

ATTACHMENT 4

TINOSORB[®] M

Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (MBBT)

Next Generation UV Filter for Sun Protection

**Information Package
Submitted with Citizen's Petition**

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Submitted by

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1. INTRODUCTION

1.1 BACKGROUND

This document summarizes the physical/chemical and toxicological data for a new sunscreen additive produced by Ciba Specialty Chemicals Corporation ("Ciba"), Consumer Care Division. Ciba's Consumer Care Division (formally Ciba-Geigy) is one of the world's leading developers and producers of technical UV-absorbers and is well known for its competence in UV-Protection.

The brand name for the product is Tinosorb[®] M. The official International Nomenclature Cosmetic Ingredient (INCI) name for this substance is: Methylene Bis-Benzotriazolyl Tetramethylbutylphenol ("MMBT"). Chemically it is known as 2,2'-Methylenebis[4-(1,1,3,3-tetramethylbutyl)-6-benzotriazolylphenol] (CASRN: 103597-45-1). The material is currently under patent and Ciba is the sole manufacturer. Tinosorb M is the first micronized organic filter sunscreen agent. It exhibits strong and broad UVA-protection with significant UVB-absorption. In addition, the micronized particles provide further protection by scattering and reflecting light. Tinosorb M exhibits extremely high photostability in contrast to Avobenzone, which is photolabile. Tinosorb M is extremely easy to formulate in many different types of sunscreen bases. The critical wavelength of Tinosorb M (λ_c) is 388 nm. The UVA/UVB-ratio of Tinosorb M is 1.0 and Tinosorb M exhibits a synergistic effect when formulated with other sunscreen agents such as Octyl Methoxycinnamate (OMC) and 4-Methylbenzylidene Camphor (MBC). As a consequence of its high photostability, MBBT is fully compatible with other UV absorbers and can be used in any combination without adverse effects. Furthermore, MBBT shows a stabilizing effect on other non-photostable UV absorbers. Adding MBBT to a conventional formulation makes the formulation more photostable (Herzog, B., 2000).

1.2 SUMMARY OF EXISTING SAFETY DATA

Tinosorb M exhibits low toxicity by dermal and oral routes of exposure. Acute rat dermal and oral LD₅₀ values are >2,000 mg/kg. Tinosorb M caused minimal irritation when applied to rabbit eyes and skin. Tinosorb M did not cause sensitization, photoirritation, or photosensitization when applied to the skin of guinea pigs or humans. Tinosorb M was not genotoxic in several different assays with and without UV activation. In an *in vitro* assay, Tinosorb M exhibited low penetration (0.14%) across human skin with 20% considered to be absorbed into the skin layers. In a 90-day subchronic oral gavage study in the rat, the No-Observable-Effect-Level (NOEL) are 1,000 mg/kg/day, which was the highest dose tested. In a developmental toxicity study, the maternal and fetal NOELs were 1,000 mg/kg, which were the highest doses tested. Detailed summaries of each study can be found in Section 3.

1.3 RISK ASSESSMENT

As summarized in the previous section, Tinosorb M exhibited very low toxicity by the dermal and oral routes of exposure. In addition, Tinosorb M did not exhibit enhanced toxicity upon exposure to UV radiation, which is critical for a UV-protectant. Tinosorb M did not exhibit compound or dose-related toxicity in subchronic and developmental toxicity studies. A safety factor of > 100 exists between NOELs in animal studies and estimated human exposures. Based on this information, Tinosorb M is safe for use as a human skin UV-protectant since it is unlikely to cause any toxic effects after dermal exposure.

As with any compound that is applied repeatedly to the skin, the potential for inducing cancer should be assessed. Tinosorb M is considered very unlikely to induce cancer and/or enhance UV-induced cancer for several reasons. First, Tinosorb M was not genotoxic in two different assays with and without UV activation. Second, Tinosorb M is very photostable (see Section 2.6)

indicating that Tinosorb M is unlikely to degrade into compounds that pose an unknown hazard. Third, Tinosorb M was not phototoxic or photoallergenic when applied to human or guinea pig skin. Fourth, Tinosorb M diminished the effects of UV irradiation on human skin compared to controls in a human phototoxicity study (see Section 3.6.1) and a human photoallergenicity study (see Section 3.6.2). Taken together, these data clearly indicate that Tinosorb M is unlikely to either induce cancer by itself or enhance UV-induced cancer.

In conclusion, the safety data clearly indicate that Tinosorb M is unlikely to pose a health hazard when applied to human skin in sunscreen formulations.

2. PHYSICAL-CHEMICAL DATA

2.1 CHEMICAL NAME

2,2'-Methylene-bis-(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)-phenol

2.2 MOLECULAR FORMULA

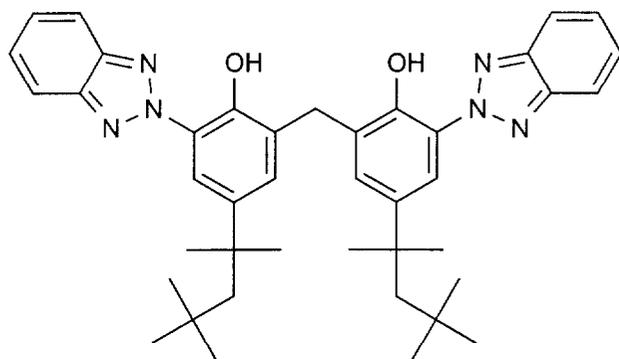
$C_{41}H_{50}N_6O_2$

2.3 MOLECULAR MASS

658.86 g/mol

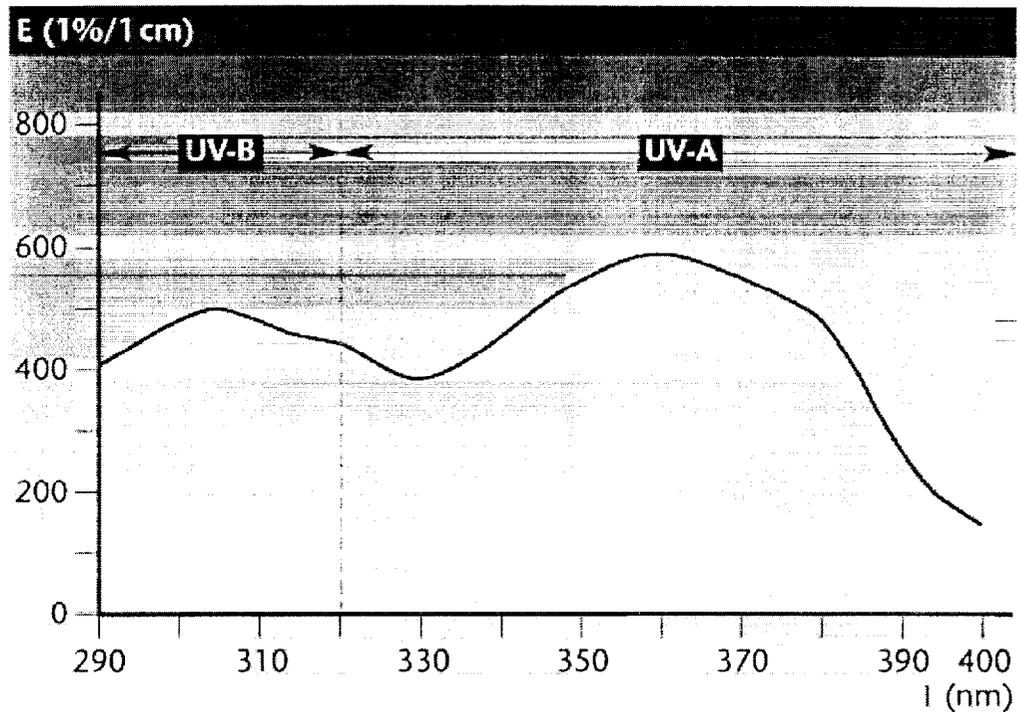
2.4 STRUCTURE

Figure 1. Structure of Tinosorb M



2.5 UV-SPECTRUM (IN ETHANOL)

Figure 2. UV-Spectrum of Tinosorb M



2.6 PHOTOSTABILITY

The photostability of Tinosorb M was measured in terms of recovery of the substance after application of different doses of UV-light. The testing was performed using two independent methods, each employing defined irradiation and adapted analysis procedures (Method A was similar to the procedure suggested by Berset, G. et al., *Int. J. Cosmet. Sci.* **18** (1996) 167 - 177; and Method B was based on the irradiation of a highly diluted UV-filter solution). Doses of UV-light were varied between 0 and 50 MED (minimal erythemal doses) and the samples were analyzed afterwards using high performance liquid chromatography (HPLC) and UV-spectroscopy, respectively. For comparison purposes: 15 MED corresponds to one summer day in the southern United States at sea level: e.g. Houston Texas; whereas up to 20 MED can be received at higher altitudes (Pathak, M.A., 1997); and a maximum of 30 MED can be obtained in tropical regions, such as Townsville, Australia (Bernhard, G., 1997).

