CONTACT SENSITIZING UV FILTERS IN SUNSCREEN PRODUCTS IN THAILAND

BY

MR. PAWIT PHADUNGSAKSAWASDI

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE (DERMATOLOGY)
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ENTITLED

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IN SUNSCREEN PRODUCTS IN THAILAND

was approved as partial fulfillment of the requirements for
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ABSTRACT

Background: Ultraviolet filters are the active ingredients in sunscreen products. Many common filters cause allergic responses. The prevalence of sensitivities to sunscreen may vary based on region due to differences in sunscreen composition.

Objective: To evaluate the presence of common contact-sensitizing ultraviolet filters in sunscreen products in Thailand.

Methods: From March to December 2016, ingredient labels on commercially available sunscreen products in Thailand were analyzed.

Results: Two hundred and forty-six sunscreen products were examined. Sixty-eight (27.6%) were manufactured in Thailand, 90 (36.6%) in Asia, and 88 (35.7%) in Western countries. Twenty-two ultraviolet filters were identified. Ethylhexyl methoxycinnamate (EHMC) was the most common in this study and in Asian products, while butyl methoxydibenzoylmethane (BMDM) was the most common in Western products. The median number of ultraviolet filters in each product was four. Seventy-six percent of sunscreens had sun protection factor ≥ 50. EHMC and benzophenone-3 (BP3) were less prevalent in products for children ($p = 0.004$ and $p = 0.029$, respectively). BP3, BMDM, and octocrylene (OCR) were not significantly different between products labeled for sensitive skin and those not.

Conclusions: This study indicates differences in ultraviolet filter exposure in Thailand. This should provide a benchmark for future studies.

Keywords: sunscreen, UV filters, photoallergic contact dermatitis, ingredient label, exposure analysis, market survey

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LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
EHMC	Ethylhexyl methoxycinnamate
TiO	Titanium dioxide
BMDM	Butyl methoxydibenzoylmethane[i]
OCR	Octocrylene
BEMT	Bis-ethylhexyloxyphenol methoxyphenyl triazine
EHS	Ethylhexyl salicylate
ZnO	Zinc oxide
DHHB	Diethylamino hydroxybenzoyl hexyl benzoate
HMS	Homomenthyl salicylate
BP3	Benzophenone-3
MBBT	Methylene bis-benzotriazolyl tetramethylbutylphenol
PBSA	Phenylbenzimidazole sulfonic acid
EHT	Ethylhexyl triazone
DMT	Drometrizole trisiloxane
TDSA	Terephthalylidene dicamphor sulfonic acid
PS15	Polysilicone-15
DHBT	Diethylhexyl butamido triazone
MBC	4-Methylbenzylidene camphor
IMC	Isoamyl p-methoxycinnamate
DPDT	Disodium phenyl dibenzimidazole tetrasulfonate

EDOP	Ethylhexyl dimethoxybenzylidene oxoimidazoline propinoate
EDPABA	Ethyl dihydroxypropyl PABA
UV	Ultraviolet
UVR	Ultraviolet radiation
UVA	Ultraviolet A
UVB	Ultraviolet B
UVC	Ultraviolet C
VL	Visible light
IR	Infrared radiation
ROS	Reactive oxygen species
MMPs	Matrix metalloproteinases
SPF	Sun protection factor
UPF	Ultraviolet protection factor
ACD	Allergic contact dermatitis
PACD	Photoallergic contact dermatitis
NACDG	North American Contact Dermatitis Group
NSAIDs	Nonsteroidal anti-inflammatory drugs

CHAPTER 1
INTRODUCTION

1.1 Background

Over the past few decades, sunscreen use and sun-protection behaviors have been rising as a result of education and marketing about the dangers of ultraviolet (UV) radiation exposure (1–4) in Western and Asian countries. The fast-growing cosmetic industry launched new sunscreen products and UV filters to market to supply the demand of consumers. Ultraviolet filters, which are the active ingredients of sunscreen products, are widely reported as causative agents of contact and photocontact allergies (5). The prevalence of sunscreen allergies may vary by country due to differences in UV filter exposure. Although a low incidence of contact/photocontact allergies to UV filters has been identified in Thai patients (6–8), this may have been underestimated due to infrequent testing and the lack of allergen testing. The definitive solution for allergic and photoallergic contact dermatitis is to avoid the allergen, so a better understanding of the common causative agents in sunscreen products is needed. Sunscreen products are complex mixtures designed to mutually protect the skin from UV radiation with maximum efficiency (9). The usage of UV filters varies by country and region due to different regulations (10). At present, there are no exposure studies of common UV filters in sunscreen products sold in Thailand, or even Asia. The aim of this study was to investigate consumer exposure to potential sensitizing UV filters in sunscreen products, to describe the characteristics of sunscreen products currently sold in Thailand, and to compare these results with other study results from Western countries.

1.2 Objectives

The primary objective is to examine the Frequency of common (in EU and USA) contact sensitizing UV-filter labelled on the products that indicated as sun protection use (sunscreen product), sold in Bangkok Metropolitan, Thailand during year 2016.

The secondary objective is to describe the characteristics of sunscreen products currently sold in Thailand and compare with the other study from western country.

1.3 Hypothesis

The consumer exposure to contact sensitizing UV filters in sunscreen products in Thailand are different from the western country.

1.4 Keywords

Sunscreen
UV filters
Photoallergic contact dermatitis
Ingredient label
Exposure analysis
Market survey

1.5 Limitation

Cannot verify the ingredients that labeled on the sunscreen products are actually existing in the products.

This survey is not able to obtain all of the sunscreen product brand that available in the market due to missing out or inaccessibility.

1.6 Expected benefit

1. To provide the data of UV filters exposure assessments

2. To evaluate the regional difference in UV filters allergy exposure
3. To be an information for establish the standard patch/photopatch test
4. To be an information for revise the local cosmetic regulation
5. To be a database for sunscreen selection

CHAPTER 2
REVIEW OF LITERATURE

2.1 Biology of sunlight

2.1.1 Spectrum of sunlight

UV radiation is in the range of electromagnetic spectrum, which divided into groups based on its frequency and wavelength as show in Figure 2.1. The atmosphere stop most of the electromagnetic radiation from space reaching Earth's surface (Figure 2.2). Radio, infrared , visible light and some UV radiation can reach to the human.

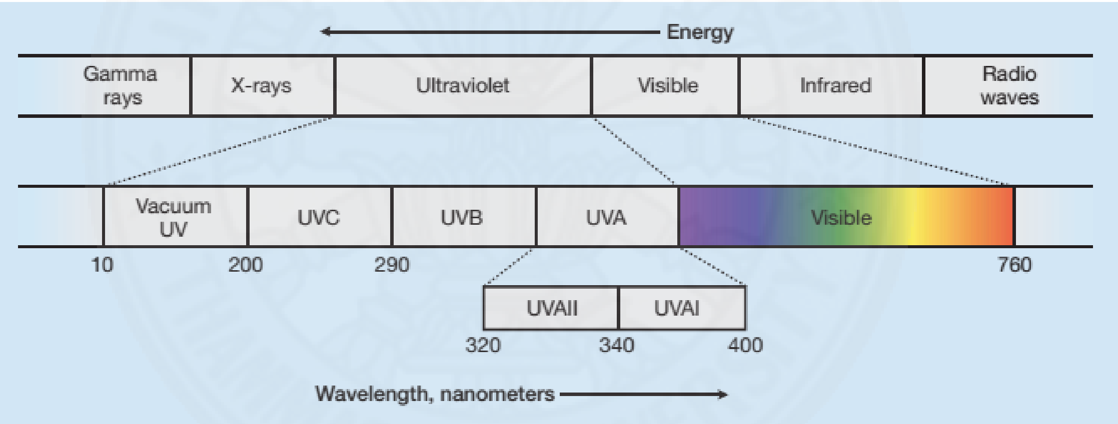

Figure 2.1 Electromagnetic spectrum and radiation types (11)

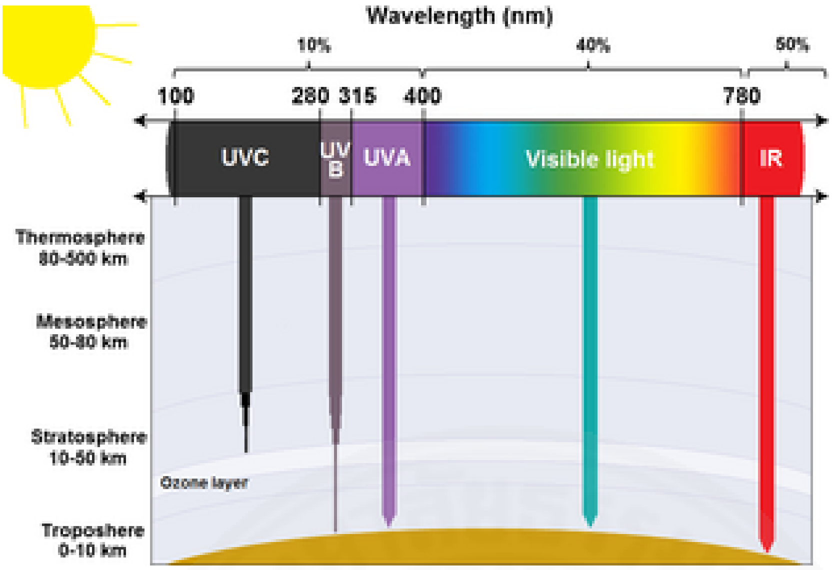

Figure 2.2 Sunlight spectrum and the atmosphere filtering effects (10).

Ultraviolet radiation (200-400nm) is divided into ultraviolet C(200-290nm), ultraviolet B(290-320nm), and ultraviolet A (320-400nm). Ultrviolet A is divided into UVA1 (400-340nm) and UVA2 (340-315nm). Reaching of ultraviolet radiation to the surface depends on the environmental factors(clouds, humidity), location and season(12). The wavelengths from the sun shorter than 290nm are filtered by in the stratosphere ozone layer and not reach to the skin. The different wavelengths of ultraviolet radiation can enter the skin in various depth and has numerous cellular effects (Figure 2.3).

2.1.2 Ultraviolet radiation

UVC (200– 290 nm), a high-energy ultraviolet range is usually filtered by stratosphere ozone layer. UVC is a powerful radiation that strongly absorbed by DNA can be harmful to the viable cells of the epidermis. Reduction of stratospheric ozone layer that caused more UV exposure, has been concerned for a while. The releasing of chlorofluorocarbons (CFCs) by ant sources could affect the ozone layer. In 1987, the Montreal Protocol was approved, leading to banning on CFC usage. Greenhouse gasses and climate change are the other important factors result in ozone layer depletion (13).

Ultraviolet B (290–320 nm) are mostly filteredby the ozone layer. The UVB constitutes only around 5% of the UV and 0.5% of total radiation reaching the earth's surface. UVB radiation, a "sunburn" spectrum, is an active wavelengths for biological effect. It enter the skin, down to the deep epidermis, where it generates reactive oxygen species, caused sunburned and inflammation and induced skin aging. ROS are produced when chromophores absorb the light that reaches the skin. The ultraviolet B is able to absorbed by DNA bases and cause mutation in DNA. Nucleotide excision repair process repairs CPDs and 6-4 PPs when it is not able to fix the exceeding mutation, leading to aggregate of mutations in skin cells that caused skin cancer (14). Delayed tanning is a defense mechanism of skin when exposing to UVB involving new melanin synthesis to reduce the effect of radiation on the skin (15). UVB at 297nm is mainly responsible for erythema while 313-nm UVB(16) primarily causes DNA damage and photocarcinogenesis (17).

UVA radiation (320–400 nm), account for ninety-five percent of ultraviolet radiation pass to the earth, less energetic than UVB but enter deeper into the skin. Immediately tanning that develops after exposing to a significant amount of UVA occurs through the reaction of existing melanin instead of new pigment synthesis. Oxidative damage from UVA caused premature skin aging and carcinogenesis via the formation of oxidized DNA bases (18)(19). Moreover, 360– 380 nm range of UVA has immunosuppressive properties that may explain the increasing risk of skin cancers (20).

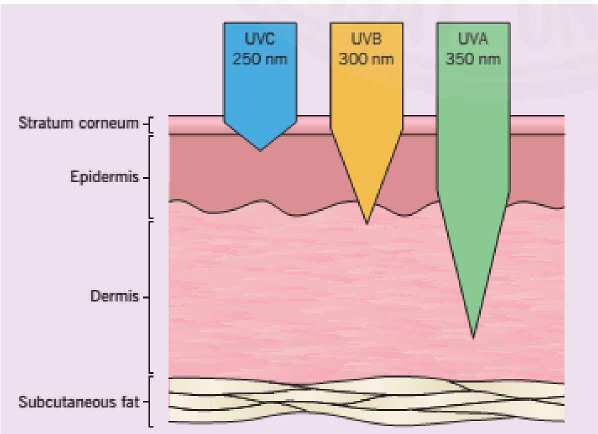

Figure 2.3 Skin penetration of different UV wavelengths (21)

2.1.3 Effects of sunlight

2.1.3.1 Positive effects

Vitamin D synthesis is the most important positive effects of sun light, especially UVB radiation, on skin(22).The 7-dehydrocholesterol in keratinocyte and fibroblasts, is converted into vitamin D3 during exposed to sunlight. The vitamin D3 is produced, then attach to binding protein and pass into the circulatory system. In the kidneys and liver ,vitamin D is metabolized into 1,25-dihydroxyvitamin D which is the biologically active form and 25(OH)D and 25-hydroxyvitamin D which is a major vitamin D form respectively (23). Metabolism of calcium and phosphorus are regulated by vitamin D3 for maintaining the metabolic functions and skeletal health. Approximately fifteen percent of calcium and sixty percent of phosphorus from dietary are absorbed if there are vitamin D3(24). Deficiency of vitamin D in children can cause growth abnormality, such as rickets disease. Osteoporosis is the consequence of vitamin D deficiency that caused bone problems in adults (25) Mostly, around ninety percent of the vitamin D necessity is enough by sunlight exposure. Thus, elderly who staying indoors and rarely expose to sunlight and strong pigmented persons are at risk of vitamin D difficiencies. The sunscreen usage with high SPF can affect the vitamin D levels (26). Moreover, vitamin D have an effect on myocardial function, insulin production, function of lymphocyte, inflammatory disease response, hormone secretion, and modulating colon cancer risk and rheumatoid arthritis (26–28). Moreover, there are many application of UV radiation in treatment of several skin diseases. The balancing of sunlight exposure is essential in order to have an optimal benifit for health.

2.1.3.2 Negative effects

Excessive sunlight exposure leads to damaging on human skin. Sunlight compose of UV radiation, IFR, visible light that all can cause the problem on the skin(29). Nowadays, it is recognized that ultraviolet radiation has an important effect on skin damage even acute or chronic exposure (Table 2.1)(30). Ultraviolet B mainly induce erythema and DNA damage, while ultraviolet A is related to tanning and photo-aging (Table 2.2).

Table 2.1 Ultraviolet radiation spectrum, penetration and effect on skin (30)

Characteristics	UVC	UVB	UVA
Wavelength	200-290 nm	290-320 nm	UVA I: 340-400 UVA II: 320-340
Depth of penetrance	Epidermis	Epidermis and papillary dermis	Papillary and reticular dermis
DNA effects	Pyrimidine dimers, pyrimidine photoadducts, strand breaks	Photodynamic actions (ROS production)	Photosensitization reactions (protein and DNA cross-links)
Clinical effects	Erythema Photocarcinogenesis	Vitamin D3 synthesis Immediate pigmentation Sunburn Delayed pigmentation Phototoxicity Immunomodulation Hyperplastic reaction Photoaging Photocarcinogenesis	Immediate pigmentation Sunburn Delayed pigmentation Phototoxicity Photoallergy Immunomodulation Hyperplastic reaction Photoaging Photocarcinogenesis

Table 2.2 Effects of Ultraviolet radiation on skin (30)

Acute effect of UV exposure	Chronic effect of UV exposure
Erythema	Photoaging
Pigment darkening	Immunosuppression
Delay tanning	Photocarcinogenesis
Epidermal hyperplasia	Photodermatoses
Free radical formation	
Vitamin D synthesis	

2.1.3.3 Visible light

Visible light (400-760 nm) accounts for fourty to fourty five percent of the electromagnetic wavelength that reaches the earth's surface. Some studies reported the biological effects of visible light on human skin, However it had reported to cause changes in erythema and pigmentation (31)(32), free radical production and thermal damage, and production of reactive oxygen species (33). In 2010, investigators performed the visible light on skin types IV to VI showed that visible light can caused darker pigment than UVA (UVA1, 340-400 nm, 20 J/cm^2) and at higher doses, surrounded by erythema that disappeared within 2 hours of exposure (34). In contrast to UVA1, pigmentation induced by visible light remaining over 2 weeks and did not disappear even at lower doses. No pigmentation could be induced in skin type II, suggesting that the response to visible light and UVA is dependent on skin type. This suggests that visible light plays a role in conditions aggravated by sun exposure such as post-inflammatory hyperpigmentation and melasma, which is especially common in darker-skinned individuals (skin phototypes III-VI). A subsequent study showed that pigmentation was induced in individuals with skin types III and IV with 415-nm, but not 630-nm radiation; the pigmentation lasted 3 months (35).

At present available chemical UV filters are not adequate to protect the skin from the effect of visible light; only physical UV filters such as non-micronized form of titanium dioxide and zinc oxide, and iron oxide, are able to protect visible light (36). These agents reflect and scatter visible light. Recently, the studies showed that adding of these agents to sunscreens offer greater protection in terms of decrease in Melasma Area and Severity Index score (37). However, these agents are matt white or red in color, water-insoluble, and leave an unpleasant white mark on th skin, which is unacceptable to many people. Topical antioxidants may also be beneficial against the effects of visible light, as suggested by the findings that use of a photostable ultraviolet A and ultraviolet B sunscreen together with antioxidant considerably less cytokines production, reactive oxygen species, and MMPs expression in vitro, and lessened oxidative stress in skin after exposed to visible light (33).

2.1.3.4 Infrared radiation

More than half of the solar radiation that reaches earth's surface is infrared radiation. The most broadly studied wavelength band is near infrared (infrared A, 760-1400 nm), which represents about one third of total solar energy and can penetrate the skin, directly affecting the epidermis, dermis, and subcutis. Irradiated to infrared generate a perceptible increase in skin temperature (38). Nowadays, Infrared is known as having biological effects on human skin (29). Infrared A exposure include the activation of mitochondrial reactive oxygen species via up-regulation of MMP-1, -3, and -13, without connected up-regulation of tissue inhibitor of metalloproteinase-1, resulting in collagen degradation. Repeated irradiance to infrared A is related to the appearance of photoaging aging signs, wrinkles, in the skin of mice and human (39)(40). In animal skin, wrinkle formation was more with infrared A plus UV radiation than with either infrared A or UV radiation alone, representing that infrared A causes photoaging via different mechanisms. Infrared A has also been shown to decrease collagen type 1 expression by inhibiting the procollagen-1-stimulating factors production (41), and to induce angiogenesis in skin through increased VEGF expression (42), and it has been shown to increase numbers of mast cells. Infrared A has been shown to confer resistance to ultraviolet induced apoptosis via antiapoptotic proteins upregulation and DNA damage reduction(43). Some studies of the effects of infrared A have been criticized for using artificial infrared A sources of higher intensity than real-life daily exposure with the result that skin damage caused by infrared A at real-world intensities has not been conclusively demonstrated (44).

Now, there are no chemical or physical UV filters definitely filtered infrared A; claims that sunscreens protect against infrared A–induced skin damage are not regulated. Sunscreens with infrared A reflecting physical UV filters such as titanium dioxide would be effective. The demonstration that ROS plays an essential role in the pathogenesis of infrared A–induced skin damage has led to the testing of antioxidant agents. Topical application of β-carotene (2 mg/cm^2) was reported to protect human skin exposed to infrared radiation (45). In a proof of principle study, topical application of a antioxidant formula containing vitamin E, vitamin C, ubiquinone, and a grape seed extract effectively prevented infrared A induced MMP-1 messenger RNA expression in vivo in human skin (40). The same mixture added to SPF 30 sunscreen applied by 30 healthy volunteers significantly reduced MMP-1 messenger RNA expression compared with SPF 30 sunscreen alone (46). Grape seed extract includes several procyanidins, flavonols and phenolic acids, are reported to act as antioxidants (47). Grape seed extract is marketed widely as a dietary supplement. Another combination being tested is a mixture of topical ferulic acid and vitamins C and E, which was reported to reduce infrared A–induced MMP-1 up-regulation in human skin by 60% (48). Ferulic acid was shown to inhibit the expression of MMPs and decreases the degradation of collagen fibers (49). However, further studies of these agents are needed, as are defined criteria by which consumers can judge the efficacy of infrared A protection of a product from its label.

2.2 Photoprotection

2.2.1 History of photoprotection and sunscreen

An early Human ancestor in were possibly dark skin, and had the help of natural protection that called melanin, to protect sunlight effects. By the gradually move to the north, around 60,000 B.C., those original populations of the human found a different climate, lower solar radiation and colder. Thus, they began to cover themselves with the animal’s skin. Then, ancient people in the Egypt and Middle East learnt how to made their own cloth by natural materials. The diverse migrations of human ancestor and atlas of solar radiation at different latitudes show in Figure 2.4. The ancient Greeks did several activities without clothing but they used robes to protect the body. The western life had changed in the Middle Ages, with Christianity and the extreme religious aspects. The human body became sinful, and was completely covered. Even many art had to be disposed by linen, so protected from solar radiation. And these circumstances continued with little revolution until the 19th century and the Victorian age. At the 20th century, when the war finished, white skin was no longer gorgeous. A day after war, wishing to live in peace, experience new sensations and enjoy life. Tanning were famous and reflecting a good health. Skin was not protected by any kind of UV filters, only helped by re-hydration with emulsions, the first being Nivea Crème (50).

In the early 20^{th} century, oils become as cosmetics to protect the skin, but it is not able to filter the solar radiation. While traveling n the sunny day in his boat L’Edelweiss, Eugene Schueler (founder of L’Oreal) discovered the happiness of sunbaths. He tested the oils product from the market at that time, but he not satisfies it. He produced the first “filtering” oil, Ambre Solaire, replacing old product recipes based on olive oil and iodine solution. Other merchants also began producing similar products (50).

In 1944, The first generally used sunscreen was formulated by Benjamin Green during the height of world war two, when it was likely that the dangers of long time sun exposure were becoming apparent to soldiers. The sunscreen product had limited efficacy, protecting as a physical UV filter. It was a red, unpleasant feeling similar to petroleum jelly. This product was famous when Coppertone company acquired the patent of this product.

The first effective sunscreen had developed by the Franz Greiter in 1938 (51) (Table 2.3). It was called Gletscher Créme and became the main product of the Piz Buin company, which still exists as a marketer of sunscreen products. In 1956, Schulze (51) is credited with introducing the concept of sun protection factor, measuring the protective efficacy of sunscreen when applied at an amount of 2 mg/cm2, and the original Greiter's cream was evaluated and the result was at SPF 2 (50) .

Table 2.3 Historical development of sunscreen (51)

Year	Development
1928	First commercial use of sunscreen in the United States: emulsion containing benzyl salicylate and benzyl cinnamate
1933	An ointment containing benzylimidazole sulfonic acid becomes the first commercial sunscreen available in Germany
1936	The future founder of L'Oreal, Eugène Schueller, markets the first commercial sunscreen available in France, an oil preparation containing benzyl salicylate
1938	Franz Greiter, the founder of Piz Buin Company, develops an effective sunscreen in Austria, Gletscher crème; he later improves upon and popularizes the concept of SPF (1974)
1943	p-Amino benzoic acid is patented
1950s	Higher incomes and expanding travel options spur emergence of the sunscreen market
1956	Schulze invents the SPF, enabling the evaluation of sunscreen performance
1970s	Introduction of oxybenzone as a broad spectrum UVB/UVA filter; broad introduction of SPF on sunscreen packaging revolutionizes marker, and products are now comparable on a quantitative basis
1980s	Avobenzone, a long-wave UVA filter, is approved by the US FDA

Year	Development
1990s-2000s	Attitude of consumers toward sun exposure changes as the public becomes increasingly aware of the potential harm from solar radiation
2000s-2010s	Role of topical sunscreens expands from mere protection against sunburn to include health prophylaxis

FDA, Food and Drug Administration; *SPF*, Sun Protection Factor; *UVA*, ultraviolet A light; *UVB*, ultraviolet B light

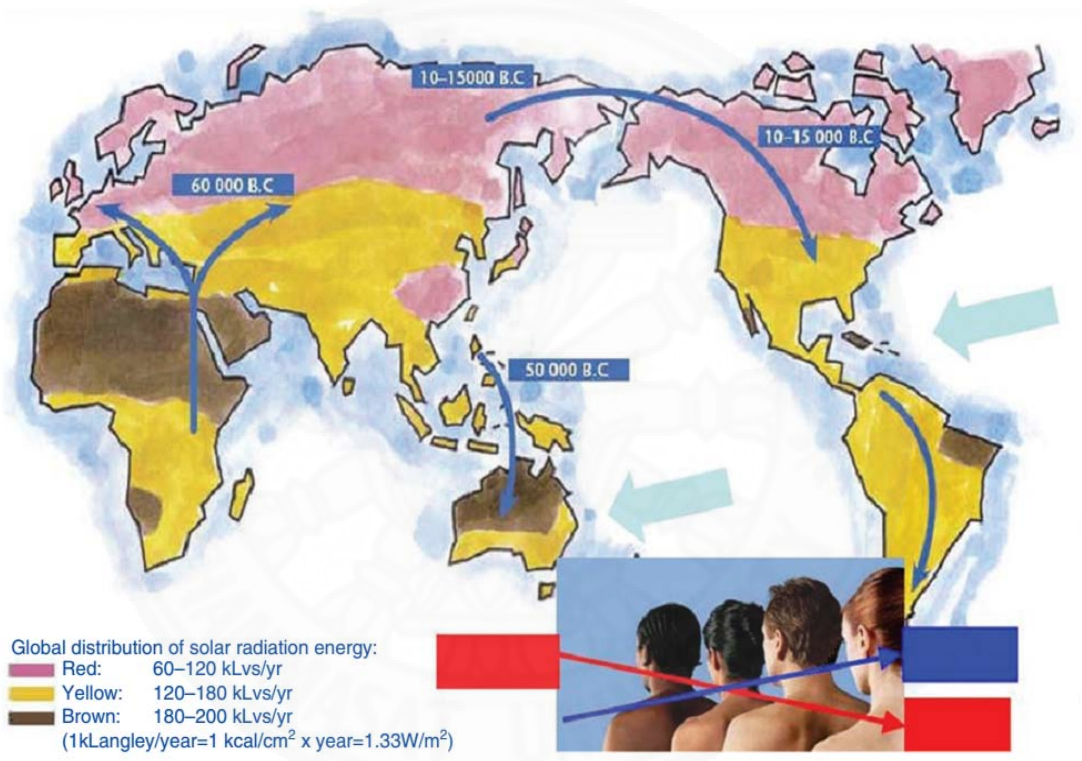

Figure 2.4 Human migration and global distribution of solar radiation (50)

2.2.2 Environmental protection factors

2.2.2.1 Atmosphere

The sunlight is absorbed by the ozone layer and molecules in the atmosphere that decrease basically all UVC radiation emitted by the sun, 90% of UVB radiation, and slightly to UVA radiation and visible light. This may explain that ultraviolet A accounts for ninety five percent of UV radiation reaching the earth's surface on a summer day and UVB radiation accounts for 4% (52). The quality and quantity of solar UV are altered as the sunlight pass through the atmosphere. The principal interactions are in the stratosphere (approx. 10–50 km above sea level) layer. In the troposphere (approx. 0–10 km above sea level) absorption by pollutants such as ozone, NO_2 and SO_2, and scattering by particle and clouds are the main attenuating processes (52). The reduction of the protective ozone layer by substances known as chlorofluorocarbons has led to substantially increased UVB radiation reaching the earth. A reduction in greenhouse gasses and ozone-depleting substances in recent years has stabilized ozone columns, and slow recovery of ozone is anticipated over the coming decades (53).

