J. Soc. Cosmet. Chem., **28**, 667–679 (November 1977)

Reduction of topical irritation

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Received November 23, 1976. Presented SCC St. Louis Chapter Meeting, September 20, 1976; and SCC New York Chapter Meeting, October 6, 1976.

Synopsis

ANTIIRRITANT effects noted since 1965 are reviewed and grouped into two major chemical categories: IMIDAZOLE and HYDROXY compounds. Several miscellaneous types are also noted: PVP (Polyvinyl pyrollidone), quaternary ammonium complexes, and amido sulfosuccinate surfactants.

The "no tears" antiirritancy effect, which results from a combination of AMPHOTERIC surfactants with lauryl sulfates is postulated as resulting from a possible difference in sorption rates which allows the amphoteric to "occupy" the cornea's available binding sites before the anionic can do so, thus preventing "denaturing" damage to the eye by the lauryl sulfate.

INTRODUCTION

Some 12 years ago Goldemberg (1) presented a paper to the Third IFSCC Congress on the use of antiirritants in cosmetic formulations. Its major thesis was that the topical irritation potential of cosmetic ingredients depends as much on their extrinsic "formulation environment" as on intrinsic properties of the ingredients themselves.

That initial paper, plus several subsequent ones touching peripherally on this subject, proposed three possible mechanisms of action by which antiirritants may function: (1) *via* complexation of the irritant; (2) by blocking otherwise chemically reactive sites of skin keratin; and (3) by preventing complete physical contact with the skin.

We have no reason to change this overall view today, and in fact, we provide in this paper a considerable expansion of the original reference section of that 1965 paper, thus bringing the subject to date. We have now had time to explore many of these phenomena in depth. Many clear cut accomplishments have been achieved in this area during the past decade—including a number of newly issued patents covering antiirritant activity of various compounds. The "desensitization" (of perfume components) *via* nonimmunologic processes is now also being actively explored (23, 59).

It is the purpose of this paper to summarize such recent developments in the field of antiirritancy, and to offer theoretical considerations linking together as many of them as possible.

GENERAL

The basic concept first enunciated in 1965 still holds: it is possible to change the irritation potential of topically applied raw materials by varying their "formula environment." Materials, which *per se* are soothing to the skin, occasionally reverse their roles and increase topical or eye irritation levels in certain types of formulations. On the other hand, strong irritants can frequently be rendered totally innocuous by combining them with precise (usually small) percentages of other ingredients. It is such other ingredients which we herein define as "antiirritants."

There are several probable mechanisms by which some compounds are able to reduce topical or eye irritation of other ingredients. Some of these processes are more or less mechanical, depending primarily on physical factors for their "activity" in this respect. However, we must not confuse such physical effects with specific antiirritancy of a chemical nature. To avoid later confusion between these two phenomena, we shall first briefly review recently noted *physical* effects, to preclude them from later discussion of antiirritancy operating *via* mechanisms of chemical reactivity.

PHYSICAL ANTIIRRITANCY

The simplest physical effect is diminution of skin contact by the irritant—applying oily substances to the skin prior to application of aqueous irritants (such as greasing the forehead and temples before applying caustic hair straighteners); and gelling (or otherwise thickening) products to reduce intimate skin contact. Gelled shampoos and bubble baths frequently are not irritants when tested "as is." Once diluted to the point where they flow readily, however, they often become primary skin and eye irritants (56). Perhaps related to viscosity and consequent skin penetration are the well known phenomena that light mineral oils (40 *visc.* and under) are irritants, medium weight (70 *visc.*) oils are neutral, and heavy mineral oils are antiirritants.

