), 15000 ppm (2 male/1 female) TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Mortality and time to death: no effect - Clinical signs: hunched appearance, localized alopecia, and urine stains

(sporadically noted in a few animals in each group including controls)
- Body weight gain:
15000 ppm, m, f: decrease (5-10 % of controls)
- Food/water consumption: no effect
- Gross pathology: no effect
- Histopathology: no effect
RESPONSE/EFFECTS BY DOSE LEVEL which are not compound related:
Lung (peribronchial or perivascular lymphoid hyperplasia, lung congestion):
m: control 8/10, 7500 ppm 3/10, 15000 ppm 1/10
f: control 4/10, 7500 ppm 6/10, 15000 ppm 6/10
These findings revealed early spontaneous respiratory disease lesions.
Kidney (interstitial nephritis, nonsuppurative pyelitis):
m: control 3/10, 7500 ppm 0/10, 15000 ppm 2/10
f: control 1/10, 7500 ppm 5/10, 15000 ppm 2/10
These findings are noted as spontaneous lesions.

Test condition : TEST ORGANISMS
- Age: 5 weeks
- Weight at study initiation: males: 16-23 g, females: 17-22g
- Number of animals/dose group: 10 male and 10 female
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
EXAMINATIONS:
- Clinical signs: appearance and behaviour was recorded weekly
- Mortality: yes (daily)
- Body weight: yes (weekly monitored)
- Food consumption: yes (weekly monitored)
- Water consumption: no
- Organ weights: no
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
- Histopathology: for the 7500 and 15000 ppm concentration groups
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and preserved mainly as described in OECD guideline 408 (Exceptions: No full histopathological examination was carried out on the aorta, peripheral nerve and spinal cord)
STATISTICAL METHODS: only standard deviations given

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: no statistics and no data on organ weights

Flag : Critical study for SIDS endpoint

07.08.2002 (38)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 13 w
Frequency of treatm. : continuously
Post exposure period : 1 w
Doses : 930, 1870, 3750, 7500, 15000 ppm
Control group : yes, concurrent vehicle
Method : other
Year : 1976
GLP : no

Test substance : other TS: USP grade was used

Result : ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX
calculated relation of % in diet to mg/kg bw/d (data obtained from detailed food consumption table given in the paper):
930, 1870, 3750, 7500 or 15000 ppm =
for male rats: 59, 114, 231, 472, 937 mg/kg bw/d
for female rats: 67, 142, 285, 521, 998 mg/kg bw/d

NOAEL for male rats: 937 mg/kg bw/d
NOAEL for female rats: 998 mg/kg bw/d

- Time of death: no deaths
- Number of deaths at each dose: none
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: no effect
- Clinical signs: hunched appearance with wheezing, localized alopecia, urine stains, soft feces, and redness of the eye (sporadically noted in a few animals in each group including controls)
- Body weight gain: no effect
- Food/water consumption: no effect
- Gross pathology: no effect
- Histopathology:
15000 ppm males: Minimal increase in the severity of spontaneous interstitial nephritis (finding of questionable significance)
No further dose-dependent observations.

Test condition : TEST ORGANISMS
- Age: 8 weeks
- Weight at study initiation: males: 166-214 g, females: 121-149 g
- Number of animals/dose group: 10 male and 10 female
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
EXAMINATIONS:
- Clinical signs: appearance and behaviour was recorded weekly
- Mortality: yes (daily)
- Body weight: yes (weekly monitored)
- Food consumption: yes (weekly monitored)
- Water consumption: no
- Organ weights: no
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
- Histopathology: yes
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and preserved as described in OECD guideline 408 (Exceptions: No full histopathological examination was carried out on the aorta, peripheral nerve and the spinal cord)
STATISTICAL METHODS: only standard deviations given

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: no statistics and no data on organ weights

Flag : Critical study for SIDS endpoint
07.08.2002 (39)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	other: diet
Exposure period	:	5.5 w
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	0, 100 or 200 mg/kg bw/d
Control group	:	other: Yes, not specified
NOAEL	:	200 mg/kg bw
Method	:	other: no data
Year	:	1961
GLP	:	no
Test substance	:	other TS: L-menthol or D/L-menthol
Remark	:	other: Repeated dose study
Result	:	No adverse effects on weight gain, excretion of glucuronides, water, or electrolytes, or interference with central nervous system reactions to stimulants were observed
Test condition	:	NUMBER OF ANIMALS: 40 rats of each sex/dose
Reliability	:	(2) valid with restrictions secondary citation from peer-reviewed expert document (FAO/WHO report 1999)
Flag	:	Critical study for SIDS endpoint

19.02.2003 (40)

Type	:	Chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	103 w
Frequency of treatm.	:	continously
Post exposure period	:	2 w
Doses	:	3750 or 7500 ppm (about 188 or 375 mg/kg bw/d)
Control group	:	yes, concurrent vehicle
NOAEL	:	= 188 mg/kg bw
NOAEL male rat	:	= 375 mg/kg bw
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	other TS: purity of 100 % is assumed
Result	:	NOAEL (NOEL), LOAEL (LOEL): the overall NOAEL (188 mg/kg bw) is based on females showing decreased body weight gain with a difference greater than 10% between dosed and control rats. TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Survival m: 31/50 (62 %), 33/50 (66 %); 34/50 (68 %) - Survival f: 36/50 (72 %), 35/50 (70 %), 38/50 (76 %) - Clinical signs: No dose-related clinical signs of toxicity. - Body weight gain: 3750 ppm, m and f: slight body weight gain suppression: < 10% (estimated from graphic) 7500 ppm, m and f: slight body weight gain suppression, m: < 10%, f: < 14% (estimated from graphic) - Food/water consumption: no effect - Gross pathology: no effect - Histopathology:

Chronic inflammation kidney:
m: 29/49, 41/50, 41/50 (effect frequently found in aged male Fischer rats; considered as of questionable significance by the authors).

Test condition : TEST ORGANISMS
- Age: 9 weeks
- Weight at study initiation: males: 165-180 g, females: 120-135 g (estimated from graphic)
- Number of animals/dose group: 50 male, 50 female
ACTUAL DOSE RECEIVED BY DOSE LEVEL
mg/kg bw/d values calculated for rats with a bw of in average 400 g, food consumption of in average 20 g/d
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (twice daily)
- Mortality: yes (twice daily)
- Body weight: yes (monitored every two weeks)
- Organ weight: no
- Food consumption: yes (monitored every two weeks)
- Water consumption: no
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
- Histopathology: yes
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and preserved as described in OECD guideline 451.
STATISTICAL METHODS:
Probabilities of survival: procedure of Kaplan and Meier.
Possible dose-related effect on survival: method of Cox.
Dose-related trends: Tarone's extensions of Cox' methods

Reliability : (2) valid with restrictions
No biochemistry/hematology performed, organ weights not determined

Flag : Critical study for SIDS endpoint

19.02.2003 (41)

Type : Chronic
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 103 w
Frequency of treatm. : continously
Post exposure period : 1 w
Doses : 2000 or 4000 ppm (about 334 or 667 mg/kg bw/d)
Control group : yes, concurrent vehicle
NOAEL : = 667 mg/kg bw
Method : other
Year : 1976
GLP : no
Test substance : other TS: purity of 100 % is assumed

Result : TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Survival m: 32/50 (62 %), 32/50 (64 %); 35/50 (70 %)
- Survival f: 45/50 (90 %), 40/50 (80 %), 36/50 (72 %)
- Clinical signs: no clinical signs of toxicity
- Body weight gain:
2000 and 4000 ppm m and f: slight body weight gain

suppression: < 10% (estimated from graphic)
- Food/water consumption: no effect
- Gross pathology: no effect
- Histopathology: see 5.7 Carcinogenicity

