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Dermatology Research

Sunscreens' Percutaneous Absorption and Ingredients Concentration in Human Plasma and Urine: A Systematic Review

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ABSTRACT

Sunscreen application is widespread and incorporated into daily life. Although FDA has approved 16 sunscreen ingredients, recent studies suggest a revaluation of their potential adverse effects. This systematic review assesses sunscreens' percutaneous absorption, toxicity, and their ingredients concentration in urine and plasma. The search was conducted in Medline (PubMed), Scopus, Embase, and Cochrane until 05/08/2021. Data from 21 studies with related inclusion criteria were extracted. 18 studies reported sunscreen complications such as rash, irritation, immune system disorders, stratum corneum DNA damage, and hormonal disruption, 4 articles reported maximum concentration of sunscreen ingredients in plasma, and 4 articles reported urinary concentration of ingredients. In 2016, the FDA suggested a plasma concern level of 0.5 ng/mL for sunscreen ingredients. Sunscreen ingredients including avobenzone, octocrylene, ecamsule, homosalate, octisalate, enzacamene, octinoxate, and oxybenzone were detected more than 0.5 ng/mL after in blood 1-4 daily applications. Sunscreen application reduces the risk of sunlight harmful effects but could have advers effects related to their percutaneous penetration. Taken together, related data provide the impetus for detailed analysis of sunscreen toxicology. Also, highly adsorbed ingredients should be replaced with less adsorbed compounds to minimize body accumulation and the associated risks. Also, life time infant and children sunscreen exposure provide furthur impetus for in-depth toxicologic investigations.

Keywords
Sunscreen, Sun protection, Sunscreens adverse effect, Sunscreens ingredient, Percutaneous penetration, Plasma concentration, Urine concentration.

Abbreviations
SPF: Sun Protection Factor, UVR: Ultraviolet Radiation, GRASE: Generally Recognized as Safe and Effective, MPPD: Minimal Persistent Pigment Darkening, MED: Minimal Erythema Dose.

Introduction
Sunscreen products especially those designed for human sun protection are available in the market as creams, gels, lotions, oils, sticks, and sprays [1] and are classified as over-the-counter drugs in the USA. The first use of primary synthetic sunscreens was in 1928 and the first major commercial product was marketed in 1936 [2]. Approximately, one-third of adults usually or always utilize sunscreens when in the sun: 14% of males and 29% of females in the US use sunscreen regularly on their faces and other body parts [3]. Sunscreens are divided into physical and chemical sunscreens [4]. Physical sunscreens such as titanium dioxide and zinc oxide function by scattering, reflecting or blocking UVA, UVB, and UVC radiations [5]. Most Sunscreens contain organic compounds such as aminobenzoic acid, avobenzone, cinoxate, dioxybenzone, ensulizole, homosalate, menthyl anthranilate, mexoryl S.X., octocrylene, octyl methoxycinnamate, octyl salicylate, oxybenzone, padimate O, phenyl benzimidazole, sulisobenzone, and trolamine salicylate which act by absorbing UV radiation and scattering solar energy [6-9]. Recently, sunscreens consumption has increased and starts from 6 months of age [10].

Repeated long-term UVR contact leads to skin aging and increasing skin cancer risk [11]. UVB affects DNA damage, epidermis hyperplasia, and skin inflammation [12]. Skin cancer is the most common cancer [13]. Almost 5 million new skin cancer cases are reported annually in the US, comprising approximately 90,000 melanomas, the deadliest skin cancer. Sunscreen's actives used in personal care and cosmetics can absorb UVA (320–400 nm) and UVB (290–320 nm) photons energies [14,15]. FDA-approved sunscreens is provided in 'supplement file' (Table 1).

Recently, reports regarding sunscreens' adverse effects have increased; around 12% of users report irritation [10-16]. Recently, concern of potentil internal organ effects has increased. Systemic exposure has been observed in *in-vitro* and *in-vivo* studies [16-22]. FDA proposed a steady-state concentration of 0.5 ng/ml in the bloodstream for the sunscreens' active ingredients as a safety threshold [23].

Benzophenone-3 (BP-3) concentration in the bloodstream by FDA is up to 6% [24,25]. The results of a study on 25 volunteers who applied a sunscreen containing 4% BP-3, twice daily, for 5 days, indicated that there was accumulation in the amount excreted with repeat administration and that 1.2-8.7% (mean 3.7%) of the total amount of BZ-3 applied was excreted in urine [26].

In-vivo research studies on BP-3 effect on children's birth weight and gestational age [27] raised concerns about sunscreen's hormonal effects [28]. BP-3 also indicated proliferative effects on MCF-7 breast cancer cells [28]. BP-3 cytotoxicity may be caused by oxidative stress relevant to high Zn^{2+} intracellular levels [29].

Objective
This review evaluates sunscreens complications in human, clinical trials, their absorption and urinary, plasma concentration after application. Intended PICO in our study are as follows; population: all people who use sunscreen (any age or race), intervention: use of sunscreen (any form), comparison: no use of sunscreen, outcome: urinary concentration, plasma concentration, or complication.

Method
Protocol and registration
We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [30].

Eligibility Criteria
Inclusion criteria included English studies on the use of sunscreen in the human population and examination of the concentration of sunscreen ingredients in the blood or urine, or the side effects after sunscreen application. Exclusion criteria were review articles, case reports, in-vitro studies, and studies that not met the inclusion criteria.