The rate of sorption of surfactants onto keratin surfaces has been shown by Garrett (2) to relate directly to their irritation potential. Another rather purely physico-chemical factor affecting irritation response is the loosening of hydrophobic bonds, discussed at length recently by both Dominguez (3) and Hall (4) at the Ninth IFSCC meeting. At this same meeting, Suzuki pointed (5) to the correlation between skin irritancy and rate of penetration (into sebaceous glands by isopropyl myristate, glyceryl trioleate, etc.). The partition coefficient between pharmaceutical vehicles and skin fat has been discussed by both Rabinowitz (6) and Goldemberg (7) as a probable factor determining substantivity and the associated irritation potential of certain active ingredients. Various proteins and partially degraded collagens have been cited for their "protective colloid" and other inactivating effects (8,9,10,11,12,13,20), while partially depolymerized chitin and/or pulverized egg shells appear to promote wound healing (14,15,16,47), perhaps simply by acting as foci for epithelial granulation. Note that Chitin contains D-Glucosamine as a major constituent.

Reduction of pH is probably the sole reason that addition of ammonium carbonate reduces irritation of thioglycolate permanent waves (17). Several authors have also pointed out (18,19) that climatic influences should not be ignored when judging the results of human irritation testing, especially large scale tests such as the Food and

Drug Administration's recent study of the cosmetic use habits and skin irritation responses of 10,000 typical American families.

Inhibition of polymerization (and/or oxidation) perhaps explains the observed usefulness of Vitamin E (30), of the reduction of lanolin sensitizations over the years (21), of the value of Na_2SO_3 in Paraphenylene diamine (PPD) hair dyes (24), and the reduction of uv-induced skin cancers *via* ingestion of antioxidants (25). The "quenching phenomenon" (22,23,27,61) has also been connected with prevention of the formation of oxidative resins in perfume aldehydes.

Keratin substantivity of compounds also affects their irritation, sensitization and/or antiirritant potential, as pointed out by Goldemberg (7,26,27) in regard to Ni^{++} and other materials. Scheuplein and Ross (28) showed that irritancy of sodium lauryl sulfate (SLS) and other surfactants correlates to their keratin denaturing ability, to their effect on its water binding capacity, and to their ability to liberate (SH) groups from keratin. Bettley (29) showed similar effects for sodium laurate, while Dominguez *et al.* (3) recently tied much of this data to the peak sorption (onto keratin), which occurs as the surfactant approaches the C_{12} chain length.

Finally, the shape of the molecule (its size and the molecular location of irritating moieties) affect the degree and type of irritancy produced. Dominguez *et al.* (3) gave us an excellent discussion of the effects of moving the SO_3 group from the first to the third carbon position in C_{12} alkyl sulfates. When the sulfonate is in the "normal" (No. 1) position, lauryl sulfate surfactants have a much smaller molecular configuration, are much more irritating, sorb more strongly onto keratin, and extract more soluble protein than do lauryl sulfates whose SO_3 group is attached to carbon No. 3. Other workers have also shown the frequent association between keratin sorption, protein extraction capability, and irritation reactions caused by alkyl sulfate surfactants.

By contrast, sucrose ester surfactants (claimed by Croda, Inc. to have almost no denaturing effect on skin proteins) apparently do not disrupt the skin's lipid layer. They are not only nonirritating *per se,* but have been shown to distinctly reduce irritation of lauryl ether sulfate formulations (Table I).

Table I
Effect of Two Ethoxylated Nonionics on an Amphoteric Shampoo Base
(Average Draize scores, 6 rabbits)

I. 30 Per Cent Shampoo base, 70 Per Cent water

24 h	7 days
18	6.5

II. 30 Per Cent Shampoo base, 5 Per Cent POE 20 sorbitan monolaurate, 65 Per Cent water

24 h	7 days
19	5.0

III. 30 Per Cent Shampoo base, 5 Per Cent sucrose monolaurate, 65 Per Cent water

24 h	7 days
18	3.0

SHAMPOO BASE

20.0	Amphoteric-10
7.0	Na lauryl ether sulfate (1 mol Et0)
1.0	Coconut DEA superamide (1:1)
2.0	Propylene glycol
30.0	

CHEMICAL ANTIIRRITANCY

During the past decade, many observed antiirritancy effects resulting from both planned investigations and fortuitous formulating practices appear to cluster around two major types of chemical compounds: *imidazole* derivatives and various *hydroxy* compounds. Investigators reporting such results have not generally appeared to be aware that their work falls into the following two major groupings.

