IRGANOX 1076

Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate

CAS No. 2082-79-3

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Date: May 2000

CONTENTS

1. MELTING POINT

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Estimated by the MPBPWIN Program (v. 1.40),[1] using the adapted Joback method and the Gold and Ogle method.
GLP:	No
Year:	2000
Results:	241.0 °C
Remarks:	The melting point calculation by an accepted method is assigned a reliability code of 2f.[2]
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [2]See general reference, p. 37.

2. BOILING POINT

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Estimated by the MPBPWIN Program (v. 1.40),[1] using the adapted Stein and Brown method.
GLP:	No
Year:	2000
Results:	560.8 °C
Remarks:	The boiling point calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

3. VAPOR PRESSURE

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Estimated by the MPBPWIN Program (v. 1.40),[1] using the modified Grain method.
GLP:	No
Year:	2000
Results:	3.4×10^{-13} mm Hg
Remarks:	The vapor pressure calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

4. PARTITION COEFFICIENT

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Estimated by the KOWWIN Program (v. 1.66).[1]
GLP:	No
Year:	2000
Results:	Log P = 13.4
Remarks:	The partition coefficient calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

5. WATER SOLUBILITY

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Estimated by the WSKOW model (v. 1.37).[1]
GLP:	No
Year:	2000
Results:	Solubility at 25 °C = 6.1 x 10^{-9} mg/L
Remarks:	The water solubility calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

6. PHOTODEGRADATION

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Estimated by the AOP program (v. 1.90),[1] which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere.
GLP:	No
Results:	For reaction with hydroxyl radicals, the predicted half-life of the chemical is moderate. Rate constant: 43.2×10^{-12} cm^3/molecule-sec Half-life: 3.0 h
Remarks:	The photodegradation calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

7. STABILITY IN WATER

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Estimated by the HYDROWIN Program (v. 1.67).[1]
GLP:	No
Year:	2000
Results:	At 25 °C, $t_{1/2}$ (pH 8) = 263.9 days $t_{1/2}$ (pH 7) = 7.2 years
Remarks:	The stability in water calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

8. THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Estimated by Level III Fugacity Model.[1]
GLP:	No
Year:	2000
Results:	Distribution using Level III fugacity model

Air	0.080%
Water	2.32%
Soil	30.7%
Sediment	66.9%

Remarks: The fugacity calculation by an accepted method is assigned a reliability code of 2f.

References: [1]Syracuse Research Corporation, Syracuse, NY

9. BIODEGRADATION

A.

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	OECD Guideline 301B "Ready Biodegradability: Modified Sturm Test (CO_2 Evolution)," 1981. The only deviations from the guideline related to the volume of test solution which was 1.5 liters instead of 3.0 liters.
Concentration of the chemical:	10 mg/L and 20 mg/L for the test substance 20 mg/L reference chemical (aniline)
Medium:	Sewage sludge (per guideline)
GLP:	Yes
Year:	1984
Results:	Degradation = 32% after 29 days
Conclusion:	The substance is partially biodegradable, but not readily biodegradable according to OECD definition.
Remarks:	Two studies were conducted to evaluate the biodegradation potential. Both studies are reliable (reliability code 1) and should be given equal weight for evaluating this endpoint.
Reference:	"Report on the Test for Ready Biodegradability of TK 10044 in the Modified Sturm Test", Project No. 840054. Ciba Geigy, Ltd., Basel, Switzerland. Dr. A. de Morsier, 05/08/84.

B.

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. 11887494
Method:	84/449/AEEAC, C.5 Biotic Degradation: Modified Zahn-Wallens/Carbon Dioxide Evolution Test [For adaptation: OECD Guideline No. 302b (12/05/81)]. Deviations from the guidelines include the following: for the CO_2 evolution test, the volume of the test solution was reduced from 3 liters to 1.5 liters. The CO_2 formed by biodegradation was absorbed with NaOH and determined on a carbon analyzer. Due to the poor solubility of the test substance in water, an emulsifier was used to achieve a better distribution in the medium, and was homogenized with polyoxyethylene-sorbitan-monooleate (Tween 80).
Inoculum:	Sewage treatment sample per guideline
Concentration:	13.3 and 25.9 mg/L for the test substance 20 mg/L for the reference (aniline)
Medium:	Activated sludge per guideline
GLP:	Yes
Year:	1991
Results:	Degradation: 13.3 mg/L: 47% after 35 days 25.9 mg/L: 21% after 35 days
Conclusion:	The test substance is inherently biodegradable according to OECD definition.
Remarks:	This study is considered reliable as it was conducted under relevant guidelines (reliability code 1).
Reference:	"Report on the Test for Inherent Biodegradability in a combined Zahn-Wallens/Carbon dioxide Evolution Test of Irganox L 107 (Irganox 1076)", Test No. 918132. Ciba Geigy, Ltd., Basel, Switzerland. Dr. A. von Schulthess, 12/10/91.