The table below summarizes the recoveries of Tinosorb M as obtained from UV-spectroscopic analysis. As seen in Table 1, even after a UV-dose of 50 MED, recoveries of >98% were detected using the different methods, indicating that Tinosorb M is an extremely photostable UV-filter.

Table 1. Recoveries of Tinosorb M as obtained from UV-spectroscopic analysis including 95% confidence intervals

Dose (MED)	Mean Recovery \pm 95% CI (%)
0	100.0 \pm 0.2
5	99.8 \pm 0.2
10	99.7 \pm 0.2
20	99.3 \pm 0.2
50	98.3 \pm 0.2

Notes: MED = minimal erythema dose; CI = confidence interval

2.7 SPF

4% Tinosorb M (*in vivo*): 4

2.8 UVA/UVB-RATIO

The UVA/UVB-ratio is the ratio of the areas under the extinction curve in the UVA-range (320 - 400 nm) and the UVB-range (290 - 320 nm), each area divided by the range of wavelengths involved.

UVA/UVB-ratio of Tinosorb M = 1.00

2.9 CRITICAL WAVELENGTH

The critical wavelength (λ_c) is the wavelength up to which from 290 nm on, the area under the extinction curve is 90% of the area of the extinction curve between 290 and 400 nm [5].

Critical wavelength of Tinosorb M (λ_c) = **388 nm**

Like the UVA/UVB-ratio, the critical wavelength depends not only on UVA- but also on UVB-absorption

2.10 SOLUBILITY

Dispersible in water (solubility $< 7 \times 10^{-6}$ g/l in water)

2.11 PARTICLE SIZE DISTRIBUTION

Less than 5% of the particles in Tinosorb M showed a particle size $< 40 \mu\text{m}$ (lowest mesh size used) using the sieving method. About 50 wt% was determined to be smaller than $218 \mu\text{m}$ (median mass diameter). The OECD Guideline for testing of chemicals, No. 110, "Particle Size Distribution/Fiber Length and Diameter," could not be used since the particle size distribution of Tinosorb M was too large.

2.12 MELTING POINT

195.7°C

2.13 OCTANOL/WATER PARTITION COEFFICIENT

Log P_{ow} > 12.7

2.14 WATER SOLUBILITY

< 7×10^{-6} g/l

2.15 VAPOR PRESSURE

6×10^{-13} Pa at 25°C

2.16 EXPLOSIVE PROPERTIES

The substance is not considered to be explosive, thermally, shock or friction sensitive.