Test condition : TEST ORGANISMS
- Age: 6 weeks
- Weight at study initiation: male: 23-25 g, female: 19-21 g (estimated from graphic)
- Number of animals/dose group: 50 male, 50 female
ACTUAL DOSE RECEIVED BY DOSE LEVEL
mg/kg bw/d values calculated for mice with a bw of in average 30 g, food consumption of in average 5 g/d
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (twice daily)
- Mortality: yes (twice daily)
- Body weight: yes (recorded every two weeks)
- Organ weights: no
- Food consumption: yes (recorded every two weeks)
- Water consumption: yes
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
- Histophathology: yes
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and preserved as described in OECD guideline 451
STATISTICAL METHODS:
Probabilities of survival: procedure of Kaplan and Meier.
Possible dose-related effect on survival: method of Cox.
Dose-related trends: Tarone's extensions of Cox' methods

Reliability : (2) valid with restrictions
No biochemistry/hematology performed, organ weights not determined

Flag : Critical study for SIDS endpoint
19.02.2003 (41)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : S. typhimurium TA 98, TA 100, TA 2637
Test concentration : 0.005, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5 mg/plate
Cycotoxic concentr. : 0.2 mg/plate
Metabolic activation : with and without
Result : negative
Method : other: according to Ames et. al (1975)
Year : 1985
GLP : no data
Test substance : other TS: purity not stated

Result : No increases in mutant frequency were seen in any strain both in the absence or in the presence of metabolic activation.
Test condition : Metabolic activation system: S9-mix from PCB induced BALB/c mice
Vehicle: DMSO
Negative control: DMSO
Positive controls: AF-2 0.02 µg/plate (for TA 100 and TA 98 without S9 mix), 9-aminoacridine 0.2 mg/plate (for TA 2637 without S9 mix), 2-

aminoanthacene 0.05 mg/plate (for all used strains with S9 mix)

Reliability : (2) valid with restrictions
purity of TS not stated

Flag : Critical study for SIDS endpoint

19.02.2003 (42)

Type : Ames test
System of testing : S. typhimurium TA 97, TA 98, TA 100, TA 1535
Test concentration : 3, 10, 33, 100, 166, 333, 666 µg/plate
Cycotoxic concentr. : 333 µg/plate
Metabolic activation : with and without
Result : negative
Method : other: see reference Zeiger et.al.
Year : 1984
GLP : no data
Test substance : other TS: D/L-menthol, purity not stated

Test condition : SYSTEM OF TESTING
- Metabolic activation system: S9, Sprague-Dawley rat and male Syrian hamster livers respectively, induced with Aroclor 1254, mix contained 10 or 30% S9
ADMINISTRATION:
- Number of replicates: 3
Vehicle and negative control: DMSO
Positive controls in the absence of metabolic activation: sodium azide (for TA 1535 and TA 100), 9-aminoacridine (TA 97 and TA 1537), 4-nitro-o-phenylenediamine (TA 98)
Positive control in the presence of metabolic activation: 2-aminoanthracene
STATISTICS: standard error of the mean

Reliability : (2) valid with restrictions
purity of TS not stated

Flag : Critical study for SIDS endpoint

04.03.2003 (43) (44) (45)

Type : Ames test
System of testing : S. typhimurium TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537
Test concentration : up to 5 mg/plate
Cycotoxic concentr. : no data
Metabolic activation : with and without
Result : negative
Method : other: according to Ames et. al (1975)
Year : 1984
GLP : no data
Test substance : other TS: 99.8 %

Test condition : Solvent: DMSO
Metabolic activation system: S9-mix from PCB induced Fischer rats
In this study 200 different compounds have been tested (pos. and neg. results)
No information on positive control.
The result was considered positive if the number of colonies found was twice the number in the control.
SATISTICS: not done

Reliability : (2) valid with restrictions
no data for positive controls

Flag : Critical study for SIDS endpoint

19.02.2003 (46)

Type : Chromosomal aberration test

System of testing	:	Chinese hamster ovary cells
Test concentration	:	100, 150, 200 µg/ml without metabolic activation, 50, 124, 250 µg/ml with metabolic activation
Cycotoxic concentr.	:	up to toxic or near-toxic levels
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	other TS: purity: no data

Result	:	Negative controls: 2% cells with aberrations Positive controls: above 30 % cells with aberrations
Test condition	:	- treatment time: 8 hours without metabolic activation 2 hours with metabolic activation - scoring: 200 cells per dose - positive controls: MMC, 0.5 µg/ml (without met. act.) CPA, 37.5 µg/ml (with met. act.)
Reliability	:	(2) valid with restrictions limited documentation
Flag	:	Critical study for SIDS endpoint

19.02.2003 (47) (48) (44)

Type	:	Sister chromatid exchange assay
System of testing	:	Chinese hamster ovary cells
Test concentration	:	up to 167 µg/ml
Cycotoxic concentr.	:	up to toxic- or near-toxic levels
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	other TS

Result	:	Positive controls led to more than 3 times the control levels. SCE without activation: TS was judged negative in the first SCE trial. Due to a low-level increase at the low dose only, a repeat test was performed. In this 2. trial none of the responses were increased over 20% above the control, but the trial was judged equivocal based on a positive trend. SCE with activation: no increase Overall, the TS was judged negative in the SCE test.
Test condition	:	- treatment time: 25 hours without metabolic activation 2 hours with metabolic activation - scoring: 50 cells per dose - Testing was performed up to or near-toxic levels as evidenced by the reduction of cell confluence at the highest dose. - positive controls: MMC, 0.01 µg/ml (without met. act.) CPA, 2 µg/ml (with met. act.)
Reliability	:	(2) valid with restrictions limited documentation
Flag	:	Critical study for SIDS endpoint

19.02.2003 (47) (48) (44)

Type	:	other: alkaline elution/rat hepatocyte assay for DNA damage
System of testing	:	primary rat hepatocytes
Test concentration	:	0.1, 0.3, 0.7, 1.0, 1.3 mM
Cycotoxic concentr.	:	up to cytotoxic concentrations
Metabolic activation	:	without

Result : negative
Method : other
Year : 1996
GLP : no data
Test substance : other TS: > 99 %

Result : Menthol showed clear evidence of a dose-related cytotoxic effect and weakly increased the frequency of DNA-double strand breaks. These genotoxic effects were considered to be a consequence of cytotoxicity.
Test condition : To discriminate between cytotoxic and genotoxic effects of chemicals, additional assays of cytotoxicity were perfomed.
SYSTEM OF TESTING
- Species/cell type: male Sprague-Dawley rats (150-300 g, Charles River Laboratories, Raleigh, NC) hepatocytes
- Cytotoxicity testing: TBDE-0 (Trypan blue dye exclusion), TBDE-3h (after 3 h recovery), Thiazol blue dye reduction (MTT), intracellular adenosine triphosphate content (ATP), intracellular potassium content (K+), cell blebbing
- Alkaline elution assays were performed described by Elia, M.C. et al., Int. J. Radiat. Biol., 63, 7-11 (1993), with several modifications.
ADMINISTRATION:
- Positive and negative control groups and treatment:
positive control: 137-Cs 3 Gy
negative control: DMSO 1%
CRITERIA FOR EVALUATING RESULTS: study was conducted to improve criteria for positivity and to reduce false-positive results.
criteria for positive result old:
>= 3.0-fold increase in elution slope
>= 70% relative viability by TBDE-0 assay
criteria for positive result new:
induced elution slope >= 0.020
>= 70% relative viability by TBDE-3 (TBDE after a further 3-h recovery incubation without test chemicals) assay
>= 50% of control ATP content
Reliability : (2) valid with restrictions
non-validated test system
Flag : Critical study for SIDS endpoint
19.02.2003 (49)

