

The Flavor And Fragrance High Production Volume Consortia

The Cyclohexyl Derivatives Consortium

Robust Summaries for Alkyl-substituted Cyclohexanol Derivatives

4-*tert*-butylcyclohexanol **CAS No. 98-52-2**

4-*tert*-butylcyclohexyl acetate **CAS No. 32210-23-4**

FFHPVC Cyclohexyl Derivatives Consortium Registration Number

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The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al.*, 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1. Reliable without restrictions
- Reliability code 2. Reliable with restrictions
- Reliability code 3. Not reliable
- Reliability code 4. Not assignable

1 CHEMICAL AND PHYSICAL PROPERTIES

1.1 Melting Point

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Melting Point	56.6-58.6 °C
Remarks for General Remarks	Handbook data (Beilstein)
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Krestinina, T. B.; Koshel', G. N.; Chabutkina, E. M.; Antonova, T. N.; Migachev, G. I.; JAPUAW; J.Appl.Chem.USSR

(Engl.Transl.); EN; 57; 9; 1984; 2138-2142; ZPKHAB;
Zh.Prikl.Khim. (Leningrad); RU; 57; 9; 1984; 2318-2324;

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
GLP	No
Year	1965
Melting Point	56-58 °C
Remarks for General Remarks	Handbook data, Beilstein data base
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	General Aniline + Film Corp.; Patent; FR 1411988; 1965; Chem.Abstr.; EN; 64;1983c; 1966;

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	55-70 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	Calculated. Mean or weighted MP.
Melting Point	4.34 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVWIN EPI Suite (2000) US Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
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CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Melting Point	41-43 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only secondary literature (review, tables, books, etc.).
References	Merck Index (1997) Merck & Co., Inc. Whitehouse Station, NJ.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Melting Point	30 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Melting Point	41 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	ASTM-D-1015
GLP	No
Melting Point	Less than -50 °C

Decomposition	No at C
Sublimation	No
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Degussa AG (2003b) Safety Data Sheet for 4- <i>tert</i> -Butylcyclohexyl acetate. Degussa AG (1998) Product information, Data Sheet 1401, 1.12.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	Calculated Mean or weighted MP
Melting Point	10.93 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVWIN EPI Suite (2000) US. Environmental Protection Agency.

1.2 Boiling Point

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Boiling Point	110 °C
Pressure	15 mm Hg
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
GLP	No
Boiling Point	224-228 °C
Pressure	1013 hPa
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Degussa AG (2003a) Safety Data Sheet for 4- <i>tert</i> -butylcyclohexanol. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	ASTM-D-1078
GLP	No
Boiling Point	223 °C
Pressure	1013 hPa
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Degussa AG (1998a) Product information for 4- <i>tert</i> -butylcyclohexanol, Data Sheet 1391, 1.12. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	Calculated. Adapted Stein & Brown method.
Boiling Point	216.91 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVPPWIN EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2

Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Boiling Point	216 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Boiling Point	212 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only secondary literature (review, tables, books, etc.).
References	Merck Index (1997) Merck & Co., Inc. Whitehouse Station, NJ.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Boiling Point	260 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	ATSDM-D-1078
GLP	No
Boiling Point	241 °C
Pressure	1013 hPa
Data Qualities Reliabilities	Reliability code 4. Not assignable.

Remarks for Data Reliability Code 4. Only short abstract available.

References Degussa AG (1998b) Product information for 4-*tert*-butylcyclohexyl acetate, Data Sheet 1401, 1.12. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
GLP	No
Boiling Point	ca. 241 °C
Pressure	1013 hPa
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Degussa AG (2003b) Safety Data Sheet for 4- <i>tert</i> -butylcyclohexyl acetate. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	Calculated/Adapted Stein & Brown method
Boiling Point	232.55 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVWIN EPI Suite (2000) U.S. Environmental Protection Agency.

1.3 Vapor Pressure

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
GLP	No

Vapor Pressure	Less than 0.1 hPa
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Degussa AG (2003a) Safety Data Sheet for 4- <i>tert</i> -butylcyclohexanol. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	Calculated
Vapor Pressure	0.005 mm Hg
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	Calculated/Mean VP of Antoine & Grain methods
Vapor Pressure	0.0263 mm Hg
Temperature	25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVPWIN EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Vapor Pressure	0.02 mm Hg

Temperature	20 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
GLP	No
Vapor Pressure	0.01 hPa
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Degussa AG (2003b) Safety Data Sheet for 4- <i>tert</i> -butylcyclohexyl acetate. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	Calculated
GLP	No
Remarks for Substance	The value at 20 °C is an estimate obtained by extrapolation of the data given in the reference: 241 °C: 1013 hPa, 200 °C: 366 hPa, 150 °C: 73 hPa, 100 °C: 8 hPa, $\log(VP) = -2866 \cdot (1/T) + 8.6061$ (T in K, VP in hPa)
Vapor Pressure	Approximately 0.067 hPa
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Huels AG (1985) Produktdatenblatt "p- <i>tert</i> -Butylcyclohexylacetat", Artikel-Nr. 002304, 01-MAR-85. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4

Method/guideline	Calculated
Vapor Pressure	0.03 mm Hg
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Fragrance Materials Association (FMA) Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	Calculated/Mean VP of Antoine & Grain methods
Vapor Pressure	0.0159 mm Hg
Temperature	25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVWIN EPI Suite (2000) U.S. Environmental Protection Agency.

1.4 n-Octanol/Water Partition Coefficients

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	OECD Guideline 107
GLP	No
Year	1981
Remarks for Test Conditions	Flask shaking method GC analysis of the test substance No further data
Log Pow	3.23

Remarks for Results	Summary report of results.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Degussa AG (1981) Unpublished Report No. 89-0514-DKP.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	Calculated
Log Pow	3.42
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (menthol)
Method/guideline	Calculated
Log Pow	3.38
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Remarks for Substance	Purity: 70.7% trans, 28.3 cis by GC
Method/guideline	Reverse phase HPLC method (OECD 117)
Year	1996
Log Pow	4.8 at 25 °C
Remarks for Results	For both isomers

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Givaudan-Roure (1996) Partition coefficient n-octanol/water of 4- <i>tert</i> -butylcyclohexyl acetate. Unpublished.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	Calculated
Log Pow	4.42
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U.S. Environmental Protection Agency.

1.5 Water Solubility

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
GLP	No
Value (mg/L) at Temperature	Less than 100 mg/L at 20 °C
Description of Solubility	Of very low solubility
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Degussa AG (2003a) Safety Data Sheet for 4- <i>tert</i> -butylcyclohexanol. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/Guideline	Calculated

Value (mg/L) at Temperature 528.9 at 25 °C

Data Qualities Reliabilities Reliability code 4. Not assignable.

Remarks for Data Reliability Code 4. Calculated.

References WSKOWIN EPI Suite (2000) US Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
GLP	No
Value (mg/L) at Temperature	ca. 90 mg/L at 20 °C
pH	7
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Degussa AG (2003b) Safety Data Sheet for 4- <i>tert</i> -butylcyclohexyl acetate. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/Guideline	Calculated
Value (mg/L) at Temperature	2.552 at 25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWIN EPI Suite (2000) U.S. Environmental Protection Agency.

2 ENVIRONMENTAL FATE AND PATHWAYS

2.1 Photodegradation

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	Calculation
Test Type	AOPWIN
Half-life t_{1/2}	6.361 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) U S Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	Calculation
Test Type	AOPWIN
Half-life t_{1/2}	8.850 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) U S Environmental Protection Agency.

2.2 Stability in Water

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method	Calculated
Half-life t 1/2	266 days at pH 8
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	HYDROWIN EPI Suite (2000) US Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method	Calculated
Half-life t 1/2	7.2 years at pH 7
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	HYDROWIN EPI Suite (2000) US Environmental Protection Agency.

2.3 Biodegradation

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method	EG-Guideline 84/449/EWG C.3
Test Type	Aerobic
GLP	No

Year	1983
Contact time (units)	19 days
Innoculum	Predominantly domestic sewage
Remarks for Test Conditions	Concentration: 20 mg/L related to DOC (dissolved organic carbon). TEST CONDITION - Additional substrate: No - Test temperature: 20 +- 2°C Kinetics: 5 d: 6% 14 d: 17% 19 d: 89 %
Degradation % After Time	90% after 19 days
Results	Readily biodegradable
Time required for 10% degradation	Approximately 9 days
10 day window criteria	Fulfilled
Total degradation	90 %
Classification	Readily biodegradable
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Degussa AG (1983) Unpublished report. Report No. 96-0464-DKO.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method	EC-Guideline 92/69/E, CO2 Evolution test
Test Type	Aerobic
GLP	Yes
Year	1992
Innoculum	Activated sludge, domestic
Remarks for Test Conditions	INOCULUM - Source: Kläranalge Marl Ost Initial cell concentration: 122 x 10exp4 colony building units/L INITIAL TEST SUBSTANCE CONCENTRATION: 20,6 to 20,8

	mg/l
	Test temperature: 20.4-23.6 °C
	- pH value: 7.5-7.6
	- suspended solids: 29.7 mg/l
Degradation % After Time	75% after 28 days
Results	Readily biodegradable
Time required for 10% degradation	Approximately 5 days
10 day window criteria	Yes
Total degradation	75%
Classification	Readily biodegradable
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
Reference	Degussa AG (1997b) Unpublished report. Report No, 97-0300-DGO.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method	ISO Draft "BOD Test for insoluble substance"
Test Type	Aerobic
GLP	No
Year	1995
Contact time (units)	28 days
Innoculum	Activated sludge, domestic
Remarks for Test Conditions	INNOCULUM - Source: Lippeverbands-Kläranlage Marl INITIAL TEST SUBSTANCE CONCENTRATION: 51.5 mg/l DURATION OF THE TEST: 28 days ANALYTICAL PARAMETER: Oxygen consumption SAMPLING: on days 0, 7, 14, 21, 28 Control: Diethylene glycol
Degradation % After Time	68% after 28 days
Time required for 10% degradation	Approximately 10 days

10 day window criteria	Not met
Total degradation	68 %
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Degussa AG (1995) Unpublished report. Report No. 95-0220-DKO.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Remarks for Substance	Purity: 70.8% trans, 28.3% cis by GC
Method	Respirometric Method, modified MITI test II (OECD Guideline No. 302 C)
GLP	Yes
Year	1995
Contact time (units)	Up to 28 days
Innoculum	Fresh activated sludge, domestic sewage
Remarks for Test Conditions	Dry weight of suspended solids=3.980 g/L; sludge concentration= 100 mg/L (d.w.); nominal concentration=30 mg/L; temperature=22 deg C; biodegradation began on day 12
Degradation % After Time	24% after 28 days
Results	Not inherently but partially biodegradable
Time required for 10% degradation	12-14 days
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Rudio J. (1996b) Inherent biodegradability of 4- <i>tert</i> -butylcyclohexyl acetate according to OECD Guideline No. 302 C. Givaudan Roure Test Report No. 96-E51. Unpublished, dated June 24, 1996.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Remarks for Substance	Purity: 70.8% trans, 28.3% cis by GC
Method	Manometric Respirometric Test (OECD Guideline No. 301 F)
Test Type	Yes

GLP	Yes
Year	1996
Contact time (units)	Up to 28 days
Innoculum	Fresh activated sludge, domestic sewage
Remarks for Test Conditions	Dry weight of suspended solids=4.366 g/L; sludge concentration= 30 mg/L (d.w.); nominal concentration=100 mg/L; temperature=22 deg C; biodegradation began on day 15
Degradation % After Time	54% after 28 days
Results	Not readily biodegradable
Time required for 10% degradation	15 days
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Rudio J. (1996a) Ready biodegradability of butylcyclohexyl acetate according to OECD Guideline No. 301 F. Givaudan Roure. Unpublished, dated January 17, 1996.

2.4 Fugacity

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input Parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Model data and results	Air = .92% Water = 37.9% Soil = 59.7% Sediment = 0.468%

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	<p>Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183.</p> <p>Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five-stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626.</p> <p>Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.</p>

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Model Conditions	Mackay
Test Type	Environmental Equilibrium Partitioning Model
Model Used	Level III Fugacity-based Environmental Equilibrium Partitioning Model
Input Parameters	MW, calculated VP, calculated MP, calculated Kow
Year	2000
Model data and results	<p>Air = 1.66%</p> <p>Water = 14.9%</p> <p>Soil = 71.3%</p> <p>Sediment = 12.1%</p>
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	<p>Mackay D. (1991) Multimedia Environmental Models; The Fugacity Approach, Lewis Publishers, CRC Press, pp 67-183.</p> <p>Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five-stage process. Environmental Toxicology and Chemistry, 15(9), 1618-1626.</p> <p>Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.</p>

3 ECOTOXICITY

3.1 Acute Toxicity to Fish

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	DIN 38412 part 15
Test Type	Static
GLP	No
Year	1987
Species/Strain/Supplier	Fish/ <i>Leuciscus idus</i> (Fresh water)
Exposure Period	48 hours
Analytical monitoring	No
Remarks for Test Conditions	TEST ORGANISMS - Strain: <i>Leuciscus idus melanotus</i> - Supplier: Fischzucht Eggert / Hohenwestedt - Size/weight/loading: 6 cm +/- 2 cm / 10 - Feeding: Tetramin before start of test - Pretreatment: 14 d prior to experiment, Zephriol 1: 1000 for 1 hour - Feeding during test: no STOCK AND TEST SOLUTION AND THEIR PREPARATION - Vehicle, solvent: no STABILITY OF THE TEST CHEMICAL SOLUTIONS: stable REFERENCE SUBSTANCE: no DILUTION WATER - Source: dechlorinated drinking water - Aeration: continuously - Hardness: no data - pH: 7.9 to 8.3 - Oxygen content: 8.3 to 9.5 mg/l
Unit	mg/L
Remarks fields for results	RESULTS:

- Nominal/measured concentrations: nominal only:

13, 16, 20 mg/l

- Effect data (Mortality):

13 mg/l: 0%

16 mg/l: 20%

20 mg/l: 100 %

Conclusion Remarks LC50 = 17 mg/L

LC0 = 13 mg/l

LC100= 20 mg/l

Data Qualities Reliabilities Reliability code 2. Reliable with restriction.