10. ACUTE TOXICITY TO FISH

A.

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 70097.34
Method:	OECD Guideline 203 "Fish, Acute Toxicity Test" Paris (1981). The highest test concentration used was 100 mg/L and the highest vehicle concentration used was 892 mg/L.
Type of test:	Static
Species:	Lepomis macrochirus (Bluegill fish, fresh water)
Exposure period:	96 hours
Analytical monitoring:	Yes
GLP:	Yes
Year:	1984
Results:	LC_0 = 50 mg/L LC_{50} = > 100 mg/L LC_{100} = > 100 mg/L
Remarks:	Two studies were conducted to assess the acute toxicity to fish. Both are considered reliable (reliability code 1) and should be given equal weight for assessing this endpoint.
Reference:	"Report on the Test for Acute Toxicity of TK 10044 to Bluegill", Project No. 840057. Ciba Geigy, Ltd. Basel, Switzerland. Dr. A. de Morsier, 04/13/84

B.

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	OECD Guideline 203 "Fish, Acute Toxicity Test" Paris (1981). The deviations from the guideline include the following: (1) the highest vehicle concentration used was 892 mg/L; (2) the fish size averaged 59 mm (50 – 70 mm). These deviations would not significantly affect the test result.
Type of test:	Static
Species:	Salmo Gairdneri (Rainbow Trout, estuary, fresh water)
Exposure period:	96 hours
Analytical monitoring:	Yes
GLP:	Yes
Year:	1984
Results:	LC_0 = > 100 mg/L LC_{50} = > 100 mg/L LC_{100} = > 100 mg/L
Remarks:	Two studies were conducted to assess the acute toxicity to fish. Both are considered reliable (reliability code 1) and should be given equal weight for assessing this endpoint.
Reference:	"Report on the Test for Acute Toxicity of TK 10044 to Rainbow Trout", Project No. 840056. Ciba Geigy, Ltd. Basel, Switzerland. Dr. A. de Morsier, 03/13/84.

11. TOXICITY TO AQUATIC PLANTS

Test substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 148638.14, Purity 99.9%
Method:	Directive 87/302/EEC, part C, p. 89 "Algal Inhibition Test" 1992. The nominal test concentrations were 0.37, 1.1, 3.3, 10 and 30 mg test substance/L.
Species:	Scenedesmus subspicatus (Green Algae)
Endpoint:	Growth rate
Exposure period:	72 hours
Analytical monitoring:	Yes
GLP:	Yes
Year:	1992
Results:	NOEC = 30 mg/L EC_{50} = > 30 mg/L
Remarks:	This study is considered reliable as it was conducted under relevant guidelines (reliability code 1). Testing at higher concentrations is unnecessary as the compound has very low solubility.
Reference:	"Report on the Growth Inhibition Test of Irganox 1076 to Green Algae (Scenedesmus subspicatus)", Test No. 928140. Ciba Geigy Ltd. Basel, Switzerland. Dr. A. von Schulthess, 11/12/92.

12. ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	OECD Guideline 202, part 1 "Daphnia sp., Acute Immobilisation Test" 1981. The only deviation from the guideline was that the highest vehicle concentration was 892 mg/L. This deviation would not significantly affect the test result.
Species:	Daphnia Magna (Crustacea)
Exposure period:	24 hours
Analytical monitoring:	Yes
GLP:	Yes
Year:	1984
Results:	EC_0 = > 100 mg/L EC_{50} = > 100 mg/L EC_{100} = > 100 mg/L
Remarks:	This study is considered reliable as it was conducted under relevant guidelines (reliability code 1).
Reference:	"Report on the Test for Acute Toxicity of TK 10044 to Daphnia Magna", Project No. 840055. Ciba Geigy, Ltd. Basel, Switzerland. Dr. A. de Morsier, 03/06/84.

