Vol 27 No. 2 February 1976

Journal of the Society of Cosmetic Chemists

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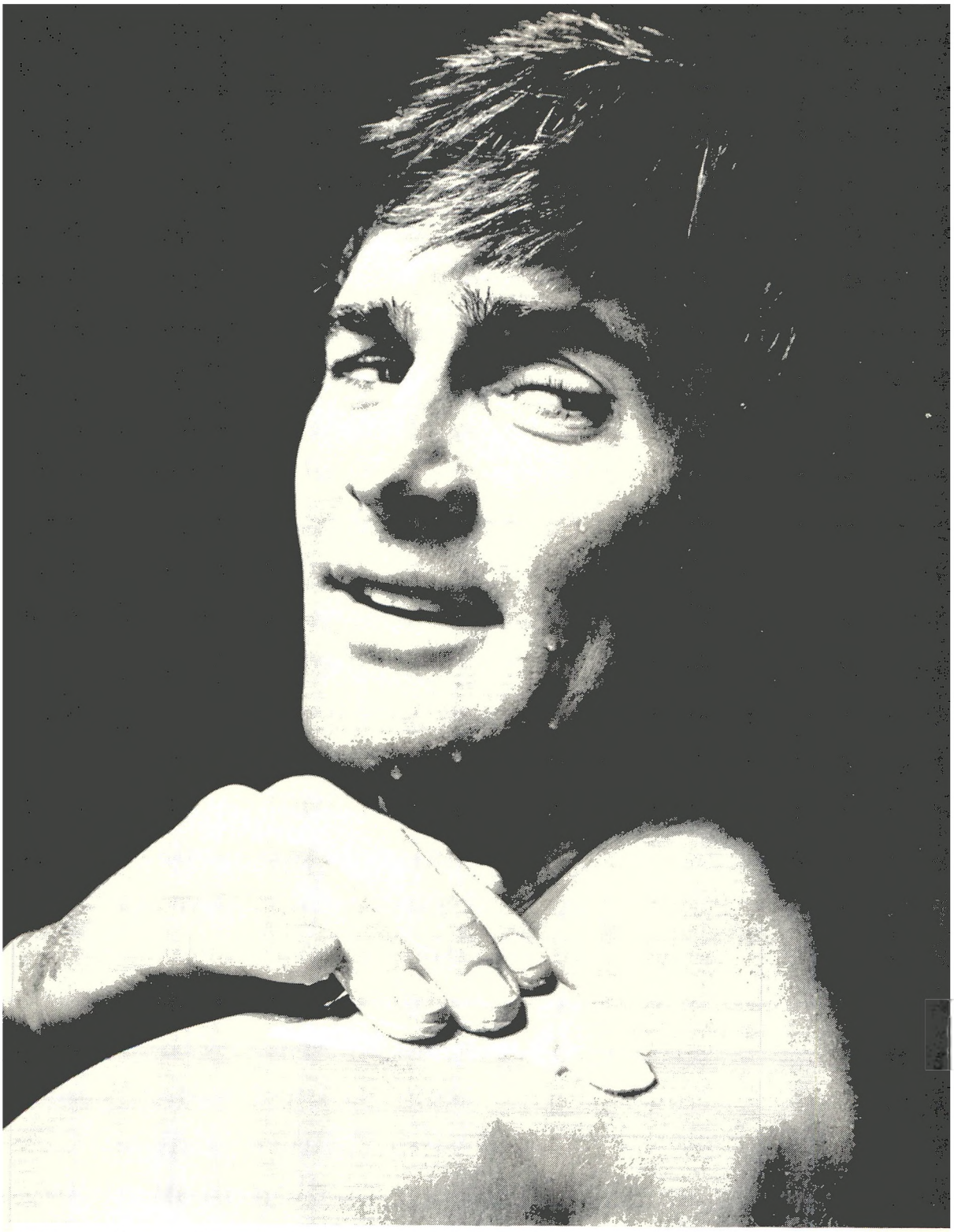

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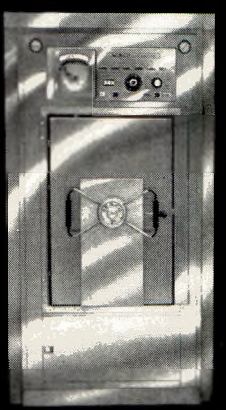

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At the December 2nd luncheon session of the Society's Annual Scientific Meeting at the Americana Hotel in New York City, 1975 President Mr. Stephen G. Hoch installed the Officers and Directors for 1976.

Left to right (standing): Dr. Stephen M. Greenberg, Director Area III; Dr. Karl Laden, President-Elect; Mr. Graham Barker, Director Area I; Mr. Warren J. Hintz, Director Area I; *(seated):* Mr. Joseph H. Kratochvil, President; Ms. Gail Phillips Bucher, Secretary; Mr. Stephen G. Hoch, Chairman of the Board; Mr. Paul Thau, Treasurer; *(Absent):* Mr. George Pollack, Director Area I; Mr. Stanley E. Allured, Director Area II; Ms. Betty Lou Day, Director Area II

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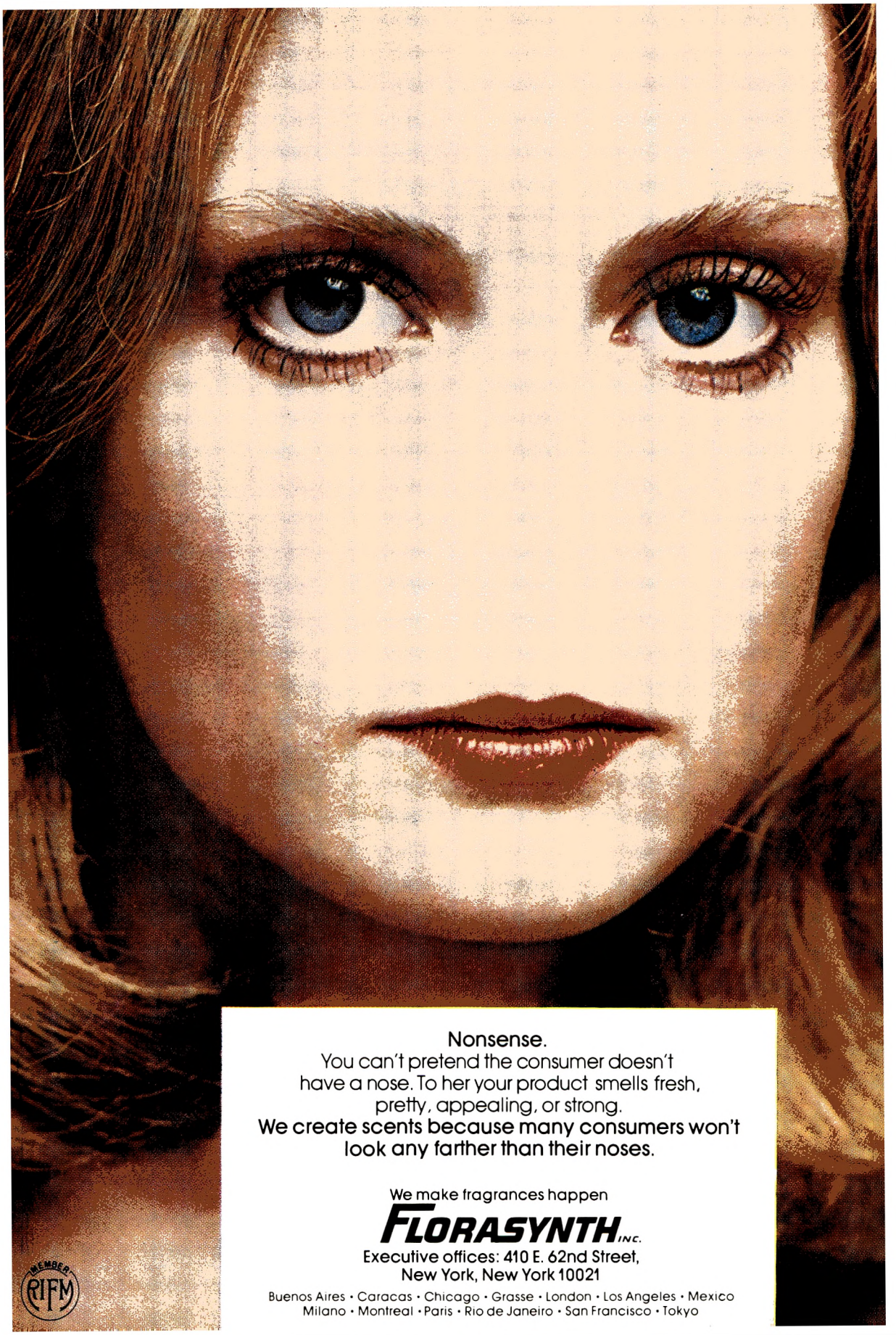
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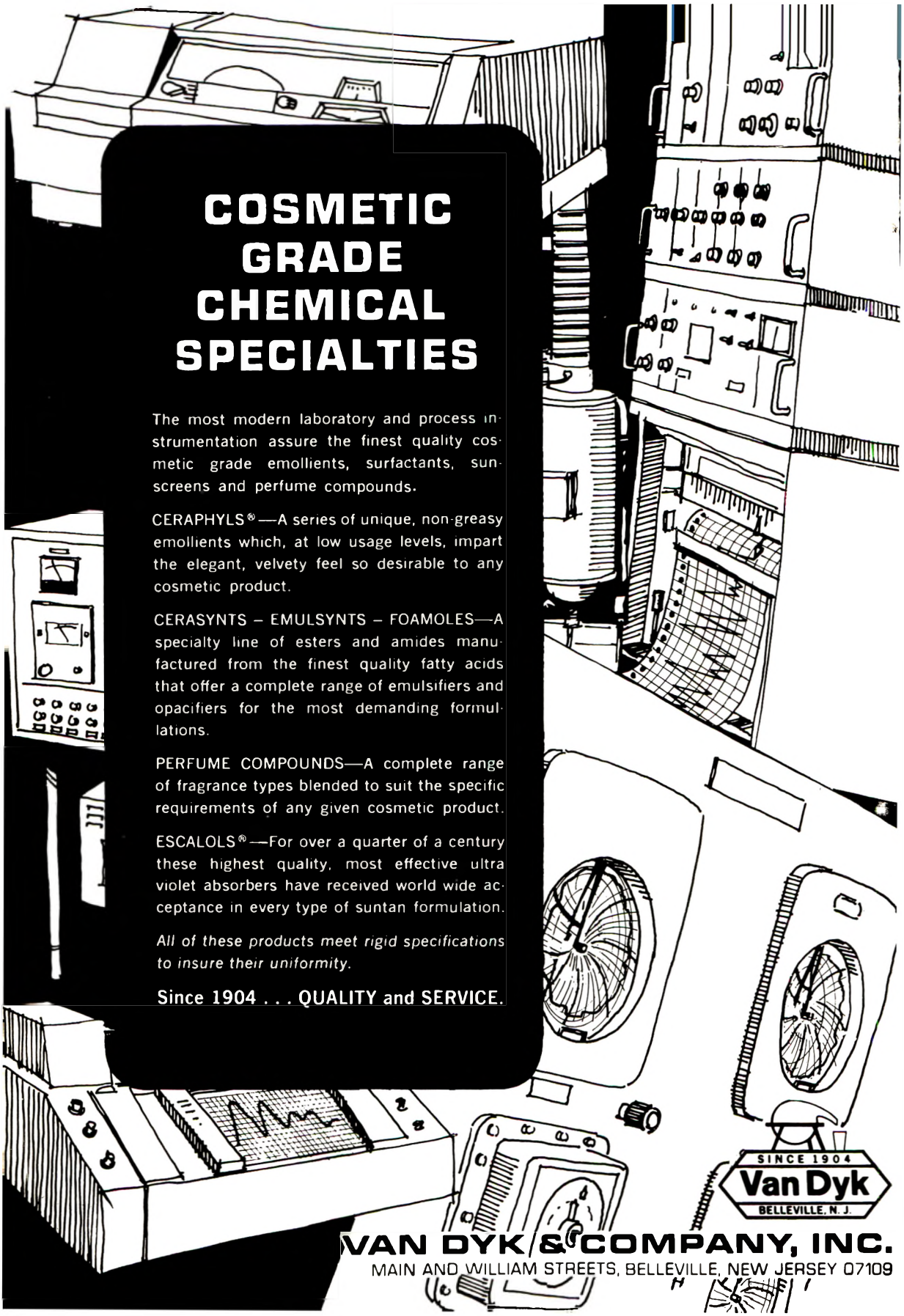