Remarks for Data Reliability Code 2. Basic data given: comparable to guidelines/standards.

Reference Degussa AG (1987) Unpublished report. Report No. 96-0394-DKO.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Remarks for Test Conditions	Based on: log KOW = 3.23, MP = 67 °C, water solubility = 100 mg/L
Unit	mg/L
Endpoint value	LC50 = 8.085
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	Fish

Exposure Period	14 days
Remarks for Test Conditions	Based on: log KOW = 3.23, MP = 67 °C, water solubility = 100 mg/L
Unit	mg/L
Endpoint value	LC50 = 17.805
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	DEV DIN 38412 part 15
Test Type	Static
GLP	No
Year	1985
Species/Strain/Supplier	Fish/ <i>Leuciscus idus</i> , fresh water
Exposure Period	48 hours
Analytical monitoring	No
Remarks for Test Conditions	<p>TEST ORGANISMS</p> <ul style="list-style-type: none"> - Strain: <i>Leuciscus idus melanotus</i> - Supplier: Fa. Ekkerts - Loading: 10 per vial - Feeding: Tetramin - Pretreatment: Zephirol 1: 50000 - Feeding during test: no <p>DILUTION WATER</p> <ul style="list-style-type: none"> - Source: Drinking water dechlorinated <p>Temperature: 20+-1°C</p> <p>pH: 7.6-7.8</p> <p>Hardness: 15°dH</p> <p>Dissolved oxygen: 7.3-8.1 mg/l</p> <p>Statistical analysis: Linear regression</p>
Nominal concentrations as mg/L	10 to 20

Measured concentrations as mg/L	4.0 to 34
Unit	mg/L
Endpoint value	Death
Remarks fields for results	Temperature: ca. 20 °C Dissolved oxygen: 85-100% saturation pH: 8.0-8.4 Hardness: 12.5-13 degree dH
Conclusion Remarks	LC0 = 6.7 mg/L, LC50 = 8.6 mg/L, LC100 = 12 mg/L.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
Reference	Degussa AG (1997c) Unpublished report. Report No. 97-0304-DGO.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Unit	mg/L
Endpoint value	LC50 = 0.954
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Purity: 99 %
Method/guideline	EC Guideline 92/69/EEC
Test Type	Experimental
GLP	Yes
Year	1992
Analytical procedures	TOC analysis
Species/Strain/Supplier	<i>Daphnia magna</i>
Test Details	48 hours
Remarks for Test Conditions	<p>TEST ORGANISMS</p> <ul style="list-style-type: none"> - Strain: <i>Daphnia magna</i> - Source/supplier: Hüls AG Prüfinstitut für Biologie, Marl, Germany - Breeding method: in M4 medium (Elendt, 1990), 1 l bakery - Age: < 24 h - Feeding: <i>Scenedesmus subspicatus</i> - Pretreatment: no - Feeding during test: no - Control group: yes <p>STOCK AND TEST SOLUTION AND THEIR PREPARATION</p> <ul style="list-style-type: none"> - Dispersion: 1 g/l in synthetic fresh water, mixing over 18 hours, filtration, DOC determination. <p>Reference substance: potassium dichromate</p> <p>STABILITY OF THE TEST CHEMICAL SOLUTIONS: stable</p> <p>DILUTION WATER</p> <ul style="list-style-type: none"> - Source: synthetic fresh water <p>CaCl₂ x 2 H₂O: 294 mg/l MgSO₄ x 7 H₂O: 123 mg/l NaHCO₃: 63 mg/l KCl: 5.5 mg/l</p> <ul style="list-style-type: none"> - Aeration: no

	- Hardness: Ca ²⁺ and Mg ²⁺ : 2.5 mmol/l
	- TOC: 0
	- Ca/Mg ratio: 4:1
	- Na/K ratio: 10:1
	- pH: 7.7 to 7.8
	- Oxygen content: 7.9 to 8.1 mg/l
Measured concentrations as mg/L	Less than 20 % deviation from nominal conc.
EC50, EL50, LC0, at 24,48 hours	EC0 = 25, EC50 = 46, EC100 = 75 mg/L.
Biological observations	EC50 (24 h): 46 mg/l EC50 (48 h): 46 mg/l
Control response satisfactory?	Yes
Appropriate statistical evaluations?	Yes
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Data Reliability Remarks	Code 1. Comparable to guideline study.
Reference	Degussa AG (1994b) Unpublished report. Report No.: 94-0228-DGO.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	<i>Daphnia Magna</i>
Test Details	48 hours
Remarks for Test Conditions	Based on: log KOW = 3.23, MP = 67 °C, water solubility = 100 mg/L
EC50, EL50, LC0, at 24,48 hours	LC50 = 9.431 at 48 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
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CAS No.	98-52-2
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	Mysid shrimp
Test Details	96 hours
Remarks for Test Conditions	Based on: log KOW=3.23, MP=67 °C, water solubility=100 mg/L
EC50, EL50, LC0, at 24,48 hours	LC50 = 0.969 at 96 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Remarks for Substance	Purity 99.1%
Method/guideline	EG EG92/69/EWG
Test Type	Static
GLP	Yes
Year	1997
Analytical procedures	DOC
Species/Strain/Supplier	<i>Daphnia magna</i>
Test Details	48 hours
Remarks for Test Conditions	<p>TEST ORGANISMS</p> <ul style="list-style-type: none"> - Strain: <i>Daphnia magna</i> - Source/supplier: Hüls AG Prüfinstitut für Biologie, Marl, Germany - Breeding method: in M4 medium (Elendt, 1990), 1 l bakers - Age: < 24 h - Feeding: <i>Scenedesmus subspicatus</i> - Pretreatment: no - Feeding during test: no - Control group: yes <p>STOCK AND TEST SOLUTION AND THEIR PREPARATION</p>

- Dispersion: 1 g/l in synthetic fresh water, mixing over 18 hours, filtration, DOC determination.

Reference substance: potassium dichromate

STABILITY OF THE TEST CHEMICAL SOLUTIONS: stable

DILUTION WATER

- Source: synthetic fresh water

CaCl₂ x 2 H₂O: 294 mg/l

MgSO₄ x 7 H₂O: 123 mg/l

NaHCO₃: 65 mg/l

KCl: 6 mg/l

- Aeration: no

- Hardness: Ca²⁺ and Mg²⁺: 2.5 mmol/l

- TOC: 0

- Ca/Mg ratio: 4:1

- Na/K ratio: 10:1

- pH: 7.7 to 7.8

- Oxygen content: 8.9 to 9.1 mg/l

Temperature: 20±1°C

Nominal concentrations as mg/L	2.8-28-4
Measured concentrations as mg/L	2.4-28-4
EC50, EL50, LC0, at 24,48 hours	EC50 = 23.4, EC10 = 8.7, EC100 > 28.1
Control response satisfactory?	Yes
Appropriate statistical evaluations?	Yes
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Data Reliability Remarks	Code 1. Guideline study.
Reference	Degussa AG (1997a) Unpublished report. Report No. 97-0302-DGO.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	DIN 38412 part 11
Test Type	Static
GLP	No

Year	1985
Analytical procedures	DOC
Species/Strain/Supplier	<i>Daphnia magna</i>
Test Details	24 hour
Remarks for Test Conditions	<p>TEST ORGANISMS</p> <ul style="list-style-type: none"> - Strain: <i>Daphnia magna</i> - Supplier: Hüls AG - Age/loading: < 1 d, 5 - Feeding: Chlorella Vulgaris - Feeding during test: no <p>STOCK AND TEST SOLUTION AND THEIR PREPARATION</p> <ul style="list-style-type: none"> - Stock solution: in water, filtration after 2 h of stirring. <p>Dilution water: synthetic: CaCl₂ x 2 H₂O: 294 mg/l MgSO₄ x 7 H₂O 123 mg/l NaHCO₃ 63 mg/l KCl 5,5 mg/l</p> <ul style="list-style-type: none"> - Test temperature: 20 +- 1 °C - Hardness: 2.5 mmol Ca²⁺ and Mg²⁺, Ca²⁺ : Mg²⁺: 4: 1 <p>DURATION OF THE TEST: 24 h</p> <p>TEST PARAMETER: Immobilisation</p> <p>MONITORING OF TEST TEST ORGANISMS</p> <ul style="list-style-type: none"> - Strain: <i>Daphnia magna</i> - Supplier: Hüls AG - Age/loading: < 1 d, 5 - Feeding: Chlorella Vulgaris - Feeding during test: no <p>STOCK AND TEST SOLUTION AND THEIR PREPARATION</p> <ul style="list-style-type: none"> - Stock solution: in water, filtration after 2 h of stirring. <p>Dilution water: synthetic: CaCl₂ x 2 H₂O: 294 mg/l MgSO₄ x 7 H₂O 123 mg/l NaHCO₃ 63 mg/l KCl 5,5 mg/l</p> <ul style="list-style-type: none"> - Test temperature: 20 +- 1 °C

- Hardness: 2.5 mmol Ca²⁺ and Mg²⁺, Ca²⁺ : Mg²⁺: 4: 1

DURATION OF THE TEST: 24 h

TEST PARAMETER: Immobilisation

MONITORING OF TEST SUBSTANCE CONCENTRATION:
yes by DOC

Measured concentrations as mg/L	2,6 to 22
EC50, EL50, LC0, at 24,48 hours	24 h EC50 = 7 mg/l, EC10= 2.6 mg/l EC100= 22 mg/l
Biological observations	Immobilization
Appropriate statistical evaluations?	Regression analysis.
Remarks for results	Results based on DOC in mg/l.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Degussa AG (1985b) Unpublished report. Report No. 85-0368-DKO.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	DIN 38412 part 11
Test Type	Static
GLP	No
Year	1985
Analytical procedures	No
Species/Strain/Supplier	<i>Daphnia magna</i>
Test Details	24 hours
Remarks for Test Conditions	TEST ORGANISMS - Strain: <i>Daphnia magna</i> - Supplier: Hüls STOCK AND TEST SOLUTION AND THEIR PREPARATION Solution using a solubiliser: Marlowet ef - Concentrations: 12, 18, 25, 35 mg/l DURATION OF THE TEST: 24 hours TEST PARAMETER: Immobilisation

Nominal concentrations as mg/L	12-35
EC50, EL50, LC0, at 24,48 hours	EC50 = 19, EC0=12, EC100= 35
Appropriate statistical evaluations?	Regression analysis
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Degussa AG (1985c) Unpublished report. Report No. 85-0378-DKO.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	<i>Daphnia magna</i>
Test Details	48 hours
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
EC50, EL50, LC0, at 24,48 hours	LC50 = 0.446 at 48 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

3.3 Acute Toxicity to Aquatic Plants

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	99.3 % purity (GC)
Method/guideline	EC 92/69/EEC

Test Type	Biomass/growth rate
GLP	Yes
Year	1992
Species/Strain/Supplier	<i>Scenedesmus subspicatus</i> (algae)
Endpoint Value	Growth
Exposure Period	72 hour
Analytical monitoring	Yes
Remarks for Test Conditions	- Initial cell concentration: 20000 cells/ml STOCK AND TEST SOLUTION AND THEIR PREPARATION - Dispersion: 1 g/l in synthetic fresh water, mixing over 18 hours, filtration, DOC determination.
Nominal concentrations as mg/L	4.4 to 148
Measured concentrations as mg/L	4.6 to 110
Unit	mg/L
Endpoint value	Growth
NOEC, LOEC or NOEL, LOEL	NOEC=14, EC10=15, and EC50= 29 mg/L.
Biological observations	EC50 for growth rate: 45 mg/l EC10 for growth rate: 21 mg/l
Control response satisfactory?	Yes
Appropriate statistical evaluations?	Yes
Conclusion remarks	EC50 (72 h, growth rate) = 45 mg/L EC10 (72 h, growth rate) = 21 mg/L
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
Reference	Degussa AG (1994a) Unpublished report. Report No.: 94-0230-DGO.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	ECOSAR
Test Type	Calculated

Species/Strain/Supplier	Green algae
Exposure Period	96 hours
Remarks for Test Conditions	Based on: log KOW = 3.23, MP = 67 C, water solubility = 100 mg/L
Unit	mg/L
NOEC, LOEC or NOEL, LOEL	EC50 = 6.329 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Remarks for Substance	Purity 99.1%
Method/guideline	EC Guideline 92/69/EEC
GLP	Yes
Year	1992
Species/Strain/Supplier	<i>Scenedesmus subspicatus</i>
Endpoint Value	Biomass and growth rate
Exposure Period	72 hour
Analytical monitoring	Yes
Remarks for Test Conditions	As the test substance was not readily soluble in water, suspension of 1 g test substance/L was stirred for 18 hours. After that a filtrate of the suspension was used for the test. Temperature: 23.3-23.8 °C; pH: 7.5-9.3
Nominal concentrations as mg/L	0.76 to 27.3
Measured concentrations as mg/L	0.76 to 27.3
Unit	mg/L
NOEC, LOEC or NOEL, LOEL	NOEC = 6.8, EC10 = 8.2, EC50 = 17 mg/L
Control response satisfactory?	Yes
Appropriate statistical evaluations?	Yes

evaluations?