Databases
The search was performed on PubMed (http:/ncbi.nlm.nih.gov / pubmed), Scopus (http:/WWW.scopus.com), Embase (http:/WWW.embase.com) and Cochrane (https:/www.cochranelibrary.com/) up to 05/08/2021, and all articles on sunscreen use in humans were studied.

Search strategy
Table 2, the 'supplement file', shows that the search was started and completed on 05/08/2021. Sunscreen agents, sun protection factor, sunscreen application and synonyms, toxicity, adverse effects, complications and synonyms, percutaneous absorption, percutaneous permeation, plasma concentration, urine concentration, circulation, and synonyms were the key search words. Search was not limited to the publication year, language, region, race, or any other conditions.

Study selection
A total of 3148 studies were included, 869 articles were duplicates and removed, and 2279 articles were screened by reviewers; articles were screened by two independent reviewers, and 358 articles remained after the title-abstract screening and evaluated in full text, stated in detail in PRISMA flow chart shown in Figure 1. Finally, 21 articles met inclusion criteria, and reviewers extracted the results. We selected studies which documented sunscreens usage complications, sunscreens ingredients concentration in

Table 1: Sunscreen Data from Articles That Reported Plasma Concentration.

Year	Num.	First author	Country	population			Follow up duration (days)	sunscreen										
				Population No.	Age (mean)	Sex ratio (Percentage of female)		Type	Avobenzone OR Butyl methoxydibenzoylmethane	Oxybenzone or benzophenone-3 or BP-3 OR BZP-3	Octocrylene (OCT)	Ecamsule	Enzacamene OR 3-(4-methylbenzylidene) camphor (4-MBC)	Octyl methoxycinnamate or ethylhexyl methoxycinnamate or octinoxate (OMC)	Amount used (mg/cm²)	Use in which parts of the body (percentage from whole body)	How many days application	How many times application per day
2020	1	Matta MK	United States	12	45.1	50%	21	lotion	3%	4%	6%	Nm	Nm	Nm	2 mg/cm²	75%	4	Once on day 1 and 4 times per day for day 2, 3, and 4
2020	2	Matta MK	United States	12	41.4	50%	21	Aerosol Spray	3%	6%	10%	Nm	Nm	Nm	2 mg/cm²	75%	4	Once on day 1 and 4 times per day for day 2, 3, and 4
2020	3	Matta MK	United States	12	39.2	50%	21	Non-aerosol Spray	3%	Nm	10%	Nm	Nm	7.5%	2 mg/cm²	75%	4	Once on day 1 and 4 times per day for day 2, 3, and 4
2020	4	Matta MK	United States	12	29	50%	21	Pump Spray	3%	Nm	Nm	Nm	Nm	7.5%	2 mg/cm²	75%	4	Once on day 1 and 4 times per day for day 2, 3, and 4
2019	5	Matta MK	United States	6	42/5	50%	7	spray	3%	6%	2/35%	0	0	0	2 mg/cm²	75%	4	4
2019	6	Matta MK	United States	6	33/7	50%	7	spray	3%	5%	10%	0	0	0	2 mg/cm²	75%	4	4
2019	7	Matta MK	United States	6	34/5	50%	7	lotion	3%	4%	6%	0	0	0	2 mg/cm²	75%	4	4
2019	8	Matta MK	United States	6	31/7	50%	7	cream	2%	0%	10%	2%	0	0	2 mg/cm²	75%	4	4
2019	9	Julia Hiller	Germany	20	24/5	50%	6	lotion	YES	0	YES	0	0	0	2 mg/cm²	Nm	NM	4
2019	10	Julia Hiller	Germany	20	24/5	50%	6	lotion	YES	0	YES	0	0	0	2 mg/cm²	Nm	NM	4
2007	11	NR Janjua	Denmark	17	65	100%	14	cream	0	10%	0	0	10%	10%	2 mg/cm²	100%	4	1
2007	12	NR Janjua	Denmark	15	26	0%	14	cream	0	10%	0	0	10%	10%	2 mg/cm²	100%	4	1

Table 2: Maximum concentration of sunscreen active ingredients observed in human plasma across

Num.	Maximum plasma concentrations																			
	Avobenzone				Oxybenzone				Octoclylene				Ecamsule				4-methylbenzylidene camphor		Octymethoxycinnamate (omc)	
	Mean (ng/ml)	Coefficient of Variation%	Min (ng/ml)	Max (ng/ml)	Mean (ng/ml)	Coefficient of Variation%	Min (ng/ml)	Max (ng/ml)	Mean (ng/ml)	Coefficient of Variation%	Min (ng/ml)	Max (ng/ml)	Mean (ng/ml)	Coefficient of Variation%	Min (ng/ml)	Max (ng/ml)	Mean (ng/ml)	Max (ng/ml)	Mean or median (ng/ml)	Max (ng/ml)
1	7.1	73.9	2.9	28	28.1	53.0	131.3	498.1	7.8	87.1	2.6	38.7	Nm	Nm	Nm	Nm	Nm	Nm	NM	NM
2	3.9	70.9	1	9	180.1	57.3	70.1	476.9	6.6	78.1	1.4	16.2	Nm	Nm	Nm	Nm	Nm	Nm	NM	NM
3	3.5	73.0	1	10	Nm	Nm	Nm	Nm	6.6	103.9	1.7	34.4	Nm	Nm	Nm	Nm	Nm	Nm	7.9	30.6
4	3.3	47.8	1.2	6.2	Nm	Nm	Nm	Nm	NM	NM	NM	NM	Nm	Nm	Nm	Nm	Nm	Nm	5.2	11.8
5	4	60/9	1/6	8/3	209/6	66/8	83/3	532	2/9	102	1	9/8	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm
6	3/4	77/3	1	7/3	194/9	52/4	89/3	350/1	7/8	113/3	2/5	20/4	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm
7	4/3	46/1	2/8	9/3	169/3	44/5	103/3	274/6	5/7	66/3	2/8	13/4	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm
8	1/8	32/1	1/1	2/7	Nm	Nm	Nm	Nm	5/7	47/1	2/9	10/3	1/5	166/1	0/5	12/1	Nm	Nm	Nm	Nm
9	4	Nm	Nm	11/3	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm
10	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	11/7	Nm	Nm	25	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm
11	Nm	Nm	Nm	Nm	187	Nm	Nm	200	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	16	20	7	10
12	Nm	Nm	Nm	Nm	238	Nm	Nm	300	Nm	Nm	Nm	Nm	Nm	Nm	Nm	Nm	18	20	16	20