I. IMIDAZOLE COMPOUNDS:

Kawakami (31) claims "antiphlogistic and antihistaminic" activity from use of 0.08 to 10 per cent hydroxyethyl-4,5 diphenylimidazole. His data (Table II) clearly show such an effect. Libby (33) reacted imidazoline with methyl acrylate and various acrylamides, forming compounds which (at 2 per cent levels) reduce the eye irritation of shampoos and hair grooms containing ethoxylated amides and/or quaternary ammonium compounds.

Imidazolidinyl urea ("Germall 115") is an active bactericide which Lanzet (34) showed to distinctly reduce the primary irritation of a liquid make-up (*via* 48-h closed human patch testing) when added at 0.2 per cent levels (Tables III & IV). Other urea compounds, clathrates of various cosmetic oils in combination with inorganic pigments, are currently being investigated for their antiirritant properties (52). A recent Canadian patent (48) describes the use of 3 per cent imidazol-3-oxyalcanoic acid (and its metal salts) in cosmetic preparations for this purpose.

The antiirritant effects of imidazoline amphoteric surfactants are also well-known, due to their current common use in baby and "no tears" shampoos. Originally produced under Hans Mannheimer's "Miranol" patents (32), they are now offered by several other firms as well.

Of particular interest in this amphoteric surfactant series is the fact that C_{10} and C_{12} mono- and di-carboxylic imidazoline surfactants (those of major commercial interest) show the least irritation *per se* and (frequently) show the most potent antiirritant properties. If keratin sorption of amphoterics eventually turns out to peak at the C_{12} chain length (as has already been demonstrated for the alkyl sulfates), one can only conclude that in this particular case, sorption is *good.* Perhaps, keratin sorption of imidazoline amphoteric surfactants occurs preferentially to that of the lauryl sulfates and similar anionics, thereby preventing denaturation *via* blocking the limited number of binding sites available on the cornea. Perhaps such preferential sorption is responsible for the well-known "no tears" effect, which results when amphoterics (plus polysorbate 20) are added to typical anionic shampoo formulations. Another possibility is that such amphoterics (and the Polysorbate?) form a complex with lauryl sulfates via hydrogen bonding, and that this complex (a new entity) simply has different irritational properties.

Manufacturers of such amphoteric compounds would be well advised to run studies designed to measure relative sorption rates of the amphoteric and anionic alone, and of combinations thereof. Such studies would tell us a great deal about the mechanism by which certain imidazoline derivatives provide antiirritancy.

Table II
1-Hydroxyethyl-4, 5-Diphenylimidazole
(Antiphlogistic and Antihistaminic Composition)

Control Scores (No Imidazole)		With Imidazole Per Cent Imidazole	Score
10	Cold cream	0.08%	1
2	Vanishing cream	0.03%	0
10	Face "milk" lotion	0.10%	0
5	Face lotion	0.04%	0

Primary skin irritation (10 skin-sensitive humans). Results reported in U.S. Pat. 3,504,090 to Iwao Kawakami (1970).

Table III
Antiirritant Effect of Imidazolidinyl Urea Preservative
(48 h Closed Patch Test of a Liquid Make-up on 100 Humans)

I. Liquid make-up (control):
94 persons showed (0) reaction
4 persons showed (+) reaction
2 persons showed (++) reaction
II. Same liquid make-up + 0.25 per cent Germall 115:
98 persons showed (0) reaction
2 persons showed (+) reaction
0 persons showed (++) reaction

Table IV
Antiirritant Effect of Acetamide MEA on SLS

	Ratio (MEA/SLS)	Conjunctival Scores* (Mean Value)
3 Per cent SLS	0	14.7
3 Per cent SLS + 0.35 per cent MEA	0.16	11.3
3 Per cent SLS + 3 per cent MEA	1.0	8.7
3 Per cent SLS + 7 per cent MEA	2.5	9.3
3 Per cent SLS + 15 per cent MEA	5.0	2.6

*Draize eye irritation scores.

II. HYDROXY COMPOUNDS

The many recent reports of antiirritant properties attributed to diverse hydroxy compounds suggest that perhaps a general principle is operating here, a broad reaction mechanism.

We summarize these reports very briefly: Polysorbate 20 has been patented for shampoo use by Bollch *et al.* (35). Esters of branched chain fatty alcohols with hydroxystearic acid have been patented by Jacobi (36,37) to reduce skin irritation and defatting of the dermis (Table V). Sucrose esters (with HLB ranges as high as 14.5) are claimed by Croda, Inc. to be nonirritating to the skin and eyes, to have no denaturing

Table V
Irritation-Reducing Effects from Topical Use of C8 Fatty Alcohol Esters of Hydroxy Fatty Acids*

		Primary Irritation Score (Skin)
1.4 Per cent	Na lauryl sulfate	4.28
5.0	Na lauryl sulfate	3.56
4.5 0.5	Na lauryl sulfate 2,6-dimethyl-octyl-hydroxy stearate	3.06
4.5 0.5	Na lauryl sulfate a-ethyl-hexyl-ricinoleate	2.73
4.5 0.5	Na lauryl sulfate 2,6-dimethyl-octyl-ricinoleate	2.57
4.5 0.5	Na lauryl sulfate a-ethyl-hexyl-12-hydroxy stearate	2.45

*(U.S. Patent 3,906,106 to Otto K. Jacobi (9/16/75).

effect on cutaneous proteins, and to act as antiirritants with effects substantially similar to those shown by Polysorbate 20 (Table I)(CTFA label designation).

Work previously reported by Goldemberg (1) demonstrated two such hydroxy compound effects: Polysorbate 20 (in combination with an acetylated monoglyceride) reduced the eye irritation of an aluminum antiperspirant preparation, and Pluronic F68, a polypropylene/polyethylene block polymer, totally nullified primary irritation otherwise produced by an alcoholic cologne. Edlich *et al.* (38) later singled out this same block polymer as having particular interest, demonstrating that the ethylene oxide content of such polyols is the determinant of tissue toxicity. It has also been found to detoxify iodine (57), as does PVP. Henkel Inc. (39) has shown that "higher ethoxylated lauryl sulfates" significantly reduce the eye irritation of shampoo formulations based on fatty alcohol sulfonates.

Riso (60) pointed out that the 7 mol EtO lauryl sulfate is completely nonirritating to the eye, but unfortunately foams poorly. It can be "boosted" with up to 5 per cent triethanolamine dodecyl benzene sulfonate, a good foamer which is very mild in the eye (up to this level.) Use of this alkyl aryl compound is restricted in the United States in bubble baths, however, due to its potential for vaginal irritation when applied in concentrated solutions.

As mentioned above, Kawakami (31) demonstrated antiirritancy for hydroxyethyl-4,5 diphenylimidazole. Peck and Spoor (40) have each confirmed that topically applied dihydroxy-phenylamine (ℓ-DOPA) reduces the number of sensitization reactions among PPD-sensitive hair dye users. They worked with formulations made according to Feier's 1972 patent (41) on PPD/ℓ-DOPA hair dye combinations.

Similar claims, though with less positive documentation, have been advanced for galacturonic acid (in aloe Vera gel), glycolic (hydroxyacetic) acid, glyceryl triacetate, allantoin polygalacturonate (42), and for the glucose trimer, "Pullulan" (44). Opdyke (45) once reported a curious phenomenon: the only discernable chemical difference in skin which has "accommodated" (to the insult of continuous immersion in SLS) is the

Table VI
Kelley-Ritter "Mildness Additive" Patents*

	Total Score, 12 Persons (24 hr Skin Patch)
6 per cent SLS (sodium lauryl sulfate)	15
6 per cent SLS + 6 per cent TEA oleate	15
6 per cent SLS + 6 per cent TEA dimerate	5
Use of Dimer Acids *via* Following U.S. Patents:	
US 3,538,009—11/3/70	US 3,798,182—3/19/74
US 3,630,934—12/28/71	US 3,813,350—5/28/74
US 3,769,242—10/30/73	US 3,947,382—3/30/76

*Tests were run with dimer and trimer acids (of oleic and linoleic), and with their esters and amides (in 1:1 ratios, at 0.15 per cent) with various detergents such as ABS, SLS, lauryl ether sulfate, and TEA laurate.

presence of glycogen, another hydroxy compound. Lipkin (8) recently reported on the use of a glycoprotein obtained from normal human epidermis to inhibit *in vitro* growth of malignant cells. *Glucan*, a yeast-derived polysaccharide, stimulates macrophage activity (and subsequent immune response) when injected directly into active tumors, according to Smith's review (46) reporting on Dr. Peter Mansell's experiments at McGill University. Zviak patented the use of thiodiglycollic acid (50) to reduce scalp irritations, while thioglycerol has also been claimed as an epithelial cell growth stimulant (51). There also exists a gluconamide quat which can be tolerated in the eye at 100 times the levels at which benzalkonium quats are tolerated.

Are all of these hydroxy compound effects just coincidence? *It seems most unlikely.*

Finally, Kelly and Ritter (43,62,63,64,65,66,67) have clearly demonstrated (Table VI) *via* guinea pig immersion and human patch testing that hydroxy derivatives (-OH and -COOH) of oleic and linoleic dimer and trimer acids are potent antiirritants.

All of these reports are highly suggestive of a prophylactic effect deriving from the presence of the hydroxyl group in topically-applied materials.

CARBOXYL COMPOUNDS

Kelly and Ritter also reported (43) that dimer acids themselves (containing 2-4 carboxyl groups) are "mildness additives which prevent or reduce skin irritation" of many surfactants. When carboxyl groups of dimer acids are replaced by weaker polar groups (such as hydroxyl) the antiirritant effects do not appear until such hydroxyl groups are separated by at least 15 atoms. Here was the first attempt at quantifying the hydroxyl ion antiirritant effect.

Kelly and Ritter's observations are most interesting in light of LeVeen (49), who patented the use of traumatic acid (1-decene-1,10-dicarboxylic acid) for its pronounced favorable effect on the ingrowth of new epithelial tissue into burned areas. LeVeen reports that the presence of traumatic acid increases ingrowth rate by 40 per cent (Table VII), whereas sebacic acid (a saturated acid with eight central carbons separating two carboxy groups) does not affect such growth rate at all, and adipic acid (having two

Table VII
Traumatic Acid
(1-decene-1,10-dicarboxylic acid)
"Ingrowth" on 1 cm^2 Human Burn Blisters (as Per cent of Control)

Control (PEG 6000)	0	(Base line)
Sebacic acid (2 per cent in PEG 6000)	0	(No change in healing rate)
Adipic acid (2 per cent in PEG 6000)	−50 per cent	(Decrease in healing rate)
Traumatic acid (2 per cent in PEG 6000)	+40 per cent	(Increase in healing rate)

*Ref: Brit. 1,013,109 to H. H. LeVeen (1965).

Table VIII
Chronic Toxicity (IP) of Phthalate Esters (Mouse)

Phthlate Ester	Acute LD_{50} (g/Kg)	Chronic LD_{50} (g/Kg)
Dimethyl	3.98	1.40
Diethyl	3.22	1.56
Dibutyl	3.57	0.89
Diisobutyl	3.99	1.94
Di-n-Octyl	65.70	3.02
Di-2-Ethylhexyl	37.77	1.35
Butyl Carbobutoxymethyl	6.88	3.34
Bis (2-Methoxyethyl)	4.18	1.65

(Lawrence *et al., Environ Res.*, 9, 1–11 (1975)).

carboxy groups separated by four central carbons) actually *decreases* ingrowth by 50 per cent. The apparent chain-length relationship shown in this series of examples is unfortunately clouded by the unsaturation of traumatic acid, whose carboxyls are at either end of a 10-carbon chain. Pacini (58) claimed that traumatic acid (and especially its cobalt salts) reduce the skin irritation of detergent compositions when used at levels as low as 0.0005 per cent.

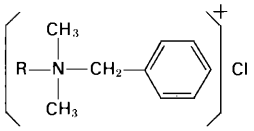
III. MISCELLANEOUS OTHER CHEMICAL IRRITANTS

Several other "chemical" antiirritant effects have been observed, which do not fall into either Imidazol or Hydroxy Compound categories.

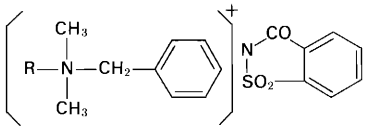
The phthalate esters, for example, were recently discussed by Lawrence of the University of Tennessee (Table VIII). It is fascinating how an apparently innocuous switch in the alcohol portion of an homologous series of esters can make such a difference in their toxicity. All of us know of similar examples, such as the sunscreen PABA-ester series, which differ drastically in the "sting" produced on mucous membranes of certain individuals.

The prime example of detoxification is PVP, perhaps the classic antiirritant and detoxicant of all time. Although its effects were noted long before the development of current theories of antiirritant mechanisms, we still do not know how or why PVP works. Yet, no one can doubt the antiirritant potency of this unique polymer.

TWO ALKYL DIMETHYL BENZALKONIUM QUATS



Chloride



Saccharinate

Table IX
Alkyl Dimethyl Benzalkonium Quats
(Comparison of Properties)

	Chloride	Saccharinate*
Taste	bitter	sweet
LD_{50} (g/Kg)	445	1130
Primary skin irritation	moderate	0
Draize eye irritation (non-irritating level)	0.1 per cent	1.0 per cent
Phenol coefficient	580	525

(*Onyxide 3300 or Hollichem HQ 3300).

The basic patent for detoxicant PVP uses was issued in 1956 to Shelanski (53), who modestly only claimed a "method for reducing the vapor pressure of free halogens." The substantial detoxification of iodine and chlorine—although clearly recognized in the introductory portion of his patent—was not claimed.

Pointing out that the PVP iodine "complex" was more active than free iodine itself, Shelanski described how its irritation and sensitization effects were now completely absent and that its oral toxicity had been reduced tenfold by formation of this "complex" with PVP. This was an astounding discovery, the basis for many commercial products in the years to follow. Imagine gargling with iodine, a material known only as a potent poison until then, carrying the skull-and-cross-bones label!

As early as 1954, Shelanski and Cantor (54) reported on the reduction of irritation of sodium alkyl sulfates *via* addition of 1 per cent PVP. Many other examples of detoxification and antiirritancy were later discovered for this material, summarized in Wood's excellent review (55) which lists 148 references.

Scher Chemical Co. recently reported that Acetamide MEA demonstrates (eye) antiirritant properties in conjunction with sodium lauryl sulfate (Table IV). This unusual material may, therefore, be of interest in shampoo formulations.

Two other major examples of antiirritancy do not fall into "simple" chemical categories: the quaternary ammonium saccarinate complexes and certain sulfo-succinate amido surfactants. In a manner reminiscent of the behavior of PVP, cationic saccarinate complexes are more effective than the "parent" benzalkonium quats from which they are derived, yet their oral toxicity is so low as to allow their use in mouth washes. Their

Table X
Ricinoleic Acid Sulfosuccinate Monoethanolamide (SS/RAM)
(Antiirritant Effect on Addition to Typical Foaming Agents *via* "Repeated Insult" Skin Testing)

I. Addition of SS/RAM to Sodium Dodecyl Benzene Sulfonate (SDBS):

10 per cent SDBS alone (control)										10 per cent SDBS + 0.5 per cent SS/RAM										10 per cent SDBS + 1 per cent SS/RAM									
Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total
	1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4	
1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
2	1	0	2	1	0	0	2	0	6	2	1	0	1	1	0	0	2	0	5	2	2	1	0	0	0	0	0	0	3
3	1	1	3	2	0	1	3	3	14	3	2	1	2	1	0	0	2	1	9	3	2	1	0	1	1	1	0	1	7
4	1	1	4	3	0	1	3	2	15	4	1	0	2	2	0	0	2	2	9	4	2	2	1	1	1	1	0	1	10
Control									35										23										20

II. Addition of SS/RAM to Sodium Lauryl Ethyl Sulfate (SLES):

10 per cent SLES alone (control)										10 per cent SLES + 0.5 per cent SS/RAM										10 per cent SLES + 1 per cent SS/RAM									
Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total
	1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4	
1	1	0	0	0	0	0	0	0	1	1	1	0	0	1	0	0	0	0	2	1	1	0	0	0	0	0	0	0	1
2	1	1	2	3	1	0	2	1	11	2	2	2	2	2	0	0	1	1	10	2	1	1	1	1	0	0	1	1	6
3	1	2	2	4	0	1	1	2	13	3	2	2	2	3	1	0	1	2	13	3	1	1	2	2	0	2	0	3	11
4	2	2	3	4	1	1	2	3	18	4	2	2	3	3	2	1	0	1	14	4	1	2	2	3	0	0	0	3	11
Control									43										39										29

III. Addition of SS/RAM to Sodium Lauryl Sulfate (SLS):

10 per cent SLS alone (control)										10 per cent SLS + 0.5 per cent SS/RAM										10 per cent SLS + 1 per cent SS/RAM									
Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total	Days	Erythema				Oedema				Total
	1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4			1	2	3	4	1	2	3	4	
1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
2	1	2	3	1	0	0	2	0	9	2	1	2	1	0	0	0	0	0	4	2	0	0	0	0	0	0	0	0	0
3	1	3	2	3	0	1	0	2	12	3	0	2	1	1	0	0	0	1	5	3	1	1	0	1	0	0	0	0	3
4	1	3	2	4	0	0	1	3	14	4	1	2	1	2	0	0	0	1	7	4	1	1	0	0	0	0	0	1	3
Control									35										16										6

5 per cent Primary Irritation index is zero, their 1 per cent solutions safe in the eye (Table IX). Formation of the saccarinate complex, whatever its mechanism, clearly reduces the normal toxicity and irritation of benzalkonium quaternary compounds.

Amido-sulfosuccinate surfactants have also recently received considerable publicity for their apparent ability to reduce the eye irritation of shampoo formulations. One such product, disodium monoricinoleamido MEA sulfosuccinate, has been shown to reduce Draize eye irritation scores by 32 to 54 per cent when added at 1 per cent to 10 per cent alkyl sulfate solutions (Table X).

CONCLUSIONS

Quite clearly, hydroxy compounds (and their related carboxy derivatives) have a special interest to those seeking topical antiirritant effects. In particular, hydroxyl compounds demonstrating keratin substantivity ("sorption") appear to be of particular interest.

A second major category, imidazole and imidazoline compounds, also repeatedly demonstrated activity in this respect—perhaps *via* preferential sorption to keratin binding sites. It is proposed that this mechanism may explain the "no tears" effect obtained from mixing amphoteric surfactants (plus Polysorbate 20) with typical anionic shampoo ingredients.

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