Type : Mouse lymphoma assay
System of testing : L5178Ymouse lymphoma cells
Test concentration : without S9-mix: 12.5, 25, 50, 100, 150, 200 g/ml, with S9-mix: 25, 50, 75, 100, 150, 200, 300 µg/ml
Cycotoxic concentr. : 0.2 mg/ml; see test conditions
Metabolic activation : with and without
Result : negative
Method : other
Year : 1987
GLP : no data
Test substance : other TS: D/L-menthol, purity not stated

Result : No evidence of mutagenicity was obtained at non-toxic and cytotoxic concentrations.
Test condition : - cytotoxic dose: 0.2 mg/plate (+ or - S9-mix; 10% relative total growth)
- relative total growth 150 µg/plate - S9-mix: 24-27%
- relative total growth 150 µg/plate + S9-mix: 52-94%
negative control and vehicle: Ethanol
positive control - S9-mix: methylmethanesulfonate (MMS, 5 µl/ml)
positive control + S9-mix: 3-methylcholanthrene (MCA, 1.5 µg/ml)

Both positive control compounds were functional and led to strongly enhanced mutant frequencies.

Reliability : (2) valid with restrictions
limited documentation

Flag : Critical study for SIDS endpoint

04.03.2003 (50) (51) (52) (48) (44)

Type : Chromosomal aberration test
System of testing : Chinese Hamster lung cells (direct method)
Test concentration : 0.1, 0.15, 0.2 mg/ml
Cycotoxic concentr. : no data
Metabolic activation : without
Result : negative
Method : other
Year : 1982
GLP : no data
Test substance : other TS: 99.8 %

Result : No TS related effects on polyploidy.
Gaps were included in the frequency of aberrations.
Test was equivocal after 24 hours of treatment:
- Vehicle control: 2 % aberrations
- 0.1 mg/ml: 5 % aberrations
- 0.15 mg/ml: 1 % aberrations
- 0.2 mg/ml: 6 % aberrations

Test was negative after 48 hours of treatment:
- Vehicle control: 3 % aberrations
- 0.1 mg/ml: 2 % aberrations
- 0.15 mg/ml: 1 % aberrations
- 0.2 mg/ml: 4 % aberrations

Overall conclusion: negative

Test condition : SYSTEM OF TESTING
- No. of metaphases analyzed: 100
- chromosomal effects evaluated: chromatid and isochromatid gaps, chromatid breaks, chromatid exchanges, chromosome breaks, chromosome exchanges including dicentric and ring chromosomes.

CRITERIA FOR EVALUATING RESULTS: negative: incidence less than 4.9 %, ambigous: incidence between 5.0 and 9.9 %, positive: incidence more than 10%.
Solvent: Ethanol
Duration of treatment: 24 and 48 hours.
In this study 25 chemicals have been tested. Acrylamide and acrylonitrile gave positive results (up to 15 % and 25 % aberrations, respectively). No further positive controls tested.
STATISTICS: not performed

Reliability : (2) valid with restrictions
limited documentation

Flag : Critical study for SIDS endpoint

19.02.2003 (46) (53) (54)

Type : Chromosomal aberration test
System of testing : CHO cells
Test concentration : 203-297 µg/ml
Cycotoxic concentr. : up to cytotoxic concentrations (see results)
Metabolic activation : with and without
Result : ambiguous
Method : other
Year : 1998
GLP : no data

Test substance : other TS: purity: commercial grade

Result : First test - without S9:
concentrations: 0.3 -1.9 mM (according to 46 to 297 µg/ml)
cytotoxicity: viability dropped to 12 % at 297 µg/ml, ATP levels dropped from 85% of controls at 47 µg/ml to 33% of controls at 297 µg/ml
- % chromosomal aberrations:
first test - without S9:
203 µg/ml (1.3 mM): 1% (80 % cell viability)
234 µg/ml (1.5 mM): 2.5% (56 % cell viability)
250 µg/ml (1.6 mM): 7% (47 % cell viability)
266 µg/ml (1.7 mM): 9.5% (39 % cell viability)
281 µg/ml (1.8 mM): 6% (33 % cell viability)
second test - without S9:
Chromosome aberrations:
reproducible with first test but only at highest scoreable dose of 250 µg/ml: 6% (34 % cell viability)
234 µg/ml: no increase (40 % cell viability)
test with S9:
only one concentration was scoreable
203 µg/ml: 3.0 % (not statistically significant)
Negative control values not listed.

Test condition : - harvest time: 20 hr
- treatment time: 3h
- vehicle: DMSO
- Criteria for positivity:
statistically significant increase over concurrent controls in the percentages of cells with chromosomal aberrations at two separate concentrations of test article, with about 50 % cytotoxicity, or a reproducible increase at one dose level.
- Cytotoxicity testing: trypan blue exclusion, ATP levels
- scoring: 200 cells with 19-23 chromosomes per point
- positve control levels: 0 - 2.25 % cells with aberrations (mean 1.50 %)
- statistics: Fisher' exact test, with the P values adjusted for multiple comparisons against a common control by the method of Dunnett (J. Am Stat Assoc 50, 1096-1121, 1955).

Reliability : (2) valid with restrictions
Study well documented.
Restrictions: no concurrent positive and negative controls

Flag : Critical study for SIDS endpoint
19.02.2003 (55)

Type : Chromosomal aberration test
System of testing : CHO cells
Test concentration : 203, 219, 234 µg/ml
Cycotoxic concentr. : 234 µg/ml = 45 % viable cells
Metabolic activation : no data
Result :
Method : other
Year : 1998
GLP : no data
Test substance : other TS: purity: commercial grade

Result : Menthol had no clastogenic activity at non-toxic concentrations. At 234 µg/ml - 7 % cells with aberrations were observed. Flow cytometric measurements showed that DNA synthesis was inhibited by menthol to 4 1 % of control level at this concentration and cell viability was reduced to 45%.

Test condition : - harvest time: 20 hr

- treatment time: 3h
- vehicle: DMSO
- Cytotoxicity testing: two-parameter flow cytometry to assess DNA synthesis inhibition (uptake of BrdUrd)
- scoring: 200 cells with 19-23 chromosomes per point
- statistics: no data

Reliability : (2) valid with restrictions
limited documentation
Flag : Critical study for SIDS endpoint
19.02.2003 (56)

Type : Chromosomal aberration test
System of testing : TK6 human lymphoblasts
Test concentration : 0.8, 1.0 and 1.2 mM
Cycotoxic concentr. :
Metabolic activation : without
Result : positive
Method : other
Year : 1998
GLP : no data
Test substance : other TS: purity: commercial grade

Result : No increase in aberrations at 0.8 and 1.0 mM (125 and 156 µg/ml), but a significant increase (11% cells with aberrations) was seen at 1.2 mM (187 µg/ml), a highly toxic dose with cell counts reduced to 20 % of control.
Test condition : - harvest time: 17-35 h, not further specified
- treatment time: 3 h
- vehicle: DMSO
- Criteria for positivity:
statistically significant increase over concurrent controls in the percentages of cells with chromosomal aberrations at two separate concentrations of test article, with about 50 % cytotoxicity, or a reproducible increase at one dose level.
- Cytotoxicity testing: trypan blue exclusion, ATP levels
- scoring: 100 cells containing 45-49 chromosomes per point
- positve control levels: 0 - 4 % cells with aberrations (mean 2 %)
- statistics: Fisher' exact test, with the P values adjusted for multiple comparisons against a common control by the method of Dunnett (J. Am Stat Assoc 50, 1096-1121, 1955).