Conclusion Remarks	Effect concentrations based on growth rate EC10 = 11 mg/L EC50 = 22 mg/L
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Degussa AG (1992) Unpublished report. Report No. 97-0308-DGO.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	Green algae
Exposure Period	96 hours
Remarks for Test Conditions	Based on: log KOW = 4.80, water solubility = 90 mg/L
Unit	mg/L
NOEC, LOEC or NOEL, LOEL	EC50 = 0.084 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

4 HUMAN HEALTH TOXICITY

4.1 Acute Toxicity

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Test Type	Acute Oral LD50
GLP	Yes
Year	1973
Species/strain	Rat
# of animals per sex per dose	10
Route of Administration	Oral
Value LD50 or LC50 with confidence limits	LD50 = 4200 mg/kg bw; Confidence limits 3620 - 4870 mg/kg.
Number of deaths at each dose level	95% confidence limit = 3620-4870 mg/kg. Toxic signs were immediate stimulation followed by ataxia.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Denine E.P. and Palanker A.C. (1973) Acute oral and dermal toxicity studies. Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	Acute Toxicity LD50
GLP	No
Year	1962
Species/strain	Mouse/CF1
Route of Administration	Intraperitoneal
Remarks for Test Conditions	Groups of 10 adult CF1 strain mice weighing 20-25 grams (6-8 weeks old) were injected with test compound and the resulting mortality was recorded for one week. The mice were housed 10 per cage in an air-conditioned room (75 to 80 F) and were provided food and water ad libitum. Vehicle was distilled H2O

when possible. Compounds insoluble in H₂O were dissolved in mixtures of H₂O and propylene glycol or cottonseed oil or suspended in 0.5% solution of carboxymethylcellulose.

Value LD50 or LC50 with confidence limits	LD50 = 50-100 mg/kg.
Conclusion remarks	LD50 = 50-100 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Doull J., V.Plzak and S.J.Brois. (1962) A survey of compounds for radiation protection. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Test Type	Acute Dermal LD50
GLP	No
Year	1973
Species/strain	Rabbit
# of animals per sex per dose	6
Route of Administration	Dermal
Value LD50 or LC50 with confidence limits	LD50 = greater than 5000 mg/kg bw
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Denine E.P. and Palanker A.C. (1973) Acute oral and dermal toxicity studies. Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute Oral LD50
GLP	No
Year	1964

Species/strain	Rat/Osborne-Mendel
Sex	Male and Female
# of animals per sex per dose	5
Vehicle	Corn oil
Route of Administration	Oral-Gavage
Value LD50 or LC50 with confidence limits	3180 mg/kg bw (2790-3620)
Remarks for Results	Slope function: 1.3 (95% CL 1.1-1.5)
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenner, P.M., Hagan, E.C., Taylor, J.M., Cook, E.L., and Fitzhugh, O.G. (1964) Food flavourings and compounds of related structure. I. Acute oral toxicity. <i>Fd Cosmet Toxicol</i> 2:327-343.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Reed-Munch method
Test Type	Acute Oral LD50
GLP	No
Year	1975
Species/strain	Mouse
Sex	Male
# of animals per sex per dose	6
Route of Administration	Oral
Remarks for Test Conditions	Doses given ranged from 2000 to 5000 mg/kg bw and given as a 37.5% (w/v) emulsion.
Value LD50 or LC50 with confidence limits	4384 mg/kg bw
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.

References

Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute Oral LD50
GLP	No
Year	1975
Species/strain	Rat
Sex	Male
# of animals per sex per dose	5
Vehicle	0.85% saline
Route of Administration	Oral-Gavage
Value LD50 or LC50 with confidence limits	940 mg/kg bw (95% CL=534-1654)
Number of deaths at each dose level	250 mg/kg bw: 0/5 500 mg/kg bw: 1/5 1000 mg/kg bw: 3/5 2000 mg/kg bw: 4/5 3000 mg/kg bw: 5/5
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Test Type	Acute Oral LD50
Year	1975

Species/strain	Rat
# of animals per sex per dose	10
Route of Administration	Oral
Value LD50 or LC50 with confidence limits	LD50 = 5000 mg/kg.
Remarks for Results	Acute oral LD50 approximately equals 5000 mg/kg. Toxic signs were lethargy, tremors and chromodacryorrhea.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Moreno O.M. (1976) Acute toxicity studies in rats, mice, rabbits and guinea pigs. Unpublished report to RIFM.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Test Type	Acute Oral LD50
GLP	No
Year	1970
Species/strain	Rat
Sex	Not reported
Vehicle	Traganth
Route of Administration	Oral
Remarks for Test Conditions	Substance administered as a 2-30% emulsion
Value LD50 or LC50 with confidence limits	Approximately 4,800 ml/kg bw
Remarks for Results	Signs included dyspnea, shivering, cramping. At necropsy, rats showed bloody snouts and anus, diarrhea, enlarged gastrointestinal tract and bladder.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Zeller and Hofmann (1970) <i>p-tert</i> -Butylcyclohexylacetat. Ergebnis der Gewerbetoxikologischen Vorpruefung. Dated 21.7.1970.
Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate

CAS No.	32210-23-4
Test Type	Acute Oral LD50
GLP	No
Year	1976
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10/dose
Route of Administration	Oral
Remarks for Test Conditions	Two doses administered: 500 or 5000 mg/kg bw
Value LD50 or LC50 with confidence limits	Less than 5 but greater than 500 mg/kg bw
Number of deaths at each dose level	500 mg/kg bw: 3 deaths/10 rats 5000 mg/kg bw: 8 deaths/10 rats
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Opdyke, D.L. (1976) Acute oral toxicity in rats, dermal toxicity in rabbits. Report to RIFM dated May 21, 1976.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Test Type	IP LD50
GLP	No
Year	1970
Species/strain	Mouse
Sex	Not reported
Vehicle	Traganth
Route of Administration	Intraperitoneal
Remarks for Test Conditions	Substance administered as a 2-30% emulsion
Value LD50 or LC50 with confidence limits	Approximately 400 ml/kg bw
Remarks for Results	Signs included dyspnea, shivering, cramping. At necropsy, lesions were reported in the forestomach.

Data Qualities Reliabilities Reliability code 2. Reliable with restriction.

Remarks for Data Reliability Code 2. Basic data given: comparable to guidelines/standards.

References Zeller and Hofmann (1970) *p-tert*-Butylcyclohexylacetat. Ergebnis der Gewerbetoxikologischen Vorpruefung. Dated 21.7.1970.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Test Type	Acute Dermal LD50
GLP	No
Year	1976
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	4/dose
Route of Administration	Dermal
Remarks for Test Conditions	One dose of 5000 mg/kg bw administered. Insufficient test material to dose 10 rabbits.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg bw
Number of deaths at each dose level	5000 mg/kg bw: 1 death/5 rabbits
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Opdyke, D.L. (1976) Acute oral toxicity in rats, dermal toxicity in rabbits. Report to RIFM dated May 21, 1976.

4.2 Genetic Toxicity

4.2.1 *In vitro* Genotoxicity

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Test Type	Ames test
System of Testing	Bacterial
GLP	No
Year	1988
Species/Strain	<i>Salmonella typhimuriums</i> TA98, TA 100, TA 1535, TA 1537, TA 1538
Metabolic Activation	With and without
Doses/Concentration	Up to 5000 ug/plate
Remarks for Test Conditions	<p>SYSTEM OF TESTING</p> <ul style="list-style-type: none"> - Metabolic activation system: Arochlor induced rat liver S9-mix of Bor: W/SW male rats (source SPF, TNO, NL) - No. of metaphases analyzed: no indicated - concentrations: 10 to 5000 micro-g/plate - Number of replicates: 2 one plate incorporation on pre-incubation test. - Positive and negative control groups and treatment: <p>Negative: Solvent, DMSO</p> <p>Positive: TA 98, TA 1528: Nitrofluorene, TA 100, TA 1535: Sodiumazide, TA 1537: Aminocridine</p> <p>Cytotoxicity: from 250 or 500 micro-g per plate</p>
Results	Negative
Cytotoxic concentration	250 to 500 micrograms/plate
Genotoxic Effects	None
Remarks for results	<p>GENOTOXIC EFFECTS:</p> <ul style="list-style-type: none"> - With metabolic activation: none - Without metabolic activation: none <p>CYTOTOXIC CONCENTRATION:</p> <ul style="list-style-type: none"> - With metabolic activation: 500 ug/plate

	- Without metabolic activation: 250 ug/plate TEST-SPECIFIC CONFOUNDING FACTORS: none STATISTICAL RESULTS: not given
Conclusion Remarks	Not mutagenic with and without metabolic activation
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Degussa AG (1988a) Unpublished report. Reg.Nr.: 88-0660-DKM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	Ames test
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	No
Year	1982
Species/Strain	<i>Salmonella typhimurium</i> strains TA100, TA2637, and TA98
Metabolic Activation	S9 mix
Doses/Concentration	0.005, 0.01, 0.02, 0.05, 0.1, 0.2, and 0.5 mg/plate
Remarks for Test Conditions	DMSO used as solvent control.
Results	No increase in his+ revertant frequency at any concentration tested.
Cytotoxic concentration	0.5 mg/plate for all strains; 0.2 mg/plate for TA100 -S9
Genotoxic Effects	None
Remarks for Results	Foreign paper, data taken from tables and brief English summary.
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol was not mutagenic when tested in <i>Salmonella typhimurium</i> strains TA100, TA2637 or TA98 with or without metabolic activation.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Nohmi, T., Miyate, R., Yoshikawa, K., and Ishidate, M. Jr. (1985) Mutagenicity tests on organic chemical contaminants in city water and related compounds. I. Bacterial mutagenicity

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Preincubation assay (Haworth <i>et al.</i> , 1983)
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	Ambiguous
Year	1988
Species/Strain	<i>Salmonella typhimurium</i> strains TA100, TA1535, TA97, and TA98
Metabolic Activation	S9 from liver of Aroclor-induced male Sprague-Dawley rat and male Syrian hamster
Doses/Concentration	0, 3, 10, 33, 100, 166, 333, and 666 ug/plate
Remarks for Test Conditions	At least 5 concentrations of test chemical tested in triplicate with metabolic activation (10% and 30% of rat or hamster S9) and without S9. Positive controls used were sodium azide, 9-aminoacridine, and 4-nitro-o-phenylenediamine. DMSO used as solvent control.
Results	No increase seen in number of his+ revertants with or without any type/concentration of S9 at any of the concentrations tested.
Cytotoxic concentration	Not given
Genotoxic Effects	None
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol was not mutagenic when tested in <i>Salmonella typhimurium</i> strains TA100, TA1535, TA97, or TA98 with or without metabolic activation.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study. Part of NTP study program.
References	Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1988) <i>Salmonella</i> mutagenicity tests: IV. Results from the testing of 300 chemicals. <i>Environ Mol Mutagen</i> 11(Suppl 12): 1-158. Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., Zeiger, E. (1983) <i>Salmonella</i> mutagenicity results for 250 chemicals. <i>Environ Mutagen</i> 5(Suppl 1): 3-142.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Ames test
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	No
Year	1984
Species/Strain	<i>Salmonella typhimurium</i> strains TA92, TA1535, TA100, TA1537, TA94, and TA98
Metabolic Activation	S9 fraction from liver of PCB-induced Fischer rats
Doses/Concentration	Max. Concentration = 5.0 mg/plate
Remarks for Test Conditions	Overnight cell cultures were preincubated at 37 °C with the test chemical and S9 for 20 minutes prior to plating. Six concentrations of the test chemical were tested in duplicate. The number of revertants was scored after the plates were incubated for 2 days at 37 °C. A chemical was considered mutagenic if the number of revertants was 2X the number of colonies in the solvent control. DMSO was the solvent control.
Results	No increase in the number of revertants.
Cytotoxic concentration	Not given
Genotoxic Effects	None
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol was not mutagenic when tested in <i>Salmonella typhimurium</i> strains TA92, TA1535, TA100, TA1537, TA94, or TA98 with metabolic activation.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Ishidate, M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsuoka, A. (1984). Primary mutagenicity screening of food additives currently used in Japan. <i>Fd Chem Toxic</i> 22(8): 623-636.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	OECD Guideline 473
Test Type	Cytogenetic assay

