

Introduction

Several excipients have to be used in cosmetic emulsions to reach the desired product requirements, e.g. physicochemical stability, a satisfactory safety profile and sensorial properties, including surfactants, preservatives and emollients. It is of crucial importance to evaluate the safety profile of the ingredients used in such vehicles.

As imposed by legislation, cosmetic emulsions, in their intended use, must be safe for the consumer. In Europe, they fall under the general requirements of the Regulation (EC) N° 1223/2009. Under this regulation, the toxicological profile of all ingredients and detailed product-specific exposure knowledge are fundamental for the safety assessment. The safety of a cosmetic product is determined based on the safety assessment of its ingredients through literature data, *in vitro* tests and *in vivo* tests in humans. Some ingredients are of special concern, e.g. preservatives and UV filters, especially those used in nano-sized form.

Aim

The aim of this study was to evaluate the safety profile and biological effects of a newly developed cosmetic emulsion containing Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (MBBT) (Tinosorb® M, obtained from BASF, S.E.) as an Ultraviolet (UV) filter, using literature data and a systematic approach for the safety assessment, comparing it with *in vitro* and *in vivo* data obtained by methods of skin bioengineering and tests on human volunteers, respectively.

Methods

The safety assessment was performed according to the Scientific Committee on Consumer Safety (SCCS) guidance [1].

Hazard identification: The results of the *in vitro* and *in vivo* tests, clinical studies, physical, chemical and toxicological properties of each ingredient were considered to recognize if the ingredient has the potential to damage human health.

Dose-response assessment: The dose-response assessment describes the change in effect on an organism caused by differing levels of exposure to a chemical after a certain time of exposure. In the case of an effect with a threshold, the dosage at which there is 'No Observed Adverse Effect Level' (NOAEL) is determined.

Exposure assessment: The amount and the frequency of human exposure to the MBBT-loaded emulsions were determined using the systemic exposure dose (SED) that was calculated for each ingredient, according to Equation 1.

$$\text{Equation 1: } SED = E(\text{mg/kg / bw/day}) \times \frac{C(\%)}{100} \times \frac{DA(\%)}{100}$$

Where, E is the amount expected to enter the blood stream per kg body weight per day, C is the concentration of the ingredient in the MBBT-loaded emulsions and DA is the dermal absorption reported as a percentage of the test dose expected to be applied under conditions simulating those of real-life.

Risk characterization: The probability that the substances under study cause damage to human health was considered. In the case of a threshold effect, the margin of safety (MoS) was calculated according to the Equation 2.

$$\text{Equation 2: } MoS = \frac{NOAEL}{SED}$$

A safety evaluation study, using the Marzully and Maibach [2] Human Repeat Insult Patch Test (HRIPT) was performed for the MBBT-loaded emulsions to evaluate the product's irritant and allergic capacity in 51 volunteers. A protocol identical to the one previously described by Marto et al was followed [3]. This protocol was approved by the local Ethical Committee and respected the Helsinki Declaration and the AFSSAPS regulations on performed HRIPT studies on cosmetic products. The study was conducted under the supervision of a dermatologist.

Results

MBBT is composed of 50.0% organic micro-fine particles, with a particle size below 200 nm; thus this ingredient is considered to be nano-sized.

The assessment of the safety for human health of the finished product took into consideration the toxicological profile of each ingredient, their chemical structures and their exposure levels.

Table 1. Summary of the safety data of Tinosorb® M.

INCI	Acute toxicity	Dermal toxicity	SED*	MoS**
Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (and) Aqua (and) Decyl Glucoside (and) Propylene Glycol (and) Xanthan Gum	LD50 (oral) rat > 2000 mg/L	LD50 (dermal) rat > 5000 mg/kg	0.724	1381.22
*C = 0.3%; **NOAEL = 1000 [4].				

Despite the high values obtained for MBBT, it should be taken in account that this ingredient has a particle size below 200 nm. The Scientific Committee on Consumer Safety issued an opinion considering this ingredient in 2013 [4].

Nevertheless, attention needs to be paid to the identification/presence in selected tissues to obtain information on potential bioaccumulation given the physical and chemical properties (namely lipophilicity) of the substance.

Table 2. Results for the Human Repeat Insult Patch Test (HRIPT).

Induction phase	
Type of reactivity on the induction site	Number and percentage of reactive volunteers
0	0/0%
Challenge phase	
Type of reactivity on the induction site and virgin site	Number and percentage of reactive volunteers
0	0/0%



The MBBT-loaded emulsion did not induce any irritant (induction phase) or allergic reactions (challenge phase) in occlusive-patch tests.

Discussion & Conclusion

Given the high lipophilicity of MBBT, attention should be given to its identification in selected tissues to obtain information on potential bioaccumulation. MBBT's use as a sunscreen ingredient might lead to environmental exposure. The SCCS noted that, due to poor biodegradation potential and high partition coefficient, long term effects in the environment cannot be excluded; MBBT is currently classified with R 53/Chronic 4 – 'may cause long term effects on the aquatic environment'.

For the intended use, the evaluation of available data on MBBT does not indicate a significant risk that outweighs its benefits.

Furthermore, clinical data, albeit largely gathered by pilot investigations, indicates very low incidence of adverse events; together with the HRIPT results it can be concluded that this product shows very good skin compatibility.

References: [1] SCCS. The SCCS'S Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation: 9th Revision. European Union, 2015; [2] MARZULLI FN, MAIBACH HI. Contact allergy: predictive testing in man. Contact Derm 1976; 2:1-17; [3] MARTO J, GOUVEIA LF, GONÇAVES L et al. Starch Pickering Emulsion: A Safe Vehicle for Topical Drug Delivery. Athens Journal of Sciences 2015; 2:77-87; [4] Scientific Committee on Consumer Safety (SCCS). SCCS/1443/11. Opinion on 2,2'- Methylene-bis-(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol), 2013.