Reliability : (2) valid with restrictions
Study well documented.
Restrictions: no concurrent positive and negative controls
Flag : Critical study for SIDS endpoint
19.02.2003 (55)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Drosophila SLRL test
Species : Drosophila melanogaster
Sex : male
Strain : other: Canton-S
Route of admin. : oral feed
Exposure period : 3 d
Doses : 50000 ppm
Result : negative
Method : other
Year : 1994
GLP : no data

Test substance : other TS: not further specified

Method : s described by Woodruff, R.C. et al., Environ. Mutagen. 6, 189-202 (1984); Zimmering, S. et al., Environ. Mutagen. 7, 87-100 (1985); Valencia, R. et al., Environ. Mutagen. 7, 325-348 (1985).

Test condition : Treatment: Males were mated to Basc females using a 2 to 3 day brooding pattern for a total of three broods spanning 7 days.
Vehicle: Ethanol
Control group: yes
Mortality: 1 %
Sterility: 4 %
Total lethals: 1 (treated group), 1 (control group)

Reliability : (2) valid with restrictions
limited documentation

Flag : Critical study for SIDS endpoint
19.02.2003 (57) (58)

Type : Drosophila SLRL test
Species : Drosophila melanogaster
Sex : male
Strain : other: Canton-S males
Route of admin. : other: injection
Exposure period : no data
Doses : 10000 ppm
Result : negative
Method : other
Year : 1994
GLP : no data
Test substance : other TS: not further specified

Method : as described by Woodruff, R.C. et al., Environ. Mutagen. 6, 189-202 (1984); Zimmering, S. et al., Environ. Mutagen. 7, 87-100 (1985); Valencia, R. et al., Environ. Mutagen. 7,325-348 (1985).

Test condition : Treatment: Males were mated to Basc females using a 2 to 3 day brooding pattern for a total of three broods spanning 7 days.
Vehicle: Ethanol
Control group: yes
Mortality: 3 %
Sterility: 43 %
Total lethals: 0 (treated group), 4 (control group)

Reliability : (2) valid with restrictions
limited documentation

Flag : Critical study for SIDS endpoint
19.02.2003 (57) (58)

Type : Micronucleus assay
Species : mouse
Sex : male
Strain : B6C3F1
Route of admin. : i.p.
Exposure period : 3 days
Doses : 250, 500, 1000 mg/kg
Result : negative
Method : other
Year : 1993
GLP : no data
Test substance : other TS: not further specified

Result : Micronucleated PCEs per 1000 PCE scored:
0 mg/kg / 2.90
250 mg/kg / 3.60
500 mg/kg / 2.20
1000 mg/kg / 3.67
Positive Control DMBA / 7.93
Positive Control MMC / 6.85
Negative Control / 2.38

Cytotoxicity
% of PCEs (No. of PCE/No of PCE + No of NCE)
0 mg/kg / 54.4
250 mg/kg / 64.2
500 mg/kg / 56.7
1000 mg/kg / 51.8

* PCE: polychromatic erythrocytes

Survival: 0 mg/kg 5/5
250 mg/kg 5/5
500 mg/kg 5/5
1000 mg/kg 3/6
p value: 0.374

Test condition : TEST ORGANISMS:
- Age: 9-14 weeks
- Weight at study initiation: 25-33 g
- No. of animals per dose: 5-7
ADMINISTRATION:
- Vehicle: corn oil
- Frequency of treatment: one injection/day
- Control groups and treatment:
Positive controls: 7,12-dimethylbenzanthracene (12.5 mg/kg) and mitomycin-C (0.2 mg/kg)
Negative control: vehicle
Time of deaths: Mice were killed 24 hrs after last injection
EXAMINATIONS:
Bone marrow smears (two slides per mouse)
The slides were evaluated for the number of MN-PCE among 2000 PCD and for the percentage of PCE among 200 erythrocytes.
STATISTICS:
Data were analysed using the Micronucleus Assay Data Management and Statistical software package (version 1.4, ILS, 1990).

Reliability : (2) valid with restrictions
no information on TS provided

Flag : Critical study for SIDS endpoint

19.02.2003 (59)

5.7 CARCINOGENICITY

Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 103 w
Frequency of treatm. : continously
Post exposure period : 1 w
Doses : 2000 or 4000 ppm (about 334 or 667 mg/kg bw/d)

Result : negative
Contrd group : yes, concurrent vehicle
Method : other
Year : 1976
GLP : no
Test substance : other TS: purity of 100 % is assumed

Result : TOXIC RESPONSE/EFFECT BY DOSE LEVEL
- Survival m: 32/50 (62%), 32/50 (64%), 35/50 (70%)
- Survival f: 45/50 (90%), 40/50 (80%), 36/50 (72%)
- Clinical signs: no clinical signs of toxicity
- Body weight gain:
2000 and 4000 ppm m and f: slight body weight gain suppression: < 10% (estimated from graphic)
- Food consumption: no effect
- Gross pathology: no effect
- Histopathology:
hepatocellular carcinomas:
m: 8/47, 8/49, 14/48; incidence was not statistically significant, within the range of historical controls; observed occasionally in groups of mice of this age and strain in this laboratory.
Alveolar/bronchiolar adenomas or carcinomas:
f: 1/49, 3/47, 5/48; incidence was not statistically significant.
No increased incidence of neoplasms compared to controls.

Test condition : TEST ORGANISMS
- Age: 6 weeks
- Weight at study initiation: male: 23-25 g, female: 19-21 g (estimated from graphic)
- Number of animals/dose group: 50 male, 50 female
ACTUAL DOSE RECEIVED BY DOSE LEVEL
mg/kg bw/d values calculated for mice with a bw of in average 30 g, food consumption of in average 5 g/d
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (twice daily)
- Mortality: yes (twice daily)
- Body weight: yes (recorded every two weeks)
- Organ weights: no
- Food consumption: yes (recorded every two weeks)
- Water consumption: no
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
- Histophathology: yes
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and preserved as described in OECD guideline 451
STATISTICAL METHODS
Probabilities of survival: procedure of Kaplan and Meier.
Possible dose-related effect on survival: method of Cox.
Dose-related trends: Tarone's extensions of Cox's methods.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restriction: no data on clinical chemistry.