System of Testing	Non bacterial
GLP	Yes
Year	1997
Species/Strain	Hamster/Chinese V79 lung cells
Metabolic Activation	With and without
Doses/Concentration	With metabolic activation: 20 - 500 micrograms/ml, without metabolic activation 20 - 200 micrograms/ml
Statistical Methods	For testing acceptable homogeneity between replicates: Binominal Dispersion Test (Richardson et al., 1989). Comparison of structural aberrations between treated and controls: Chi-square Test ($p < 0.05$).
Remarks for Test Conditions	Cytotoxicity screening test between 10 to 2000 micrograms/ml, solubility limit in Ethanol 1%. SYSTEM OF TESTING <ul style="list-style-type: none"> - Cell type: Chinese Hamster lung cells V79 - Metabolic activation system: Arochlor induced liver S9 fraction of male Spraque Dawley Rats. - No. of metaphases analyzed: 100 from each culture: - Cocentrations: without S9: 10, 60, 100 micro g/ml (test 1 and 2) with S9: 50, 250, 500 (test 1) and 20, 100, 200 micro g/ml (test 2) - Number of replicates: 2 per culture, 2 independent experiments. - Positive and negative control groups and treatment: Negative control: MEM 4 medium with and without S9 mix. Positive controls: Without metabolic activation: Mitomycin C 0.03 to 0.04 micro g/ml With metabolic activation: Cyclophosphamide, 3 and 4 micro g/ml Harvest time: 18 and 28 hours CRITERIA FOR EVALUATING RESULTS: The chemical is regarded as clastogenic if: <ul style="list-style-type: none"> - it induces chromosomal aberrations in a statistically significant manner in one or more concentrations. - the induced proportion of aberrant cells at such test substance concentrations exceeds the normal rang of the test system (greater than 5%). - positive results can be verified in an independent experiment.

STATISTICAL METHODS:

For testing acceptable homogeneity between replicates:
Binominal Dispersion Test (Richardson et al., 1989).

Comparison of structural aberrations between treated and controls: Chi-square Test ($p < 0.05$).

Results

Negative.

No biologically significant increases in chromosomal aberrations (excluding gaps) in both experiments with and without metabolic activation at both sampling times. A statistically significant increase in the highest concentration with S9 at the 28 hour sampling time was within the normal range of chromosomal aberrations of the test system and related to the low control incidence of the experiment (0%) . As no dose related increase in chromosomal aberrations could be detected in the other experiments, this result was not considered biologically significant. 4-*tert*-Butylcyclohexanol was not clastogenic in this experiment.

Cytotoxic concentration	Without S9 mix 60 to 100 ug/ml, with S9 mix 200 to 500 ug/ml
Genotoxic Effects	None detected
Appropriate statistical evaluations?	Yes
Conclusion Remarks	The test substance was not clastogenic under the described experimental conditions
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Degussa AG (1997) Unpublished report. Report No. 97-0366-DGM.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Chromosomal Aberration assay
System of Testing	Non bacterial
GLP	Ambiguous
Year	1991
Species/Strain	Human lymphocyte
Metabolic Activation	S9 from liver of Aroclor-induced male Sprague-Dawley rat
Doses/Concentration	0.1, 1.0, 10 mM with and without S9

Statistical Methods	Chi-square test
Remarks for Test Conditions	Lymphocytes were obtained from healthy donors (12 of each sex) and cultured at ~0.5-1.0E6 isolated cells. Cultures were incubated in the dark at 37 °C for 72 hours after which cells were exposed for 1 hour to colchicine and slides were prepared and chromosomal aberrations were scored in 100 metaphase cells. Solvent control was DMSO and positive control was MMC.
Results	Total structural aberrations (no./100 cells) for DMSO, DMSO+S9, MMC, 0.1 mM, 0.1 mM+S9, 1.0 mM, 1.0 mM+S9, 10 mM, and 10 mM+S9 was 1.76, 2.00, 9.13, 1.90, 2.03, 2.18, 2.02, 2.11 and 2.23, respectively.
Appropriate statistical evaluations?	Yes
Genotoxic Effects	None
Remarks for Results	Results were not affected by the presence or absence of S9.
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol did not induce chromosomal aberrations in human lymphocytes.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Murthy, P.B.K., Ahmed, M.M., and Regu, K. (1991) Lack of genotoxicity of menthol in chromosome aberration and sister chromatid exchange assays using human lymphocytes in vitro. Toxic In Vitro 5(4): 337-340.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Sister Chromatid Exchange
System of Testing	Non bacterial
GLP	Ambiguous
Year	1991
Species/Strain	Human lymphocyte
Metabolic Activation	S9 from liver of Aroclor-induced male Sprague-Dawley rat
Doses/Concentration	0.1, 1.0, 10 mM with and without S9
Remarks for Test Conditions	Lymphocytes were obtained from healthy donors (12 of each sex) and cultured at approximately 0.5-1.0E6 isolated cells. All cultures contained BrdU and metaphase preparations were stained with Hoechst-Giemsa stain. From each culture, a

	minimum of 25 2nd-division cells were scored and the mean no. of SCEs/cell were compared with solvent controls. Solvent control was DMSO and positive control was MMC.
Results	Total no. of SCEs/cell (mean) for DMSO, DMSO+S9, MMC, 0.1 mM, 0.1 mM+S9, 1.0 mM, 1.0 mM+S9, 10 mM, and 10 mM+S9 was 7.90, 8.00, 21.46, 7.39, 8.25, 8.00, 8.10, 8.50, and 8.60, respectively.
Appropriate statistical evaluations?	Yes
Genotoxic Effects	None
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol did not affect the frequency of SCEs in human lymphocytes.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Murthy, P.B.K., Ahmed, M.M., and Regu, K. (1991) Lack of genotoxicity of menthol in chromosome aberration and sister chromatid exchange assays using human lymphocytes in vitro. Toxic In Vitro 5(4): 337-340.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Galloway et al. (1985, 1987)
Test Type	Sister Chromatid Exchange
System of Testing	Non bacterial
GLP	Ambiguous
Year	1989
Species/Strain	Hamster/Chinese ovary cell
Metabolic Activation	S9 from liver of Aroclor-induced male Sprague-Dawley rat
Doses/Concentration	Trial 1: 0, 5, 16.7, or 50 ug/ml Trial 2: 0, 2.5, 5, 10, or 25 ug/ml Trial 3: 0, 16.7, 50, or 167 ug/ml
Remarks for Test Conditions	Positive controls used were mitomycin C (MMC) and cyclophosphamide (CP). Without S9, cultures were exposed to test substance for 25 hours. With S9, cultures were exposed for 2 hours. All cultures contained BrdU, which was added 2 hours after initial exposure, and cultures were exposed to BrdU until harvest. Typically, total incubation was 27.5-28 hours with Colcemid present 2-2.5 hours prior to harvest. Mitotic cells were

obtained and slides were prepared and examined by fluorescence microscopy after staining with Hoescht 33258 to evaluate cell cycle kinetics. For SCEs, cells were stained and scored. 50 cells were scored in trial 1 and 25 cells were scored in trials 2 and 3.

Results

SCE/cell for

Trial 1 (-S9) at 0, 5, 16.7, and 50 ug/ml: 7.72, 9.34, 8.06, and 7.94

Trial 2 (-S9) at 0, 2.5, 5, 10, and 25 ug/ml: 8.36, 7.78, 9.02, 9.75, and 10.04

Trial 3 (+S9) at 0, 16.7, 50, and 167 ug/ml: 8.42, 8.10, 8.74, and 8.48

Genotoxic Effects

In trial 1, a less than 20% increase in SCEs was reported at the low dose only. In trial 2, none of the concentrations showed an increase over 20%, but the test was considered equivocal based on a positive trend. No effects were reported in the presence of S9 in trial 3.

Conclusion Remarks

2-Isopropyl-5-methylcyclohexanol did not induce SCE in Chinese hamster ovary cells.

Data Qualities Reliabilities

Reliability code 2. Reliable with restriction.

Remarks for Data Reliability

Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles. Part of NTP study program.

References

Ivett J.L., Brown B.M., Rodgers C., Anderson B.E., Resnick M.A., and Zeiger E. (1989) Chromosomal aberrations and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. IV. Results with 15 chemicals. *Envir. Molecular Mut.*, 14(3), 165-187.

Galloway, S.M., Bloom, A.D., Resnick, M., Margolin, B.H., Nakamura, F., Archer, P., and Zeiger, E. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. *Environ Mutagen* 7:1-51.

Galloway, S.M. Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987) Chromosome aberration and sister chromatid exchange tests in vitro in Chinese hamster ovary cells: Results for 108 chemicals. *Environ Molec Mutagen* 10 (Suppl. 10):1-175.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Galloway <i>et al.</i> (1985, 1987)

Test Type	Chromosomal Aberration assay
System of Testing	Non-bacterial
GLP	Ambiguous
Year	1989
Species/Strain	Hamster/Chinese ovary cell
Metabolic Activation	S9 from liver of Aroclor-induced male Sprague-Dawley rat
Doses/Concentration	Trial 1: 100, 150, or 200 ug/ml Trial 2: 50, 125, or 250 ug/ml
Remarks for Test Conditions	Positive controls used were mitomycin C (MMC) and cyclophosphamide (CP). Without S9, cells were cultured with test article for 8 hours, then washed, then treated with Colcemid for 2-2.5 hours. With S9, cells were cultured with test article and S9 for 2 hours, washed, incubated for 8 hours then treated with Colcemid for 2-2.5 hours. Cells were harvested and slides prepared using Giemsa stain. 100-200 cells from each of the 3 highest scorable doses were analyzed and all aberrations were individually classified. Only the total percent cells with aberrations was considered in the statistical evaluation.
Results	Total percent cells with aberrations: Trial 1 at 0, 100, 150, or 200 ug/ml: 4, 2, 2, or 4 Trial 2 at 0, 50, 125, or 250 ug/ml: 4, 2, 1, or 4.
Genotoxic Effects	None
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol did not induce chromosomal aberrations in Chinese hamster ovary cells.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles. Part of NTP study program.
References	Ivett J.L., Brown B.M., Rodgers C., Anderson B.E., Resnick M.A., and Zeiger E. (1989) Chromosomal aberrations and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. IV. Results with 15 chemicals. <i>Envir. Molecular Mut.</i> , 14(3), 165-187. Galloway, S.M., Bloom, A.D., Resnick, M., Margolin, B.H., Nakamura, F., Archer, P., and Zeiger, E. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. <i>Environ Mutagen</i> 7:1-51. Galloway, S.M. Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimp, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987) Chromosome aberration and sister chromatid exchange tests in vitro in Chinese hamster ovary cells: Results for 108 chemicals. <i>Environ Molec Mutagen</i> 10

(Suppl. 10):1-175.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Ishidate and Odashima, 1977
Test Type	Chromosomal Aberration assay
System of Testing	Non bacterial
GLP	No
Year	1984
Species/Strain	Hamster/Chinese fibroblast cell line
Metabolic Activation	Max. Concentration = 0.2 mg/ml
Remarks for Test Conditions	Cells were exposed to 3 different concentrations of the test substance for 24 or 48 hours after which colcemid was added 2 hours before harvesting. Cells were trypsinized, suspended in a hypotonic KCl solution (13 min at room temperature), centrifuged, fixed with acetic acid-methanol and applied to slides. Preparations were stained with Giemsa solution and 100 well-spread metaphases were microscopically observed. The incidence of polyploid cells and cells with structural chromosomal aberrations were counted. Controls consisted of solvent-treated or untreated cells. Test chemicals were considered positive if the incidence of aberrations was greater than 10%, equivocal if between 5.0 and 9.9%, and negative if less than 4.9%. For positive samples, the D20 (dose in mg/ml at which structural aberrations were detected in 20% of the metaphases observed) was calculated to assess the clastogenic potential. The frequency of cells with exchange-type aberrations per unit dose (mg/ml) was also calculated and expressed as "TR".
Results	0% polyploid 4.0% structural aberrations
Cytotoxic concentration	Not given
Genotoxic Effects	None
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol did not induce chromosomal aberrations in Chinese hamster fibroblasts.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Ishidate, M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsuoka, A. (1984). Primary mutagenicity

screening of food additives currently used in Japan. *Fd Chem Toxic* 22(8):623-636.