2.2.2.2 Location

UV radiation exposure is highest at the high altitudes and equator. The intensity of UVB radiation that pass along the atmosphere before reaching the earth's surface decline by 3% for every degree increase in latitude. There are approximate 8% to 10% increase in UV radiation strength for each 1000 feet of elevation across the altitudes. The association between altitude and UVB strength seems to have an exponential form at higher elevations because of less UV radiation filtering atmosphere (54).

2.2.2.3 Time

The UV radiation are strongest in the 4 hours period around the noon, 10 am to 2 pm (Table 2.4), with highest transmission at the solar zenith when the way of UV radiation through the absorptive ozone layer is shortest (55). The transmission of UVA radiation is quite constant throughout the daylight hours because the better penetration of UVA radiation and also slightly affected by the cloud. Seasonal differences in solar radiation are caused by the elliptical orbit of the sun; global UV radiation is strongest in the summer.

Table 2.4 The percentage of UV radiation during a daylight hour in summer day from tropical (20°) to temperate (60°) latitudes. (52)

Hourly interval	% daily UV
Before 9:30 a.m.	6
9:30 a.m. to 10:30 a.m.	8
10:30 a.m. to 11:30 a.m.	12
11:30 a.m. to 12:30 p.m.	15
12:30 p.m. to 1:30 p.m.	17
1:30 p.m. to 2:30 p.m.	15
2:30 p.m. to 3:30 p.m.	12
3:30 p.m. to 4:30 p.m.	8
4:30 p.m. to 5:30 p.m.	4
5:30 p.m. to 6:30 p.m.	2
After 6:30 p.m.	1

2.2.2.4 Clouds

Water is a poor absorber of UV radiation, clouds, which are mainly composed of water droplets, weaken UV radiation primarily by scattering. Cloud cover reduces the strength of UV radiation, infrared radiation and visible light. The water in clouds reduces infrared radiation much more than ultraviolet and so increase the risk of overexposure to UV radiation, especially UVA radiation because lessening of heat warning sensation. (52)(56). The assumption of calculated UV index in different pattern of clouds show that overcast skies allow 31% of UV radiation transmission, broken clouds 73%, scattered clouds 89% , and clear skies 100% (57).

2.2.2.5 Pollutants

Pollutants and scattering particulates in the atmosphere, especially troposphere decrease the short wavelength UV radiation effect more than longer wave (56). Great decline in UV irradiance was detected in polluted urban areas (58). Substantial reductions in UVB radiation can happen with pollutants, such as dust, wildfire and volcanic ash (59). Whereas metal , glass, sand and snow can reflect up to eighty five percent of UVB radiation, reflection of UV radiation from most earthly surfaces is usually lower than 10% (60).

2.2.2.6 Shade

Shading can reduce ultraviolet radiation from the sun by fifty to ninety percent. Half of UVA radiation exposure occurs in the shade (61). Small shading area such as umbrellas provide only low UV radiation protection. A dense foliage tree providing superior UV protection to a beach umbrella (61). Sun protection factor of trees range from 4 to 50, depending on foliage density and proximity to the shadow border (62) (Figure 2.5).

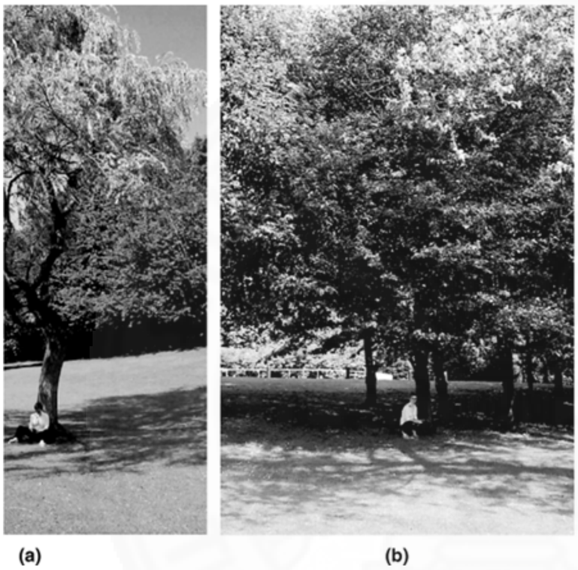

Figure 2.5 Example of the tree shade (a) protection factor 4 and (b) protection factor 20. (62)

2.2.3 Natural photoprotection of the skin

Since ultraviolet radiation does not enter deeper than the skin, human skin shields the rest of the body from damaging solar radiation. Factors that impact the effects of UV radiation on the skin barrier include penetrative depth of specific wavelengths, skin type, and the skin chromophores (32). The skin chromophores at epidermis level determine the decrease of radiation in these layers, superior than skin scattering effect. Thickness of epidermis and melanin are important factors for light wavelengths less than 300 nm, while the UVA reduction and visible light is mainly by melanin. Human skin absorbs UVB radiation, scatters most visible light, and reflects up to 10% of all solar radiation from 250 to 3000 nm (63). Most UVB radiation penetrate limit in the epidermis, whereas UVA radiation can reach deep to dermis. Dark-skin types have lessened UV radiation penetration, because of increased melanin. Normally, five times less UVB and UVA radiation penetrate the epidermis of dark skin compared to white skin. Within individuals, solar radiation penetration are varies depend on skin sites because of differences in epidermal thickness(64,65).

2.2.3.1 Melanin

Melanin in the epidermis is a large dense molecule that reduces reactive oxygen species, UV radiation and visible light penetration into the skin by scattering, blocking and converting the energy of UV radiation. The degree of photoprotection provided by melanin associates with skin thickness and degree of skin pigmentation. Thin facial skin develops erythema more easily than thicker skin, and darkly skin is less sensitive to the effects of UV radiation than white skin.

2.2.3.2 Other agents

Other chromophores in the skin including heme, porphyrins, and water also protect the skin form the solar radiation. Oxyhemoglobin and reduced hemoglobin in blood absorb bands in the UV, blue, green, and yellow visible light regions. Infrared radiation is mainly absorbed by water. An endogenous photosensitizing molecule, porphyrin, can create a reactive oxygen species when expose to the Soret band (400-410 nm), accumulates to high levels in cutaneous porphyrias can causes photosensitivity (66).

2.2.4 Physical protective agents

2.2.4.1 Clothing and hats

Hats and clothing are an important things in order to achieve a high photoprotection (67). Clothing is the major strategy of photoprotection used by the public and has numerous benefits. First, hats and clothing offer an effective protection for all UV radiation range. Next, hats and clothing are cheaper than sunscreens (67), and they are lacking of any side effects such as contact or photoallergic dermatitis.

As predictable, the degree of UV protection offered by hats and clothing are varies. The commercial clothes and photoprotection study, demonstrated that one-third of summer clothing provided bad UV protection, and only 75 % of fabrics clothes were able to provide an adequate UV protection (68). Some studies show that

25% of clothes provided at least a SPF 15 (67). To exactly measure protection of U radiation by clothes, UV protection factor or UPF is a standard measurement. To achieve the UPF value, UV penetration through the clothes is measured using spectrophotometer (69). In 1996, This standard was first established in Australia and in 2003 it was approved by the European Committee for Standardization (70). The Committee specified the clothes with UV protecting factor label have to protect the area from the neck to the hip, shoulders, and upper arm. In addition, the minimum allowed UPF value is 40. It also established a condition for ultraviolet A transmission, that had to be lower than five percent. Though, the standard assessment did not mention in the consequence of wetness and stretching in the UV protecting facor measurement; clothing with a UPF more than 40 could be enough to compensate the negative factors. American Society for Testing and Materials and the American Association of Textile Chemists and Colorists published a regulations of testing and labeling a UV protective clothing (71).

Many factors limit the UPF of garment (Table 2.5). Fabric is an important material. Wool and polyester have the greatest UV protection, and they have higher protection capacity than linen, rayon and cotton. A clothing for summer, polyester usually used together with other materials to provide comfort and greater ultraviolet protection. The fabric thickness provide better UV protection (55). Black and blue colors can augment UV protection (72)(73). Knit density is an another major factor that determinant protection capacity (74,75). Dress-shirt means the clothes that the fabric is interlaced with each other. Space between separated fibers allow entering of light, but theultraviolet radiation penetrated the fiber, particularly cotton is usually more important.

Table 2.5 Factors determining the ultraviolet protection factor (UPF) of clothing (76)

Increase UPF	Decrease UPF
Fabric material (polyester, nylon)	Thinner fabric
Tightly woven fabric	Lighter colors
Thicker fabric	Wetting
Darker colors	Stretching
Washing	Bleaching
Washing with optical whitening agents	
Washing with UV absorbing chemicals (Tinosorb FD)	

The sun protection for hats depending on the hat material, weaving and brim width. Wide-brimmed hats (7.5 cm) provide SPF seven for the nose, five for neck, three for cheek, and two for chin, but hat with narrow-brimmed has only SPF below two for the nose, and slight protection for other areas (30).

Wearing and washing also effect the UV protecting factor value of the garments. After garment washing, the space of each fibers decreases and its become thicker, so UV protecting factor is increased. This outcome is usually obvious in the first washing (77) and is more noticeable with garmentmade with rayon, cotton, and flax materials (67). In contrary, wet-clothes reduce the UV protecting factor value for most garments (78), as the existence of water reduces the scattering of ultraviolet radiation (79). Thus, a summer t-shirts may have a low protecting capacity when they are wet. This change related mostly for fabrics which has lighter colored; darker colour garments are less affected, due to absorption is greater than scattering protection(79).

Chemical agents with brightening agents, UV filter, and bleach can alter UPF value. Brightening chemical are the agents that absorb ultraviolet radiation and change it to fluorescence in the visible light range. These compounds absorb UV radiation and increase UPF values, and they are found in many everyday laundry detergents (67). The Tinosorb FD is a UV absorber which bind to the individual fibers of garment. The UPF value of cotton fabric used for T-shirts production increased by more than 4 times with the addition of UV absorber (73). In contrast, bleaching fabrics such as rayon and cotton reduces the value of UPF.

2.2.4.2 Sunglasses

photokeratoconjunctivitis is a short term ocular complications of UV radiation exposure, while long term complications include keratopathy, pinguecula, pterygium, cortical cataract formation, and certain types of ocular melanoma (80–84). An example of ocular complication in different electromagnetic spectrum shown in Table 2.6 and Figure 2.6. Even though UV radiation not able to reach the retina except in young children and people with aphakia, blue light can induced a macular degeneration (85). Sunglasses are particularly important for children whose ocular lenses transmit more visible light when compared with adult, increasing the risk of developing macular degeneration (86,87). The time of the day for maximum UVR risk differs for eyes and skin. Maximum UV radiation exposure to the eye occurs when solar radiation is parallel to the eye, usually during early morning or later afternoon, but does vary with latitude and season (88).

Table 2.6 Non-ionizing radiation hazard to eye (55)

Eye damage	Clinical description	Structure involved	Risk factor
Photokeratoconjunctivitis	Transient ocular pain with tearing and photophobia	Corneal epithelium	Excessive UVR below 315 nm
Photoretinitis	Photochemical injury with a scotoma and can be sight-threatening	Retina	Blue/violet light
Cortical cataract	Lens opacity leads to vision loss	Lens	UV radiation
Pterygium	Abnormal growth of the conjunctiva that can extend onto cornea	Conjunctiva	UV radiation
Macular degeneration	Loss of central vision	Retina	Blue light

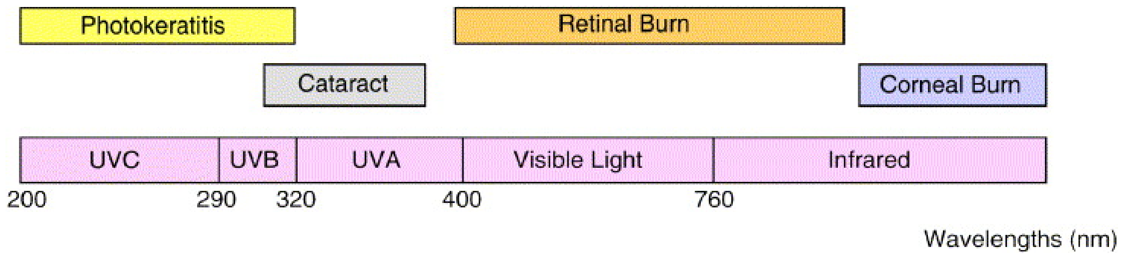

Figure 2.6 Eyes complications causing from exposure to different wavelengths of electromagnetic wave. (89)

Three sunglasses standard exist: The American standard ANSI Z80.3, the Australian standard AS/NZS 1067:2003, and the European standard EN 1836:2005, which was last updated in 2010. While the Australian and European standards differ in the determined amount of UVB light transmission allowed and the definition of UVA light, they are overall very similar (90,91). Compliance with the ANSI standard is voluntary in the United States, whereas compliance with the respective standards in Australia and Europe is mandatory. Only the Australian standard is mandated by law to be assessed by an independent party.

According to the US FDA, sunglasses should meet a standard of <0.001% permissiveness for UVB light and <0.01% for UVA light radiation (92). UVR protection by sunglasses depends on sunglass size and distance from face (93). The best protection from UVR is achieved by sunglasses with a wraparound style or side shields (94).Mirror coating reduces the amount of VL that reaches the eyes, but neither this nor gradient tint, color, or darkness is indicative of UV protection. Tinted lenses with good UV protection intended for outdoor use can eliminate nearly all UV transmittance (95). Dark lenses result in pupil dilatation, which can potentially result in more exposure to UV if the lenses are not UV protective. Expensive brands do not guarantee good UVA protection (96). The use of UVR-blocking contact lenses can increase the time the wearer can be exposed to solar UVR before a toxic ocular dose is achieved (97).

Polycarbonate is a thermoplastic that was first developed and used in the aerospace industry. A study of airplane window screens found that polycarbonate airplane windshields transmitted almost no UVR below 380 nm. The material offers a lightweight, impact resistant, photoprotective option for eyeglass. A newer plastic, developed in 2001 and marketed as Trivex (PPG Optical Products, Pittsburgh, PA), provides a lightweight, strong, high index eyeglass lens. According to the manufacturer, urethane-based monomer Trivex lenses block “100%” of UVR (30).

2.2.4.3 Glass

A lot of people spending much time in vehicles or indoors, the potential for UV radiation exposure through car and building windows is often unnoticed. Existing photoprotection strategies and educational operations target warning UV radiation exposure during outdoor activities. The variety of UV radiation pass through vehicle glass, window glass, and sunglasses offers an important occasion for improved photoprotection. Standard residential and commercial window glass blocks the transmission of UVB. The newer types of window glass can also partially block the transmission of UVA light and VL (89). The clinical relevance of UVR exposure via glass-filtered sunlight is supported by studies documenting an increased prevalence of facial photodamage, actinic keratoses, NMSCs, and malignant melanoma in situ on the driver’s exposed side (98–101). In the United States, 2 recent retrospective studies identified a significant increase in left-sided distribution of BCCs, SCCs, Merkel cell carcinomas, and malignant melanoma (99,102).

Transmission of UVR through windows depends on glass type, thickness, and color. For details on commonly used glass types, show in Table 2.7 and Figure 2.7. The combination of low E–coated glass and lamination yields the best performance for comfort, security, safety, and health (103). The effect of glass colors on the properties of solar, visible light, and UV transmission is show in Figure 2.8.

Table 2.7 Type of glass (103)

Type	Properties
Annealed	Low level of residual stress; breaks into large pieces
Tempered	Four time stronger than annealed glass in bending; breaks into small pieces resulting in less risk for injury
Tinted/heat-absorbing	Contains special color components that reduce unwanted heat gain by reflecting<comma> transmitting<comma> or absorbing solar radiation
Reflective	Has mirror-like appearance; reflects both infrared and visible light
Laminated	Blocks ultraviolet radiation, reduces sound transmission, and increase security; breakage pieces adhere to the polyvinyl butyral layer
Low Emissivity	Reflects infrared while selectively transmitting visible light
Insulating	The glass with air- or gas-filled space; decreases heat transfe

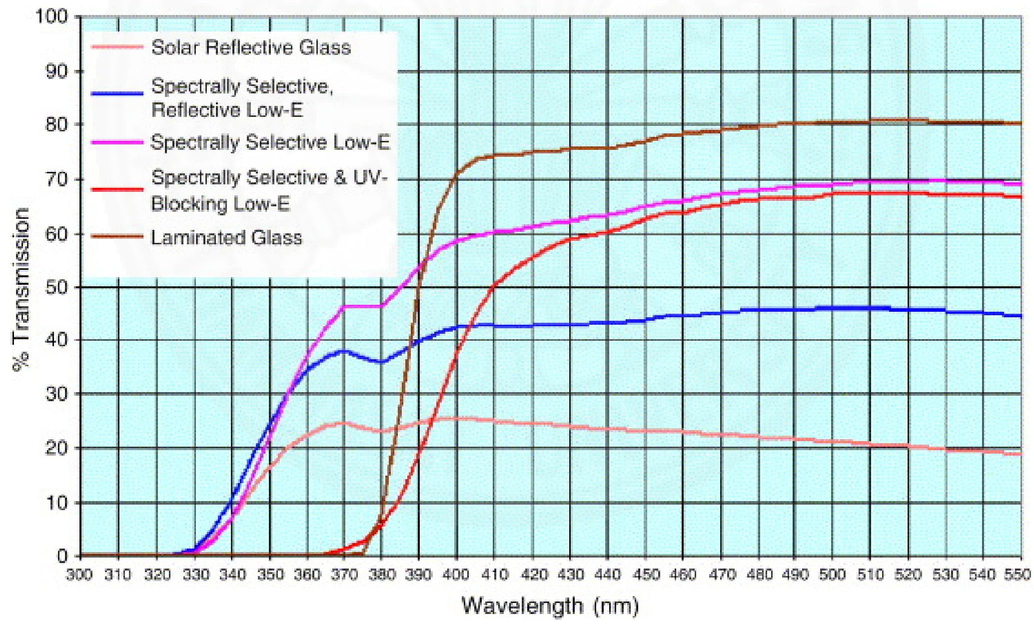

Figure 2.7 UV and short-wavelength visible light transmittance (300-550 nm) of different types of commercial architectural glass (89)

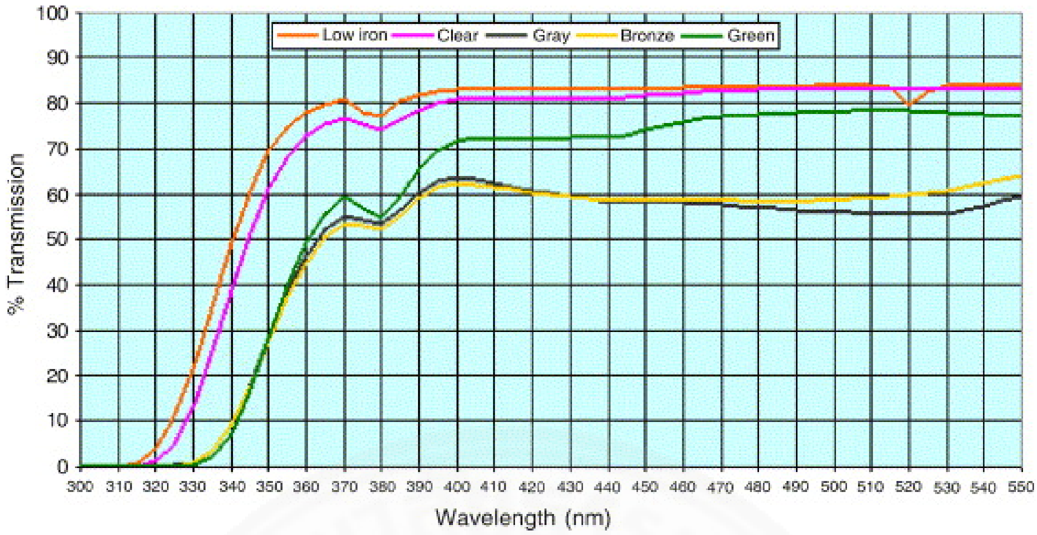

Figure 2.8 UV and short wavelength visible light transmittance (300-550 nm) of common glass with different colors (89)

2.2.5 Systemic photoprotection

There is rising attention in the possible for oral and subcutaneous agents to provide supplementary protection the ultraviolet radiation and to further decrease harmful that usually caused skin cancer and skin aging. These interesting agents have different protecting mechanism from sunscreens, in the term of efficacy evaluation, and the usage benefit. Numerous orally and subcutaneously injecction agents have been shown to have the potential to decrease photosensitivity, reduce the sunburn, and prevent photodamage. However, larger studies need to be conducted to approve safety and efficacy. Several of these agents are in late stages of clinical development.

2.2.5.1 Polypodium leucotomos extract

A native fern plant in Central and South America, botanically known as Polypodium aureum, Phlebodium aureum, *or* Polypodium leucotomos that it is used in traditional medicine. Polypodium leucotomos extract is commercially available in many parts of the world as over the counter products in oral and topical formulations (104). Studies with the oral formulation have demonstrated that it can protect the ultraviolet B and psoralen plus ultraviolet A induced toxicity (105,106), development of PMLE, and probably also solar urticaria (107,108). Polypodium leucotomos extract increases the ultraviolet density required for minimal erythemal dose, immediate pigment darkening, and minimal phototoxic dose (106). A recently concluded short-term study of this oral agent extract prescribed at 240 mg twice daily for two months in healthy individuals resulted in suppression of UVB-induced erythema (109). The primary activities of Polypodium leucotomos extract appear to be anti-inflammatory and antioxidative; it has a low SPF 3-8.

2.2.5.2 Nicotinamide

Nicotinamide is an active amide form of vitamin B_3 generally available as an oral dietary supplement. It is a precursor of nicotinamide adenine dinucleotide, an important cofactor for production of adenosine triphosphate that is vital for DNA repair and skin immunity. Dissimilar niacin, oral nicotinamide does not have vasodilatory effects and is not associated with a cutaneous flushing reaction. Nicotinamide is able to prevent UV radiation induced intracellular depletion of adenosine triphosphate, enhancing cellular energy and DNA repair and preventing immunosuppression (110–113). In phase II trials, subjects with sun damaged skin who took 500 mg of oral nicotinamide once or twice daily had, respectively, 29% and 35% fewer actinic keratoses at 4 months compared with patients on placebo (114). In a recently reported phase III, double-blind, randomized controlled trial, Oral Nicotinamide to Reduce Actinic Cancer, patients with a history of 2 or more nonmelanoma skin cancers who were given nicotinamide 500 mg twice daily had 23% lower rates of new nonmelanoma skin cancers and 11% fewer actinic keratoses than the placebo group after 12 months (115). This broad chemopreventive effect persisted with continuous treatment, but not after discontinuation of nicotinamide. There were no differences in side effects between the treatment and the control groups.

2.2.5.3 Afamelanotide

Afamelanotide is a structural similarity of α-melanocyte-stimulating hormone that was demonstrated to be helpful as an adjunctive photoprotective agent in patients with Erythropoietic protoporphyria and solar urticaria (EPP). As an agonist of the melanocortin-1 receptor, afamelanotide promotes synthesis of melanin, which is a natural protecting agent in skin. In clinical trials, using subcutaneous afamelanotide implant that controlled release the drug for 2 weeks, after 2 days the melanin concentration was increased, with the effect lasting up to 2 months

(116). After undergoing phase II and III clinical trials in Europe and the United States (117–119), afamelanotide, administered as 16 mg subcutaneously every 60 days, received regulatory approval in Europe for prevention of phototoxicity in adult patients with EPP. In 2 randomized, double-blind, placebo-controlled phase III studies, in 74 European patients with EPP and in 94 US patients with EPP who each received 5 or 3 subcutaneous implants, respectively, every 60 days, those who received afamelanotide experienced significant improvements in duration of pain-free time under direct sun exposure compared with placebo (119). Quality of life was also improved in both treatment groups, and adverse effects were mostly mild (consisting of headache, nausea, nasopharyngitis, and back pain). In the longer European study, phototoxic reactions were significantly less severe, with shorter recovery time in patients on afamelanotide. Afamelanotide has also been investigated as treatment of solar urticaria in a small study of 5 patients; it resulted in increased synthesis of melanin and an increase in tolerance to artificial light exposure (120).

2.2.5.3 Nonsteroidal anti-inflammatory drugs

Although many studies have different concluding evidence about an relation of nonsteroidal antiinflammatory drug (NSAID) use and decreased squamous cell carcinoma (SCC) risk (121–123), several recent studies have proposed an effects of NSAIDs in cutaneous chemoprevention. A population-based study show that NSAIDs possibly will reduce the risk of cutaneous SCC and melanoma by inhibiting cyclooxygenase-2 enzymes that are involved in carcinogenesis (124). A double blind, placebo controlled, randomized controlled trial demonstrated that celecoxib could prevent basal cell carcinoma(BCC) and SCC in individuals with extensive photodamage who are at high risk for developing NMSCs (125).

2.3 Sunscreen

The first effective sunscreen available since 1946 and today play a major role in skin photoprotection(50). Over a past few decades sunscreen use and sunprotection behavior have been rising as a result of worldwide education and promotion about UV radiation exposure(1,3,4,126,127). Growing consumer awareness over skin cancer and aging skin is resulting in strong demand for sunscreen product.

The global market for sun care is continuously growing during the past decade (Figure 2.9). Using sunscreen with board-spectrum SPF≥15 regularly and properly can decrease the risk of skin cancer and early skin sign aging caused by the sun (128).

Since the first commercial sunscreen was introduced in 1928, the use of sunscreens as an important part of photoprotection strategy has expanded worldwide. UV filters are the most important part of the product technology. In addition to UVB filters, a lot of UVA filters are now available worldwide. Although the SPF is well established and many methods have been developed for measure UVA protection, the performance evaluation of sunscreens is still far from perfect. Cosmetic pleasant texture of sunscreen is a key element in improving UV protection. Two factors must be considered to develop an ideal sunscreen (129). It should have a protection across the range of UVB and UVA, a property referred to as "spectral homeostasis," which assures that the natural spectrum of sunlight is attenuated in a uniform manner. This is particularly useful for protection against immunosuppression, which has a broad action spectrum (130). An "ideal" sunscreen should also have pleasing sensory and tactile profiles that enhance the user's compliance.

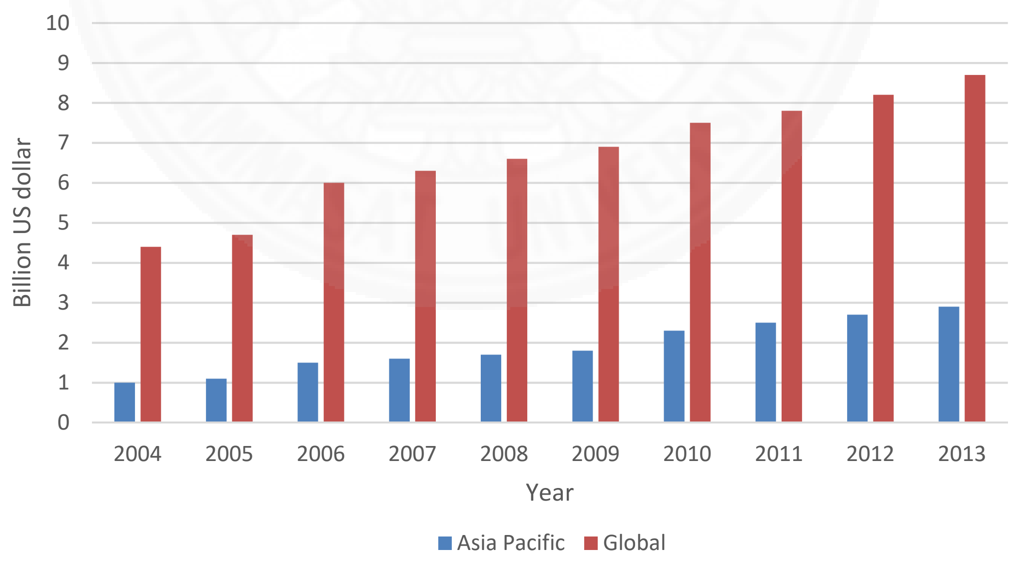

Figure 2.9 Suncare market trends in the past decade; adapted from Market Line industry profile suncare year 2004-2013 (131–133)

2.3.1 Sunscreen measurement

2.3.1.1 UVB protection measurement

Sun protection factor (SPF) is mainly a measure of ultraviolet B protection. An SPF 15 sunscreen blocks ninety four percent of UVB rays, while SPF30 filters ninety seven percent (60). The minimal dose of UV that can cause sunburn is called minimal erythemal dose (MED). SPF is a MED ratio of protected to non-protected skin. In concept, SPF5 product can protect the skin from sunburn 5 times longer than non-protected skin. But, the value is not totally accurate (134,135). The SPF testing standard by FDA needs application of 2 mg/cm^2 to protected skin. True application thickness is around 0.5 to 1.0 mg/cm^2, which lowers the SPF level (136–139).