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SYNOPSES FOR CARD INDEXES

The following synopses can be cut out and mounted on 3 x 5 in. index cards for reference, without mutilating the pages of the Journal.

Water and the horny layer: Thomas S. Spencer. *Journal of the Society of Cosmetic Chemists* **27,** 63 (February 1976)

Synopsis—Water content of human stratum corneum (SC) has been studied by gravimetric analysis *in vitro* as a function of temperature, relative humidity (RH), and aqueous exposure. SC samples obtained by trypsin digestion and cantharidin blister techniques have similar hydration properties, while sunburn exfoliated tissue absorbs more water at 97 per cent RH and is more susceptible to damage by aqueous solution. As one increases the humidity from 30 to 60 per cent, there is little change in water content of SC. Low temperature and low relative humidity reduce the bound water fraction in the SC, which has been identified as one of the factors in dry skin observed during cold dry weather.

Microbial quality control for the manufacture of cosmetic emulsions: C. Kano et al. *Journal of the Society of Cosmetic Chemists* **27,** 73 (February 1976)

Synopsis—Various aspects of a quality control system intended to insure the production of microbial free cosmetics or cosmetics containing a minimum number of organisms are discussed. This subject has received world-wide attention and, at present, a great deal of time and effort is devoted to establishing such a system. The authors indicate the various sources and potential sources for microbial contamination of cosmetics. Microbial contamination of cosmetics can result either from the raw materials or during the actual manufacturing, processing, and packaging operations; or from both of these things. Emulsions contain many ingredients which will support the growth of microorganisms. Therefore, attention is given to a discussion of the quality control procedures concerning the manufacture of large-scale cosmetic emulsions.

The quality control program will be discussed as follows: (a) standardization of techniques which will reduce the microbial levels found in cosmetic raw materials; (b) sterilization, sanitizing, and cleansing procedures for use during the manufacturing process; (c) sterilization or sanitization of the packaging components and filling equipment so as to prevent microbial contamination during the packaging process; and (d) establishment of test methods useful for microbial quality assurance. Finally, consideration is given to other aspects of a quality control system including on-the-job training programs for plant employees and plant maintenance and sanitation.

The evaluation of a sunscreening agent for safety and activity: Lester I. Conrad. *Journal of the Society of Cosmetic Chemists* **27,** 87 (February 1976)

Synopsis—In the light of current and proposed legislation on safety and efficacy, each new cosmetic raw material requires extensive testing before it is introduced to the market. The evolution and evaluation of a highly active alkoxylated para-aminobenzoic acid (PABA) derivative is discussed in detail. Animal studies are employed to provide basic toxicity data. Clinical studies employ maximization techniques to expose possible hazards. Laboratory, clinical, and field tests are used to study efficacy. All the above comprise a case study of the considerations involved in the introduction of a new chemical raw material to the cosmetic industry.

J. Soc. Cosmet. Chem., **27**, 63-72 (1976)

Water and the Horny Layer

THOMAS S. SPENCER, Ph.D.*

Presented, May 29, 1975, SCC Annual Seminar, St. Louis, Missouri

Synopsis: WATER content of HUMAN STRATUM CORNEUM (SC) has been studied by gravimetric analysis *in vitro* as a function of TEMPERATURE, RELATIVE HUMIDITY (RH), and AQUEOUS EXPOSURE. SC samples obtained by trypsin digestion and cantharidin blister techniques have similar hydration properties, while sunburn exfoliated tissue absorbs more water at 97 per cent RH and is more susceptible to damage by aqueous solution. As one increases the humidity from 30 to 60 per cent, there is little change in water content of SC. Low temperature and low relative humidity reduce the bound water fraction in the SC, which has been identified as one of the factors in dry skin observed during cold dry weather.

Introduction

An understanding of water binding in the SC is necessary to develop preventive measures for dry skin; for without a minimum water content of 0.10 to 0.15 mg water per milligram dry skin, the corneum is less pliable, which contributes to the mechanical cracking and fissuring of dry skin (1,2). The current paper is an evaluation of hydration studies involving samples obtained using various harvest methods.† In addition, kinetic analysis of hydration and previous results (3), indicating direct relation between temperature and water content of SC, are related to water binding in SC.

Materials and methods

The SC was obtained by three methods: cantharidin blister; trypsinization of autopsy skin; and sunburn exfoliated tissue. Cantharidin blister tops were formed by application of cantharidin at 0.1 mg/cm^2 under an occlusive dress-

*Department of Dermatology Research, Letterman Army Institute of Research, Presidio of San Francisco, CA 94129.

†J. M. Mueller, T. S. Spencer, and W. A. Akers, Stratum corneum harvest methods and hydration, Technical Report, Department of Dermatology Research, Letterman Army Institute of Research, Presidio of San Francisco, CA 94129.

ing on the backs of human subjects. After 6 hours of occlusion, treated sites were covered with a sterile bandage and the blister tops were allowed to fill overnight. Blister tops were cut off with scissors, remaining epidermal tissue was removed with a wool-tipped stick, and samples were stored in a desiccator. Trypsinized SC was obtained from the abdominal region of cadavers and separated by the method of Kligman and Christophers (4). Epidermal tissue was gently removed with a wool-tipped stick and samples were stored in a desiccator until they were used. Sunburn exfoliated tissue was obtained in a single sheet from the back of an individual 10 days after 1.5 hours of exposure to summer sun and was stored in a desiccator.