Flag : Critical study for SIDS endpoint
17.07.2002 (60) (41)

Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	103 w
Frequency of treatm.	:	continously
Post exposure period	:	2 w
Doses	:	3750 or 7500 ppm (about 188 or 375 mg/kg bw/d)
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	other TS: purity of 100 % is assumed

Result :

TOXIC RESPONSE/EFFECT BY DOSE LEVEL
- Survival m: 31/50 (62%), 33/50 (66%), 34/50 (68%)
- Survival f: 36/50 (72%), 35/50 (70%), 38/50 (76%)
- Clinical signs: no clinical signs of toxicity
- Body weight gain:
3750 ppm, m and f: slight body weight gain suppression: < 10% (estimated from graphic)
7500 ppm, m: slight body weight gain suppression: < 10% (estimated from graphic), f: < 14% (estimated from graphic)
- Food consumption: no effect
- Gross pathology: no effect
- Histopathology:
Chromophobe adenomas of the pituitary gland:
f: 28/48, 25/42, 19/43
Mammarygland fibroadenomas:
f*: 20/50, 20/49, 7/49
Mammary adenocarcinomas:
f: 1/50, 3/49, 0/49).
In male rats chronic inflammation of the kidney was found with greater frequency in dosed males than in control males (controls: 29/49; low-dose: 41/50; high-dose 41/50).
* = statistically significant (p=0.003; 0.028; 0.004

Test condition :

TEST ORGANISMS
- Age: 9 weeks
- Weight at study initiation: males: 165-180 g, females: 120-135 g (estimated from graphic)
- Number of animals/dose group: 50 male, 50 female
ACTUAL DOSE RECEIVED BY DOSE LEVEL
mg/kg bw/d values calculated for rats with a bw of in average 400 g, food consumption of in average 20 g/d
ADMINISTRATION / EXPOSURE
- Vehicle: corn oil
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes (twice daily)
- Mortality: yes (twice daily)
- Body weight: yes (recorded every two weeks)
- Organ weight: no
- Food consumption: yes (recorded every two weeks)
- Water consumption: no
- Ophthalmoscopic examination: no
- Haematology: no
- Biochemistry: no
- Urinalysis: no
- Histopathology: yes

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
Organs examined and preserved as described in OECD guideline 451.
STATISTICAL METHODS
Probabilities of survival: procedure of Kaplan and Meier.
Possible dose-related effect on survival: method of Cox.
Dose-related trends: Tarone's extensions of Cox's methods.

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restriction: no data on clinical chemistry.

Flag : Critical study for SIDS endpoint
04.03.2003 (60) (61)

5.8.1 TOXICITY TO FERTILITY

Type : other: Chronic (in detail reported in chapter 5.4 and 5.7)
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 103 w
Frequency of treatm. : continuously
Premating exposure period
Male :
Female :
Duration of test :
No. of generation studies :
Doses : 3750, 7500 ppm (= ca. 188, 375 mg/kg bw/d)
Control group : yes, concurrent vehicle
Result : No pathological changes in reproductive organs
Method : other
Year : 1979
GLP : no
Test substance : other TS: purity of 100% is assumed

Test condition : Microscopic examination of prostate, uterus, testis, ovaries, mammary glands and adrenals.
Details of the study design under 5.7 Carcinogenicity and 5.4 Repeated dose toxicity.
ACTUAL DOSE RECEIVED BY DOSE LEVEL
mg/kg bw/d values calculated for rats with a bw of in average 400 g, food consumption of in average 20 g/d

Reliability : (2) valid with restrictions
see 5.7

Flag : Critical study for SIDS endpoint
04.03.2003 (41)

Type : other: Chronic (in detail reported in chapter 5.4 and 5.7)
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 103 w
Frequency of treatm. : continuously
Premating exposure period
Male :
Female :

Duration of test	:	
No. of generation studies	:	
Doses	:	2000, 4000 ppm (= ca. 334, 667 mg/kg bw/d)
Control group	:	yes, concurrent vehicle
Result	:	No pathological changes in reproductive organs
Method	:	other
Year	:	1979
GLP	:	no
Test substance	:	other TS: purity of 100% is assumed
Test condition	:	Microscopic examination of prostate, uterus, testis, ovaries, mammary glands and adrenals. Details of the study design under 5.7 Carcinogenicity and 5.4 Repeated dose toxicity. ACTUAL DOSE RECEIVED BY DOSE LEVEL mg/kg bw/d values calculated for mice with a bw of in average 30 g, food consumption of in average 5 g/d
Reliability	:	(2) valid with restrictions see 5.7
Flag	:	Critical study for SIDS endpoint

04.03.2003 (41)

Type	:	other: sub-chronic (in detail reported in chapter 5.4)
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	13 w
Frequency of treatm.	:	continuously
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	
Doses	:	930, 1870, 3750, 7500 or 15000 ppm (m: 59, 114, 231, 472, 937 mg/kg bw/d; f: 67, 142, 285, 521, 998 mg/kg bw/d)
Control group	:	yes, concurrent vehicle
Result	:	no pathological changes in reproductive organs
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	other TS: purity of 100% is assumed
Test condition	:	Microscopic examination of prostate, uterus, testis, ovaries, mammary glands and adrenals. Details of the study design under 5.4 Repeated dose toxicity.
Reliability	:	(2) valid with restrictions see 5.4
Flag	:	Critical study for SIDS endpoint

19.02.2003 (39)

Type	:	other: sub-chronic (in detail reported in chapter 5.4)
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	13 w

Frequency of treatm.	:	continuously
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	
Doses	:	930, 1870, 3750, 7500 or 15000 ppm (m: 243, 488, 978, 1956, 3913 mg/kg bw/d, f: 290, 595, 1193, 2386, 4773 mg/kg bw/d)
Control group	:	yes, concurrent vehicle
Result	:	No pathological changes in reproductive organs
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	other TS: purity of 100% is assumed
Test condition	:	Microscopic examination of prostate, uterus, testis,
Reliability	:	(2) valid with restrictions see 5.4
Flag	:	Critical study for SIDS endpoint

19.02.2003 (62)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

Endpoint	:	other: Induction of S-phase cells
Study descr. in chapter	:	
Reference	:	
Type	:	other: in vivo-in vitro replicative DNA synthesis test (RDS)
Species	:	rat
Sex	:	male
Strain	:	Fischer 344
Route of admin.	:	gavage or i.p. injection
No. of animals	:	
Vehicle	:	other: corn oil
Exposure period	:	
Frequency of treatm.	:	single treatment
Doses	:	725, 1450 mg/kg
Control group	:	yes
Observation period	:	
Result	:	positive
Method	:	other
Year	:	1994
GLP	:	no data
Test substance	:	other TS: not further specified
Result	:	RDS incidences: control: 0.7 % 725 mg/kg: 24 hours: 6.0 % (cell viability: 75%) 39 hours: 0.8 % (cell viability: 74 %) 48 hours: 0.6 % (cell viability: 67 %)

1450 mg/kg
24 hours: 0.6 % (cell viability: 66 %)
39 hours: 3.9 % (cell viability: 72 %)
48 hours: 0.5 % (cell viability: 73 %)

Test condition : Examination: Hepatocyte isolation and measurement of RDS incidence 24, 39 and 48 hrs after dosage
RDS incidences were calculated as the percentage of Tritium thymidine-incorporating cells relative to 2000 hepatocytes.
Judgement criteria for RDS incidence:
Maximum RDS incidence was 2.0% or above - positive response
Incidence less than 1.0% - negative response
Incidence between 1.0 and 2.0 % - equivocal
Cell viability - trypan blue exclusion test

Reliability : (2) valid with restrictions
limited documentation

19.02.2003 (63)

5.10 EXPOSURE EXPERIENCE

Type of experience : Human

Result : 0.3 %: significant decrease in perceived intensity, but not for cooling

Test condition : 15 persons (10f, 5m, aged 24-33 years)
Concentrations of d/l-menthol: 0.03% and 0.3%
10 menthol solution at one of the two concentrations were given to subjects; the rate of intensity of irritaion and coolness in mouth was recorded.

Reliability : (2) valid with restrictions
limited documentation

19.02.2003 (64)

5.11 ADDITIONAL REMARKS

Type : Metabolism

Result : D,l-menthol inhibited metabolic cooperation between 6-thioguanine-sensitive and -resistant V79 Chinese hamster lung cells.