2.17 FLAMMIBILITY

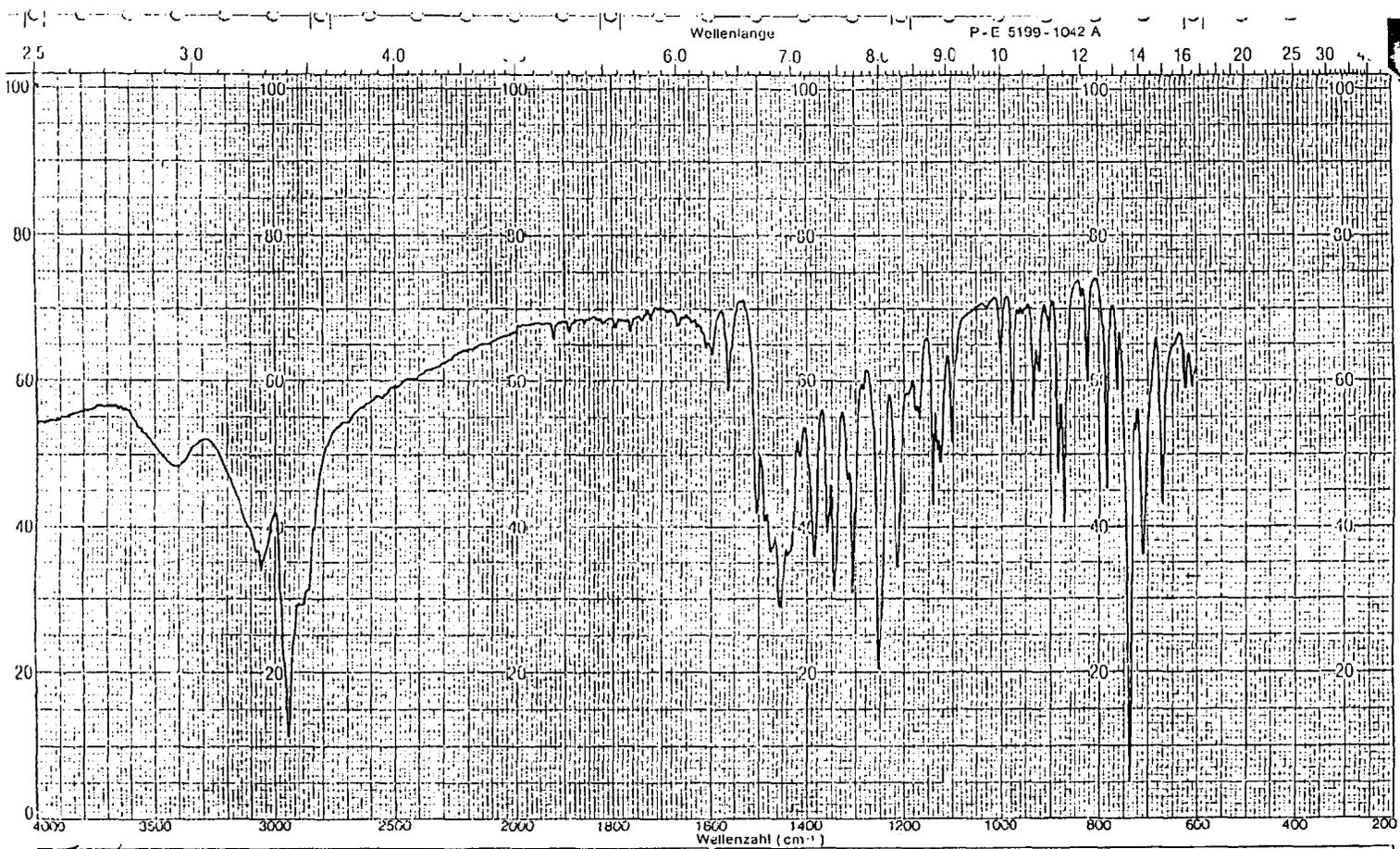
Not Flammable

2.18 RELATIVE DENSITY

1.20 g/cm³ at 22°C

2.19 FT-IR ABSORPTION SPECTRA

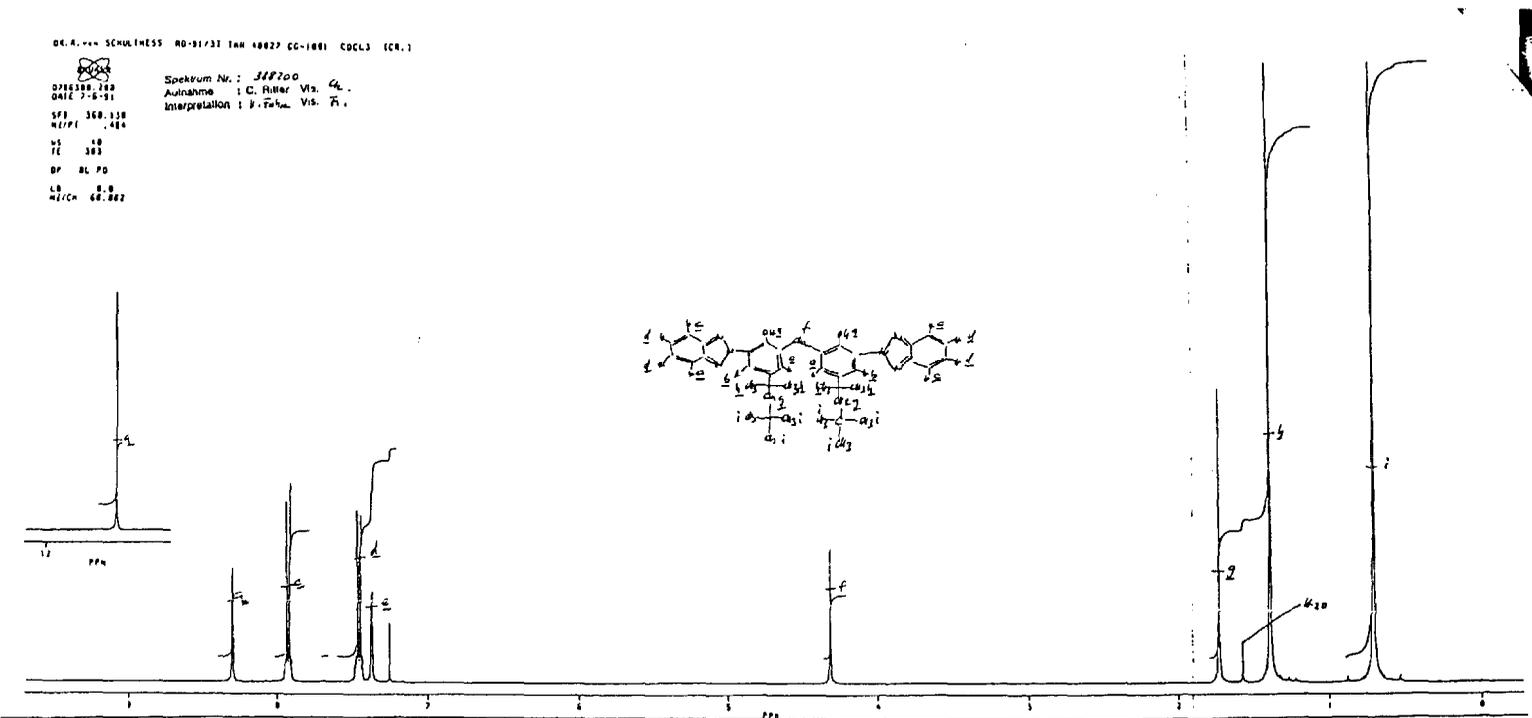
Figure 3. FT-IR Spectra for Tinosorb M



An. No. 102505		Wellenzahl (cm ⁻¹)	
Muster: CG30-1881 TKA 40027 EN 302690.12	Aufnahmetechnik: HBr	Bemerkungen: 1.0mg / 300mg Perkin Elmer 299	Operator: E. Ackli Frau E. Ackli
Herkunft: Dr. H. von Schulthess	Schichtdicke:	Datum: 3. 7. 89 R-1062.2.17 73818	Spektrum Nr.:
	Spaltprogramm: mittel		
	Registrierzeit: 8 Min.		

2.20 ¹H-NMR-SPECTRUM

Figure 4. ¹H-NMR-spectrum for Tinosorb M



DE.A. SCHULTHEISS RD-91/31 IAH 48827 GC-1881 CDCL3 (CDCl3)

Spektrum Nr.: 3117200
 Aufnahme: C. Riller Vis. CL
 Interpretation: B. Fehle Vis. F.

0716338.282
 DATE 7-5-91
 SFS 368.128
 NS 18
 TE 103
 OF AL PD
 LO 6.0
 MHz 62.882

3. SUMMARY OF PRE-CLINICAL AND CLINICAL STUDIES

Below is a summary of the various pre-clinical and clinical studies conducted on Tinosorb M (Table 2). Detailed study summaries follow the table.

Table 2. Summary of Tinosorb M Pre-Clinical and Clinical Studies

Study	Results
Acute	
Acute Dermal Toxicity in Rats	LD ₅₀ > 2000 mg/kg
Acute Oral Toxicity in Rats	LD ₅₀ > 2000 mg/kg
Irritation/Sensitization	
Primary Skin Irritation Study in Rabbits	Not Irritating
Primary Eye Irritation Study in Rabbits	Not Irritating
Skin Sensitization (Guinea Pig Maximization Test)	Not Sensitizing
Phototoxicity in Guinea Pigs	Not Phototoxic
Photoallergenicity in Guinea Pigs	Not Photoallergenic
Sub-Chronic	
14-Day Oral Gavage Range Finding Study	NOEL = 1000 mg/kg
28-Day Oral Gavage Toxicity Study in the Rat	NOEL = 1000 mg/kg
90-Day Oral Gavage Toxicity Study in the Rat	NOEL = 1000 mg/kg
Range Finding Developmental Study in Rats	NOEL = 1000 mg/kg
Developmental Toxicity Study in Rats	NOEL = 1000 mg/kg
Genotoxicity	
S. typhimurium and E. coli Reverse Mutation Assay	Negative
In Vitro Chromosome Aberration Assay in Chinese Hamster Ovary Cells	Negative
Photomutagenicity: S. typhimurium and E. coli Reverse Mutation Assay	Negative
Photomutagenicity: In Vitro Chromosome Aberration Assay In Chinese Hamster V79 Cells	Negative
Absorption	
In Vitro Human Skin Distribution	≈20% Penetrated Into Skin
In Vitro Human Skin Penetration	0.14% Penetrated Across Skin
Clinical	
Phototoxicity in Humans	Not Phototoxic
Photoallergenicity in Humans	Not Photoallergenic

¹ Note: Human tests conducted on trade form (50% a.i.), while tox. tests conducted on pure form (100% a.i.)

3.1 ACUTE STUDIES

3.1.1 Acute Dermal Toxicity in Rats

Tinosorb M was applied to the shaved skin of five male and five female albino (Tif: RAI f1 (SPF)) rats at a dose of 2000 mg/kg and covered with a semi-occlusive dressing. Tinosorb M was suspended in a vehicle (0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80) at a concentration of 0.5 g/ml and administered at a volume of 4 ml/kg. After 24 hours of exposure, the dressing was removed and the treated skin washed with water. No deaths occurred during the study. The only clinical signs noted were piloerection and hunched posture, which cleared within 3 days after termination of exposure. No local effects of the test article on the skin at the application site were noted during the observation period of 15 days. The body weight of the animals were within the range of physiological variability known for rats of this

strain and age. No macroscopic organ findings were observed at necropsy. Since no deaths occurred during the study, the LD₅₀ is >2000 mg/kg (Hartmann, 1991a).

3.1.2 Acute Oral Toxicity in Rats

Tinosorb M was administered to five male and five female albino (Tif:RAI f1 (SPF)) rats at a dose of 2000 mg/kg by oral gavage. Tinosorb M was suspended in vehicle (0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80) at a concentration of 0.2 g/ml and administered at a volume of 10 ml/kg. The animals were observed for a period of 15 days. The only clinical signs noted were piloerection, hunched posture, and dyspnea, which cleared within 4 days after termination of exposure. The body weights of the animals were within the range of physiological variability known for rats of this strain and age. No macroscopic organ findings were observed at necropsy. Since no deaths occurred during the study, the LD₅₀ was >2000 mg/kg (Hartmann, 1991b).

