AR201-13209

on 10/10/2001 09:58:04 AM

To: NCIC OPPT/DC/USEPA/US@EPA
cc:

Subject: Robust Summary for CAS#1843-05-6

Administrator
US Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116
Attention: Chemical Right-to-Know Program

Please find attached a Robust Summary being submitted for the HPV Challenge Program, AR-201. This test plan/data summary is attached as a WORD file: 1843056.doc.

Cytec Industries Inc. Registration number:
Ciba Specialty Chemicals Corporation Registration Number:

The Robust Summary being submitted is for CAS# 1843-05-6, 2-hydroxy-4-n-octoxybenzophenone.

If you have any questions please call me directly at .

Regards,
Lisa Navarro, Ph.D.

1843056.doc

DATA SUMMARY & TEST PLAN
For
2-Hydroxy-4-n-Octoxybenzophenone

October 10, 2001

OVERVIEW

Cytec Industries Inc. and Ciba Specialty Chemicals Corporation hereby submit for review a test plan for 2-Hydroxy-4-n-Octoxybenzophenone under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of these companies to use existing data to adequately fulfill the Screening Information Set (SIDS) for environmental fate endpoints, ecotoxicity tests, and human health effects for this substance. We believe that adequate data exist to fulfill all the requirements of the HPV program without the need for additional testing.

US EPA High Production Volume (HPV)
Chemical Challenge Program

Data Summary
&
Test Plan

2-Hydroxy-4-n-Octoxybenzophenone
CAS No. 1843-05-6

October 10, 2001

Names of Sponsoring Companies:

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CONTENTS

DATA SUMMARY TABLE

CAS No. 1843-05-6	DATE	RESULTS	FULFILLS REQUIREMENT
PHYSICAL/CHEMICAL ELEMENTS			
Melting Point	2000	47 -49 ^{o}C	Yes
Boiling Point	1968	> 300 ^{o}C (Decomposes)	Not applicable
Vapour Pressure		--	Not applicable
Partition Coefficient	2000	Log Kow > 6.00	Yes
Water Solubility	2001	<7.3 x 10^{-7} g/L of solution at 20.0±0.5°C	Yes
ENVIRONMENTAL FATE AND PATHWAYS ELEMENTS			
Photodegradation	2001	For reaction with hydroxyl radical, predicted rate constant = 218.14 x 10^{-12} cm^3/molecule-sec predicted half-life = 0.59 h [EPIWIN Program]	Yes
Stability in Water	2001	The estimated half-life at pH 4, 7, and 9 at 25°C is > 1 year.	Yes
Fugacity	2000	Predicted distribution using Level III Fugacity model Air 0.09% Water 8.2% Soil 29.5% Sediment 62.2% [EPIWIN Program]	Yes
Biodegradation	1989	Not Biodegradable	Yes
ECOTOXICITY ELEMENTS			
Acute Toxicity to Fish	1988	Zebra fish (Brachydanio rerio): LC_{50} (96 h) > 100 mg/L	Yes
Toxicity to Aquatic Plants	1992	Green Algae (Scenedesmus subspicatus) EC_{50} (0 -72 h) > 100 mg/L	Yes
Acute Toxicity to Aquatic Invertebrates	1988	Daphnia magna Straus 1820 EC_0 (24 h) > 10 mg/L EC_{50} (24 h) > 52 mg/L	Yes
MAMMALIAN TOXICITY			
Acute Toxicity	1965	>10 g/kg (rats)	Yes
Genetic Toxicity: Gene Mutations	1991	Non-mutagenic to bacterial cells	Yes
Genetic Toxicity: Chromosomal Aberration	2001	Non-clastogenic to human lymphocytes *in vitro*	Yes
Repeated Dose Toxicity	1965	Rat 30-day Dietary	Yes
	1965	Rat 90-day Dietary NOEL = 0.6 % (6000 ppm)	Yes
	1965	Dog 120-day Dietary NOEL = 0.6% (6000 ppm)	Yes
	1968	Rat 90-day Dietary NOEL = 0.15 % (1500 ppm)	Yes
	1969	Rats 90-day Dietary NOEL = 1000 ppm	Yes
Reproductive/ Developmental Toxicity	1969	Rats NOEL = 0.6% (6000 ppm) for 4 Successive Generations	Yes

PROPOSED TEST PLAN

CAS# 1843-05-6	Data Available	Data Acceptable	Testing Required
Study	Y/N	Y/N	Y/N
Physical/Chemical Characteristics			
Melting Point	Y	Y	N
Boiling Point	NA	NA	N
Vapor Pressure	NA	NA	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
Environmental Fate			
Photodegradation	Y	Y	N
Hydrolysis	Y	Y	N
Fugacity	Y	Y	N
Biodegradation	Y	Y	N
Ecotoxicity			
Acute Toxicity to Fish	Y	Y	N
Acute Toxicity to Invertebrates	Y	Y	N
Acute Toxicity to Algae	Y	Y	N
Mammalian Toxicity			
Acute Toxicity	Y	Y	N
Repeat Dose Toxicity	Y	Y	N
Genetic Toxicity: Gene Mutations	Y	Y	N
Genetic Toxicity: Chromosomal Aberration	Y	Y	N
Developmental Toxicity	Y	Y	N
Reproductive Toxicity	Y	Y	N

GENERAL INFORMATION

A. INTRODUCTION

On November 22 and 29, 1999, respectively, Cytec Industries Inc. (Cytec) and Ciba Specialty Chemicals Corporation (Ciba) agreed to participate in the Environmental Protection Agency's (EPA) High Production Volume Chemical Challenge Program. By participating in this program, Cytec and Ciba agreed to assess the adequacy of existing data, design and submit test plans to fill data gaps where necessary and appropriate, provide test results, and prepare summaries of the data characterizing each chemical sponsored.