Table 3; sunscreen ingredients in articles that reported urine sample

Year	First author	Country	Population			Type	Sunscreen ingredient																					
			Number of sunscreen users	Age (mean)	Sex ratio (percentage of female)		Avobenzone*[1]	Oxybenzone*[2]	Octocrylene*[3]	Enzacamene*[4]	Octinoxate*[5]	Titanium dioxide	Octyl salicylate*[6]	Silicon dioxide*[7]	Acrylates*[8]	Dioxybenzone*[9]	disodium edta or trisodium edta	Dimethicone*[10]	Tocopherol*[11]	Propylheptyl caprylate	vp/hexadecene copolymer	Panthenol	Coumarin*[12]	Citronellol*[13]	Benzyl salicylate*[14]	Linalool*[15]	Sodium hydroxide	Ethylhexylglycerin*[16]
2019	Julia hiller	Germany	20	24/5	50%	lotion	yes		yes			yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
2019	Julia hiller	Germany	20	24/5	50%	lotion	yes		yes			yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
2007	nr janjua	Denmark	17	65	100%	cream		yes		yes	yes																	
2004	nr janjua	Denmark	15	26	0%	cream		yes		yes	yes																	
2002	gustavsson gonzalez, h.	Sweden	11	26	36%	lotion		yes																				

[1]* avobenzone or butyl methoxy dibenzoyl methane
[2]* oxybenzone or benzophenone-3 or bp-3 or bzp-3
[3]* octocrylene or oct
[4]* enzacamene or 3-(4-methylbenzylidene) camphor (4-mbc)
[5]* octyl methoxycinnamate or ethylhexyl methoxycinnamate or octinoxate (omc)
[6]* octyl salicylate, or 2-ethylhexyl salicylate or butyloctyl salicylate or ethylhexyl salicylate
[7]*hydrated silica or silicon dioxide
[8]* c12-22 alkyl methacrylene copolymer or c10-30 alkyl acrylate or acrylates
[9]* c12-15 alkyl benzoate or dioxybenzone
[10]* dimethicone or polydimethylsiloxane, stearoxy dimethicone
[11]* tocopheryl acetate or tocopherol or vit e acetat
[12]* coumarin or 2h-chromen-2-one
[13]* citronellol or dihydrogeraniol
[14]* benzyl salicylate or salicylic acid benzyl ester
[15]* terpene alcohol or linalool
[16]* ethylhexylglycerin, or octoxyglycerin, or glyceryl ether

Table 4: sunscreen ingredients in urine samples according to studies which shows the high absorption of these substances

First author	The amount used (mg/cm^2)	Use in which parts of the body (percentage)	How many days use	How many times a day	Follow up duration (days)	urine concentration														
						Avobenzone			Benzophenone-3				Enzacamene OR 3-(4-methylbenzylidene) camphor 4-mbc			Octyl methoxycinnamate or ethylhexyl methoxycinnamate or octinoxate (omc)			Octocrylene (OCT)		
						mean (ng/ml)	min	max	percentage	mean (ng/ml)	min	max	mean	min	max	mean	min	max	mean	min	max
Tatsuya kunisue	Not report								6%												
Julia hiller	2			4	6	1/7	1/5	1/9													
Julia hiller	2			4	6														7/9	6/9	8/9
Nr janjua	2	100%	4	1	14					44		60	4		5	6	5				
Nr Janjua	2	100%	4	1	14					81		140	4		7	4		8			
Gustavsson Gonzalez	4	100%			2				5%	9/8		11									

Table 5: characteristics of articles that reported adverse effects

Year	Num.	First author	Country	Population				Sunscreen
				Population number		Age (mean)	Sex ratio	Type
				Sunscreen Users	Control group		percentage of female	
2020	1	Matta MK	United States	12	0	45.1	50%	Lotion
2020	2	Matta MK	United States	12	0	41.4	50%	Aerosol Spray
2020	3	Matta MK	United States	12	0	39.2	50%	Nonaerosal Spray
2020	4	Matta MK	United States	12	0	29	50%	Pump Spray
2019	5	Matta MK	United States	6	0	42/5	50%	spray
2019	6	Matta MK	United States	6	0	33/7	50%	spray
2019	7	Matta MK	United States	6	0	34/5	50%	lotion
2019	8	Matta MK	United States	6	0	31/7	50%	cream
2019	9	Lindstrom, A. R.	Nambour	812	809	Nm	44%	Nm
2014	10	Katie Beleznay	Canada	23	0	41/5	100%	Nm
2009	11	ALASTAIR C. KERR	France	94	0	44	Nm	Nm
2010	12	Numano, K.	Japan	41	0	7/8	Nm	Nm
1987	13	English, J. S. C.	United Kingdom	280	0	Nm	Nm	Nm
2003	14	Choi, J.	South Korea	200	0	Nm	Nm	ointment
2017	15	Anežka Sharma	Nm	2	2	28	100%	lotion
2015	16	Boonchai, W.	Thailand	30	0	34/1	93/30%	cream
1998	17	Berne, B.	Sweden	355	0	43/9	69%	Nm
1998	18	Berne, B.	Sweden	355	0	43/9	69%	Nm
1998	19	Berne, B.	Sweden	355	0	43/9	69%	Nm
1998	20	Berne, B.	Sweden	355	0	43/9	69%	Nm
1998	21	J. FARRERONS	spain	24	19	71	58%	cream
2016	22	Jorge Aburto-Corona,	USA	10	10	22/3	50%	Nm
2016	23	Jorge Aburto-Corona,	USA	10	10	22/3	50%	Nm
2012	24	A. Faurschou	Denmark	Nm	10	Nm	54%	Nm
2012	25	A. Faurschou	Denmark	7	Nm	Nm	54%	Nm
2012	26	A. Faurschou	Denmark	7	Nm	Nm	54%	Nm
2012	27	A. Faurschou	Denmark	7	Nm	Nm	54%	Nm
2012	28	A. Faurschou	Denmark	6	Nm	Nm	54%	Nm
2007	29	NR Janjua	Denmark	32	32	Nm	53%	cream
2004	30	NR Janjua	Denmark	32	32	65	53%	cream
1997	31	Hayag, M. V.	USA	9	9	40	33%	Nm
1995	32	marks.r	Australia	113	113	Nm	Nm	Nm

Table 6: Sunscreen's adverse effect

Num.	SPF	The amount used (mg/cm^2)	Use in which parts of the body	How many days use	How many times a day	Follow up duration (days)	Complications															
							Rash	Irritation	Deaths			Cardiovascular disease deaths			Cancer deaths			Immune system disorder	Significant DNA damage in stratum corneum	Hormonal disruption	Decrease 25-hydroxy vitamin D levels	Hindered effective sweating
							percentage	percentage	percentage in case group	percentage in control	hazard ratio	percentage in case	percentage in control	hazard ratio	percentage in case group	percentage in control group	hazard ratio					
1		2	75%	4	4	21	8.3%	8.3%														
2		2	75%	4	4	21	50%	0														
3		2	75%	4	4	21	42%	0														
4		2	75%	4	4	21	17%	0														
5		2	75%	4	4	7	17%															
6		2	75%	4	4	7	17%															
7		2	75%	4	4	7	17%															
8		2	75%	4	4	7	17%															
9			27%	1460	1	7665			20%	21%	0/94	7%	9%	0/77	8%	7%	1/09					
10		patch	9%	2	1	5		17/39%														
11		patch	9%	2	1			5%														
12			99%	28	0/43		0%															
13		Patch test		4	1		5%															
14					1		4%															
15		26/4	9%	1	3	0/33		yes										yes	yes	yes		
16	60		5%	90		90		30%														
17			patch	2	1	3		4/22%														
18			patch	2	1	3		3/38%														
19			patch	2	1	3		1/70%														
20			patch	2	1	3		0/56%														
21	15		27%	730	1																yes	
22	50	1	9%																			
23	50	1	9%																			yes
24	8		25%			3															yes	
25	8	0/5	25%			3															yes	
26	8	1	25%			3															yes	
27	8	1/5	25%			3															yes	
28	8	2	25%			3															yes	
29		2	100%	4	1	14														yes		
30		2	100%	4	1	14														yes		
31	30		10%	7	1	30		90%														
32	17				1																yes	

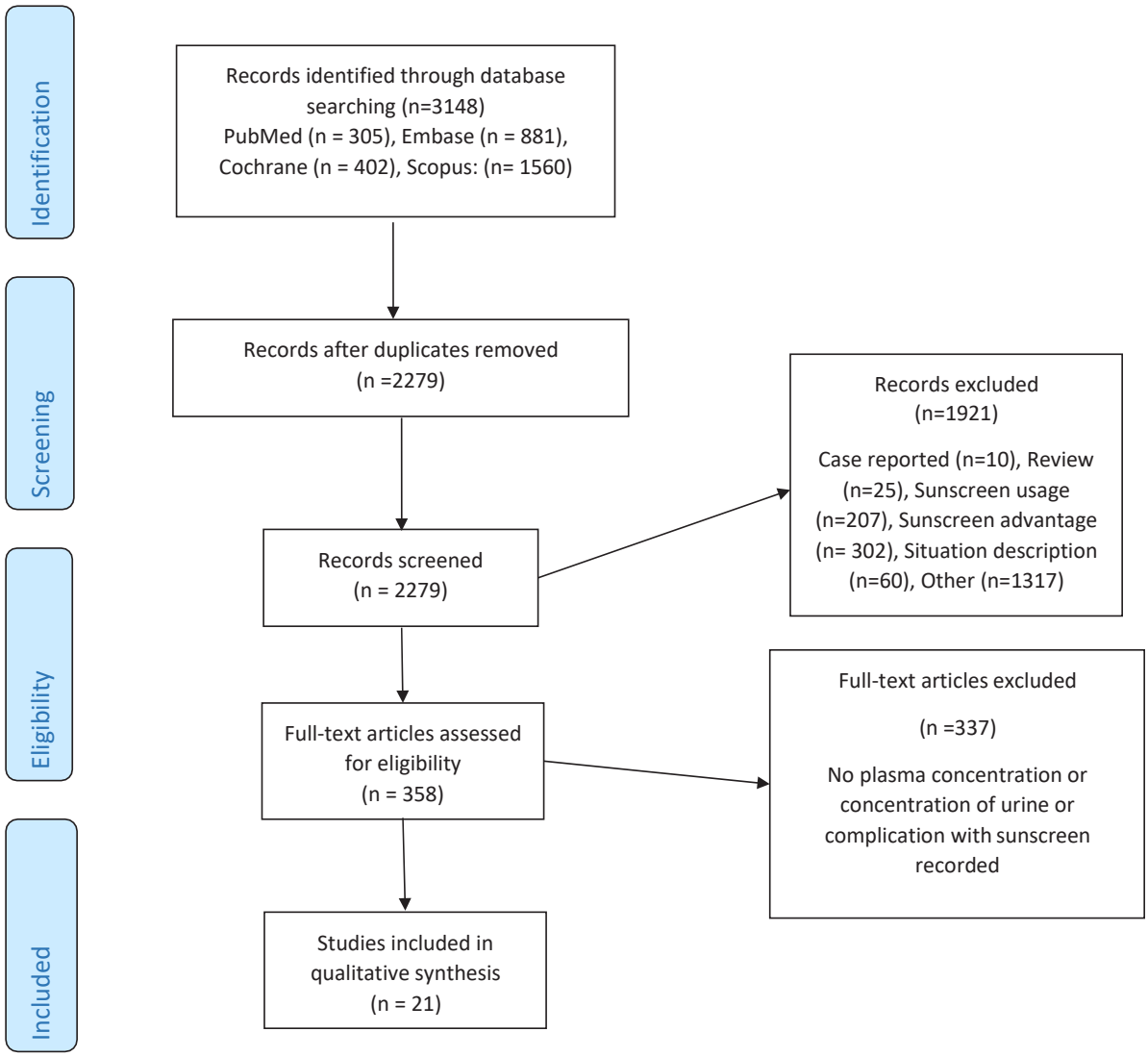

Figure 1: PRISMA flow diagram of study selection

human plasma and urine within one day to several years in the partial or whole body.

Result

The study screening process is summarized in the flow diagram (tableure 1). Among 21 articles for data extraction, 4 reported maximum plasma concentrations of sunscreen ingredients (Tables 1 and 2), 4 articles reported ingredients concentration in urine (Tables 3 and 4), and 18 articles reported sunscreen usages complications (Tables 5 and 6).

Sunscreens Plasma concentrations

Sunscreen active ingredients - avobenzone, oxybenzone, octoclylene, ecamsule, homosalate, octisalate, enzacamene, and octinoxate - are systematically absorbed when applied to human skin. In 2008, Janjua et al. showed that sunscreens with 10% of each benzophenone-3, octinoxate and enzacamene were absorbed into the blood at maximum plasma concentrations of 187, 7, 16 ng/mL for females and 300, 20, 20 ng/mL for males, respectively [7]. Benzophenone-3 provided higher plasma concentrations than others. According to Matta et al., using 2 mg/cm^2 of several sunscreen preparations (lotions and sprays) in 75% of the body (containing oxybenzone, avobenzone, octocrylene, homosalate, octisalate, octinoxate, ecamusla) showed plasma concentrations of oxybenzone 169 to 209 ng/ml, avobenzone 1.8 ng/ml, octocrylene 5.7 ng/ml, homosalate 23 ng / ml, octisalate 5.8 ng/ml octinoxate 7.9 ng/ml, and ecamusla 1.5 ng/ml [31]. In a comparison between lotion and spray formulations used in this study, the lotions yielded higher active ingredients' concentrations in plasma. Systemic exposures of all ingredients remained above 0.5 ng/mL for more than 50% of participants up to 7 days for avobenzone, octisalate, and octinoxate; 10 days for octocrylene; and 21 days for homosalate and oxybenzone [31].

Matta et al. then studied with 48 participants to provide additional data on the systemic exposure of the active sunscreens ingredients

following a single application; residual skin amounts during the wash-out phase; plasma concentrations up to 17 days after the last application; and the systemic exposure to additional commonly used sunscreen ingredients, including octisalate, homosalate, and octinoxate. Systemic exposure of all the sunscreens in all products exceeded 0.5 ng/mL on a single application and remained above the threshold until 23 hours after application. Systemic exposures of all tested actives remained above 0.5 ng/mL in more than 50% of participants up to 7 days for avobenzone, octisalate, and octinoxate; 10 days for ocotocrylene; and 21 days for homosalate and oxybenzone [32]. Hiller et al. collected plasma and urine samples from 20 healthy volunteers before, during, and after a real-life exposure scenario (1st application: 2 mg/cm^2; 2nd and 3rd (after 2 and 4 h): 1 mg/cm^2 each) using a commercial sunscreen formulation for one day. They reported avobenzone concentrations as 11.7 ng / mL and octocrylene as 25.0 ng /mL in human plasma [33].

Urine Concentration

Kunisue et al. reported the highest concentration of hydroxylated benzophenone metabolite (2, 4 dihydroxybenzophenone) in urine (23 ng/ml) [34]. The average excreted benzophenone-3 in urine was 11 mg/ml, upon sunscreen application containing 4% BP-3 after 48 h which showed high skin permeability [35]. The lipophilic UV filter octocrylene and its metabolite 2-cyano-3, 3-diphenylacrylic acid showed much slower elimination than other hydrophilic UV filters, avobenzone, and octocrylene were detected in more than 20% of urine samples [33].

Accumulation of sunscreens and their metabolites in the human body occurs when exposures were repeated for several consecutive days. Application of sunscreen preparations containing 10% of each BP-3, octinoxate, and enzacamene (2 mg/cm^2) in the total body per day for a week resulted in mean urine concentrations of 60, 5, 5 ng/ml for females and 140, 7, 8 ng/ml for males, respectively [7]. Repeated whole-body benzophenone-3 application increased BP3 excretion after 2 days, which reached steady-state after 3 to 5 days, and then decreased [7]. Average urinary levels of octocrylene and avobenzone were 7.9 and 1.7 ng / ml, respectively, after 6 days of application, 4 times daily [33].

Adverse Effect

The adverse effect reported with sunscreens applications were rash, irritation, immune system dysfunction, significant stratum corneum DNA damage, hormonal disruption, decreased levels of 25-hydroxy vitamin D, and hindered effective sweating. In a randomized controlled trial conducted by Lindstrom, long-term sunscreen use was assessed on mortality of 1,621 Australian adults over 21 years old [36]. Results showed a higher mortality rate in the discretionary sunscreen group, but cancer death was higher in the daily sunscreen group [36]. Four studies reported skin rash, six irritation, three vitamin D decrease, and three hormonal disruption as an adverse effect following sunscreen use. In a study performed on 23 women by Beleznay K et al., after application of sunscreen including sulisobenzone (benzophenone-4) and para-aminobenzoic acid (PABA) on the face for 2 days, 18% irritation was observed [37]. Hayag applied a sunscreen including 10% octocrylene (OCT), 7.5% octyl methoxycinnamate (OMC), and 5% meradimate with SPF of 30 in 10% of the body area for 7 days and 30 days of follow-up caused 90% irritation [38]. Kerr et al., found sulisobenzone (benzophenone-4) and bisoctrizole caused 5% irritation [39]. Sunscreen lotion containing octyl methoxycinnamate (OMC), three times a day, caused irritation, immune system disorder, hormonal disruption, and significant stratum corneum DNA damage [40]. Sunscreens as a spray, lotion, and cream including avobenzone, oxybenzone, octocrylene, and ecamsule ingredients with different combinations applied on 75% of the body caused 17% rash [31]. In addition, 30% of participants using sunscreen containing polyethylene glycols, octyl salicylate, bemotrizinol, ensulizole, methyl methacrylate (MMA), homosalate, titanium dioxide, and avobenzone reported rash in a 90-day follow-up study in Thailand [41]. In the conducted studies by English et al., a patch test containing 2% chemical UV filters was used for 2 days on 280 participants, Choi et al. used to patch and photopatch containing 25% octylmethoxycinnamate, butylmethoxydibenzoylmethane, and octyltriazone for 2 weeks, on 200 participants, 5 and 4 % of the participants showed rash respectively [42,43]. Also, using 2 mg/cm^2 of sunscreen cream in the full-body for 4 days induced hormonal disturbance [7]. Daily sunscreen use with SPF 8 and 15, 17 caused a reduction in 25-hydroxyvitamin D levels [44-46].

Discussion

Plasma concentration

Sunscreen preparations are considered cosmetics in some countries, and there appears minimal in-depth toxicity evaluations to support their life long use safety. FDA recognizes certain requirements to support sunscreen safety and effectiveness [47]. Most sunscreens contain organic chemicals [6-8] with various amounts in sunscreen products, but acceptable levels are as high as 15% [23]. FDA issued a proposed regulation that considers most sunscreen active ingredients which are currently used are not classified as generally recognized as safe and effective (GRASE) due to a lack of adequate safety information in the US [48]. The rule also discussed the safety evidence recommended to support a decision on whether certain active ingredients are GRASE, including the need for information on human absorption. The key objective of the maximum usage trial is to help the FDA assess the expected level of human risk [48]. As mentioned, FDA sunscreen guidance on safety and efficacy accepted 0.5 ng/ml in the bloodstream as the regulatory threshold of sunscreen active ingredients [47]. Nonetheless, the public Access for Sunscreens Coalition proposed a higher concentration of sunscreen active ingredients in the bloodstream as a safety threshold of 20–200 folds (10–100 ng/ml). Ingredients absorption in the bloodstream can vary depending on factors including physicochemical characteristics of the active ingredient, formulation properties, and stratum corneum thickness, and structure [49-52].

Eight active ingredients - avobenzone, octoclylene, ecamsule, homosalate, octisalate, enzacamene, octinoxate, and oxybenzone - were found in the blood more than 0.5 ng/mL after 1-4 daily application on 75% of the body's surface. Oxybenzone (benzophenone-3) was detected at a higher level than other UV filters in plasma. Relatively, low human skin penetration was observed for octyl salicylate [53]. Oxybenzone, one of the most lipophilic UV filters highly penetrates into the skin. Data on safety assessment, internal organ carcinogenicity potential and reproductive effects, and clinical studies are essential.

Skin penetration studies on titanium dioxide (TiO_2) nanoparticles showed that they cannot infuse unbroken skin and can only be found in the stratum corneum and epidermis and do not reach the blood or peripheral organs [54,55]. Consequently, mineral sunscreens such as zinc oxide and TiO_2 do not significantly penetrate the skin and bloodstream and are usually considered safe [51].

According to this review, most organic sunscreen ingredients are absorbed to a greater extent than FDA anticipated and may accumulate in internal tissues.

Urine concentration

After sunscreen application on skin, organic sunscreens such as avobenzone, benzophenone-3, octocrylene, enzacamene, and octinoxate were found in urine [7,26,33,34]. Benzophenone-3 indicated the highest urine concentration among the UV filters [34].

Adverse Effect

Irritation and rash are common sunscreen complications widely reported [26,31,32,37-39,42,43). Sunscreens containing avobenzone, oxybenzone, ecamsule, para-aminobenzoic acid (PABA), and octocrylene cause rash and irritation [31,38,42,43]. A sunscreen lotion containing octyl methoxycinnamate (OMC) caused immune system dysfunction, stratum corneum DNA damage, hormonal disruption, and hindered effective sweating [40,56]. A decreased level of hydroxyl vitamin D levels was observed when using a sunscreen containing titanium dioxide. Due to the minimal knowledge in children about skin permeability, physical filters such as titanium dioxide and zinc oxide might be appropriate.

Safety and Tolerance

If the minimal persistent pigment darkening (MPPD) and minimal erythema dose (MED) are higher, the skin is less sensitive and more tolerant to solar radiation. Sunscreen acts as a first-line protection against ultraviolet radiation (UVR). It helps to delay the process of aging and reduce the incidence of skin cancer. The detrimental effect of frequent sub-erythematic exposure to human skin can be prevented by daily care and broad-spectrum sunscreen [57-59]. If the patients use sunscreen and are exposed to ultraviolet in small doses, their MPPDs and MEDs will be improved and UV tolerance will be enhanced [60].

Weaknesses and Strengths

The trials presented in this review have various weaknesses and strengths [7,31-46,56,61]. In most studies presented, the number of participants was small and the results are likely to be incomplete. In most studies, the research environment was the external environment to make the effect of sunlight on the cases more realistic, but in these studies, influential factors such as heat, humidity, wind, and cloud cover are not controlled. The type of formulation and the type of Fitzpatrick skin may affect sunscreen absorption. However, in some studies, Fitzpatrick skin types were not considered. Utilizing strengths and weaknesses of previous studies will aid planning the next generation of research.

Conclusion

Sunscreens reduce the harmful sunlight risks on skin. Adverse effects of sunscreen have not been conclusively documented in long term. To reduce the potential adverse effects, high systemic absorption ingredients might be substituted with less penetrating substances and those that can fully excreted.

Consumers should use these substances just in sun-exposed body areas to minimize their potential accumulation.

Sunscreen prescribers should pay close attention to sunscreen ingredients, particularly in children, pregnant women, and people with a history of skin diseases, hormonal disorders and vitamin D deficiency. Also, consider combining these substances with nanotechnology that remain only in the epidermis and may not enter the blood and circulation system, and prevent their accumulation in the body tissues and potential side effects. Together, life long use of sunscreens and high organic compounds percutaneous penetration suggest a wisdom need of additional acute and long term toxicologic evaluations.

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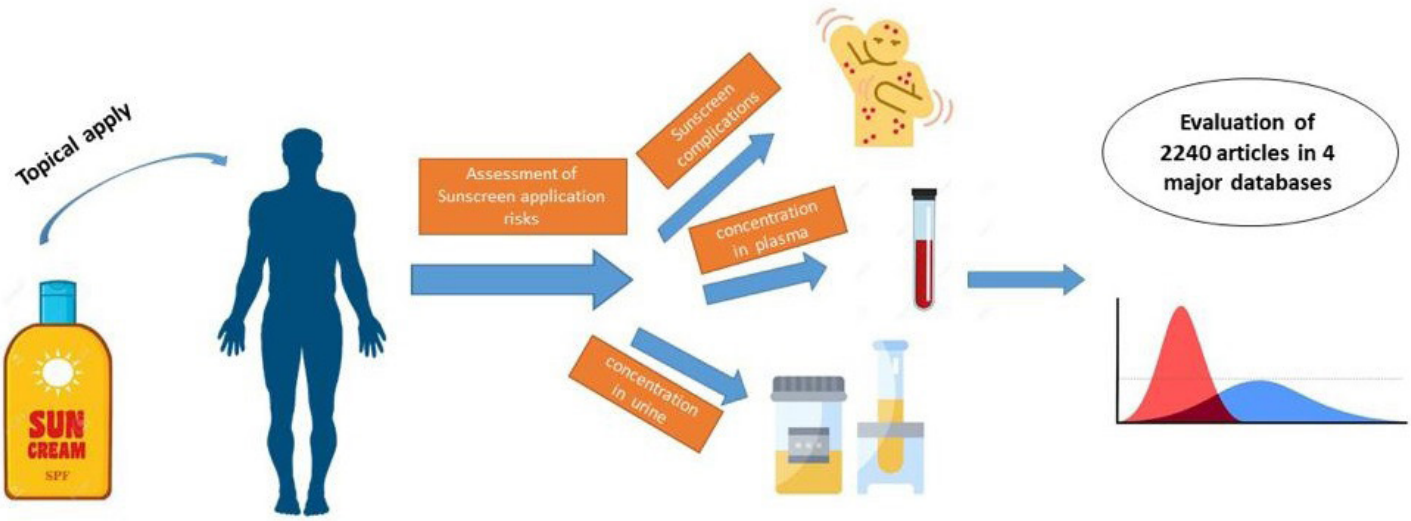
Graphic Abstract



Supplement Table 1: Active sunscreen ingredients are approved by the FDA (Preclinical PK/PD and Toxicology Services for Sunscreen). All are chemical except Titanium dioxide and Zinc Oxide.

FDA Monograph Sunscreen Ingredients	Mechanism of sun prevention	
	UVA	UVB
Aminobenzoic acid (PABA)		✓
Avobenzone	✓	✓
Cinoxate	✓	✓
Dioxybenzone	✓	✓
Ecamsule	✓	✓
Homosalate		✓
Menthylanthranilate	✓	✓
Octocrylene	✓	✓
Octyl methoxycinnamate	✓	✓
Octyl salicylate		✓
Oxybenzone	✓	✓
Padimate O		✓
Phenylbenzimidazole		✓
Sulisobenzone	✓	✓
Titanium dioxide	✓	✓
Trolamine salicylate		✓
Zinc Oxide	✓	✓

Supplement Table 2: Search Strategies.

Database	Search strategy
PubMed	((("sunscreen" OR "sun-screen" OR "sunscreen application" OR "Sunscreening Agents" [Pharmacological Action] OR "Sun Protection Factor"[Mesh]) AND ("adverse effects" OR "Sunscreening Agents/adverse effects"[Mesh] OR "adverse drug reaction" OR "poisoning" OR "Sunscreening Agents/ poisoning"[Mesh] OR "intoxication" OR "Toxi*" OR "Sunscreening Agents/toxicity"[Mesh] OR "Permeability" OR "skin permeability" OR "hazard" OR "health hazard" OR "Safety"[Mesh] OR "risk assessment" OR "drug concentration" OR "Blood Circulation"[Mesh] OR "circulation")) AND ("Pragmatic Clinical Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "Clinical Trial, Phase II" [Publication Type] OR "Clinical Trial, Phase I" [Publication Type] OR "Randomized Controlled Trial" [Publication Type] OR "Clinical Trial" [Publication Type] OR "Clinical Trial Protocol" [Publication Type]))
Scopus	TITLE-ABS-KEY (({sunscreen} OR {sun-screen} OR {sunscreening agents} OR {sun protection factor}) AND ({adverse effects} OR {adverse drug reaction} OR {poisoning} OR {intoxication} OR {toxicity} OR {permeability} OR {skin permeability} OR {hazard} OR {health hazard} OR {safety} OR {risk assessment} OR {drug concentration} OR {blood circulation} OR {circulation}) AND ({human} OR {man} OR {men} OR {woman} OR {women})) AND (LIMIT-TO (DOCTYPE , "ar"))
Embase	('human'/exp OR 'homo sapiens' OR 'human' OR 'human being' OR 'human body' OR 'human race' OR 'human subject' OR 'humans' OR 'man (homo sapiens)') AND ('sunscreen'/exp OR 'anti sunburn preparation' OR 'antisunburn agent' OR 'sun burn protective agent' OR 'sun cream' OR 'sun protection factor' OR 'sun protective agent' OR 'sun protective factor' OR 'sun screen' OR 'sunburn oil' OR 'sunburn protecting agent' OR 'suncream' OR 'sunscreen' OR 'sunscreen agent' OR 'sunscreen product' OR 'sunscreen products' OR 'sunscreening agents') AND ('adverse event'/exp OR 'adverse effect' OR 'adverse effects' OR 'adverse event' OR 'adverse events' OR 'adverse reaction' OR 'intoxication'/ exp OR 'mptp poisoning' OR 'acute intoxication' OR 'carbon tetrachloride poisoning' OR 'chronic intoxication' OR 'endogenous intoxication' OR 'intoxication' OR 'intoxification' OR 'overdose' OR 'poisoning' OR 'poisoning, mptp' OR 'toxic injury' OR 'toxicosis' OR 'toxicity'/ exp OR 'hypertoxicity' OR 'subacute toxicity' OR 'tissue toxicity' OR 'toxic actions' OR 'toxic effect' OR 'toxicity' OR 'toxigenicity' OR 'permeability'/ exp OR 'permeability' OR 'permeability constant' OR 'tissue permeability' OR 'skin permeability'/exp OR 'cutaneous permeability' OR 'permeability, skin' OR 'skin permeability' OR 'skin water permeability' OR 'hazard'/exp OR 'danger' OR 'dangerousness' OR 'hazard' OR 'health hazard'/exp OR 'hazard, health' OR 'health hazard' OR 'health risk' OR 'safety'/exp OR 'safety' OR 'safety management' OR 'safety precaution' OR 'safety protection' OR 'safety regulation' OR 'risk assessment'/exp OR 'assessment, safety' OR 'risk adjustment' OR 'risk analysis' OR 'risk assessment' OR 'risk evaluation' OR 'safety assessment' OR 'circulation'/exp OR 'blood circulation' OR 'circulation' OR 'circulatory tract' OR 'blood level'/exp OR 'blood concentration' OR 'blood level' OR 'plasma concentration' OR 'plasma level' OR 'serum concentration' OR 'serum level' OR 'urine level'/exp OR 'urinary level' OR 'urine level') AND ('clinical trial'/exp OR 'clinical drug trial' OR 'clinical trial' OR 'major clinical trial' OR 'trial, clinical' OR 'randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled')
Cochrane	('sunscreen' OR 'sun-screen' OR 'sunscreen application' OR 'sunscreening agents' OR 'sun protection factor') AND ('adverse effects' OR 'adverse drug reaction' OR 'poisoning' OR 'intoxication' OR 'toxi*' OR 'permeability' OR 'skin permeability' OR 'hazard' OR 'health hazard' OR 'safety' OR 'risk assessment' OR 'drug concentration' OR 'blood circulation' OR 'circulation') AND ('humans' OR 'human')