Ishidate, M., Jr., and Odashima, S. (1977). Chromosome tests with 134 compounds on Chinese hamster cells in vitro--A screening for chemical carcinogens. *Mutat Res* 48:337.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Clive <i>et al.</i> (1979); Mitchell <i>et al.</i> (1988); Myhr and Caspary (1988)
Test Type	Forward mutation assay
System of Testing	Non-bacterial
GLP	Ambiguous
Species/Strain	Mouse/L5178Y lymphoma cell
Metabolic Activation	S9 from liver of Aroclor-induced male Sprague-Dawley rat
Doses/Concentration	+ and -S9: 0, 12.5, 25, 50, 75, 100, 150, 200, and 300 ug/ml
Remarks for Test Conditions	Two trials (3 reps/concentration) were conducted for each: non-activated cultures and activated cultures. RPMI 1640 medium used for growth, expression and cloning. Ethanol used as vehicle control.
Results	<p>Test substance cytotoxic at 200 ug/ml and higher with or without S9.</p> <p>Without S9,</p> <p>Trial 1 at 0, 12.5, 25, 50, 100, and 150 ug/ml: 37, 36, 27, 38, 29, and 33 mutant cells/10E6 cells</p> <p>Trial 2 at 0, 25, 50, 75, 100, and 150 ug/ml: 27, 30, 24, 19, 28, and 29 mutant cells/10E6 cells</p> <p>With S9,</p> <p>Trial 1 at 0, 25, 50, 75, 100, 150, and 200 ug/ml: 35, 42, 43, 45, 33, 33, and 35 mutant cells/10E6 cells</p> <p>Trial 2 at 0, 25, 50, 75, 100, and 150 ug/ml: 48, 54, 58, 53, 64, and 37 mutant cells/10E6 cells</p>
Cytotoxic concentration	200 ug/ml
Genotoxic Effects	None
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol did not increase mutation frequency in mouse lymphoma cells.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.

Remarks for Data Reliability Code 1. Comparable to guideline study. Part of NTP study program.

References Myhr, B.C. and Caspary, W.J. (1991) Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: Results for 31 coded compounds in the National Toxicology Program. *Environ Mol Mutagen* 18:51-83.

Clive, D., Johnson, K.D., Spectory, J.F.S., Batson, A.G., Brown, M.M.M. (1979) Validation and characterization of the L5178Y TK-/- mouse lymphoma mutagen assay system. *Mutat Res* 59:61-108.

Mitchen, A.D., Myhr, B.C., Rudd, C.J., Caspary, W.J., Dunkel, V.C. (1988) Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Methods used and chemicals evaluated. *Environ Mol Mutagen* 12(Suppl 13):1-18.

Myhr, B.C., Caspary, W.J. (1988) Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Intralaboratory results for sixty-three coded chemicals tested at Litton Bionetics, Inc. *Environ Mol Mutagen* 12(Suppl13):103-194.

Substance Name	4- <i>tert</i> -Butylcyclohexyl acetate
CAS No.	32210-23-4
Method/guideline	Ames Test
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	No
Year	1975
Species/Strain	<i>Salmonella typhimurium</i> TA 1535, TA 1537, TA 1538, TA98, TA 100
Metabolic Activation	With and without
Doses/Concentration	8-5000 ug/plate
Remarks for Test Conditions	<ul style="list-style-type: none"> - Metabolic activation system: Arochlor induced rat liver S9 mix - Number of replicates: 2 Preincubation method - Application: 8 to 5000 microg/plate - Positive and negative control groups and treatment: positive controls: TA 98, TA 158: 2.5 ug Nitrofluorene/plate TA 100, TA 1535: 2.5 ug Sodium-azid/plate TA1537: 50 ug aminoacridine/plate Negative control: solvent: Dimethylsulfoxide
Results	Negative

Cytotoxic concentration	200 and 400 micrograms/plate
Genotoxic Effects	GENOTOXIC EFFECTS: - With metabolic activation: not genotoxic - Without metabolic activation: not genotoxic
Remarks for Results	Toxic effects were observed at concentrations 200 ug/plate or higher.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Degussa AG (1989) Unpublished report. Report No, 89-350-DKM.

4.2.2 *In vivo* Genotoxicity

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Chromosomal aberration
Test Type	Cytogenetic assay-Acute study
GLP	No
Year	1975
Species/Strain	Rat/Albino
Sex	Male
Route of Administration	Oral-Gavage
Doses/Concentration	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 500 or 3000 mg/kg bw
Exposure Period	6, 24 or 48 hours
Remarks for Test Conditions	Groups of rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 3000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) and groups of rats were killed at 6, 24 and 48 hours. 4 hours after administration and 2 hours prior to termination, rats were intraperitoneally injected with 4 mg colcemid/kg bw. Bone

marrow was removed and slides were prepared and analyzed.

Genotoxic effects	None
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol did not induce chromosomal aberrations.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Chromosomal aberration
Test Type	Cytogenetic assay-Subacute study
GLP	No
Year	1975
Species/Strain	Rat/Albino
Sex	Male
Route of Administration	Oral-Gavage
Doses/Concentration	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 1150 mg/kg bw
Exposure Period	Five doses 24 hours apart
Remarks for Test Conditions	Groups of rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 1150 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) for 5 consecutive doses, 24 hours apart and were killed 6 hours after last dose. 4 hours after administration and 2 hours prior to termination, rats were intraperitoneally injected with 4 mg colcemid/kg bw. Bone marrow was removed and slides were prepared and analyzed.
Genotoxic effects	None
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol did not induce chromosomal aberrations.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-

444 (FDA 71-268).

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Micronucleus test
GLP	Ambiguous
Year	1993
Species/Strain	Mouse/B6C3F1
Sex	Male
Route of Administration	Intraperitoneal
Doses/Concentration	0, 250, 500, and 1,000 mg/kg bw
Exposure Period	3 daily exposures
Remarks for Test Conditions	Groups of 5-6 mice were intraperitoneally injected on 3 consecutive days with 1X, 0.5X and 0.25X of the test chemical. A positive control and solvent control were also used. 24 hours after the last treatment, mice were killed, bone marrow removed and slides were prepared. For each mouse, the number of MN-PCE in 2,000 PCE and the percent PCE in 200 erythrocytes were determined.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	0 mg/kg bw: survival=5/5 mice; MN-PCE/1000=2.90; %PCE=54.4 250 mg/kg bw: survival=5/5 mice; MN-PCE/1000=3.60; %PCE=64.2 500 mg/kg bw: survival=5/5 mice; MN-PCE/1000=2.20; %PCE=56.7 1000 mg/kg bw: survival=3/6 mice; MN-PCE/1000=3.67; %PCE=51.8
Genotoxic effects	None
Appropriate statistical evaluations	Yes
Conclusion Remarks	2-Isopropyl-5-methylcyclohexanol was negative in the micronucleus test.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions. Part of NTP study program.
References	Shelby, M.D., Erexson, G.L., Hook, G.J., and Tice, R.R. (1993) Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. Environ Mol

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Host-mediated-Acute study
GLP	No
Year	1975
Species/Strain	Mouse/ICR
Sex	Male
Route of Administration	Oral-Gavage
Doses/Concentration	Test 1: 1.45, 14.5 and 145 mg/kg bw; Test 2: 500 and 5000 mg/kg bw
Exposure Period	Single exposure
Remarks for Test Conditions	Indicator organisms were <i>Salmonella typhimurium</i> strains G46 and TA1530, and <i>Saccharomyces cerevisiae</i> D3. Groups of mice were given 1.45, 14.5 and 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 5000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) by gavage followed by intraperitoneal injection of 2 ml indicator organism. Three hours later, mice were killed and intraperitoneally injected with 2 ml of sterile saline. As much fluid as possible was removed from the peritoneal cavity and dilutions were made from each exudate. Dilutions were plated and incubated for 18-40 hours. Further dilutions were made, plated and incubated at 30 °C for 40 hours after which bacterial scoring was conducted for calculation of mutation frequency and recombinant frequency.
Genotoxic effects	Only at 5000 mg/kg bw in <i>Salmonella</i> TA1530.
Remarks for Results	In vitro tests using same organisms were all negative.
Conclusion Remarks	No significant increase in mutant and recombinant frequency at any dose in <i>Salmonella</i> G46 and <i>Saccharomyces</i> D3. At the highest dose tested in <i>Salmonella</i> TA1530 a significant increase in mutant frequency was reported.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Host-mediated-Subacute study
GLP	No
Year	1975
Species/Strain	Mouse/ICR
Sex	Male
Route of Administration	Oral-Gavage
Doses/Concentration	Test 1: 1.45, 14.5 and 145 mg/kg bw; Test 2:1150 mg/kg bw
Exposure Period	Five doses 24 hours apart
Remarks for Test Conditions	Indicator organisms were <i>Salmonella typhimurium</i> strains G46 and TA1530, and <i>Saccharomyces cerevisiae</i> D3. Groups of mice were given 1.45, 14.5 and 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 1150 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) by gavage for 5 consecutive doses, 24 hours apart. Thirty minutes after the last dose, mice were given an intraperitoneal injection of 2 ml indicator organism. Three hours later, mice were killed and intraperitoneally injected with 2 ml of sterile saline. As much fluid as possible was removed from the peritoneal cavity and dilutions were made from each exudate. Dilutions were plated and incubated for 18-40 hours. Further dilutions were made, plated and incubated at 30 °C for 40 hours after which bacterial scoring was conducted for calculation of mutation frequency and recombinant frequency.
Genotoxic effects	Elevated recombinant frequency in <i>Saccharomyces</i> D3
Conclusion Remarks	No significant increase in mutant and recombinant frequency at any dose in <i>Salmonella</i> G46 and TA1530, but in <i>Saccharomyces</i> D3 an elevation of recombinant frequency was reported. In vitro tests using same organisms were all negative.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).
Substance Name	4- <i>tert</i> -Butylcyclohexanol

CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Dominant lethal assay-Acute study
GLP	No
Year	1975
Species/Strain	Rat/Random bred
Sex	Male
Route of Administration	Oral-Gavage
Doses/Concentration	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 500 or 3000 mg/kg bw
Exposure Period	Single dose
Remarks for Results	Groups of male rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 3000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2). Male rats were mated with 2 female rats per week for 8 weeks. Fourteen (14) days after mating, females were killed and the uterus was examined for early deaths, late fetal deaths and total implantations.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

4.3 Repeated Dose Toxicity

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Method/guideline	OECD Guideline 407
GLP	Yes
Year	1998

Species/strain	Rat/Wistar
Sex	Male and Female
Route of Administration	Oral-Gavage
Doses/concentration Levels	50, 150, 300 mg/kg bw/day
Exposure Period	28 days
Frequency of Treatment	Once daily
Control Group	Yes, concurrent vehicle
Post exposure observation period	14 days
Remarks for Test Conditions	<p>TEST ORGANISMS</p> <ul style="list-style-type: none"> - Age: 6 to 8 weeks - Weight at study initiation: 183-188.9 g variation less than 20% - Number of animals: 30 male, 30 female <p>ADMINISTRATION / EXPOSURE</p> <ul style="list-style-type: none"> - Duration of test/exposure: 28 day - Type of exposure: gavage - Post exposure period: 14 days - Vehicle: corn oil - Concentration in vehicle: 10, 30, 60 mg/ml - Total volume applied: 5 ml/kg - Doses: 50, 150, 300 mg/kg per day <p>CLINICAL OBSERVATIONS AND FREQUENCY:</p> <ul style="list-style-type: none"> - Clinical signs: general health: twice daily, general clinical observations: once daily. <p>A detailed FOB in home, cage and open field was conducted once per week. During the final week of the dosing period all animals were subject to an extended FOB, extended open field observation test, sensory reactivity to different stimuli, motor activity assessment, landing foot splay, grip strength, rearing behaviour.</p> <ul style="list-style-type: none"> - Body weight: At allocation of the groups, prior to first dose, weekly. - Food consumption: weekly - Water consumption: daily - Haematology, at the end of the treatment period/recovery period: <p>RBC, WBC, Platelet count, Haemoglobin, Hematocrit, MCV, Mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration. Differential WBC, coagulation.</p> <ul style="list-style-type: none"> - Biochemistry: at the end of the treatment period/recovery

period: sodium, potassium, calcium, AST, ALT, AP, Glucose, Triglycerides, cholesterol, total bilirubin, BUN, Creatinine, total protein, albumin.

- Urinalysis: after 6 hours in metabolic cages before termination, Volume, pH, specific gravity, colour, protein, glucose, ketones, urobilinogen, blood, sediment analysis for leukocytes, erythrocytes, bacteria, epithelial cells squamous and renal, oxalate crystals, triple phosphate crystals, carbonate, granular cylinder, urate crystals.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):

- Macroscopic:

Organ weights of following organs were determined: liver, kidney, adrenals, spleen, heart, thymus, brain, male gonads and epididymis.

- Microscopic:

The following organs and all gross lesions were preserved in formalin for all dose groups. In high dose and controls all organs were examined histopathologically and selected organs of the other dose groups were also examined.

