UVA phototoxicity evaluation of a combination of organic and inorganic UV filters

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Introduction:

Photoprotective formulations should provide even broad-spectrum protection, minimizing and not altering the natural sunlight spectrum [1]. For this, one must consider not only the amount or quality of the UV filters, as this does not directly imply photostability, but also the interactions between all the UV filters and the other components of the formulation [2]. In fact, depending on the interaction, synergistic effects can occur that result in either photostabilization or acceleration of photodegradation reactions [3,4].

In this sense, optimizing photoprotective efficacy in terms of UV filters' phototoxicity and photostability, ensures broad and uniform protection of the solar spectrum, reduced amounts of UV filters incorporated into formulations, reduced production of free radicals related to irritation, penetration, as well as the prevention of environmental accumulation of these compounds [1-5].

In this context, this study aimed to assess the phototoxic potential of a combination of UV-filters containing a titanium dioxide (TiO_2) with silica and dimethicone coating, bis-ethylexyloxyphenol methoxyphenyl triazine (BEMT) and avobenzone, by means of a validated in vitro phototoxicity test as an alternative to animal testing.

Materials & Methods:

After solubility assessment of the UV filters combination, the *in vitro* phototoxicity of the UV filter combination was evaluated in duplicate by the 3T3 Neutral Red Uptake Phototoxicity Test (3T3 NRU PT), in accordance to the INVITTOX protocol No. 78 [6].