13. ACUTE TOXICITY

ACUTE DERMAL TOXICITY

Test substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 148638.14, 99.9% purity
Method:	OECD Guideline 402 "Acute Dermal Toxicity", adopted February 24, 1987. No significant deviations that would affect the results occurred in this study.
Species/strain:	Tif: RAI f ((SPF)) Albino Rats
Sex:	Male and Female
No. Animals/Group:	5/sex
Dose:	2000 mg/kg (limit test)
Vehicle:	0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate
GLP:	Yes
Year:	1992
Results:	No significant adverse effects were noted and no animals died during the study. Piloerection and hunched posture were noted, being common symptoms in acute dermal tests.
Conclusion:	$LD_{50} > 2000$ mg/kg b.w.
Remarks:	This study was conducted under GLP and OECD guidelines and is considered reliable (reliability code 1).
Reference:	"Acute Dermal Toxicity in the Rat, Test No. 924057, TK 10044 (Irganox 1076) Report", Ciba Geigy Limited, Basel, Switzerland. Dr. phil H. R. Hartman, 06/22/92.

ACUTE INHALATION TOXICITY

Test substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	Inhalation toxicity was tested according to the method of Sachsse *et al* (1973). Male and female rats were placed in nose-only exposure chambers, and exposed to an aerosol of the test material for 4 hours. All animals were observed for signs and symptoms of systemic toxicity and mortality for 14 days.
Species/strain:	Tif: RAIf (SPF) Rats
Sex:	Male and Female
No. Animals/Group:	10 Male/10 Female/group
Doses:	500 mg/m^3 1025 mg/m^3 1811 mg/m^3
Exposure period:	4 hours
Post exposure observation period:	14 days
GLP:	No
Year:	1978
Results:	No significant adverse toxicity or mortality was observed.
Conclusion:	The $LC_{50} > 1811$ mg/m^3
Remarks:	This study is assigned a reliability code of 2e. The study was not conducted under GLP or OECD guidelines, but does meet generallly accepted scientific standards, is well documented, and is acceptable for assessment.
References:	"Acute aerosol inhalation toxicity in the rat of TK 10044," Ciba-Geigy Limited, Basel, Switzerland, 1978. Sachsse, K., Ullmann, L., Voss, G., and Hess, R., "Measurement of inhalation toxicity of aerosols in small laboratory animals. In Proceedings of the European Society for the Study of Drug Toxicity, Vol. XV, pp. 239-251, Zurich, 1973.

ACUTE ORAL TOXICITY

Test substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 10124.12
Method:	Although this study was not carried out under OECD or EPA guidelines, the methods closely parallel those described in OECD Guideline 401 "Acute Oral Toxicity". Male and female rats were administered the test substance by oral gavage at a dose of 5000 mg/kg bw. All animals were observed for signs and symptoms of systemic toxicity and mortality for 14 days.
Species/strain:	Tif: RAIf (SPF) Rats
Sex:	Male and Female
No. Animals/Group:	5/sex
Doses:	5000 mg/kg (20 mL/kg bw)
Vehicle:	Polyethylene glycol 400
GLP:	No
Year:	1981
Results:	No significant adverse effects were noted, except for mild dyspnoea, ruffled fur, and curved body position. These symptoms are common in acute toxicity studies. No animals died during the study.
Conclusion:	The $LD_{50} > 5000$ mg/kg/bw.
Remarks:	This study is considered reliable, and assigned a reliability code of 2c (comparable to guideline study with acceptable restrictions). The study was not conducted under GLP or OECD guidelines, but methods were comparable to OECD guideline 401. Males and females of an adequate number were included, but the clinical symptoms were not separated by sex. However, the symptoms were minor and of questionable toxicological significance. The results from this study confirm earlier studies in hamster which found the LD_{50} to be greater than 6000 mg/kg bw.
Reference:	"Report on Acute Oral LD_{50} in the Rat of TK 10044", Ciba Geigy, Limited, Basel, Switzerland. Dr. Phil II G. Sarasin, 12/18/81