2.3.1.2 UVA protection measurement

The SPF value principally measures the level of protection against erythemogenic spectra of UV radiation. Better understanding of the adverse effects of ultraviolet A radiation has underpinned the development of better UVA filters and testing standards for measuring UVA protection.

Methods for testing UVA protection were accepted by regulatory bodies in United States, European Union, Japan, United Kingdom, and the Australia. However, the testing methods vary by country (140) (Table 2.8). Persistent pigment darkening (PPD) is used in japan, PPD measures the lowest dose of UVA radiation that required to induce pigmentation on protected skin compared to unprotected skin. Sunscreen products protection value for UVA are rated as PA+, PA++, PA+++, or PA++++ (141). The UVA protection factor in EU are required to be one-third of the SPF value, with PPD method as the measurenemt. For instance, a sunscreen with a SPF of 30 must have a UVA protection factor of at least 10 (142). In the UK, the ratio of UVA absorbance to mean UVB absorbance is measured in vitro; a star rating system is used. Australia adopted the in vitro test procedure ISO 24443:2012 for determining broad-spectrum performance, which is similar to the European assessment. The adoption of this UVA testing method, which determines the spectral absorbance characteristics of UVA protection in a reproducible manner, has led to the development of sunscreens with 10 to 20 times the protection against UVA radiation when compared to sunscreens complying with the old standard (143).

In 2011, the US FDA mandated the use of in vitro CW for testing of UVA protection (144). Briefly, the CW test is conducted by applying the test product to 3 different polymethylmethacrylate plates at a density of 0.75 mg/cm^2. To take into account the photostability of the product, a preirradiation dose of 800 J/m^2 is used to the test product. UV transmittances are then measured from 290 to 400 nm. The wavelength that ninety percent of the total area under the absorbance curve occurs is called CW. Any sunscreens product that have a critical wavelength more or equal 370 nm are then able to claim broad-spectrum status.

Table 2.8 UVA determination methods in different countries (10)

	UVA measurement method
ASEAN	ISO 24442:2012 (PPD) ISO 24443:2011 (in vitro) + critical wavelength ≥ 370 nm
Japan	JCIA Standard (PPD)
China	JCIA Standard (PPD)
Europe	ISO 24442:2012 (PPD) ISO 24443:2011 (in vitro) + critical wavelength ≥ 370 nm
USA	FDA Final Rule 2011; critical wavelength ≥ 370 nm

2.3.1.3 Immunosuppression measurement

It is gradually recognized that sunscreens should protect the skin from UV radiation induced immunosuppression, with an indicator of protection that can correlate with the sun protection factor (SPF). Immune protection factor can be assessed by measuring the UV radiation induced suppression of either the induction or elicitation arms of the delayed-type or contact hypersensitivity responses (130). However, standardization of both the definition and the method for determination of immune protection factor has yet to be established.

2.3.2 Sunscreen efficacy and usage

2.3.2.1 Sunscreen formulation

Sunscreen products ingredients are a complex mixtures intended to form a solution which protect the skin from UV radiation(9). The initial consideration to develop a sunscreen product is the protecyion efficacy, followed by features such as water/ resistance or moisturization. The efficacy goal will determine the UV filters that will be used and vehicle/formulae raw materials. The UV filter combination is a key point to reach the protection targets with maximum efficiency, cost reduction, skin feel (9). Notably, to achieve maximum protection, photostability have to be considered.

2.3.2.1 Sunscreen vehicle type

Vehicles of sunscreen usually determine product efficacy. A vehicle has to minimize the interaction between inert and active ingredients in order to maintain the photoprotection capacity of UV filters. Vehicles of sunscreen include creams/lotions, gels, sprays, stick, and cosmetics. Creams and lotions, containing either water-in-oil or oil-in-water emulsions, are most commonly used vehicles due to permit the greatest variety of formulations. Gels are preferred by consumer with oily skin or acne prone skin, although it easily washed out by sweat and water. Sticks are used for a small area such as lips or nose. Sprays are convenient, but are often used inadequately.

Vehicle type also determines sunscreen durability and water resistance. It often plays a role in cosmetic satisfactoriness, application, and compliance. The opacity and greasiness of inorganic and organic agents respectively, may contribute to inappropiate application and following SPF reduction (145). Inadequet protection may be from insufficient application. (136–138,146). In order to improve patient compliance, the daily reminders and sunscreen education on appropriate use are important(147).

2.3.2.2 Water resistant statement

The terms “sunblock”, “water proof,” or “sweat proof” are not approved to claim on the label of sunscreen. The “proof” may misunderstand consumers to understand that the products can protect the skin remain for a long duration without reapplication, the currently claim use can only contain either the statement “water resistant (40 minutes)” or “water resistant (80 minutes).” This claim must be labeled at the front of the package. Resistant time duration on the label indicate the water resistant property that is required to be tested: SPF value requires to be determined after test subjects are immersed in a whirlpool for 2 times 20 minutes or 4 times 20 minutes. The stated of water resistant time on the label would help consumers understand the protecting duration of the sunscreen products.

2.3.2.3 Use claims

The important point in the present ruling concerns the use and advantage claims of sunscreens. The broad-spectrum sunscreen SPF ≥15 can show on the label the claim "if used as directed with other sun protection measures, sunscreens decrease the risk of skin cancer and early skin aging caused by the sun". The permission for claim use is mainly based on the evidence that most of nonmelanoma and melanoma skin cancer are caused by excessive sun light exposure (148–151). The conclusion by the US FDA in suggesting the SPF lower limit to 15 is based on the studies from Australia show that regularly used of broad-spectrum sunscreen (SPF 16) can reduce the incidence of squamous cell cancer (150,152). Notably, the sunscreen with at least 30 of SPF was recommened by AAD; because the actual use, most people apply sunscreens at 0.5 to 1.0 mg/cm^2, which is considerably less than the FDA instructed amount of 2.0 mg/cm^2 used in SPF testing.

In addition to benefits of SPF ≥15 broad-spectrum sunscreens the appropriate amount and duration of sunscreen application are important. Another effective photoprotection stratergies includes seeking shade, avoiding sun exposure, wearing hats and clothing, and using sunscreens. Nowaday, some people, sunscreens use is a mainly form of sun protection. Since inappropriate use, many people do not reach the best UV protection, more exposure to the sun, and do not use other more reliable sun protection methods (153). Thus, sunscreen use may lead to increased amounts of UV exposure.

As above-mentioned, the benefit claims are only used for broad-spectrum sunscreens with SPF ≥15. For sunscreens that SPF lower than 15 and not broad-spectrum , these claims are not permited. The skin cancer alert message states that "spending time in the sun increases our risk of skin cancer and early skin aging," and "This product has been shown only to prevent sunburn not skin cancer or early aging." The sunburn prevention claim are allowed in any sunscreen products.

2.4 Adverse reactions to sunscreen

There are 4 types of contact dermatitis that caused by sunscreen ingredients: irritant, allergic, phototoxic, and photoallergic. The UV filters allergy prevalence is low when patient were referred for patch testing, maybe less than one percent (154). The incidence of PACD were reported as uncommon but is possible underestimated because of misleading clinical presentation, causative substances, and the infrequent use of photopatch testing(155). Moreover, UV filters list in photopatch testing kit are vary, the agents used for testing are different by countries (156). A lot of UV filters are allergenic agents that caused allergic and photoallergic reaction account for 55-80% reactions on photopatch testing (157–159). Irritant and phototoxic contact dermatitis are less frequent than photoallergic/allergic reactions maybe due to underreported(160,161).

2.4.1 Allergic and photoallergic contact dermatitis

Allergic contact dermatitis (ACD) is a delayed-type (type IV) hypersensitivity response resulting from a response of T-cell mediated immune to an allergens that exposed to the skin (Figure 2.10). ACD has two phases of reaction: the sensitizing phase and the expression phase. The sensitizing phase could take a days to a years, depending on the allergens that have different allergenic potential. In the sensitizing phase, small allergens enter the skin. Some allergens are primarily non-allergenic allergens but turn out to be potent haptens due to enzymatic processes or photoactivation. (162,163).

The allergic contact and photoallergic contact dermatitis to sunscreens are not able to distinguish by clinical presentations, because sunscreens are typically applied to sun exposed area. Both reactions present as eczema that might present at any stages of eczema. Photoallergic contact dermatitis reasonably affects sun-exposed areas. Usually, the upper lip, eyelids, postauricular and submental areas are spared. The skin location that received adequate sun light and is exposed to a photosensitizing agent possibly will be affected. The characteristics of four type of contact dermatitis show in Table 2.9 and Table 2.10.

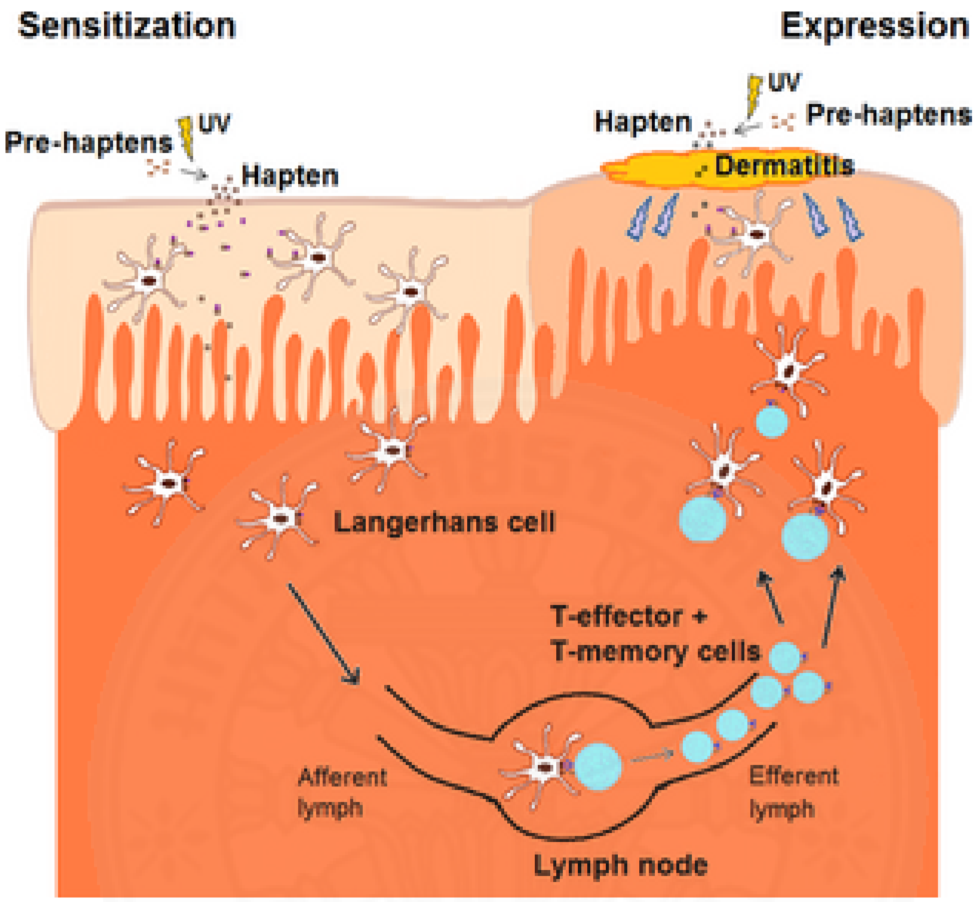

Figure 2.10 The sequence of skin allergic response (10)

Table 2.9 Characteristics of allergic and photoallergic contact dermatitis (5,154)

Characteristic	Allergic contact dermatitis	Photoallergic contact dermatitis
Occurrence	requires previous sensitization	requires presence of both UV light and antigen
Onset	usually within 48 hours	usually within 48 hours
Dose dependence	Not crucial	Not crucial
Pathophysiology	Type IV cell-mediated, delayed hypersensitivity reaction	Type IV cell-mediated, delayed hypersensitivity reaction to photoproduct or hapten
Clinical presentations	Pattern: confined to area of exposure with possible spread to immediate surrounding area	Pattern: confined to areas exposed to both light and allergen with possible spread to immediate surrounding area
	Morphology: acute erythema, induration, vesicles; chronic scaly plaques and/or lichenification	Morphology: acute erythema, induration, vesicles; chronic scaly plaques and/or lichenification
	Symptoms: pruritus	Symptoms: pruritus
Diagnosis	Patch test	Photopatch testing

Table 2.10 Characteristics of irritant and phototoxic contact dermatitis (5,154)

Characteristic	Irritant contact dermatitis	Phototoxic contact dermatitis
Occurrence	At first exposure	At first exposure with UV light
Clinical time course	within minutes to days	within minutes to days
Dose dependence	Yes: chemical concentration and duration	Yes: chemical concentration and radiation dose
Pathophysiology	Direct, cytotoxic action	Cytotoxic via releasing energy from photoproduct
Clinical presentations	Pattern: confined to area of exposure, sharply marginated, no spreading	Pattern: confined to areas exposed to both light and allergen with possible spread to immediate surrounding area
	Morphology: erythema, fissuring, vesicles	Morphology: ''exaggerated sunburn,'' erythematous, bullous, residual hyperpigmentation
	Symptoms: pain	Symptoms: pain
Diagnosis	Clinical history, excluded contact allergy	Clinical history, excluded contact allergy

2.4.2 Sunscreen allergy risk factors

The sunscreen allergy risk factors are unclear but may include sex, preexisting photodermatoses, daily activities, and atopy history (154). Women are reported having more number of allergy, due to many factors such as frequently use of cosmetic or sunscreen products containing UV filters and other inactive ingredients, or more common use of dermatologic services (164). The most common photodermatoses condition that associated with sunscreen allergy was chronic actinic dermatitis (164,165). Photosensitivity reaction are more common in adults than children, probably due to adult are normally exposed to more allergens (166).

At the present day, we are not able to program a person's immunity to not cause contact dermatitis when the person exposed to an allergen. So, the prevalence/incidence of allergy and allergens are important data for management of allergic(photo) contact dermatitis. Photopatch/patch test are a gold standard diagnostic implement for ACD/PACD. The photopatch test series should be reviewed in 5-10 years, depending on trends in sunscreen development and changes in the patterns of exposure to allergens. In 2012, nineteen UV filters are included to the European photopatch test baseline series(167).

2.4.3 Prevalence of sunscreen allergy

The incidence of PACD and the sunscreen allergens is also likely to change, as new UV filters are introduced. In the mid of 20th century, para-aminobenzoic acid and sulfonic acid were broadly used to protect skin from harmful effects of ultraviolet B, but as the harmful effects of ultraviolet A were concerned in late 20th century, dibenzoylmethanes and benzophenones were used to provide protection for ultraviolet radiation. Timing of the chemical UV filters were used in European countries, correlated with the period of time when contact allergy and photocontact allergy to UV filters were reported, show a variable time delay from emerging time of use in Europe to reported allergy(168).

The prevalence study of sunscreen allergy in Singapore in 1998, show that sixty-one patients who were suspected sunscreen allergy had patch or photopatch testing, two were positive for photoallergy, and three were allergic to UV filters in sunscreens. The key allergens were ethylhexyl methoxycinnamate and benzophenone-

3. The study conclude that allergy to sunscreen is uncommon in Singapore(169). Recently, in 2013 in Singapore, a study of photopatch testing in Asians report that, sunscreen is the most common photoallergen to date. The frequencies of the positive photopatch test reactions were benzophenone-3 and benzophenone-10 (170).

The photopatch test study in Thailand during 2000-2009, show that a 72 positive photopatch test patients, oxybenzone was the most common causative agent, followed by promethazine hydrochloride, chlorpromazine hydrochloride, fragrance mix, triclocarban and fenticlor(6).

The photopatch test study in China during 2010 to 2014, show that a total of 3767 positive for photopatch test reaction, chlorpromazine was the most causative agent, followed by para-aminobenzoic acid, thimerosal, potassium dichromate(171).

A series of 157 children study in sunscreen photopatch testing in 2014 found that allergic reactions were found in 9 children (5·7%), with 16 children (10·2%) showing photoallergic/allergic reaction to UV filters and/or sunscreen products. The causative UV filters that usually identified were benzophenone-3 and ethylhexyl methoxycinnamate(172). A summary of photopatch test studies, focused on UV filters shown in Table 2.11.

The allergy to UV filters is infrequent but not rare. Sunscreen allergy prevalence possibly will rise as sunscreen use continue to become more widespread(154). Recently, study about adverse reaction to sunscreen agents, the most reported agent that caused contact and photocontact allergy are listed in (Table 2.12 and Table 2.13)(5).The common non UV filters contact sensitizing in sunscreen are Fragrance mix I, DL-alpha-tocopherol, M. Pereirae and diazolidinyl urea(173).

Table 2.11 Summary of photopatch test studies

Study period	Country	n	Most frequent UV filters allergens
1991-1999	Australia(174)	81	Oxybenzone, Sulisobenzone
1994-1999	India(175)	50	-
1995-1999	Netherlands(176)	55	Eusolex 8020, Avobenzone, Oxybenzone
2000-2002	United kingdom(177)	1155	Oxybenzone, Avobenzone, Amiloxate, octinoxate
2000-2005	United states(178)	182	Sulisobenzone, Oxybenzone, PABA, octinoxate
2004-2006	Italy(179)	1082	Octocrylene, Mexenone, Benzophenone-3, Octinoxate, Avobenzone
2008-2011	Europe(180)	1031	Octocrylene, Oxybenzone, Avobenzone, Octinoxate, Bisoctrizole
2005-2014	China(171)	6153	PABA
2012-2013	India(181)	35	-
2007-2011	Singapore(170)	22	Oxybenzone, Mexenone, Padimate O
2000-2009	Thailand(6)	270	Oxybenzone
2001-2014	Thailand(182)	168	Oxybenzone, Mexenone

Table 2.12 Review of photocontact/contact allergy reactions to UV filters(5)

UV filters	Photocontact allergy (documented reactions)	Contact allergy (documented reaction)
Benzophenone-3, Oxybenzone	318	100
Butyl methoxy dibenzoyl methane, Avobenzone	111	83
Isopropyl dibenzoylmethane, Eusolex8020	96	69
Octocrylene	81	64
Ethylhexyl methoxycinnamate, Octinoxate	60	61
PABA	55	57
Ethylhexyl dimethyl PABA, Padimate O	49	49
Isoamyl p-methoxycinnamate, Amiloxate	35	40
Benzophenone-4, Sulisobenzone	29	40
4-methylbenzylidene camphor, Enzacamene	23	33
Phenylbenzimidazole sulfonic acid, Ensulizole	18	24
Benzophenone-10, Mexemome	17	14

2.5 UV filters

UV filters are classified into physical agent and chemical agent by the mechanism of blocking. Physical UV filters block the UV radiation by reflection and scattering that leads to a protection across UVR spectrum(183).The major physical agents are zinc oxide and titanium dioxide, which are photostable and require a thick application to achieve the efficacy(184). Chemical UV filters block the UV radiation by absorbing UVR and convert it to heat energy. Chemical UV filters can be classified into UVA and UVB filter by the specific UVR range absorption. There are a hundred of agents that can be a UV filters. This review focuses on the common UV filters in commercial use (5,10).

2.5.1 Physical UV filters

The physical UV filters are zinc oxide and titanium dioxide, listed in the Cosmetics Regulation were allowed to use in cosmetic product up to 25% concentration. Titanium dioxide reduces mainly UVB and UVA II (320–340 nm), whereas zinc oxide can also filter UVA I radiation (340–400 nm)(2). Physical UV filters leaving an undesired white marks on the skin that limited their use in cosmetic products. Owing to new technology , the physical UV filters are now obtained on a nano sized(<100 nm) and demonstrated light diffraction and refraction properties, subsequent in a thin layer that is easy to spread with even better protection abilities(185). For both nano TiO2 and nano ZnO are determined that their usage in sun protection products can be considered as safe(186). The only exception is made for the usage of ZnO and TiO2 nano sized in cosmetic spray products, because there is evidence that these particles may induced inflammation in the lungs upon inhalation(187). However, an effective assessment, the usage of nano sized is still questioned. The concerning is the toxic of a very small particles, their possible deep penetration, particularly through damaged skin barrier, and their other effects in the body (188)(189).

Possible toxicity concern about of ZnO and TiO2 nanoparticles are realized that it can evade immunological defence mechanisms, to form complexes with proteins and free radical formation(190)(191). In fact, the toxicity is determined by its surface reactivity. The nanoparticles structure display more reactivity surface area than larger particles, that why ROS formation under UV radiation are more frequent. The toxicity mainly concern on ROS formation because these nanoparticles are capable to photocatalysts. These agent release an electrons inducing potentially reactive oxygen species When they are exposed to UV radiation (192). The ability to cross stratum corneum of particle is defined by its size. Intercellular spaces between stratum corneum measure is approximately between 0.5–7 and 20–30 nm(193). These intercellular spaces can be adjusted and widened by various topical products or after exposed to UV radiation (194)(195).

These nanoparticles are able to damage on different mammalian cell lines, such as human mesothelioma, alveolar epithelial cells, neural cells, vascular endothelial cells, rodent fibroblasts, and are therefore cytotoxic (196–198). The crystal forms of TiO2, the amorphous and the anatase form show greater totoxicity than the rutile form (199–201). In order to decrease the photoreactivity of TiO2 and ZnO nanoparticles, the material coating such as silica, aluminum oxide and dimethicones were used to reduce the surface activity of the particles (202)(203). The possible toxicity pathogenesis of ZnO and TiO2 on human epidermal cell are shown in the Figure 2.11 and Figure2.12, respectively.

Penetration of nano sized particles at the stratum corneum can happen via different routes such as intracellular space, sweat pores and hair follicles (190). Because of the impermeable property of corneocytes, skin penetration of titanium dioxide or zinc oxide is unlikely. Despite accumulation of these particles in hair follicles , the particles are slowly excreted out along with sebum without additional skin penetration (204,205). The shedding and turnover of stratum corneum further prevents accumulation of nanoparticles (206). The skin penetration of nano-sized particle has been conducted in many studies and the result are vary. Nowadays, numerous studies using both animal and human skin, have shown that TiO2 and ZnO nanoparticles confined to the stratum corneum layers either intact or impaired barrier function of skin (207,208) (Table 2.14). However, until further research in side effects, sunscreen usage on damaged skin with weakened barrier functions should be aware.

The physical UV filters have not been reported to cause any types of contact dermatitis. Of interest, these UV filters may block the allergic process to other sunscreen agents because of their UV filtering effects(209).

Table 2.13 Titanium oxide and zinc oxide human skin penetration studies; adapted from Newman et al. (187)

Study	Particle size	Results
TiO2 studies		
Tan et al, (210) 1996	Not specified	No penetration into skin
Lademann et al, (205) 1999	150-170 nm	Penetration into upper layers of stratum corneum; ~1% of particles in ostium of follicle
European Union, (211) 2000	14 nm-200µm	Penetration limited to stratum corneum
Pflucker et al, (212) 2001	10-100 nm	Penetration into upper layers of stratum corneum
Schulz et al, (213) 2002	10-100 nm	Particles in and on upper layers of stratum corneum
Mavon et al, (214) 2007	20 nm	Penetration in upper layers of stratum corneum
ZnO studies		
Pirot et al, (214) 1996	Not specified	0.36% Penetration in 72 h
European Union, (215) 2003	Not specified	No change in plasma zinc levels; in vitro<comma> penetration <1% of dose; most ZnO recovered from stratum corneum
Cross et al, (216) 2007	15-30 nm	No penetration in epidermis or dermis; <0.03% of applied Zn recovered in stratum corneum
TiO2 and ZnO combined studies		
Dussert and Gooris, (217) 1997	TiO2: 50-100 nm	Penetration into upper layers of stratum corneum
Gontier et al, (218) 2004	ZnO: 20-200 nm	TiO2 found in intercellular space between corneocytes of upper layers of stratum corneum

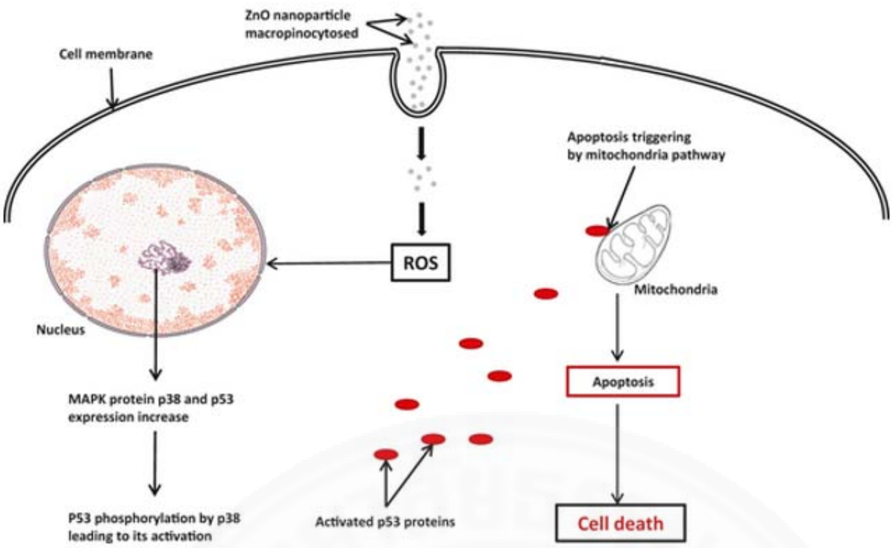

Figure 2.11 Schematic representation of a possible toxicity model of ZnO nanoparticles on human epidermal cells. ZnO nanoparticles are macropinocytosed by skin cell. They induce ROS formation in cell cytoplasm. Oxidative stress leads lead to MAPK p38 and p53 expression increase. P38 MAPK phosphorylates p53 triggering its activation. p53 MAPK activated trigger mitochondrial pathway apoptosis of skin cell. (191)

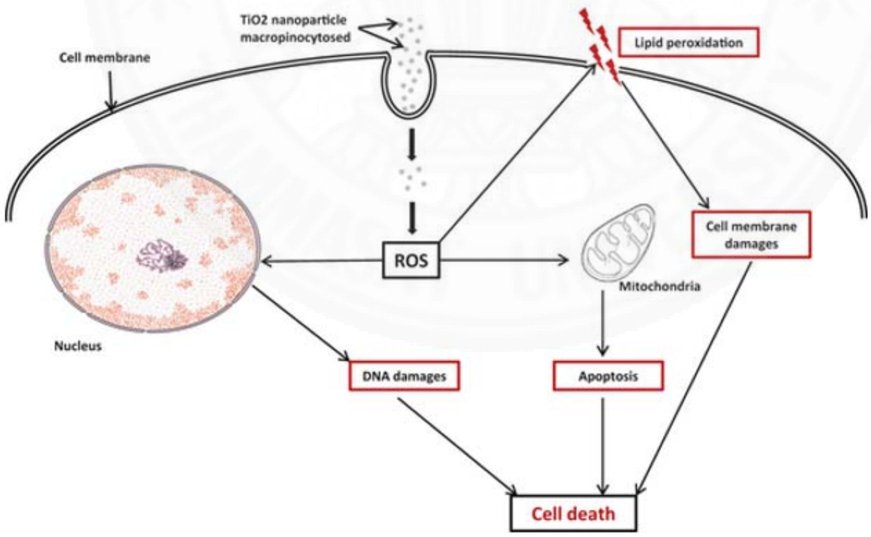

Figure 2.12 Schematic representation of a possible toxicity model of TiO2 nanoparticles on human epidermal cells. TiO2 nanoparticles are macropinocytosed by skin cell. They induce ROS formation in cell cytoplasm. Oxidative stress leads to DNA damages and membrane lipid peroxidation that enhance cell apoptosis. (191)

2.5.2 Chemical UV filters

2.5.2.1 Benzophenones

Benzophenones, chemical ultraviolet filters, are mostly UVB absorbers (290-320nm), while benzophenones-3, -4 also absorb UVA II (320–340nm) (154). Nowadays, there are 12 benzophenones, all of them are derivatives of 2-hydroxybenzophenone, the aromatic ketones that are able to absorb the UV radiation. Only benzophenones-3, -4, -8, and -10 are commonly used in personal care products. Cosmetic and toiletry products, apart from sunscreens, such as moisturizers, hair products, detergent bars, and nail products may also contain benzophenones. At first, Benzophenones were used as agents to preserve the industrial products such as paints, varnishes, and plastics to protect the products from color changes. Moreover, the material such as rubber, acrylic and polystyrene are also use benzophenone to avoid darkening and loss of structural integrity. These agents were first used as UV filter in sunscreen products in 1950 (210). The source of each benzophenones is shown in Table 2.15.