Reliability : (4) not assignable
Documentation insufficient.

17.01.2002 (65)

Type : other: antimutagenic effect

Result : D/L-Menthol showed no antimutagenic effect.

Test condition : The inhibitory effects of flavourings (d/l-menthol among others) on mutagenesis induced by chemical in bacteria is studied.

Reliability : (2) valid with restrictions
limited documentation

19.02.2003 (66)

6. Analyt. Meth. for Detection and Identification Id 89-78-1
Date 18.03.2003

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7. Eff. Against Target Org. and Intended Uses Id 89-78-1
Date 18.03.2003

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8. Meas. Nec. to Prot. Man, Animals, Environment Id 89-78-1
Date 18.03.2003

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

9. References Id 89-78-1
Date 18.03.2003

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10. Summary and Evaluation Id 89-78-1
Date 18.03.2003

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

I U C L I D Data Set

Existing Chemical	:	ID: 15356-60-2
CAS No.	:	15356-60-2
EINECS Name	:	(+)-menthol
EC No.	:	239-387-8
Molecular Formula	:	C10H20O

Producer related part

Company	:	Bayer AG
Creation date	:	15.11.2001

Substance related part

Company	:	Bayer AG
Creation date	:	15.11.2001
Status	:	
Memo	:	ICCA D-menthol
Printing date	:	18.03.2003
Revision date	:	
Date of last update	:	18.03.2003
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1. General Information Id 15356-60-2
Date 18.03.2003

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : solid
Purity :
Colour : white
Odour : minty

Flag : Critical study for SIDS endpoint
17.07.2002

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

5-METHYL-2-(1-ETHYLETHYL)-CYCLOHEXANOL

Flag : Critical study for SIDS endpoint
03.06.2002

CYCLOHEXANOL, 5-METHYL-2-(1METHYLETHYL)-(1S-(1ALPHA,2BETA,5ALPHA))

Flag : Critical study for SIDS endpoint
03.06.2002

D-MENTHOL

Flag : Critical study for SIDS endpoint
03.06.2002

MENTHOL D

Flag : Critical study for SIDS endpoint
17.07.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Labelling : provisionally by manufacturer/importer
Specific limits :
Symbols : Xi, , ,
Nota : , ,
R-Phrases : (38) Irritating to skin
S-Phrases : (25) Avoid contact with eyes

Flag : Critical study for SIDS endpoint
17.07.2002

1.6.2 CLASSIFICATION

Classified : provisionally by manufacturer/importer
Class of danger : irritating
R-Phrases : (38) Irritating to skin
Specific limits :

Flag : Critical study for SIDS endpoint
17.07.2002

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Non dispersive use

Remark : Pure D-menthol is used for scientific purposes only. Industrial D-menthol from separation of L-menthol is used as the starting material for racemization to yield (D- and) L-menthol
Flag : Critical study for SIDS endpoint
17.07.2002

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Remark : D/L-menthol is produced via reaction of m-cresol with propen to thymol, and hydrogenation of thymol, resulting in 4 isomers: D/L-neomenthol, D/L-neoisomenthol, D/L-menthol and D/L-isomenthol. D/L-menthol is isolated by fractional distillation.
To produce L-menthol, D/L-menthol is transesterificated with methylbenzoate and further manufactured. Resulting products are L- and D-menthol

Flag : Critical study for SIDS endpoint
03.06.2002

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External

Chapters covered : 5
Date of search : 01.09.2001

Remark : Human Health: last literature search September 2001: CAS number search in external and internal databases, e.g. Biosis, Embase, Toxline, Scisearch
Flag : Critical study for SIDS endpoint
10.07.2002

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 14.01.2002

Remark : Physico-chemical properties / Environment / Ecotoxicology :
Flag : Critical study for SIDS endpoint
29.07.2002

1.13 REVIEWS

Memo : Its Origins, Chemistry, Physiology and Toxicological Properties

Flag : Critical study for SIDS endpoint
03.06.2002 (1)

2.1 MELTING POINT

Sublimation :
Method :
Year : 2002
GLP : no data
Test substance : other TS

Remark : Freezing temp.: minimum 36.0 degrees C
18.03.2003 (2)

Value : 43 °C
Sublimation :
Method :
Year : 1993
GLP : no data
Test substance : no data

Remark : Review article, no information on data source but excellent compilation of major data
Flag : Critical study for SIDS endpoint
18.03.2003 (1)

2.2 BOILING POINT

Value : ca. 216 °C at 1013 hPa
Decomposition :
Method :
Year : 2002
GLP : no data
Test substance : no data

18.03.2003 (2)

Value : 216.5 °C at
Decomposition :
Method :
Year : 1993
GLP : no data
Test substance : no data

Flag : Critical study for SIDS endpoint
18.03.2003 (1)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : 3.4 at °C
pH value :
Method : other (calculated)
Year : 1999
GLP :
Test substance : other TS: D/L-menthol and L-menthol

Method : D/L-Menthol and L-menthol were both measured by reversed-phase high-performance liquid chromatography. Since they had the same log Kow (3.40), D-menthol also has the log kow 3.40
Flag : Critical study for SIDS endpoint
11.03.2003 (3)

Partition coefficient : octanol-water
Log pow : 3.38 at °C
pH value :
Method : other (calculated): SRC-KOWWIN v. 1.66
Year : 2002
GLP :
Test substance :

18.03.2003 (4)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 431 mg/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Remark : for L-Menthol
Flag : Critical study for SIDS endpoint
18.03.2003 (2)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : 98 °C
Type : closed cup

25.01.2002 (2)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : alpha D20 + 50.1 degree C

Flag : Critical study for SIDS endpoint
30.07.2002 (1)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Method	:	structure estimation method
Result	:	Rate constant: k = 2.4 E -11 cm3/molecule/sec at 25 degrees C; considering an atmospheric OH-radical concentration of 5 E5 OH-radicals/cm3, the half-life is about 16 h
Reliability	:	(2) valid with restrictions accepted calculation procedere
Flag	:	Critical study for SIDS endpoint

29.07.2002 (5)

3.1.2 STABILITY IN WATER

Result	:	volatilization half-lives for a model river (1 m deep, flow-rate 1 m/sec, wind velocity 3 m/sec) and a model lake (1 m deep, flow-rate 0.05 m/sec, wind velocity 0.5 m/sec) are estimated to be 2 and 18 days
Reliability	:	(2) valid with restrictions accepted calculation procedure derived from l-menthol cause of strucutral similarities
Flag	:	Critical study for SIDS endpoint

26.07.2002 (6)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	volatility
Media	:	water - air
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	
Year	:	2003
Result	:	Based on a water solubility of 431 mg/l and a vapour pressure of 8.5 Pa (see chapter 2), the Henry's law constant is calculated to be 3.08 Pa x m3/mol
Reliability	:	(2) valid with restrictions Generally accepted calculation method, parameters for calculation from L-menthol

Flag : Critical study for SIDS endpoint
14.03.2003 (7)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2003

Result : Air: 43.2 %
Water: 40.6 %
Soil: 8.0 %
Sediment: 8.1 %
Biota: 0.005 %

Test condition : Base data for calculation:
temperature: 20 °C
molar mass: 156.27 g/mol
vapour pressure: 8.5 Pa
water solubility: 431 g/m3
log Kow: 3.4
environmental compartments:
- air: 6*10^9 m³, 1.2 kg/m³
- water: 7*10^6 m³, 1000 kg/m³
- soil: 4.5 *10^4 m³, 1500 kg/m³, 2 % org. C
- sediment: 2.1*10^4 m³, 1300 kg/m², 5 % org. C
- susp. sediment: 35 m³, 1500 kg/m³, 16.7 % org. C
- aerosol: 0.12 m³, 1500 kg/m³
- aquatic biota: 7 m³, 1000 kg/m³, 5 % fat