14. GENETIC TOXICITY IN VIVO

A. DOMINANT LETHAL ASSAY

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 28303
Method:	Male mice were administered a single gavage dose of 0, 1000 or 3000 mg/kg. Males were mated with females for up to 6 weekly mating periods. Pregnant females were necropsied on Day 14 of pregnancy.
Type:	Dominant lethal assay
Species/strain:	Albino mice (NMRI derived)
Sex:	Male
No Animals/Group:	20
Route of administration:	Gavage
Exposure period:	Single exposure
Doses:	1000 and 3000 mg/kg in carboxymethylcellulose (0.2ml/kg bw)
Control:	Concurrent, vehicle only
GLP:	No
Year:	1975
Results:	No evidence of dominant lethal effects was noted. There were no differences in mating ratio, number of implantations or embryonic deaths between controls and treated.
Remarks:	Although not conducted under GLP or OECD guidelines, this study does meet generally accepted scientific standards, is well documented, and is acceptable for assessment (reliability code 2e). The findings of this study are consistent with those of other in vitro and in vivo studies for this chemical.
Reference:	Dominant Lethal Study on TK 10044, Mouse (Test for Cytotoxic or Mutagenic Effects on Male Germinal Cells), Experiment No. 327540. Ciba Geigy, Limited, Basel, Switzerland. Dr. H. Fritz, 09/12/75.

B. SOMATIC MUTATION ASSAY

Test substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 28303
Method:	This study was not conducted under OECD or GLP guidelines. Animals were gavaged with either 500, 1000 or 2000 mg/kg test material. Positive controls were administered cyclophosphamide (128 mg/kg). Treatment consisted of daily administration on 2 consecutive days. Twenty-four hours after the second application, animals were sacrificed and bone marrow was harvested from the shaft of both femurs. Bone marrow cells (1000/animal) were scored for chromosomal anomalies.
Species/strain:	Chinese hamster
Sex:	Male/Female
No. Animals/group:	6
Route of administration:	Gavage
Exposure period:	2 days
Doses:	500, 1000 and 2000 mg/kg
Vehicle:	0.5 % carboxymethylcellulose (20 mL/kg)
Controls:	Concurrent Positive: 128 mg/kg cyclophosphamide Negative: Vehicle only
GLP:	No
Year:	1976
Results:	In all groups the percentage of cells displaying anomalies of nuclei did not differ significantly from the negative control. The test material is considered to be nonmutagenic.
Remarks:	Although not conducted under GLP or OECD guidelines, this study meets generally accepted scientific standards, is well documented, and is acceptable for assessment (reliability code 2e). The findings are consistent with those of other in vitro and in vivo studies for this chemical.

Reference: "Nucleus Anomaly Test on Somatic Interphase Nuclei, TK 10044, Chinese Hamster (Test for Mutagenic Effects on Bone Marrow Cells)", Ciba Geigy, Limited, Basel-Switzerland. Dr. M. Langauer, 09/22/76.

C. SOMATIC MUTATION ASSAY

Test Material:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 28303
Method:	This study was not conducted under OECD guidelines. Animals were gavaged once daily for 2 consecutive days with the test material. Positive controls were administered cyclophosphamide (64 mg/kg). The animals were injected with colcemide (10 mg/kg) 2 hours after administration of the second dose and sacrificed 4 hours later. Bone marrow was harvested and analyzed for chromosomal aberrations (100 metaphases/animal).
Type:	Somatic mutation assay
Species/strain:	Chinese Hamsters (Cricetulus griseus)
Sex:	Male/Female
No. Animals/Group:	4/sex/dose group
Route of Administration:	Gavage
Exposure period:	2 days
Doses:	500, 1000 and 2000 mg/kg
Controls:	Concurrent Positive: cyclophosphamide (64 mg/kg)
Vehicle:	2% aqueous solution sodium carboxymethylcellulose 20 mL/kg
GLP:	No
Year:	1981
Results:	The chromosome displays from the negative control group and of the intermediate and high dose group showed no aberrations. In the animals of the low dose group, one metaphase per 400 cells with chromatid-type aberration in the form of a break was detected. This incidence is within the frequency observed in historical controls and is therefore considered to be spontaneous in origin. The test material is considered to be nonmutagenic.
Remarks:	Although not conducted under GLP or OECD guidelines, this study does meet generally accepted scientific standards, is well documented, and is acceptable for assessment (reliability code 2e). The findings of

this study are consistent with those of other in vitro and in vivo studies for this chemical.