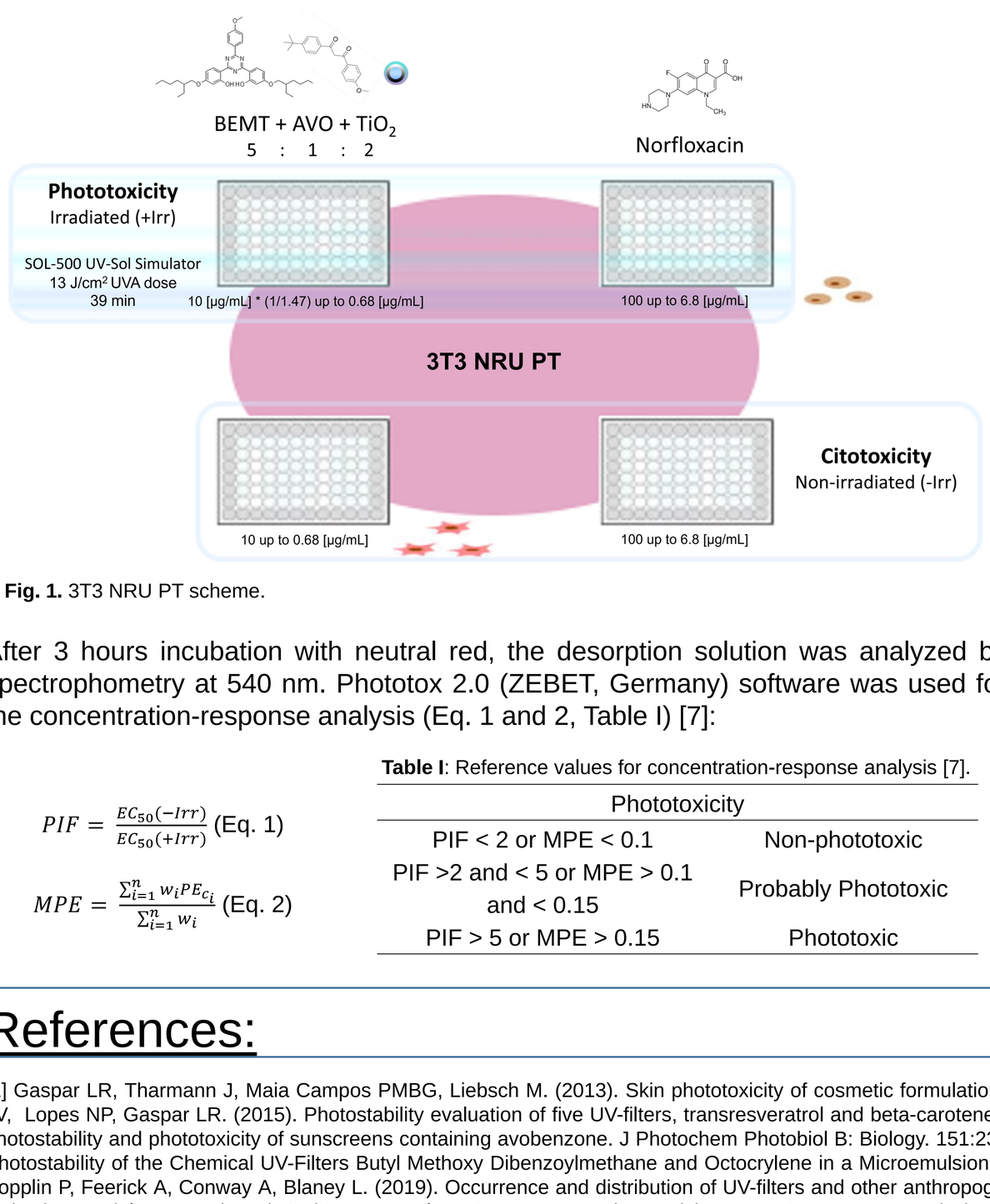

Fig. 1. 3T3 NRU PT scheme.

After 3 hours incubation with neutral red, the desorption solution was analyzed by spectrophometry at 540 nm. Phototox 2.0 (ZEBET, Germany) software was used for the concentration-response analysis (Eq. 1 and 2, Table I) [7]:

$$PIF = \frac{EC_{50}(-Irr)}{EC_{50}(+Irr)} \text{ (Eq. 1)}$$

$$MPE = \frac{\sum_{i=1}^{n} w_i PE_{c_i}}{\sum_{i=1}^{n} w_i} \text{ (Eq. 2)}$$

Table I: Reference values for concentration-response analysis [7].

Phototoxicity	
PIF < 2 or MPE < 0.1	Non-phototoxic
PIF >2 and < 5 or MPE > 0.1 and < 0.15	Probably Phototoxic
PIF > 5 or MPE > 0.15	Phototoxic

Results & Discussion:

Although the UV filter combination exhibited a concentration-dependent photo effect, it was not deemed phototoxic [7]. PIF of both test runs were of 1.000 ± 0.000, indicating that the half maximum inhibitory concentration could not be identified for the concentrations under study.