Reliability : (2) valid with restrictions
Generally accepted calculation method, parameters for calculation from L-menthol

Flag : Critical study for SIDS endpoint
14.03.2003 (7)

Media : water - air
Method : other (calculation)
Year :

Result : Using the equation log Koc = 0.52 log Kow + 1.02 and based on a log Kow of 3.4 (see chapter 2) a Koc value of 614 can be calculated for the distribution between the organic phase of soil and pore water

Reliability : (2) valid with restrictions
Generally accepted calculation method

07.03.2003 (8)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : .84 mg/l related to Test substance
related to
Contact time : 28 day(s)
Degradation : 92 (±) % after 28 day(s)
Result : readily biodegradable
Kinetic of testsubst. : 0 day(s) 0 %
7 day(s) 64 %

14 day(s) 92 %
21 day(s) 90 %
28 day(s) 92 %

Control substance : Acetic acid, sodium salt
Kinetic : 7 day(s) 86 %
14 day(s) 100 %
Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 2003
GLP : yes
Test substance : other TS: purity 99.834 %

Remark : Measured degradation of sodium acetate was 103 % after 14 d
Result : The biodegradation in the toxic controls exceeded 25 %. According to the guideline, the test substance is not toxic to the medium
Test condition : Two concentrations of the test substance (0.84 mg/l, 2.01 mg/l) a control (blank medium), an inoculum activity control (sodium acetate) and a toxicity control (sodium acetate and D-menthol) were prepared with mineral medium, saturated with oxygen, placed in approximately 300 ml BOD bottles, and incubated for 28 d in the dark at about 20 °C, except for the activity control and the toxicity control which were incubated for 14 d. To prevent leakage of gases out of the BOD bottles the bottles were incubated upside down. The O2 concentration was determined with an oxygen electrode after 0, 7, 14, 21, and 28 d of incubation
Reliability : (1) valid without restriction
Guideline study in accordance with the OECD principles of GLP
Flag : Critical study for SIDS endpoint
12.02.2003 (9)

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 2.01 mg/l related to Test substance
related to
Contact time : 28 day(s)
Degradation : 76 (±) % after 28 day(s)
Result : readily biodegradable
Kinetic of testsubst. : 0 day(s) 0 %
7 day(s) 61 %
14 day(s) 72 %
21 day(s) 76 %
28 day(s) 76 %
Control substance : Acetic acid, sodium salt
Kinetic : 7 day(s) 86 %
14 day(s) 100 %
Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 2003
GLP : yes
Test substance : other TS: purity 99.834 %

Remark : Measured degradation of sodium acetate was 103 % after 14 d
Result : The biodegradation in the toxic controls exceeded 25 %. According to the guideline, the test substance is not toxic to the medium
Test condition : Two concentrations of the test substance (0.84 mg/l, 2.01 mg/l) a control (blank medium), an inoculum activity control (sodium acetate) and a toxicity control (sodium acetate and D-menthol) were prepared with mineral medium, saturated with oxygen, placed in approximately 300 ml BOD bottles, and incubated for 28 d in the dark at about 20 °C, except for the activity control and the toxicity control which were incubated for 14 d. To

prevent leakage of gases out of the BOD bottles the bottles were incubated upside down. The O2 concentration was determined with an oxygen electrode after 0, 7, 14, 21, and 28 d of incubation

Reliability : (1) valid without restriction
Guideline study in accordance with the OECD principles of GLP
Flag : Critical study for SIDS endpoint
12.02.2003 (9)

Type : anaerobic
Inoculum : other: enrichment culture from a forest ditch
Deg. product :
Method :
Year : 1992
GLP : no
Test substance : other TS: (+)-isomenthol, analytical grade

Method : Determination of nitrification under nitrate-reducing conditions
Result : Denitrification was stimulated by the presence of TS after 12 weeks.
Test condition : Culture tubes contained 100 ml water-mud mixture from the forest ditch, 350 ml anoxic mineral salt medium and 400 mg TS (HMN as carrier), N2/CO2-atmosphere, incubation at 28 degrees C in the dark
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards
28.07.2002 (10)

Type : anaerobic
Inoculum : other bacteria: Pseudomonas citronellolis
Deg. product :
Method :
Year : 1995
GLP : no
Test substance : other TS: (+)-isomenthol, analytical grade

Method : Determination of growth of P. citronellolis under nitrate-reducing conditions
Result : Test organisms did not grow with TS as the sole carbon and energy source.
Test condition : Culture tubes contained 15 ml anoxic mineral salt medium and 20 mg TS (HMN as carrier), N2/CO2-atmosphere
Reliability : (2) valid with restrictions
No standard test procedure, but in accordance with generally accepted scientific standards
30.07.2002 (10)

Deg. product :
Method :
Year :
GLP :
Test substance : other TS: (+)-isomenthol

Remark : Based on the previous literature it can be stated that the bacteria species: Thauera terpenica, strain 21 Mol may degrade (+)-isomenthol
Reliability : (4) not assignable
Review, no experimental data given
28.07.2002 (11)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	
Type	:	Metabolism
Species	:	
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Remark	:	data are reported in chapter 5.11

01.07.2002

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 2046 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	female
Number of animals	:	10
Vehicle	:	peanut oil
Doses	:	1000, 1500, 2000, 2500, 3000 mg/kg bw
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	other TS: d-Menthol dest.
Result	:	MORTALITY: - Time of death: 1-2 days after application - Number of deaths at each dose: dose (mg/kg) number of deaths 1000 0/10 1500 1/10 2000 5/10 2500 7/10 3000 10/10 CLINICAL SIGNS: narcotic status (no data available on exposure levels at which the clinical signs were observed)
Test condition	:	ADMINISTRATION: - Volume administered or concentration: 10-20 ml/kg - Post dose observation period: 14 days EXAMINATIONS: deaths, clinical signs No information on statistical methods and confidence limits.
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles, acceptable for assessment. Restrictions: No information on statistical methods and confidence limits.
Flag	:	Critical study for SIDS endpoint

01.07.2002 (12)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	100 %
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	4
Vehicle	:	other: diethylphthalate (DEP)
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1989
GLP	:	yes
Test substance	:	other TS: menthol-d, HR 89/620005, purity: no data
Result	:	AVERAGE SCORE 100%/50%/25%/5%/1%/Vehicle 2.5/1.9/0.7/0.0/0.0/0.0 (erythema) 2.4/1.3/0.0/0.0/0.0/0.0 (oedema) REVERSIBILITY: yes Day 7: 100%: 3/4 - treated sites were covered with a layer of white to white-brown scales, 1/4 - massive layer of white-brown scales 50%: 4/4 - thin layer of white scales 25%: 2/4 - thin layer of white scales Day 14: 100%: 4/4 - treated sites were covered with white to white-brown scales, underlaying skin was intact 50%: 3/4 - treated sites showed scattered scale formation on intact skin.
Test condition	:	TEST ANIMALS: - Strain: Chbb:HM (C.H.Boehringer/Biberach - Sex: female - Source: Dr. Karl Thomae GmbH, Biberach an der Riss - Age: no data - Weight at study initiation: 2200-2900 - Number of animals: 4 - Controls: internal control (one part of skin) ADMINISTRATION/EXPOSURE - Preparation of test substance: dilutions of substance with DEP, concentrated test substance was moistened with DEP in the ratio 6:1 - Area of exposure: six different fields on back (two anterior, two centrally located and two posterior treatment sites) - Concentration in vehicle: 100, 50, 25, 5 and 1 %, Vehicle - Total volume applied: 0.5 ml - Postexposure period: up to 14 days - Removal of test substance: skin was washed with luke warm water and soap
Reliability	:	(2) valid with restrictions purity of test substance not stated

Flag : Critical study for SIDS endpoint
24.02.2003 (13)

Species : guinea pig
Concentration : no data
Exposure : Open
Exposure time : 14 day(s)
Number of animals : 20
Vehicle : no data
PDII :
Result : not irritating
Classification : not irritating
Method : other
Year : 1974
GLP : no
Test substance : other TS: d-menthol dest.