Reference:

"Chromosome Studies in Somatic Cells, TK 10044, Chinese Hamster (Test for Mutagenic Effects on Bone Marrow Cells." Experiment No. 764028. Ciba Geigy, Limited, Basel, Switzerland. Dr. D. Muller, 08/27/81.

15. GENETIC TOXICITY IN VITRO

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	This study was not conducted under OECD guidelines but was conducted using the methods described by Ames *et al* (1973, 1975). The material was tested for mutagenic effects on histidine auxotrophic mutants of Salmonella typhimurium. Cultures were prepared from frozen stock, and on the following day the standard plate test was carried out. The concentrations of the test substance used were: without microsomal activation: 10, 25, 50, 100 and 250 µg/0.1 mL; with microsomal activation: 5, 10, 25, 50 and 100 µg/0.1 mL. In the experiments in which the substance was metabolically activated, 0.5 mL of the activation mixture (S9 fraction of liver from rats induced with Aroclor 1254 plus co-factors) was added. Positive controls in the form of spot tests were also included.
Type:	Reverse mutation
System of testing:	S. typhimurium TA 98, 100, 1535, 1537
Concentration:	10 – 250 microgram/plate
Metabolic activation:	With and without S9 fraction of liver from rats induced with Aroclor 1254 plus co-factors
GLP:	No
Year:	1977
Results:	Negative Cytotoxicity conc: Not reported Precipitation conc: 100 µg/0.1 mL
Genotoxic effects:	No increase in mutations, with or without metabolic activation.
Remarks:	This study is considered scientifically sound and follows methods described by Ames *et al* (1973, 1975). The study meets generally accepted scientific standards, is well documented, and is acceptable for assessment (reliability code 2e). The low solubility of the test compound limited the range of test concentrations.

References:

"Salmonella/mammalian Microsome Mutagenicity Test with TKA 10044 (Test for Mutagenic Properties in Bacteria." Ciba Geigy, Limited, Basel, Switzerland. Dr. P. Arni, 04/20/77.

Ames, B.N., Lee, F.D., and Durston, W.E., "An improved bacterial test system for the detection and classification of mutagens and carcinogens, Proc. Natl. Acad. Sci. USA, 70, 782-786, 1973.

Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D., "Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection," Proc. Natl. Acad. Sci. USA, 70, 2281-2285, 1973.

Ames, B.N., McCann, J., and Yamasaki, E., "Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test, Mutat. Res., 31, 347-364, 1975.

16. REPEAT DOSE TOXICITY

Test substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 132812.82, 99 % purity
Method:	Although not formally conducted under OECD guidelines, the method parallels that described under "OECD Guideline 407, Repeat Dose 28-Day Oral Toxicity Study in Rodents" adopted by the Council on 27th July, 1995. Male and female rats were gavaged daily for 28 days. All animals were observed twice daily for morbidity and mortality, and were observed daily for any clinical signs of toxicity. Body weights were measured twice weekly. Food consumption was measured weekly. Hematology, urinalysis and clinical chemistry were performed at the end of week 4 on all animals. Following the final treatment, all animals were sacrificed, and macroscopic and microscopic analyses were performed. Organs obtained for pathological analysis included the adrenals, heart, kidneys, liver, lung, spleen, testes and any tissue with evidence of gross lesions. Statistical analysis of mean data was performed.
Species/strain:	Sprague-Dawley Rat
Sex:	Male/Female
No. Animals/group:	5/sex
Route of Administration:	Oral gavage
Exposure period:	28 days
Frequency of treatment:	Daily
Post exposure observation period:	No
Dose:	5, 30, 100, 300 mg/kg/day
Vehicle:	0.5% hydroxypropylcellulose in water
Dosing volume:	10 mL/kg
Control group:	Yes; Concurrent vehicle
GLP:	Yes
Year:	1991

Results	NOAEL = 30 mg/kg bw No animals died during the study, nor were there any treatment related clinical signs of toxicity. There were no significant differences in body weights or food consumption that were attributed to treatment. There were no differences in the hematological parameters that could be attributed to treatment. In females, a statistically significant decrease in blood urea nitrogen in the high dose group was observed, but the absolute values were within normal background range. Thus, the toxicological significance of this finding is questionable. A statistically significant increase in relative liver weight was observed in females of the high and intermediate dose groups. A significant dose response in liver weight increases was observed in males. All high dose animals had minimal centrilobular hepatocytic hypertrophy. No other findings occurred which could be attributed to treatment.
Remarks:	This study is considered reliable (reliability code 1b). Although this study was not conducted under OECD guidelines, the methods closely parallel the OECD guideline for repeat dose toxicity testing. Moreover, the study was conducted under GLP guidelines. Additional testing is considered unnecessary.
Reference:	"4 Week Oral Gavage Toxicity Study in the Young Rat" Study No. 380/563. Hazelton France. N. Pickersgill, 04/26/91.

