

Ciba



September 5, 2000

Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Resources  
Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

Via Next Day Courier  
Return Receipt Requested

**Re: Citizen Petition: Addition of Two New UV-A Active Ingredients for Sunscreen Drug Products for Over-the-Counter Human Use**

Dear Madam or Sir:

On behalf of Ciba Specialty Chemicals Corporation (formally Ciba-Geigy), Consumer Care Division ("Ciba"), the undersigned submits this petition under 21 CFR § 10.30 requesting that the Commissioner of Food and Drugs re-open the administrative record to allow for the addition of two new active ingredients to the list of UV filters currently allowed for use under the Final Monograph for Sunscreen Drug Products for Over-the-Counter (OTC) Human Use (64 FR 27666-27693, May 21, 1999; Docket No. 78N-0038).

Ciba realizes that the FDA officially reopened the administrative record and extended the effective date of this Monograph on June 8, 2000 (65 FR 36319) to allow for the development of a comprehensive ultraviolet B (UVB) and ultraviolet A (UV-A) final monograph and to solicit comments addressing formulation, labeling, and testing requirements for both UVB and UV-A radiation protection. Ciba wishes to inform the FDA that this petition is being submitted independent from the comments solicited under the June 8, 2000 *Federal Register* Notice. However, Ciba believes that it would be appropriate for the FDA to consider this petition in concurrence with its plans to develop a comprehensive final monograph for UVB and UV-A radiation protection as our petition primarily addresses the need for more photostable and UV-A-effective sunscreen ingredients.

We also request that the Agency consider this petition in light of our comments relating to the Agency's current approach to regulating OTC drug products submitted under separate cover on August 24, 2000 to Docket No. 001N-1256.

#### Overview of Ciba's Request and Underlying Rationale

Since the publication of the Sunscreen Tentative Final Monograph on May 12, 1993 (58 FR 28194), FDA medical groups and consumer interest groups have continued to document the significance of, and expressed increasing concern about, exposure to UV-A radiation. Exposure to UV-A radiation has been causally linked with the high incidence of skin cancer in the United States.

78N-0038

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UV-A radiation has also been demonstrated to contribute to both acute and chronic skin damage such as erythema, melanogenesis, carcinogenesis, drug-induced photosensitivity, photoaging, and morphological alterations of Langerhans cells (58 FR 28233). Moreover, the large amount of UV-A radiation present in the solar spectrum at the earth's surface also results in a significant contribution to the generation of erythema.

According to public health experts, skin carcinomas and melanoma rates have reached epidemic levels in the U.S. and are expected to rise. The most recent estimates of the American Cancer Society predict 1.3 million new cases of basal cell and squamous cell carcinomas in 2000. In response to this threat, FDA has repeatedly stated that:

*"protection against UV-A radiation is much more important than previously realized. Protection against UV-A radiation may be as important to consumers' well-being as protection against UVB radiation" (Baker, D.E., FDA Response to CTFA Petition, Docket No. 78N-0038/CP11, October 1, 1999).*

Thus, it is clear that as the significance of UV-A radiation in terms of public health concerns continues to mount, the need for more effective UV-A filters that provide protection from the deleterious effects of UV-A exposure also increases.

Ciba's interest lies in the finalization of a comprehensive, scientifically sound final sunscreen monograph that addresses both UVB and UV-A exposure. It is our firm belief that the availability of photostable and effective UV-A absorbers is extremely limited under the existing Final Monograph. Thus, we are herein proposing that the FDA take action to include two new and unique photostable and UV-A-effective active ingredients in the final monograph for UVB and UV-A protection.

### **Why Ciba Is Pursuing this Course of Action**

As stated in our comments relating to the Agency's current approach to regulating OTC drug products on August 24, 2000 (Docket No. 001N-1256), we believe that the OTC monograph process should be a flexible mechanism that is periodically updated to reflect current scientific developments, adopt safer and more efficacious active ingredients, and include improved test methods when necessary.

We also believe that OTC monograph decisions should continue to be based on the totality of data supporting the safety and efficacy of active ingredients. Currently, it is virtually impossible to add a new active ingredient to a finalized monograph unless the NDA route is followed. We firmly believe that it is inappropriate to categorically apply NDA standards, which relate to specific final formulations, to OTC Monograph active ingredients and conditions. Moreover, it should not be automatically assumed that OTC availability can only be accomplished via an NDA.

Hence, we believe that the present NDA route, as applied to actives such as sunscreens, prevents the widespread use of safer and more efficacious products as any product approved under the NDA will be restricted to a particular formulation.

From a public health perspective, it is critical that the current monograph process be re-engineered to allow the addition of new OTC drug active ingredients which can be safely and effectively used by consumers to self-treat ailments, or prevent disease.

Moreover, it is essential for FDA to realize that non-pharmaceutical companies, such as ours, are interested in offering more efficacious OTC active ingredients and products for all to use, but currently cannot add an ingredient to a finalized monograph unless the NDA-route is used.

However, costs are high to develop an NDA (which is formulation specific). This, combined with the reality that the UV filter is the major cost element in a sunscreen, prohibits amortization of the NDA costs by manufacturers of sunscreens when compared to first generation OTC-monographed ingredients. We have therefore elected to file a Citizen's petition as a way to make two new unique photo-stable products which protect against UV-A rays available to the public. Our efforts to this end are being pursued in good faith and for legitimate public health reasons.

### **Active Ingredients Being Proposed Under This Petition**

Ciba proposes that FDA take action to add the following two UV-A absorbers to the list of active ingredients currently allowed for use under the Final OTC Sunscreen Monograph:

- Bis-Ethylhexyloxyphenol Methoxyphenol Triazine (BEMT)
- Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (MBBT)

Ciba requests this action in order to enhance the public health, allow for the use of superior active ingredients which have been demonstrated as being photostable and safe, and which afford consumers with a better spectrum of protection against UV-A radiation. A summary of the efficacy and safety for each of these substances is presented below.

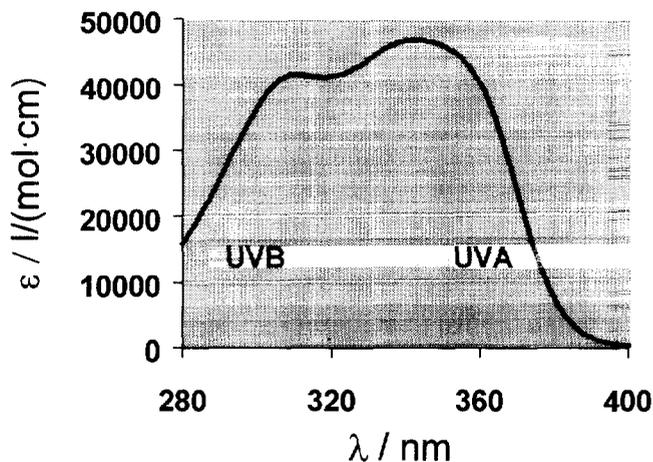
#### **Bis-Ethylhexyloxyphenol Methoxyphenol Triazine**

Bis-Ethylhexyloxyphenol Methoxyphenol Triazine ("BEMT") is the official International Nomenclature Cosmetic Ingredient (INCI) name for a substance chemically known as 2,4-Bis-[[4-(2-ethyl-hexyloxy)-2-hydroxy]-phenyl]-6-(4-methoxyphenyl)-(1,3,5)-triazine (CASRN: 187393-00-6). The material is currently under patent and Ciba is the sole manufacturer. The trade name for this substance is Tinosorb™ S. A summary of the ingredient's efficacy and safety is presented below.

#### **Efficacy**

BEMT is the first "true" broadband-type UV-absorber on the market. It provides overall protection, fully covering the UV-A and UVB spectrum in contrast to other UV filters on the market today; is indeed photostable - in contrast to other currently available UV-A filters; has a favorable safety profile; and is extremely easy to formulate in W/O or O/W emulsions. Our test data indicate that BEMT has a much higher efficacy than what is currently available on the market. The UV-spectrum of BEMT is presented in Figure 1.

Figure 1. UV-Spectrum of Tinosorb S (in ethanol)



$$\epsilon_{343 \text{ nm}} = 46750 \text{ M}^{-1} \text{ cm}^{-1}$$

$$E_{343 \text{ nm}} (1\%, 1\text{cm}) = 745$$

The photostability of BEMT has been 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). Doses of UV-light were varied between 0 and the extremely high 50 MED (minimal erythemal doses) and the samples were analyzed afterwards using UV-spectroscopy and high performance liquid chromatography (HPLC), 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; Reference 1); and a maximum of 30 MED can be obtained in tropical regions, such as Townsville, Australia (Bernhard, G., 1997; Reference 2).

Table 1 summarizes the recoveries of BEMT 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 BEMT is an extremely photostable UV-filter.

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

Dose (MED)	Mean Recovery ± 95% CI (%)
0	100.0 ± 0.2
5	99.8 ± 0.2
10	99.7 ± 0.2
20	99.4 ± 0.2
50	98.4 ± 0.2

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

The Sunscreen Protection Factor (SPF) of BEMT has been calculated as 9.4, using a 4% *Tinosorb S* in o/w- emulsion, measured *in vitro* by the method of Diffey and Robson (*J. Soc. Cosmet. Chem.*, 40, 1989, 127 - 133) using an Optometrix SPF290-analyzer.

The UV-A/UVB-ratio of BEMT is 0.73. The UV-A/UVB-ratio is the ratio of the areas under the extinction curve in the UV-A-range (320 - 400 nm) and the UVB-range (290 - 320 nm), each area divided by the range of wavelengths involved. In the case of a UV-A-filter with very weak UVB-absorption the UV-A/UVB-ratio may be of a value higher than 1. The lower ratio of BEMT is due to its rather strong absorption in the UVB-range.

The Critical wavelength of BEMT ( $\lambda_c$ ) is 370 nm. The critical wavelength ( $\lambda_c$ ) 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. Like the UV-A/UVB-ratio, the critical wavelength depends not only on UV-A- but also on UVB-absorption. UV-A-filters with very weak UVB-absorption approach a  $\lambda_c$  of 380 nm. Again, the somewhat lower value of BEMT is caused by its relatively strong UVB-absorption.

A recent study of the photostability of BEMT in comparison to the photostabilities of different UV-filters (i.e., UV-A-filter Butyl Methoxydibenzoylmethane (BMDDBM), the UVB-absorbers Octyl Methoxycinnamate (OMC) and 4-Methylbenzylidene Camphor (MBC), and the organic micronised UV-A-filter Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (MBBT)) indicates that BEMT is more photostable than all other UV filters tested (with the exception of MBBT, which is the second active ingredient being proposed under this petition).

A copy of this study, entitled: "*Investigations of Photostability of UV-absorbers for Cosmetic Sunscreens*" (Herzog, B., 2000; Reference 3) is enclosed as Attachment 1.

As a consequence of its high photostability, BEMT is fully compatible with other UV absorbers and can be used in any combination without adverse effects. Furthermore, BEMT shows a stabilizing effect on other non-photostable UV absorbers. Indeed, adding BEMT to a conventional formulation makes the formulation more photostable.

From a safety perspective, as a result of BEMT's high photostability, sunscreen products with superior broadband protection can be achieved, without using complex formulations. Moreover, the potential for interaction amongst formulation ingredients and overall consumer exposure to additives in sunscreen formulations may also be significantly reduced.

### Safety

Our current toxicological assessment indicates that BEMT does not show any unusual acute toxic effects up to the highest doses. The oral and dermal LD<sub>50</sub> values are >2,000 mg/kg bw. It is not an irritant to the skin or eyes and there is no sensitizing potential. It is also not mutagenic, phototoxic or clastogenic. It also does not readily penetrate human skin. In a 90-day subchronic toxicity study in the rat, no effects were noted up to the top dose of 1,000 mg/kg bw/day. In a developmental toxicity study, no observable adverse effects were noted for maternal, embryo, or fetal toxicity up to the top dose of 1,000 mg/kg. A summary of the Pre-clinical and clinical studies conducted on BEMT is presented in Table 2.

**Table 2. Summary of Tinosorb S Pre-Clinical and Clinical Studies**

Study	Results
<b>Acute</b>	
Acute Dermal Toxicity in Rats	LD <sub>50</sub> > 2000 mg/kg
Acute Oral Toxicity in Rats	LD <sub>50</sub> > 2000 mg/kg
<b>Irritation/Sensitization</b>	
Primary Skin Irritation Study in Rabbits	Not Irritating
Primary Eye Irritation Study in Rabbits	Minimally Irritating
Skin Sensitization (Guinea Pig Maximization Test)	Not Sensitizing
Phototoxicity in Guinea Pigs	Not Phototoxic
Photoallergenicity in Guinea Pigs	Not Photoallergenic
<b>Sub-Chronic</b>	
14-Day Oral Gavage Range Finding Study	NOAEL = 2000 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
<b>Genotoxicity</b>	
S. typhimurium Reverse Mutation Assay	Negative
In Vitro Chromosome Aberration Assay in Chinese Hamster V79 Cells	Negative
Photomutagenicity: S. typhimurium and E. coli Reverse Mutation Assay	Negative
Photomutagenicity: In Vitro Chromosome Aberration Assay In Chinese Hamster V79 Cells	Negative
<b>Absorption</b>	
In Vitro Human Skin Penetration	<0.1% Penetrated Across Skin
In Vitro Human Skin Penetration and Distribution	<0.1% Penetrated Across Skin
<b>Clinical</b>	
Phototoxicity in Humans	Not Phototoxic
Photoallergenicity in Humans	Not Photoallergenic

A full summary of the physical-chemical, efficacy, safety data and global registration status of BEMT may be found in Attachment 2 (D'Ruiz, C.D.; 2000).

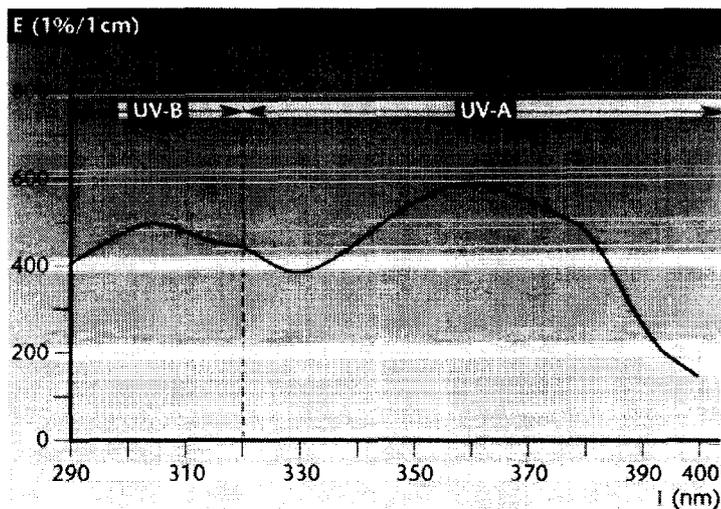
### **Methylene Bis-Benzotriazolyl Tetramethylbutylphenol**

Methylene Bis-Benzotriazolyl Tetramethylbutylphenol ("MMBT") is the official International Nomenclature Cosmetic Ingredient (INCI) name for a substance chemically known as 2,2'-Methylenebis[4-(1,1,3,3-tetramethylbutyl)-6-benzotriazolylphenol] (CASRN: 103597-45-1). Ciba currently sells this product as Tinosorb™ M and holds a patent for the micronization process under which it is manufactured. A summary of the ingredient's efficacy and safety data is presented below.

#### **Efficacy**

MMBT is a superior UV filter that is an extremely photostable. The UV-spectrum of MMBT is presented in Figure 2.

Figure 2. UV-Spectrum of MMBT (in water)



The photostability of MMBT 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; Reference 1); and a maximum of 30 MED can be obtained in tropical regions, such as Townsville, Australia (Bernhard, G., 1997; Reference 2).

The table below summarizes the recoveries of MMBT as obtained from UV-spectroscopic analysis. As seen in Table 3, even after a UV-dose of 50 MED, recoveries of >98% were detected using the different methods, indicating that MMBT is an extremely photostable UV-filter.

**Table 3. Recoveries of MMBT 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 erythemal dose; CI = confidence interval

The UV-A/UVB-ratio of MMBT is 1.0.

The critical wavelength of MMBT ( $\lambda_c$ ) has been calculated as 388 nm. Like the UV-A/UVB-ratio, the critical wavelength depends not only on UV-A- but also on UVB-absorption.

The photostability of MMBT was recently compared to the photostabilities of different UV-filters (i.e., UV-A-filter Butyl Methoxydibenzoylmethane (BMDBM), the UVB-absorbers Octyl Methoxycinnamate (OMC) and 4-Methylbenzylidene Camphor (MBC), and Bis-Ethylhexyloxyphenol Methoxyphenol Triazine (BEMT)). The results of this study indicate that MMBT was the most photostable substance.

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. A copy of this study, entitled: "*Investigations of Photostability of UV-absorbers for Cosmetic Sunscreens*" (Herzog, B., 2000), is enclosed as Attachment 1.

Further analysis of the photostability, performance, and photo-protection attributes of MBBT may be found in Attachment 3 (Osterwalder, U., et al., 2000).

### Safety

MMBT has been demonstrated to be safe in pre-clinical and clinical studies. A summary of these results is presented in Table 4.

**Table 4. Summary of Tinosorb M Pre-Clinical and Clinical Studies**

Study	Results
<b>Acute</b>	
Acute Dermal Toxicity in Rats	LD <sub>50</sub> > 2000 mg/kg
Acute Oral Toxicity in Rats	LD <sub>50</sub> > 2000 mg/kg
<b>Irritation/Sensitization</b>	
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
<b>Sub-Chronic</b>	
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
<b>Genotoxicity</b>	
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
<b>Absorption</b>	
In Vitro Human Skin Distribution	≈20% Penetrated Into Skin
In Vitro Human Skin Penetration	0.14% Penetrated Across Skin
<b>Clinical<sup>1</sup></b>	
Phototoxicity in Humans	Not Phototoxic
Photoallergenicity in Humans	Not Photoallergenic

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

Further information regarding MMBT's physical-chemical properties, efficacy, safety and global registration status may be found in Attachment 4 (D'Ruiz, C.D., 2000) and in the product brochure for Tinosorb M (Attachment 5).

### Conclusion and Request For Further Action

Recent medical evidence has made it clear that UV-A protection may be the most important factor in preventing skin cancer and other effects caused by sun exposure. OTC sunscreen products are important to the health and well-being of the American consumer. There is recent evidence to suggest that there is a public health need for new active ingredients that are photostable, broad-spectrum, and control the risks of overexposure to UV-A radiation.

Ciba acknowledges that FDA accepted two sunscreen UV-A active ingredients (Avobenzone and Zinc Oxide) prior to the finalization of the sunscreen monograph on May 21, 1999. However, even these substances do not offer the same level of photostability and UV-A protection that the two substances being proposed under this petition do. Given the deleterious effects associated with sun exposure, we firmly believe that the American public deserves to receive maximum level of UVB and UV-A protection available today. Thus, it is for this reason that Ciba asks FDA to take action to add these substances to the final monograph covering UVB and UV-A sunscreen protection.

Ciba truly believes that the actions requested herein are in the best interest of public health. These actions, if promptly implemented, will assure the availability of superior, state-of-the-art . photostable and safe UV-A radiation protection products for consumer use. Ciba would be more than happy to work with the FDA to fulfill this need. Please contact the undersigned at (336) 801-2493 if there are any further questions or comments regarding this petition.

Sincerely,



Carl D. D'Ruiz, MPH  
Director, Product Stewardship & Regulatory Affairs  
Ciba Specialty Chemicals  
Consumer Care & Colors

Attachments

Desk copy:

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Johnathan Wilkin, MD  
John Lipnicki  
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OTC Docket No. 78N-0038

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U. Osterwalder  
J. Plautz  
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W. Salminen

### References

1. Pathak M.A. *Photoprotection Against Harmful Effects of Solar UV-B and UV-A Radiation*. In: Lowe N.L., Shaat N.A. and Pathak M.A., *Sunscreens, Development, Evaluation, and Regulatory Aspects*, 2<sup>nd</sup> ed., Marcel Dekker, New York (1997) 59-79.
2. Bernhard G., Mayer B., Seckmeyer G., Moise A., *Measurements of spectral solar irradiance in tropical Australia*, *Journal of Geographical Research*, Vol.102, No. D7 (1997) 8719-8730.

### Attachments

1. Herzog B. and Sommer K., *Investigations on Photostability of UV-Absorbers for Cosmetic Sunscreens*, Proceedings: 21<sup>st</sup> IFSCC Congress, Berlin, 11-14 September 2000.
2. D'Ruiz, C.D., Plautz, J. Salminen, W., TINOSORB™ S, *Bis-Ethylhexyloxyphenol Methoxyphenol Triazine (BEMT)* - Next Generation UV Filter for Sun Protection, Information Package Submitted with Citizen's Petition, 5 September 2000.
3. Osterwalder U., Herzog B. Luther H., *UV-A PROTECTION WITH NEW CLASS OF UV ABSORBER*, Proceedings: 14<sup>th</sup> Congresso Nacional de Cosmetologia, Sao Paulo, 5-7 July, 2000.
4. D'Ruiz, C.D., Plautz, J. Salminen, W., TINOSORB™ M, *Methylene Bis-Benzotriazolyl Tetramethylbutyl phenol (MBBT)* - Next Generation UV Filter for Sun Protection, Information Package Submitted with Citizen's Petition, 5 September 2000.
5. Ciba Specialty Chemicals, *Ciba Tinosorb™ M, A microfine UV-A absorber with Triple Action*, Technical Brochure, Basel Switzerland, August 2000.