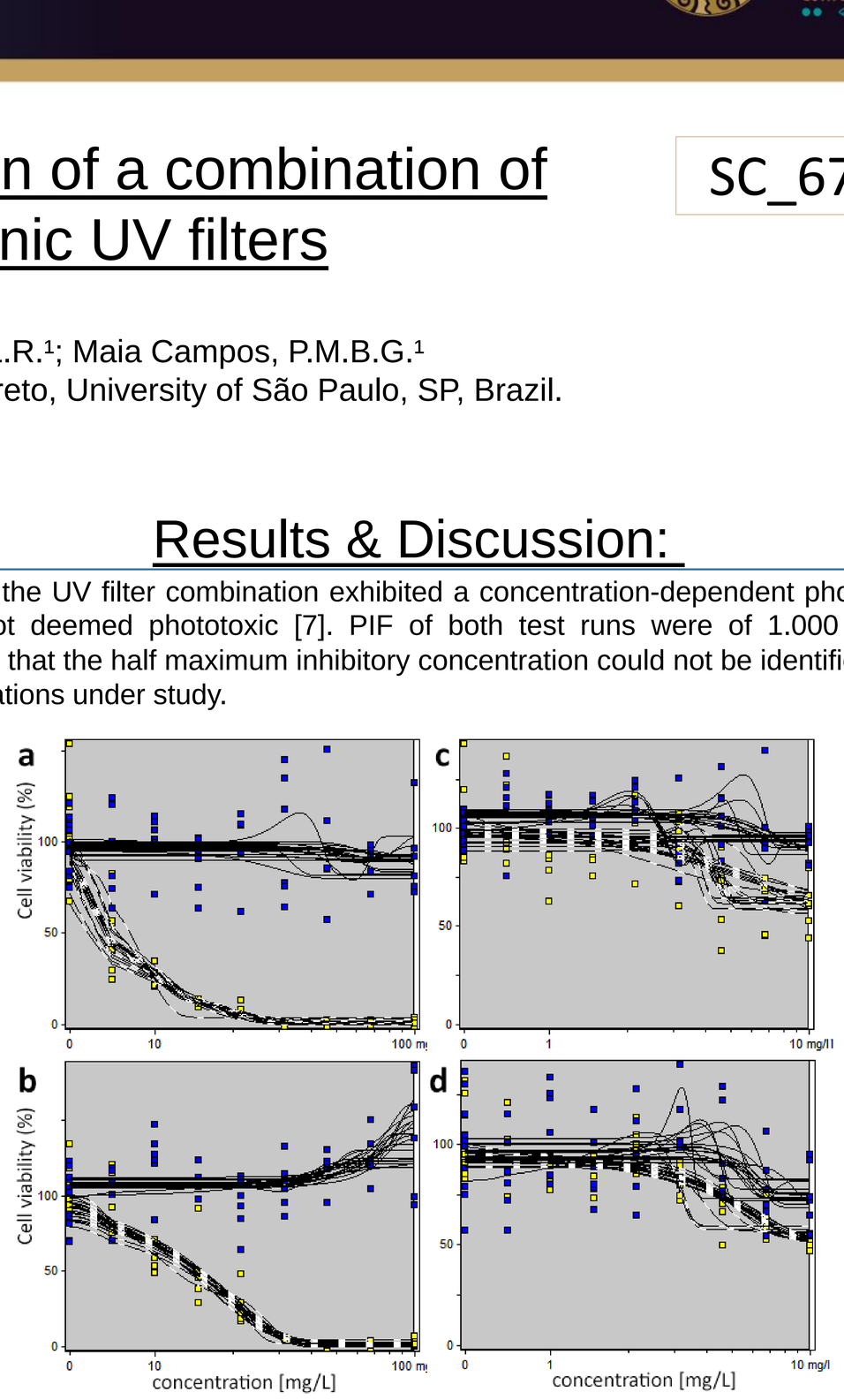

Fig. 2. Dose-response curves of (a,b) norfloxacin, (c,d) combination of UV filters. Blue and yellow dots refer to non-irradiated (-Irr) and irradiated (+Irr) substances, respectively.

The concentration range evaluated in this study, due to the lipophilic coating of the inorganic particle, the maximum concentration used in serial dilutions was 10 µg.mL^{-1}. Confirmation in reconstituted skin models is still recommended for prevention of the solubility bias and adequate portray of the skin barrier function.

Table II. Mean-Photo-Effect (MPE) and Photo-Irritation-Factor (PIF) values.

Sample	Run	MPE	PIF	MPE_m	PIF_m
Norfloxacin	1 a	0.762[a]	18.039[a]	0.790[a]	12.585[a]
	2 b	0.818[a]	7.130[a]		
UV Filters	1 c	0.151[a]	1.000	0.114	1.000
	2 d	0.077	1.000		

[a] Phototoxic [7].

Conclusions:

The UV filter combination was characterized as probably phototoxic. The methodology applied supports the development of safer photoprotection products, since the 3T3 NRU PT allows early risk assessment and can be complemented by other alternative methods, preventing unnecessary risks for human subjects, the enviroment and animal testing.

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