AR 201-12966

Ciba Specialty Chemicals
North America
Additives
Legal and Regulatory Affairs

Ciba

February 20, 2001

Christine Todd Whitman, Administrator
U. S. Environmental Protection Agency
P. O. Box 1473
Merrifield, VA 22116

Attn: HPV Program

Dear Administrator Whitman,

Ciba Specialty Chemicals Corporation, Additives Division (HPV Registration #) acknowledges receipt of EPA's comments on the robust summaries and test plans that we submitted for the following chemicals:

- Octadecyl 3,5-di(tert)-butyl-4-hydroxyhydrocinnamate, CAS No. 2082-79-3
- Tetrakis-(methylene-(3,5-di-(tert)-butyl-4-hydrocinnamate))methane, CAS No. 6683-19-8
- Tris(2,4-di-(tert)-butylphenyl)phosphite, CAS No. 31570-04-4

We have addressed EPA's comments, and are pleased to submit the revised robust summaries. The documents are being provided as hardcopies and electronically as Microsoft Word files. We expect that the revised documents will be acceptable to EPA. Please feel free to contact me if you have additional comments or questions regarding our submissions. Ciba remains committed to supporting EPA's HPV Challenge Program, and looks forward to our continued participation.

Sincerely,

David La
Senior Toxicologist

MR 45009

540 White Plains Road
Tarrytown, New York 10591

Tel. 914-785-2000
Fax 914-785-4147

AR 201-12966 B1

IRGANOX 1076

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

CAS No. 2082-79-3

Name of Sponsoring Organization: Ciba Specialty Chemicals Corporation
HPV Registration Number:
Contact Persons: Richard Balcomb and David La
Address: Additives, Legal and Regulatory Affairs
540 White Plains Road
Tarrytown, New York 10591
USA
Tel: (914) 785-2000
Fax: (914) 785-4147

Date: May 2000; revised February 2001

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SUMMARY TABLE

CAS No. 2082-79-3 PHYSICAL/CHEMICAL ELEMENTS	DATE	RESULTS	FULFILLS REQUIREMENT
Melting Point	1978	49 - 54 °C	Yes
Boiling Point	2000	560.8 °C	Yes
Vapor Pressure	2000	4.2×10^{-11} mm Hg (25 °C)	Yes
Partition Coefficient	2000	log P = 13.4	Yes
Water Solubility	2000	3.9×10^{-8} mg/L (25 °C)	Yes
ENVIRONMENTAL FATE ELEMENTS			
Photodegradation	2000	For reaction with hydroxyl radical, predicted rate constant = 43.2×10^{12} cm^3/molecule-sec predicted half-life = 3.0 h	Yes
Stability in Water	2000	$t_{1/2}$ at pH 8 = 264.0 days $t_{1/2}$ at pH 7 = 7.2 years	Yes
Fugacity	2000	Predicted distribution using Level III fugacity model Air 3.33×10^{-5} % Water 5.74×10^{-3} % Soil 99.3 % Sediment 0.66 % Persistence = 3.69×10^{6} h	Yes
Biodegradation	1984	Partially biodegradable 32% after 29 days	Yes
	1991	Inherently biodegradable 13.3 mg/L: 47% after 35 days 25.9 mg/L: 21% after 35 days	Yes
ECOTOXICITY ELEMENTS			
Acute Toxicity to Fish	1984	Bluegill fish (Lepomis macrochirus) EC_0 (96 h) = 50 mg/L EC_{50} (96 h) => 100 mg/L EC_{100} (96 h) => 100 mg/L	Yes
	1984	Rainbow trout (Salmo gairdneri) EC_0 (96 h) => 100 mg/L EC_{50} (96 h) => 100 mg/L EC_{100} (96 h) => 100 mg/L	Yes
Toxicity to Aquatic Plants	1992	Green algae (Scenedesmus subspicatus) EC_{50} (72 h) => 30 mg/L NOEC = 30 mg/L	Yes
Acute Toxicity to Aquatic Invertebrates	1984	Daphnia magna EC_0 (24 h) => 100 mg/L EC_{50} (24 h) => 100 mg/L EC_{100} (24 h) => 100 mg/L	Yes

SUMMARY TABLE, CONTINUED

CAS No. 2082-79-3 **HEALTH ELEMENTS**	**DATE**	**RESULTS**	FULFILLS **REQUIREMENT**
Acute Toxicity	1992	Rat: LD_{50} (Dermal) > 2000 mg/kg	Yes
	1978	Rat: LC_{50} (Inhalation) > 1800 mg/m^3	Yes
	1981	Rat: LD_{50} (Oral) > 5000 mg/kg	Yes
Genetic Toxicity in vivo	1975	Mouse: No evidence of dominant lethal effects (single gavage dose of 1000 or 3000 mg/kg). No effect on mating ratio, implantations, or embryonic death	Yes
	1976	Chinese hamster: Nonmutagenic in somatic mutation assay (exposed by gavage 500, 1000, or 2000 mg/kg/day for 2 days)	Yes
	1981	Chinese hamster: No evidence of chromosomal aberrations (exposed by gavage 500, 1000, or 2000 mg/kg for 2 days)	Yes
Genetic Toxicity in vitro	1977	Salmonella typhimurium: No increase in mutations with or without metabolic activation (at doses of 10 – 250 µg/0.1 mL)	Yes
Repeated Dose Toxicity	1991	Rat: NOAEL = 30 mg/kg (28-days exposure, gavage)	Yes
Reproductive Toxicity	1986	Rat: NOAEL parental = 1500 ppm LOAEL F1 offspring = 500 ppm LOAEL F2 offspring = 500 ppm	Yes
Developmental Toxicity/Teratogenicity	1975	Rat: NOAEL maternal toxicity = 150 mg/kg NOAEL teratogenicity > 1000 mg/kg	Yes
	1975	Mouse: NOAEL maternal toxicity = 1000 mg/kg NOAEL teratogenicity = 1000 mg/kg	Yes