Hydration measurements were carried out on 6 or 8 mm punches of dry SC mounted on nichrome wire hooks. Samples were weighed in one of two $15 \times 15 \times 20$ cm chambers which had controlled environments. Within the chambers, up to 6 SC samples could be manipulated from storage hooks to a balance wire extending down from a Cahn RG Electrobalance° mounted on top of the chambers. In addition, samples could be transferred from one chamber to the other with a slidewire via a sliding door so that all measurements could be made without disturbing the environment in the chamber.

Humidity was maintained by a salt solution within each chamber, which generated a constant RH (5). The following saturated solutions were used: magnesium nitrite (RH equals 30 per cent), potassium carbonate (RH equals 40 per cent), sodium nitrite (60 per cent), sodium chloride (75 per cent), potassium chloride (83 per cent), potassium nitrite (93 per cent), and potassium sulphate (97 per cent). The hydration chamber was mounted within a modified Hydro-Jac† incubator, which was coupled with a water bath to regulate the temperature of the incubator ($\pm 0.2°C$). The temperature was monitored with a 46-TU Telethermometer Thermistor‡ and the humidity was monitored by means of Hygrodynamics°° narrow-range sensors located within the chamber. Changes in temperature, humidity, and sample weight were recorded simultaneously throughout the experiments on strip-chart recorders. Water content was measured as milligram H_2O per milligram dry SC (mg H_2O/mg SC).

To study the effects of heat exposure, two 8 mm punches were cut from one sample harvested by each of the 3 methods. A dry weight was taken for each sample. The samples were transferred to the second chamber at 97 per cent RH for 48 hours, and hydrated weights were recorded. The samples were then wrapped in plastic and immersed in water at 60°C for 10 min. after which dry

°Ventron Instruments Corp., Paramount, Calif. 90723.
†Forma Scientific, Marietta, Ohio 45750.
‡Yellow Springs Instrument Co., Yellow Springs, Ohio 45387.
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and hydrated weights were again recorded.

Effects of aqueous exposure were studied by immersing 8 mm punches of SC in distilled water for specified lengths of time. Each of 5 punches from a single piece of SC was immersed for 0, 1, 3, 10, or 24 hours. Following immersion, dry weights and water uptakes (97 per cent RH and 30°C for 48 hours) were recorded as described previously. Three sets of 5 were run, using the following 3 SC specimens: trypsin, cantharidin, and sunburn.

Results

The relationship between hydration of SC and RH or activity of water is shown in Fig. 1 for cantharidin blister and trypsin samples. Average dry weights and equilibrium hydrations for samples harvested by all three methods are shown in Table I with statistical significance determined by analysis of variance and F-ratio test. Effects of exposure to water and to heat at 60°C are shown in Tables II and III.

The effect of temperature on the equilibrium water content at various relative humidities has been discussed in detail by Spencer *et al* (3). The ability of the SC to retain water at equilibrium *in vitro* decreases with decreasing temperature at humidities below 60 per cent. Above 60 per cent RH, this temperature dependence decreases with increasing RH until there is essentially no temperature effect on the equilibrium water content above 90 per cent.

Kinetics of hydration of the SC from a dry weight to a steady state (SS) water content at 97 per cent RH were recorded for more than 45 samples. Analysis of hydration can be accomplished by treating the system as either diffusion of vapor into a membrane or pseudo-first order reaction of water with the membrane.

Analysis of SC hydration as a diffusion problem can be defined as the sorption of vapor by a plane sheet. Using an approximation for determining the average diffusion coefficient D from initial sorption data as described by described by Crank (6) and Scheuplein (7), one obtains the equation

$$\frac{W}{W_{max}} = 4\left[\frac{Dt}{\pi l^2}\right]^{1/2} \tag{1}$$

where W equals mg H_2O/mg SC at time t after the dry sample has been placed in the hydration chamber; W_{max} equals the SS water weight (mg H_2O/mg SC) at 48 hours, $\overline{D}$ equals the average diffusion coefficient for the hydration; t equals time (in minutes); and l is one-half the thickness of the SC. A plot of W/W_{max} versus $t^{1/2}$ will yield $\overline{D}$ from the slope (m) squared as $m^2 \times \frac{\pi l^2}{16}$.

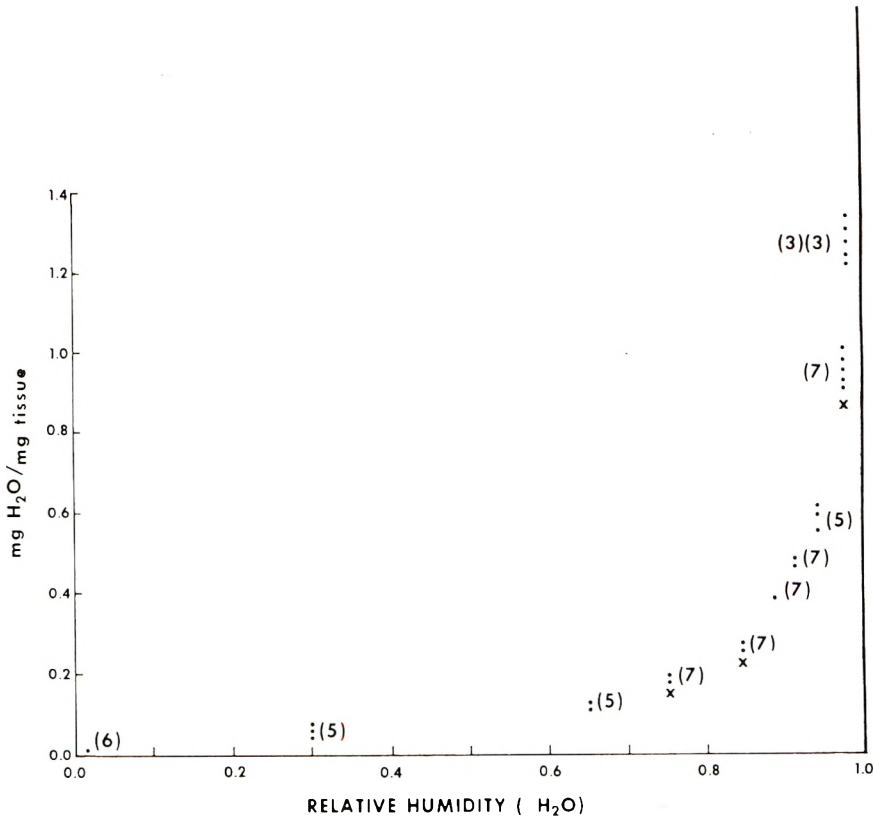

Figure 1. Effect of humidity on SC hydration: (•) cantharidin or trypsin samples; (x) callus sample. Since most of data points were superimposed on each other, number of experimental points at each RH is indicated by number in parentheses

Table I

Effect of Harvest Method on SC Hydration

Sample[a]	Dry Weight (mg)	Hydrated[b] (mg H_2O/mg SC)
Cantharidin (23)	0.48 ± 0.07	0.77 ± 0.14
Trypsin (9)	0.50 ± 0.07	0.84 ± 0.17
Sunburn exfoliated (11)	0.38 ± 0.17[c]	1.08 ± 0.08[c]

[a]Harvest method (number of samples).

[b]Eight mm punch hydrated for 48 hours at 97 per cent RH, 30° C, mean ± s_d.

[c]Statistically different from cantharidin and trypsin harvested samples at the 99 per cent level of significance ($\alpha < 0.01$).

Table II

Effect of Heat on SC Hydration

Sample[b]		Hydration (mg H_2O/mg SC)[a] Control	After 10 min. at 60°C
Trypsin	– 10	0.57	0.62
	– 11	0.63	0.57
Cantharidin	– 10	0.68	0.71
	– 11	0.88	0.75
Sunburn exfoliate	– 10	1.03	1.14
	– 11	1.12	1.16

[a]Hydration from dry weight to hydrated weight at 97 per cent RH and 30°C for 48 hours.
[b]Samples harvested by the techniques indicated; numbers 10 and 11 designate 2 different 8 mm punches from the same specimen.

Table III

Effect of Aqueous Exposure with Different Harvest Methods

Harvest Method	Control: 0	Dry Weight following Aqueous Exposure (hour)[a] 1 hour	3 hours	10 hours	24 hours
Trypsin	0.522	0.518	0.537	0.507	0.497
Cantharidin	0.469	0.457	0.480	0.457	0.463
Sunburn exfoliate	0.362	0.349	0.312	0.259	0.337
		Hydration following Aqueous Exposure (hour)[b]			
Trypsin	0.91	0.92	0.85	0.72	0.51
Cantharidin	0.90	0.86	0.89	0.76	0.85
Sunburn exfoliate	1.22	1.07	0.97	0.63	0.67

[a]Dry weight (in milligrams) of 1 of 5, 8 mm punches from the same specimen, following water exposure by immersion in distilled water for the time indicated.
[b]Hydration at 97 per cent RH, 30°C for 48 hours (mg H_2O/mg SC).