17. REPRODUCTIVE TOXICITY

Test Material:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	OECD Guideline 416 "Two-generation Reproduction Toxicity Study" 1986
Species/strain:	Charles River Rats: COBS ® CD ®
Sex:	Male/Female
Route of Administration:	Dietary
Exposure period:	10 months
Frequency of treatment:	Daily
Premating exposure period:	Male: 10 weeks; Female: 10 weeks
Duration of the test:	10 months
Doses:	500, 1500, 5000 ppm
Control group:	Yes; Concurrent vehicle (diet without test material)
GLP:	Yes
Year:	1986
Res ults:	NOAEL Parental: 1500 ppm LOAEL F1 Offspring: 500 ppm LOAEL F2 Offspring: 500 ppm

5000 ppm: At 5000 ppm, there were no obvious signs of reaction to treatment among adults. Findings at 5000 ppm among adults of both generations (F0 and F1) which did appear treatment related were as follows: (1) slight reduction in food consumption, weekly weight gain and weight gain among pregnant females; (2) increase in liver weights and reduction in spleen weight. Histological analysis of livers from F1 adult animals revealed minimal centrilobular hepatocyte enlargement. Mating performance, pregnancy rate and the duration of gestation were unaffected by treatment. Of the litters from the high dose group, the litter size of the F0 generation was slightly reduced. Postpartum pup loss was increased and pup weight gain was reduced. In the F1 generation, initial litter size was reduced. Organ weight analysis of

selected F1 and F2 weanlings showed effects on brain, liver and spleen weights, but histological analysis revealed no adverse abnormalities.

1500 ppm: Organ weight analysis of F0 and F1 adults showed significant reduction in spleen weight. However, histological analysis revealed no treatment-related changes. Overall there was no clear indication of an adverse effect of treatment on litter data. Among selected F1 and F2 weanlings, statistically significant increases in liver weights and reductions in spleen weights were noted but deviations from controls were less than at 5000 ppm. Slight reductions in brain weights were observed among F1 weanlings.

500 ppm: No effect on adults, other than a statistically significant reduction in spleen weight among adult F0 males and F1 females was noted. There were no treatment-related effects on reproductive performance or on litter data. Among weanlings, an increase in liver weight and a decrease in spleen weight were observed among F2 females only. A slightly lower brain weight was observed among F1 males only.

Remarks: This study is considered reliable as it was conducted under relevant guidelines (reliability code 1).

Reference: "Effect of TK 10044 on Reproductive Functions of Two Generations in the Rat", Report No. CBG 337/831043, Huntingdon Research Centers, Cambridge, England. J. Edwards, 01/03/86.

18. DEVELOPMENTAL TOXICITY/ TERATOGENICITY

A. TERATOGENICITY IN RATS

Test substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 28303
Method:	Although this study was not formally carried out under OECD Guidelines, the methods parallel those described in OECD Guideline 414 "Teratogenicity", adopted May 12, 1981. The compound was administered by oral gavage on Days 6 through 15 of pregnancy. During the treatment, general condition, weight gain, food consumption and symptomology were checked daily. Dams were necropsied and fetuses were removed by Cesarean section on Day 21 of pregnancy. The examinations were carried out in accordance with the World Health Organization (WHO) recommendations (WHO, 1967) and the technique described by Wilson, 1965.
Species/strain:	Sprague-Dawley Rats
Sex:	Female
Route of Administration:	Gavage
Duration of the test:	10 Days
Exposure period:	Days 6 through 15 of gestation
Frequency of treatment:	Daily
Doses:	150, 500, 1000 mg/kg
Control group:	Yes; Concurrent vehicle
GLP:	No
Year:	1975
Results:	NOAEL Maternal Toxicity: = 150 mg/kg bw NOAEL Teratogenicity : > 1000 mg/kg bw Maternal general toxicity: A dose-related reduction in food intake was noted during the treatment period. Pregnancy/litter data: No effects on pregnancy or litter data were noted.