1. MELTING POINT

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3
Method:	From Kirk-Othmer Encyclopedia of Chemical Technology.'
GLP:	No
Year:	1978
Results:	49 - 54 °C
Remarks:	The melting point determination was assigned a reliability code of 2g (data from handbook or collection of data).* Similar data were reported by Aldrich (50-52 °C) and the MSDS from Ciba Specialty Chemicals Corp (50-55 °C). The methods of determination by these sources were unreported.
References:	'Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Edition, Vol. 2, p. 88. [2]See general reference, p. 49.

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),[1,2] using the adapted Stein and Brown method.
GLP:	No
Year:	2000
Results:	560.8 °C
Remarks:	In the absence of reliable experimental data, the boiling point was calculated using an accepted method and was assigned a reliability code of 2f.[3]
References:	[1]Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 49.

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),[1,2] using the modified Grain method.
GLP:	No
Year:	2000
Results:	4.2×10^{-11} mm Hg (25 °C)
Remarks:	The MSDS from Ciba Specialty Chemicals Corp reported a vapor pressure of approximately 2×10^{-9} mm Hg at 20 °C, but the method of determination was not reported. In the absence of this information, the vapor pressure was calculated using an accepted method and was assigned a reliability code of 2f.[3]
References:	'Syracuse Research Corporation, Syracuse, NY *Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 49.

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).[1,2]
GLP:	No
Year:	2000
Results:	Log P = 13.4
Remarks:	The MSDS from Ciba Specialty Chemicals Corp reported a partition coefficient of > 6, but the method of determination was not reported. In the absence of this information, the partition coefficient was calculated using an accepted method and was assigned a reliability code of 2f.[3]
References:	[1]Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 49.

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).[1,2]
GLP:	No
Year:	2000
Results:	Solubility at 25 °C = 3.9 x 10^{-8} mg/L
Remarks:	The MSDS from Ciba Specialty Chemicals Corp reported a solubility of < 0.2 ppm at 20 °C, but the method of determination was not reported. In the absence of this information, the water solubility was calculated using an accepted method and was assigned a reliability code of 2f.[3]
References:	'Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 49.

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),[1,2] 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 x 10^{-12} cm^3/molecule-sec Half-life: 3.0 h
Remarks:	In the absence of reliable experimental data, the photodegradation was calculated using an accepted method and was assigned a reliability code of 2f.[3]
References:	[1]Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 49.

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).[1,2]
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:	In the absence of reliable experimental data, the stability in water was calculated using an accepted method and was assigned a reliability code of 2f.[3]
References:	[1]Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [3]See general reference, p. 49.

8. THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Test Substance: Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate
CAS No. 2082-79-3

Method: Estimated by EQC Level III Fugacity Model.'

GLP: No

Year: 2000

Results: Distribution using EQC Level III Fugacity Model

Air	3.33 x 10^{-5} %
Water	5.74 x 10^{-3} %
soil	99.3 %
Sediment	0.66 %

Persistence = 3.69 x 10^{6} h

Remarks: In the absence of reliable experimental data, the fugacity was calculated using an accepted method and was assigned a reliability code of 2f.[2]

References: 'Environmental Modelling Centre, Trent University, Peterborough, Ontario, 1997.

[2]See general reference, p. 49.

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.[2]
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.

[2]See general reference, p. 49.

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 included 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
Medium	Activated sludge per guideline
Concentration:	13.3 and 25.9 mg/L for the test substance 20 mg/L for the reference (aniline)
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 was considered reliable as it was conducted under relevant guidelines (reliability code 1).[2]
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.

[2]See general reference, p. 49.

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 Purity: Commercial grade
Method:	OECD Guideline 203 "Fish, Acute Toxicity Test" Paris (1981). Fish averaged 27 mm (24-30 mm) in length, and 0.16 g (0.10-0.28 g) in weight. Aquaria of 20 L (filled with 15 L) were used. The water source was dechlorinated tap water (carbon filtered). Hardness was 179 mg $CaCO_3$/L; pH ranged from 8.0 to 8.3; O_2 ranged from 94 to 101% saturation; water temperature was 23 ± 1 "C. Test concentrations of 10, 18, 32, 58, and 100 mg/L (nominal) were used. The test substance precipitated immediately at concentration > 100 mg/L. The vehicle contained 887 mg tetrahydrofuran, 3 mg Arkopal N150, and 2 mg Marlopon AT50 per liter water. Samples for analysis were taken at 0 h and 96 h exposure. There were 10 fish per concentration and control, and 10 fish per aquarium
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 LC50 was > 100 mg/L (nominal concentration). Mortality in blanks was 0% and in vehicle controls 10%.