Alternately, hydration of the SC has been treated as a pseudo-first order process, since H_2O is present in excess (8,9). The water weight gain is expressed

$$dW/dt = K_1^H (W_{max} - W) \tag{2}$$

Rearranging eq. 2 gives

$$\frac{dW}{(W_{max} - W)} = K_1^H \, dt \tag{3}$$

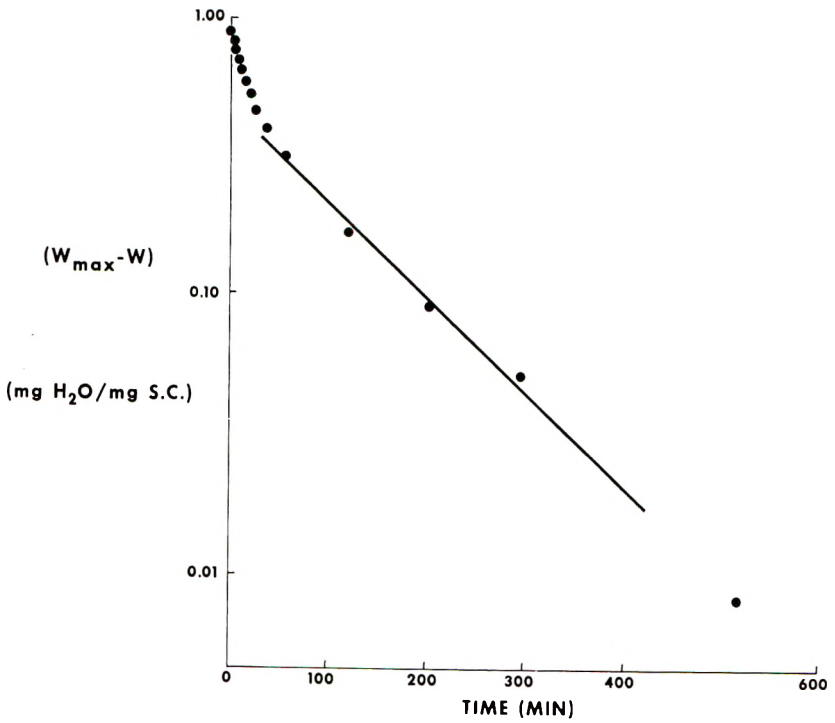

Figure 2. First-order hydration kinetics of SC. Plot of ln ($W_{max} - W$) vs. t with slope m equals K_1^H for trypsin-harvested 8 mm punch of SC (lateral thigh of caucasian male, age 45 years). W_{max} equals 0.90 mg H_2O/mg SC after 2280 min at 97 per cent RH and 30° C

Integration from initial hydration at t equals 0 to time t when W_{max} water has been absorbed yields

$$\ln\left[\frac{W_{max} - W}{W_{max}}\right] = -K_1^H t \qquad (4)$$

where K_1^H equals the first-order rate constant for hydration. A typical plot of the hydration process using the variable ln ($W_{max} - W$) versus time is illustrated in Fig. 2. The first nonlinear portion of the curve has been explained by Anderson *et al* (8) as the initial hydration of tightly bound water; however, this nonlinearity leads to an alternate treatment of hydration kinetics.

If the hydration occurs from a constant surface concentration determined by the constant RH, and if the rate of reaction is limited by both diffusion into the membrane and by reaction of available hydration sites, then the rate constant of the rate expression (2) will be a function of the diffusion constant of water into the membrane, and consequently, a function of the dif-

ference between the water content at the surface and water within the membrane. Allowing for a suitable lag time for equilibrium to be established, the surface layer of the SC is in equilibrium with the water vapor in the atmosphere. Therefore, k will be large initially and decrease as hydration approachs an equilibrium SS. The surface layer, at equilibrium with water vapor in the atmosphere, will have a water content of Wmax (mg H_2O/mg surface layer). The interior water content, taken as an average, is represented by W. If K_1^H is not actually a constant but rather a function of the water content, one might express the rate function K(W) in terms of the degree of hydration as

$$K(W) = K' (W_{max}/W) \tag{5}$$

which is large initially, decreasing as the extent of hydration increases. Substituting eq. 1 in 5 gives

$$K(W) = K' \left[\frac{\pi l^2}{16Dt}\right]^{1/2} \tag{6}$$

Applying the resulting expression K(W) for K_1^H in eq. 3

$$\frac{dW}{(W_{max} - W)} = K' \left[\frac{\pi l^2}{16D}\right]^{1/2} t^{-1/2}\, dt \tag{7}$$

Integrating over the limits of 0 to W_{max} and 0 to t

$$\ln\left[\frac{(W_{max} - W)}{W_{max}}\right] = K' \left[\frac{\pi l^2}{4D}\right]^{1/2} t^{1/2} \tag{8}$$

which is constrained to description of initial sorption data as is 1. A typical plot of eq. 8 is linear over the initial 300 min. of hydration. It should be noted that the linear portion of the curve begins after t equals 1 min, as a result of a lag time for formation of equilibrium between water vapor and the surface of the sample.

Discussion

Comparison of hydration parameters in Table I indicates that average dry weights and water content at 97 per cent RH are similar for SC samples harvested by cantharidin blister or trypsin techniques. Sunburn exfoliated samples have lower dry weight, indicating a lower density than samples harvested by the other methods. In addition, sunburn samples retain more water than either cantharidin or trypsin samples. Some harvest methods involve immersion in water at 60°C for separation of epidermis from dermis (7). In the current work, exposure to 60°C had no detectable effect on hydration of any samples at 97 per cent RH (Table II). However, SC samples were pro-

tected from water exposure by plastic; therefore, no statement can be made concerning the wash effect of warm water on water soluble fraction in the membrane.

Excessive aqueous exposure of SC causes a reduction in dry weight and ability of the SC to retain water at 97 per cent RH (Table III). With 3 hours of exposure, the effect is small in both cantharidin and trypsin harvested samples; however, sunburn exfoliated tissue loses weight and ability to absorb water with increasing water exposure. The trend in weight loss indicates that sunburn exfoliated membranes lose more water soluble components and that the ability of sunburn membrane to retain water is reduced by the loss of these components. Since sunburn exfoliated skin has been reported to have incompletely formed keratin, caution should be taken in comparing data from sunburn exfoliated SC with normal SC harvested by other methods.

The hydration of SC has been described in terms of three types of water (8, 10, 11). The first type, primary bound water, is tightly bound water associated with strong protein hydrogen-bonded interactions. Primary bound water constitutes the first 0.10 to 0.15 mg H_2O/mg SC absorbed by dry SC at 60 per cent RH (Fig. 1) and is necessary for normal pliability of SC (1). As the activity of water (RH) increases above 60 per cent, water sorption appears to increase exponentially in relation to RH (Fig. 1). The water absorbed in this region is secondary water, bound to the primary water layer, constituting 0.40 to 0.50 mg H_2O/mg SC (Fig. 1). At RH above 94 to 96 per cent, water content increases rapidly as free water, not directly bound to the membrane, is absorbed. In this region, SC will continue to absorb water until the tissue begins to break down mechanically (7,8). Spectroscopic observations by Hansen and Yellin (12) indicate that continued water uptake in this region results in an increase in primary water binding also; hence, excessive free water opens up the molecular lattice exposing more primary hydration sites. Irreversible alteration of these primary binding sites or hydroscopic components affecting these sites may play a role in the effect of water exposure on the loss of mechanical integrity when the SC is hydrated (13,14).