The sponsored chemical addressed in this test plan is 2-hydroxy-4-n-octoxybenzophenone, (CAS # 1843-05-6).

B. GENERAL SUBSTANCE INFORMATION

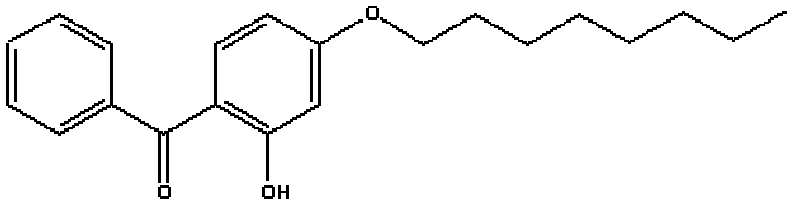
Chemical Name: 2-hydroxy-4-n-octoxybenzophenone

Description: The substance is a pale, cream-to-white powder with friable lumps.

Chemical Abstract Service Registry Number: CAS # 1843-05-6

Common Name: Benzophenone-12

Chemical Formula: $C_{21}H_{26}O_3$
Molecular Weight: 326.42
Structure:



C. GENERAL USE INFORMATION

2-Hydroxy-4-n-octoxybenzophenone is an effective photostabilizer for a variety of plastic systems. It may be used in food packaging materials as an antioxidant and stabilizer and in addition may be used as a stabilizer in petroleum wax. As such, it is cleared under the 21 CFR (Code of Federal Regulations) §178.2010 for use as a stabilizer in polypropylene, polyethylene, olefin copolymers, and poly(methylpentene) complying with limitations set forth in §177.1520c and also under 21 CFR §178.3710. When used in packaging materials, 2-hydroxy-4-n-octoxybenzophenone prevents UV-radiation from reaching the stored product and increases the stability of the container. In order to be approved by the FDA for such uses, 2-hydroxy-4-n-octoxybenzophenone has been thoroughly evaluated for its potential toxicity.

DATA SUMMARIES

1. MELTING POINT

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	Directive 84/449/EEC, A.1 “Melting point/ melting range” From Material Safety Data Sheet[1]
GLP:	Yes
Year:	1993
Results:	47 - 49 °C
Remarks:	The melting point was obtained from MSDS of Ciba Specialty Chemicals Corporation and is consistent with that on the MSDS of Cytec Industries Inc. The method of determination and other details were not reported. The melting point estimate is assigned a reliability code of 2g[2] (data from handbook or collection of data).
References:	[1]Ciba Specialty Chemicals Corp. [2]See listing of codes, p.38.

2. BOILING POINT

Test substance: 2-Hydroxy-4-n-Octoxybenzophenone
CAS No. 1843-05-6

Not applicable. This substance is a solid and decomposes at temperatures >300 ºC[1]

References: [1]Patel, Y.M. Levinskas, G.J., and Shafer, C.B. 1968. Toxicity and Metabolism of 2-Hydroxy-4-n-Octoxybenzophenone. *Fd Cosmet. Toxicol*. Vol. 6, pp. 199-208.

3. VAPOR PRESSURE

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
	Not applicable. This substance is a solid

4. PARTITION COEFFICIENT

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	From Material Safety Data Sheet[1]
GLP:	Yes
Year:	2000
Results:	Log Kow > 6.00
Remarks:	The partition coefficient was obtained from the MSDS of Ciba Specialty Chemicals Corporation. The method of determination and other details were not reported. The partition coefficient estimate by this method is assigned a reliability code of 2g[3] (data from handbook or collection of data). The partition coefficient was also estimated by KOWWIN Program (V1.66)[2]. The calculated value is 6.96.
References:	[1]Ciba Specialty Chemicals MSDS [2]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 listing of codes, p.38.

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	Estimated using TOPKAT[1] v.3.05
GLP:	Does not apply to estimated data based on Structure Activity Relationship
Year:	1999
Results:	Log Kow = 6.416
Remarks:	The partition coefficient estimated by this method is assigned a reliability code of 2f[2].
References:	[1]Health Designs, Inc. Rochester, NY. 1999. [2]See listing of codes, p.38.

5. WATER SOLUBILITY

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	Column Elution Method, Method A6 of Commission Directive 92/69/EEC and OECD Guideline Method 105
Temperature:	20.0 ± 0.5°C
GLP:	Yes
Year:	2001
Results:	$<7.3 \times 10^{-7}$ g/L of solution
Remarks:	Preliminary Test: An aliquot (0.300 g) of test material was diluted to 900 ml with glass double-distilled water. After shaking at 30°C for 68 hours and standing at 20°C for 24 hours, the solution was centrifuged, filtered and analysed. The preliminary estimate of water solubility was $<6.44 \times 10^{-5}$ g/L. Definitive Test: An aliquot (0.1051 g) of test material was dissolved in acetone (20 ml). Glass beads were added and the solvent removed using a rotary evaporator. The elution apparatus was set up consisting of glass micro-column fitted with a plug of glass wool, and connected to a recirculating pump and a reservoir capable of holding approximately 2 L of water. The circulating water was maintained at 20.0 ± 0.5°C by means of a water bath. The whole system was flushed for 2 hours, and the water was discarded. The reservoir was re-filled with fresh glass double-distilled water and the coated bead loaded into the micro-column. After allowing the coated beads to soak for ~15 hours, the re-circulating pump was switched on and the first 25 ml of eluate discarded. Aliquots (~250 ml) of sample solution were taken from the column at intervals of at least ten bed volumes of eluate and centrifuged. This procedure was carried out in duplicate. Analysis of the test material in the sample solutions was determined by high performance liquid chromatography (HPLC). The water solubility determination by this method is assigned a reliability code of 1a[2].
References:	[1]SafePharm Laboratories Limited. Determination of Abiotic Degradation, Hydrolysis as a function of pH and Water Solubility. SPL Project Number: 971/121. Sponsored by Cytec Industries Inc., 2001. [2] See listing of codes, p.38.