Test condition : Substance was rubbed into the skin for 30 s once daily.
Substance was applicated 2 x 5 days, results were taken after 14 days.
Reliability : (3) invalid
Significant methodological deficiences. e.g. concentration and amount of substance is unclear; lack of control experiment.
17.12.2001 (14)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : 29 %
Dose : .1 ml
Exposure time : 24 hour(s)
Comment : rinsed after (see exposure time)
Number of animals : 4
Vehicle : other: diethylphthalate (DEP)
Result : slightly irritating
Classification :
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1989
GLP : yes
Test substance : other TS: menthol-d, HR 620005 DEP, purity: no data

Result : AVERAGE SCORE
- Cornea: 0.4
- Iris: 0.0
- Conjunctivae (Redness): 1.3
- Conjunctivae (Chemosis): 0.1

REVERSIBILITY: yes, no reaction observed after 7 days
Test condition : TEST ANIMALS:
- Strain: Chbb:HM (C.H.Boehringer, Biberach: Himalaya)
- Sex: female
- Source: Dr. Karl Thomae GmbH, Biberach an der Riss
- Age: no data
- Weight at study initiation: 2500-2900 g
- Number of animals: 4
- Controls: internal control (right eye)

Reliability : (2) valid with restrictions
purity of test substance not stated
Flag : Critical study for SIDS endpoint
24.02.2003 (15)

Species	:	rabbit
Concentration	:	64 %
Dose	:	.1 ml
Exposure time	:	24 hour(s)
Comment	:	rinsed after (see exposure time)
Number of animals	:	4
Vehicle	:	other: 29 % solution of d-menthol in DEP (HR 89/620005 DEP)
Result	:	slightly irritating
Classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1989
GLP	:	yes
Test substance	:	other TS: menthol-d, HR 620005
Result	:	AVERAGE SCORE HR 89/620005 64%/Vehicle (29% d-menthol in DEP) 0.9/0.5 (cornea) 0.0/0.0 (iris) 2.1/1.2 (redness of conjunctivae) 0.3/0.0 (chemosis, conjunctivae) The right eyes were treated with the vehicle and the left eyes with the test article solution. Both articles had almost the same eye-irritating potential. REVERSIBILITY: yes, no reactions ovserved after 7 days
Test condition	:	TEST ANIMALS: - Strain: Chbb:HM (C.H.Boehringer, Biberach: Himalaya) - Sex: female - Source: Dr. Karl Thomae GmbH, Biberach an der Riss - Age: no data - Weight at study initiation: 2300-3000 - Number of animals: 4 - Controls: internal control with vehicle (right eye) ADMINISTRATION/EXPOSURE - Preparation of test substance: Test article was pulverized in a mortar and then diluted with vehicle (absolute concentration of substance in DEP is 64%) - Vehicle: 29% d-menthol in DEP (HR 89/620005 DEP; previously tested by Scantox, lab.no.: 11755) EXAMINATIONS according guideline
Reliability	:	(2) valid with restrictions purity of test substance not stated, no untreated control
Flag	:	Critical study for SIDS endpoint

24.02.2003 (16)

Species	:	rabbit
Concentration	:	60 %
Dose	:	.1 ml
Exposure time	:	1 minute(s)
Comment	:	other: see test conditions
Number of animals	:	8
Vehicle	:	other: olive oil
Result	:	not irritating
Classification	:	not irritating
Method	:	Draize Test
Year	:	1974
GLP	:	no
Test substance	:	other TS: d-menthol dest.

Test condition : Substance was initially applied in 10, 20 and 30 % solution.
The eyes of 4 animals were rinsed 1 minute after application with physiological saline, substance remained in the eyes of 4 animals. In a second step animals were treated with the substance in concentrations of 40, 50 and 60 %.
Reliability : (2) valid with restrictions
limited documentation
24.02.2003 (14)

5.3 SENSITIZATION

Type : other: open repetetive dermal test
Species : guinea pig
Number of animals : 20
Vehicle : no data
Result : not sensitizing
Classification : not sensitizing
Method : other
Year : 1974
GLP : no
Test substance : other TS: d-menthol dest.

Test condition : Substance was rubbed into shaved skin for 30 sec once daily for 3x5 days.
After 5 days without application the test substance was rubbed into an untreated part of the skin.
Results were taken after 24 h, 2 and 3 days.
Reliability : (3) invalid
Significant methodological deficiences. e.g. concentration and amount of substance is unclear; lack of control experiment.
17.12.2001 (14)

5.4 REPEATED DOSE TOXICITY

5.5 GENETIC TOXICITY 'IN VITRO'

Type : other: Alkaline single cell gel test (comet assay)
System of testing : V79 Chinese hamster cells
Test concentration : 0; 0.5; 1; 2 mmol/l
Cycotoxic concentr. : >= 1 mmol/l
Metabolic activation : with and without
Result : negative
Method : other: as decribed by Singh et al. (1988), Exp. Cell Res. 175, 184-191, with the modifications as in: Hartmann and Speit (1995), Mut. Res. 346, 49-56
Year : 1997
GLP : no data
Test substance : other TS: D-Menthol purchased from Sigma

Reliability : (2) valid with restrictions
non-validated test system
Flag : Critical study for SIDS endpoint
04.03.2003 (17) (18)

Type : other: Alkaline single cell gel test (comet assay)

System of testing	:	Human lymphocytes
Test concentration	:	0; 0.2; 0.5; 1; 2 mmol/l
Cycotoxic concentr.	:	>= 1 mmol/l
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: as described by Singh et al. (1988), Exp. Cell Res. 175, 184-191, with the modifications as in: Hartmann and Speit (1995), Mut. Res. 346, 49-56
Year	:	1997
GLP	:	no data
Test substance	:	other TS: D-Menthol purchased from Sigma
Reliability	:	(2) valid with restrictions non-validated test system
Flag	:	Critical study for SIDS endpoint

04.03.2003 (17) (18)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type	:	Metabolism
Result	:	(-)-/(+)-menthol glucuronidation ratio: 2.6/1 Vmax (-)/(+)-menthol glucuronidation ratio: 2.8/1 Data suggest, that monkey UGT2B9 and human UGT2B7 are functionally similar (89 % identity in cDNA library).
Test condition	:	Enantioselective glucuronidation for (+)- and (-)-menthol was studied using expressed monkey UGT2B9 (UDP-glucuronosyltransferase)
Reliability	:	(2) valid with restrictions non-standard in vitro test system

24.02.2003 (19)

6. Analyt. Meth. for Detection and Identification Id 15356-60-2
Date 18.03.2003

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7. Eff. Against Target Org. and Intended Uses Id 15356-60-2
Date 18.03.2003

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT