# ATTACHMENT 5

Ciba Specialty Chemicals

Ciba

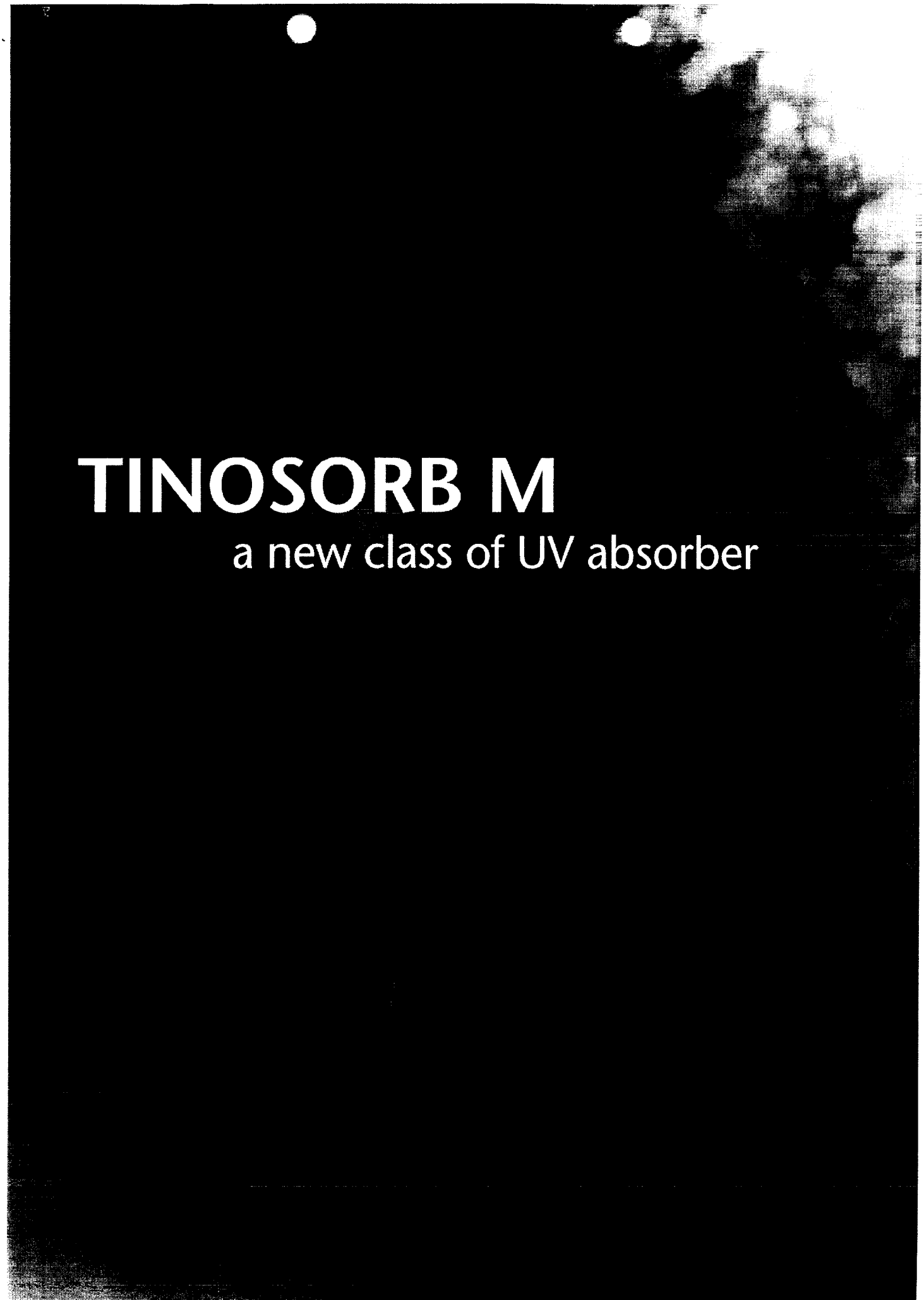
# Ciba® TINOSORB™ M

A microfine UV-A absorber with triple action

**Personal Care**

Value beyond chemistry

# Contents


TINOSORB M
a new class of UV absorber

# TINOSORB M

introduces a **new technology** of UV skin protection. It is the first sun filter using microfine particle technology wich acts both as micro pigment and organic UV absorber.

# TINOSORB M

derives from a colourless, UV-absorbing organic solid, which has been micronised to **particles** below 200 nm in diameter. It is inherently photostable.

# TINOSORB M

is a highly efficient sunscreen due to its **triple action:** UV *absorption* by a photostable organic molecule, light *scattering* and light *reflection* by its microfine structure.

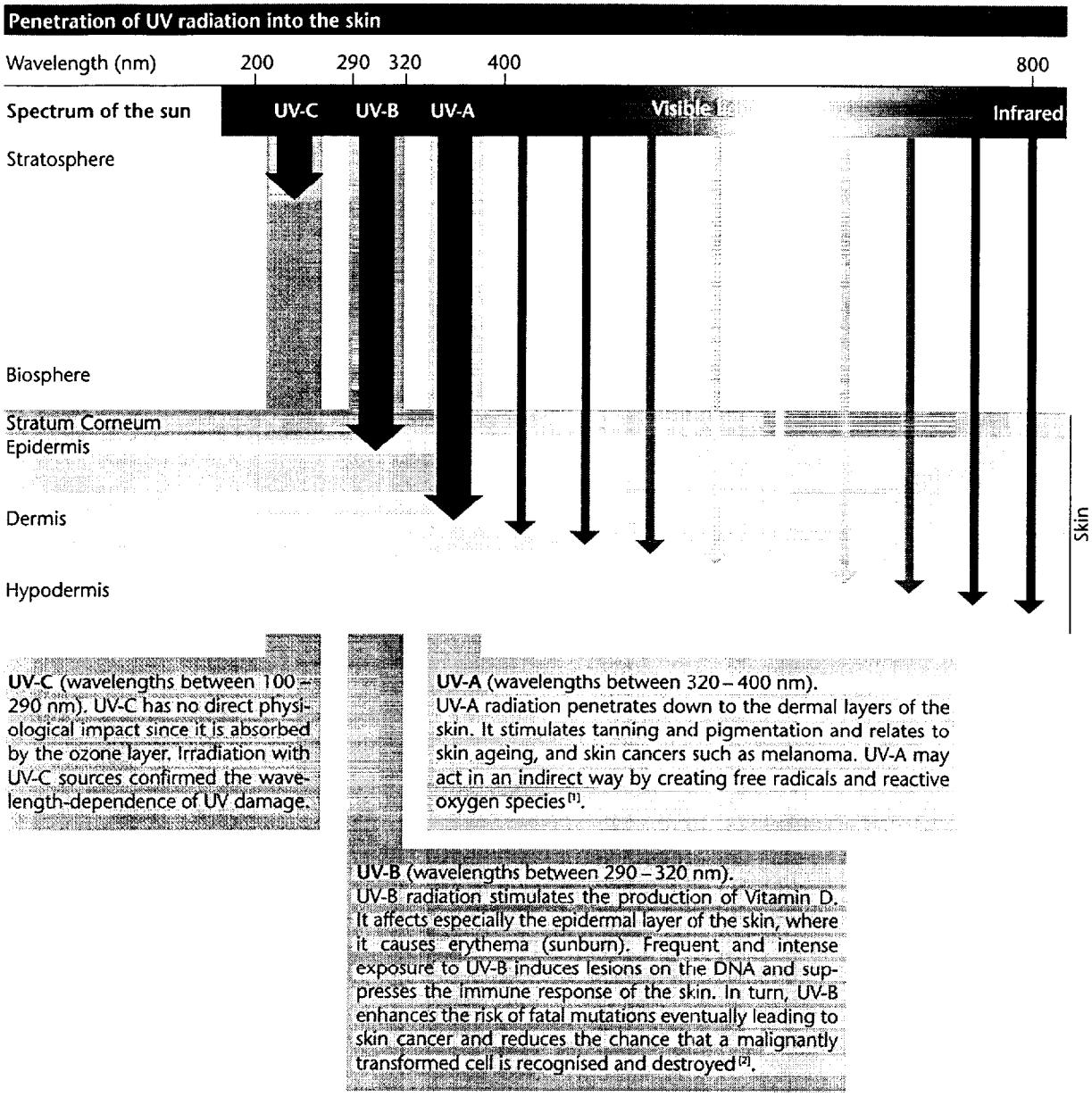
# Background of photoprotection

The UV radiation of sunlight induces skin damage. The nature of the damage relates to the wavelength.

Solar radiation in the range of infrared is perceived as heat, in the visible as colour, and in the ultraviolet as the result of photobiological reactions. Such reactions may ultimately stimulate melanin production and tanning, or lead to altered genetic information and to aberrant cell behaviour.

The fact that the radiation energy increases with the decrease of the wavelength, and that longer waves are less reflected by an object also holds true for UV radiation (UVR). Short wave UVR is more likely to induce photochemical reactions. Long-wave UVR will penetrate deeper into the skin. Hence, the biological effects induced by UVR may change with the wavelength.

In consequence, and based on empirical observation, the spectrum of ultraviolet light with a wavelength between 100 nm and 400 nm has been divided into three different ranges: UV-C, UV-B and UV-A.




The chance of developing permanent damage increases with the dose of sunlight accumulated over a life time. The risk of detrimental UV induced effects eventually depends on the accumulated dose and not only on the UV wavelength. This holds especially true in the context of exposure to natural sunlight where UV-A contributes to about 95% and UV-B only to 5% of the radiation.

UV related health hazards can be minimised by proper protection and shielding.

Sun protective agents have been on the market for more than 60 years. They were first developed to protect the skin against sunburn, i. e. to shield the skin preferentially from UV-B and to permit tanning by UV-A. Conventional sun protection factors (SPF) still relate to the protection from UV induced erythema.

With the growing awareness of UV-A damage accumulating the risks for the development of melanoma and other tumours, it became obvious that to reduce the risk of sun exposure-related cancers the skin was to be protected not

only from UV-B but from the whole UV-A/UV-B range[3,4]. In consequence, a new concept has evolved: an efficient sunscreen should not only prevent sunburn, but also minimise the accumulation of all radiation induced damage in the skin which eventually increase the risk of fatal alterations[5-7].

UV protection means conversion of the radiation energy of sunlight into a harmless form.

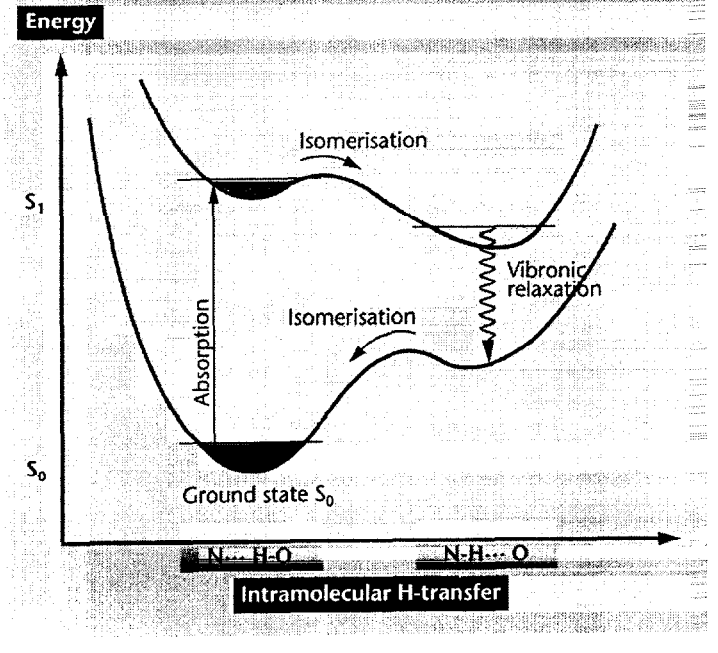
## Triple action of TINOSORB M

### UV protection by absorption

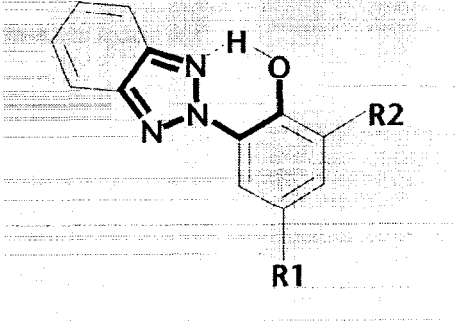
Absorption of UV light promotes organic molecules from the electronic ground singlet state $S_0$ into an excited electronic state ($S_1$ or higher). There are different ways to dissipate this energy.

The most important energy dissipation mode is ***internal conversion followed by vibronic relaxation.*** In contrast to the energy of excited electrons, vibration energy can be dissipated into heat by collisions with surrounding molecules. Internal conversion is an intramolecular process by which the electronic excitation energy is transferred to molecular vibrations. The probability for internal conversion is strongly enhanced when the molecule in its excited electronic state can switch between isomeric structures such as by cis/trans-isomerisation or by intramolecular H-transfer.[8,9] The latter is the case for TINOSORB M.

**UV protection by absorption (Energy dissipation cycle)**



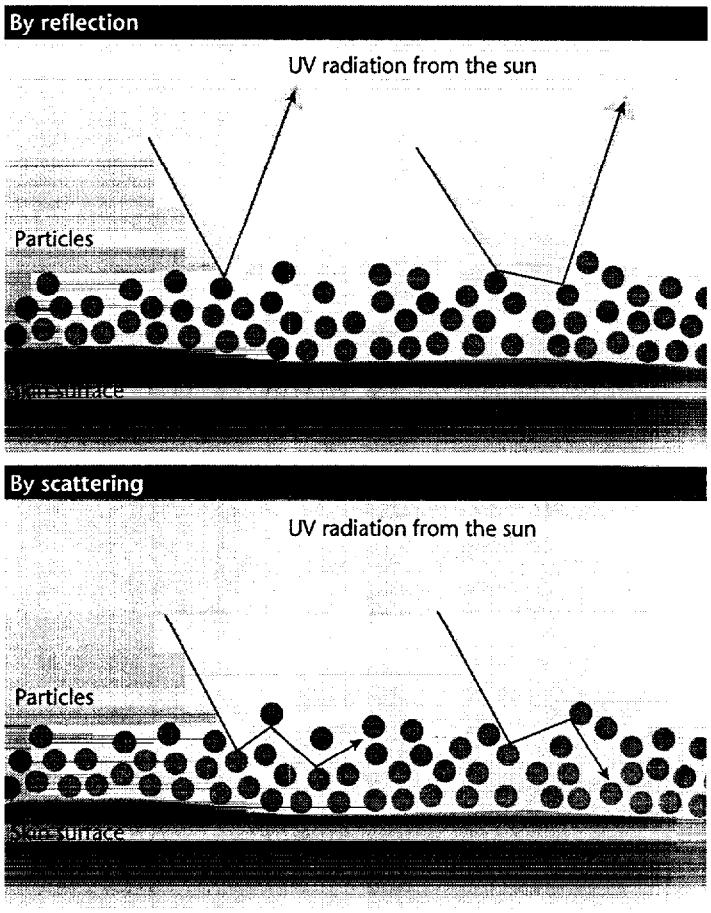

**Structure of TINOSORB M**




UVR is absorbed and leads to the excited state $S_1$. Within a very short time, in the order of $10^{-12}$ seconds, isomerisation takes place. During this short time span no other chemical reactions can be triggered. After the energy is dissipated vibronically isomerisation back to the original ground state $S_0$ takes place.

## UV protection by reflection and scattering

Particulate UV absorbers can in addition attenuate radiation by reflection or scattering. Both of these processes involve dipole oscillation of the electrons, a feature depending much on the polarisability of the particles and their refractive index. Since no energy is absorbed by scattering or reflection photochemical processes are absent.




## Undesired modes of energy dissipation

Other theoretical modes of energy dissipation are: fluorescence, phosphorescence, triplet/triplet energy transfer and photodegradation. They should not play a significant role in photoprotection.

Fluorescence and phosphorescence are not dangerous. Yet, since such radiative dissipation processes are visible effects, they are not desirable for cosmetic applications.

## Requirements for cosmetic UV absorbers

UV absorbers for cosmetics must be chemically and photochemically inert. If they are not, chemical bonds may be rearranged leading to new molecules, the UV absorbance of which might be diminished or even lost, and the toxicological properties may be altered. Radicals may react to form reactive oxygen species leading to biological damage. Moreover, fluorescence and phosphorescence, though not dangerous, are not desirable. Therefore, the light energy absorbed by UV filters (if not scattered or reflected) should only be transformed into harmless thermal energy as described.

# Product data

TINOSORB M is a 50% aqueous dispersion of colourless organic microfine particles with a size below 200 nm

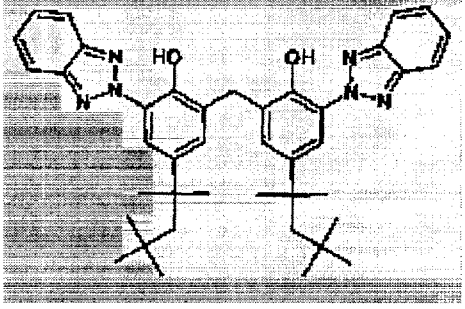
| Composition | |
|---|---|
| Organic microfine particles | 50.0% |
| Surfactant (Decyl glucoside) | 7.5% |
| Thickener (Xanthan gum) | 0.2% |
| Propylene glycol | 0.4% |
| Water | ad 100.0% |

pH adjusted to 10.5–11.5 by NaOH
Preservation: by alkaline pH

## Chemical data

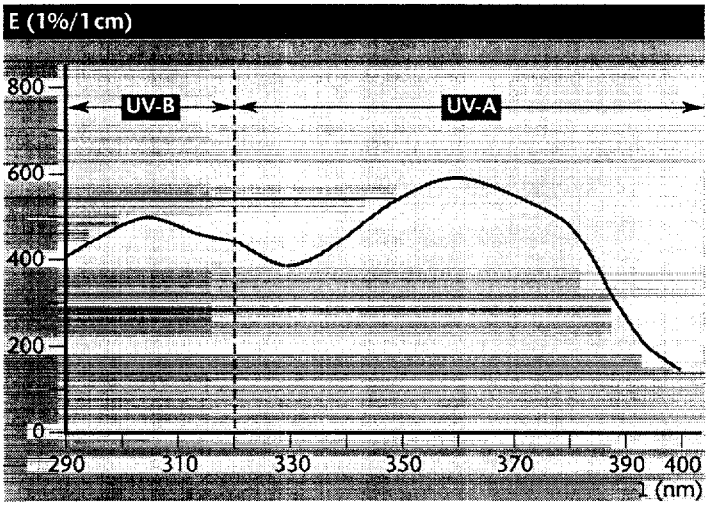
| | |
|---|---|
| **Chemical name** | 2,2'-Methylene-bis-(6-(2H-benzotriazole-2-yl)-4-(1,1,3,3-tetramethylbutyl)-phenol) |
| **INCI name** | Methylene Bis-Benzotriazolyl Tetramethylbutylphenol |
| **Molecular formula** | $C_{41}H_{50}N_6O_2$ |
| **Molecular mass** | 658.86 g/mol |
| **$T_M$** | 195° C |
| **Solubility** | in $H_2O$: < $10^{-8}$ g/l |

**Structure**




## Absorption spectrum of TINOSORB M

UV spectrum of TINOSORB M recorded using a Perkin Elmer Lambda 20 Spectrometer with integration sphere attachment. The integration sphere detects the directly transmitted light as well as the light that is scattered in forward direction.




Extinction of 1% active ingredient at an optical path length of 1 cm

## Particle size of TINOSORB M


Photo taken by Atomic Force Microscopy (AFM)

# Performance efficacy

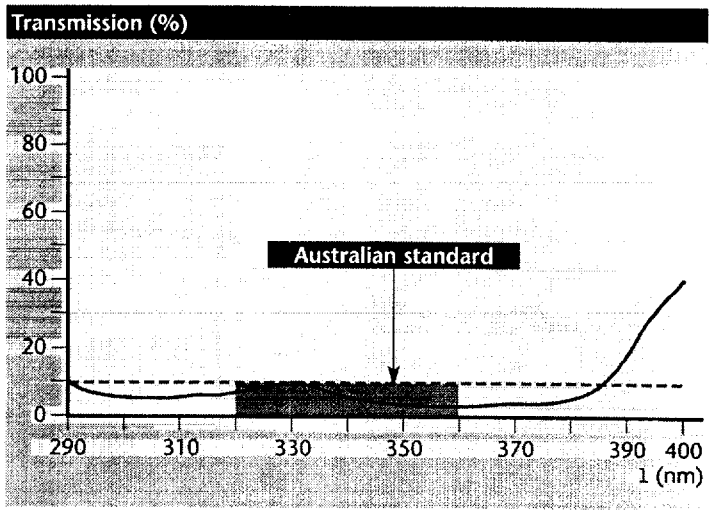
TINOSORB M is an efficient UV-A absorber and SPF booster. It proved extremely photostable and has a stabelising effect on other UV filters.

## UV-A assessment

The efficacy of a modern sunscreen is characterised not only by its UV-B shielding capacity but also by its UV-A attenuation. Three methods are widely used to document the UV-A performance of a sunscreen. The method required by the Australian authorities, the 'Australian standard', relates directly to the absolute reduction of UV-A reaching the skin. In contrast, the $l_c$ concept and the UV-A/UV-B ratio are measures for the amount of UV-A protection by a specific sunscreen in relation to its protection in the UV-B or to its overall protection, respectively.

## Australian standard

In Australia, UV-A protection is recognised when a sunscreen preparation transmits between a wavelength of 320 nm and 360 nm (at a pathlength of 8 µm) less than 10% of the incoming light[10]. 3.3% active ingredient (6.6% *TINOSORB M*) is necessary to fulfill this requirement.



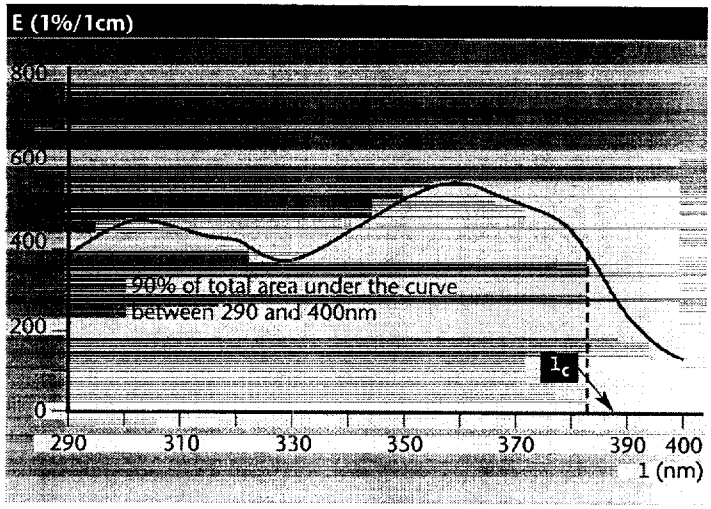

The green bar indicates the threshold value of the Australian standard $T_{320-360\ nm}$.

## Critical wavelength

The critical wavelength $l_c$ is a measure of a sunscreen's extinction capacity in the UV-A range in relation to its overall extinction between 290 nm and 400 nm. The extinction capacity is given by the area under the extinction curve. $l_c$ is defined as the wavelength at which this area corresponds to 90% of the total area $A_{290-400}$. The higher the critical wavelength of a sunscreen, the better its UV-A performance[9].

The critical wavelength is calculated as:

$$\int_{290}^{l_c} E(l)dl = 0{,}9 \cdot \int_{290}^{400} E(l)dl$$

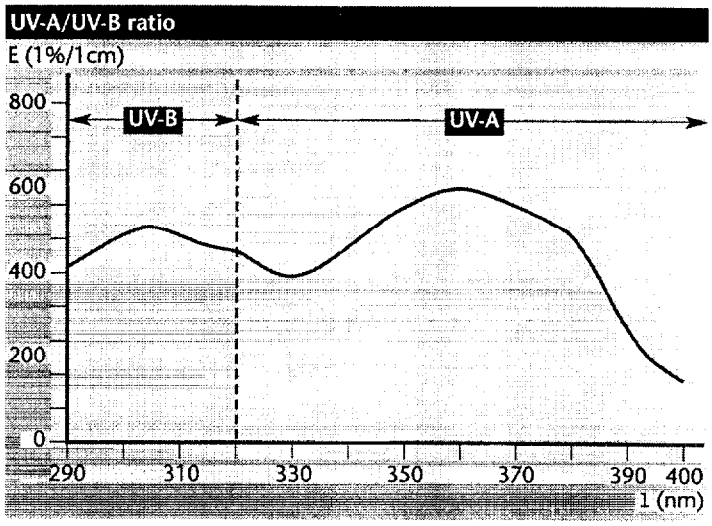



The critical wavelength $l_c$ for TINOSORB M comes to 388 nm.

## UV-A/UV-B ratio

The UV-A/UV-B ratio defines the performance of a sunscreen in the UV-A range (320–400 nm) in relation to its performance in the UV-B range (290–320 nm). It is calculated as the ratio between the area defined by the UV-A and UV-B extinction capacity. Both areas are normalised to the range of wavelength involved[9]:

$$\text{UV-A/UV-B ratio} = \frac{\int_{320}^{400} A(\lambda)\,d\lambda \;\cdot\; \int_{320}^{400} d\lambda}{\int_{290}^{320} A(\lambda)\,d\lambda \;\cdot\; \int_{290}^{320} d\lambda}$$



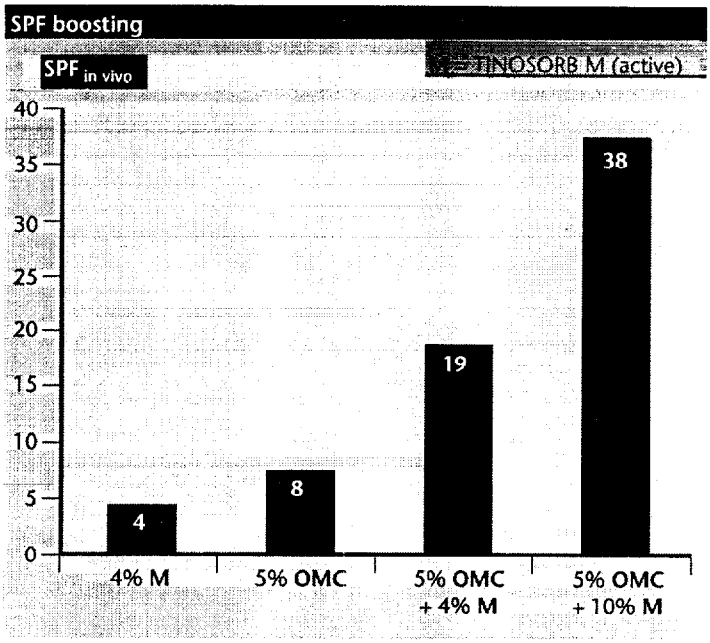

The UV-A/UV-B ratio of TINOSORB M alone amounts to 1.0.

The ratio 1, indicating a UV filter to absorb comparably in UV-A and UV-B does not refer to the absolute filtering capacity of a product. If a sunscreen absorbs poorly in the UV-B, the UV-A/UV-B ratio may be higher than 1. If UV-B protection is high, even high absorption in UV-A will lead to a ratio of <1.

# Synergistic effect of TINOSORB M + OMC

## SPF boosting

In combination with UV-B absorbers such as Octyl Methoxycinnamate (OMC), TINOSORB M causes boosting of the SPF.



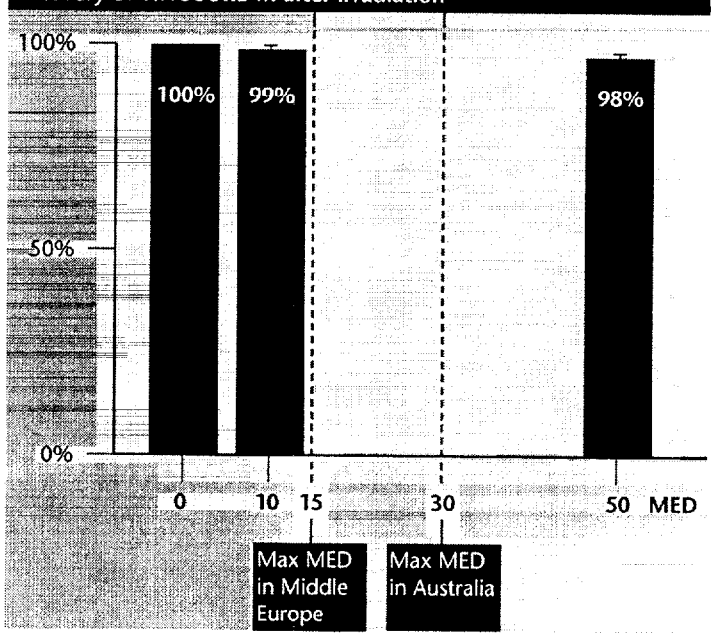
## Photostability

TINOSORB M proved extremely photostable. Its photostability was measured according to Berset et al.[12] in a solar simulator.

The recovery of TINOSORB M (7% active ingredient in aqueous suspension, 2 µl/cm² on a rough quartz plate) after irradiation by 10 MED amounted to >99% and by 50 MED to >98%.

Efficient energy dissipation of the active ingredient is responsible for the high photostability (see background of photoprotection).

**Recovery of TINOSORB M after irradiation**



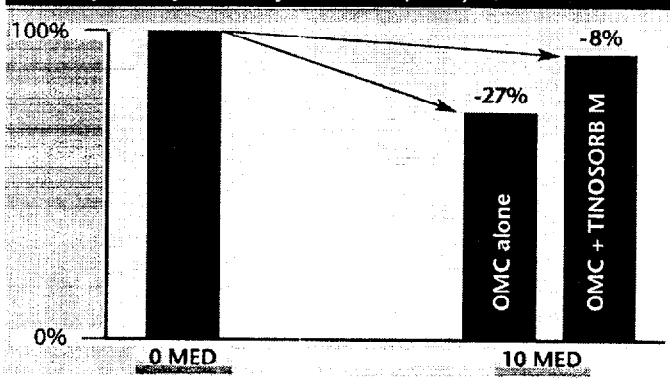

**Ultraviolet radiation (UVR) and Erythema (sunburn)** [4,15]

| | |
|---|---|
| MED | The Minimal Erythemal Dose defines the unity of UVR exposure for sun-sensitive individuals (skin phototype II). Its value is **200 J/m²**. |
| Erythema flux | The maximum erythema flux in middle European summer is about **0.2 W/m²**. In a tropical Australian summer it can be double this value. |
| MED/hour | In middle European summer a maximum of **3.5 MED/hour** can be received at midday and about **15 MED** during the whole day. In tropical regions these values must be doubled. |
| Exposure time $t_{EXP}$ | **MED divided by the erythema flux** gives the exposure time until the first reddening occurs. At midday in middle European summer this time is about **17min.** for skin phototype II. $t_{EXP}$ = 200 J/m²/(0.2 W/m²*60sec/min) |

## Stabilisation of Octyl Methoxycinnamate (OMC)

TINOSORB M has a stabilising effect on other UV filters. The experiment with Octyl Methoxycinnamate, (OMC) shows the positive effect of TINOSORB M. After irradiation with 10 MED, 27% of the OMC alone is lost. In the presence of TINOSORB M this loss is only 8%.

**Recovery of Octyl Methoxycinnamate (OMC) O/W**



# Safety

## TINOSORB M Active is

- not irritating to skin and eyes
- not phototoxic
- not sensitising
- not photosensitising
- no acute toxicity
- subchronic toxicity:
  not toxic up to very high dose levels
- not mutagenic
- not photomutagenic
- not teratogenic
- well tolerated in human skin applications

## Registration status

TINOSORB M is approved as UV filter on part I of Annex VII of the European cosmetics directive 76/768/EEC in a concentration of active ingredient up to 20% (10% Active)*.

TINOSORB M Active is approved as UV filter by the Swiss "Bundesamt für Gesundheit", listed in "Anhang 2 der Verordnung über kosmetische Mittel (VKos)" in a concentration of up to 20% (10% Active).

* The use of TINOSORB M Active as an ingredient in sunscreen products in the United States requires prior review and approval by the United States Food and Drug Administration "FDA". Ciba is committed to seek registration of TINOSORB M with all the necessary regulatory agencies, including the FDA, in the USA.

# References


1. K. Scharfetter-Kochanek, J. Wenk, B. Brenneisen, R. Blaudschun and M. Wlaschek. Molecular Role of Reactive Oxygen Species in Photoageing and Tumor Progression. *In*: P. Altmeyer et al. (Eds.). Skin Cancer and Radiation. Springer, Berlin-Heidelberg (1997) pp. 115–127

2. J.W. Streilein, J.R. Taylor, V. Vincek, I. Kurimoto, T. Shimizu, C. Tie, and C. Coulomb . Immune surveillance and sunlight-induced skin cancer. *Immunology Today*. 15.(1994) 174–179

3. A. Ziegler, A.S. Jonason; D.J. Leffeli; J.A. Simon; H.W. Sharma; J. Kimmelmann; L. Remington; T. Jacks; and D.A. Brash . Sunburn and p53 in the onset of skin cancer. *Nature* 372.(1994) 773–776

4. H. N. Ananthaswamy, S.M. Loughlin; P. Cox; R.L. Evans; S.E. Ullrich; and M.L. Kripke . Sunlight and Skin cancer: Inhibition of p53 mutations in UV-irradiated mouse skin by sunscreens. *Nature Medicine* 3.(1997) 510–514

5. M. Fukuda and S. Takata. The Evolution of Recent Sunscreens. *In*: P. Altmeyer et al. (Eds.). Skin Cancer and Radiation. Springer, Berlin-Heidelberg (1997) 265–275

6. S. Schrauder. Sunscreens in Europe: Recent Developments. *In*: P. Altmeyer et al. ( Eds.). Skin Cancer and Radiation. Springer, Berlin-Heidelberg (1997) 276–295

7. G. Sauermann, T. Mann, and M. Wochnowski. UV Protection by Sunscreens. *In*: P. Altmeyer et al. ( Eds.). Skin Cancer and Radiation. Springer, Berlin-Heidelberg (1997) 296–313

8. Otterstedt J-E, Photostability and molecular structure, J. Phys. Chem. 58 (1973) 5716-5725

11. Diffey, B.L., A method for broad spectrum classification of sunscreens. Int. J. Cosm. Sci., 16 (1994) 47–52

10. Australian/New Zealand Standard, AS/NZS 2604 (1993)

12. Berset, G., Gonzenbach, H., Christ, R., Martin, R., Deflandre, A., Mascotto, R. E., Jolley, J. D. R., Lowell, W., Pelzer, R., and Stiehm, T., Int. J. Cosmet. Sci. 18 (1996) 167–177

9. McGarry, P. F., Jockusch, S., Fujiwara, Y., Kaprinidis, K., and Turro, N. J., J. Phys. Chem. A 101 (1997) 764–767

13. B.L. Diffey, Dosimetry of Ultraviolet Radiation. *In:* N.L. Lowe, N.A. Shaath, M.A. Pathak, Sunscreens, Development, Evaluation, and Regulatory Aspects, 2nd ed., Marcel Dekker, New York (1997) 175–188

14. M.A., Pahtak, Photoprotection Against Harmful Effects of Solar UV-B and UV-A Radiation: An Update. *In:* N.L. Lowe, N.A. Shaath, M.A. Pathak, Sunscreens, Development, Evaluation, and Regulatory Aspects, 2nd ed., Marcel Dekker, New York (1997) 59–79

15. Bernhard G., Mayer B., Seckmeyer G., Moise A., Meanrements of spectral solar irradiance in tropical Australia, Journal of Geophysical Research, Vol.102, No.D7 (1997) 8719-8730

# Recommendations for use

## Principles for handling Tinosorb M

As Tinosorb M is an aqueous dispersion, it should not be allowed to dry completely in vessels and other equipment. During drying Tinosorb M tends to agglomerate, making cleaning difficult.

It is also good practice to close the storage tank after working with Tinosorb M to reduce drying.

If Tinosorb M has become dry, clean the equipment by brushing with plenty of water.

During the preparation of a batch agglomeration of Tinosorb M by drying should be avoided because, once in the product, agglomerates cannot be redispersed by means of a homogeniser (Ultra Turrax).

## Incorporation of Tinosorb M in o/w emulsion

Tinosorb M can be incorporated into o/w-emulsion but is not recommended for use in w/o-emulsions.

A minimum concentration of 3.3% active substance (i.e. 6.6% Tinosorb M) is necessary – when used alone – in order to fulfill the Australian Standard for UV-A protection.

Tinosorb M should be blended into the water phase by continuous stirring. Continuous stirring is also required during the subsequent heating of the water phase.

Incorporation of Tinosorb M into the oil phase of emulsions is not recommended because of its tendency to agglomerate.

Alternatively TINOSORB M can be incorporated into the final emulsion (after emulsification).

Because of the alkaline pH of Tinosorb M it is best to neutralise either the water phase after incorporation of Tinosorb M or the made-up emulsion. Please note that all raw materials incorporated prior to the neutralisation step must be stable to alkaline conditions.

# Formulary

The information given in our circulars is based on the present state of our knowledge. It shows without lability on our part the uses to which our product can be put.

**For further information please call your local representative.**



**Ciba Specialty Chemicals**

Ciba Specialty Chemicals is a global leader in the discovery, manufacture and marketing of innovative specialty chemicals. Our products hold leading positions in their chosen markets. We add value beyond chemistry for our customers, employees and shareholders through our state-of-the-art environmentally compatible technologies and proven international marketing expertise.

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Value beyond chemistry

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* FedEx Letter Rate not available. Minimum charge: One-pound rate

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