Foetal data: A slight and non-specific retardation of physiological growth of the fetuses at the intermediate and high-dose levels, as well as an increase in the number of not yet ossified phalangeal nuclei of the hind-limb in the high-dose group were found. Pups in the low dose group were unaffected.

Conclusion: The material is considered nonteratogenic under the test conditions.

Remarks: This study is considered reliable (reliability code 2b). Although it was not conducted formally under OECD or GLP guidelines the methods employed are standard techniques and paralleled OECD guidelines for assessing teratogenicity. An additional teratogenicity study was conducted in mice which supports the conclusion of this study and is given equal weight for assessing this endpoint.

References:

"Reproduction Study – TK 10044, Rat, Segment II (Test for Teratogenic or Embryotoxic Effects)', Test No. 227513. Ciba Geigy Limited, Basel, Switzerland. Dr. H. Fritz, 06/19/75.

World Health Organization Technical Report Service 364, 1967

Wilson, J.G., in: Teratology, Principles and Techniques; J.G. Wilson and J. Warkany eds., The University of Chicago Press, Chicago, 1965, pp. 262-277.

B. TERATOGENICITY IN MICE

Test substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Batch No. EN 28303
Method:	Although this study was not formally carried out under OECD guidelines, the methods parallel those described in OECD Guideline 414 "Teratogenicity", adopted May 12, 1981. The compound was administered by oral gavage on Days 6 through 15 of pregnancy. During the treatment, general condition, weight gain, food consumption and symptomology were checked daily. Dams were necropsied and fetuses were removed by Cesarean section on Day 18 of pregnancy. The examinations were carried out in accordance with the World Health Organization (WHO) recommendations (WHO, 1975) and the technique described by Wilson, 1965.
Species/strain:	Albino Mice (NMRI derived)
Sex:	Female
Route of administration:	Gavage
Duration of the test:	10 Days
Exposure period:	Days 6 through 15 of gestation
Frequency of treatment:	Daily
Doses:	150, 500, 1000 mg/kg
Vehicle:	2% aqueous carboxymethylcellulose (0.1 mL/kg bw)
Control group:	Yes; Concurrent vehicle
GLP:	No
Year:	1975
Results:	NOAEL maternal toxicity: 1000 mg/kg bw NOAEL teratogenicity : 1000 mg/kg bw Maternal general toxicity: No reaction to treatment was noted. Pregnancy/litter data: The rates on implantation and embryotoxicity were not significantly affected by treatment. Foetal data: No teratogenic effects were noted.

Remarks: This study is considered reliable (reliability code 2b). Although it was not conducted formally under OECD or GLP guidelines, the methods employed are standard techniques and paralleled OECD guidelines for assessing teratogenicity. An additional teratogenicity study was conducted in rats which supports the conclusion of this study and is given equal weight for assessing this endpoint.

References:

"Reproduction Study – TK 10044, Mouse, Segment II (Test for Teratogenic or Embryotoxic Effects)', Test No. 327533. Ciba Geigy Limited, Basel, Switzerland. Dr. H. Fritz, 06/19/75.

World Health Organization Technical Report Service 563, 1975

Wilson, J.G., in: Teratology, Principles and Techniques; J.G. Wilson and J. Warkany eds., The University of Chicago Press, Chicago, 1965, pp. 262-277.

GENERAL REFERENCE

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25:1-5, 1997.

Definition of codes

1 = Valid without restriction
1a: GLP guideline study
1b: Comparable to guideline study
1c: Meets national standard methods (AFNOR/DIN)
1d: Meets generally accepted scientific standards and is described in sufficient detail

2 = Valid with restriction
2a: Guideline study without detailed documentation
2b: Guideline study with acceptable restrictions
2c: Comparable to guideline study with acceptable restrictions
2d: Meets national standard methods with acceptable restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment
2f: Accepted calculation method
2g: Data from Handbook or collection of data

3 = Invalid
3a: Documentation insufficient for assessment
3b: Significant methodological deficiencies
3c: Unsuitable test system

4 = Not assignable
4a: Abstract
4b: Secondary literature
4c: Original reference not yet available
4d: Original reference in foreign language
4e: Documentation in sufficient for assessment