Table 1. Analytical data of test concentrations

Sample time	Nominal concentration (mg/L)	Measured concentration (mg/L)
Oh	10	13.4
	18	19.3
	32	32.9
	58	60.5
	100	96.3
96 h	10	6.4
	18	12.3
	32	32.7
	58	47
	100	90.3

Table 2. Mortality data

Nominal Concentration (mg/L)	Cumulative Mortality at Different Time Points			
	24 h	48 h	72 h	96 h
Blank	0	0	0	0
Vehicle	0	0	0	1
10	0	0	0	0
18	0	0	0	0
32	0	0	0	0
58	0	0	0	0
100	0	0	1	1

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.[2]

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

[2]See general reference, p. 49.

B.

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Purity: Commercial grade
Method:	OECD Guideline 203 "Fish, Acute Toxicity Test" Paris (198 1). Deviations from the guideline included 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 results. Aquaria of 20 L (filled with 15 L) were used. The water source was dechlorinated tap water (carbon filtered). Hardness was 168 mg $CaCO_3$/L; pH ranged from 7.8 to 8.1; O_2 ranged from 82-101% saturation; water temperature was 14 $\pm$ 1 "C. Test concentrations of 10, 18, 32, 58, and 100 mg/L (nominal) were prepared. The test substance precipitated immediately at concentrations > 100 mg/L. The vehicle contained 887 mg tetrahydrofuran, 3 mg Arkopal N150, and 2 mg Marlopon AT50 per liter water. Samples were analyzed at 0 and 96 h exposure. There were 10 fish per concentration and control, with 5 fish per aquarium
Type of test:	Static
Species:	Salmo gairdneri (Rainbow trout)
Exposure period:	96 hours
Analytical monitoring:	Yes
GLP:	Yes
Year:	1984
Results:	LC_0 = > 100 mg/L (nominal concentration) LC_{50} = > 100 mg/L LC_{100} = > 100 mg/L

Table 1. Analytical data of test concentrations

Sample time	Nominal concentration (mg/L)	Measured concentration (mg/L)
Oh	10	22
	18	25
	32	29
	58	50
	100	92
96 h	10	9
	18	15
	32	29
	58	38
	100	80

Table 2. Mortality data

Nominal Concentration (mg/L)	Cumulative mortality			
	24 h	48 h	72 h	96 h
Blank	0	0	0	0
Vehicle	0	0	0	0
10	0	0	0	0
18	0	0	1	1
32	0	0	0	0
58	0	0	0	0
100	0	0	0	0

Remarks: Two studies were conducted to assess the acute toxicity to fish. Both were considered reliable (reliability code 1) and should be given equal weight for assessing this endpoint.[2]

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.

[2]See general reference, p. 49.

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. Tests were conducted in 100 mL Erlenmeyer flasks containing 50 mL of the test solution and stoppered with aluminum caps. Composition of the water was according to guidelines. A stock solution was prepared by mixing 2 g of the test substance and 18 g of a solution of 0.4% lecithin in water, and adding 1 mL of this blend to 1000 mL water. The nominal test concentrations were 0.37, 1.1, 3.3, 10 and 30 mg test substance.&. Each test concentration was tested in 3 replicates and the blank control in 6. Temperature was 23 ± 2 °C; pH ranged from 7.8 to 7.9 at 0 h and from 8.5 to 9.0 at 72 h. Additional information such as total hardness, TOC, and dissolved oxygen was not provided. Continuous illumination was provided by cold white fluorescent light.

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

Table 1. Analytical data of test concentrations

Concentration, nominal mg/L	Measured concentration, mg/L	
	Oh	72 h
Blank	< 0.5	< 0.5
Vehicle	< 0.5	< 0.5
0.37	< 0.5	< 0.5
1.1	1	< 0.5
3.3	2.5	< 0.5
10	9.0	0.8
30	19.7	2.9

Table 2. Cell density data

Concentration, nominal mg/L	Mean cell density/mL * 10^4		
	24 h	48 h	72 h
Blank	4.5	25.6	184.5
Vehicle	5.1	25.4	227.7
0.37	4.7	26.7	196.0
1.1	3.3	25.6	202.3
3.3	4.0	21.2	149.2
10	2.5	24.7	166.2
30	-0.3	15.2	185.3

Remarks: This study was considered reliable as it was conducted under relevant guidelines (reliability code 1).[2] Testing at higher concentrations was 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.

[2]See general reference, p. 49.

12. ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test Substance:	Octadecyl 3,5-Di(tert)-butyl-4-hydroxyhydrocinnamate CAS No. 2082-79-3 Purity: Commercial grade
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. Reconstituted water was produced by dissolving 65 mg $NaHCO_3$, 294 mg $CaCl_2$ (2 H_2O), 123 mg $MgSO_4$ (7 H_2O), and 6 mg KCl in 1 L bidistilled water. Hardness was 240 mg $CaCO_3$/L; pH ranged from 7.7 to 7.9. O_2 ranged from 93-98% saturation; temperature was 20 ± 1 "C. 20 mL test tubes covered with steel caps were used as exposure vessels. Test concentrations of 10, 18, 32, 58, and 100 mg/L (nominal) were prepared. The test substance precipitated immediately at concentrations > 100 mg/L. The vehicle contained 887 mg tetrahydrofuran, 3 mg Arkopal N150, and 2 mg Marlopon AT50 per liter water. Samples were analyzed at 0 and 24 h exposure. The study used 20 daphnia per concentration and control (4 replicates of 5 daphnia).
Species:	Daphnia Magna (Crustacea)
Type of test:	Static
Exposure period:	24 hours
Analytical monitoring:	Yes
GLP:	Yes
Year:	1984
Results:	EC_0 = > 100 mg/L (nominal concentration) EC_{50} = > 100 mg/L EC_{100} = > 100 mg/L

Table 1. Analytical data of test concentrations

Sample time	Nominal concentration (mg/L)	Measured concentration (mg/L)
Oh	10	12
	18	22
	32	29
	58	47
	100	92
24 h	10	22
	18	20
	32	31
	58	43
	100	102

Table 2. Immobiition data

Nominal Concentration (mg/L)	Immobilization after 24 h (replicates 1-4)				
	1	2	3	4	Total
Blank	0	0	0	0	0
Vehicle	0	0	0	0	0
10	0	0	0	0	0
18	0	0	0	0	0
32	0	0	0	0	0
58	0	0	0	0	0
100	0	0	0	0	0

Remarks: This study is considered reliable as it was conducted under relevant guidelines (reliability code 1).[2]

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.

[2]See general reference, p. 49.

13. ACUTE TOXICITY

A. 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. Rats, weighing 211 to 274 g, were shaved on the back (an area on the back of at least 10% of the body surface) 24 h before treatment. The test article was evenly dispersed on the skin, and was covered with a gauze-lined semiocclusive dressing. After 24 h, the dressing was removed and the skin was cleaned with water. Signs and symptoms were examined daily for 14 days. The animals were submitted to a gross necropsy at the end of the observation period.
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. No deviation from normal morphology was noted at necropsy.
Conclusion:	LD_{50} > 2000 mg/kg body weight
Remarks:	This study was conducted under GLP and OECD guidelines and considered reliable (reliability code 1)[2].
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.

[2]See general reference, p. 49.

B. 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.*[2] Male and female rats, weighing 199 to 244 g, were placed in nose-only exposure chambers, and exposed to an aerosol of the test material for 4 hours. During the exposure, the following parameters were controlled inside the inhalation cylinder: temperature (27-28 °C), relative humidity (46-49%), and oxygen content (19-21%). The concentration and the particle size distribution of the aerosol was monitored at 1 h intervals throughout the exposure. Concentrations were determined gravimetrically by sampling the test atmosphere. After a 4 h exposure the rats were returned to their cages. Physical condition and incidence of death were monitored throughout an observation period of 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} > 18 11 mg/m^3
Remarks:	This study is assigned a reliability code of 2e.[3] 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.

[2]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. 239-25 1, Zurich, 1973.

[3]See general reference, p. 49.

C. 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 formal guidelines, the methods closely paralleled that described in OECD Guideline 401 "Acute Oral Toxicity". Male and female rats, 7-8 weeks old, were administered the test substance by oral gavage at a dose of 5000 mg/kg body weight. All animals were observed for signs and symptoms of systemic toxicity and mortality for 14 days. Surviving animals were submitted to a necropsy at the end of the observation period.
Species/strain:	Tif: RAIf (SPF) Rats
Sex:	Male and Female
No. Animals/Group:	5/sex
Doses:	5000 mg/kg (20 mL/kg body weight)
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. No compound related gross organ changes were noted.
Conclusion:	The LD_{50} > 5000 mg/kg body weight
Remarks:	This study was 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 40 1. 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.
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

[2]See general reference, p. 49.

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:	This study was not conducted under OECD guidelines. 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. Each group consisted of 20 males, each of which was placed in a cage with 2 untreated females immediately after treatment. At the end of 1 week, the females were removed from the cages and replaced by another group of 2 females. The procedure was continued for 6 consecutive weeks. The females were examined daily for successful mating. Pregnant females were necropsied on Day 14 of pregnancy. The number of live embryos and embryonic deaths were recorded. In addition, the uteri were examined for early embryonic resorptions. Experimental data, particularly the numbers of implantations and embryonic deaths also were compared with cumulative data of untreated controls observed over a longer period of time.
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
Vehicle:	Aqueous carboxymethylcellulose (0.2 mL/kg body weight)
Control:	Concurrent Positive: None Negative: 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.