Organs: Adrenals, aorta, anus, brain, all parts of the intestinal tract, epididymides, eyes, exorbital lacrimal glands, heart, kidneys, larynx, liver, lungs, lymph nodes (skin, cervical, mesenteric), mammary gland, muscle, ovaries, oesophagus, pancreas, pituitary, prostate, salivary glands, sciatic nerve, seminal vesicles, skin, spinal cord, spleen, stomach, sternum, testes, thymus, thyroid, parathyroid, Tongue, Trachea, urinary bladder, uterus, vagina.

STATISTICAL METHODS:

For FOB: Kruskal Wallis non parametric analysis of variance, in case of significance: pairwise comparison with Wilcoxon, Mann, Whitney U-Test.

Other data: ANOVA or Kruskal Wallis test if heterogenous

NOAEL(NOEL)

50 mg/kg bw

LOAEL(LOEL)

150 mg/kg/bw

Toxic Response/effects by Dose Level

Mortality: 2 animals of the high-dose group died due to an application failure and were replaced by two recovery animals. Clinical symptoms: 15 min after test substance administration high and medium dose group: convulsions, squatting position, straub tail (one female animal of the high-dose group) and vocalization. Some animals were walking on tiptoes. The symptoms disappeared within a few hours to 1 day. No clinical abnormalities were observed in the controls and recovery animals. FOB: After the first and second day of the treatment period no abnormalities were observed. After 2, 3 and 4 weeks of treatment clinical symptoms were observed in individual animals predominantly in the high-dose group. The effects included ataxia, fasciculations, padding movements, defense against touching, aggressiveness, hunchback/squatting

position, reduced respiration, hyperactivity, straub tail, slight convulsions. In the recovery period (week 5 and 6) no significant treatment-related clinical signs were observed in all dose groups. Extended FOB week 4: Reactivity to standard stimuli was normal in the control, low and medium dose animals. Individual animals of the high-dose group showed minimal to high sensitivity of pain. One male showed catalepsy. Rearing, landing foot splay and grip strength was normal in the control, low, medium and high-dose groups and in the recovery group females. High-dose male recovery group animals showed a statistically significant increase of group mean values of landing-foot-splay and rearing and a decrease of group mean values of grip strength compared to recovery controls, but these differences were minor and did not show a consistent pattern in the individual animals. The effects were also not seen in the high-dose group males that were not allocated to the recovery group at the same examination time. Therefore the findings were considered of minor toxicological importance. No statistically significant increase in motor activity was observed in all dose groups comparing group mean values to that of controls. A statistically non-significant increase was observed in high-dose animals, in particular females. Body weights: A slight decrease in body weight and body weight changes was observed in the high-dose males (statistically significant only for high-dose recovery group males in week 4. The females of the high-dose recovery group showed an increase of group mean body weight change at the beginning of the study. In the recovery period no statistically significant differences in body weights and body weight gains were observed. Food intake: A slight reduction was seen in treated males and an increase in treated females when compared to controls. During the recovery period the food consumption of the treated animals was increased compared to controls. Water consumption was not different between treated and control groups. Alterations in clinical chemistry, urinalysis and hematology parameters were minor and within the normal range of the historical data. All differences observed were considered of minor toxicological importance. Organ weights: At the end of the treatment period male high-dose group animals showed a statistically significant increase in relative adrenal weight when compared with controls. At the end of the recovery period the treated males revealed a statistically significant increase in relative epididymis weight compared to the controls. Histopathology: Treatment-related findings were restricted to an increased number of male animals of the high-dose group with eosinophilic hyaline droplets in the epithelial cell cytoplasm of the proximal tubules (5 treated compared to 1 control). This could be indicative of the alpha-2 microglobulin nephropathy syndrome in male rats that is a rat-specific effect. The deaths were not treatment related.

Remarks for Results

Based on the clinical signs a NOAEL of 50 mg/kg bw and a LOAEL of 150 mg/kg bw were derived. *Alpha-2*-microglobulin effects in males were reported at the highest dose levels.

Conclusion Remarks

The main effects of the test substance are clinical signs of neurotoxicity ant the high and mid dose. No histopathological changes that are considered relevant for humans were

observed.

Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Degussa AG (1999) Unpublished report. Report No. 98-0184-DGT.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data for mixture of structurally related alkyl-substituted cyclohexanols and cyclohexanones: 1) 46.8% (1a, 2beta, 5a)-2-isopropyl-5-methylcyclohexanol 2) 3.97% (1a, 2a, 5a)-2-isopropyl-5-methylcyclohexanol 3) 0.86% (1 beta, 2beta, 5a)-2-isopropyl-5-methylcyclohexanol 4) 21.81% (2beta, 5a)-2-isopropyl-5-methylcyclohexanone 5) 3.07% (2beta, 5beta)-2-isopropyl-5-methylcyclohexanone 6) 5.11% (1a, 2beta, 5a)-2-isopropyl-5-methylcyclohexyl acetate 7) 1.55% (1beta, 2beta, 5 beta)-2-isopropyl-5-methylcyclohexyl acetate. The other constituents accounting for approximately 10% of the oil include aliphatic terpene hydrocarbons (<i>e.g.</i> , <i>alpha</i> -pinene) and ethers (eucalyptol) (Vollmuth, 1989).
Method/guideline	28-Day Oral Toxicity Study
GLP	Yes
Year	1990
Species/strain	Rat/Sprague Dawley
Sex	Male and Female
Route of Administration	Oral Gavage
Doses/concentration Levels	0, 100, 200, or 400 mg/kg bw
Exposure Period	29 or 30
Frequency of Treatment	Once daily
Control Group	Yes, vehicle only
Remarks for Test Conditions	Groups (10/sex/group) of male and female Sprague-Dawley rats were given daily dose levels of 0, 100, 200, or 400 mg/kg bw of a mixture of alkyl-substituted cyclohexanol by gavage in corn oil (10 ml/kg) daily for 29 or 30 days. Clinical signs were monitored twice weekly and body weights and food consumption were measured weekly. At the initiation of the study, 10 animals were randomly selected from the pool of

animals not selected from the study. They were fasted overnight and blood samples were drawn and analyzed for baseline clinical chemistry and hematology parameters. Prior to termination, animals were injected with ketamine and blood samples were drawn for clinical chemistry and hematology. At necropsy, organ weights (brain, spleen, liver, heart, kidneys, testes with epididymides, adrenals, ovaries, and pituitary) were measured, and tissues (26) were preserved in 10% formalin. All tissues from the control and high-dose groups and tissues from the heart, liver, kidneys, and gross lesions from the low- and mid-dose group were embedded in paraffin, stained with hematoxylin and eosin, and examined microscopically.

NOAEL(NOEL)	Less than 100 mg/kg bw per day for males and 400 mg/kg bw per day for females
LOAEL(LOEL)	100 mg/kg bw per day (based on appearance of alpha-2-microglobulin effect in males)
Actual dose received by dose level and sex	0, 100, 200, or 400 mg/kg bw
Toxic Response/effects by Dose Level	All animals survived to study termination with high dose males showing increased incidence of urine staining during clinical observations. Except for a non-statistically significant decrease in mean body weight in high-dose males, there were no statistically significant differences in body weight or food consumption between treated and control groups. A significant decrease in serum glucose levels was reported in the mid- and high-dose males that the authors, in part, attribute to change in nutritional status as revealed by a decreased body weights in the high-dose group. A treatment-related increase in alkaline phosphatase was reported in high-dose males.
	Measurement of body weight, food consumption, hematology and clinical chemistry parameters revealed no significant changes between test and control female rats. There were statistically significant increases in relative kidney weights in high-dose males. Histopathological findings revealed renal tubule protein droplets in all groups of treated male rats. The authors considered these findings related to the lysosomal handling of alpha-2-micro-globulin, a protein specific to the male Sprague-Dawley rat. Absolute and relative liver weights in high-dose females also were significantly increased but these changes were not confirmed by histopathological examination.
Appropriate statistical evaluations?	Dunnett's Control versus Treatment Comparison.
Remarks for Results	Based exclusively on the renal pathology (<i>alpha-2-microglobulin</i> effect) reported in all dosed groups of male rats, the authors concluded that the no observable adverse effect level (NOAEL) for the mixture is less than 100 mg/kg bw per day in male rats and 400 mg/kg bw per day in female rats
Conclusion Remarks	The NOAEL is less than 100 mg/kg bw in male Sprague-Dawley rats and 400 mg/kg bw per day for female rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability Code 2. Comparable to guideline study with acceptable restrictions.

References Serota D. G. (1990) 28-Day oral toxicity study in rats: B100. HLA Study No. 642-477. Private Communication to FEMA. Unpublished Report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	90-Day Toxicity Study
GLP	Yes
Year	1979
Species/strain	Mousr/B6C3F1
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	0, 930, 1870, 3750, 7500, or 15000 ppm (~0, 140, 281, 563, 1125 or 2250 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw/day)
Exposure Period	13 weeks
Frequency of Treatment	Daily
Control Group	Basal diet with 2% corn oil
Remarks for Test Conditions	Groups of 10 male and 10 female B6C3F1 mice were maintained on diets containing dl-2-isopropyl-5-methylcyclohexanol at dietary concentrations of 0, 930, 1870, 3750, 7500, or 15000 ppm for 13 weeks. Dietary concentrations were calculated to provide average daily intake levels of 0, 140, 281, 563, 1125 or 2250 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw, respectively. Necropsies were performed on all animals at the end of the study. Histopathological examination was performed on tissues from the control animals, the 2250 mg/kg bw/day group, and selected tissues from the 1125 mg/kg bw/day group.
NOAEL(NOEL)	1125 mg/kg bw/day
LOAEL(LOEL)	563 mg/kg bw/day
Toxic Response/effects by Dose Level	Six mice (sex not specified) died during the study but the deaths could not be attributed to compound administration. Final mean body weights of the male mice and female mice were not statistically different from those of the controls except for the high-dose female group which showed statistically significant decreased body weights. A slight increase in the incidence of perivascular lymphoid hyperplasia and interstitial nephritis was

reported in the female mice given the two highest dose levels. No adverse effects were reported for male or female mice administered 140, 281 or 563 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw/day.

Data Qualities Reliabilities Reliability code 1. Reliable without restriction.

Remarks for Data Reliability Code 1. Comparable to guideline study.

References National Cancer Institute, NCI (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	90-Day Toxicity Study
GLP	No
Year	1979
Species/strain	Rat/F344
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	0, 930, 1870, 3750, 7500, or 15000 ppm (~0, 93, 187, 375, 750 or 1500 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw/day)
Exposure Period	13 weeks
Frequency of Treatment	Daily
Control Group	Basal diet with 2% corn oil
Remarks for Test Conditions	Groups of 10 female and 10 male Fischer 344 rats per group were maintained on diets containing dl-menthol at concentrations of 0, 930, 1870, 3750, 7500, or 15000 ppm for 13 weeks. Dietary concentrations were calculated to provide corresponding average daily intake levels of 0, 93, 187, 375, 750 or 1500 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw, respectively. Necropsies were performed on all animals at the end of the study. Histopathological examination was performed on tissues from the control animals, the highest dose group, and selected tissues from the second highest dose group.
NOAEL(NOEL)	750 mg/kg bw/day
LOAEL(LOEL)	1500 mg/kg bw/day
Toxic Response/effects by Dose Level	Final mean body weights of the male and female rats at all dose levels were similar to those of the controls. A slight increase in the incidence of interstitial nephritis was observed in high-dose

male rats. No adverse effects were reported for male or female rats administered 93, 187, 375, or 750 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw/day.

Data Qualities Reliabilities Reliability code 1. Reliable without restriction.

Remarks for Data Reliability Code 1. Comparable to guideline study.

References National Cancer Institute, NCI (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Carcinogenicity Study
GLP	No
Year	1979
Species/strain	Rat/F344
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	0, 3750, or 7500 ppm (approximately 0, 187 or 375 mg/kg bw, respectively)
Exposure Period	103 weeks
Frequency of Treatment	Daily
Control Group	Basal diet with 2% corn oil
Post exposure observation period	2 weeks
Remarks for Test Conditions	Groups of 50 Fischer 344 rats of each sex were administered 0, 3750 or 7500 ppm dl-2-isopropyl-5-methylcyclohexanol in their feed daily for 103 weeks. Dietary concentrations were calculated to provide corresponding average daily intake levels of approximately 0, 187 or 375 mg/kg bw, respectively. Animals were housed five per cage until week 48 when the male rats were divided into groups of two to three per cage. The animals were observed twice daily for signs of toxicity. Body weight and food consumption were recorded every two weeks for the first twelve weeks, and once a month thereafter. Necropsies and histological examinations were performed on all animals at the termination of the study and on those found dead during the study.
NOAEL(NOEL)	375 mg/kg bw/day

Toxic Response/effects by Dose Level

The mean body weights of the male and female rats administered 187 or 375 mg/kg dl-menthol were slightly lower when compared to the controls. Survival of the high- and low-dose groups of male (controls, 31/50; low-dose, 33/50; high-dose, 34/50) and female (controls, 36/50; low-dose, 35/50; high-dose, 38/50) rats was similar to the control animals. Chronic inflammation of the kidney observed in the dosed older males was not considered by the authors to be related to the administration of dl-2-isopropyl-5-methylcyclohexanol since the effect is commonly observed in aged male Fischer 344 rats. There was no increase in the incidence of neoplasms of dosed females compared to that of control animals. In the low-dose (10/49) and high-dose (7/49) female groups, fibroadenomas of the mammary glands occurred at a lower incidence than in the control group (20/50). Alveolar/bronchiolar adenomas or carcinomas were reported only for the female control rats. Under the conditions of this study, it was concluded that dl-2-isopropyl-5-methylcyclohexanol was neither carcinogenic nor toxic for either sex of Fischer 344 rats at dose levels of 187 or 375 mg dl-2-isopropyl-5-methylcyclohexanol /kg bw.