Table 2.14 The source of benzophenones (211)

Benzophenones	Source
BP-1	Personal care products
BP-2	Personal care products, Herbicides
BP-3	Personal care products, Agriculture films
BP-4	Personal care products, Hair care products
BP-5	Personal care products
BP-6	Personal care products
BP-7	Grain fungicide
BP-8	Personal care products
BP-9	Personal care products, Grain insecticide
BP-10	Personal care products
BP-11	Personal care products
BP-12	Food stabilizer in petroleum wax, Stabilizer in olefin polymers

BP, Benzophenones

Benzophenone-3 (2-hydroxy-4-methoxybenzophenone) is the most common found benzophenone in the United States. In 2011, Scheman *et al.* examined the frequency of contact allergens in skin care products, 68% of sunscreens products contained benzophenone-3 (212). While , the other study from United kingdom in 2011 shows that benzophenone-3 was found in 15% of sunscreen products(213). There are no data on the prevalence of benzophenone-3 use in Thailand from the review literature. Benzophenone-3 can pass through the skin, and its metabolites had found in urine after few hours of widespread topical application(214). However, recently studies show that There is no correlation between benzophenone-3 in urine and sunscreen usage (215)(216). The Estrogenic effect of benzophenone-3 had been reported in vitro studies(217,218) but the dosage of benzophenone-3 in the study was too high than actually application(219). Janjua N. *et al.* showed that benzophenone-3 exposure not related to the hormone levels in human(220).

In 1972, Ramsay *et al* first documented the allergic contact dermatitis to benzophenone-3 (221). Recently, the 10-year retrospective study of the North American Contact Dermatitis Group Data (NACDG; 2001-2010) found that allergic to benzophenone-3 account for 70.2% of patients who had positie reaction to sunscreen.(173). According to 2009-2010 NACDG data, positive reaction to benzophenone-3 was higher than 1995–1996 NACDG data. Benzophenone-3 was also the major chemical UV filter in a large patch tested study in Australia with suspicious to sunscreen allergy, causing 28% of positive reactions. In addition, Canadian and European studies reported that benzophenone-3 is the most significant UV filter that cause allergy(155,158,222).

Eight years after the report of allergic contact dermatitis to benzophenone-3, the PACD to benzophenone-3 was reported in 1980 (223). This UV filter is implicated in more photoallergy than any available UV filters. The photoallergic reactions to benzophenone-3 in European studies (180,224,225) are greater than studies in the United States(223,226,227). Shaw *et al.* demonstrated that most patients with photoallergic reactions to benzophenone-3 had the moisturizer as the source of allergen(228). Another reported case of photoallergic contact dermatitis to benzophenone-3 was secondary to contact the printing ink on magazine. The patient had positive photopatch test to benzophenone-3, octocrylene, and ketoprofen , but benzophenones was a only component of the printing on magazine that patient was exposed(177). In addition to allergic and irritant reactions to benzophenone-3, It has been reported to cause contact urticaria, photocontact urticaria and anaphylaxis(214)(229)(230).

Cross-reactions within the benzophenones group are possible due to sharing chemical structure, but from the literature's review there are no reported case(231). Notably, benzophenone-3 shows high frequent of cross-reactivity with ketoprofen(a topical NSAID) and octocrylene(a commonly use UVB filter)(232). Benzophenone-3, ketoprofen and octocrylene have similar structures, but ketoprofen when exposed to sunlight, it break down to various fragment that related to benzophenone-3(233). All three of these agents are strong photosensitizers. Although there are no evidence show that other benzophenones cross-react with ketoprofen or octocrylene, NSAIDs such as tiaprofenic acid and the fenofibrate have been shown to cross-react(161). Topical NSAIDs are commonly used in Europe but are less common in the United states. In 2012, A European multicenter photopatch test study show that ketoprofen cause the most positive photopatch test of all agent test. Moreover, benzophenone-3 and octocrylene were the top five photosensitizers in this study, this may reflect the cross-reactivity rather than individual sensitization(180).

Benzophenone-4 has been reported that can caused irritant, allergic and urticarial reactions (221). This UV filter is also a top 5 sunscreen allergens in many western studies(177,234). A many photopatch testing studies in United states and Europe have suggested that benzophenone-4 is also a leading cause of photoallergy in patients with allergy to sunscreens (177,223,228). Cosmetic allergy study in Thailand, Boonchai *et al.* reported that positive patch test reaction to benzophenone-4 in the past ten year is 18.8%. The survey study of UV filters in sunscreen in Europe showed that the benzophenone-4 is less common in sunscreen products (235)(213). Recently, Uter *et al.* conducted a survey in cosmetic product in Germany, show that benzophenone-4 usually found in hair products but not found in sunscreen products(236). Benzophenone-4 is used not only in sunscreen or hair products, but also to prevent photodegradation of other ingredients in cosmetic products(237).

In the past, benzophenones-8 and -10 were commonly used in sunscreen products but the documented reactions to these agents is rare. Benzophenone-

8 were reported as a cause of ACD just a few cases(238,239). Photoallergy to benzophenone-8 have not been reported. However, this agent is not regularly included in photopatch testing series. This may reflect the barely use of benzophenone-8 as UV filter in sunscreen products today(236). Benzophenone-10 is no longer used in sunscreen products. Benzophenone-10 was the top three photoallergen in photopatch testing study conducted in Europe from 1983 to 1998(240). But recently study have not reported any reaction to this agent. Benzophenone-2 has been reported to cause a photopatch test reaction in a patient with self-proclaimed "sunscreen allergy"(226). The others benzophenones that are not mention above has not been reported as eliciting allergic contact dermatitis. And There are no reports of photoallergic reactions to benzophenones -1, -5, -6, -7, -9, -11, or -12(211). This might be due to less common use in products or lack of testing to these agents.

2.5.2.2 Dibenzoylmethanes

The dibenzoylmethane group include 4-isopropyl-dibenzoylmethane (Eusolex 8020) and butyl methoxydibenzoylmet (BMDM). The Eusolex 8020 were introduced in Europe in 1980 as a UVA filter in sunscreen for photodermatoses patient and facial cosmetics(241). In 1997, BMDM was approved for use as UV filter in the USA. Dibenzoylmethanes have a broad spectrum and mainly coverage the UVA range. Increasingly use this UV filers, because of reported sensitivities to benzophenones and PABA products(222). The sun protection that covered UVB and UVB range was recommened worlwide, so the usage of avobenzone has increased more importance. Currently, Avobenzone is the most common dibenzoylmethane used in sunscreen sold in the USA. Allergy to avobenzone was also reported, but ht ereaction could be from cross-reaction caused by previous exposure to the Eusolex 8020(242,243). Avobenzone has replaced the former Eusolex 8020, the Eusolex 8020 production was discontinued in 1993 because of its high allergic potential. But, Avobenzone is also known as a allergenic agents among the UV filters(177,180). The other concerning point is the photoinstability of avobenzone, particularly when it combined with Octinoxate(EHMC)(244). The consequent of photodegradation products have a potential reaction and may lead to contact allergies.

2.5.2.3 para-Aminobenzoic acid

The para-aminobenzoic acid(PABA) was one of the first commercially available UV filters and became popular worlwide. PABA is an effective UVB filter but does not UVA(245). Vehicle for PABA is alcohol. Oxidation of this agent causes it to turn yellow, it may stain the clothes. The important property of PABA is its ability to enter the stratum corneum. This accumulation property can offer a long protective duration even after exposed to water (246). Derivatives of para-aminobenzoic acid include glycerol PABA, amyl dimethyl PABA (padimate A), and octyl dimethyl PABA. These derivatives became famous for use in sunscreen products due to a compatible property with many cosmetic vehicles and a reduced tendency for staining. P-phenylenediamine and benzocaine share structural similarities that are able to cross-react with PABA (247). Both the haptens concerned in development of allergy to PABA and the PABA cross-reacting compounds are quinine amines, the oxidation products of para-amino compounds.

Though, Thess agents became apparent that cause photoallergic reactions (158,248), and sensitization was documented in 1947(249). PABA was banned in 2008 as a UV filter for cosmetic purpose in the EU. Nowadays, PABA are hardly used in sunscreen products. The recent update reported show that around two percent of sunscreens in the USA contained para-aminobenzoic acid or a derivative(250).

In a study at the Mayo Clinic of photopatch testing from 2000 to 2005, PABA was the second most common UV filters caused photoallergic reactions, after benzophenone-4 (178). PABA also documented as the most common UV filter that caused photoallergic reactions in a recent study of photocontact allergy at New York University(227). Octyl dimethyl PABA (Padimate O) is the most common used PABA in sunscreens in the USA(246). In 2010-2011, the European Multicenter Photopatch Test Study, octyl dimethyl PABA were used for photopatch and patch tested, the result did not show any reactions(180). This is probably due to decreased use of this filter in Europe since 2005 to 2010 (213). Moreover, patients may have a transient burning sensation after use the products that contain PABA or derivative. A cross-reacting compounds of PABA are quinine amines, para-amino chemicals oxidative product(245). It is not available for commercial use in Europe and USA but these agents still is found in other countries. So, its used in patch and photopatch testing allergen series are still not concluded(251).

2.5.2.4 Salicylates

Salicylates are weak UVB filter usually used to enhance other UVB filters or used in high concentration. These agents are able to mix insoluble UV filter such as the benzophenones but are themselves insoluble in water, so they are usually combined together. Because its simply incorporated into other agents, salicylates are often used in cosmetic products such as makeup, moisturizers, and lip balm (154). In 192, benzyl salicylate was firsly used in sunscreen product and in 1968, was reported as a contact allergen in detergents and soap (252). The most frequently used salicylates are octyl salicylate, trolamine salicylate, homomenthyl salicylate, and benzyl salicylate. Benzyl salicylate was the first filter used in sunscreen in the USA(253). At present, the main salicylate used in sunscreens is octyl salicylate (254). Homosalate is not as commonly combined into topical products as octyl salicylate (255) and has less reports of photoallergy and allergy. Salicylates are hardly associated with photoallergic or allergic reactions in term of cosmetic used(180,256,257).

2.5.2.5 Camphor derivatives

Terephthalylidene dicamphor sulphonic acid (ecamsule, Mexoryl SX), a derivative of camphor, is a great UVA filter, which was developed by L'Oreal (Paris, France) in 1982 and was approved in Europe in 1991 as cosmetic compound. Mexoryl SX was approved in 2006 as part of the sunscreen named Anthelios SX. Since 1988, This agent was the first approval of a product with a new UV filter. In addition, Mexoryl SX has good stability and shows no risk for skin penetration(258). The allergy to Mexoryl SX have only recently been reported(259). The another camphor derivatives, 3-(4-methylbenzylidene) camphor (enzacamene), mainly for UVB filter and was approved in Europe. There were many reports of allergic reaction to Enzacamene(260,261).

2.5.2.6 Cinnamate

Octinoxate (EHMC), another famous ultraviolet filters and is usually used with other ultraviolet B filter to reach the target SPF value. Octinoxate is well tolerated but has a firm photodegradation potential, specifically in combination with avobenzone, related to decrease the protection ability(180,262,263). Cinnamate allergy in sunscreen ingredients is uncommon; possible cross-reactivity with another agents is generally the main clinical problem(264). All the reactions of contact dermatitis to this octinoxate have been reported. The irritant and phototoxic contact dermatitis to octinoxate were found in one study and just only 3 and 1 reaction respectively(5). Allergy and photoallergy to octinoxate have been reported quite extensively. Isoamyl p-methoxycinnamate (amiloxate) is not approved for use in the USA(265). Allergic reaction to amiloxate is also reported, especially photoallergic reaction. 2-ethoxyethyl-p-methoxycinnamate (cinoxate) is permitted for use in the USA with concentrations up to 3% but not in the Europe(266). The photoallergic reaction to cinoxate have been hardly reported(267–269).

2.5.2.7 Diphenylcyanoacrylate derivatives

The octocrylene is produced by the condensation of ethylhexanol with 2-diphenylcyanoacrylic acid, and is classified in cinnamate group. Octocrylene is a good UVB filter that has been used in sunscreens for many years(270). The protecting spectrum of octocrylene (290–360 nm, peak at 303 nm) covers entirely ultraviolet B length, but also ultraviolet A II length (271). But, octocrylene is not an effective UV filter, so, is typically used with other UVB filters to increase the sun protection factor, especially cinnamates group (272).

Photostability is an outstanding property of octocrylene , and is used for stabilize other unstable UV filters (273), and increase their overall stability and resistance to water (271). This applies mostly to the avobenzone, which has an very unstable property under sunlight exposure, leading to a reduction in the protection efficacy of the products that use avobenzone (274). Octocrylene can mix with many cosmetic oils, so this UV filters can easily be combined into gel sunscreens (272).

In 2003,Carrotte-Lefebvre and colleagues reported the photoallergy to octocrylene (270); After that the allergic contact dermatitis to octocrylene was reported afterward(275). Octocrylene has become famous e in recent years and is allowed in sunscreens up to 10% concentration in USA and Europe. Ketoprofen, benzophenone-3, and ctocrylene, have shared mlecular structure; so can induce the cross-reaction. Photo/contact allergy to octocrylene have been reported in children(276). Karlsson et al, Ten years of patch and photopatch review study, two thirds of octocrylene allergy in children were allergic in nature versus photoallergic(277). The another photopatched test study of 11 children showed that ten had patch tests positive to octocrylene, and one had a photopatch test positive(271). Positive patch tests to octocrylene have also presented in children that never exposed to ketoprofen(278). Photopatch test reactions to ketoprofen often presented with not only to benzophenone-3 and octocrylene, but also to many chemicals. These include NSAIDs, such as etofenamate, suprofen, and tiaprofenic acid , the fenofibrate drug (279), and photoallergens such as fenticlor, chlorpromazine, triclosan, bithionol, and tetrachlorosalicylanilide; such reactions are usually not relevant (232,280). Cross-reactivity to benzophenone-3 and fenofibrate is regularly considered to be photo-cross-reactivity, that shared a double benzene rings linked by a ketone group (Figure 2.13) (232,279), and the key photodegradation product from ketoprofen is 3-ethylbenzophenone (281).

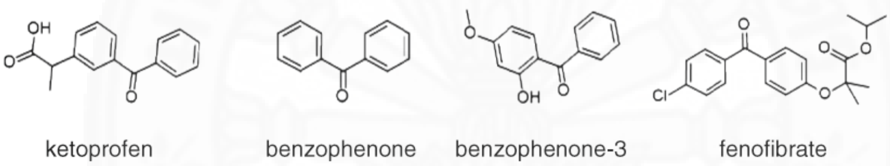

Figure 2.13 Chemical structures of ketoprofen, benzophenone, benzophenone-3, and fenofibrate (282)

2.5.2.8 Benzotriazole derivatives

Bemotrizinol (Tinosorb S, bis-ethylhexyloxyphenol methoxyphenyl triazine) is in the benzotriazole group that have a broad spectrum and photostbility properties, UV filters that h organic and insoluble (283). This agent is not approved in the USA but available in Europe. The photostable property of this filter lets it be photostabilizer to other UV filters such as avobenzone (284). Irritant and phototoxic reactions have not been documented to this agent but photopatch and patch test reaction were reported in the recent European multicenter photopatch test study (180).

Bisoctrizole (Tinosorb M, methylene bis-benzotriazolyl tetramethylbutylphenol) is another benzotriazole derivatives approved for use in used Europe (285) and South America. Bisoctrizole is a combination of methylene bis-benzotriazolyl tetramethylbutylphenol which is an active agent and decyl glucoside, propylene glycol, and xantham gum (286). This agent have both physical and chemical filter properties and absorbs the UVB and UVA I spectrums (287). Bisoctrizole has cosmetically desirable property better than titanium dioxide and zinc oxide.

The study in 2009 performed by Kerr et al,(288) show that bisoctrizole cause the irritant/phototoxic contact reaction around five percent of patients, though reactions did not determine a dose-related pattern. Photoallergic/allergic dermatitis to bisoctrizole have also been reported. In the recent European multicenter patch study, bisoctrizole was the most common UV filter that cause an ACD (180). One study documented bisoctrizole allergy with only patch testing to the sunscreen product as formulated and no individual testing (283). Another study reported one patient with bisoctrizole allergy whose tested positive to lauryl glucoside and one patient who had a positive patch test to the sunscreen agents without glucoside reaction(289). The other two studies show that positive patch tested to both bisoctrizole and glucoside have found together in all patients tested (286,290).

2.5.2.9 Triazines

Drometrizole trisiloxane is a ultraviolet A II filter. This UV filter produced in 1999 and allowed using in cosmetics prodcut up to fifteen percent concentration in Europe (285), but it is not allowed for use in USA (265). The contact allergy to this agent first emerged in 2005, and positive photopatch/patch tests reaction to Mexoryl XL have also been reported(180,234,291).

Drometrizole (2-(2-hydroxy-5-methylphenyl) benzotriazole) has protecting range at 243, 298, and 340 nm. It is commonly use as a UV filter and stabilizer in polyesters, plastics, celluloses, rubber, acrylates, dyes, synthetic and natural fibers, orthodontic adhesives, waxes, detergent, insecticides snd agricultural products (292). USA and Europe do not approve dometrizole as a UV filter in sunscreens, and have no reported the reaction to this agent.

2.5.2.10 Other chemical UV filters

Ensulizole is a UVB filter allowed for use in the Europe and USA. It is soluted in water and usually used in products that formulated for less oily and lighter feeling on the skin. Because of it is new sunscreen agents, reports of reactions to ensulizole are relatively few (5).

Polysilicone-15 (Parsol SLX) is an chemical agent found in many hair products such as shampoos, hair conditioners and hair sprays. This agent was approved for use in sunscreens and cosmetics up to ten percent in Europe (285). One photopatch reaction to polysilicone-15 was recently reported(180).

Uvinul A Plus (diethylamino hydroxybenzoyl hexyl benzoate) has a peak protective range in UVA II spectrum. In 1977, The first case of allergic contact dermatitis to this agent was documented.(293), with few other adverse reaction reports to uvinul A plus emerging in the last few years (180). This UV filter is approved for use in Europe up to ten percent concentration (285).

Octyl triazone (Uvinul T 150; BASF Corporation, Florham Park, NJ) has a protective range mainly in UVB. It is not soluted in water but has light-stable property, octyl triazone was approved for use in Europe up to five percent concentration(285). Due to its polarity, it has a good affinity to keratin. In 2002, The photoallergic reaction to octyl triazone was first reported(294). Recent multicenter European studies have also reported photoallergic/allergic reactions to octyl triazone (177,180).

Bisdisulizole disodium (disodium phenyl dibenzimidazole tetrasulfonate, Neo Heliopan AP; Symrise, Teterboro, NJ) has a peak protective range in UVA I spectrum. It is not allowed for use in USA. There is one ACD reaction to this filter has been reported (180).

2.5.3 Photostability of UV filters

UV filters stability is an important issue for formulated the sunscreen products. If possible, the lowest number of UV filters and concentration to reach the protecting target would be combined into a cosmetically pleasing formula. The UV filters should absorb the radiation, and the absorbed cycle would be repeated over and over again with minimal loss of the chromophores. Photo-unstable of UV filters or sunscreen products is not a new issue. It is important to evaluated the human safety of UV filters/sunscreen products as many of these studies have been conducted with photo-unstable UV filters, alone and in combination.

The human safety attentions should be in response short-term product use with sunlight exposure because it is an expected use situations. This might present as phototoxicity/photoirritation and photoallergic reactions caused by exposure to photo-degradation products. Also, long-term health effects may include the problem from long time exposure to such photo-degradation products which could have toxicological effect. Additional, an higher sun light exposure owing to decrease UV protection while using photoinstability product, could increased the risk of adverse reaction to UV radiation even acute or chronic effect.

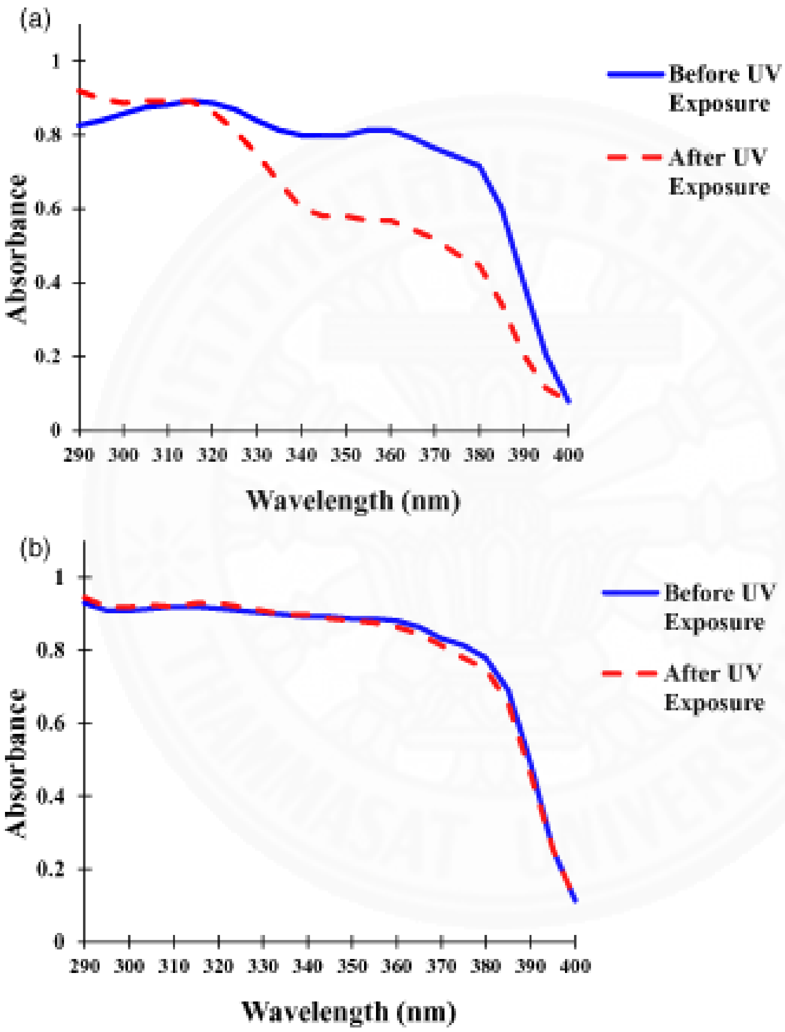

Figure 2.14 Absorbance curves for photo-unstable 7.5% OMC + 2% avobenzone oil/water sunscreen formula (a) and photostable 10% octocrylene + 2% avobenzone oil/water formula (b) before and after irradiation with 30 J/cm^2 of solar-simulated UV light (244)

2.5.4 Prevalence of UV filters

UV filters in sunscreen were change time to time, in the past decade the 5 most common UV-filter found in sunscreen in Denmark are EHMC, BMDM, Octocrylene, benzophenone-3, TDSA(295) (Table 2.16). In 2012 , personal care products survey in Switzerland (Table 2.17), the most common UV filters found in sunscreen are BMDM, Octocrylene, BEMT, Octyl salicylate, Octyl triazone(235). A survey of sunscreen products in UK, in 2010. In total, 337 products were identified, with a median SPF of 30. In these products, 19 UV filters were identified, of which the most common was Avobenzone. Compared with data from 2005, most filters had an increase in frequency of inclusion, with a trend towards broader spectrum protection(213) (Table 2.18). In 2014, cosmetic products survey in Germany (Table 2.19), the common UV filters found in sunscreen are BMDM, Octocrylene, Titanium dioxide, EHMC, BEMT(236). Oxybenzone and Octinoxate are less common because of adverse reaction. According to review of literature, there has no study on the prevalence UV filters in sunscreen product in Asia.

Table 2.15 A survey of UV filters in sunscreen products in Denmark (2002) (295)

UV filters (INCI)	(%) n=75
Octyl methoxycinnamate	49.3
Butyl methoxydibenzoylmethane	44
4-methylbenzylidene camphor	22.7
Octocrylene	22.7
Terephthalylidene dicamphor sulfonic acid	21.3
Benzophenone 3	18.7
Drometrizole trisiloxane	16
Octyl salicylate	10.7
Isoamyl p-methoxycinnamate	5.3
Homosalate	4
Octyl triazone	4
Ohenylbenzimidazole sulfonic acid	2.7
Octyl dimethyl PABA	1.3
PEG-25 PABA	1.3

Table 2.16 A survey of UV filters in personal care products in Switzerland (2012) (235)

UV filters (INCI)	UV filters in personal care products (%)							
	Total n=116	LC n=19	LS n=8	FC n=29	LMF n=11	AS n=3	HC n=7	SC n=39
Butyl methoxydibenzoylmethane	70.7	63.2	50	65.5	9.1	66.7	100	94.9
Ethylhexyl methoxycinnamate	50.9	73.7	100	44.8	100	66.7	71.4	15.4
Octocrylene	43.1	10.5	0	37.9	0	0	57.1	84.6
Bis-ethylhexyloxyphenol methoxyphenyl triazine	34.5	21.1	0	24.1	0	0	0	74.4
Ethylhexyl salicylate	25.0	0	37.5	34.5	18.2	66.7	14.3	28.2
Ethylhexyl triazone	12.9	10.5	0	10.3	0	0	0	25.6
Phenylbenzimidazole sulfonic acid	11.2	0	0	10.3	0	0	14.3	23.1
Methylene bis-benzotriazolyl tetramethylbutylphenol	9.5	5.3	0	3.4	0	0	0	23.1
Diethylhexyl butamido triazone	9.5	15.8	0	3.4	0	0	0	17.9
Drometrizole trisiloxane	6.9	5.3	0	6.9	0	0	0	12.8
Terephthalylidene dicamphor sulfonic acid	5.2	0	0	3.4	0	0	0	12.8
Homosalate	4.3	0	0	6.9	0	0	0	7.7
Benzophenone-3	3.4	15.8	0	3.4	0	0	0	0
Ethylhexyl dimethyl PABA	1.7	10.5	0	0	0	0	0	0
Isoamyl-p-methoxycinnamate	0.9	0	0	0	0	0	0	2.6
Benzophenone-4	0.9	0	0	0	0	33.3	0	0
4-Methylbenzylidene camphor	0.9	5.3	0	0	0	0	0	0

INCI: International Nomenclature of Cosmetic Ingredients; LC: lip care; LS: lipstick; FC: face cream; LMF: liquid makeup foundation; AS: aftershave; HC: hand cream; SC: sunscreen.

Table 2.17 A survey of UV filters in sunscreen products in UK (2005) and UK (2010) (213,296)

UV filters (INCI)	UK 2005 (%) n=308	UK 2010 (%) n=337
Butyl methoxy dibenzoylmethane	73.4	96.4
Ethylhexyl methoxycinnamate	53.6	17.8
Octocryolene	36.4	90.5
4-Methylbenzylidene camphor	25.3	1.2
Ethylhexyl salicylate	20.8	32.6
Benzophenone 3	16.9	15.1
Bis-ethylhexyloxyphenol methoxyphenyl triazine	15.9	58.5
Ethylhexyl triazone	14.9	16
Terephthalylidene dicamphor sulfonic acid	14.6	14.2
Benzyl salicylate	13.6	N
Drometrizole trisiloxane	11	13.4
Diethylhexyl butamido triazone	10.4	32
Methylene *bis*-benzotriazolyl tetramethylbutylphenol	7.8	N
Phenylbenzimidazole sulfonic acid	3.6	5.6
Ethyl methoxycinnamate	3.2	N
Octyl dimethyl PABA	3.2	N
Benzophenone 4	2.9	N
Polysilicone-15	2.6	3.3
Homosalate	2.3	15.7
Disodium phenyl dibenzimidazole tetrasulfonate	1.9	0.9
Sodium phenylbenzimidazole sulfonate	1.3	N
Diethylamino hydroxybenzoyl hexyl benzoate	1	5
PABA	0.6	N
Isoamyl-p-methoxycinnamate	0	0.9
Titanium dioxide	45.1	49
Zinc oxide	4.9	N

N, not mentioned; INCI, International Nomenclature of Cosmetic Ingredients

Table 2.18 A survey of UV filters in sunscreen products in Germany (2006-2009) (236)

UV filters (INCI)	UV filters in cosmetic products (%)							
	Total	SC	C	LC	MU	PF	NA	HA
	n=4447	n=19	n=8	n=29	n=11	n=3	n=7	n=39
Benzophenone-3	8.8	3.2	5.6	16.1	3.6	28.6	78.8	9.3
Benzophenone-4	5.5	0	2.6	1.6	0	0	6.1	57.4
3-Benzylidene camphor	0.1	0	0.4	0	0	0	0	0
Benzylidene camphor sulfonic acid	0	0	0	0	0	0	0	0
Bis-ethylhexyloxyphenol methoxyphenyl triazine	16.4	34.4	2.2	0	0	0	0	0
Butyl methoxydibenzoylmethane	48.7	74	38.5	33.9	0	64.3	0	0
Camphor benzalkonium methosulfate	0	0	0	0	0	0	0	0
Diethylamino hydroxybenzoyl hexyl benzoate	1.8	2.6	0	1.6	0	4.8	0	1.9
Polysilicone-15	0.1	0	0.4	0	0	0	0	0
Diethylhexyl butamido triazone	6	11.3	0	12.9	0	0	0	0
Disodium phenyl dibenzimidazole tetrasulfonate	0.4	0.9	0	0	0	0	0	0
Drometrizole trisiloxane	6.1	11.5	2.2	3.2	0	0	3	0
Ethylhexyl methoxycinnamate	38.5	36.6	51.1	40.3	18.2	85.7	3	16.7
Ethylhexyl triazone	13.7	22.7	7.4	22.6	0	0	0	0
Homosalate	0.4	0.9	0	0	0	0	0	0
Isoamyl *p*-methoxycinnamate	4.1	7.1	2.2	3.2	0	0	0	0
4-Methylbenzylidene camphor	5.9	10	2.6	8.1	0	0	0	1.9
Methylene bis-benzotriazolyl tetramethylbutylphenol	5.4	10	3.5	0	0	0	0	0
Octocrylene	30.7	58.2	16	0	1.8	0	0	0
Ethylhexyl dimethyl PABA	0.5	0.2	0	1.6	0	0	0	0
Ethylhexyl salicylate	12.6	15.4	11.7	1.6	0	61.9	3	0
PABA	0.4	0	0.4	0	0	0	0	0
PEG-25 PABA	1	0	0.9	0	0	0	0	14.8
Phenylbenzimidazole sulfonic acid	11.6	15.8	15.6	0	9.1	0	3	0
Polyacrylamidomethyl benzylidene camphor	0	0	0	0	0	0	0	0
Terephthalylidene dicamphor sulfonic acid	6.1	12.1	2.2	0	0	0	0	0
Titanium dioxide	40.1	55.8	34.6	30.6	40	0	9.1	1.9
Zinc oxide	10.6	12.8	5.6	11.3	34.5	0	6.1	3.7

INCI: International Nomenclature of Cosmetic Ingredients; SC: sunscreen; C: cream; LC: lip care; MU: make-up; PF: perfume; NA: nail; HA: hair.

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Materials

3.1.1 Sunscreen products

Sunscreen products information are collected during the March to December 2016 from a random location and various stores in Bangkok Metropolitan region as follow;

1) Supermarket: Tesco Lotus, Big C, Max Valu, Villa market

2) Department store: Central plaza, The mall

3) Specific Cosmetic Store: Watsons, Beauty buffet, EveandBoy, Yves rocher, Oriental princess, The face shop, Skinfood, Matsumoto kiyoshi, Etude house

4) Convenience store: Seven-eleven

5) Drug store: Boots, Tsuruha.

3.1.1.1 Sample size

All available products that Primarily indicated as sun protection use.

3.1.1.2 Inclusion criteria

1) A product that primarily indicated as sun protection use.

2) The sample has a Thai FDA registration number.

3) The sample have an ingredient label.

3.1.1.3 Exclusion criteria

1) The sample discontinue from the market during the study.

3.1.2 Data recording form

The data user-form, according to the prepared data was created by Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) (Figure 3.1).

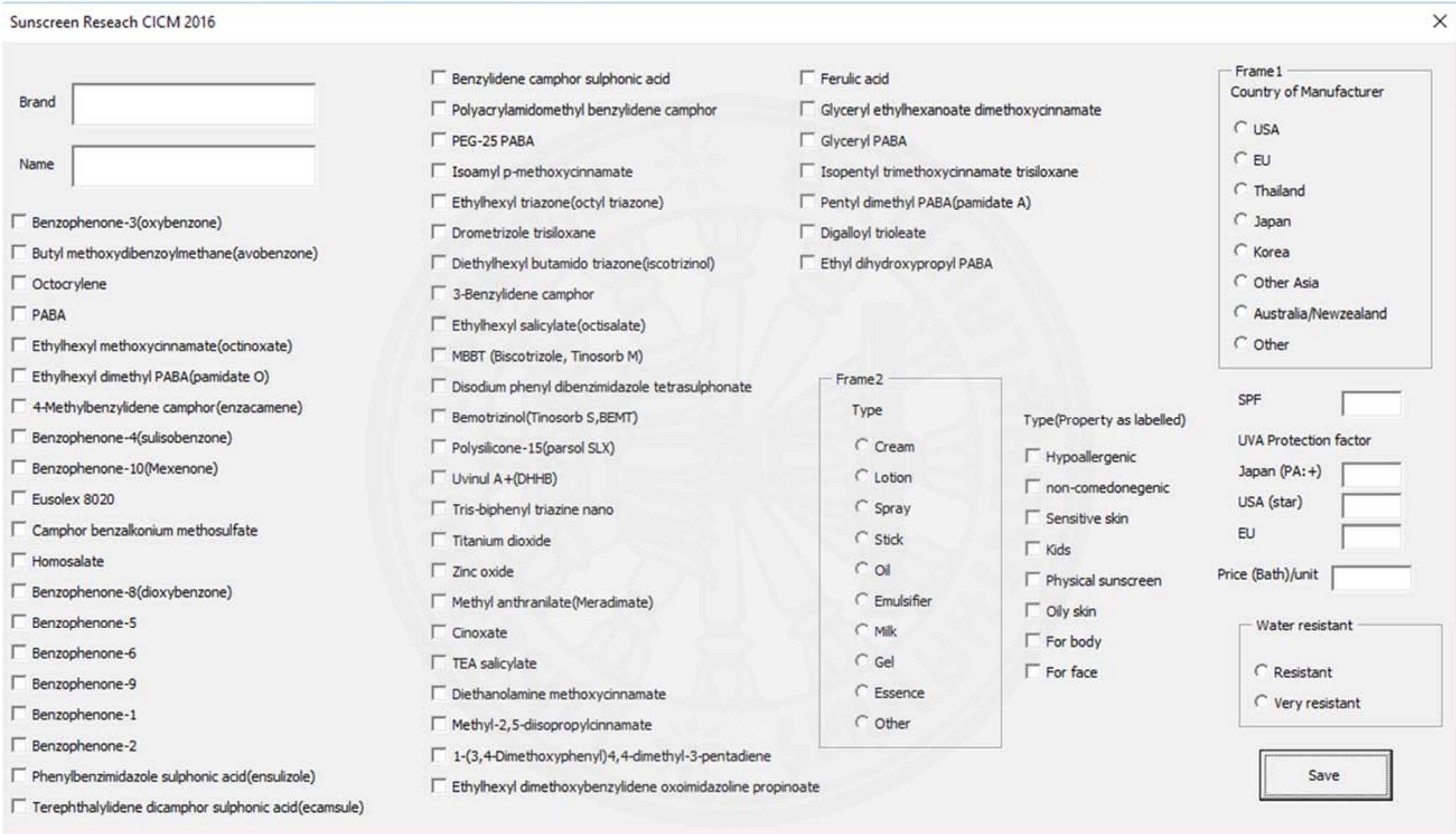

Figure 3.1 The data user-form of this study created by Microsoft Excel (Microsoft Corporation, Redmond, WA, USA

3.2 Research design

3.2.1 Market survey experiment

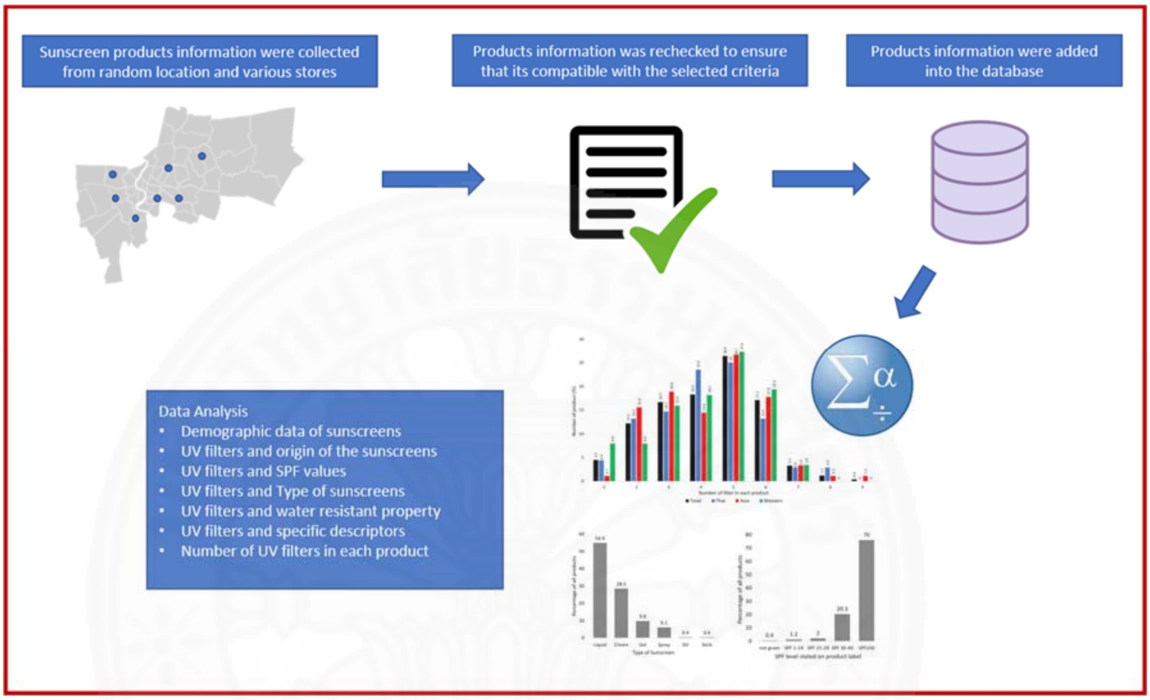

Figure 3.2 Flow chart of research methodology

Labeled ingredients and sunscreen information from various stores from random locations in the Bangkok metropolitan area were collected and reviewed during March to December 2016. The data were entered into a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet and analyzed.

The ingredients and properties of the sunscreen products (Figure 3.3) that were commercially available on the Thai market were collected and recorded. To obtain a representative sampling of sunscreens used by all types of consumers in the Bangkok metropolitan area, sunscreen ingredients were recorded from products sold in supermarkets, department stores, specific cosmetic stores, convenience stores, and drug stores. The inclusion criteria for samples were as follows: (i) the product was primarily designated for sun protection use, (ii) the product had a Thai FDA registration number, and (iii) the sample had an ingredient label. If the product was removed from the market during the study, it was excluded.

Figure 3.3 An example of product information that was collected form the store

For each product, the following data were recorded; UV filter, brand, name, country of manufacture (i.e., origin), sun protection factor (SPF), type (cream, liquid, spray, gel, oil and stick), price (Baht per unit, g, or mL), and the specific descriptors, “Kids/Children/Baby,” “Sensitive/Hypoallergenic,” and “Water resistant/Waterproof. The liquid type of sunscreen includes lotion, milk, essence and emulsifier.

3.2.2 Outcome measurement

3.2.2.1 Characteristics of sunscreen

Describe the general data of the study sample as follow;

1) Country of manufacturer (origin)
2) Brand of products
3) UV filters
4) Sun protection factor (SPF)
5) Type of products
6) Water resistant products
7) Specific descriptors
8) Number of UV filters in each product
9) Price

3.2.2.2 Relation of UV filters and sunscreen properties

(1) UV filters and product origin

Describe the frequency of UV filters between different country and regional origin (Figure 3.4).

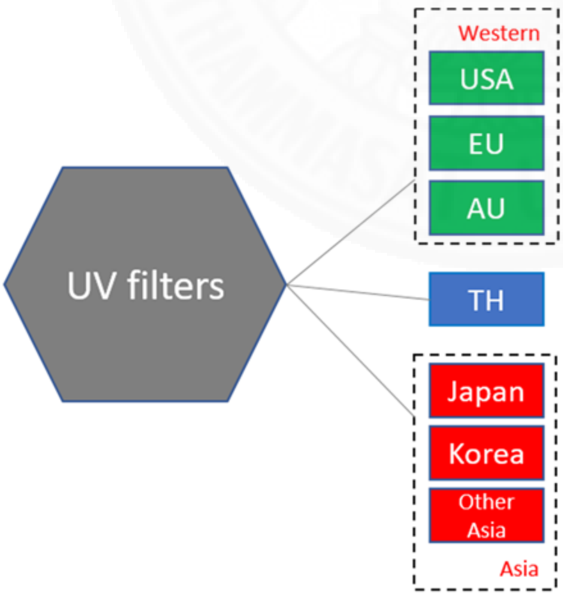

Figure 3.4 Illustrative relation of UV filters and product origin

(2) UV filters and sun protection factor (SPF)

Describe the frequency of UV filters between different SPF level (Figure 3.5).

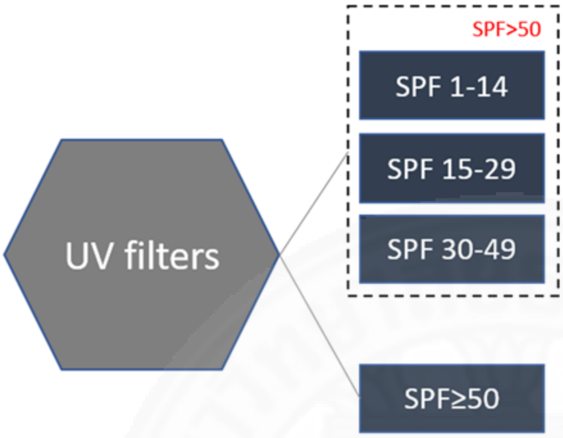

Figure 3.5 Illustrative relation of UV filters and SPF level

(3) UV filters and type of products

Describe the frequency of UV filters between different type of products (Figure 3.6).

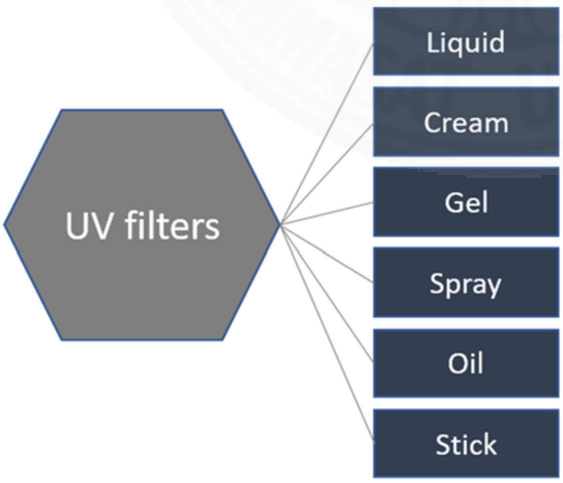

Figure 3.6 Illustrative relation of UV filters and type of products

(4) UV filters and water resistant property

Describe the frequency of UV filters between the product labeled "water resistant" and those not (Figure 3.7).

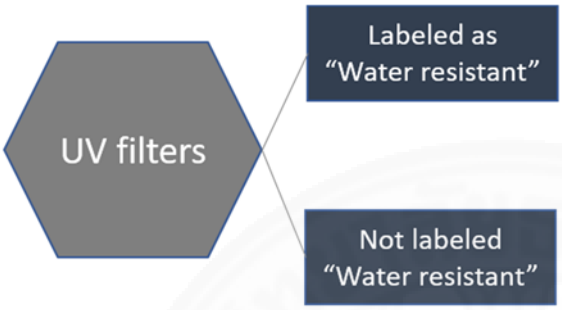

Figure 3.7 Illustrative relation of UV filters and water resistant property

(5) UV filters and specific descriptors

Describe the frequency of UV filters between the product labeled for "sensitive skin" or "kids" or "physical sunscreen" and those not (Figure 3.8).

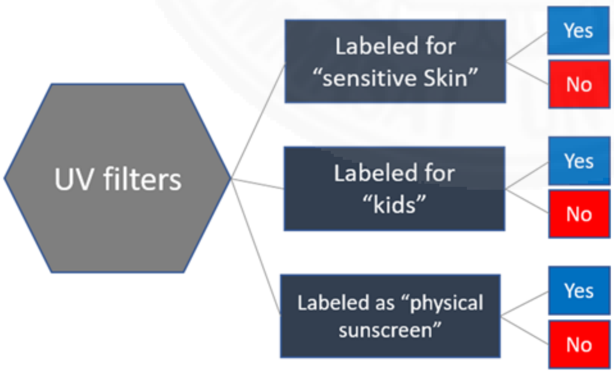

Figure 3.8 Illustrative relation of UV filters and specific descriptors

3.2.2.3 Relation of number of UV filters and sunscreen properties

(1) Number of UV filters and product origin

Describe the number of UV filters in each product between different regional origin (Figure 3.9).

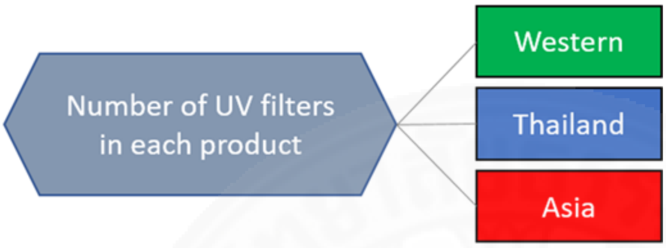

Figure 3.9 Illustrative relation of number of UV filters and product origin

(2) Number of UV filters and sun protection factor (SPF)

Describe the number of UV filters in each product between SPF <50 and SPF ≥50 products (Figure 3.10).

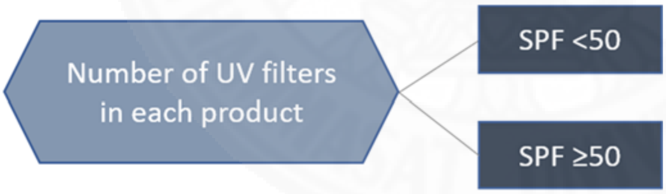

Figure 3.10 Illustrative relation of number of UV filters and SPF level

(3) Number of UV filters and type of products

Describe the number of UV filters in each product between type of products (Figure 3.11).

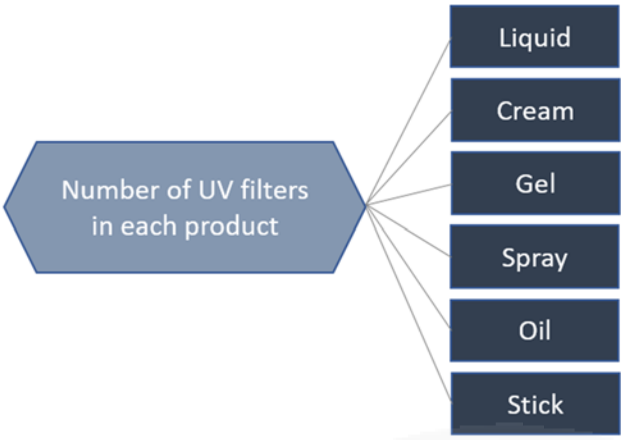

Figure 3.11 Illustrative relation of number of UV filters and type of products

(4) Number of UV filters and price

Describe the correlation between price and number of UV filters in each product.

3.3 Data analysis

The data were analyzed using descriptive analyses. Statistical analysis was performed with PASW STATISTICS version 20.0 (SPSS Inc., Chicago, IL, USA). Pearson's chi-square test was performed for comparison of UV filters and number of UV filters according to origin of manufacture, SPF, "Kids", "Sensitive", and "Water resistant". ANOVA test was performed for comparison of number of UV filters according to origin of manufacture, SPF, types of product and "water resistant". A p-value < 0.01 was considered statistically significant. Spearman's rho was performed to evaluate the relation between number of UV filter and price per unit.

CHAPTER 4
RESULTS

The sample information was collected from the stores located in Bangkok Metropolitan region as follow;

1) Supermarket including; Tesco Lotus, Big C, Max Valu and Villa market; from Bangyai, Bang kruai, Ratchathewi districts

2) Department store including; Central plaza, The mall; from Pathumwan, Bangyai, Bangna, Bang khae districts

3) Specific Cosmetic Store including; Watsons, Beauty buffet, EveandBoy, Yves rocher, Oriental princess, The face shop, Skinfood, Matsumoto kiyoshi, Etude house; from Pathumwan, Bangrak, Bangna, Bangyai, Bang kruai districts

4) Convenience store; Seven-eleven; from Pathumwan, Bangna, Bangyai districts

5) Drug store including; Boots, Tsuruha; from Bangrak, Bangna, Bangyai districts

Investigators selected the survey location that near the working place and home.

4.1 Characteristic of sunscreen

4.1.1 Brand and national/regional origin of sunscreen products

Of 246 sunscreen products from 97 brands, 68 products (27.6%) were domestically produced in Thailand. Ninety products (36.6%) from 32 brands were made in Asia, specifically Japan (15.9%), Korea (11.8%) and other Asian countries (8.9%). Eighty-eight products (35.7%) from 27 brands were made in Western regions, specifically the USA (11.8%), European countries (21.5%), and Australia (2.4%). There are 4 brands that manufacture in multiple country include: cathy doll (Korea and Thailand), nivea (Europe and Thailand), biore (Japan and other Asian country) and neutrogena (Korea and USA). The percentage of products in different country and region are shown in Figure 4.1 and Figure 4.2. The list of brands in different country and region shown in Table 4.1.

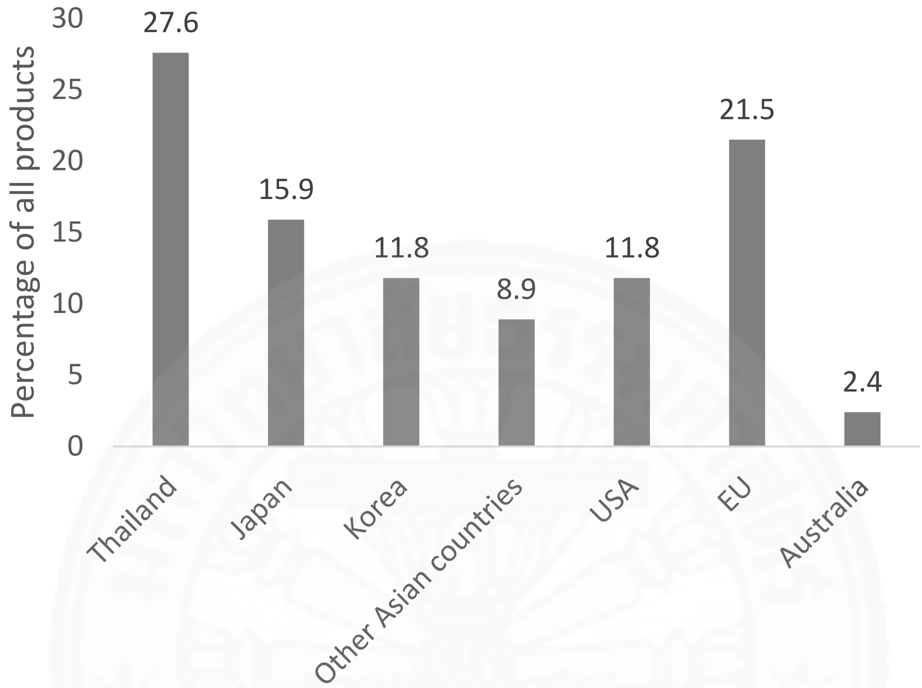

Figure 4.1 Frequency of UV filters in different country origin

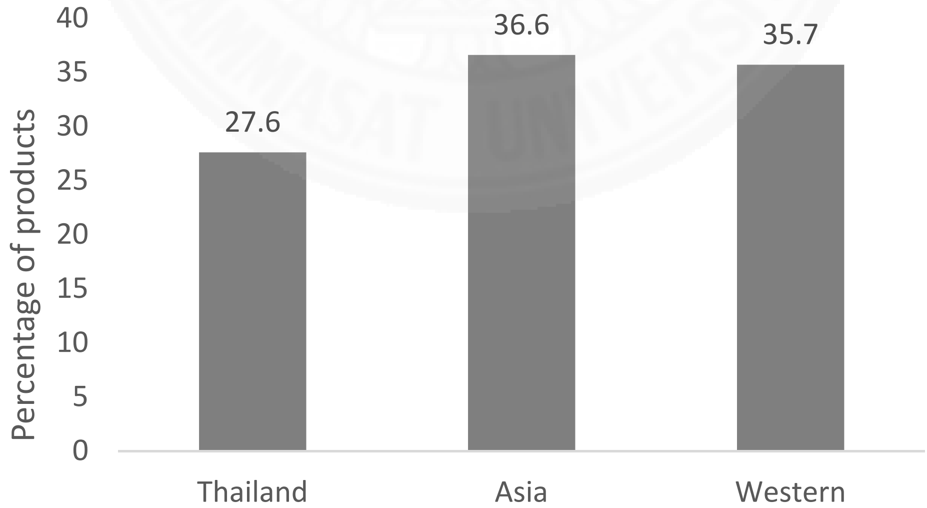

Figure 4.2 Frequency of UV filters in different regional origin

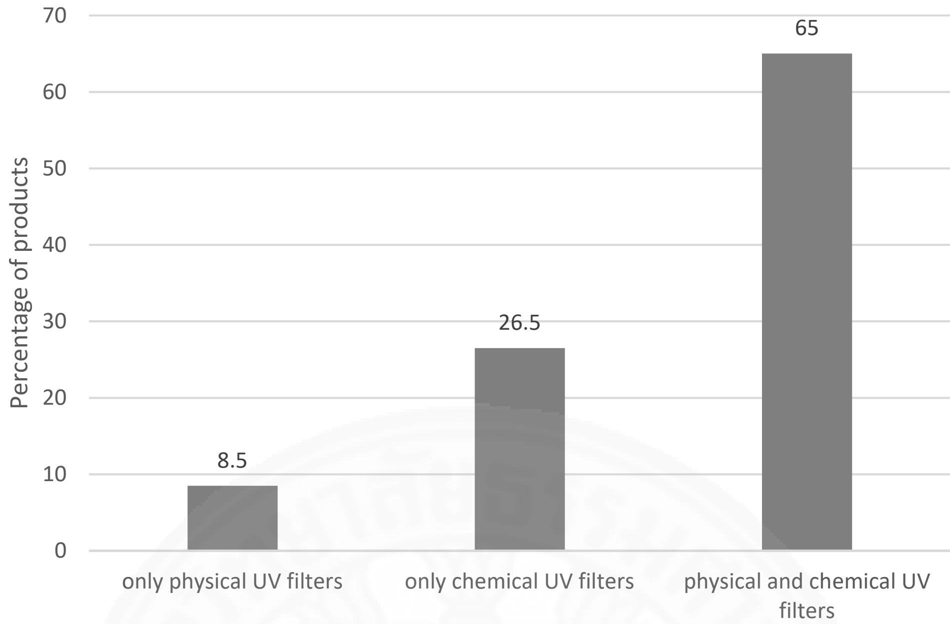

Figure 4.3 Frequency of type of UV filters in each sunscreen product

4.1.2 UV filters

Among the 246 examined products, 8.5% contained only physical UV filters, 26.5% contained only chemical UV filters, and 65% contained both physical and chemical UV filters (Figure 4.3). The 11 products that had only one UV filter contained physical UV filters (10 products) and a chemical UV filter (1 product).

None of the examined products was devoid of UV filters. Twenty-two UV filters were found in this study (Table 4.2 and Figure 4.4), 11 were UVB protectors, 6 were UVA protectors, and 5 were broad-spectrum (UVA+UVB) protectors (Figure 4.5). The 5 most common found UV filters in this study are EHMC, TiO, BMDM, OCR and BEMT.

Table 4.1 Brands and national/regional origin of examined sunscreen products available for sale on Thai market

Thailand		Asia						Western					
		Japan		Korea		Other Asian countries		USA		EU		Australia	
Brand	No.	Brand	No.	Brand	No.	Brand	No.	Brand	No.	Brand	No.	Brand	No.
Aliz Pauline	2	Allie	4	Cathy doll	1	1028 visual therapy	1	Babyganics	1	Avene	5	Cancer council	6
Amela-Ex	1	Anessa	8	Dr.Jart	1	Biore	7	BananaBoat	7	Bioderma	4	-	-
BB care	1	Aqualabel	2	Etude house	7	Divinia	1	Bobbi brown	1	Cetaphil	3	-	-
Beauty buffet	2	Biore	4	It's skin	1	Garnier	1	Dermalogica	2	Chanel	2	-	-
Beauty wise	1	Canmake	1	Laneige	3	Hada Labo	1	Elizabeth arden	1	Clarins	4	-	-
Bm.B	1	DHC	2	Neutrogena	4	Loreal paris	3	Estee lauder	2	Clinique	5	-	-
Boots	1	Kiss me	6	Premedica	1	Mentholatum	7	Hawaiian tropical	4	Eucerin	8	-	-
BSC	1	Lancome	2	Pure beauty	1	Za	1	Kiehl's	4	La roche-posay	6	-	-
C care	3	Senka	2	Saem	2	-	-	kiss my face	1	Nivea	2	-	-
Cathy doll	1	Shiseido	4	Skinfood	3	-	-	MAC	1	Papulex	1	-	-
Chohm	1	SK-II	3	Sulwhasoo	1	-	-	Neutrogena	1	Sebamed	1	-	-
COS	1	Suncut	1	The face shop	4	-	-	Paula's choice	4	Soltan	8	-	-
Cute press	2	-	-	-	-	-	-	-	-	Vichy	2	-	-
Dermaction	1	-	-	-	-	-	-	-	-	Yves rocher	2	-	-
Dermocare	2	-	-	-	-	-	-	-	-	-	-	-	-
D-nee	2	-	-	-	-	-	-	-	-	-	-	-	-
Dr.Somchai	1	-	-	-	-	-	-	-	-	-	-	-	-
Equilibrium	1	-	-	-	-	-	-	-	-	-	-	-	-
Ing organic	1	-	-	-	-	-	-	-	-	-	-	-	-
KA	1	-	-	-	-	-	-	-	-	-	-	-	-
Kodomo	1	-	-	-	-	-	-	-	-	-	-	-	-
Laurence	1	-	-	-	-	-	-	-	-	-	-	-	-
Luminese	1	-	-	-	-	-	-	-	-	-	-	-	-
Merci	1	-	-	-	-	-	-	-	-	-	-	-	-
Mistine	2	-	-	-	-	-	-	-	-	-	-	-	-
Nivea	8	-	-	-	-	-	-	-	-	-	-	-	-
Olay	1	-	-	-	-	-	-	-	-	-	-	-	-
Oriental princess	1	-	-	-	-	-	-	-	-	-	-	-	-
Origina	1	-	-	-	-	-	-	-	-	-	-	-	-
PO care	2	-	-	-	-	-	-	-	-	-	-	-	-
Poompuksa	1	-	-	-	-	-	-	-	-	-	-	-	-
Provamed	3	-	-	-	-	-	-	-	-	-	-	-	-
Rayshi	1	-	-	-	-	-	-	-	-	-	-	-	-
smooth E	1	-	-	-	-	-	-	-	-	-	-	-	-
Snail white	1	-	-	-	-	-	-	-	-	-	-	-	-
SpectraBan	3	-	-	-	-	-	-	-	-	-	-	-	-
The body shop	1	-	-	-	-	-	-	-	-	-	-	-	-
Vaseline	2	-	-	-	-	-	-	-	-	-	-	-	-
Viv skin	1	-	-	-	-	-	-	-	-	-	-	-	-
Watsons	7	-	-	-	-	-	-	-	-	-	-	-	-
Yura	1	-	-	-	-	-	-	-	-	-	-	-	-
Total	68	Total	39	Total	29	Total	22	Total	29	Total	53	Total	6

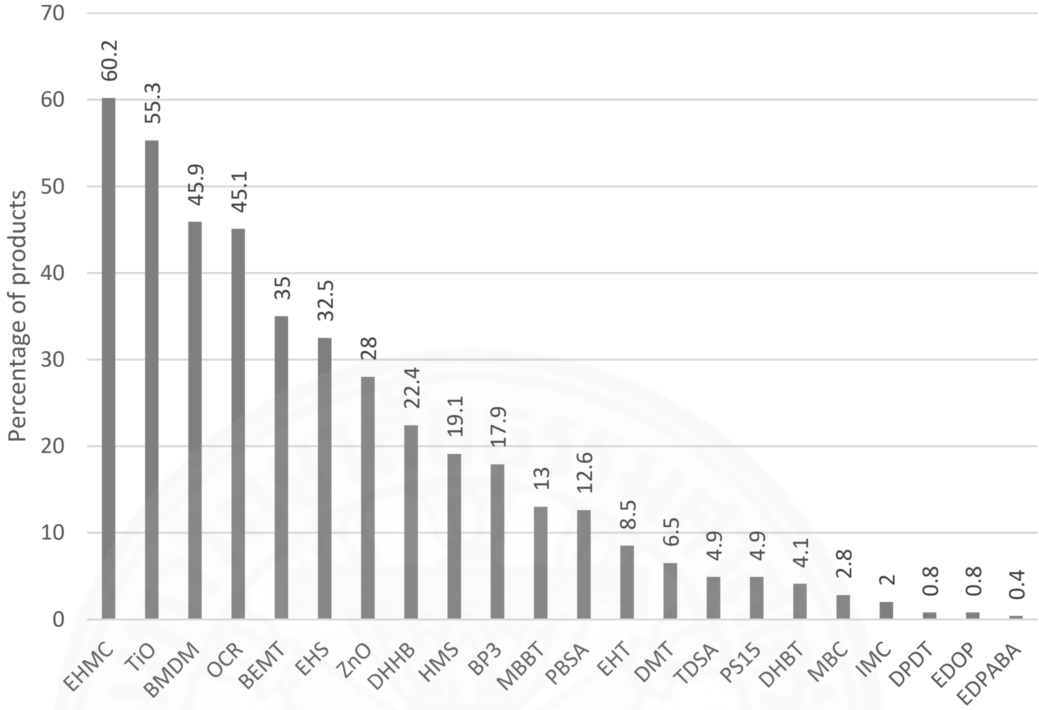

Figure 4.4 Frequency of 22 UV filters found in this study

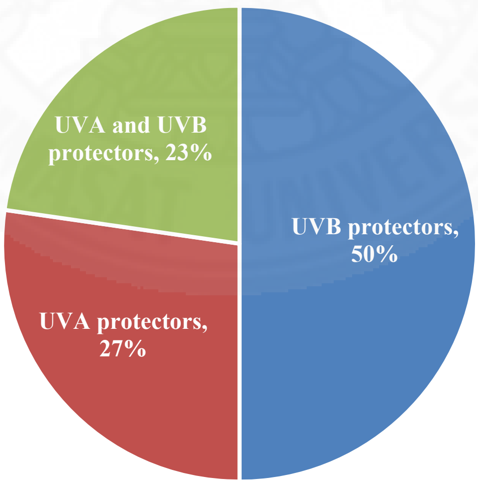

Figure 4.5 Protecting spectrum of UV filters found in this study

Table 4.2 Frequency of UV filters found in the study

INCI	Acronym	Spectrum	(%) n=246
Ethylhexyl methoxycinnamate[i]	EHMC	UVB	60.2
Titanium dioxide[i]	TiO	UVB, UVA2	55.3
Butyl methoxydibenzoylmethane[i]	BMDM	UVA1, UVA2	45.9
Octocrylene[i]	OCR	UVB, UVA2	45.1
Bis-ethylhexyloxyphenol methoxyphenyl triazine	BEMT	UVB, UVA1, UVA2	35.0
Ethylhexyl salicylate[i]	EHS	UVB	32.5
Zinc oxide	ZnO	UVB, UVA1, UVA2	28.0
Diethylamino hydroxybenzoyl hexyl benzoate	DHHB	UVA1	22.4
Homomenthyl salicylate[i]	HMS	UVB	19.1
Benzophenone-3[i]	BP3	UVB	17.9
Methylene bis-benzotriazolyl tetramethylbutylphenol	MBBT	UVB, UVA1	13.0
Phenylbenzimidazole sulfonic acid[i]	PBSA	UVB	12.6
Ethylhexyl triazone	EHT	UVB	8.5
Drometrizole trisiloxane	DMT	UVA2	6.5
Terephthalylidene dicamphor sulfonic acid	TDSA	UVA2	4.9
Polysilicone-15	PS15	UVB	4.9
Diethylhexyl butamido triazone	DHBT	UVB	4.1
4-Methylbenzylidene camphor	MBC	UVB	2.8
Isoamyl p-methoxycinnamate	IMC	UVB	2.0
Disodium phenyl dibenzimidazole tetrasulfonate	DPDT	UVA2	0.8
Ethylhexyl dimethoxybenzylidene oxoimidazoline propinoate	EDOP	UVA	0.8
Ethyl dihydroxypropyl PABA	EDPABA	UVB	0.4

INCI, International Nomenclature of Cosmetic Ingredients; SPF, Sun protection factor; UV, ultraviolet; [i] Worldwide approved UV filters

4.1.3 Sun protection factor (SPF)

The stated SPF ranged from 4 to 60 and was divided into four groups. Seventy-six percent of products were SPF ≥ 50 (Figure 4.6). One product stated "High UV protection," instead of SPF. The sunscreen products seemed to have higher SPF values, compare with those previously reported (213).

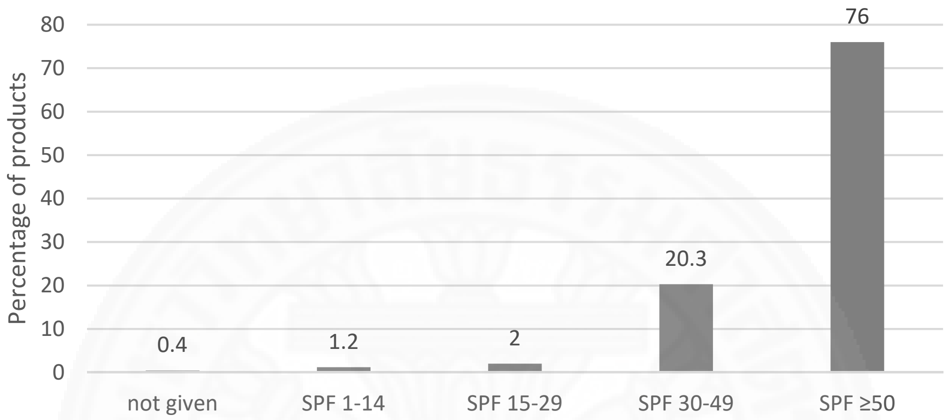

Figure 4.6 Frequency of SPF level stated on product label

4.1.4 Type of products

The types of sunscreen products investigated are shown in Figure 4.7, the most common type of sunscreen was in liquid form (54.9%).

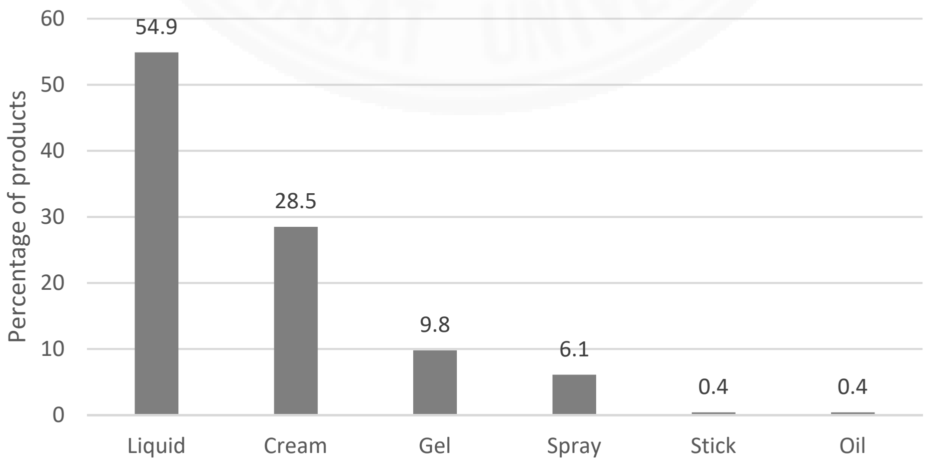

Figure 4.7 Frequency of type of sunscreen products

4.1.5 Water resistant properties

Ninety-nine products (40.2%) were labeled as "water resistant" or "waterproof" (Figure 4.8).

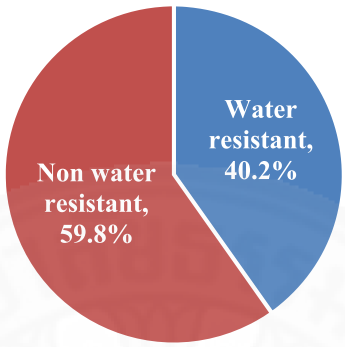

Figure 4.8 Frequency of water resistant products found in this study.

4.1.6 Specific descriptors

Twenty products (8.1%) were marketed for use in "children," "kids," or "babies"; forty-one products (16.6%) were labeled as being "sensitive" or "hypoallergenic"; and ten products (4.1%) were labeled as "physical sunscreen" (Figure 4.9).

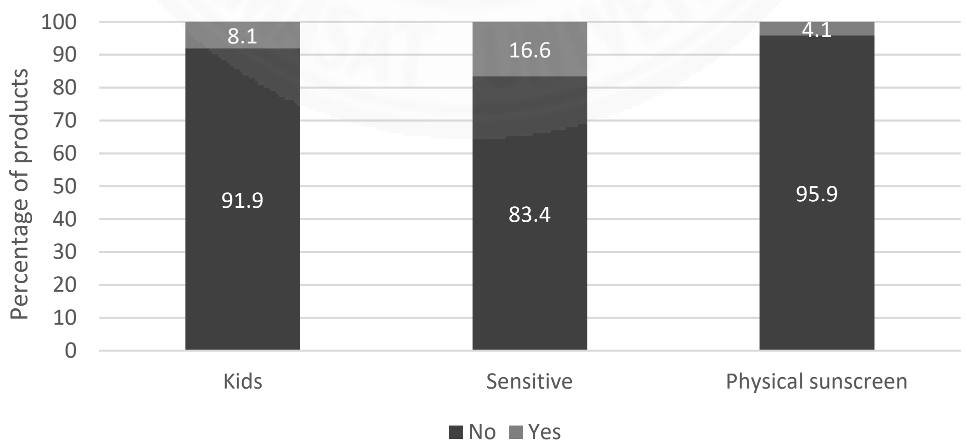

Figure 4.9 Frequency of Specific descriptors; Kids, Sensitive and physical sunscreen

4.1.7 Number of UV filters in each product

The number of UV filters in each product ranged from 1 to 9 (median of 4) (Figure 4.10).

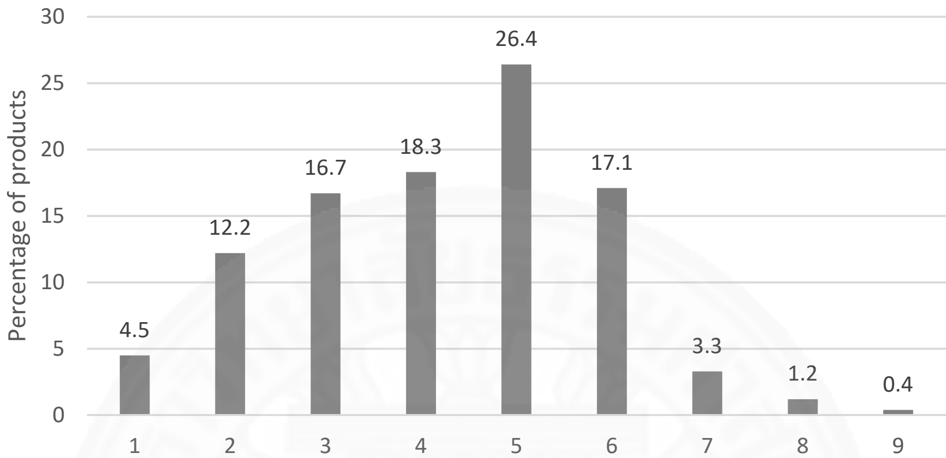

Figure 4.10 Number of UV filters in each sunscreen product

4.1.8 Price

The price of each product ranged from 0.4 to 105 Baht/unit (gram or mL), with a mean 17.1 (SD=17.48) Baht/unit.

4.2 Relation of UV filters and sunscreen properties

4.2.1 UV filters and product origin

In Thailand and Asia, the most common UV filter was ethylhexyl methoxycinnamate (EHMC), but EHMC was not common in the USA and Europe. Butyl methoxydibenzoylmethane (BMDM) was the most common UV filter found in Europe, USA, and Australia. BMDM was less common in Japan compared with the other regions. Benzophenone-3 (BP3), the most common UV filter allergen, was found in one-half and one-third of the sunscreen products from the USA and Thailand, respectively. BP3 was less common in products from Asia. The frequency of all UV filters in different origin found in this study are shown in Table 4.3 and Table 4.4

Table 4.3 The frequency of UV filters between different country origin

UV filters	All (%) N=246	Origin (%) Thailand N=68	Japan N=39	Korea N=29	Other Asian N=22	USA N=29	EU N=53	Australia N=6
EHMC	60.2	79.4	82.1	79.3	95.5	20.7	18.9	33.3
TiO	55.3	76.5	43.6	62.1	59.1	37.9	45.3	16.7
BMDM	45.9	55.9	5.1	37.9	4.5	65.5	67.9	100
OCR	45.1	44.1	41	37.9	4.5	58.6	56.6	100
BEMT	35.0	17.6	51.3	34.5	50	6.9	58.5	0
EHS	32.5	27.9	0	72.4	9.1	44.8	43.4	33.3
ZnO	28.0	26.5	56.4	34.5	40.9	17.2	9.4	0
DHHB	22.4	8.8	61.5	17.2	54.5	3.4	13.2	0
HMS	19.1	14.7	5.1	31	0	34.5	26.4	33.3
BP3	17.9	30.9	0	13.8	0	51.7	5.7	16.7
MBBT	13.0	13.2	7.7	3.4	9.1	0	28.3	33.3
PBSA	12.6	10.3	15.4	17.2	9.1	0	18.9	16.7
EHT	8.5	1.5	5.1	0	36.4	0	17	16.7
DMT	6.5	0	5.1	0	18.2	3.4	17	0
TDSA	4.9	0	2.6	0	13.6	3.4	13.2	0
PS15	4.9	1.5	20.5	0	13.6	0	0	0
DHBT	4.1	0	0	0	0	0	18.9	0
MBC	2.8	5.9	0	3.4	0	0	0	33.3
IMC	2.0	2.9	0	10.3	0	0	0	0
DPDT	0.8	0	0	0	9.1	0	0	0
EDOP	0.8	0	5.1	0	0	0	0	0
EDPABA	0.4	0	0	0	4.5	0	0	0

Table 4.4 The frequency of UV filters between different regional origin

UV filters	All (%) N=246	Regional origin (%)		
		Thailand N=68	Asia N=90	Western N=88
EHMC	60.2	79.4*	84.4*	20.5*
TiO	55.3	76.5*	53.3*	40.9*
BMDM	45.9	55.9*	15.6*	69.3*
OCR	45.1	44.1*	31.1*	60.2*
BEMT	35.0	17.6*	45.6*	37.5*
EHS	32.5	27.9	25.6	43.2
ZnO	28.0	26.5*	45.6*	11.4*
DHHB	22.4	8.8*	45.6*	9.1*
HMS	19.1	14.7*	12.2*	29.5*
BP3	17.9	30.9*	4.4*	21.6*
MBBT	13.0	13.2	6.7	19.3
PBSA	12.6	10.3	14.4	12.5
EHT	8.5	1.5	11.1	11.4
DMT	6.5	0	6.7	11.4
TDSA	4.9	0	4.4	9.1
PS15	4.9	1.5*	12.2*	0*
DHBT	4.1	0*	0*	11.4*
MBC	2.8	5.9	1.1	2.3
IMC	2.0	2.9	3.3	0
DPDT	0.8	0	2.2	0
EDOP	0.8	0	2.2	0
EDPABA	0.4	0	1.1	0

*$p<0.01$, compared between the same UV filter

4.2.2 UV filters and protection factor (SPF)

The frequency of UV filters between different SPF levels is shown in Table 4.5. EHMC is the most common found UV filter among all SPF levels. OCR, BEMT and DHHB are significantly ($p<0.01$) different between SPF<50 and SPF≥50 products (Figure 4.11).

Table 4.5 The frequency of UV filters between different SPF level

UV filters	All (%) N=246	SPF levels (%)			
		SPF 1-14 N=3	SPF15-29 N=5	SPF 30-49 N=50	SPF≥50 N=187
EHMC	60.2	66.7	60	70	57.8
TiO	55.3	33.3	40	54	56.1
BMDM	45.9	33.3	20	38	49.2
OCR	45.1	33.3	40	22	51.9
BEMT	35.0	0	20	20	40.1
EHS	32.5	0	20	22	36.4
ZnO	28.0	0	40	34	26.2
DHHB	22.4	0	0	8	27.3
HMS	19.1	0	20	10	21.9
BP3	17.9	33.3	0	12	19.8
MBBT	13.0	0	20	6	15
PBSA	12.6	0	40	14	11.8
EHT	8.5	0	0	2	10.7
DMT	6.5	0	0	0	8.6
TDSA	4.9	0	0	0	6.4
PS15	4.9	0	0	0	6.4
DHBT	4.1	0	0	2	4.8
MBC	2.8	0	0	2	3.2
IMC	2.0	0	0	4	1.6
DPDT	0.8	0	0	0	1.1
EDOP	0.8	0	0	2	0.5
EDPABA	0.4	0	0	0	0.5

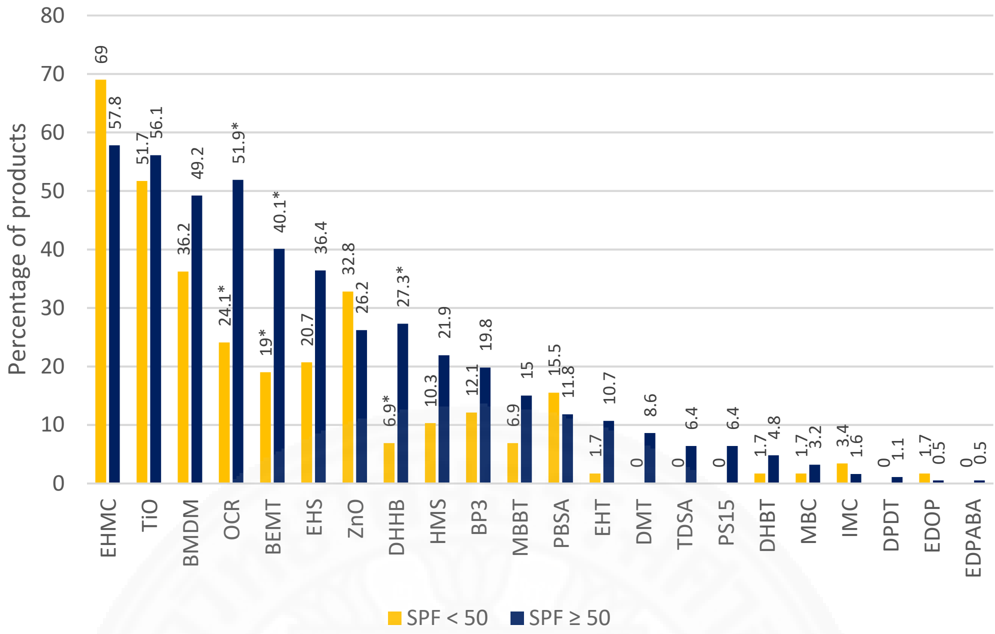

Figure 4.11 Comparison of UV filters between SPF<50 and SPF≥50 products
*p<0.01, compared between the same UV filter

4.2.3 UV filters and type of products

EHMC is the most common UV filter in liquid and gel type of sunscreen, while TiO and BEMT are the most common UV filter in cream and spray type, respectively. The frequency of all UV filters in different type of products are shown in Table 4.6 and Figure 4.12

Table 4.6 The frequency of UV filters between different type of products

UV filters	All (%) N=246	Type of sunscreen (%)					
		Liquid N=135	Cream N=70	Gel N=24	Spray N=15	Stick N=1	Oil N=1
EHMC	60.2	59.3	54.3	91.7	40	100	100
TiO	55.3	53.3	72.9	37.5	56.1	100	0
BMDM	45.9	48.1	45.7	16.7	80	0	0
OCR	45.1	49.6	35.7	25	80	100	0
BEMT	35.0	29.6	28.6	62.5	66.7	100	0
EHS	32.5	29.6	35.7	20.8	60	100	0
ZnO	28.0	28.9	34.3	20.8	6.7	0	0
DHHB	22.4	18.5	7.1	83.3	26.7	100	0
HMS	19.1	21.5	12.9	8.3	46.7	0	0
BP3	17.9	22.2	17.1	4.2	6.7	0	0
MBBT	13.0	14.1	12.9	8.3	13.3	0	0
PBSA	12.6	16.3	5.7	8.3	20	0	0
EHT	8.5	7.4	4.3	16.7	26.7	0	0
DMT	6.5	6.7	5.7	8.3	6.7	0	0
TDSA	4.9	5.9	5.7	0	0	0	0
PS15	4.9	2.2	1.4	20.8	20	0	0
DHBT	4.1	3.7	5.7	0	6.7	0	0
MBC	2.8	3.7	2.9	0	0	0	0
IMC	2.0	1.5	2.9	4.2	0	0	0
DPDT	0.8	0.7	0	4.2	0	0	0
EDOP	0.8	1.5	0	0	0	0	0
EDPABA	0.4	0	0	4.2	0	0	0

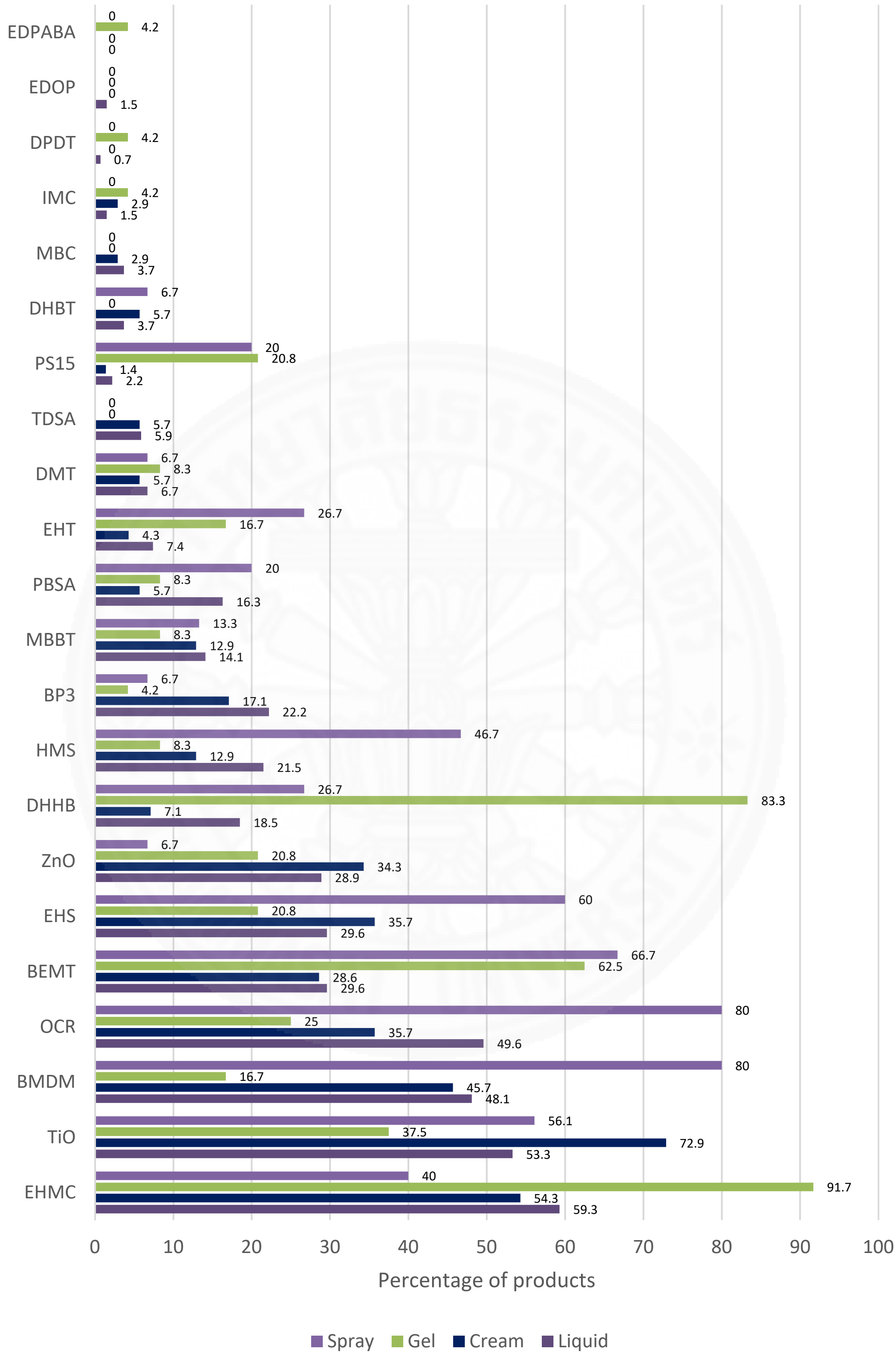

Figure 4.12 Comparison of UV filters between type of sunscreen products

4.2.4 UV filters and water resistant property

Bis-ethylhexyloxyphenol methoxyphenyl triazine (BEMT) and diethylhexyl butamido triazone (DHBT) were found more frequently (p = 0.001 and p = 0.009, respectively) in water resistance products than the groups that did not declare water resistance (Figure 4.13).

