

# Toxicological Profile of Homosalate as Cosmetic Ingredients

Selma Yazar Urek<sup>1,\*</sup>, Merve Bilgin<sup>2</sup> and B. Ufuk Halli<sup>3</sup>

<sup>1</sup>Dept. of Pharmacology and Toxicology, Faculty of Pharmacy, Yeni Yuzyil University, Istanbul, Turkey

<sup>2</sup>Dept. of Pharmaceutical Microbiology, Faculty of Pharmacy, Yeni Yuzyil University, Istanbul, Turkey

<sup>3</sup>Dep. of Pharmaceutical Technology, Faculty of Pharmacy, Yeni Yuzyil University, Istanbul, Turkey

**Abstract:** UV filters are widely used in many cosmetic products. They are added in order to protect from acute (sunburn-photo-ageing) or chronic (skin cancer) toxic effects of sunlight exposure. Although, acute and subchronic toxicity of these compounds is considered to be rather low, in the long-term exposure can cause some problems such as effects on reproductions, ontogeny, endocrine diseases and photoallergic reactions. In addition, the bioaccumulation of these the lipophilic chemicals in wildlife and human oes not seem to be considered in earlier publised toxicity studies. Homosalate (HMS) is a member of the UV filters. HMS has many industrial uses, as a vehicle for fragrance and cosmetic ingredients like sunscreen agent, ultraviolet light absorber. There are some studies regarding hormone-disrupting properties of homosalate. The aim of mini review was to collect data about toxicological effects on animal, human and aquatic biota, including studies the variety routes of exposure, and the risk assessment of usage of HMS as cosmetic ingredients.

**Keywords:** Homosalate, cosmetics, toxic effect, UV filters.

## 1. INTRODUCTION

UV filters are used by every socio class of human being for skin protection, light stability, durability and also to expand the shelf life of beauty cosmetics products such as creams, lipstick, skin lotions, hair sprays, hair dyes, shampoos, bubble baths. They can be found not only in cosmetics but also in other personal care products, pharmaceuticals, vehicle maintenance products to prevent photodegradation of polymers and pigments. These chemicals are added in concentrations up to 10% in EU or 15% depending upon where product is used. Humans can be exposed to UV filters through two pathways; directly through using cosmetics (dermal absorption) and indirectly through the food chain [1-6].

Many UV filters products are in use, but their safety, efficacy and toxicological profile are still not clear. Recently, according to the published literature toxicological effects of UV filters have raised concern about the long-term safety, UV radiation and growing skin cancer. It is estimated that every year approximately 60.000 people die worldwide because of malignant melanoma and other types of skin cancer. Chronic exposure to UV filters is important for increasing the risk of skin cancer in childhood and during teenage years. On the one hand, it is crucial to use to protect ourselves from photocarcinogenesis, the p53 tumor suppressor gene from sun-DNA-damage

and prevent UV-induced immune suppression, photodermatoses, such as polymorphic light eruption, and, photoaging. On the other hand, while using them, we should be care of toxicological effects, the safety of UV filters and other effects such as sunburns, cutaneous degeneration, photosensitivity, phototoxicity, photo-aging, immunosuppression and skin cancer [2, 4, 7-11].

Although the toxicologic classification of UV filters is rather complex, toxicologic studies of UV are generally needed for a global registration include acute and chronic toxicity, genotoxicity, *in vitro/in vivo* toxicity, fetal toxicity, peri/postnatal toxicity, carcinogenicity, immunosuppression, photocarcinogenesis and photoaging [7, 12, 13].

There are approximately 55 UV filters licensed for usage in UV filters in United States, European Union, Japan, South America, South Africa. Homosalate also is approved in FDA for use as UV filter product which is one of the most common active ingredients used in UV filters [6, 14, 15].

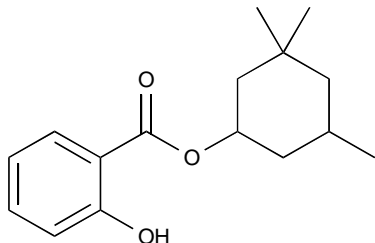
So, we wanted to evaluate possible toxic effects resulting from of HMS exposure on human, animal and in aquatic biota.

## 2. CHEMICAL STRUCTURE

Salicylates (Octisalate, Homosalate, Trolamine salicylate) are weaker UVB absorbers so they must be used in relatively high concentration. These chemicals are used to increase the effect of other UVB absorbers. Homosalate is a member of Salicylates. Homosalate (homomenthyl salicylate;  $\lambda_{max}$ , 306 nm) [15].

\*Address correspondence to this author at the Dept. of Pharmacology and Toxicology, Faculty Pharmacy, Yeni Yuzyil University, Istanbul, Turkey; Tel: 0090 212 444 50 01; Fax: 0090 212 481 40 58; E-mail: selma.yazar@yeniyyuzuil.edu.tr

Homosalate chemical structure (HMS; CAS No. 118-56-9) is given Figure 1. It is a viscous or light yellow, to slight tan liquid or oil. It has a boiling point of 161-165 °C. HMS is likely converted to salicylic acid and is highly photostable agents used to reduce photodegradation of other active sunscreen ingredients [7].



**Figure 1:** Chemical structure of Homosalate.

### 3. *IN VIVO* AND *IN VITRO* TOXICITY STUDIES (IN HUMAN AND IN ANIMAL)

The safety margin of new UV filters for apply to humans is estimated by comparing the potential systemic exposure with the no-effect level from *in vivo* toxicity tests. Before to marketing new UV filters undergo rigorous human testing to confirm their efficacy as well as local toxicity such as irritation, sensitization, phototoxicity and photogenotoxicity, photocarcinogenicity in man [10, 16].

UV filters are needed to a rigorous risk/benefit assessment including acute skin injury such as sunburn, chronic skin damage, including cellular DNA damage, photoinduced immune suppression, reproductive toxicity, genotoxicity, carcinogenicity and mutagenesis. As addition, UV filters should be determined a stringent toxicological safety evaluation prior to approval [10, 16].

UV filters can be absorbed and accumulated in body, after their dermal application. UV filters absorb from skin and reach to kidneys, where they are metabolized and then excreted. Urine is the first route, feces is the second route for elimination of both parent compounds and metabolites [17]. Authors evaluated four common used UV filters including HMS in human volunteers (in plasma, urine, skin tissues). It was also declared that all UV filters had shown significant penetration in skin [14].

Researchers compared the skin penetration of HMS with two vehicles (an oil-in-water emulsion gel and petrolatum jelly) both *in vitro* using Franz cells and *in vivo* using a standardized tape-stripping method for human skin penetration. *In vitro* HMS did not diffused

the skin after 6 h from application and very little could be found in the skin. When using the right vehicle or optimizing, UV filters can be significantly improved in terms of pharmacological efficacy as well as the potential toxicological risk associated with the skin penetration of UV filters may be significantly reduced [18].

It was evaluated skin-irritant capacity such as redness (cumulative irritation score) and fluid accumulation (changes in skinfold thickness) of UV filters in rabbit. Then, they compared the result of this study on animals and humans. Results of 60 UV filters including HMS showed a significant correlation between the cumulative irritation scores obtained on rabbits and those obtained on human [19].

Although metabolism of UV filters is extreme importance, little is known about accumulation metabolism and excretion of them [17] Schlumpf *et al.* (2010) studied about UV filters in human milk. They found that HMS was present in three of eight samples. They indicated that the user reports showed a significant correlation between usage of UV filters and their present in milk [20].

A recent study by Jimenez *et al.* (2013) indicated that HMS didn't take place in human placental tissues. They stated that the reason of this absence is exposure level and metabolism. Also these researchers studied on cytotoxic activity of HMS and found that HSM didn't show any cytotoxic effect [21].

Photoallergy studies are extremely important for UV filters. The photoallergic potential of HMS researched using the mouse for ear-swelling model and it was indicated that this UV-filters did not generally associated with as photoallergy in humans or animals using this model [22].

In another study, HMS which lead to photoallergy was tested using the modified Harber guinea pig photoallergy model and the result of this study was negative [23].

### 4. ENDOCRINE DISRUPTORS

In recent years, studies showed that UV filters including homosalate can alter endocrine signaling by mimicking or inhibiting the actions of endogenous hormones. These chemicals are classified as endocrine disruptors chemicals (EDCs). As a result, EDCs are potential threat to human being and animals reproduction as well as even they can make epigenetic

changes that can be transmitted to future generations [6, 12, 24].

The nuclear hormone receptors is widely believed to be key factor causing endocrine disruption. In addition, nuclear hormone receptor family makes up estrogen receptors, androgen receptor (AR), progesterone receptor (PR), glucocorticoid receptor (GR), thyroid receptor (TR), mineralocorticoid receptor (MR), retinoic acid receptor (RAR), and Vitamin D receptor [12, 25].

In several literature, *in vitro* and *in vivo* studies were found exhibit to be weak estrogenic activity of HMS.

Ma *et al.* (2003) studied estrogenic activity of 8 UV filters including HMS. As a result of HMS and benzophenone-3 was found to have antiandrogenic activity and estrogenic activity in the human breast carcinoma cell line MDA-kb2. These chemicals were also studied about the coaction with glucocorticoid receptors (GR) activation. The authors emphasized that HMS didn't play a role on the effect of dexamethasone on luciferase activity [26]. In another *in vivo* study, Schlumpf *et al.* (2004) found that estrogenic activity of HMS measured as 1.56  $\mu\text{M}$  in MCF-7 cells [27].

Schreurs *et al.* (2005) informed that HMS didn't show effect toward the androgen receptor and progesterone receptor using sensitive and specific reporter gene cell lines [25].

Schreurs *et al.* (2004) studied on 10 UV filters for identification of endocrine activity *in vitro*. They also found that HMS was eliminated for estrogenic activity on MCF-7 cells. Another *in vitro* and *in vivo* studies were investigated UV filters exhibiting estrogenic activity *in vitro* and in uterotrophic assay immature rats. This chemical was given to Long Evans rats for 4 days. They found that HMS was inactive in this study [4].

## 5. ECOTOXICITY

Accumulation and increase release of UV filters into the environment has prompted them to be considered this new a class of organic pollutants in the aquatic environment, especially in bathing waters such as rivers, lakes, sea water [6, 28].

Studies have shown that UV filters may be accumulated in the aquatic environment through direct and indirect pathways. The first pathway is by direct input to natural waters stems from swimming, bathing,

industrial wastewater discharges. The second pathway is by indirect input. Indirect input occurs when UV filters are washed off individuals when those individuals shower or released from towels and clothing during laundering [1, 3, 28].

UV filters also have determined in surface waters, river, swimming pool and tap water samples, wastewater, drinking water, soil, sludge and fish [1, 29, 30].

Studies indicate that certain organisms have a strong tendency to bio-accumulation of UV filters [28]. Fish are suitable organisms that can be used to monitor the presence of persistent lipophilic contaminants in aquatic organism. Moreover, humans may be exposed to such chemicals including UV stabilizers not only by use of personal care products but also through the consumption of fish [31].

Although their extensive use, there are a few studies about the environmental occurrence, distribution and toxic effects of UV filters.

UV filters are highly lipophilic and therefore can be expected to bioaccumulate in the environment. Gago-Ferrero and Diaz-Cruz, (2012) determined levels of UV filters in fish (lipid in perch and roach) of Maarfeder Lake (Germany). The results indicated that HMS can be selectively accumulated depending on the species; perch accumulated HMS in offal. In contrast, roach had higher levels of HMS in muscle and they measured 3100  $\text{ng g}^{-1}$  lipids HMS in fish [5].

Kameda *et al.* (2011) measured levels of eight UV filters including HMS in surface waters and sediments in Japanese rivers and lakes. The researchers found that HMS was an important correlated with Galaxolide in sediments [32].

## 6. PHARMACOLOGY EFFECT

The effect of UV filters can be measured using two indicators, SPF (sun protection factor) and UVA-PF (UVA-protection factor). These indicators was studied *in vivo* (using volunteers) and *in vitro*. The studies demonstrated that *in vivo* levels are higher than *in vitro* levels for SPF. Couteau *et al.* (2012) thought that this difference can be explained with having anti-inflammatory effect of the UV filters. Same authors researched the anti-inflammatory effect of 21 UV filters in Swiss male mice. These filters was topically applied

to mice. It was found that HMS demonstrated a significant anti-inflammatory effect because of it belongs to the salicylate family [33].

## 7. CONCLUSIONS

Personal care products including UV-filters have two different toxicological aspects. On one hand, they may apply dermal in humans when they are used as UV filters. On the other hand, they may play an ecotoxicologic role in wildlife and humans (intake *via* the food chain).

Although UV filters can be released at levels greater than many other compounds, little research has been carried out to determine potential toxicity as result of their accumulation in the human body. A great deal of additional data is needed to understand the significance of Homosalate in the aquatic environment. The bioaccumulation of this substance in humans and wildlife is important.

A few studies at the molecular level and *in vivo* have shown the interaction of HMS with antiandrogenic and estrogenic receptors. Homosalate has an endocrine disruptors activity. The long-term exposure to HMS can still cause to serious toxic effects including mutations and genetic instability. As a consequence, this compound should be tested for with regard to endocrine activity.

While using these chemicals, risk/benefit relationship should be cared. In conclusion, Homosalate must be researched in animal and human for the possible long-term toxic effects of homosalate in cosmetics.

## REFERENCES

- [1] Diaz-Cruz MS, Barcelo D. Chemical analysis and ecotoxicological effects of organic UV-absorbing compounds in aquatic ecosystems. *Trends Analyt Chem* 2009; 28: 708-17. <http://dx.doi.org/10.1016/j.trac.2009.03.010>
- [2] Nash JF. Human safety and efficacy of ultraviolet filters and sunscreen products. *Dermatol Clin* 2006; 24: 35-51. <http://dx.doi.org/10.1016/j.det.2005.09.006>
- [3] Grabicova K, Fedorova G, Burkina V, Steinbach C, Schmidt-Posthaus H, Zlabek V, et al. Presence of UV filters in surface water and the effects of phenylbenzimidazole sulfonic acid on rainbow trout (*oncorhynchus mykiss*) following a chronic toxicity test. *Ecotoxicol Environ Saf* 2013; 96: 41-47. <http://dx.doi.org/10.1016/j.ecoenv.2013.06.022>
- [4] Schlumpf M, Cotton B, Conscience M, Haller V, Steinmann B, Lichtensteiger W. *In vitro* and *in vivo* estrogenicity of UV screens. *Environ Health Perspect* 2011; 109: 239-44. <http://dx.doi.org/10.1289/ehp.01109239>
- [5] Gago-Ferrero P, Diaz-Cruz MS, Barcelo D. An overview of UV-absorbing compounds (organic UV filters) in aquatic biota. *Anal Bioanal Chem* 2012; 404: 2597-10. <http://dx.doi.org/10.1007/s00216-012-6067-7>
- [6] Santos AJM, Miranda MS, Esteves da Silva JCG. The degradation products of UV filters in aqueous and chlorinated aqueous solutions. *Water Res* 2012; 46: 3167-76. <http://dx.doi.org/10.1016/j.watres.2012.03.057>
- [7] Sambandan D, Ratner D. Sunscreens: An overview and update. *Rev J Am Acad Dermatol* 2010; 64: 748-58. <http://dx.doi.org/10.1016/j.jaad.2010.01.005>
- [8] Lohezic-Le Devehat F, Legouin B, Couteau C, Boustie J, Coiffard L. Lichenic extracts and metabolites as UV filters. *J Photochem Photobiol B: Biol* 2013; 120: 17-28. <http://dx.doi.org/10.1016/j.jphotobiol.2013.01.009>
- [9] Kapoor S, Saraf S. Risk analysis tools for toxicological profile of cosmetics. *Internet J Toxicol* 2008; 5(2).
- [10] Nohynek GJ, Schaefer H. Benefit and risk of organic ultraviolet filters. *Regul Toxicol Pharmacol* 2001; 33: 285-99. <http://dx.doi.org/10.1006/rtp.2001.1476>
- [11] Krause M, Klit A, Blomberg Jensen M, Søeborg T, Frederiksen H, Schlumpf M, et al. Sunscreens: Are they beneficial for health? An overview of endocrine disrupting properties of UV-filters. *Int J Androl* 2012; 35(3): 424-36. <http://dx.doi.org/10.1111/j.1365-2605.2012.01280.x>
- [12] Hexsel CL, Bangert SD, Hebert AA, Lim HW. Current sunscreen issues: 2007 Food and Drug Administration sunscreen labelling recommendations and combination sunscreen/insect repellent products. *J Am Acad Dermatol* 2008; 59: 316-23. <http://dx.doi.org/10.1016/j.jaad.2008.03.038>
- [13] Tuchinda C, Lim HW, Osterwalder U, Rougier A. Novel emerging sunscreen technologies. *Dermatol Clin* 2006; 24: 105-17. <http://dx.doi.org/10.1016/j.det.2005.09.003>
- [14] Sarveiya V, Risk S, Benson HAE. Liquid chromatographic assay for common sunscreen agents: Application to *in vivo* assessment of skin penetration and systemic absorption in human volunteers. *J Chromatogr B* 2004; 803: 225-31. <http://dx.doi.org/10.1016/j.jchromb.2003.12.022>
- [15] Kullavanijaya P, Lim HW, Photoprotection. *J Am Acad Dermatol* 2005; 52: 937-58. <http://dx.doi.org/10.1016/j.jaad.2004.07.063>
- [16] Nohynek GJ, Antignac E, Re T, Toutain H. Safety assessment of personal care products/cosmetics and their ingredients. *Toxicol Appl Pharmacol* 2010; 243: 239-59. <http://dx.doi.org/10.1016/j.taap.2009.12.001>
- [17] Diaz-Cruz MS, Llorca M, Barcelo D. Organic UV filters and their photodegradates, metabolites and disinfection by-products in the aquatic environment. *Trends Analyt Chem* 2008; 27: 873-87. <http://dx.doi.org/10.1016/j.trac.2008.08.012>
- [18] Chatelain E, Gabard B, Surber C. Skin penetration and sun protection factor of five UV filters: effect of vehicle. *Skin Pharmacol Appl Skin Physiol* 2003; 16: 28-35. <http://dx.doi.org/10.1159/000068291>
- [19] Marzulli FN, Maibach HI. The Rabbit as a model for evaluating skin irritants: A comparison of results obtained on animals and man using repeated skin exposures. *Fd Cosmet Toxicol* 1975; 13: 533-40. [http://dx.doi.org/10.1016/0015-6264\(75\)90008-5](http://dx.doi.org/10.1016/0015-6264(75)90008-5)
- [20] Schlumpf M, Kypke K, Wittassek M, Angerer J, Mascher H, Mascher D, et al. Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlor pesticides, PBDEs, and PCBs in human milk: Correlation of UV filters with use of cosmetics. *Chemosphere* 2010; 81: 1171-83. <http://dx.doi.org/10.1016/j.chemosphere.2010.09.079>

- [21] Jimenez-Diaz I, Molina-Molina JM, Zafra-Gomez A, Ballesteros O, Navalon A, Real M, *et al.* Simultaneous determination of the UV- filters benzyl salicylate, phenyl salicylate, octyl salicylate, homosalate, 3-(4-methylbenzylidene) camphor and 3- benzylidene camphor in human placental tissue by LC-MS/MS. Assessment of their *in vitro* endocrine activity. *J Chromatogr B* 2013; 936: 80-7. <http://dx.doi.org/10.1016/j.jchromb.2013.08.006>
- [22] Gerberick GF, Ryan CA. A predictive mouse ear-swelling model for investigating topical photoallergy. *Fd Chem Toxic* 1990; 28: 361-68. [http://dx.doi.org/10.1016/0278-6915\(90\)90110-9](http://dx.doi.org/10.1016/0278-6915(90)90110-9)
- [23] Gerberick GF, Ryan CA. Contact photoallergy testing of sunscreens in guinea pigs. *Contact Dermatitis*. 1989; 20(4): 251-9. <http://dx.doi.org/10.1111/j.1600-0536.1989.tb03141.x>
- [24] Cooke PS, Simon L, Denslo ND. Endocrine Disruptors. Haschek and Rousseaux's Handbook of Toxicologic Pathology (Third Edition) 2013; II: 123-1154.
- [25] Schreurs RHMM, Sonneveld E, Jansen JHJ, Seinen W, Burg B. Interaction of polycyclic musks and UV filters with the estrogen receptor (ER), androgen receptor (AR), and progesterone receptor (PR), in reporter gene bioassays. *Toxicol Sci* 2005; 83: 264-72. <http://dx.doi.org/10.1093/toxsci/kfi035>
- [26] Ma R, Lichtensteiger W, Schlumpf M. UV filters with antagonistic action at androgen receptors in the MDA-kb2 cell transcriptional-activation assay. *Toxicol Sci* 2003; 74: 43-50. <http://dx.doi.org/10.1093/toxsci/kfg102>
- [27] Schlumpf M, Schmid P, Durrer S, Conscience M, Maerkel K, Henseler M, *et al.* Endocrine activity and development toxicity of cosmetic UV filters-an update. *Toxicol* 2004; 205: 113-22. <http://dx.doi.org/10.1016/j.tox.2004.06.043>
- [28] Giokas DL, Salvador A, Chisvert A. UV Filters: From sunscreens to human body and the environment. *Trends Analyt Chem* 2007; 26: 360-74. <http://dx.doi.org/10.1016/j.trac.2007.02.012>
- [29] Zhang Y, Lee HK. Ionic liquid-based ultrasound-assisted dispersive liquid-liquid microextraction followed high-performance liquid chromatography for the determination of ultraviolet filters in environmental water samples. *Anal Chim Acta* 2012; 750: 120-6. <http://dx.doi.org/10.1016/j.aca.2012.04.014>
- [30] Zhang Y, Lee HK. Determination of ultraviolet filters in environmental water samples by temperature-controlled ionic liquid dispersive liquid-phase microextraction. *J Chromatogr A* 2013; 1271(1): 56-61. <http://dx.doi.org/10.1016/j.chroma.2012.11.047>
- [31] Kim JW, Isobe T, Ramaswamy BR, Chang KH, Amano A, Miller TM, *et al.* Contamination and bioaccumulation of benzotriazole ultraviolet stabilizers in fish from Manila Bay, the Philippines using an ultra-fast liquid chromatography-tandem mass spectrometry. *Chemosphere* 2011; 85: 751-58. <http://dx.doi.org/10.1016/j.chemosphere.2011.06.054>
- [32] Kameda Y, Kimura K, Miyazaki M. Occurrence and profiles of organic sun- blocking agents in surface waters and sediments in Japanese rivers and lakes. *Environ Pollut* 2011; 159: 1570-6. <http://dx.doi.org/10.1016/j.envpol.2011.02.055>
- [33] Couteau C, Chauvet C, Papis E, Coiffard L. UV filters, ingredients with a recognized anti-inflammatory effect. *Plos One* 2012; 7: 1-6. <http://dx.doi.org/10.1371/journal.pone.0046187>

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