6. PHOTODEGRADATION

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
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
Year:	2000
Results:	For reaction with hydroxyl radicals, the predicted half-life of the chemical is rapid. Rate constant: 218.14 x 10^{-12} cm^3/molecule-sec Half-life: 0.59 h
Remarks:	The photodegradation 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 listing of codes, p.38.

7. STABILITY IN WATER

Test substance: 2-Hydroxy-4-n-Octoxybenzophenone
CAS No. 1843-05-6

Method: Method C7 of Commission Directive 92/69/EEC and OECD Guidelines Method 111

GLP: Yes

Year: 2001

Results: The estimated half-life of the test material at 25°C is shown in the table below:

pH	Estimated half-life at 25°C
4	> 1 year
7	> 1 year
9	> 1 year

Remarks:

Preparation of buffer solutions:
The buffer solutions were filtered through a 0.2 mm membrane filter to ensure they were sterile before commencement of the test. Also, these solutions were subjected to ultrasonication and degassing with nitrogen to minimize dissolved oxygen content.

Buffer pH	Components	Concentration (mol dm^{-3})
4	Potassium hydrogen phthalate	0.01
7	Disodium hydrogen othrophosphate (anhydrous) Potassium dihydrogen othrophosphate Sodium chloride	6.00×10^{-3} 4.00×10^{-3} 4.00×10^{-3}
9	Disodium tetraborate Sodium chloride	2.00×10^{-3} 4.00×10^{-3}

Preparation of samples:
Sample solutions were prepared in stoppered glass flasks at a nominal concentration of 3.44×10^{-7} g/l in the three buffer solutions. Solutions were shielded from light and maintained at the test temperature.

Results:
Sample solutions at pH 4, 7, and 9 were maintained at 50.0 ± 0.5°C for 5 days. Aliquots of sample solutions were taken at various times

and pH recorded. The concentration of the sample solution was determined by HPLC.

Less than 10% hydrolysis after 5 days at 50°C, equivalent to a half-life greater than 1 year at 25°C was the result for each of the buffer solutions tested.

The Abiotic Degradation, Hydrolysis as a function of pH determination by this method is assigned a reliability code of 1a[2].

References:

[1]SafePharm Laboratories Limited. Determination of Abiotic Degradation, Hydrolysis as a function of pH and Water Solubility. SPL Project Number: 971/121. Sponsored by Cytec Industries Inc., 2001.

[2] See listing of codes, p.38.

8. THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	EPI WIN level III Fugacity model. [1]
Year:	2000
GLP:	No
Results:	Distribution using level III fugacity model

Air	0.09 %
Water	8.2%
Soil	29.5 %
Sediment	62.2%

Remarks: The fugacity calculation by an accepted method is assigned a 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 listing of codes, p.38.

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9. BIODEGRADATION

Test substance: 2-Hydroxy-4-n-Octoxybenzophenone
CAS No. 1843-05-6
Batch No. EN 130125.82

Method: The protocol generally followed OECD Guideline 301 B, algae growth inhibition test. Instead of centrifuged sludge, settled sludge was used. The substance was not dissolved but distributed in the test medium. The sludge concentration in the test bottle was reduced from 3.0 L to 1.5 L.

Species: Bacteria collected from activated sludge of the sewage treatment plant.

Duration: 28 days

Temperature: 22 ± 2^0 C

Reference Substance: Aniline MERCK No.: 1261

Concentrations: Reference substance: 20 mg/L
Test substance: 10.7 mg/ L, and 20.2 mg/ L.

GLP: No

Year: 1989

Results: The observed biodegradation was:

Test Material	***Dose***	***Result (in 28 days)***
reference substance	20 mg/L	84.3 %
test substance	10.7 mg/L	6 %
test substance	20.2 mg/L	5 %

The test substance is not biodegradable under these experimental conditions.

Remarks: This study is assigned a reliability code of 2c[2] (comparable to guideline study with acceptable restrictions) according the criteria established by Klimisch *et al* (1997).

Reference: [1]Report On The Test For Ready Biodegradability Of TK 10050 In The Modified Strum Test; Project No: 188 45 60; U. Bader, Dr. A. De Morsier; Ciba-Geigy Ltd. Basle, Switzerland.

[2] See listing of codes, p.38.

10. ACUTE TOXICITY TO FISH

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6 Batch No. EN 130125.82
Method:	OECD Guideline No. 203 (Paris 1984).
Species:	Zebra Fish (Brachydanio rerio)
Supplier:	West-Aquarium, D-3422 Bad Lauterberg
Length:	26 mm (22-29 mm)
Weight:	0.17 g (0.12 - 0.23 g)
Loading:	0.11 g/L
Test Concentrations:	10, 18, 32, 58, 100 mg/L (nominal)
Controls:	Blank: Water Vehicle: 100 mg DMF and 0.8 mg alkylphenol-polyglykol-ether per liter water
Exposure period:	96 h
Analytical monitoring:	No
GLP:	No
Year:	1988
Results:	LC_{50} (96 h): > 100 mg/L LC_0 (96 h): > 100 mg/L Mortalities in blank and in vehicle: 0%
Remarks:	This study is assigned a reliability code of 2b[2] (guideline study with acceptable restrictions) according the criteria established by Klimisch *et al* (1997), as it was conducted under OECD Guidelines.
Reference:	[1]Report Test For Acute Toxicity Of TK 10050 To Zebra Fish; Project No.: 884561; Drs H. Rufli, A. De Morsier; Ciba-Geigy Ltd. Basle, Switzerland.

[2] See listing of codes, p.38.

11. TOXICITY TO AQUATIC PLANTS

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6 Batch No. EN 253644.02
Method:	According to the guidelines 87/302/EEC Algal growth inhibition test. The static Scenedesmus subspicatus toxicity screen was conducted in 100-mL Erlenmeyer flasks containing 50 mL of algae nutrient media or test solution. The temperature was maintained at 24 ± 1^0 C with continuous illumination with cold white fluorescent light. Each test concentration was tested in 3 replicates and the blank control in 6. Cell densities were measured at 24, 48 and 72 hours exposure.
Species:	Green Algae (Scenedesmus subspicatus)
Initial cell density	10400 cells/mL
Test concentrations :	Test substance: 1.23, 3.7, 11, 33, and 100 mg/L (Nominal) Controls: Blank: Water Vehicle: 96.0 mg n-methyl-2-pyrrolidone and 4.0 mg polyoxy-ethylene-sorbitan-monooleate (TWEEN 80)/1
Exposure period:	72 h
Analytical monitoring:	No
GLP:	No
Year:	1992
Results:	EbC_{50} (0-72 h): > 100 mg/L (growth inhibition) $NOEbC_{50}$ (0-72 h): 100 mg/L
Remarks:	This study is assigned a reliability code of $2c^2$ (comparable to guideline study with acceptable restrictions) according the criteria established by Klimisch *et al* (1997).
Reference:	[1]Report On The Inhibition Test Of Chimassorb 81 to green algae (Scenedesmus subspicatus); Dr. A. Von Schulthess, Ciba-Geigy Ltd., Additives Division, CH-4002, Basel, Switzerland. [2] See listing of codes, p.38.

12. ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6 Batch No. 130125.82
Method:	OECD Guideline No. 202 (Part I, 1984).
Species:	Daphnia magna Straus 1820
Exposure period:	24 hours
Test Concentration:	0.58, 1.0, 1.8, 3.2, 5.8,10, 18, 32, 58 mg/L (nominal)
Controls:	Vehicle: 94.5 mg 1-methyl-2-pyrrolidon and 0.6 mg alkylphenol-polygycol ether per liter water Blank: Water.
Analytical monitoring:	No.
GLP:	No.
Year:	1988
Results:	EC_{50} (24 h) calculated: 52 mg/L (confidential limits: 36-100 mg/L) EC_0 (24h): 10 mg/L Immobilization in blank 0 % Immobilization in vehicle 0 %
Remarks:	The study is assigned a reliability code of $2c^2$ (comparable to guideline study with acceptance restrictions). Values are based on nominal concentrations.
Reference:	[1]Report On The Test For Acute Toxicity of TK 10050 To Daphnia Magna; OECE-Guideline No. 202, Part I, 1984; Project No.: 884562; Drs. A. de Morsier, H. Rufli; CIBA-GEIGY Ltd., Basel, Switzerland. [2]See listing of codes, p.38.

13. ACUTE TOXICITY

Acute Rat Oral LD50

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	Test material dosed as a 20% aqueous dispersion.
Species/strain:	Carworth Farm Nelson strain Albinos Rats
Sex:	Male
No. Animals/Group:	10
Doses:	A single 10 g/kg dose
Post dosing observation period:	Dosing was followed by a 7-day observation period. No signs of intoxication were observed post-dosing. In addition, no abnormal findings were noted following gross autopsy.
GLP:	Conducted prior to GLP.
Year:	1965
Results:	**Oral LD_{50} (rat) > 10 g/kg.** 10 male CF Nelson albino rats were dosed with a 20% aqueous dispersion of the product at a dose of 10.0 g/kg. 0/10 died, and there were no signs of intoxication; the gross autopsy was normal.
Remarks:	This study is assigned a rating code of $2e^{2}$ (meets generally accepted scientific standards, well documented and accepted for assessment).
References:	[1]American Cyanamid Company, Wayne, New Jersey. Report 65-58. June 30, 1965. [2]See listing of codes, p.38.

14. GENETIC TOXICITY

A. Ames Salmonella Mutagenicity Assay(1)

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6 Batch No. EN 254644.02
Method:	This study was not conducted under OECD guidelines, but was conducted using the methods described by Ames *et al* (1973, 1975).[2,3,4] The mutagenicity test was performed with the Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 with and without microsomal activation according to Standard Operating Procedures of Genetic Toxicology.
Type:	Bacterial mutagenicity
System of testing:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
GLP:	No
Year:	1991
Results:	In the experiments performed with and without microsomal activation, comparison of the number of histidine-prototrophic mutants in the controls and after treatment with TK 10050 revealed no marked differences.
Remarks:	This study is assigned a rating code of 2e[5] (meets generally accepted scientific standards, well documented and accepted for assessment).
References:	[1]Bacterial Mutagenicity Screening Test; CIBA-GEIGY Limited, Basel, Switzerland; September 02, 1991. [2]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. [3]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 Salmonella/mammalian-microsome mutagenicity test, Mutat. Res., 31, 347-364, 1975. [5]See listing of codes, p.38.

B. Ames Salmonella Mutagenicity Assay (2)

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6 Lot # W-8720
Method:	This study was not conducted under OECD guidelines, but was conducted using the methods described by Ames *et al* (1973, 1975).[2,3,4] The mutagenicity test was performed with the strains Salmonella typhimurium TA 98, TA 100, TA 1535 and TA 1537, and Escherichia coli WP-2 uvrA- with and without microsomal activation according to Standard Operating Procedures of Genetic Toxicology.
Type:	Bacterial mutagenicity
System of testing:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537; Escherichia coli WP-2 uvrA-
GLP:	No
Year:	1981
Results:	In the experiments performed with and without microsomal activation, no mutagenic activity was noted at doses up to 1000 µg/plate. Doses tested were 100, 333, 1000, 2500, and 5000 µg/plate. Precipitate on plates was noted at 2500 and 5000 µg/plate doses. Background lawns appeared intact.
Remarks:	This study is assigned a rating code of 2e[5] (meets generally accepted scientific standards, well documented and accepted for assessment).
References:	[1]Bacterial Mutagenicity Screening Test; American Cyanamid Company, Report M81-28. February 6, 1981. [2]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. [3]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 Salmonella/mammalian-microsome mutagenicity test, Mutat. Res., 31, 347-364, 1975. [5]See listing of codes, p.38.

C. Chromosome Aberration Test in Human Lymphocytes In Vitro

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	Method B10 of Commission Directive 92/69/EEC and OECD Guidelines Method 473
Type:	Genetic Toxicology: Chromosome Aberration Test
System of testing:	Cultured human lymphocytes
GLP:	Yes
Year:	2001
Results:	Cells/Cell Culture: Cells obtained from the peripheral circulation of suitable volunteers. The human lymphocytes were grown in supplemented Eagle's minimal essential medium (MEM) with HEPES buffer. Test and Control Materials: The test material was dissolved in acetone and serially diluted. Final concentrations of the test material included 0, 51, 102, 204, 408, 612, and 816 µg/ml (Concentrations selected were based on results of a preliminary assay). Vehicle and positive controls were used in parallel with the test material. The vehicle control was acetone. The positive controls were mitomycin C dissolved in MEM at 0.4 and 0.2 µg/ml, in the absence of S9 and Cyclophosphamide dissolved in dimethyl sulphoxide at 12.5 µg/ml, in the presence of S9. Treatment: Treated lymphocytes were evaluated for chromosomal aberrations at up to four dose levels, together with vehicle and positive controls. Four treatment conditions were used for the study. In Experiment 1, 4 hours in the presence of an induced rat liver homogenate metabolising system (S9), at a 1% final concentration with cell harvest after a 20-hour expression period, or a 4-hour exposure in the absence of metabolic activation (S9) with a 20-hour expression period. In Experiment 2, the 4-hour exposure with the addition of S9 was repeated (using a 2% final S9 concentration) whilst in the absence of metabolic activation the exposure time was increased to 24 hours. Results: All vehicle (solvent) controls gave frequencies of cells with aberrations excluding gaps within the range expected for normal human lymphocytes. All positive control treatments gave statically significant increase in the frequency of cells with aberrations indicating the satisfactory performance of the test and of the activity of the metabolizing system. The test material did not induce any statistically significant increase in the frequency of cells with aberrations, in either of two separate experiments, using a dose range that included a dose level that induced approximately 50% mitotic

inhibition. However, in the 4-hour exposure group without metabolic activation the limiting factor was the presence of test material precipitate where maximum exposure was achieved at 816 µg/ml.

Conclusion: The test material was shown to be non-clastogenic to human lymphocytes *in vitro* both in the presence or absence of S9.

Remarks: This study is assigned a rating code of 1a[2].

References:

[1]Chromosome Aberration Test in Human Lymphocytes In Vitro; SPL Project Number 971/120. Safepharm Laboratories Ltd, Derby, UK; 2001.

[2]See listing of codes, p.38.

15. REPEATED DOSE TOXICITY

A. Subchronic (30 day) toxicity test in rats

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	This study was conducted to determine the potential oral toxicity of the test article upon continuous administration in feed for 30 days to rats. The test material was fed at dietary levels of 0, 1.25, 2.5, or 5.0% to groups consisting of 10 males each. The body weight and food consumption of each rat was recorded, permitting mean food intake and weight gain to be determined. After 30 days, rats were killed and examined grossly.
Species/strain:	Albino CF Nelson rats
Weight at initiation:	Mean weight gain: Control: 156 g 1.25%: 142 g 2.50%: 129 g (Significantly different from controls) 5.00%: 131 g (Significantly different from controls)
Sex:	Male
No. animals/group:	10 males / group
Route of admininstration:	Dietary
Exposure period:	30 days
Frequency of treatment:	Daily
Dose:	0, 1.25, 2.5, and 5% in food
GLP:	No
Year:	1965
Results:	During the feeding period, animals at the 1.25% level were comparable to the controls, but dietary levels of 2.5% and 5.0% were not well tolerated. Animals at these 2 higher levels had a poor appearance. Some rats in each test group showed signs of gross hematuria, and one death occurred in the 5.0% group. At autopsy, intact kidneys of animals for the two high dose groups appeared normal, but cut suctions revealed yellow masses in the renal tubules. Similar yellow masses were noted in the urinary bladders of several animals at these levels. The masses are believed to be glucuronides which have been observed with other benzophenone derivatives.

Mean weight gain of the 2.5% and 5.0% groups, and mean food intake of the 2.5% feeding level, were significantly lower than corresponding values for the controls. Mean daily dosage was calculated as 1.22 g/kg, 2.29 g/kg, and 4.78 g/kg for the 1.25%, 2.5% and 5.0% dietary levels, respectively.

The no-toxic-effect level (NOEL) was not determined.

Remarks: This study is assigned a reliability code of 2e[2] (meets generally acceptable scientific standards, is well documented, and acceptable for assessment) according to the guidelines described by Klimisch *et al* (1997).

Reference: [1]American Cyanamid Company. Subchronic (30 day) toxicity test in rats; Report No: 65-58, June 30, 1965.

[2]See listing of codes, p.38.

B. Subchronic (90 day) toxicity test in rats

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone, 99.0% LOT # 8072 CAS No. 1843-05-6
Method:	This study was conducted to determine the potential oral toxicity of the test article upon continuous administration in feed for 3 months to rats. The test material was fed at dietary levels of 0, 0.2, 0.6, or 1.8% to groups consisting of 20 males and 20 females. The diet was prepared at weekly intervals and was available ad lib. The body weight of each rat was recorded twice a week. The food consumption of each group was determined weekly. Haematological data were collected from 5 animals of each sex animals in the 11th week.. At the time of autopsy, liver and kidney weights were determined for 10 animals of each sex/group. 15 animals of each sex/group were examined grossly, weights of organs were recorded, and extensive histopathological examinations were conducted.
Species/strain:	Carworth Farms, Nelson strain albino rats, approximately 5 weeks of age at start of study.
Weight at initiation:	Mean weight: males: 77-125 g females: 75-110 g
Sex:	Male/Female
No. animals/group:	20 males & 20 females/ group
Route of administration:	Dietary
Exposure period:	90 days
Frequency of treatment:	Daily
Dose:	0, 0.2, 0.6 and 1.8% in feed
GLP:	Conducted prior to GLPs
Year:	1965
Results:	The overall appearance and behaviour of all animals were good throughout the feeding period. Only 2 deaths occurred during the study period, a 0.2% female found dead on day 5 and a 0.6% male which lost weight in week 11 and died in week 12. Advanced autolysis prevented the determination of the cause of death in both instances. However, since no deaths occurred at the maximum feeding level of 1.8% it was concluded that the deaths were not related to the test article. There were no significant differences in mean weight gain between any test group and its corresponding control. There were no significant

differences in mean food intake between test and control animals. There were no significant differences in mean hemoglobin or mean hematocrit between and of the test groups. Females in the 0.2% group had a very slight but significant decrease in total leukocyte, but was judged to be coincidental and unrelated to feeding of the test material as not differences in leukocyte counts were noted in the two higher dietary levels.

Mean liver weight of the 0.2% males and of both sexes at 0.6% was significantly increased, but no effect on liver weight was noted in the 1.8% dietary groups. Thus this was determined to be unrelated to the test article.

Mean kidney weight was significantly decreased for the 0.2% females and significantly increased for the 1.8% males. There was a slight, but not significant increase in the kidney weights of the 1.8% females. The observed increases in kidney weight at the 1.8% dietary levels could be test article related.

No significant lesions were encountered at the time of autopsy. The no-toxic-effect level (NOEL) was 0.6% in the diet.

Remarks: This study is assigned a reliability code of 2e[2] (meets generally acceptable scientific standards, is well documented, and acceptable for assessment) according to the guidelines described by Klimisch *et al* (1997).

Reference: [1]American Cyanamid Company. Sub-Chronic (90-day) toxicity test with UV-531 in rats. Report # 65-64. July 15, 1965.

[2]See listing of codes, p.38.

C. Subchronic (90 day) toxicity test in rats

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6
Method:	This study was conducted to determine the potential oral toxicity of the test article upon continuous administration in feed for 3 months to rats. The test material was fed at dietary levels of 0, 0.065, 0.1, or 0.15% to groups consisting of 10 males and 10 females. The diet was prepared bi-weekly, and was constantly available. The body weight of each rat was recorded once a week. The food consumption of each group was determined in the first 4 weeks and in the 11^{th} and 12^{th} weeks. Haematological data were collected from all animals in the 13^{th} week, and biochemical data collected in the 14^{th} week. At 14 weeks, rats were sacrificed, examined grossly, and weights of organs were recorded. Extensive histopathological examinations were conducted.
Species/strain:	Wistar rats
Weight at initiation:	Mean weight: males: 41 - 62 g females: 43 - 61 g
Sex:	Male/Female
No. animals/group:	40 males & 40 females/ group
Route of admininstration:	Dietary
Exposure period:	90 days
Frequency of treatment:	Daily
Dose:	0, 0.065, 0.1 and 0.15% in food
GLP:	No
Year:	1968
Results:	No deaths or untoward reactions were recorded throughout the 90-day feeding study. Gain in body weight, food intake, food efficiency, haematology, glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase and alkaline phosphotase in the serum showed no treatment related abnormalities at any dietary level. Organ-to-body weight ratios were slightly increased for the kidney at the highest feeding level in females and for the thyroid at the two highest levels in males. Gross and microscopic examination did not reveal pathological changes attributed to the feeding. The no-toxic-effect level (NOEL) was 0.15% in the diet.

Remarks: This study is assigned a reliability code of 2e[2] (meets generally acceptable scientific standards, is well documented, and acceptable for assessment) according to the guidelines described by Klimisch *et al* (1997).

Reference: [1]Sub-Chronic (90-day) toxicity test with "V 67-531" in rats. Report # 2769; Drs H.P. Til, Miss Drs. H.C. van der Meulen, Drs. J.W. Huismans and Dr. A.P. de Groot; November 1968; Central Institute for Nutrition and Food Research.

[2]See listing of codes, p.38.

D. Subchronic (90 day) toxicity test in rats

Test substance:	2-Hydroxy-4-n-Octoxybenzophenone CAS No. 1843-05-6; Batch No. EN
Method:	This toxicity study was conducted to determine the potential oral toxicity of the test article upon continuous administration in feed for 3 months to rats. The diet for each test group was prepared weekly by blending the appropriate amount of the test compound with standard rat diet. Concentrations of the test compound in the feed were 1000 and 6000 ppm. Food and water were available ad libitum. Abnormal reactions and deaths were recorded daily. Body weights and food consumption were recorded weekly. Haematology, clinical blood chemistry, and urine were analyzed after 45 and 84 days. Surviving animals were sacrificed after 90 days and subject to gross examination. Organ weights were recorded and microscopic examination was conducted.
Species/strain:	Albino Rats, Charles River strain
Sex:	Male/Female
No. animals/group:	15 males & 15 females/ group
Route of administration:	Dietary
Exposure period:	90 days
Frequency of treatment:	Daily
Dose:	1,000 and 6,000 ppm
GLP:	No
Year:	1969
Results:	No outstanding differences in food consumption, body weight, or weight gain were observed between test and control rats. There were no effects of treatment on haematology, blood chemistry, or urinalysis. The liver and kidney weights were higher among males in the 6000 ppm group compared to controls. The gonad weights were higher among females in the 1000 ppm group relative to controls. There were no effects of treatment on gross pathology.
Remarks:	This study is assigned a reliability code of $2e^2$ (meets generally acceptable scientific standards, is well documented, and acceptable for assessment) according to the guidelines described by Klimisch *et al* (1997)
Reference:	[1]Ninety-Day Subacute Oral Toxicity Of TU-1103 In Albino Rats; IBT No: B6680, January 8, 1969, Industrial Bio-test laboratories, Inc.

[2] See listing of codes, p.38.

E. Subchronic (120 day) toxicity test in dogs

Test substance: 2-Hydroxy-4-n-Octoxybenzophenone
CAS No. 1843-05-6, Lot # 8072, 99.0% Purity.

Method: This study was conducted to determine the potential oral toxicity of the test article upon continuous administration in feed for 124-127 days to beagle dogs. The test material was initially fed at dietary levels of 0, 0.2, 0.6, or 1.8%. Due to unpalatability of the 1.8% dietary level it was reduced to 0.4% at the end of week 2. Each test group consisted of 2 males and 2 females, while 2 animals of each sex served as controls.

There were no deaths and the appearance and behaviour of the dogs were good during the test period. Except for food refusal by the group started on the 1.8% diet, the acceptance of the diet was good. Body weight was determined at weekly intervals and food consumption was recorded daily, permitting mean food intake and weight gain to be determined. Water was provided ad libitum. All animals were observed daily with full physical examinations at 1-2 month intervals.

Hematology: Prior to start of the study, hematocrit, total hemoglobin and total and differential leukocyte counts were performed, and then repeated at week fourteen.

Clinical Chemistry: Prior to the start and at week 14, alkaline phosphatase, glucose and urea nitrogen were determined in blood plasma from all animals. In addition, BSP (bromosulfopthalein) clearance was determined on each of the 16 dogs prior to the start and at week 15.

Species/strain: Pure-bred Beagle Dogs, 4½ 6 months of ages at start of study.

Mean Body Weight at Initiation:

Treatment Group	Males (kg)	Females(kg)
Control	3.92	5.06
0.2%	4.65	4.93
0.4%	4.87	4.12
0.6%	4.70	4.70

Sex: Male/Female

No. animals/group: 2/sex/group

Route of administration: Dietary

Exposure period: 124-127 days

Frequency of treatment: Daily

Dose: 0, 0.2, 0.4, and 0.6% in food

GLP: No; Conducted prior to GLP Standards.

Year: 1965

Results: General Observations: During the feeding period, the overall condition of the dogs was good, and their appearance and behavior was normal. Several of the dogs had intestinal parasitic infestations that were treated with various remedies until apparently cured or controlled.

Food Intake: Except for the refusal of the high dietary concentration at the start of the study, the acceptance of the diets was quite good. Most of the animals ate essentially all of the food offered to them. The relatively elevated food refusals of a few of the dogs were judged to reflect individual differences in appetite among the animals. There was no correlation between food refusal and dietary concentration of the test materials at 0.6% or lower.

Mean weight gain/
Mean terminal body weights:

Treatment Group	Mean Weight Gain	Terminal Body Weight	Mean Weight Gain	Terminal Body Weight
	Males (kg)		Females(kg)	
Control	2.38	6.30	1.23	6.29
0.2%	2.54	7.19	1.35	6.28
0.4%	2.48	7.35	2.00	6.12
0.6%	2.40	7.10	1.31	6.01

While there were individual differences in the percentage weight gain, there was no evident correlation between weight gain and either food consumption or dietary level of the test material. The smallest weight gain was recorded for a control female in which an abnormally elongated lower jaw interfered with eating.

Hematology: Mild absolute, as well as relative, eosinophilia was present in many of the blood samples taken toward the end of the study. However, this was also found in the smears from the controls. It was determined that there was no apparent correlation between the degree of eosinophilia and dietary concentrations of the test material. An occasional lymphocyte in the blood smear from a 0.4% male dog after 14 weeks on the test showed abnormal morphology and staining. This is not an uncommon finding in blood smears and it occurs in dogs as well as in humans. It is of little or no importance unless associated with other evidence of blood dyscrasia or with other clinical signs. Such lymphocytes were not found in smears from the other 3 dogs at the 0.4% dose level, nor were they observed in the 4 dogs at the higher dietary concentration and (0.6%). Therefore it is concluded that the observed lymphocyte changes in this dog are unrelated to ingestion of the test material.

Except for the above observations, there were no other abnormalities in the leukocytes, and no aberrations were seen in wither erythrocytes or thrombocytes. Mean hematocrits, total hemoglobin concentrations, and total leukocyte counts for each dietary group did not differ significantly from the corresponding control mean. Therefore it was determined that the test material feed to dogs at dietary concentrations up to 0.6% for 14 weeks had no effect on hematocrit, total hemoglobin concentrations, or total leukocyte count.

Clinical Chemistry: As an expected result of maturation, the plasma alkaline phosphatase levels of every dog decreased during the 14 weeks of the feeding interval. At the end of the study, only 3 dogs had phosphatase levels above the acceptable range for adults. The highest level occurred in a control females and the other 2 values occurred in one male and one female of the 0.4% treatment group. Since none of the dogs at the 0.6% treatment group had elevated alkaline phosphatase levels, and since all group means were within the 95% confidence limits for that measurement, it was concluded that the test material did not affect alkaline phosphatase. All individual values for plasma glucose, urea nitrogen, and percent retention of BSP were within acceptable ranges, and the corresponding mean values did not differ significantly from control means.

Gross and Microscopic Findings: Complete autopsies, including opening of the cranium were performed. Organ weights were recorded for the spleen, pancreas, liver, adrenal, kidney, thyroid, heart, pituitary, brain and testes. At autopsy all animals were in good general condition with the exception of one control female. This animal had developed an over-elongation of the lower jaw (prognathism) with resultant misalignment of teeth, impaired feeding and smallness of stature. Although no statistical evaluation was made, organ weights were comparable for each group and treatment with test material was judged to be without adverse effect on the organ weights.

No lesions, gross or microscopic, could be attributed to ingestion of the test material.

It was concluded that feeding this material to dogs at levels as high as 0.6% (6000 ppm) for 120 days did not result in either gross or microscopic lesions referable to ingestion of the product..

Remarks: This study is assigned a reliability code of 2e[2] (meets generally acceptable scientific standards, is well documented, and acceptable for assessment) according to the guidelines described by Klimisch *et al* (1997).

Reference: CYASORB® UV-531 Light Absorber: Repeated Feeding Study in Dogs. American Cyanamid Company, Report # 65-63, July 14, 1965.

[2]See listing of codes, p.24.

16. REPRODUCTIVE/DEVELOPMENTAL TOXICITY

Test substance: 2-Hydroxy-4-n-Octoxybenzophenone
CAS No. 1843-05-6
99.0% Pure, WB-0785

Method: This toxicity study was conducted to determine whether ingestion of the test material would interfere with reproduction, lactation, or development of offspring. The reproduction and lactation performance, which was evaluated in terms of the criteria proposed by Oser and Oser (1959), is summarized below for each mating for the 4 generations combined. The study followed the general recommendations in "The Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" (The Association of Food and Drug Officials of the Untied States, pp 43, ff., (1959).

Methods:
Young adults, approximately 4-6 weeks of age were received in the laboratory and subsequently mated when they were ~3 months of age. This initial mating was conducted to ensure that the progenitors of the study were fecund. At 21 days of age, the offspring of the stock animals were placed on the study as the F_0 generation. The series of generations were managed according to the outline below:

F_0 Generation
⇒F_1Generation
⇒F_2Generation
⇒F_{3a}Generation (Used for microscopic pathology ad skeletal examination)
⇒F_{3b}Generation
⇒F_4 Generation

Diet:
At weaning, the offspring produced by mating of the stock animals were placed on the study as the F_0 Generation. They were assigned to diets containing 0 (control) or 0.6% (6000 ppm) dietary concentration (~523.9 mg/kg/day (males) and ~614.3 mg/kg/day (females)). The test material was incorporated into ground lab chow on a weight basis, prepared weekly. Pups were weaned directly onto the diets their parents had been receiving.

Management:
Animals were housed singly after weaning; as pairs for mating. Food and water were available ad libitum. Abnormal reactions and deaths were recorded daily. Body weights were recorded periodically for all generations and food consumption was measured to time of mating for the F_0 Generation.

Species/strain: Albino Rats, Charles River CD strain

Sex: Male/Female

No. animals/group:	16 males & 16 females/ group; 80 matings cumulatively.
Route of administration:	Dietary
Exposure period:	4 Generations
Frequency of treatment:	Daily
Dose:	0 and (0.6%) 6,000 ppm
GLP:	No
Year:	1969
Results:	The fertility, gestation, viability and lactation indices for the test and control groups were comparable and quite high in most instances. An occasional dip in one of the indices was followed by a higher value in a subsequent mating, thus indicating that there was no impairment of reproduction or lactation performance. Overall, there was an identical distribution of values for both groups. Consequently, it was concluded that a diet containing 0.6% (6000 ppm) of the test material had no adverse effect on the reproduction and lactation performance of rats. There were no apparent differences in the number of live births or the number of pups weaned between the control and test groups. The average pup from rats fed the test material weighed slightly more than the average control pups. Pups of all litters, including those which died before weaning, were examined for gross defects. However, autopsies were performed only on pups from the first mating of the F2 animals (F3a Generation). The latter pups were killed at weaning. Immediately after death, the 2 males and 2 females which were the smallest or least healthy appearing of each litter were set aside while the others were autopsied and examined for gross lesions. One of each sex of those set aside was autopsied, and portions of all organs were taken for histologic processing and examination. The other 2 animals were examined for skeletal defects using skeletal staining. The only condition which occurred frequently was hydronephrosis. This is a known spontaneous lesion in rats. Most cases were unilateral, involving the right kidney, and males were afflicted more frequently than females. The incidence of this condition was higher in control animals. Microscopic findings were few and clearly not related to treatment. No skeletal abnormalities were seen in the control or treated pups. A group of 3 treated pups was sacrificed at 12 days of age after the mother had eaten their littermates. Their cleared skeleton appeared normal except for an apparent reduction in length of all bones, as compared to control animals of the same age. This may have resulted from maternal mineral deficiency. It is concluded that feeding the test material to rats from weaning through reproductive age for 4 successive generations at a level of

0.6% did not produce lesions in the parents or anomalies in the offspring which could be attributed to the compound.

Remarks: This study is assigned a reliability code of 2e[2] (meets generally acceptable scientific standards, is well documented, and acceptable for assessment) according to the guidelines described by Klimisch *et al* (1997).

Reference:

[1]Oser and Oser (1959) J. Nutrition, 60: 498-505.

[2]American Cyanamid Company. .Four Generation Reproduction and Lactation Study in Charles River Albino Rats; Report No: 69-251, December 18, 1969.

[3]See listing of codes, p.38.

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

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 acceptance 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 a foreign language
4e: Documentation insufficient for assessment