Since hydration can be described in terms of a single function (Fig.3), which holds over the region in which bound water is being absorbed, both primary and secondary water are defined by a single parameter, implying that they are interchangeable. Nuclear magnetic resonance (NMR) results discovered by Hansen and Yellin (12) also indicate that the interchange between primary and secondary bound water is very rapid. Hence, if a significant amount of secondary water is present, one can assume that all the primary bound sites are hydrated due to the rapid equilibrium

As observed in a previous report (3), low temperatures on the order of 10 to 20°C reduce the ability of the SC to retain water at relative humidities below 60 per cent. For example, a SC sample at 60 per cent RH retains

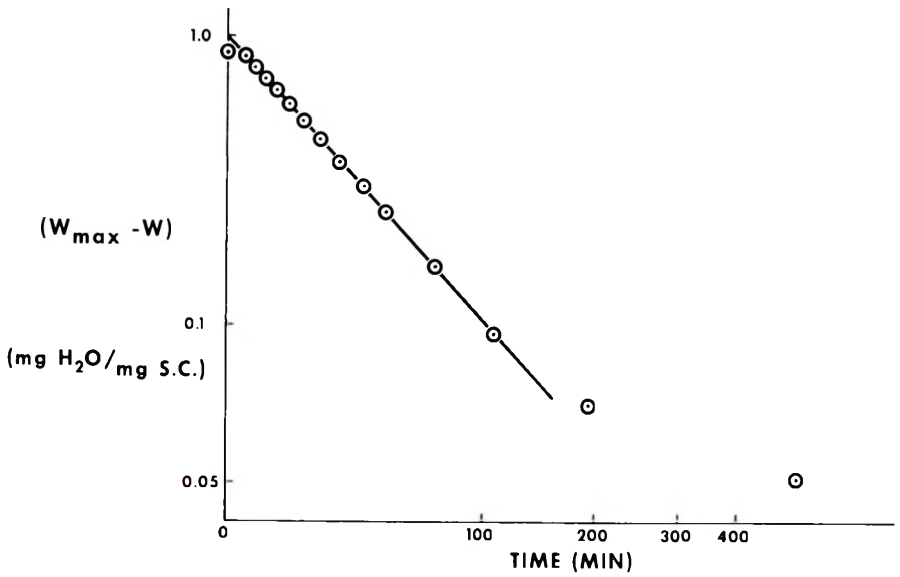

Figure 3. Plot of ln ($W_{max} - W$) vs. $t^{1/2}$. Hydration data is same as in Fig. 2. Trypsin-harvested 8 mm punch of SC from male caucasian, age 45 years, hydrated at 97 per cent RH, 30° C to W_{max} equals 0.90 mg H_2O/mg SC

approximately 0.11 mg H_2O/mg SC versus 0.06 mg H_2O/mg SC at 20°C. The sample has enough water to be pliable at 30°C, but less than the necessary 0.10 to 0.15 mg H_2O/mg SC (1) to be pliable at 20°C. At higher RH, when secondary bound water is present, the temperature effect is reduced, possibly due to the rapid interchange between the secondary water and the primary bound water necessary for pliability. In addition, Middleton and Allen (13) indicated that reduced temperature causes a reduction in the extensibility of SC exclusive of water content. The effects of temperature on both water content and extensibility indicate that temperature should be considered as one factor in the increased incidence of dry skin (2) observed in cold dry weather.

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Microbial Quality Control for the Manufacture of Cosmetic Emulsions

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Synopsis: Various aspects of a QUALITY CONTROL SYSTEM intended to insure the production of MICROBIAL FREE COSMETICS or cosmetics containing a minimum number of organisms are discussed. This subject has received world-wide attention and, at present, a great deal of time and effort is devoted to establishing such a system. The authors indicate the various sources and potential sources for MICROBIAL CONTAMINATION of cosmetics. Microbial contamination of cosmetics can result either from the raw materials or during the actual manufacturing, processing, and packaging operations; or from both of these things. Emulsions contain many ingredients which will support the growth of microorganisms. Therefore, attention is given to a discussion of the quality control procedures concerning the manufacture of LARGE-SCALE COSMETIC EMULSIONS.

The quality control program will be discussed as follows: (a) standardization of techniques which will reduce the microbial levels found in cosmetic raw materials; (b) sterilization, sanitizing, and cleansing procedures for use during the manufacturing process; (c) sterilization or sanitization of the packaging components and filling equipment so as to prevent microbial contamination during the packaging process; and (d) establishment of test methods useful for microbial quality assurance. Finally, consideration is given to other aspects of a quality control system including on-the-job training programs for plant employees and plant maintenance and sanitation.

Introduction

In recent years the incidence of skin irritation caused by the application of cosmetics has been on the increase in Japan, and hence, the need for a non-irritant type of cosmetic has become increasingly popular.

In order to manufacture such a cosmetic, careful selection of raw materials and particular attention to formulation are essential factors. Utmost care is necessary throughout the various stages of the manufacturing process, which must be carried out in a microbially free environment. This is an important factor and has come to represent what the consumer expects from a modern cosmetic manufacturer.

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Raw materials and processing equipment must be sterilized prior to use. The working environment, the use of efficient facilities, as well as the necessity of personnel education and training, etc., are all necessary factors if we are to achieve our goal; a microbially free manufacturing process and a microbially free product.

In order to obtain this microbially free condition in large-scale production each product has to be individually considered with regard to its characteristic properties during all steps of the manufacturing process (1-6).

Through the use of ultraviolet (uv) sterilization, heating, disinfectant solution, ethylene oxide gas, microporous filters, and a properly equipped clean room, we can set the standards and procedures for each single phase of the manufacturing process and their control. On the basis of the above considerations, we were able to produce a microbially free emulsion on a large scale. Some of our experiences gained during our work on this project will be discussed.

Moreover, Morrish (7) has previously discussed this topic with regard to the development of a hypoallergenic cosmetic and its manufacturing process.

Experimental

Microbial Contamination of Raw Materials

In order to manufacture a microbially free cosmetic, the raw materials utilized must be relatively free from microbial contamination. Table I shows the results obtained from studies conducted on carefully refined raw materials before their use in the manufacture of low-irritant cosmetics.

Each cosmetic product was manufactured by formulating these approved raw ingredients with a minimum quantity of preservatives, which had

Table I
Results of Microbial Contamination Check in Raw Material

Raw Material	Contamination	Raw Material	Contamination
Squalane	−[a]	Glyceryl monostearate	−[a]
Vaseline	−[a]	Polyoxyethylene sorbitan monostearate	−[a]
Glyceryl trimyristate	−[a]	Polyethylene glycol 400	−[a]
Propylene glycol	−[a]	Solid paraffin	−[a]
Cellulose gum	+[b]	Microcrystalline wax	−[a]
Polyethylene glycol 1500	−[a]	Ceresin	−[a]
Sorbitol	−[a]	Bees wax	−[a]
Cetyl alcohol	−[a]	Deionized water	+[b]
Hydrogenated oil	−[a]		

[a]Free of microbial contamination.
[b]Microbial contamination noted.

previously been shown to be dermatologically safe and capable of preventing secondary contamination of the product. While formalin and mercurial germicides are recognized as very powerful preservatives; their use in cosmetic products is not permitted in Japan. We have also found that some of the halogenated salicylanilides were photoallergenics, therefore, they were not used in our formulations for these particular products.

Microbial Contamination During Manufacturing Process

In order to accomplish the production of a microbially free cosmetic, it is necessary to have microbially free materials and manufacturing facilities with no contamination during processing.

Figure 1 shows an outline of the various manufacturing steps carried out before various controls for microbiological contamination were established. Thus far, microbial contamination was found during deaeration, cooling, storage, and filling.

In the deaeration stage, the contamination was caused by airborne microorganisms after air discharge and when new air was supplied. During the cooling process, the contamination was caused by residual liquid after washing. Due to imperfect closure during storage, as well as because of the incomplete cleansing of the tank, airborne microorganisms were found to be causes of contamination. Finally, during the filling operation, due to the fact that no clean room was available, contamination was caused by airborne

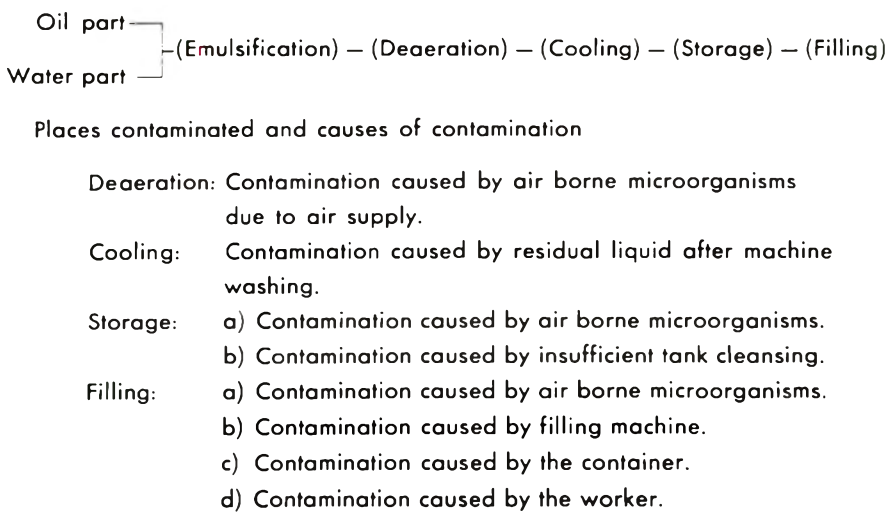


Figure 1. Possible areas for introduction of microbial contamination during manufacturing process

microorganisms, insufficient cleansing of the filling machine, contamination of the containers, and by the use of unskilled and careless workers.

Preventing Microbial Contamination of Raw Materials

A. *Sterilization of Deionized Water*

Based upon the contamination noted in the raw materials, we considered various methods of sterilization for those raw materials, which had previously caused particular trouble. Table II shows these results, which were obtained using the sterilizer shown in Fig. 2.

As deionized water is considered to be one of the most important raw materials used in the formulation and manufacture of cosmetic products, we adopted the uv sterilization treatment for the deionized water, which is used widely in other in-plant general purpose applications.