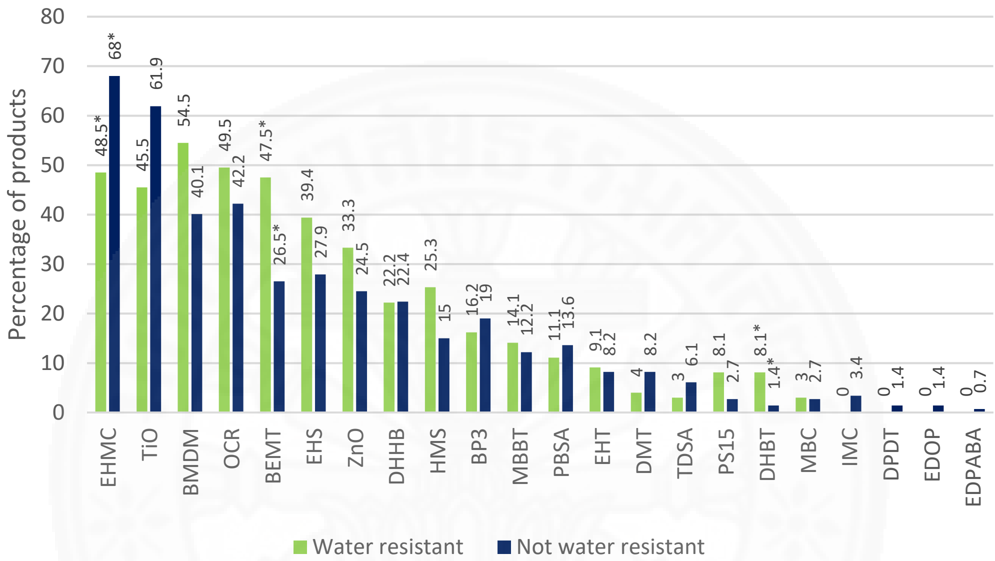

Figure 4.13 Comparison of UV filters between water resistant and non-water resistant products; *p<0.01, compared between the same UV filter

4.2.5 UV filters and specific descriptors

Forty-one products (16.6%) were labeled as being "sensitive" or "hypoallergenic." EHMC and diethylamino hydroxybenzoyl hexyl benzoate (DHHB) were found less frequently (p = 0.000 and p = 0.003, respectively) in this group, while methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT) was found more frequently (p = 0.001) (Figure 4.14 and Table 4.7). The presence of BP3, BMDM, and octocrylene (OCR) was not significantly different between "sensitive" and not "sensitive" products. There were 10 products that were labeled "Physical sunscreen product", and all of them contained only physical UV filters.

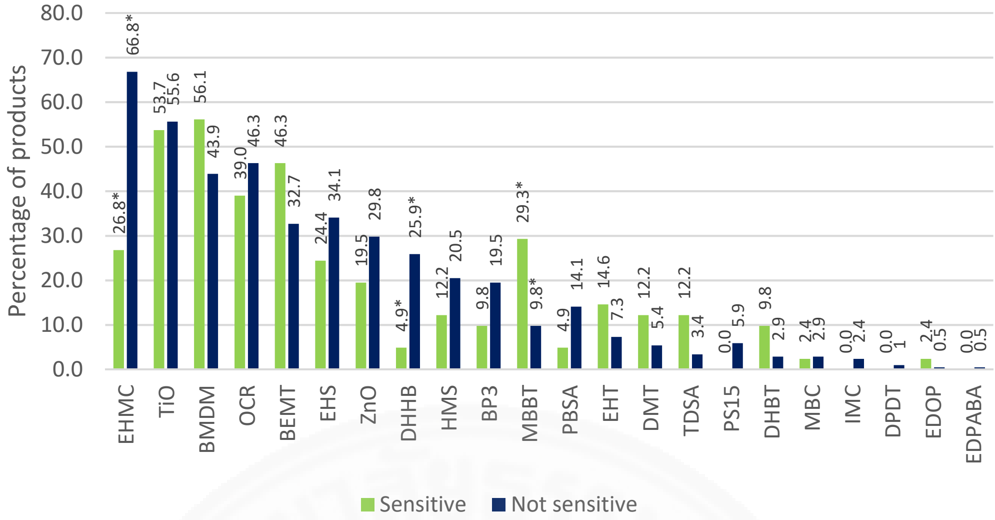

Figure 4.14 Comparison of UV filters between sensitive and non-sensitive products
*p<0.01, compared between the same UV filter

The usage of physical UV filters was not different between "Kids" and not "Kids" products. EHMC and BP3 were found less frequently in product labeled for kids ($p = 0.004$ and $p = 0.029$, respectively) (Figure 4.15).

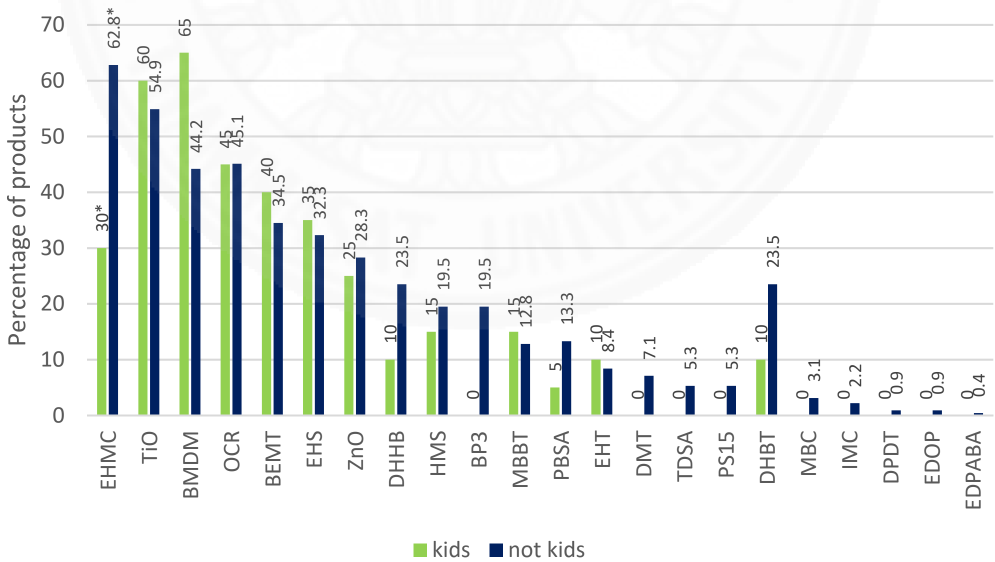

Figure 4.15 Comparison of UV filters between kids and non-kids products
*p<0.01, compared between the same UV filter

Table 4.7 The frequency of UV filters between water resistant, sensitive and kids

UV filters	All (%)	Water resistant (%)		Sensitive (%)		Kids (%)	
		Not indicated	Yes	Not indicated	Yes	Not indicated	Yes
	N=246	N=147	N=99	N=205	N=41	N=226	N=20
EHMC	60.2	59.3	54.3	91.7	40	100	100
TiO	55.3	53.3	72.9	37.5	56.1	100	0
BMDM	45.9	48.1	45.7	16.7	80	0	0
OCR	45.1	49.6	35.7	25	80	100	0
BEMT	35.0	29.6	28.6	62.5	66.7	100	0
EHS	32.5	29.6	35.7	20.8	60	100	0
ZnO	28.0	28.9	34.3	20.8	6.7	0	0
DHHB	22.4	18.5	7.1	83.3	26.7	100	0
HMS	19.1	21.5	12.9	8.3	46.7	0	0
BP3	17.9	22.2	17.1	4.2	6.7	0	0
MBBT	13.0	14.1	12.9	8.3	13.3	0	0
PBSA	12.6	16.3	5.7	8.3	20	0	0
EHT	8.5	7.4	4.3	16.7	26.7	0	0
DMT	6.5	6.7	5.7	8.3	6.7	0	0
TDSA	4.9	5.9	5.7	0	0	0	0
PS15	4.9	2.2	1.4	20.8	20	0	0
DHBT	4.1	3.7	5.7	0	6.7	0	0
MBC	2.8	3.7	2.9	0	0	0	0
IMC	2.0	1.5	2.9	4.2	0	0	0
DPDT	0.8	0.7	0	4.2	0	0	0
EDOP	0.8	1.5	0	0	0	0	0
EDPABA	0.4	0	0	4.2	0	0	0

4.3 Relation of number of UV filters and sunscreen properties

4.3.1 Number of UV filters and product origin

The number of UV filters in each product were not significantly different between product origin. The number of UV filters in each product according to their origin shown in Figure 4.16.

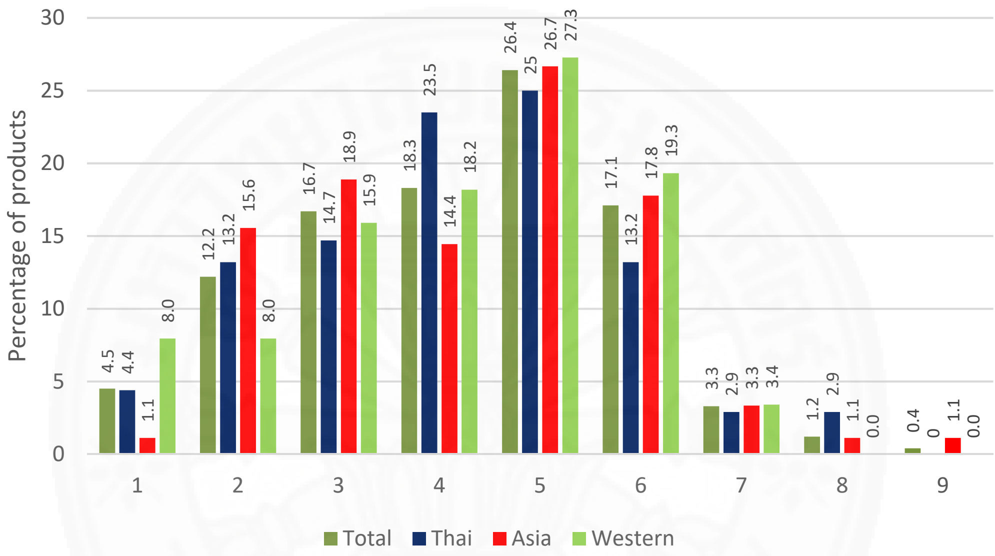

Figure 4.16 The number of ultraviolet filters in each sunscreen product according to their origin of manufacture

4.3.2 Number of UV filters and sun protection factor

High SPF levels significantly correlated with high numbers of UV filters ($p<0.001$). The number of UV filters in each product according to SPF levels shown in Figure 4.17.

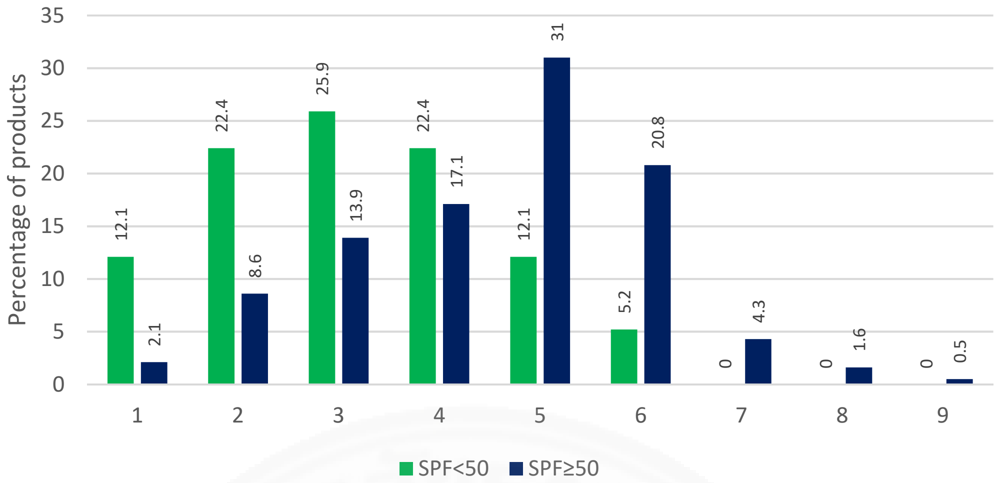

Figure 4.17 The number of ultraviolet filters in each sunscreen product according to SPF levels

4.3.3 Number of UV filters and type of products

The number of UV filters in each product were significantly ($p=0.021$) different between type of products. Spray type sunscreen has the highest mean of number of UV filters in each product. The number of UV filters in each product according to type of sunscreen products shown in Figure 4.18 and Table 4.8.

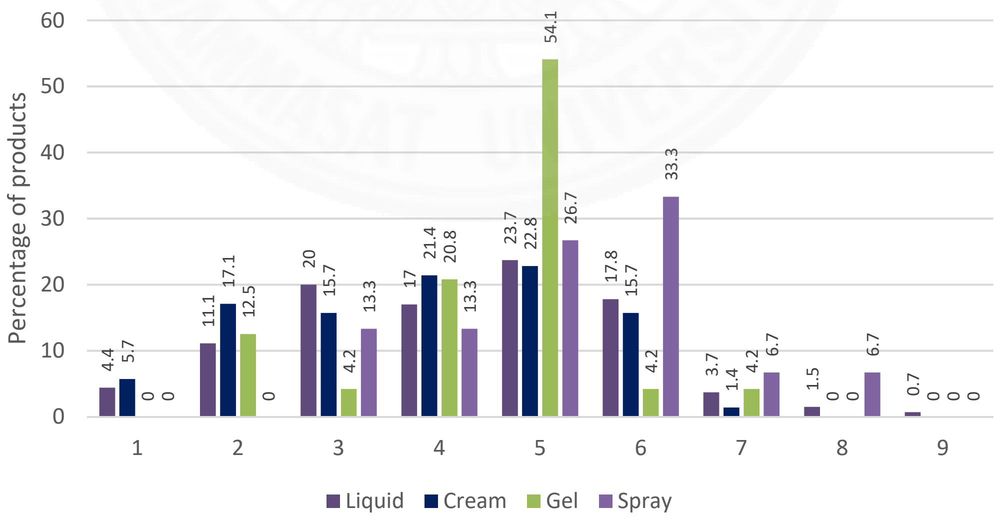

Figure 4.18 The number of ultraviolet filters in each sunscreen product according to type of sunscreen products

Table 4.8 Mean of the number of ultraviolet filters in different type of sunscreen products

Type	Number of UV filters in each product		
	N	Mean	S.D.
Cream	70	3.91	1.54
Liquid	135	4.24	1.65
Spray	15	5.27	1.39
Gel	24	4.46	1.22
p-value		0.021	

P-value corresponds to ANOVA test.

4.3.4 Number of UV filters and price

The price of each product ranged from 0.4 to 105 Baht/unit (gram or mL), with a mean 17.1 Baht/unit. There was no significant correlation (r = -0.122, p = 0.056) between price and number of UV filters in each product (Figure 4.19).

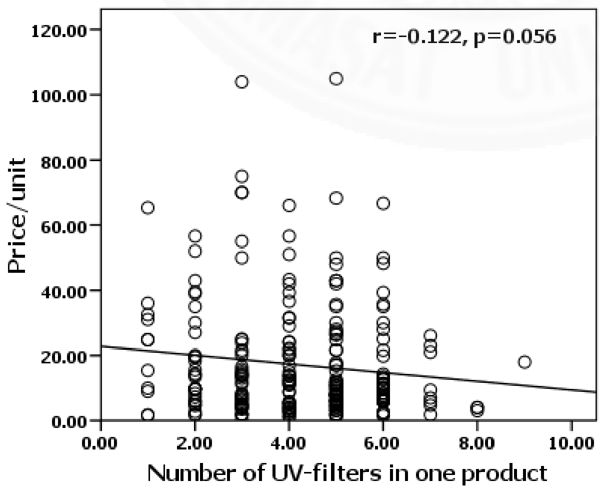

Figure 4.19 Correlation between price and number of UV filters in each product

CHAPTER 5
DISCUSSION AND RECOMMENDATION

5.1 Discussion

This is the first market survey of sunscreen ingredients and properties from Asia. Market surveys of sunscreen ingredients have been conducted in Denmark, the United Kingdom, Switzerland, and Germany (213,235,236,295). More than half of the sunscreen products that we evaluated were produced in various countries across three continents. In this study, the median number of UV filters in each sunscreen product was four, which is similar to that found in other studies (213,235,236). The high number of UV filters explains why sunscreens are the main cause of photoallergic contact dermatitis (180). Co-exposure to many chemical filters, mainly in sunscreens, may explain the multiple allergic reactions to UV filters, often from unrelated chemical groups (177). In this study, sunscreen products that were manufactured in Europe, have common UV filters that are similar to those found in many European studies (213,235,236). In a previous review about adverse reactions to sunscreen agents, the common UV filters that caused allergic reactions were BP3, isopropyl dibenzoylmethane, BMDM, OCR, para-aminobenzoic acid (PABA), EHMC, ethylhexyl dimethyl PABA, benzophenone-4, 4-methylbenzylidene camphor (MBC), benzophenone-10, MBBT, and phenylbenzimidazole sulfonic acid (PBSA) (5). Five of these; namely isopropyl dibenzoylmethane, PABA, ethylhexyl dimethyl PABA, benzophenone-8, and benzophenone-10, were not available for our study.

EHMC was the most common UV filter found in this study (60.2%). EHMC is significantly more common in sunscreens that are produced in Asia than those produced in Europe and USA. This chemical has poor water solubility and is often used in sunscreens marketed as waterproof (154). However, our results demonstrated that EHMC are frequently found in sunscreen products that are not labeled as water-resistant. Moreover, products that are labeled for sensitive skin or for Kids/Children frequently contain EHMC. Sensitivities to EHMC in children have been reported in photopatch testing in children (172). Although EHMC is common in sunscreen products from Asia, photopatch test studies in Asia did not show positive reactions to EHMC (6,170,181). However, there was a reported positive patch test reaction to EHMC in Thailand (8). Compared to the frequency of exposure to EHMC, the incidence allergic contact dermatitis and photoallergic contact dermatitis is low (222). Therefore, EHMC is regarded as a weak sensitizer (5).

BP3 is the most common UV filter to cause allergic reactions in many studies (173). The benzophenone group was named allergen of the year for 2014 by the American Contact Dermatitis Society (211). BP3 was found in 17.9% of sunscreen products in our study. Half of the sunscreen products from the USA were labeled as containing BP3 , which is consistent with that reported in other studies (297). One-third of sunscreen products from Thailand were labeled as containing BP3. We did not find BP3 in Japanese sunscreen products. BP3 was less commonly found in products from Europe, which is similar to that found in other studies (213,235,236). Both sensitive and non-sensitive sunscreen products were found to contain BP3. A recent photopatch test study in Thailand showed that BP3 is the most common causative agent of skin sensitivity (6). Considering the low prevalence of BP3 in Thailand compared to that of other UV filters, the high allergy incidence may be due to cross-reactions with ketoprofen or OCR, information that is still lacking in Thailand. Therefore, cross-reactions between BP3 and ketoprofen or OCR might be a concern to patients who have sensitivities to BP3.

Benzophenone-4 has been reported as a contact allergen in many studies (177,178,298). A study in Thailand has also reported allergic reactions to benzophenone-4 (7). However, Benzophenone-4, although found in other non-sunscreen cosmetics, was not found in our study , which is similar to the findings of other recent studies (235,236,295).

An increasing number of patients have been reported with photocontact allergies to OCR, another common UV filter, especially adults who have been previously sensitized to ketoprofen (282). Contact allergies to OCR are more common in children than in adults (224,271). OCR is used to stabilize other UV filters (273). From our study, OCR was found in 45.1% of investigated sunscreen products, lower than recently reported from Europe (213,236). The “SPF $\geq$ 50” sunscreens more frequently contained OCR than "SPF < 50" sunscreens did ($p < 0.001$). There were no differences in OCR frequency between "Kids" and non-"Kids" products.

BMDM was the most common UV filter from a European study (213,235,236). In our study, BMDM was found in 45.9% of investigated products, the fourth most common filter, yet only one-half the frequency observed in the abovementioned European study. The sunscreen products from Asia, except Thailand, had the lowest prevalence of BMDM. Allergies to BMDM have been widely reported in Europe and the USA (177,178,299). This UV filter is rarely reported to caused allergy in Thailand and Asia, which may be the reason that "patch tests" and "photopatch tests" used in many Asian studies did not include BMDM (6,170,171). Based on this information, BMDM should be a concern to cause allergic reactions because it was found in a large number of sunscreen products sold in Thailand.

MBBT is a newer agent that can act both as a physical and chemical blocker (287). A recent European multicenter patch study revealed that MBBT was the most common UV filter leading to allergic contact dermatitis (299). MBBT induces contact dermatitis because of the surfactant, decyl glucoside, which is necessary to solubilize MBBT (300,301). MBBT was found in 13% of our investigated products, a similar frequency to that of some other studies (235,236). From our study, this agent was more commonly found in sensitive products than in non-sensitive products, a difference that was statistically significant ($p = 0.001$).

Photo-instability of UV filters leads to reduced protective capacity and generates toxic photodegradation products (302). BMDM and EHMC are major photo-unstable UV filters, especially when combined together (273). OCR and BEMT are used to stabilize BMDM. In our study, BMDM and EHMC were found together in 47 products (19.1%). Thirty-three domestic products (48.5%) contained these two agents together. Ninety-two products (81.4%) that contain BMDM also have OCR and/or BEMT. More than 90% of products from Western countries that contain BMDM also have OCR and/or BEMT. Therefore, although many sunscreen products contain photo-unstable UV filters, especially BMDM, most also have UV filter stabilizers, such as OCR and BEMT, which should minimize photo-instability.

The largest reported series of photopatch testing in children, 157 children in the UK, showed that the most frequent allergens are BP3 and EHMC (172). These

UV filters were found to be less common in “Kids” products analyzed in our study. Although BP3, the most common photoallergy UV filter in children, was not commonly found in the “Kids” sunscreen in our study, OCR was found and cross-reaction may occur. Therefore, despite “Kids” sunscreens having fewer apparent allergenic UV filters, cross-reaction should still be a concern. From literature’s review, there is no regulation for claim use in “kids”, “babies” or “sensitive/hypoallergenic skin” on sunscreen product neither the USA or Europe. So, claim use for these words should be regulated in order to represent the proper ingredients.

The frequency of UV filters labeled on sunscreen products was compared with that of other UK studies, which surveyed the ingredients from product labels in 2005 (296) and 2010 (213) (Table 5.1). The common potential sensitizing UV filters were compared among studies during the past 10 years, including any that surveyed product labels or used laboratory analyses of the ingredients. The results are shown in Figure 5.1.

Comparing to the photopatch/patch test study in Thailand (Table 5.2), the frequency of UV filters is not correlated with a number of allergic reaction of that UV filters. This may be due to the allergic reaction of UV filters that mainly depend on its own allergic capacity and the photopatch test study in Thailand are a single center study and the sample are small.

The limitation of this study, unable to verify the ingredients that labeled on the sunscreen products are actually existing in the products and not able to obtain all of the sunscreen product brand that available in the market due to missing out or inaccessibility**.**

This study has provided current consumer exposure data to UV filters in sunscreen products that are available in Thailand, which is the first market survey of UV filters in sunscreens in Asia. This should be useful information to determine which agents to include in patch or photopatch test series and to provide benchmark data for future studies in this field.

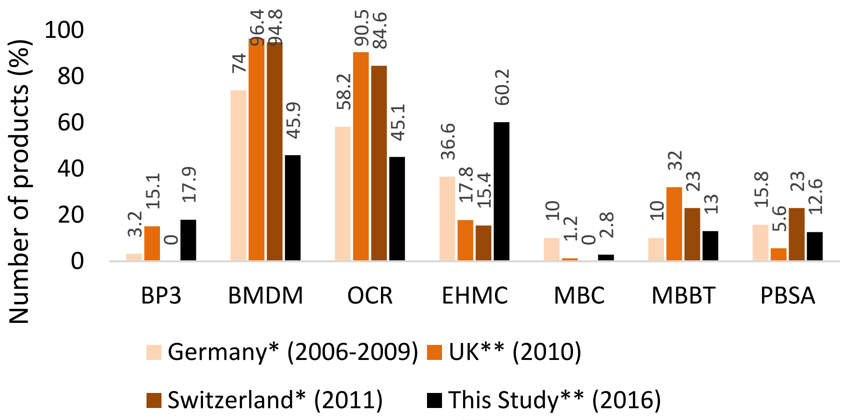

Figure 5.1 Comparison of common potential sensitizing ultraviolet filters during the past 10 years of available studies. *survey products and laboratory analysis study. **survey products label study.