Table 1. Reproductive parameters

Dose group (mg/kg)	Mating Ratio	Number Pregnant	Mean Implantations	Live Embryos	Embryonic Deaths
Mating period 1					
0	35/40	29	11.97	91.4%	8.6%
1000	40/40	30	11.47	93.9%	6.1%
3000	38/40	33	11.55	92.9%	7.1%
Mating period 2					
0	37/40	30	11.30	93.5%	6.5%
1000	39/40	32	13.56	93.3%	6.7%
3000	38/40	32	12.88	95.2%	4.8%
Mating period 3					
0	35/40	33	12.55	93.7%	6.3%
1000	38/40	32	11.69	93.6%	6.4%
3000	32/40	29	12.66	94.6%	5.4%
Mating period 4					
0	39/40	34	11.56	92.9%	7.1%
1000	40/40	33	11.82	92.8%	7.2%
3000	36/40	30	12.33	91.4%	8.6%
Mating period 5					
0	35/40	31	11.65	87.0%	13.0%
1000	36/40	30	12.93	93.6%	6.4%
3000	35/40	34	12.94	92.3%	7.7%
Mating period 6					
0	34/40	30	11.43	89.8%	10.2%
1000	38/40	31	13.10	95.8%	4.2%
3000	38/40	34	11.62	92.7%	7.3%

Remarks: Although not conducted under GLP or OECD guidelines, this study did meet generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[2] The findings of this study were 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.

[2]See general reference, p. 49.

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. Chinese hamsters weighing 20-30 g of either sex were used. Animals (6 per group) were gavaged with either 500, 1000 or 2000 mg/kg test material. Positive controls were administered cyclophosphamide. Treatment consisted of daily administration on 2 consecutive days. Twenty-four hours after the second application, animals were sacrificed, bone marrow was harvested from the shaft of both femurs, and transferred to slides. The slides were stained in undiluted May-Grunwald solution and subsequently with Giemsa solution. 1000 bone marrow cells were scored from each animal, and the following anomalies were registered: single Jolly bodies, fragments of nuclei in erythrocytes, micronuclei in erythroblasts, micronuclei in leucopoietic cells, bizarre forms of nuclei, polyploid cells, andnecrobiotic cells.
Species/strain:	Chinese hamster
Sex:	Male or Female
No. Animals/group:	6/group
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 was considered to benonmutagenic.

Table 1. Percent of cells with anomalies of nuclei.

Dose	Animal No.	% Cells with Anomalies of Nuclei
Control	1	0.2
	2	0.2
	4	0.1
		0.2
		0.1
Cyclophosphamide	1	6.4
	2	6.8
	3	9.1
	4	7.3
	5	7.8
	6	5.2
500 mg/kg	1	0.1
	2	0
	3	0
	4	0.2
	5	0.1
	6	0.2
1000 mg/kg	1	0.1
	2	0.1
	3	0
	4	0.2
	5	0.1
	6	0.2
2000 mg/kg	1	0.2
	2	0.3
	3	0
	4	0.1
	5	0.3
	6	0.1

The total represents the sum of single Jolly bodies, fragments of nuclei in erythrocytes, micronuclei in erythroblasts, micronuclei in leucopoietic cells, bizarre forms of nuclei, polypolid cells, and necrobiotic cells. The study reported separate incidences for each endpoint. Only the total is represented in this table.

Remarks: Although not conducted under GLP or OECD guidelines, this study met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[2] The findings were 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.

[2]See general reference, p. 49.

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. Chinese hamsters weighing 23-30 g (females) and 27-38 g (males) were used. The treated groups consisted of 4 female and 4 male animals each. The control groups consisted of 6 female and 6 males each. 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. Four animals (2 females and 2 males) from each group were analyzed for the following: chromatid-type aberrations, chromosome-type aberrations, chromatid gaps, chromosome pulverations. Bone marrow from the shafts of both femora were removed, fixed, and transferred onto slides. Slides were stained with acetic-orcein. There was no indication whether slides were coded. 100 metaphases *were* analyzed per animal.
Type:	Somatic mutation assay
Species/strain:	Chinese Hamsters (Cricetulus griseus)
Sex:	Male/Female
No. Animals/Group:	4/sex/dose gmup
Route of Administration:	Gavage
Exposure period:	2 days
Doses:	500, 1000 and 2000 mg/kg
Controls:	Concurrent Positive: Cyclophosphamide (64 mg/kg) Negative: Vehicle only
Vehicle:	2% aqueous solution sodiumcarboxymethylcellulose 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 was within the frequency observed in historical controls and was therefore considered to be spontaneous in origin. Cyclophosphamide (64 mg/kg) the positive control caused an increase in all types of aberrations (chromatid-type aberrations 22.0%), chromosome-type aberrations (0.25%). The test material was considered to benonmutagenic.

Remarks: Although not conducted under GLP or OECD guidelines, this study did meet generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[2] The findings of this study were 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.

[2]See general reference, p. 49.

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 method described by Ames et *al.*[2-4] 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. The low solubility of the test compound limited the range of test concentrations. 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) were added. The DMSO vehicle was used for the negative control. Positive controls included N-methyl-N'-nitro-*N*-nitrosoguanidine for TA1535, 9(5)-aminoacridine hydrochloride monohydrate (for TA 1537), daunoblastin (for TA 98), and 4-nitroquinoline-N-oxide (for TA 100). The activation mixture was tested with TA 100 and cyclosphosphamide. In experiments without the addition of microsomal activation mixture, 3 Petri plates were prepared per strain and per group. In the experiments with activation mixture, 6 Petri plates were used per strain and per group. Three of each set of 6 were preincubated. Details of incubation time and temperature were not reported, but were based on the method reported by Ames *et al.*
Type:	Reverse mutation
Species:	S. typhimurium TA 98, 100, 1535, 1537
Concentration:	10 - 250 µg/plate (without metabolic activation) 10 - 250 @plate (with metabolic activation)
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
Conclusions:	No increase in mutations, with or without metabolic activation.

Table 1. Mean number of revertant colonies from experiments without metabolic activation

Dose	TA 98	TA 100	TA 1535	TA 1537
Control (DMSO)	21	116	13	5
10 µg/0.1 mL	27	96	18	5
25 µg/0.1 mL	25	103	20	7
50 µg/0.1 mL	28	95	14	6
100 µg/0.1 mL	22	107	15	3
250 µg/0.1 mL	24	94	16	7

Table 2. Mean revertants from experiments with metabolic activation (without/with preincubation

Dose	TA 98	TA 100	TA 1535	TA 1537
Control (DMSO)	34/29	208/190	22/19	10/9
5 µg/0.1 mL	30/36	187/169	19/19	6/7
10 µg/0.1 mL	26/30	194/172	16/22	8/7
25 µg/0.1 mL	35/30	197/196	20/22	8/10
50 µg/0.1 mL	39/31	193/197	17/16	8/10
100 µg/0.1 mL	32/36	162/188	16/20	8/9

Remarks: This study is considered scientifically sound and follows methods described by Ames et al. The study met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).[5]

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.

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

[5]See general reference, p. 49.

16. REPEATED 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 paralleled 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 (4 weeks old and weighing 71.4 to 93.7 g for males and 67.1 to 82 g for females) 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, loo, 300 mg/kg/day
Vehicle:	0.5% hydroxypropylcellulose in water
Dosing volume:	10 mL/kg body weight
Control group:	Concurrent vehicle
GLP:	Yes
Year:	1991

Results

NOAEL = 30 mg/kg body weight

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. A statistically significant increase in relative liver weight was observed in females of the high and intermediate dose groups. All high dose animals had minimal centrilobular hepatocytic hypertrophy. No other findings were observed that could be attributed to treatment.

Table 1. Summary liver weight data

Group	Liver weight (g)	Organ/Body weight (%)
Male		
Control	9.0 ± 0.7	3.57 ± 0.12
5 mg/kg	8.6 ± 0.9	3.41 ± 0.12
30	8.6 ± 0.8	3.44 ± 0.25
100	8.5 ± 0.8	3.45 ± 0.28
300	10.0 ± 0.7	3.84 ± 0.16
Female		
Control	5.7 ± 0.4	3.47 ± 0.08
5 mg/kg	6.6 ± 0.5	3.44 ± 0.13
30	6.1 ± 0.8	3.46 ± 0.20
100	6.6 ± 0.9	3.82 ± 0.25'
300	6.8 + 0.8	3.78 + 0.23'

*Statistically significant difference from control

Table 2. Incidence of centrilobular hypertrophy

Group	Incidence of hepatic hypertrophy
Male	
Control	0/5
5 mg/kg	0/5
30	0/5
100	0/5
300	4/5
Female	
Control	0/5
5 mg/kg	0/5
30	0/5
100	0/5
300	2/5

Remarks: This study was considered reliable (reliability code lb).* Although this study was not conducted under OECD guidelines, the methods closely paralleled the OECD guideline for repeat dose toxicity testing. Moreover, the study was conducted under GLP guidelines. Additional testing was considered unnecessary.

Reference: "4 Week Oral Gavage Toxicity Study in the Young Rat" Study No. 380/563. Hazelton France. N. Pickersgill, 04/26/9 1.

[2]See general reference, p. 49.

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:	Concurrent (diet without test material)
GLP:	Yes
Year:	1986
Results:	NOAEL Parental: 1500 ppm LOAEL F_1 Offspring: 500 ppm LOAEL F_2 Offspring: 500 ppm

5000 ppm: Findings at 5000 ppm among adults of both generations (F_0 and F_1) which appeared treatment related were as follows: (1) slight reduction in food consumption (Tables 1,2), weekly weight gain (Tables 3.4); (2) increase in liver weights and reductions in brain and spleen weights (Table 5). Histological analysis of livers from F_1 adult animals revealed minimal centrilobular hepatocyte enlargement. Histological analysis of the brain and spleen revealed no adverse abnormalities. Mating performance, pregnancy rate and the duration of gestation were unaffected by treatment (Tables 7-10). Of the litters from the high dose group, the litter size of the F_0 generation was slightly reduced. Postpartum pup loss was increased and pup weight gain was reduced. In the F_1 generation, initial litter size was reduced. Organ weight analysis of selected F_1 and F_2 weanlings showed effects on brain, liver

and spleen weights, but histological analysis revealed no adverse abnormalities (Table 6).

1500 ppm: Organ weight analysis of F_0 and F_1 adults showed significant reduction in spleen weight (Table 5). However, histological analysis revealed no treatment-related changes. Overall there was no clear indication of an adverse effect of treatment on litter data (Tables 7-10). Among selected F_1 and F_2 weanlings, statistically significant increases in liver weights and reductions in spleen weights were noted but deviations from controls were less than at 5000 ppm (Table 6). Slight reductions in brain weights were observed among F_1 weanlings. There were no treatment-related histological changes.

500 ppm: No effect on adults, other than a statistically significant reduction in spleen weight among adult F_0 males and F_1 females was noted (Table 5). There were no treatment-related effects on reproductive performance or on litter data (Tables 7-10). Among weanlings, an increase in liver weight and a decrease in spleen weight were observed among F_2 females only (Table 6). A slightly lower brain weight was observed among F_1 males only. There were no histological changes related to treatment.

Table 1. Weekly mean group food consumption F_0 adults (control and 5000 ppm groups)

Week	Control		5000 ppm	
	Male	Female	Male	Female
1	168 g	108 g	150 g	98 g
2	186	126	171*	116*
3	191	127	173*	119*
4	193	133	178*	122*
5	166	129	151*	125*
6	184	131	178*	121*
7	181	123	172*	114*
8	178	123	174*	109*
9	174	111	169*	104*
10	183	122	175*	116*

*Statistically significant difference from control

Table 2. Weekly mean group food consumption F_1 adult males (control and 5000 ppm groups)

Week	Control	5000 ppm
5	113 g	95 g
6	150	134*
7	173	159*
8	187	175*
9	191	185*
10	192	189*
11	192	195
12	186	185
13	178	180
14	182	182
15	176	178
16	170	173

*Statistically significant difference from control

Table 3. Mean body weight, F_0 adults (control and 5000 ppm groups)

Week	Control		5000 ppm	
	Male	Female	Male	Female
0	215 g	152 g	212 g	150 g
3	376	218	357	207
10	535	288	522	270
20	638	366	643	323

Among males, weight gains between weeks O-3 and 10-20 were significantly different from controls. Among females, weight gains between weeks O-3 and O-10 were significantly different from controls.

Table 4. Mean body weight, F_1 adult males

Week	Control	5000 ppm
4	83 g	68 g
8	304	268
16	511	498
24	591	587

Weight gains between weeks 4-8 and 8-16 were significantly different from controls.

Table 5. Organ weights (g)

	Brain Weight		Liver Weight		Spleen Weight	
	Male	Female	Male	Female	Male	Female
F_0 adults						
0 ppm	2.08	1.87	25.6	12.9	0.86	0.49
500 ppm	2.02	1.84	24.5	13.3	0.77	0.49
1500 ppm	2.07	1.87	25.8	13.5	0.81*	0.48
5000 ppm	2.08	1.86	28.1*	14.7*	0.76"	0.49
F_1 adults						
0 ppm	2.11	1.91	23.4	13.2	0.80	0.54
500 ppm	2.05	1.88	22.0	12.9	0.74	0.48*
1500 ppm	2.07	1.87	22.4	13.0	0.75	0.48*
5000 ppm	2.04*	1.84*	25.8"	14.5*	0.67"	0.44*

*Statistically significant difference from control

Table 6. Organ weights (g)

	Brain Weight		Liver Weight		Spleen Weight	
	Male	Female	Male	Female	Male	Female
F_1 weanlings						
0 ppm	1.40	1.34	2.35	2.29	0.20	0.20
500 ppm	1.36"	1.33	2.56*	2.52*	0.21	0.19
1500 ppm	1.37*	1.30"	2.65"	2.51"	0.18"	0.16"
5000 ppm	1.33*	1.30"	2.85	2.81*	0.17	0.16
F_2 weanlings						
0 ppm	1.43	1.37	2.49	2.49	0.22	0.21
500 ppm	1.42	1.37	2.72*	2.49	0.21	0.19
1500 ppm	1.41	1.39	2.85	2.72"	0.18"	0.18
5000 ppm	1.43	1.37	3.15*	3.12	0.18*	0.17

*Statistically significant difference from control

Table 7. Reproductive parameters at birth, F_0

	#Pregnant/ #Mated	Litter Size	Live Litter	Loss %	Litter Weight, g	Mean Pup Weight, g
Control	26/28	13.2	13.1	1.0	76.5	5.9
500 ppm	23/28	11.7	11.5*	2.0	68.1*	6.0
1500 ppm	22/28	11.8	11.4*	4.1	66.0*	5.9
5000 ppm	23/28	11.6*	11.0*	5.2*	61.8*	5.7

*Statistically significant difference from control

Table 8. Reproductive parameters at Day 21, F_0

	Litter Size	Cumulative Loss, %	Litter Weight, g	Mean Pup Weight, g
Control	12.2	7.3	464.6	38.8
500 ppm	10.9	6.8	426.9	40.4
1500 ppm	10.7	9.9	385.5	37.5
5000 ppm	9.9*	14.4*	321.9*	33.2*

*Statistically significant difference from control

Table 9. Reproductive parameters at birth, F_1

	#Pregnant/ #Mated	Litter Size	Live litter	Loss %	Litter Weight, g	Mean Pup Weight, g
Control	19/24	12.2	12.1	1.1	67.2	5.7
500	21/24	11.5	11.2	2.7	65.1	5.9
1500	21/24	12.1	11.7	3.4	66.4	5.7
5000	19/24	10.4	10.2	2.2	56.9	5.8

*Statistically significant difference from control

Table 10. Reproductive parameters at Day 21, F_1

	Litter size	Cumulative Loss, %	Litter Weight, g	Mean Pup Weight, g
Control	11.7	4.1	241.4	21.1
500	11.0	4.4	229.1	21.5
1500	11.1	7.4	230.4	21.0
5000	9.4*	8.0	187.3*	20.4

*Statistically significant difference from control

Remarks: This study was considered reliable as it was conducted under relevant guidelines (reliability code 1).[2]

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.