B. Sterilization of Cellulose Gums

The cellulose gums, used as raw materials, are often found to be contaminated and are sources of contamination in the finished product. They may be readily sterilized by ethylene oxide gas, and under these conditions it is possible to get good sterilization. Moreover, sterilization by the ethylene oxide gas method results in a product having no noticeable change in quality and does not affect the end product. These results are shown in Table III.

Prevention of Microbial Contamination During the Manufacturing Process

A. *Microbially Free Condition During Manufacturing*

In consideration of a microbially free condition, processing equipment such as kettles, pipes, and cooler, etc., were automatically cleansed in a closed system, and a standardized operational method of cleansing was set up. All processing equipment (before each pieces' use in the manufacturing process) was sterilized as is indicated in Table IV.

In order to prevent microorganisms from contaminating the kettle, all the air which was drawn into the kettle was filtered by a highly efficient

Table II
Sterilization[a] of Deionized Water by uv

Untreated Water		Treated Water	
Flow (Kg/hour)	Microorganism count (cells/ml)	Flow (Kg/hour)	Microorganism count (cells/ml)
2400	0	2100	0
6400	0	6000	0
8800	0	10000	0
10000	0	Before uv	3.6×10^3
Before uv	6×10		

[a]Sterilizer employed: Steroline Sterilizer: Steroline System Co., Model C-4-S, Capacity: 10T/hour.

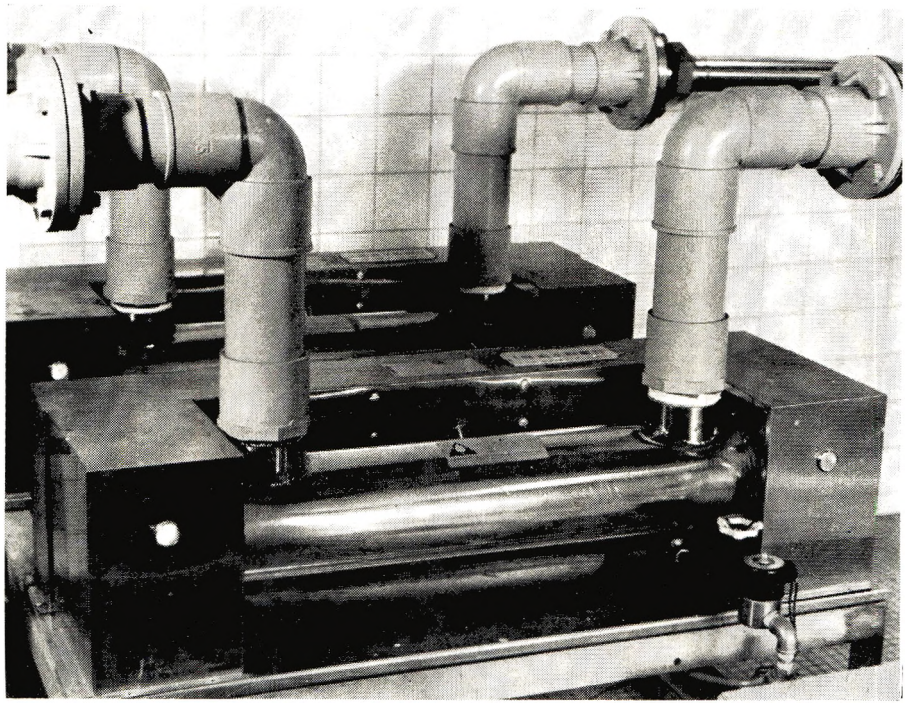


Figure 2. Uv sterilizer

Table III
Sterilization of Cellulose Gums by Ethylene Oxide Gas[a]

Lot Number	Microorganism Count (cells/g)	
	Untreated	EO Gas Treatment
23666	1.6×10^2	0
26264	1.2×10^2	0

[a]EO gas treatment conditions: Gas density = 20 per cent (diluted with carbon dioxide); Pressure, 1.0 Kg/cm^2; Temperature, 50-55°C; Time, 4 hours.

microporous filter mounted on the air inlet. This filter has the capability to filter out any foreign matter larger than 0.08 μm, thereby preventing organisms from entering the unit. The storage tank is also equipped with a microporous filter and as is shown in Fig. 3.

B. *Microbially Free Condition During Filling Operation*

1. Clean Room: It is well known that a clean room must be utilized in order to obtain a microbially free condition during the filling operation of cosmetics and pharmaceuticals. According to the results of this investigation,

Table IV
Sterilizing Method used for the manufacturing Equipment

Equipment	Sterilizing Method	Method used to Prevent Contamination Caused by Air Supply
Kettles	Hot water sterilization Disinfectant solution[a] (in joints)	Microporous filter
Pipes	Hot water sterilization Disinfectant solution[a] (in joints)	
Cooling equipments	Hot water sterilization	
Storage tanks	After hot water sterilization, drying by microbially free filtered air Disinfectant solution[a] (in joints)	Microporous filter

[a]The disinfectant solution used for sterilization was chlorhexidine in 70 per cent alcoholic solution.

a clean room as is shown in Fig. 4 is satisfactory. The room is 10.8 m x 5.4 m wide and 2.6 m in height. This clean room is equipped with a horizontal laminar flow system. The air is passed through high efficiency particulate filters and enters the room from the right side, passes through the clean room and is discharged at the exhaust grill arranged on the left side wall.

Entry to the room is from the left side through the air shower and in order to limit entry of microorganisms, every person or large material and equipment entering the room must be exposed for a minimum of 30 sec to an air shower, which has a 15 m/sec wind velocity. This can be seen in Fig. 5.

One can notice on the upper side of the room, two pass boxes, which are used to bring packaging material into the room. There is also an opening for taking out the filled products. The position of the filling machines is near the filtering air wall, where there is the least degree of contamination, while the storage tank, which is a closed system and least prone to contamination, is arranged nearest the air discharge grill. In between the filter and the storage tank, the materials (such as collapsible metal tubes) and working personnel are located. To maintain the constant efficiency of the clean room, the number of working personnel entering the room is limited to a minimum. Before being brought into the clean room, material and machinery are sterilized, and the whole facility is checked at constant intervals for microbial contamination.

2. Operation: To prevent microbial contamination in the clean room, after it is sterilized, all filling equipment is transported through the air shower tunnel into the clean room. Table V shows the sterilizing method used for this equipment.

To impede contamination in the clean room, all working personnel (before they enter the room) must wear sterile dust-free garments complete with head

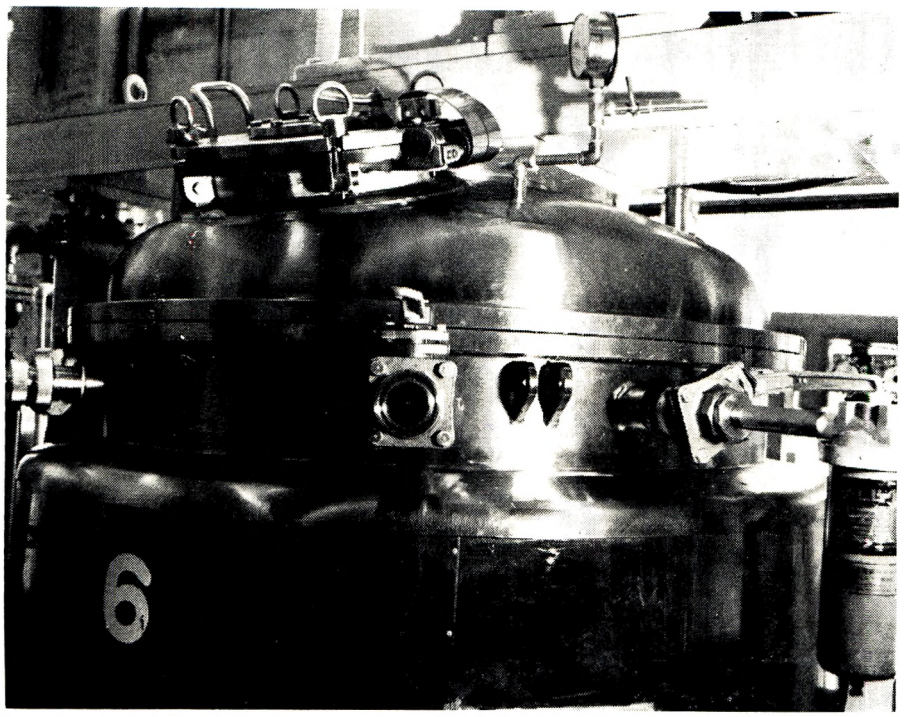


Figure 3. Highly efficient microporous filter mounted onto air inlet of kettle

cover and mouth mask. Their shoes must be changed and their hands disinfected with chlorhexidine in 70 per cent alcoholic solution. Only healthy working personnel are selected, and they are required to have periodic health checkups. After proper indoctrination with regard to the purpose for manufacturing this particular type of cosmetic, they are instructed in the fundamentals of preventing microbial contamination. Figure 6 illustrates these uniforms.