Appropriate statistical evaluations?

Yes

Data Qualities Reliabilities

Reliability code 1. Reliable without restriction.

Remarks for Data Reliability

Code 1. Comparable to guideline study.

References

National Cancer Institute, NCI (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Test Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Method/guideline	Carcinogenicity Study
GLP	No
Year	1979
Species/strain	Mouse/B6C3F1
Sex	Male and Female
Route of Administration	Oral-Diet
Doses/concentration Levels	0, 2,000 or 4,000 ppm (approximately 0, 300 or 600 mg/kg bw, respectively)
Exposure Period	103 weeks
Frequency of Treatment	Daily

Control Group	Basal diet with 2% corn oil
Post exposure observation period	1 week
Remarks for Test Conditions	A carcinogenicity study was conducted in which groups of 50 B6C3F1 mice of each sex were administered 0, 2,000 or 4,000 ppm dl-2-isopropyl-5-methylcyclohexanol in their feed daily for 103 weeks. Dietary concentrations were calculated to provide corresponding average daily intake levels of 0, 300 or 600 mg/kg bw, respectively. Animals were housed five per cage and were observed twice daily for signs of toxicity. Body weights and food consumption were recorded every two weeks for the first twelve weeks, and once a month thereafter. Necropsies and histological examinations were performed on all animals at the termination of the study and on those found dead during the study.
NOAEL(NOEL)	300 mg/kg bw/day
LOAEL(LOEL)	600 mg/kg bw/day
Toxic Response/effects by Dose Level	The mean body weights of the male and female mice administered 300 or 600 mg dl-2-isopropyl-5-methylcyclohexanol/kg bw were slightly lower when compared to the controls. Survival of the high- and low-dose groups of male mice was similar to the vehicle control animals (controls, 32/50; low-dose, 32/50; high-dose, 35/50). Survival of the high-dose group of female mice was significantly less than that of the control animals (controls, 36/50; high-dose, 45/50). However, decreased survival was not accompanied by any evidence of toxicity in the high-dose group. Survival of the low-dose female mice was similar to the control animals (controls, 36/50; low-dose, 40/50). An increase in the incidence of hepatocellular carcinomas was observed in high-dose male mice (controls, 8/47; low-dose, 8/49; high-dose, 14/48), but was not statistically different from that observed historically in mice of that age and strain [Haseman <i>et al.</i> , 1986]. A low incidence of alveolar/bronchiolar adenomas of the lung was observed in both the low- and high-dose females but was not statistically different from the incidence of this neoplasm in historical control groups. Under the conditions of this study, it was concluded that dl-2-isopropyl-5-methylcyclohexanol was not carcinogenic and did not produce any organ-specific toxicity for either sex of B6C3F1 mice at dose levels of 300 or 600 mg/kg bw.
Appropriate statistical evaluations?	Yes
Remarks for results	NOAEL based on decreased survival in female mice.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	National Cancer Institute, NCI (1979) Bioassay of dl-menthol for possible carcinogenicity. U.S. Department of Health, Education and Welfare. National Technical Report Series No. 98.

Haseman J.K., Winbush J.S. and O'Donnell M.W. (1986) Use of dual control groups to estimate false positive rates in laboratory animal carcinogenicity studies. *Fundamental and Applied Toxicology* 7, 573-584.

4.4 Reproductive Toxicity

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	<p>Data for mixture of structurally related alkyl-substituted cyclohexanols and cyclohexanones:</p> <ol style="list-style-type: none"> 1) 46.8% (1 <i>alpha</i>, 2 <i>beta</i>, 5 <i>alpha</i>)-2-isopropyl-5-methylcyclohexanol 2) 3.97% (1 <i>alpha</i>, 2 <i>alpha</i>, 5 <i>alpha</i>)-2-isopropyl-5-methylcyclohexanol 3) 0.86% (1 <i>beta</i>, 2 <i>beta</i>, 5 <i>alpha</i>)-2-isopropyl-5-methylcyclohexanol 4) 21.81% (2 <i>beta</i>, 5 <i>alpha</i>)-2-isopropyl-5-methylcyclohexanone 5) 3.07% (2 <i>beta</i>, 5 <i>beta</i>)-2-isopropyl-5-methylcyclohexanone 6) 5.11% (1 <i>alpha</i>, 2 <i>beta</i>, 5 <i>alpha</i>)-2-isopropyl-5-methylcyclohexyl acetate 7) 1.55% (1 <i>beta</i>, 2 <i>beta</i>, 5 <i>beta</i>)-2-isopropyl-5-methylcyclohexyl acetate. <p>The other constituents accounting for approximately 10% of the oil include aliphatic terpene hydrocarbons (e.g., <i>alpha</i>-pinene) and ethers (eucalyptol) (Vollmuth, 1989).</p>
Method/Guideline	<i>in vivo</i> Reproductive and Developmental Toxicity Screening Test
GLP	Yes
Year	1989
Species/Strain	Rat/Sprague Dawley
Sex	Female
Route of Administration	Oral-Gavage
Duration of Test	39 days
Doses/Concentration	0, 150, 750, or 1,500 mg/kg bw

Premating Exposure period for females	7 days
Control Group and Treatment	Yes, vehicle only (corn oil)
Frequency of Treatment	Daily
Remarks for Test Conditions	Groups of ten female rats were orally administered an oil containing a mixture of alkyl-substituted cyclohexanol derivatives via gavage at dose levels of 0, 150, 750 or 1500 mg/kg bw/d for seven days prior to and through cohabitation, gestation, delivery and a four day lactation period. The vehicle was corn oil. Body weights, food consumption and clinical signs were recorded throughout the observation period. All dams were necropsied and examined for gross lesions on Day 25 of presumed gestation for rats not delivering a litter and four days postpartum for rats delivering a litter. Pups delivered were sacrificed on day 4 post partum, any pups dying during the lactation period were necropsied.
NOAEL(NOEL)	150 mg/kg bw
Actual dose received by dose level and sex	0, 150, 750, or 1,500 mg/kg bw
Appropriate statistical evaluations	Yes
Parental data and F1 as Appropriate	<p>Deaths or moribund sacrifice were reported in 2/10 females at 750 mg/kg bw per day and 5/10 females at 1,500 mg/kg bw per day. Additional clinical observations included decreased motor activity, ataxia, dyspnea, rales, chromorrhinorrhea, un-groomed coat and thin appearance at the 750 and 1500mg/kg bw per day dose levels. Urine stained fur and excess salivation were observed at all dose levels. Significant ($P < \text{or} = 0.05$) decreases in body weight and food consumption were reported during the pre-mating period in the 750 and 1500 mg/kg bw per day groups compared to those for control group. A non-statistically significant decrease in maternal body weight gain was reported in the 750 mg/kg bw per day group compared to the control group. The single dam that delivered a litter in the high-dose group also showed less weight gain.</p> <p>Absolute and relative feed consumption were comparable between the low-, mid, and control groups.</p> <p>On day 1 of lactation, the average body weight of dams in the mid-dose group and the single dam in the high-dose group was significantly ($P < \text{or} = 0.01$) less than in the control group. During lactation, dams in the mid-dose group gained weight while the weight gain in the single dam in the high-dose group were comparable to that for the control group. Compared to control animals, feed consumption in the mid- and high-dose group decreased significantly ($P < \text{or} = 0.01$) during premating but was increased significantly ($P < \text{or} = 0.01$ to 0.05) during lactation. Of the rats surviving the cohabitation period 4 of 5 became pregnant at the highest dose level (1500 mg/kg bw per day).</p>

Live litters were reported for 9/19, 8/10, 5/6, and 1/4 pregnant females in the control, 150, 750, and 1500 mg/kg bw per day groups, respectively. Increased number of dams with stillborn pups, stillborn pups, and late resorptions in utero were reported in the 750 mg/kg bw per day group.

At 1500 mg/kg bw per day, 2 rats had only resorptions in utero when found dead on gestation day 23 and one rat possessed only empty implantation sites in utero on day 25 of presumed gestation.

Offspring toxicity F1 and F2

On day 1 postparturition, litters of dams in the 750 and 1500 mg/kg bw per day groups showed non-statistically significant decreases in pup weight which by day 4 were comparable to controls in the mid-dose group, but less than the control value in the high dose group. On day 4 postparturition, significant ($P < \text{or} = 0.01$) increases in pup mortality were reported in the mid- and high-dose groups compared to controls. However, even at the highest dose level, there was no evidence of an effect of the test article on implantation, duration of gestation, pup sex ratio, or gross morphology of pups.

Conclusion remarks

Authors concluded that the maternal NOAEL for reproductive effects was 150 mg/kg bw per day and the offspring NOAEL for developmental effects is higher than 150 mg/kg bw per day, but less than 750 mg/kg bw per day

Data Reliabilities Qualities

Reliability code 2. Reliable with restriction.

Remarks for Data Reliability

Code 2. Comparable to guideline study with acceptable restrictions.

References

Hoberman A. M. (1989) Reproductive and developmental toxicity screening of B100 administered orally *via* gavage to Crl:CD(SD)Br female rats. Argus Research Laboratories, Inc. Protocol 412-015. Private Communication to FEMA. Unpublished Report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Dominant lethal assay-Acute study
GLP	No
Year	1975
Species/Strain	Rat/Random bred
Sex	Male
Route of Administration	Oral-Gavage

Frequency of treatment	Single dose
Doses/Concentration	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 500 or 3000 mg/kg bw
Control Group and Treatment	Saline
Remarks for Test Conditions	Groups of male rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 500 or 3000 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2). Male rats were mated with 2 female rats per week for 8 weeks. 14 days after mating, females were killed and the uterus was examined for early deaths, late fetal deaths and total implantations.
Conclusion remarks	No effect on early deaths, late fetal deaths and total implantations was reported when 2-isopropyl-5-methylcyclohexanol was administered to male rats prior to mating.
Data Reliabilities Qualities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Dominant lethal assay- Subacute study
GLP	No
Year	1975
Species/Strain	Rat/Random bred
Sex	Male
Route of Administration	Oral-Gavage
Doses/Concentration	Test 1: 1.45, 14.5, or 145 mg/kg bw; test 2: 1150 mg/kg bw
Control Group and Treatment	Saline
Frequency of Treatment	Five doses 24 hours apart
Remarks for Test Conditions	Groups of rats were gavaged with 1.45, 14.5 or 145 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 1) or 1150 mg 2-isopropyl-5-methylcyclohexanol/kg bw (test 2) for 5 consecutive doses, 24 hours apart. After the last dose, male rats were mated with 2 female rats per week for 7 weeks. 14 days after mating, females were killed and the uterus was examined for

early deaths, late fetal deaths and total implantations.

Conclusion remarks	No effect on early deaths, late fetal deaths and total implantations was reported when 2-isopropyl-5-methylcyclohexanol was administered to male rats prior to mating.
Data Reliabilities Qualities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Food and Drug Administration (FDA) (1975) Mutagenic evaluation of compound FDA 71-57, menthol. NTIS PB-245-444 (FDA 71-268).

4.5 Developmental/Teratogenicity Toxicity

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Teratology study
GLP	Pre GLP
Year	1973
Species/strain	Mouse/CD-1 outbred
Sex	Female
Route of Administration	Gavage
Duration of Test	10 days
Doses/concentration Levels	0(negative control), 0, 1.85, 8.59, 39.9, 185 mg/kg bw/day and a positive control of 150 mg/kg bw/day of aspirin
Exposure Period	Days 6 to 15 of gestation
Frequency of Treatment	Daily
Control Group and Treatment	Control group received corn oil vehicle (10 ml/kg); Positive control received 150 mg/kg bw/day of aspirin in corn oil
Remarks for Test Conditions	Study measured parameters for reproductive and developmental toxicity. In the study, virgin adult female CD-1 outbred mice were gang-housed in plastic disposable cages in

a temperature- and humidity-controlled room. Animals were given free access to food and fresh tap water. There were mated with untreated young adult males and observation of vaginal sperm plugs was considered day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, groups (22-23/group) of pregnant females were given 0, 1.85, 8.59, 39.9, 185 mg/kg bw of the test material (FDA 71-57) by gavage in corn oil. A positive control group received 150-mg/kg bw/day of aspirin. Body weights were recorded on days 0, 6, 11, 15, and 17 of gestation. Females were observed daily for appearance and behavior. Food consumption and body weight were monitored to eliminate any abnormalities that may be associated with anorexia in pregnant females. On Day 17 all dams were subjected to Caesarian section and the number of implantation sites, number of resorptions, % of live and % partial live resorptions, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. One-third of fetuses of each litter underwent detailed visceral examination at 10x magnification. The remaining two-thirds were stained with alizarin red S dye/KOH and examined for skeletal defects.