[2]See general reference, p. 49.

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 paralleled that described in OECD Guideline 414 "Teratogenicity", adopted May 12, 1981. Rats were mated overnight in a ratio of 1 male to 3 females. The day on which spermatozoa were detected in the vaginal smear was designated as Day 0 of pregnancy. Successfully mated females were kept in groups of 5, with 25 dams per dose and 30 for the control. 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 and the technique described by Wilson.[2,3]
Species/strain:	Sprague-Dawley Rats
Sex:	Female (initial body weight 240 g)
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
Control group:	Concurrent vehicle, 1 mL/100 g body weight
GLP:	No
Year:	1975
Results:	NOAEL Maternal Toxicity: = 150 mg/kg body weight NOAEL Teratogenicity : > 1000 mg/kg body weight

Maternal general toxicity: A dose-related reduction in food intake was noted during the treatment period (Table 1). Body weight gain was slightly depressed following the 500 and 1000 mg/kg doses (Table 2).
Pregnancy/litter data: No effects on pregnancy or litter data were noted (Table 3).
Fetal 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 (Table 4). Pups in the low dose group were unaffected.

Table 1. Mean group food consumption

Dose	Days 1-6	Days 7-11	Days 12-16	Days 17-21
Control	127.0 g	117.9	126.1	110.8
150 mg/kg	132.3	108.3	128.0	115.1
500 mg/kg	136.3	81.1	118.2	119.5
1000 mg/kg	126.4	75.7	106.9	117.4

Table 2. Mean body weight of females, g

Dose	Day 0	Day 15	Day 21
Control	212.3 ± 19.4	304.5 ± 25.4	363.4 ± 38.0
150 mg/kg	223.6 ± 22.4	310.5 ± 23.2	371.8 ± 42.2
500 mg/kg	215.9 ± 17.6	293.2 ± 20.9	358.8 ± 38.3
1000 mg/kg	215.9 ± 17.6	293.2 ± 20.9	349.9 ± 50.0

Table 3. Reproductive parameters

	Control	150 mg/kg	500 mg/kg	1000 mg/kg
#Surviving to Term	30/30	25/25	25/25	25/25
# with Implantations	28/30	22/25	23/25	22/25
Mean # Implantations	13.61	13.95	13.43	13.73
% Embryonic Resorptions	5.2	4.6	4.5	3.6
% Fetal Resorptions	0.3	0	0	0.3
% Dead Fetuses	0	0.3	0.3	0.3
% Live Fetuses	94.5	95.1	95.2	95.7
Live Fetuses with Malformations	0	0	1*	1*
Mean Weight of Live Fetuses, g	5.18	5.16	5.09'''	5.05**

*Cranioschisis, unilat. "open eyes"
**Statistically significant difference from control

Table 4. Incidence of unossified phalaugeal nuclei of the hind limb

Dose	Unossified phalangeal nuclei of the hind limb (%)
Control	15.1
150 mg/kg	26.9
500 mg/kg	15.8
1000 mg/kg	38.5

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

Remarks: This study was considered reliable (reliability code 2b).[4] Although it was not conducted 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 supported the conclusion of this study and was 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.

[2]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.

[4]See general reference, p. 49.

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 paralleled that described in OECD Guideline 4 14 "Teratogenicity", adopted May 12, 198 1. Mice were mated overnight at a ratio of 1 male to 4 females. The day on which a vaginal plug was observed was designated as Day 0 of pregnancy. Successfully mated females were kept in groups of 5, with 30 per dose group and 60 for the control. The compound was administered by oral gavage on Days 6 through 15 of pregnancy. During the treatment, general condition, weight gain, food consumption and symptornology 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 and the technique described by Wilson.[2,3]
Species/strain:	Albino Mice (NMRI derived)
Sex:	Female (initial body weight 30 g)
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/10 g bw)
Control group:	Concurrent vehicle
GLP:	No
Year:	1975
Results:	NOAEL maternal toxicity: 1000 mg/kg body weight NOAEL teratogenicity : 1000 mg/kg body weight

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.

Table 1. Reproductive paramaters

	Control	150 mg/kg	500 mg/kg	1000 mg/kg
#Surviving to Term	60/60	30/30	30/30	30/30
# with Implantations	51/60	25/30	26/30	25/30
Mean # Implantations	11.57	11.25	11.29	11.67
% Embryonic Resorptions	7.3	5.5	7.4	7.5
% Fetal Resorptions	1	0	0	0
% Dead Fetuses	0.2	0.4	0	0.4
% Live Fetuses	91.6	94.1	92.6	92.1
Live Fetuses with Malformations	1/540	0/254	1/251	1/540
Mean Weight of Live Fetuses, g	1.13	1.11	1.12	1.20

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

[2]World Health Organization Technical Report Service 563, 1975

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

[4]See general reference, p. 49.

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
la: GLP guideline study
lb: Comparable to guideline study
lc: 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 restictions
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