Countermeasure for Preventing Microbial Contamination of Container

In order to avoid any contamination during distribution and also to impede to the utmost any other secondary contamination, the container has an unique packaging structure. The collapsible tubes are small in size with closed nozzles. To open the nozzles, the loose blue ring at the base of the cap is removed, and the tube is pierced by the sharp protrusion on the inner side of the cap when the cap is screwed down completely. This is seen in Fig. 7.

Upon delivery only a few microbial cells were found in the tubes, which is quite a low degree of contamination; however, the tubes are sterilized to

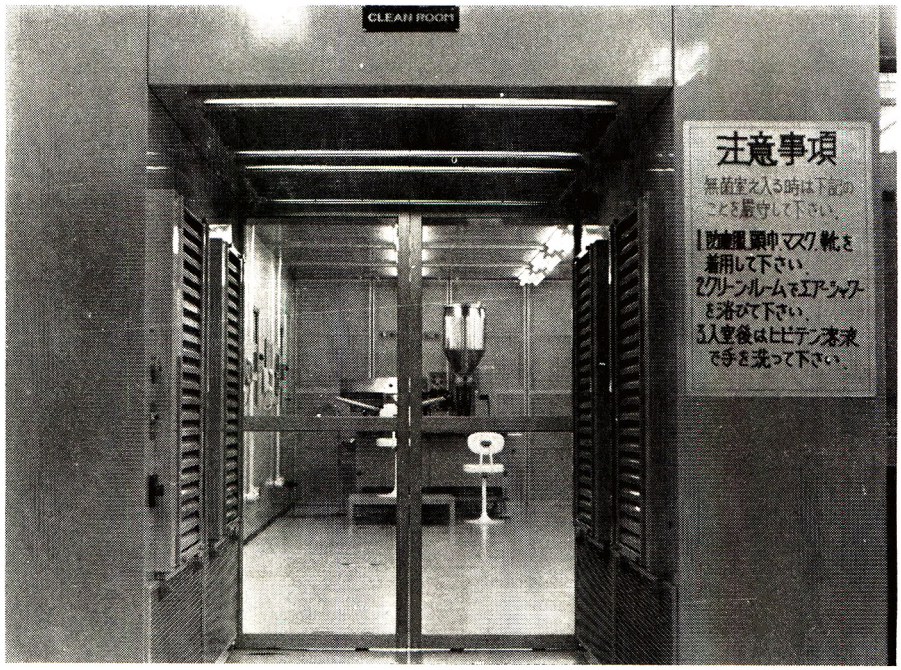


Figure 4. View of clean room from entrance. Translation of Japanese sign in picture: Caution, when entering the clean room, take the following precautions: (1) wear sterile dust-free garments complete with head cover and mouth mask; (2) take air shower and (3) disinfect hands with chlorhexidine solution

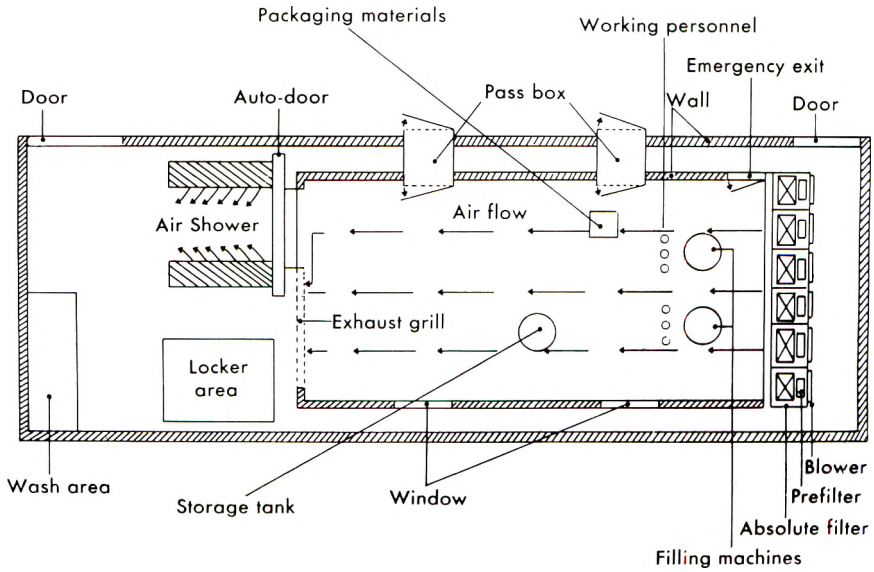


Figure 5. Layout of clean room

Table V
Sterilizing Method for the Filling Equipment

Equipment	Sterilizing method
Storage tank	Disinfectant solution (chlorhexidine in 70 per cent alcoholic solution)
Filling machine	Disinfectant solution (iodine type)
Pump	Disinfectant solution (iodine type)
Pipes	Hot water
Tools	Disinfectant solution (chlorhexidine in 70 per cent alcoholic solution)

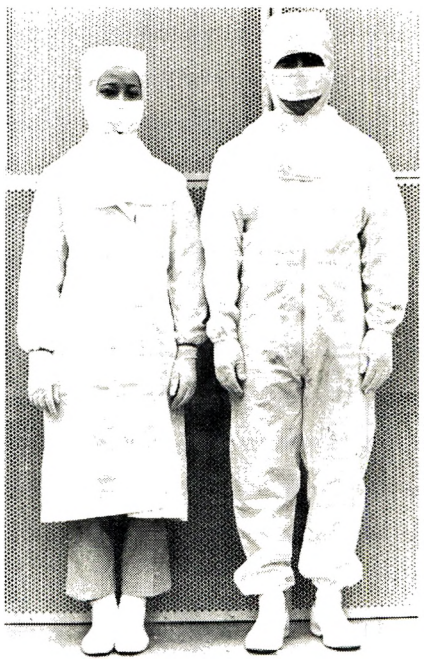


Figure 6. Working personnel wearing sterile dust-free garments

prevent any contamination of the product from this source. Ethylene oxide gas sterilization conditions are the same as those described under cellulose gums. The microbial count found in these tubes is shown in Table IV.

The collapsible tubes are received wrapped in a polyethylene protective film and then packaged in corrugated cartons. In this packaged form, the collapsible tubes are sterilized by ethylene oxide gas and subsequently conveyed in the polyethylene wrapped form through the pass box into the clean room.

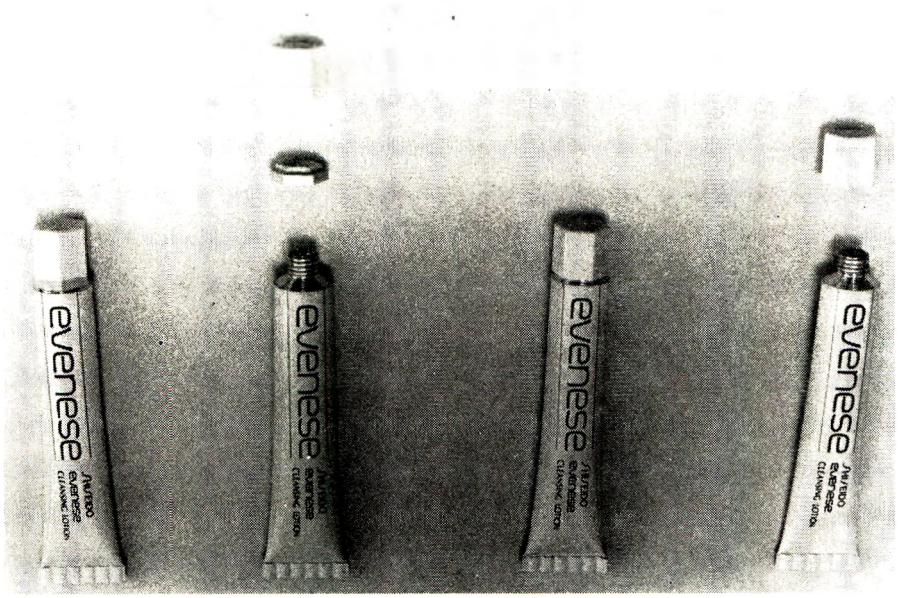


Figure 7. Container structure

Table VI
Results of Metal Tube Sterilization by Ethylene Oxide Gas

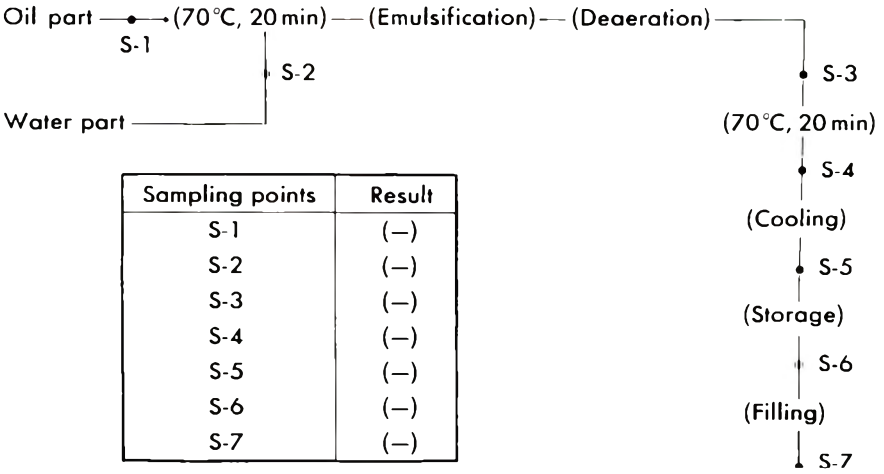
	Microorganisms Check Result	
Before sterilization	n equals 45 tubes	+[a] : 4 tubes −[b] : 41 tubes
After sterilization	n equals 45 tubes	+[a] : 0 tubes −[b] : 45 tubes

[a]Contamination.
[b]Noncontaminated.