3.2 IRRITATION/SENSITIZATION STUDIES

3.2.1 Primary Skin Irritation in Rabbits

Tinosorb M was applied to the shaved skin of three adult male New Zealand white rabbits (Chbb:NZW) for four hours using a semi-occlusive exposure. Five hundred milligrams of Tinosorb M was applied to a gauze patch (approximately 12-16 cm²) moistened with vehicle (0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80). The patch was applied to a shaved area of skin for four hours after which the dressing was removed and the application site washed with water. A control patch moistened with vehicle was applied on a separate area of shaved skin. The scoring of skin reactions was performed 1, 24, 48, 72, and 168 hours after removal of the dressing. Mean erythema scores (on a scale of 0 [none] to 4 [severe]) at 1, 24, 48, 72, and 168 hours were 1, 0.33, 0.33, 0, and 0 for Tinosorb M-treated skin, respectively. Mean edema scores (on a scale of 0 [none] to 4 [severe]) at 1, 24, 48, 72, and 168 hours were 1, 0, 0, 0, and 0 for Tinosorb M-treated skin, respectively. No erythema or edema were noted on vehicle-treated skin. The primary irritation score (PIS) was calculated by adding the mean erythema to the mean edema scores at 24, 48, and 72 hours and dividing by the number of figures. The primary irritation score was 0.11 (max. 8.0). Based on the PIS, Tinosorb M is, according to the EEC system, not irritating to the skin. By EPA guidelines it is considered minimally irritating to the skin (Hagemann, 1991a).

3.2.2 Primary Eye Irritation in Rabbits

Tinosorb M (60 mg) was instilled into one eye of each of three adult male New Zealand white rabbits (Chbb:NZW). The treated eyes were not rinsed after application. Scoring of irritation effects was performed 1, 24, 48, 72, and 168 hours after application. No corneal or iris effects were noted at any time. Mean conjunctival redness scores (on a scale of 0 [none] to 3 [severe]) at 1, 24, 48, 72, and 168 hours were 1, 1, 1, 0.33, and 0, respectively. Mean conjunctival chemosis scores (on a scale of 0 [none] to 4 [severe]) at 1, 24, 48, 72, and 168 hours were 1, 0, 0, 0, and 0, respectively. The primary irritation score (PIS) was calculated by totaling the individual cumulative scores at 24, 48, and 72 hours and then dividing the resulting total by the number of figures. The primary irritation score was 0.78 (max 13). Based on the PIS, Tinosorb M is, according to the EEC system, not irritating to the skin. By EPA guidelines it is considered minimally irritating to the eye (Hagemann, 1991b).

3.2.3 Skin Sensitization (Guinea Pig Maximization Test)

Tinosorb M was administered to Albino guinea pigs (10 per sex/group) using a skin Maximization-Test protocol. Five male and five female guinea pigs served as controls. Induction occurred over the first two weeks. At the start of the first week, the animals received three intradermal injections (0.1 ml/site) in separate areas of the skin in the neck region. The injections consisted of 1) 1:1 (v/v) mixture of Freund's Complete Adjuvant (FCA) and physiological saline, 2) 5% (w/v) Tinosorb M in oleum arachidis, and 3) 5% (w/v) Tinosorb M in a 1:1 (v/v) mixture of FCA and physiological saline. Control animals received the same three injections without Tinosorb M. One day prior to the start of the second week, the injection sites were treated with a 10% solution of sodium-lauryl-sulfate to enhance sensitization by provoking a mild inflammatory reaction. At the start of the second week, approximately 0.4 g of a mixture of 30% (w/w) Tinosorb M in white petrolatum was topically applied on a filterpaper patch (2x4 cm) to the neck of the animals using an occlusive exposure for 48 hours. Control animals received the same topical application without Tinosorb M. During weeks 3 and 4 no treatments were performed.

Following the rest period, the challenge phase started. Two hundred milligrams of 10% (w/w) Tinosorb M in white petrolatum was topically applied to one flank using a 24-hour occlusive exposure (2x2 cm patch). The other flank received 200 mg of white petrolatum only. Control animals received the same challenge treatment. Skin reactions were evaluated 24 and 48 hours after removal of the challenge exposure patch. During the induction phase, irritant reactions that are normally induced by the adjuvant, the high test article concentration, and/or the sodium-lauryl-sulfate, were observed. No atypical irritant reactions were noted during the induction phase. During the challenge phase, no erythema or edema was noted in any Tinosorb M-induced animal after the challenge exposure. Only one control animal exhibited any reaction after challenge with Tinosorb M, which consisted of very slight erythema 24 hours after the challenge exposure. In conclusion, under the test conditions, Tinosorb M was not a skin sensitizer (Hagemann, 1991c).

3.2.4 Phototoxicity in Guinea Pigs

Tinosorb M was tested in a phototoxicity study according to the Cosmetic, Toiletry, and Fragrance Association (CTFA) Safety Testing Guidelines. Tinosorb M in PEG 400 was applied to four separate 2 cm² sites on the shaved skin of the left flank of 10 male Dunkin Hartley guinea pigs at the following concentrations: 15, 25, 50, and 75%. For the 15 and 25% exposures, 0.0125 ml/cm² of test article was applied. Due to the high viscosity of the test material at 50 and 75%, a fixed volume could not be applied to each site. Instead, a thin layer of the test article was applied to saturate each test site. Five control male guinea pigs received PEG 400 only. Thirty to 50 minutes prior to test article application, the test sites were pretreated with 2% DMSO diluted in ethanol (0.0125 ml/cm²) to enhance skin penetration of the test article. Thirty minutes after application of the test material, the left flank of each animal in the control and treatment groups was exposed to 20 J/cm² UVA irradiation. After irradiation, the right flank received the same test-material applications as the left flank, but the sites were not exposed to UVA irradiation. Skin reactions were observed 24, 48, and 72 hours after application. No skin reactions, including erythema and edema, were observed during the experiment. In conclusion, under the test conditions, Tinosorb M was not phototoxic (Arcelin, 1997b).

3.2.5 Photoallergenicity in Guinea Pigs

Tinosorb M was tested in a photoallergenicity study according to the CTFA Safety Testing Guidelines. Induction occurred over the first 10 days. On test day one, each of 20 male Dunkin Hartley guinea pigs received four intradermal injections (0.1 ml/site) of a 1:1 (v/v) mixture of Freund's Complete Adjuvant (FCA) and physiological saline in the four corners of the 8 cm² test site located on the nuchal skin area. After injection, 0.1 ml of 75% Tinosorb M in PEG 400 was topically applied to the test site. The site was then exposed to 1.8 J/cm² UVB and 10 J/cm² UVA irradiation. The topical application followed by irradiation was repeated four times within two weeks on days 3, 6, 8, and 10. Control animals only received the four intradermal FCA injections without any further treatment during the induction phase. The challenge phase started on day 22. For both control and treatment groups, Tinosorb M in PEG 400 was applied to four separate 2 cm² sites on the shaved skin of the left flank at the following concentrations: 15, 25, 50, and 75%. A dose of 0.0125 ml/cm² was applied to each site. After application, the left flank was exposed to 10 J/cm² UVA irradiation only. After irradiation, the right flank was treated like the left flank, but without UVA irradiation. Skin reactions were assessed 24, 48, and 72 hours after application. One animal of the treatment group died on test day 10 of the experiment. At necropsy, several dark red foci were observed in the dark red discolored lungs. The death did not appear to be test material-related. During the topical induction phase, no skin reactions, including erythema and edema, were observed. During the challenge phase, no effects on the skin, including erythema and edema, were noted. In conclusion, under the test conditions, Tinosorb M was not a photosensitizer (Arcelin, 1997a).

3.3 SUBCHRONIC STUDIES

3.3.1 14-Day Oral Gavage Range-Finding Study in Rats

Tinosorb M in vehicle (0.5% [w/v] carboxymethylcellulose in 0.1% [w/v] aqueous polysorbate 80) was administered to groups of rats (5 per sex/group) by oral gavage at daily doses of 10, 100, and 1000 mg/kg for 14 days. Controls received vehicle only. No treatment-related effects on survival, food consumption, body weights, hematology and clinical chemistry values, organ weights, and gross pathology were noted. The only clinical sign noted was slight piloerection in the 100 and 1000 mg/kg groups on day 1 only. This finding is considered to be of no toxicological relevance in the absence of any abnormal clinical laboratory parameters and histopathology findings. In conclusion, under the test conditions, the No-Observable-Effect-Level (NOEL) for this study is 1000 mg/kg (Hartmann, 1991c).

3.3.2 28-Day Oral Gavage Toxicity Study in Rats

Tinosorb M in vehicle (0.5% carboxymethylcellulose in 0.1% aqueous Tween 80) was administered to groups of albino rats (Tif:RAIf [SPF]) by oral gavage at daily doses of 50, 200, and 1000 mg/kg for 28 days. For the control and 1000 mg/kg groups, 10 animals/sex/group were used and for the 50 and 200 mg/kg groups, 5 animals/sex/group were used. Controls received vehicle only. In the control and 1000 mg/kg groups, 5 animals/sex/group were allowed to recover for 4 weeks after the last exposure (recovery group). No treatment-related effects on clinical appearance, survival, body weights, food consumption, hematology and clinical chemistry values, organ weights, and macroscopic or microscopic findings were noted. Any significant differences in the various parameters were not considered treatment-related since they were not correlated with any morphological changes and they were within the range of normal biological variability for the strain and age of rat used and/or did not exhibit a dose-response. In

conclusion, under the test conditions, the No-Observable-Effect-Level (NOEL) for this study is 1000 mg/kg (Fankhauser, 1992).

3.3.3 90-Day Oral Gavage Toxicity Study in Rats

Tinosorb M in vehicle (0.5% carboxymethylcellulose in 0.1% aqueous Tween 80) was administered to groups of Wistar rats (SPF) (10 animals/sex/group) by oral gavage at daily doses of 100, 300, and 1000 mg/kg for at least 93 days. Controls received vehicle only. No treatment-related effects on clinical appearance; functional observational battery testing and grip strength; survival; food consumption; body weights; ophthalmoscopy findings; hematology, clinical chemistry, and urinalysis values; organ weights; and macroscopic or microscopic findings were noted. Any significant differences in the various parameters were not considered treatment-related since they were not correlated with any morphological changes and they were within the range of normal biological variability for the strain and age of rat used and/or did not exhibit a dose-response. In conclusion, under the test conditions, the No-Observable-Effect-Level (NOEL) for this study is 1000 mg/kg (Allard and Schmid, 1998).

3.3.4 Range Finding Developmental Toxicity Study in Rats

Tinosorb M in vehicle (0.5% [w/v] carboxymethylcellulose in 0.1% [w/v] aqueous polysorbate 80) was administered by oral gavage to groups of pregnant female Wistar rats (5/group) from days 6 – 17 of gestation at 100, 300, and 1000 mg/kg. Controls received vehicle only. Animals were sacrificed on day 21 of gestation and the fetuses removed by Caesarian section. No treatment-related effects on clinical appearance, survival, food consumption, body weight gain, or macroscopic findings were noted in any dam. No treatment-related reproductive effects (mean numbers of corpora lutea and implantation sites, and percent of pre- and post-implantation loss) were noted. No treatment-related fetal effects (external abnormalities, sex ratios, and body weights) were noted, with the exception of an incidental increase in fetal body weights (on an individual basis) at 1000 mg/kg. In conclusion, under the test conditions, the maternal and fetal NOELs were 1000 mg/kg (Becker and Biedermann, 1998).

3.3.5 Developmental Toxicity Study in Rats

Tinosorb M in vehicle (0.5% carboxymethylcellulose in 0.1% aqueous Tween 80) was administered by oral gavage to groups of pregnant female Wistar rats (22 animals/group) from days 6 – 17 of gestation at 100, 300, and 1000 mg/kg. Controls received vehicle only. Animals were sacrificed on day 21 of gestation and the fetuses removed by Caesarian section. No treatment-related effects on clinical signs, survival, food consumption, body weight gain, or macroscopic findings were noted in any dam. No treatment-related reproductive effects (mean number of implantation sites, mean post-implantation loss, and mean number of fetuses per dam) were noted. No treatment-related fetal effects (external, visceral, and skeletal abnormalities; sex ratios; body weights; and stage of development) were noted. Any significant differences in the various maternal or fetal parameters were not considered treatment-related since they were within the range of normal biological variability for the strain and age of rat used and/or did not exhibit a dose-response. In conclusion, under the test conditions, the maternal and fetal NOELs were 1000 mg/kg (Becker and Biedermann, 1998).

3.4 GENOTOXICITY STUDIES

3.4.1 *S. typhimurium* and *E. coli* Reverse Mutation Assay

Tinosorb M was tested in the Ames assay (*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay) to determine if it induces base pair or frameshift mutations in *Salmonella typhimurium* strains TA 98, TA 100, 1535, and TA 1537 and *E. Coli* strain WP2uvrA. The assay was performed using the plate incorporation method and repeated in an independent experiment. Tinosorb M, suspended in dimethyl sulfoxide, was tested at the following concentrations in both experiments: 313, 625, 1250, 2500, and 5000 µg/plate. Each concentration, including the controls, was tested in triplicate and was tested with and without exogenous rat liver microsomal (S9 mix) activation. Precipitation of the test material was noted at all concentrations. In the first experiment, growth inhibition (reduction in colony counts of more than 50%) was noted for strain TA 1535 at 5000 µg/plate without S9 mix, strain WP2uvrA at ≥2500 µg/plate without S9 mix, and strain WP2uvrA at 5000 µg/ml with S9 mix. No growth inhibition was noted in the confirmatory experiment. In both experiments, no significant increase in revertant colony numbers of any of the tester strains was observed following treatment with Tinosorb M at any dose level, with or without S9 mix. Appropriate reference mutagens were used as positive controls and produced a distinct increase of induced revertant colonies. In conclusion, under the test conditions, Tinosorb M did not induce base pair or frame shift mutations (Ogorek, 1991).

3.4.2 *In Vitro* Chromosome Aberration Assay in Chinese Hamster Ovary Cells

Tinosorb M, suspended in dimethyl sulfoxide, was assessed for its potential to induce structural chromosome aberrations in Chinese Hamster Ovary cells. Two independent experiments were performed with and without exogenous rat liver microsomal (S9 mix) activation. Based on the limited solubility of the test material in the solvent (i.e., 50 mg/ml), the following Tinosorb M concentrations were tested: 3.9, 7.8, 15.6, 31.3, 62.5, 125.0, 250.0, and 500.0 µg/ml with and without S9 mix. In both experiments, duplicate plates of exponentially growing cells were exposed to each concentration of the test material for 18 hours without S9 mix or 3 hours with S9 mix followed by 15 hours in normal culture medium. In addition, in the confirmatory experiment, cells were exposed for 42 hours without S9 mix or 3 hours with S9 mix followed by 39 hours in normal culture medium. Two hours prior to harvesting, colcemid was added to the cultures to arrest the cells in metaphase. The cells from the three highest dose groups were fixed, stained, and analyzed for structural chromosome aberrations. Chromosome gaps and numerical aberrations were recorded, but not included in the analysis. No significant increase in structural chromosome aberrations was noted for any treatment group. Positive control treatments produced a distinct increase in cells with structural chromosome aberrations in both experiments. In conclusion, under the test conditions, Tinosorb M did not induce structural chromosome aberrations (Ogorek, 1992).

3.4.3 Photomutagenicity: *S. typhimurium* and *E. coli* Reverse Mutation Assay

Tinosorb M was tested in a modified Ames assay (*Salmonella typhimurium* and *Escherichia coli* reverse mutation assays) to determine if it induces base pair mutations in *S. typhimurium* strain TA 102 and *E. coli* strain WP2 after UV irradiation. These strains were chosen since they tolerate

relatively high doses of UV irradiation. The assay was performed using the plate incorporation method (experiment I) and repeated in an independent experiment using the pre-incubation method (experiment II). Tinosorb M, suspended in dimethyl sulfoxide, was tested at the following concentrations in both experiments: 33; 100; 333; 1000; 2500; and 5000 $\mu\text{g}/\text{plate}$. Each concentration, including the controls, was tested in triplicate. Immediately after treating the cells with the test material, the cells were exposed to doses of UVA/UVB irradiation that were determined in preliminary experiments to produce a doubling in the background revertant frequency. WP2 cells were exposed for 10 seconds to 20 mJ/cm^2 UVA and 1 mJ/cm^2 UVB irradiation. TA 102 cells were exposed for 40 seconds to 80 mJ/cm^2 UVA and 4 mJ/cm^2 UVB irradiation. Normal background bacterial growth was observed at up to 5000 $\mu\text{g}/\text{plate}$. No toxic effects, evident as a reduction in the number of revertants, occurred in the test groups. In both experiments, no significant increase in revertant colony numbers of either tester strain was observed following treatment with Tinosorb M at any dose level. Appropriate reference mutagens were used as positive controls and produced a distinct increase of induced revertant colonies. In conclusion, under the test conditions, Tinosorb M did not induce base pair mutations after exposure to UVA/UVB irradiation (Wollny, 1998).

3.4.4 Photomutagenicity: *In Vitro* Chrom Ab Assay in Chinese Hamster V79 Cells

Tinosorb M was assessed for its potential to induce structural chromosome aberrations in Chinese hamster V79 cells with and without UVA/UVB irradiation in two independent experiments. Based on the limited solubility of the test material in the phosphate buffered saline (PBS) solution (containing 1% (v/v) dimethyl sulfoxide with the test material), the following Tinosorb M concentrations were tested: 7.81, 15.63, 31.25, 62.5, 125.0, and 250.0 $\mu\text{g}/\text{ml}$ with and without UVA/UVB irradiation. Precipitation of the test material was noted at ≥ 31.25 $\mu\text{g}/\text{ml}$. In both experiments, duplicate plates of exponentially growing cells were exposed to each concentration of the test material in a PBS solution for 30 minutes followed by irradiation with 200 mJ/cm^2 UVA and 22 mJ/cm^2 UVB for 30 minutes. Additional groups in experiment II were exposed to 300 mJ/cm^2 UVA and 33 mJ/cm^2 UVB for 30 minutes. After irradiation, the PBS solution was replaced with culture medium. Concurrent solvent and positive controls were run in parallel. In experiments I and II, the cells were harvested 18 and 28 hours after the start of the experiments, respectively. Approximately 2 hours prior to harvesting, colcemid was added to the cultures to arrest the cells in metaphase. In experiments I and II, cells were fixed, stained, and analyzed for structural chromosome aberrations from the 7.81, 15.63, 31.25, and 250.0 $\mu\text{g}/\text{ml}$ groups and 15.63, 31.25, 62.5, and 250.0 $\mu\text{g}/\text{ml}$ groups, respectively. Chromosome gaps and numerical aberrations were recorded, but not included in the analysis. The only sign of toxicity was a decreased mitotic index (41.7% compared to solvent control) in experiment II for the 62.5 $\mu\text{g}/\text{ml}$ group with 200/22 mJ/cm^2 irradiation. In both experiments, with and without UVA/UVB irradiation, the test material did not increase the frequency of cells carrying structural chromosome aberrations. Positive control treatments produced a distinct increase in cells with structural chromosome aberrations in both experiments. In conclusion, under the test conditions, Tinosorb M did not induce structural chromosome aberrations in the presence or absence of UVA/UVB irradiation (Czich, 1998).

3.5 ABSORPTION STUDIES

3.5.1 *In Vitro* Human Skin Distribution

This study was designed to determine the *in vitro* skin distribution of Tinosorb M (10% w/w in a representative sunscreen formulation) over a 24 hour period after application to epidermal

sections of human skin. The sunscreen formulation containing 10% Tinosorb M was applied to human epidermal skin membranes mounted in Franz type diffusion cells at a target dose of 2 mg/cm². The receptor phase consisted of 6% Oleth 20 in phosphate buffered saline (pH 7.4). After the 24-hour exposure period, residual amounts of test material were washed off of the skin. The level of Tinosorb M in the skin was determined by stripping layers of the skin with adhesive tape. Two samples were excluded from the analysis on the basis of anomalously high recovery of Tinosorb M compared to the remaining cells. Approximately 80% of the dose was recovered from the skin after washing. The following distribution of Tinosorb M, expressed as percent of applied dose, was measured in the skin: 55.4% (strips 1-3), 8.1% (strips 4-6), 4.7% (strips 7-12), 2.4% (strips 13-20), and 6.8% remaining skin. In conclusion, considering test material present in tape strips 1-3 as surface material, approximately 20% (40 µg/cm²) of the applied dose penetrated epidermal sections of human skin (Watkinson et al., 1998a).

3.5.2 *In Vitro* Human Skin Penetration and Distribution

This study was designed to determine the *in vitro* skin penetration and distribution of Tinosorb M (10% w/w in a representative sunscreen formulation) over a 24 hour period after application to epidermal sections of human skin. The sunscreen formulation containing 10% Tinosorb M was applied to human epidermal skin membranes mounted in Franz type diffusion cells at a target dose of 2 mg/cm². The receptor phase consisted of 6% Oleth 20 in phosphate buffered saline (pH 7.4). Of the twelve skin samples treated with Tinosorb M, five showed some permeation of Tinosorb M through the skin and into the receptor phase; however, one of the samples was excluded from further analysis on the basis of anomalously early and high permeation. Overall permeation through the skin was very low (300±250 ng/cm² representing 0.14±0.12% of the applied dose after 24 hours). In conclusion, under the test conditions, 0.14% of the applied Tinosorb M penetrated through epidermal sections of human skin over a 24-hour period (Watkinson et al., 1998b).

3.6 CLINICAL STUDIES

3.6.1 Phototoxicity In Humans

Tinosorb M, formulated in a white cream base common to cosmetic lotions, was topically applied to 28 human volunteers. Two hundred microliters of the test material, vehicle control (white cream base), and saline were topically applied to separate sites on each volunteer on one side of the spine. Duplicate applications were made on the opposite side of the spine. The treatment sites were covered with an occlusive dressing. After 24 hours of exposure, the patches and excess test material from the left paraspinal region were removed. The test sites were then exposed to 16 J/cm² UVA irradiation followed by exposure to 0.75 times the volunteer's minimum erythema dose (MED) of UVB irradiation. The patches from the right paraspinal region were then removed. Skin reactions were assessed 1, 24, 48, and 72 hours following irradiation and patch removal. For the irradiated sites, on a scale of 0-3 (0 representing no reaction and 3 representing strong erythema), grade 1 reactions were noted at 1, 24, 48, and 72 hours in 3, 1, 1, and 0 volunteers for the test material treatment, 8, 3, 1, and 0 volunteers for the vehicle control treatment, and 10, 0, 0, and 0 volunteers for the saline treatment, respectively. The remaining skin reactions were all less than grade 1. For the non-irradiated sites, grade 1 and 2 reactions were noted at 1 hour in 3 and 1 volunteers for the test material treatment, 3 and 1 volunteers for the vehicle control treatment, and 5 and 1 volunteers for the saline treatment, respectively. The remaining skin reactions were all less than grade 1. On average, the irradiated test material-treated sites exhibited lower skin reactions than the irradiated vehicle control and

saline treatment sites. In conclusion, under the test conditions, the test material was not phototoxic and is not an irritant to human skin (Pariße, 1998a).

3.6.2 Photoallergenicity in Humans

Tinosorb M was tested for photoallergenicity using a human repeated insult patch test (HRIPT). The induction phase consisted of two topical applications per week over a three week period (total of six topical applications over weeks 1-3) of 200 µl of the test material (Tinosorb M in a white cream base common to cosmetic lotions), vehicle control (white cream base), and saline to separate sites on each of 26 volunteers. The treatment sites were covered with an occlusive dressing. Twenty-four hours after each induction exposure, the patches were removed and exposed to 2 times the volunteer's UVA/UVB minimum erythral dose (MED). For a given induction treatment, the same site was used for each exposure unless unacceptable reactions were noted. In that case, the next induction exposure used a naïve site. After the last induction exposure, volunteers were not treated for two weeks (weeks 4-5). On week 6, duplicate topical applications of 200 µl of the test material, vehicle control, and saline were made to naïve sites on both sides of each volunteer's spine. The test sites were covered with an occlusive dressing. After 24 hours of exposure, the patches and excess test material from one side of the spine were removed. The test sites were then exposed to 16 J/cm² UVA irradiation followed by exposure to 0.75 times the volunteer's MED of UVB irradiation. The remaining patches were then removed. Skin reactions were assessed 1, 24, 48, and 72 hours following irradiation and patch removal. Two adverse reactions were reported, one of which was determined to be not treatment-related. The treatment-related effect consisted of burning and itching and was resolved with application of Aclovate Cream. Skin reactions were graded on a scale of 0-3 (0 representing no reaction and 3 representing strong erythema). After the challenge phase, grade 2 reactions were noted at 1, 24, 48, and 72 hours for the irradiated sites in 1, 0, 0, and 0 volunteers for the test material treatment, 1, 1, 0, and 1 volunteers for the vehicle control treatment, and 1, 1, 1, and 1 volunteers for the saline treatment, respectively. Grade 1 reactions were noted at 1, 24, 48, and 72 hours for the irradiated sites in 5, 2, 1, and 1 volunteers for the test material treatment, 8, 2, 2, and 1 volunteers for the vehicle control treatment, and 7, 1, 1, and 1 volunteers for the saline treatment, respectively. The remaining skin reactions were less than grade 1. For the nonirradiated sites, grade 1 reactions were noted in 1 volunteer at 1 hour for the vehicle control and saline treatments. The remaining skin reactions were less than grade 1. On average, the irradiated test material-treated sites exhibited lower skin reactions than the irradiated vehicle control and saline treatment sites. In conclusion, under the test conditions, the test material is not a photosensitizer or sensitizer to human skin (Pariße, 1998b).

4 GLOBAL REGULATORY/REGISTRATION STATUS

4.1 EUROPE

Tinosorb M as 2,2'-methylene-bis-(6-(2H-benzotriazole-2-yl)-4-(1,1,3,3-tetramethylbutyl)-phenol, was reviewed by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) of the European Commission. The SCCNFP concluded Tinosorb M is safe for use without restrictions as a UV absorber in cosmetic products, including sunscreen products, at a concentration of up to 10%. The UV filter is now included for cosmetic products under the Twenty-Fourth Commission Directive 2000/6/EC of the Commission of the European Communities on March 1, 2000. A copy of this Directive is enclosed as Attachment 1.

Tinosorb M is also approved for use in Switzerland.

Examples of Formulations with Tinosorb M

Formula No. RD 00 22 92

TINOSORB™ M**Ciba****UV-A/UV-B Daily Care UV Protection Lotion****SPF 14*, λ_c = 374 nm****

Excellent UV-A protection due to the photostable UV-A filter TINOSORB™ M Light O/W emulsion with silky touch and quick rub in.

	Trade name	INCI-Name	w/w %
A	Crodafos® N3A	Oleth-3 Phosphate	0.6 1)
	Brij 721	Steareth-21	2.5 2)
	Brij 72	Steareth-2	1.0 2)
	Lanette® 16	Cetyl Alcohol	0.8 3)
	Tego Alkanol® 18	Stearyl alcohol	1.5 4)
	Syncrowax® HRC	Tribehenin	0.8 1)
	Arlamol® HD	Isohexadecane	8.0 2)
	Tinosorb™ OMC	Ethylhexyl Methoxycinnamate	5.0 5)
B	Water Deionized	Aqua	qsp
	Glycerine	Glycerin	2.0
	Tinosorb™ M	Methylen Bis-Benzotriazolyl Tetramethylbutylphenol (and) Aqua (and) Propylene Glycol (and) Decyl Glucoside (and) Xanthan Gum	3.0 5)
	Disodium® EDTA	EDTA	0.1
	C	Water Deionized	Aqua
Germaïl Plus®		Diazolidinyl Urea/ Isopropynyl Butylcarbamate	0.15 6)
Propylene Glycol		Propylene Glycol	4.0
D	Salcare® SC 91	Sodium Acrylates Copolymer and Paraffinium Liquidum and PPG-1 Trideceth-6	1.5 5)
	SF 1202	Cyclomethicone	4.5 7)
	SF 1288	Dimethicone Copolyol	2.0 7)
	Citric acid 10 % solution	Citric Acid	qs
	Vitamin E acetate	DL-α-Tocopherol Acetate	0.45 8)
	pH value		5.5-6.5
Appearance		White light lotion	
Viscosity (Brookfield DVIII+LV4/25°C/15 rpm)		15000-20000 mPas	

* in vitro measurement

** critical wavelength as measure for UV-A performance (after Diffey's method)

Manufacturing instruction

Heat part A and part B separately till 75°C. Poor part A into part B under stirring. Immediately after the emulsification, incorporate SF 1202 and SF1288 from part D into the mixture and then homogenize (30 sec. at 10000 rpm). Let the mixture

cool down to 65°C under stirring, and then incorporate Salcare SC91. After cooling down below 50°C, add part C and let the product cool under stirring. Incorporate Vitamin E acetate at a temperature of 35°C or below and subsequently adjust the pH.

- 1) Croda
- 2) Uniqema
- 3) Cognis
- 4) Goldschmidt
- 5) Ciba
- 6) ISP
- 7) GE Silicones
- 8) BASF

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TINOSORB™ M**Ciba****UV-A/UV-B Sun Protection Lotion with Tinosorb™ M****SPF 20*, T_c = 380 nm****

Lotion with a high SPF an excellent UV-A protection due to the photostable UV-A filter TINOSORB™ M
Cold manufacturing process developed by Goldschmidt

	Trade name	INCI-Name	w/w %
A	Tego Care® 450	Polyglyceryl Methyl Glucose Distearate	3.0 1)
	Tego Alkanol® 18	Stearyl Alcohol	0.5 1)
	Tegosoft® P	Isopropyl Palmitate	3.5 1)
	Tegosoft® DC	Decyl Cocoate	4.0 1)
	Tegosoft® CT	Caprylic/Capric Triglyceride	5.0 1)
	Vitamin E-Acetat	Tocopheryl Acetate	0.5 2)
	Tinosorb™ OMC	Ethylhexyl Methoxycinnamate	4.0 3)
	Uvinul® T-150	Ethylhexyl Triazone	1.0 2)
B	Aqua	Aqua	66.0
	Glycerin	Glycerin	3.0
C	Tego Carbomer® 141	Carbomer	0.2 1)
	Tegosoft® P	Isopropyl Palmitate	0.8 1)
D	Tinosorb™ M	Methylen Bis-Benzotriazolyl Tetramethylbutylphenol (and) Aqua (and) Propylene Glycol (and) Decyl Glucoside (and) Xanthan Gum	8.0 2)
E	Sodium Hydroxide (10% solution)	Sodium Hydroxide	0.5
	Preservative, Perfume		q.s.

Manufacturing instruction

Charge with part B and heat to approx. 80°C. Heat part A to approx. 80°C and add to part B with stirring***.

Homogenize and cool with gentle stirring to approx. 60°C and add part C. Homogenize for a short time. Cool with gentle stirring, add part D**** and E below 40°C and stir well.

1) Goldschmidt
2) Ciba
3) BASF

- * In vivo according to the COLIPA method (5 subjects)
** critical wavelength as measure for UV-A performance (after Diffey's method)
*** Important: If it is charged with part A, part B must be added to part A without stirring
**** Before Adding part D, adjust pH value of Tinosorb M to 5.5 with citric acid

TINOSORB™ M**Ciba****UV-A/UV-B Sun Protection Lotion with TINOSORB™ M****SPF 36*, λ_c=380 nm****

Lotion with a very high SPF and excellent UV-A protection due to the photostable UV-A filter Tinosorb™. O/W emulsion with good rub-in properties and pleasant skin feeling. Formulation is produced by a cold manufacturing process***.

	Trade name	INCI-Name	w/w %	
A	Salcare SC91	Sodium Acrylates Copolymer and Paraffinium Liquidum and PPG-1 Trideceth-6	1.0	1)
	Tegosoft® TN	C12-15 Alkyl Benzoate	3.0	2)
	Tegosoft® DC	Decyl Cocoate	2.0	2)
	Tegosoft® P	Isopropyl Palmitate	2.0	2)
	Jjoba Oil	Buxus Chinensis	1.0	3)
	Tinosorb™ OMC	Ethylhexyl Methoxycinnamate	5.0	1)
	Neo Heliopan® E 1000	Isoamyl p-Methoxycinnamate	5.0	4)
	Vitamin E-Acetat	Tocopheryl Acetate	0.5	5)
B	Water	Aqua	61.1	
	Glycerin	Glycerin	2.0	
	Phenonip®	Phenoxyethanol (and) Methylparaben (and) Butylparaben (and) Ethylparaben (and) Propylparaben	0.7	6)
	Tego® SMO 80V	Polysorbate 80	0.2	2)
	Keltrol® RD	Xanthan Gum	0.5	7)
C	Tinosorb™ M	Methylen Bis-Benzotriazolyl Tetramethylbutylphenol (and) Aqua (and) Propylene Glycol (and) Decyl Glucoside (and) Xanthan Gum	16.0	1)
pH value			6.5-7.0	
Appearance			white	
Viscosity (Brookfield DVIII+LV4/5 rpm)			55000-65000 mPas	

- * In vitro measurement
- ** critical wavelength as measure for UV-A performance (after Diffey's method)
- *** Formulation developed by Goldschmidt AG and Ciba Specialty Chemicals.

Manufacturing instruction

Mix part B until it is homogenous.
Afterwards add part C to part B under continuous stirring and homogenize 30sec at 11.000 rpm. Add part A slowly under continuous stirring.

- 1) Ciba
- 2) Goldschmidt
- 3) E. Wagner
- 4) H & R
- 5) BASF
- 6) Nipa
- 7) Rahn

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**TWENTY-FOURTH COMMISSION DIRECTIVE 2000/6/EC
of 29 February 2000**

**adapting to technical progress Annexes II, III, VI and VII to Council Directive 76/768/EEC on the
approximation of the laws of the Member States relating to cosmetic products**

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products ⁽¹⁾, as last amended by Commission Directive 98/62/EC ⁽²⁾, and in particular Article 8(2) thereof,

After consulting the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers,

Whereas:

- (1) Tallow derivatives, such as fatty acids, glycerine, esters of fatty acids and soaps and fatty alcohols, fatty amines and fatty amides derived therefrom, are considered safe for use in the manufacture of cosmetic products with regard to the risk of contracting transmissible spongiform encephalopathies if they are prepared in strict accordance with specific physico-chemical processes in which temperature is the decisive parameter on which the corresponding pressure conditions depend. Annex II to the abovementioned Directive should therefore be amended accordingly.
- (2) Harmful secondary effects have been shown to arise following prolonged use of hydroquinone as skin-lightening cream. This particular use of hydroquinone must not therefore be authorised, meaning that Part I of Annex III to the abovementioned Directive needs to be amended. Studies also show that the concentration of hydroquinone used in hair dyes does not have harmful effects for health if it does not exceed 0,3 %. Part I of Annex III to the abovementioned Directive must be amended accordingly.
- (3) On the basis of new scientific data, benzalkonium chloride, bromide and saccharinate have recently been added to the list of substances which may be used as preservatives in the manufacture of cosmetic products set out in Part 1 of Annex VI to the abovementioned Directive. In the light of experience, it is also acceptable for these benzalkonium salts to be used for other purposes in cosmetic products, according to the length of their carbon chain, provided that the maximum authorised concentrations are observed. These specific characteristics therefore justify their inclusion in the list Part 1 of Annex III.
- (4) The cosmetics industry has supplied new scientific data based on studies of the percutaneous absorption of aqueous solutions of boric acid, borates and tetraborates at various pH numbers and at various concentrations showing that the requirement that pH should be neutral or slightly alkaline in order to minimise the percutaneous absorption of these boron derivatives is not justified. The list of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down, set out in Part 1 of Annex III, should therefore be amended accordingly.
- (5) In the concentrations in which it is normally used as a preservative in cosmetic products intended to be removed by rinsing, benzylhemiformal is not likely to cause harmful effects for human health. Therefore it should be removed from Part 2 of Annex VI to the abovementioned Directive which sets out the list of preservatives provisionally allowed in cosmetic products and included in Part 1 of Annex VI which contains the list of preservatives allowed in cosmetic products.

⁽¹⁾ OJ L 262, 27.9.1976, p. 169.

⁽²⁾ OJ L 253, 15.9.1998, p. 20.

- (6) In the concentrations in which it is normally used as a preservative in cosmetic products, 3-iodo-2-propynyl butylcarbamate is not likely to have harmful effects on human health. Therefore, it should be removed from the list in Part 2 of Annex VI and entered in the list in Part 1 of Annex VI.
- (7) In the concentrations in which it is normally used as a UV filter for sunscreen cream, 4-dimethyl-amino-benzoate of ethyl-2-hexyl (octyl dimethyl PABA) is not likely to have harmful effects on the health of users. Therefore, it should be removed from Part 2 of Annex VII to the abovementioned Directive which sets out the list of UV filters that cosmetic products may provisionally contain and entered in Part 1 of Annex VII which contains the list of UV filters allowed in cosmetic products.
- (8) In the concentrations in which it is normally used as a UV filter for sunscreen cream, 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid (benzophenone-5) and its sodium salt is not likely to give rise to harmful effects for human health. Therefore, 2-hydroxy-4-methoxybenzophenone-5-sulfonic (benzophenone-5) and its sodium salt should be removed from Part 2 of Annex VII and entered in Part 1 of Annex VII.
- (9) 4-isopropyl-benzyl salicylate is no longer used as a UV filter for sunscreen products. Consequently, 4-isopropyl-benzyl salicylate must be removed from Part 2 of Annex VII.
- (10) Within the concentration limits and under the conditions adopted by the cosmetic industry for its use as a UV filter for sunscreen products, 2,2'-methylene-bis-6-(2H-benzotriazol-2-yl)-4-tetra-methyl-butyl-1,1,3,3-phenol, is not likely to produce harmful effects for the health of users. Therefore, it may be included in the list in Part 1 of Annex VII.
- (11) Within the concentration limits and under the conditions adopted by the cosmetic industry for its use as a UV filter for sunscreen products, the monosodium salt of 2-2'-bis-(1,4-phenylene)1H-benzimidazole-4,6-disulfonic acid is not likely to have harmful effects on the health of users. Therefore, it may be included in the list in Part 1 of Annex VII.
- (12) Within the concentration limits and under the conditions adopted by the cosmetic industry for its use as a UV filter for sunscreen products, (1,3,5)-triazine-2,4-bis-((4-(2-ethyl-hexyloxy)-2-hydroxy)-phenyl)-6-(4-methoxyphenyl) is not likely to have harmful effects on the health of users. Therefore, it may be included in the list in Part 1 of Annex VII.
- (13) The measures provided for in this Directive are in accordance with the opinion of the Committee on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Cosmetic Products Sector,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 76/768/EEC is hereby amended as indicated in the Annex to this Directive.

Article 2

Member States shall adopt the necessary measures to ensure that cosmetic products containing the substances listed in Annexes II, III, VI and VII to Directive 76/768/EEC, as set out in the Annex to this Directive, which are supplied to the final consumer after 1 January 2001, comply with the provisions of this Directive.