Table 5.1 Frequency of UV filters present in sunscreen products labeled in the current study compared with those in the 2010 and 2005 UK studies

UV filter (INCI name)	UV filters present in percentage of products		
	Current survey (2016) n=246	UK (2010) n=316	UK (2005) n=308
Ethylhexyl methoxycinnamate	60.2	17.8	53.6
Titanium dioxide	55.3	49	45.1
Butyl methoxydibenzoylmethane	45.9	96.4	73.4
Octocrylene	45.1	90.5	36.4
Bis-ethylhexyloxyphenol methoxyphenyl triazine	35.0	58.5	15.9
Ethylhexyl salicylate	32.5	32.6	20.8
Zinc oxide	28.0	N	N
Diethylamino hydroxybenzoyl hexyl benzoate	22.4	5	1
Homomenthyl salicylate	19.1	15.7	2.3
Benzophenone-3	17.9	15.1	16.9
Methylene bis-benzotriazolyl tetramethylbutylphenol	13.0	32	7.8
Phenylbenzimidazole sulfonic acid	12.6	5.6	4.9
Ethylhexyl triazone	8.5	16	14.9
Drometrizole trisiloxane	6.5	13.4	11
Terephthalylidene dicamphor sulfonic acid	4.9	14.2	14.6
Polysilicone-15	4.9	3.3	2.6
Diethylhexyl butamido triazone	4.1	32	10.4
4-Methylbenzylidene camphor	2.8	1.2	25.3
Isoamyl p-methoxycinnamate	2.0	0.9	0
Disodium phenyl dibenzimidazole tetrasulfonate	0.8	0.9	1.9
Ethylhexyl dimethoxybenzylidene oxoimidazoline propinoate	0.8	N	N
Ethyl dihydroxypropyl PABA	0.4	N	N

Table 5.2 Frequency of UV filters present in sunscreen products labeled in the current study compared with the frequent of allergic reaction to UV filters in photopatch test study conducted in Thailand and Europe.

UV filters	Frequency in sunscreen products in this study (%)	Number of allergic reaction to UV filters					
		PACD			ACD		
		IOD[1] 2000-2009 n=72	RAMA[2] 2001-2014 n=34	EU[3] 2008-2011 n=346	IOD[1] 2000-2009 n=48	RAMA[2] 2000-2014 n=64	EU[3] 2008-2011 n=55
Ethylhexyl methoxycinnamate, Octinoxate	60.2	-	1(2.9%)	7(2%)	-	-	2(3.6%)
Butyl methoxydibenzoylmethane, Avobenzone	45.9	-	1(2.9%)	18(5.2%)	-	-	3(5.5%)
Octocrylene	45.1	-	-	41(11.8%)	-	-	7(12.7%)
Bis-ethylhexyloxyphenol methoxyphenyl triazine, Bemotrizinol	35	-	1(2.9%)	3(0.9%)	-	-	1(1.8%)
Ethylhexyl salicylate, Octisalate	32.5	-	-	2(0.6%)	-	3(4.7%)	1(1.8%)
Diethylamino hydroxybenzoyl hexyl benzoate, Uvinul A plus	22.4	-	-	4(1.2%)	-	-	1(1.8%)
Homosalate	19.1	-	-	1(0.3%)	-	-	-
Benzophenone-3, Oxybenzone	17.9	5(6.9%)	5(14.7%)	37(10.37%)	6(12.5%)	-	6(10.9%)
Methylene bis-benzotriazolyl tetramethylbutylphenol, Bisoctrizole	13	-	1(2.9%)	5(1.4%)	-	-	11(20%)
Phenylbenzimidazole sulfonic acid, Ensulizole	12.6	-	-	-	-	1(1.6%)	-
Terephthalylidene dicamphor sulfonic acid, Ecamsule	4.9	-	-	-	-	-	4(7.3%)
4-Methylbenzylidene camphor, Enzacamene	2.8	-	-	3(0.9%)	-	-	4(7.3%)
Isoamyl p-methoxycinnamate	2	-	1(2.9%)	10(2.9%)	-	-	2(3.6%)
PABA	-	-	-	-	-	-	-
Benzophenone-4, Sulisobenzone	-	-	-	3(0.9%)	-	2(3.1%)	-
Benzophenone-10 ,Mexenone	-	-	4(11.7%)	-	-	-	-

[1] Photopatch test study by Institue of Dermatology Thailand, test substances (Chemotechnique Diagnosis®, Vellinge, Sweden) include 7 UV filters

[2] Photopatch test study by Ramathibodi hospital Thailand, Patch tested allergens(modified European baseline series with additional allergens relevant in our centre), photopatch allergens(Scandinavian standard photopatch series, NSAIDS and sunscreen series)

[3] Photopatch test study in Europe, test substances (Chemotechnique Diagnosis®, Vellinge, Sweden) include 19 UV filters

PACD; Photoallergic contact dermatitis, ACD; Allergic contact dermatitis

5.2 Recommendations

1) Further studies in the prevalence of UV filters in personal care products other than sunscreen.
2) Further studies in the prevalence of UV filters by using laboratory analysis.
3) Further studies in multicenter photopatch testing in Thai population.
4) Clinical application: The regulation of claim use for “kids/baby” or “sensitive/hypoallergenic” on sunscreen product shold be established in order to represent a proper ingredient.

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APPENDICES

APPENDIX A
LIST OF UV FILTERS NAME AND SYNONYMS

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
Benzophenone-2	Benzophenone-2	BP2	-AEC Benzophenone-2 (A & E Connock (Perfumery & Cosmetics) Ltd, Hampshire, UK) -Helisorb-10 (Norquay Technology Incorporated, Chester, PA) -OriStar BP2 (Orient Stars LLC, Carson, CA) -Protaphenone-2 (Protameen Chemicals, Totowa, NJ)	UVB
Benzophenone-3	Oxybenzone	BP3	-2-hydroxy-4-methoxybenzophenone -AEC Benzophenone-3 (A & E Connock Perfumery & Cosmetics, Ltd) -CSS-II Sun Screening Agent (Spec-Chem Industry Inc, Nanjing, People's Republic of China) -Eusolex 4360 (EMD Chemicals, Philadelphia, PA) -Escalol 567 (Ashland, Inc, Wilmington, DE) -EUSORB 228 (Aceto Corporation, Lake Success, NY) -Jeescreen Benzophenone 3 (Jeen International Corporation, Fairfield, NJ) -Neo Heliopan BB (Symrise, Teterboro, NJ) -OriStar BP3 (Orient Stars LLC, Carson, CA) -Protaphenone-3 (Protameen Chemicals, Totowa, NJ) -Uvasorb MET/C (3V Group, Georgetown, SC)	UVB, UVA2

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
Benzophenone-4	Sulisobenzone	BP4	-AEC Benzophenone-4 (A & E Connock (Perfumery & Cosmetics) Ltd) -Chemysorb 4 (Chemyunion Quı´mica Ltda) -CSS-IV Sun Screening Agent (Spec-Chem Industry Inc) -Custom B-4 (Custom ngredients, Inc.) -Escalol 577 (Ashland Inc) -OriStar BP4 (Orient Stars LLC) -Protaphenone-4 (Protameen Chemicals) -Uvasorb S5 (3V Group) -Uvinul MS 40 (BASF Corporation) -UVSOB 340 (LC United Chemical Corp)	UVB, UVA2
Benzophenone-8	Dioxybenzone	BP8	-2,2'-dihydroxy-4-methoxybenzophenone -AEC Benzophenone-8 (A & E Connock Perfumery & Cosmetics, Ltd, Fording Bridge, UK)	UVB, UVA2
Benzophenone-10	Mexenone	BP10	-Uvistat 2-hydroxy-4-methoxy-4'- methylbenzophenone	UVB
Benzyl salicylate	Benzyl salicylate	BZS	-Benzyl 2-hydroxybenzoate -Phenylmethyl 2-hydroxybenzoate	UVB
Bis-ethylhexyloxyphenol methoxyphenyl triazine	Bemotrizinol	BEMT	-Tinosorb S (BASF Corp, Florham Park, NJ)	UVB, UVA1, UVA2

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
Butyl methoxy-dibenzoyl-methane	Avobenzone	BMDM	-Parsol 1789 (DSM Nutritional Products, Inc., Parsippany, NJ) -Eusolex 9020 (EMD Chemicals, Philadelphia, PA) -OriStar ABZ (Orient Stars LLC, Carson, CA) -Neo Heliopan 357 (Symrise, Teterboro, NJ) -UVSOB A (LC United Chemical Corp, Taiwan, People's Republic of China)	UVA1, UVA2
Cinoxate	Cinoxate	CNX	-2-ethoxyethyl p-methoxycinnamate -GivTan F	UVB
Diethylamino hydroxybenzoyl hexyl benzoate	Uvinul A Plus (BASF Corporation, Florham Park, NJ)	DHHB	-Alpha-glycerol ester of ortho-amino-meta (2,3 dihydroxypropoxy) benzoic acid	UVA1
Diethylhexyl butamido triazone	Iscotrizinol	DHBT	-Uvasorb HEB (3V Group, Georgetown, SC)	UVB
Disodium phenyl dibenzimidazole tetrasulfonate	Bisdisulizole disodium	DPDT	-Neo Heliopan AP (Symrise, Teterboro, NJ)	UVA1
Drometrizole trisiloxane	Mexoryl XL (Chimex, Le Thillay, France)	DMT	-	UVA2
Ethyl cinnamate	Ethyl cinnamate	EHC	-Ethyl Benzylideneacetate -AEC Ethyl Cinnamate (A & E Connock (Perfumery & Cosmetics) Ltd, Hamphire, UK)	UVB

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
Ethylhexyl dimethyl PABA	Padimate O	EPABA	-Octyl dimethyl PABA -Escalol 507 (Ashland, Inc, Wilmington, DE) -Uvasorb DMO (3V Group, Georgetown, SC)	UVB
Ethylhexyl methoxycinnamate	Octinoxate	EHMC	-Octyl methoxycinnamate -AEC ethylhexyl methoxycinnamate (A & E Connock Perfumery & Cosmetics Ltd, Hampshire, UK) -Custoscreen OMC (Custom Ingredients, Inc, Chester, SC) -Escalol 557 (Ashland, Wilmington, DE) -Heliosol 3 (Laboratoires Prod'Hyg, Houdan, France) -Jeescreen OMC (Jeen International Corporation, Fairfield, NJ) -Neo Heliopan AV (Symrise, Teterboro, NJ) -Nomcort TAB (The Nisshin Oillio Group, Ltd, Yokohama, Japan) -OriStar OMC (Orient Stars LLC, Torrance, CA) -Parsol MCX (DSM Nutritional Products, Parsippany, NJ) -Uvinul MC 80 (BASF Corporation, Florham Park, NJ)	UVB
Ethylhexyl salicylate	Octisalate	EHS	-Octyl salicylate -AEC ethylhexyl salicylate (A & E Connock Perfumery & Cosmetics, Ltd, Hampshire, UK) -Custoscreen OS (Custom Ingredients, Inc, Chester, SC) -Escalol 587 (Ashland Inc, Wilmington, DE) -Eusolex OS (Merck KGaA/EMD Chemicals, Darmstadt, Germany) -Heliosol 2 (Laboratoires Prod'Hyg, Houdan, France) -Jeescreen OS (Jeen International Corporation, Fairfield, NJ) -Neo Heliopan OS (Symrise, Teterboro, NJ) -Neotan L (Fabriquimica S.R.L., San Martin, Argentina) -OriStar OS (Orient Stars LLC,Torrance, CA)	UVB

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
			-Parsol EHS (DSM Nutritional Products, Inc, Parsippany, NJ) -UVSOB 300 (LC United Chemical Corp, Taiwan, People's Republic of China)	
Ethylhexyl triazone	Octyl triazone	EHT	-Uvinul T 150 (BASF Corporation, Florham Park, NJ)	UVB
Glyceryl PABA	Glyceryl PABA	GPABA	-Glyceryl p-Aminobenzoate 4-aminobenzoate lisadimate -Escalol 106 (Ashland, Inc, Wilmington, DE)	UVB
Homosalate	Homosalate	HMS	-Homomenthyl salicylate -Eusolex HMS (EMD Chemicals, Philadelphia, PA) -Neo Heliopan HMS (Symrise,Teterboro, NJ) -OriStar HMS (Orient Stars LLC, Carson, CA) -Parsol HMS (DSM Nutritional Products, Inc, Parsippany, NJ) -Uniderm HOMSAL (Universal Preserv-A-Chem, Inc, Somerset, NJ)	UVB
Isoamyl p-methoxycinnamate	Amiloxate	IMC	-Neoheliopan E 1000 (Symrise, Teterboro, NJ) -UVSOB 360 (LC United Chemical Corp, Taiwan, People's Republic of China)	UVB
Isopropyl dibenzoylmethane	Eusolex 8020	IDM		UVA

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
4-methylbenzylidene camphor	Enzacamene	MBC	-Enacamene-3-(4-methylbenzylidene)-camphor -Neo Heliopan MBC (Symrise, Teterboro, NJ) -Parsol 5000 (DSM Nutritional Products, Inc, Parsippany, NJ) -Eusolex 6300 (EMD Chemicals, Philadelphia, PA) -UVSOB MBC (LC United Chemical Corp, Taiwan, People's Republic of China)	UVB
Menthyl anthranilate	Meradimate	MHA	-Neo Heliopan MA (Symrise, Teterboro, NJ)	UVA2
Methylene bis-benzotriazolyl tetramethylbutylphenol	Bisoctrizole	MBBT	-Tinosorb M (BASF Corp, Florham Park, NJ)	UVB, UVA1
Octocrylene	Octocrylene	OCR	-Octocrilene -2-ethylhexyl-2-cyano-3, 3-diphenylacrylate Custoscreen OC (CustomIngredients, Inc, Chester SC) -Escalol 597 (Ashland Inc, Wilmington, DE) -Eusolex OCR (EMD Chemicals, Philadelphi a, PA) -Jeescreen OC (Jeen International Corporation, Fairfield, NJ) -Neo Heliopan 303 (Symrise, Teterboro, NJ) -OriStar OCR (Orient Stars LLC, Torrance, CA) -Parsol 340 (DSM Nutritional Products, Inc, Parsippany, NJ) -Uvinul N 539 T (BASF Corporation, Florham Park, NJ) -UVSOB 320 (LC United Chemical Corp, Taiwan, People's Republic of China)	UVB

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
PABA	Aminobenzoic acid	PABA	-4-aminobenzoic acid -p-aminobenzoic acid -aniline-4-carboxylic acid -p-carboxyaniline	UVB
Pentyl dimethyl PABA	Padimate A	PPABA	-Amyl Dimethyl PABA -Ecalol 506 (Ashland, Inc, Wilmington, DE)	UVB
Phenylbenzimidazole sulfonic acid	Ensulizole	PBSA	-2-phenyl-benzimidazole-5-sulfonic acid -Eusolex 232 (EMD Chemicals, Philadelphia, PA) -Neo Heliopan Hydro (Symrise, Teterboro, NJ) -Parsol HS (DSM Nutritional Products, Inc, Parsippany, NJ)	UVB
Polysilicone-15	Parsol SLX (DSM Nutritional Products, Inc, Parsippany, NJ)	PS15	-Diethylbenzylidene malonate dimethicone	UVB
TEA-salicylate	Trolamine salicylate	TES	-Triethanolamine salicylate -Neo Heliopan TS (Symrise, Teterboro, NJ) -Neotan W (Fabriquimica S.R.L., San Martin, Argentina)	UVB
Terephthalylidene dicamphor sulfonic acid	Mexoryl SX (Chimex, Le Thillay, France)	TDSA	-TDSA Ecamsule	UVA2

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
Titanium dioxide	Titanium dioxide	TiO	-CI 77891 -Pigment white 6 -A310 Tudor Aspen (Kingfisher Colours Ltd, Berkshire, UK) -AEC Titanium Dioxide (A & E Connock (Perfumery & Cosmetics) Ltd, Hampshire, UK) -Aeroxide TiO2 P25 (Evonik Industries AG, Hanau-Wolfgang, Germany) -C47-5175 Cosmetic White (Sun Chemical Corporation, Cincinnati, OH) -Creawhite R (Creations Couleurs, Dreux, France) -Hombitan AFDC (Sachtleben Pigments OY, Pori, Finland) -Kronos 1025 (Kronos Canada, Inc, Varennes, QC, Canada) -NanoGard AQ (Nanohybrid Co, Ltd, Seoul, Republic of South Korea) -OriStar TDO (Orient Stars LLC, Carson, CA) -Oxyde De Titane Standard (Sensient Cosmetic Technologies, Saint Ouen L'Aumone, France) -Puricolor White PWH6 (BASF Corporation, Florham Park, NJ) -Tronox A-Z (Kerr-McGee Chemical LLC, Oklahoma City, OK) -Uniwhite AO (Universal Preserv-A-Chem, Inc, Somerset, NJ)	UVB, UVA2

INCI	US adopted Name	Acronym	Other Names	Wavelength protection
Zinc oxide	Zinc oxide	ZnO	-CI 77947 -Pigment white 4 -Zinc white -Zinc gelatin -Creazinc (Creations Couleurs, Dreux, France) -Grillo Sun (Grillo Zinkoxid Gmbh, Niedersachsen, Germany) -NanoGard Zinc Oxide (Nanohybrid Co, Ltd, Seoul, Republic of South Korea) -Nano-Zinc SL (Sino Lion (USA) Ltd, East Hanover, NJ) -OriStar ZO (Orient Stars LLC, Carson, CA) -Oxyde de Zinc Micropure (Sensient Cosmetic Technologies, Saint Ouen L'Aumone) -Unichem ZO (Universal Preserv-A-Chem, Inc, Somerset, NJ) -USP-1, j2, j511 (Zinc Corporation of America, Monaca, PA) -Z-Cote (BASF Corporation, Florham Park, NJ)	UVB,UVA1, UVA2

APPENDIX B

LEGISLATION OF UV FILTERS IN THAILAND

ประกาศกระทรวงสาธารณสุข

(ฉบับที่ ๔๖) พ.ศ. ๒๕๕๐

เรื่อง ผลิตภัณฑ์เครื่องสำอางที่มีสารป้องกันแสงแดด

โดยที่เป็นการสมควรปรับปรุงประกาศกระทรวงสาธารณสุขเกี่ยวกับผลิตภัณฑ์เครื่องสำอางที่มีสารป้องกันแสงแดดให้เหมาะสมยิ่งขึ้น

อาศัยอำนาจตามความในมาตรา ๕ (๒) และ (๔) ประกอบกับมาตรา ๒๗ แห่งพระราชบัญญัติเครื่องสำอาง พ.ศ. ๒๕๓๕ รัฐมนตรีว่าการกระทรวงสาธารณสุขออกประกาศไว้ ดังต่อไปนี้

ข้อ ๑ ให้ยกเลิก

๑.๑ ประกาศกระทรวงสาธารณสุข (ฉบับที่ ๘) พ.ศ. ๒๕๓๖ ออกตามความในพระราชบัญญัติเครื่องสำอาง พ.ศ. ๒๕๓๕ เรื่อง ผลิตภัณฑ์ที่มีสารป้องกันแสงแดด ลงวันที่ ๓๑ พฤษภาคม พ.ศ. ๒๕๓๖

๑.๒ ประกาศกระทรวงสาธารณสุข (ฉบับที่ ๓๕) พ.ศ. ๒๕๔๕ ออกตามความในพระราชบัญญัติเครื่องสำอาง พ.ศ. ๒๕๓๕ เรื่อง ผลิตภัณฑ์ที่มีสารป้องกันแสงแดด (ฉบับที่ ๒) ลงวันที่ ๒๘ พฤษภาคม พ.ศ. ๒๕๔๕

ข้อ ๒ ในประกาศนี้

"ผลิตภัณฑ์เครื่องสำอางที่มีสารป้องกันแสงแดด" หมายความว่า ผลิตภัณฑ์เครื่องสำอางที่มีส่วนผสมของสารป้องกันแสงแดดเพื่อปกป้องร่างกายจากรังสีอัลตราไวโอเล็ต

"สารป้องกันแสงแดด" หมายความว่า สารที่ใช้ทำหน้าที่ปกป้องร่างกายจากอันตรายที่จะเกิดจากรังสีอัลตราไวโอเล็ต

ข้อ ๓ ให้ผลิตภัณฑ์เครื่องสำอางที่มีสารป้องกันแสงแดดเป็นเครื่องสำอางควบคุม

ข้อ ๔ สารป้องกันแสงแดดที่ให้ใช้ได้จะต้องเป็นไปตามที่กำหนดไว้ในบัญชีแนบท้ายประกาศ ฯ นี้

ข้อ ๕ ผลิตภัณฑ์เครื่องสำอางที่มีสารป้องกันแสงแดดที่ใช้สารป้องกันแสงแดดไม่เป็นไปตามที่กำหนดในข้อ ๔ ให้ถือว่าเป็นเครื่องสำอางที่มีวัตถุที่ห้ามใช้เป็นส่วนผสมในการผลิตเครื่องสำอาง

ข้อ ๖ ประกาศนี้ให้ใช้บังคับเมื่อพ้นกำหนดหนึ่งร้อยแปดสิบวันนับแต่วันที่ประกาศในราชกิจจานุเบกษาเป็นต้นไป

ประกาศ ณ วันที่ ๒๘ พฤษภาคม พ.ศ. ๒๕๕๐

มรกต กรเกษม

รัฐมนตรีช่วยว่าการ ฯ ปฏิบัติราชการแทน

รัฐมนตรีว่าการกระทรวงสาธารณสุข

หน้า ๗
เล่ม ๑๒๙ ตอนพิเศษ ๓๙ ง ราชกิจจานุเบกษา ๒๓ กุมภาพันธ์ ๒๕๕๕

ประกาศกระทรวงสาธารณสุข

เรื่อง ผลิตภัณฑ์เครื่องสำอางที่มีสารป้องกันแสงแดด (ฉบับที่ ๒)

โดยที่เป็นการสมควรแก้ไขเพิ่มเติมประกาศกระทรวงสาธารณสุขเกี่ยวกับผลิตภัณฑ์เครื่องสำอางที่มีสารป้องกันแสงแดด ให้เหมาะสมยิ่งขึ้น

อาศัยอำนาจตามความในมาตรา ๕ (๒) และ (๔) มาตรา ๒๗ และมาตรา ๖๘ แห่งพระราชบัญญัติเครื่องสำอาง พ.ศ. ๒๕๓๕ อันเป็นกฎหมายที่มีบทบัญญัติบางประการเกี่ยวกับการจำกัดสิทธิและเสรีภาพของบุคคล ซึ่งมาตรา ๒๙ ประกอบกับมาตรา ๓๒ มาตรา ๓๓ มาตรา ๔๑ มาตรา ๔๓ และมาตรา ๔๕ ของรัฐธรรมนูญแห่งราชอาณาจักรไทย บัญญัติให้กระทำได้โดยอาศัยอำนาจตามบทบัญญัติแห่งกฎหมาย รัฐมนตรีว่าการกระทรวงสาธารณสุขออกประกาศไว้ ดังต่อไปนี้

ข้อ ๑ ให้ยกเลิกช่องลำดับที่ ๑ แห่งบัญชีท้ายประกาศกระทรวงสาธารณสุข (ฉบับที่ ๔๖) พ.ศ. ๒๕๕๐ เรื่อง ผลิตภัณฑ์เครื่องสำอางที่มีสารป้องกันแสงแดด ลงวันที่ ๒๘ พฤษภาคม พ.ศ. ๒๕๕๐

ข้อ ๒ ประกาศนี้ให้ใช้บังคับเมื่อพ้นกำหนดหนึ่งร้อยแปดสิบวันนับแต่วันประกาศในราชกิจจานุเบกษาเป็นต้นไป

ประกาศ ณ วันที่ ๓๐ ธันวาคม พ.ศ. ๒๕๕๔
วิทยา บุรณศิริ
รัฐมนตรีว่าการกระทรวงสาธารณสุข

บัญชีท้ายประกาศกระทรวงสาธารณสุข (ฉบับที่ ๔๖) พ.ศ. ๒๕๕๐

ลำดับ	ชื่อสารป้องกันแสงแดด	อัตราส่วนสูงสุดที่ให้ใช้
1	4-Aminobenzoic acid (PABA)	5%
2	*N,N,N*-Trimethyl-4-(2-oxoborn-3-ylidenemethyl) anilinium methyl sulfate	6%
3	Homosalate	10%
4	Oxybenzone	10%
5	2-Phenylbenzimidazole-5-sulfonic acid and its potassium, sodium and triethanolamine salts	8% (คำนวณในรูปกรด)
6	3,3'-(1,4-Phenylenedimethylene)- bis(7,7-dimethyl-2-oxobicyclo-[2,2,1]hept-1-ylmethanesulfonic acid) and its salts	10% (คำนวณในรูปกรด)
7	1-(4-*tert*-Butylphenyl)-3-(4-methoxyphenyl) propane-1,3-dione	5%
8	alpha-(2-Oxoborn-3-ylidene) toluene-4-sulfonic acid and its salts	6% (คำนวณในรูปกรด)
9	2-Cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester (Octocrylene)	10% (คำนวณในรูปกรด)
10	Polymer of *N*-{(2 and 4)-[(2-oxoborn-3-ylidene) methyl] benzyl} acrylamide	6%
11	Octyl methoxycinnamate	10%
12	Ethoxylated ethyl-4-aminobenzoate (PEG-25 PABA)	10%
13	Isopentyl-4-methoxycinnamate (Isoamyl *p*-methoxycinnamate)	10%
14	2,4,6-Trianilino-(*p*-carbo-2'-ethylhexyl-1' oxy)-1,3,5-triazine (Octyl triazone)	5%
15	Phenol,2-(2H-benzotriazol-2-yl)-4-methyl-6-(2-methyl-3-(1,3,3,3-tetramethyl-1-(trimethylsilyl)oxy)-disiloxanyl)propyl) (Drometrizole trisiloxane)	15%

ลำดับ	ชื่อสารป้องกันแสงแดด	อัตราส่วนสูงสุดที่ให้ใช้
16	Benzoic acid, 4,4-[[6-[[(1,1-dimethylethyl)amino] carbonyl]phenyl]amino] 1,3,5-triazine-2,4-diyl]diimino)bis-,bis-(2-ethylhexyl)] ester	10%
17	3-(4'-Methylbenzylidene)-d-1 camphor (4-Methylbenzylidene camphor)	4%
18	3-Benzylidene camphor	2%
19	2-Ethylhexyl salicylate (Octyl salicylate)	5%
20	4-Dimethyl-amino-benzoate of ethyl-2-hexyl (Octyl dimethyl PABA)	8%
21	2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid and its sodium salt	5% (คำนวณในรูปกรด)
22	2,2'-Methylene-bis-6-(2H-benzotriazol-2yl)-4-(tetramethyl-butyl)-1,1,3,3-phenol	10%
23	Monosodium salt of 2-2'-bis-(1,4-phenylene)-*1H*-benzimidazole-4,6-disulfonic acid	10% (คำนวณในรูปกรด)
24	(1,3,5)-Triazine-2,4-bis((4-(2-ethyl-hexyloxy)-2-hydroxy)-phenyl)-6-(4-methoxyphenyl)	10%
25	Dimethicodiethylbenzalmalonate (CAS No 207574-74-1)	10%
26	Titanium dioxide	25%
27	Benzoic acid, 2-[-4-(diethylamino)-2-hydroxybenzoyl]-, hexylester (INCI name : Diethylamino hydroxybenzoyl hexyl benzoate; CAS No 302776-68-7)	10%
28	Menthyl anthranilate	5%
29	Zinc oxide	25%

BIOGRAPHY

Name	Mr. Pawit Phadungsaksawasdi
Date of Birth	December 15, 1988
Educational Attainment	2015-present: Master of Science (Dermatology) Chulabhorn International College of Medicine, Thammasat University
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