NOAEL(NOEL) maternal toxicity	185 mg/kg bw/day
NOAEL (NOEL) developmental toxicity	185 mg/kg bw/day
Actual dose received by dose level and sex	0, 1.85, 8.59, 39.9, 185 mg/kg bw of the test material (FDA 71-57)
Maternal data with dose level	Daily clinical observation and measurement of body weight gain failed to show any differences between control and test groups of female mice. The number pregnant and % pregnancy were similar for all dose and control groups. No abortions were observed in any group. The number of live litters, average implant sites per dam were similar for both test and control groups. The % partial resorptions and % complete resorption were increased for the 1.85 and 8.59 mg/kg bw groups, but higher dose levels exhibited lower resorption rates compared to the control groups.
Fetal Data with Dose Level	The average fetal weight of treatment and control groups were not statistically different ($p>0.05$). The total number of live fetuses was similar for test and control groups. Also, there was no significant difference in the number of dead fetuses between test and control groups. Skeletal examination of sternbrae showed no significant differences in the incidence of incomplete ossification or missing sternbrae for test and negative control groups. There was evidence of incomplete ossification in the positive control group. Likewise the incidences of fetuses with more than 13 ribs, incomplete ossification of vertebrae and extremities, incomplete skull closure were similar for test and negative control animals. Visceral examination failed to reveal any evidence of soft tissue abnormalities at any dose level.

Conclusion remarks	There was no evidence of maternal toxicity or developmental toxicity at dose levels up to and including 185 mg/kg bw/day of test material.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Morgareidge K. (1973a) Teratologic evaluation of FDA 71-57 in mice. Contract No. FDA 71-260. Unpublished Report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Teratology study
GLP	Pre GLP
Year	1973
Species/strain	Rat/female Wistar
Sex	Female
Route of Administration	Gavage
Duration of Test	10 days
Doses/concentration Levels	0(control), 2.18, 10.15, 47.05, 218 mg/kg bw/day and a positive control of 250 mg/kg bw/day of aspirin
Exposure Period	Days 6 to 15 of gestation
Frequency of Treatment	Daily
Control Group and Treatment	Control group received corn oil vehicle (10 ml/kg); Positive control received 250 mg/kg bw/day of aspirin in corn oil
Remarks for Test Conditions	Study measured parameters for reproductive and developmental toxicity. In the study, virgin adult female rats were individually housed in mesh bottom cages in a temperature- and humidity-controlled room. Animals were given free access to food and fresh tap water. They were mated with untreated young adult males and observation of vaginal sperm plugs was considered day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, groups (22-25/group) of pregnant females were given 0, 2.18, 10.15, 47.05, 218 mg/kg bw of the test material (FDA 71-57) by gavage in corn oil. A positive control group received 250 mg/kg bw/day of aspirin. Body weights were recorded on days 0, 6, 11, 15, and 20 of gestation. Females were observed daily for appearance and behavior. Food consumption and body weight were monitored to eliminate any abnormalities that may be associated with anorexia in pregnant females. On Day 20 all

dams were subjected to Caesarian section and the number of implantation sites, number of resorptions, % of live and % partial live resorptions, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. One-third of fetuses of each litter underwent detailed visceral examination at 10x magnification. The remaining two-thirds were stained with alizarin red S dye/KOH and examined for skeletal defects.

NOAEL(NOEL) maternal toxicity	218 mg/kg bw/day
NOAEL (NOEL) developmental toxicity	218 mg/kg bw/day
Actual dose received by dose level and sex	0, 2.18, 10.15, 47.05, 218 mg/kg bw of the test material (FDA 71-57)
Maternal data with dose level	Daily clinical observation and measurement of body weight gain failed to show any differences between control and test groups of female rats. The number pregnant and % pregnancy were similar for all dose and control groups. No abortions were observed in any group. The number of live litters, average implant sites per dam were similar for both test and control groups. The % partial resorptions and % complete resorption were increased only for the positive control group.
Fetal Data with Dose Level	The average fetal weight of treatment and control groups were not statistically different ($p>0.05$). The total number of live fetuses was similar for test and negative control groups. Also, there were no dead fetuses in either the test or negative control groups. The positive control group did show dead fetuses (3) and dams with more than one dead fetus. The positive control group also exhibited a decreased number of live fetuses and decreased average fetal weight compared to those for the negative control. Skeletal examination of sternbrae, vertebrae, skull, ribs, extremities, and soft tissues showed no significant differences between test and negative control groups. The positive control group showed a significant increase in incidence of missing sternbrae. Likewise, the positive control exhibited an increase in the incidence of fetuses with more than 13 ribs, incomplete ossification of vertebrae and extremities, incomplete skull closure. Visceral examination failed to reveal any evidence of abnormalities in either negative control or test groups. In the positive control group, meningoencephalocele and spina bifida were reported.
Conclusion remarks	There was no evidence of maternal toxicity or developmental toxicity at dose levels up to and including 218 mg/kg bw/day of test material.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Morgareidge K. (1973b) Teratologic evaluation of FDA 71-57 in rats. Contract No. FDA 71-260. Unpublished Report.

rats. Contract No. FDA 71-260. Unpublished Report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Teratology study
GLP	Pre GLP
Year	1973
Species/strain	Hamster/female golden
Sex	Female
Route of Administration	Gavage
Duration of Test	5 days
Doses/concentration Levels	0(control), 4.05, 21.15, 98.2, or 405 mg/kg bw/day and a positive control of 250 mg/kg bw/day of aspirin
Exposure Period	Days 6 to 10 of gestation
Frequency of Treatment	Daily
Control Group and Treatment	Control group received corn oil vehicle (10 ml/kg); Positive control received 250 mg/kg bw/day of aspirin in corn oil
Remarks for Test Conditions	Study measured parameters for reproductive and developmental toxicity. In the study, virgin adult female hamsters were individually housed in mesh bottom cages in a temperature- and humidity-controlled room. Animals were given free access to food and fresh tap water. They were mated one to one with untreated young adult males and the appearance of motile sperm in the vaginal smear was considered day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, groups (19-23/group) of pregnant females were given 0, 4.05, 21.15, 98.2, or 405 mg/kg bw of the test material (FDA 71-57) by gavage in corn oil. A positive control group received 250 mg/kg bw/day of aspirin. Body weights were recorded on days 0, 8, 10, and 14 of gestation. Females were observed daily for appearance and behavior. Food consumption and body weight were monitored to eliminate any abnormalities that may be associated with anorexia in pregnant females. On Day 14 all dams were subjected to Caesarian section and the number of implantation sites, resorption sites, % of live and % partial live resorptions, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. One-third of fetuses of each litter underwent detailed visceral examination at 10x magnification. The

	remaining two-thirds were stained with alizarin red S dye/KOH and examined for skeletal defects.
NOAEL(NOEL) maternal toxicity	405 mg/kg bw/day
NOAEL (NOEL) developmental toxicity	405 mg/kg bw/day
Actual dose received by dose level and sex	0, 4.05, 21.15, 98.2, or 405 mg/kg bw of the test material (FDA 71-57)
Maternal data with dose level	Daily clinical observation and measurement of body weight gain failed to show any differences between control and test groups of female rats. The number pregnant and % pregnancy were similar for all dose and control groups. No abortions were observed in any group.
Fetal Data with Dose Level	The average fetal weight of treatment and control groups were not statistically different ($p>0.05$). The total number of live fetuses was similar for test and control groups. There was one dead fetus in the negative control and the 4.05 and 21.15 dose groups, but none in the higher dose groups. There were 18 dead fetuses in the positive control group. Skeletal examination of sternbrae showed no significant differences in the incidence of incomplete ossification or missing sternbrae for test and control groups. Likewise the incidences of fetuses with more than 13 ribs, incomplete ossification of vertebrae and extremities, incomplete skull closure were similar for test and control animals. An increased incidence of incomplete ossification of the vertebrae was reported in the two mid-dose groups but not in the highest (405 mg/kg bw) group. Visceral examination of tissues failed to reveal any evidence of significant abnormalities at any dose level.
Conclusion remarks	There was no evidence of maternal toxicity or developmental toxicity at dose levels up to and including 405 mg/kg bw/day of test material.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Morgareidge K. (1973c) Teratologic evaluation of FDA 71-57 in hamsters. Contract No. FDA 71-260. Unpublished report.

Substance Name	4- <i>tert</i> -Butylcyclohexanol
CAS No.	98-52-2
Remarks for Substance	Data are for isomeric alcohol 2-Isopropyl-5-methylcyclohexanol (dl-menthol)
Test Type	Teratology study
GLP	Pre GLP
Year	1973

Species/strain	Rabbit/virgin, adult, Dutch belted
Sex	Female
Route of Administration	Gavage
Duration of Test	13 days
Doses/concentration Levels	0(control), 4.25, 19.75, 91.7, 425 mg/kg bw/day and a positive control of 250 mg/kg bw/day of aspirin
Exposure Period	Days 6 to 18 of gestation
Frequency of Treatment	Daily
Control Group and Treatment	Control group received corn oil vehicle (10 ml/kg); Positive control received 2.5 mg/kg bw/day of 6-aminonicitineamide in corn oil on Day 9
Remarks for Test Conditions	<p>Study measured parameters for reproductive and developmental toxicity. In the study, virgin adult female rabbits were individually housed in mesh bottom cages in a temperature- and humidity-controlled room. Animals were given free access to food and fresh tap water. On day 0, does were given an injection of 0.4 l of human chorionic gonadotropin (400 IU). Three hours later, each doe was artificially inseminated with 0.3 ml of semen from a buck using approximately 20×10^6 motile sperm. Beginning on Day 6 and continuing daily through Day 18 of gestation, groups (11-14/group) pregnant females were given 0, 4.25, 19.75, 91.7, 425 mg/kg bw of the test material (FDA 71-57) by gavage in corn oil. A positive control group received 2.5 mg/kg bw/day of 6-aminonicotinamide. Body weights were recorded on days 0, 6, 8, 12, 18, and 29 of gestation. Females were observed daily for appearance and behavior. Food consumption and body weight were monitored to eliminate any abnormalities that may be associated with anorexia in pregnant females. On Day 29 all dams were subjected to Caesarian section and the number of corpora lutea, implantation sites, resorption sites, live fetuses, dead fetuses, and body weight of live pups were recorded. Gestation index, mortality, litter size and weights, sex and sex ratio of pups, and gross abnormalities to pups were reported. The urogenital tract of each dam was examined for anatomical abnormalities. All live fetuses were placed in an incubator for 24 hours and evaluated for survival. All surviving pups were sacrificed and subjected to detailed visceral examination at 10x magnification. All fetuses were cleared with KOH, stained with alizarin red S dye, and examined for skeletal defects.</p>
NOAEL(NOEL) maternal toxicity	425 mg/kg bw/day
NOAEL (NOEL) developmental toxicity	425 mg/kg bw/day
Actual dose received by dose level and sex	0, 4.25, 19.75, 91.7, 425 mg/kg bw of the test material (FDA 71-57)
Maternal data with dose level	Survival of dams at term was similar for test, positive, and negative control groups. Daily clinical observation and measurement of body weight gain failed to show any

differences between control and test groups of female rabbits. The number pregnant and % pregnancy were similar for all dose and control groups. One to four pregnant female died in both control groups and in the four test groups. There was no dose response relationship for mortality in the test groups. There was no statistical difference in the number of live litters, corpora lutea, implantation sites, or resorption sites between the negative control group and any test group.

Fetal Data with Dose Level

The average fetal weight of treatment and control groups were not statistically different ($p>0.05$). The total number of live fetuses was similar for test and control groups. Also, there was no significant difference in the number of dead fetuses between test and control groups. Except for positive control group, skeletal examination of sternbrae and vertebrae showed no significant differences in the incidence of incomplete ossification or missing sternbrae for test and untreated control group. Likewise the incidences of fetuses with more than 13 ribs, incomplete ossification of vertebrae and extremities, incomplete skull closure were similar for test and the untreated control group. The positive 6-aminonicotinamide-treated control group showed increases in incidence of fused and split ribs. Visceral examination failed to reveal any evidence of abnormalities in either negative control or test groups. In the positive control group, medial rotation of the hind limb and anopia were reported in pups from 7 of the 11 litters.

Conclusion remarks

There was no evidence of maternal toxicity or developmental toxicity at dose levels up to and including 425 mg/kg bw/day of test material.

Data Qualities Reliabilities

Reliability code 2. Reliable with restrictions.

Remarks for Data Reliability

Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.

References

Morgareidge K. (1973d) Teratologic evaluation of FDA 71-57 in rabbits. Contract No. FDA 71-260. Unpublished report.