Check of Microorganisms at Pilot Production Scale During Processing

As shown in Fig. 8, a special study has been conducted to determine the means to prevent microbial contamination in raw and packaging materials during processing and filling procedures.

The results, as can be observed from the pilot production scale, indicate that there are no signs of contamination whatsoever in the various samples at the different sites of the process.



Sampling points	Result
S-1	(−)
S-2	(−)
S-3	(−)
S-4	(−)
S-5	(−)
S-6	(−)
S-7	(−)

Figure 8. Testing of final product for microbial contamination

Table VII
Sampling Time and Sampling Unit in the Course of Actual Production

	Sampling Time	Sampling Unit
Unfilled product	Immediately after manufacturing	Each batch
	One week after manufacturing	Each batch
Finished product	Immediately after filling	Half-day
	One week after filling	Half-day

Microbially Free Assurance

In order to assure a microbially free product in actual production, samples were taken during the pilot production scale. These were studied as shown in Table VII.

Filling is carried out after confirmation that the unfilled product passes all tests. Shipment (as a finished product) is done only after it is determined that the product meets all other rigid standards set for it.

The tests performed to confirm the number of microorganisms and their species in unfilled products and finished products are shown in Fig. 9.

Results in Actual Production

Check Results of Products

Based upon the experimental results obtained, we standardized the microbially free techniques in the various stages of manufacturing process and

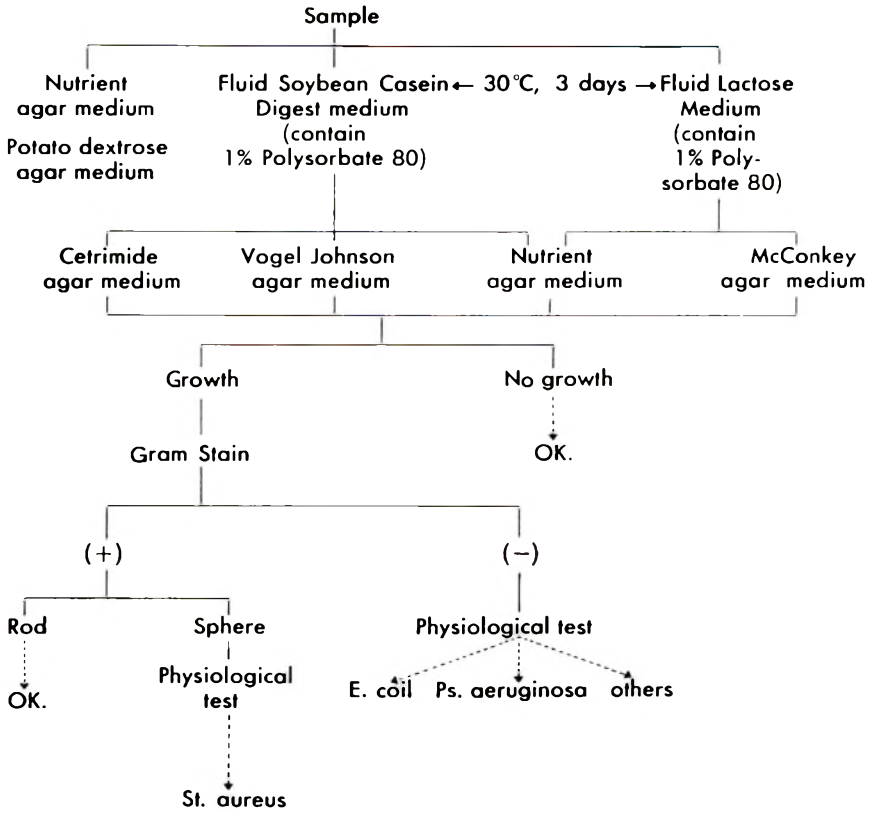


Figure 9. Microorganisms check-test method for unfilled and finished products

Table VIII
Results of A Emulsion in Actual Production

Lot Number	Unfilled Products	Finished Products
1	(−)	n[a] = 12, all (−)
2	(−)	n = 12, all (−)
3	(−)	n = 12, all (−)
4	(−)	n = 16, all (−)
5	(−)	n = 12, all (−)
6	(−)	n = 12, all (−)
7	(−)	n = 16, all (−)
8	(−)	n = 12, all (−)
9	(−)	n = 4, all (−)
10	(−)	n = 4, all (−)

[a]n equals number of samples.

Table IX
Results of B Emulsion in Actual Production

Lot Number	Unfilled Products	Finished Products
1	(—)	n[a] = 12, all (—)
2	(—)	n = 12, all (—)
3	(—)	n = 16, all (—)
4	(—)	n = 8, all (—)
5	(—)	n = 16, all (—)
6	(—)	n = 8, all (—)
7	(—)	n = 16, all (—)
8	(—)	n = 16, all (—)
9	(—)	n = 16, all (—)
10	(—)	n = 8, all (—)
11	(—)	n = 12, all (—)
12	(—)	n = 4, all (—)
13	(—)	n = 4, all (—)
14	(—)	n = 4, all (—)

[a]n equals number of samples.

Table X
Check Results of Products after Prolonged Storage on the Markets

Name / Time held / Place	A Emulsion		B Emulsion	
	6 months	18 months	6 months	18 months
Hokkaido	(—)	(—)	(—)	(—)
Toyama	(—)	(—)	(—)	(—)
Tokyo	(—)	(—)	(—)	(—)
Oaska	(—)	(—)	(—)	(—)
Kyushu	(—)	(—)	(—)	(—)

produced Emulsion A and B. Tables VIII and IX show the results obtained in the production of the emulsions during the 1971 to 1973 period. All were found to meet the predetermined standard level for microbial contamination.

Results of Quality Check on Products After Prolonged Storage on the Markets

After a lapse of 6 and 18 months while the product was on the markets of 5 different areas throughout the country, samples were collected and checked for possible microorganisms' growth; however, as Table X shows, none was found.

Summary and Conclusions

1. For microbially free raw material, uv and ethylene oxide gas sterilization methods were employed.

2. For a microbially free condition during the manufacturing processs, the following sterilizing systems were adopted: heating, disinfectant solution, and microporous filters.

3. To get a microbially free condition during the filling operation, full and proper use was made of the clean room, while establishing new control methods.

4. The assurance of a microbially free condition was obtained by the use of sampling and various test methods.

Our purpose which was to produce an emulsion on a large scale in a microbially free state has been successfully attained.

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The Evaluation of a Sunscreening Agent for Safety and Activity

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Presented August 1974, 8th IFSCC Congress, London, England

Synopsis: In the light of current and proposed legislation on SAFETY and efficacy, each new COSMETIC RAW MATERIAL requires extensive testing before it is introduced to the market. The evolution and evaluation of a highly active alkoxylated PARA-AMINOBENZOIC ACID (PABA) derivative is discussed in detail. Animal studies are employed to provide basic toxicity data. Clinical studies employ maximization techniques to expose possible hazards. Laboratory, clinical, and field tests are used to study efficacy. All of the above comprise a case study of the considerations involved in the introduction of a new chemical raw material to the cosmetic industry.

Introduction

In the light of current trends in the cosmetic industry, each new raw material requires extensive testing before its introduction to the cosmetic market. Raw materials, which are therapeutically active, must be tested as extensively as pharmaceuticals. The development of propoxylated ethyl p-aminobenzoate† at Amerchol as a new highly functional sunscreen can be considered as a case study of the considerations involved in the introduction of a new chemical raw material to the cosmetic industry.

Solar radiation has a broad band character extending in the ultraviolet (uv) range from 290 to 400 nm at sea level in midsummer. The intensity of sunlight in this range varies greatly with wavelength as does the sunburn effect and the tanning effect of the sun's radiation. Luckiesh (1) and Bener (2) investigated these factors and determined an erythemal flux for various wavelengths measured in E-vitons. This erythemal flux is obtained by multiplying intensity in microwatts per square centimeter for the wavelengths by one-tenth of an erythemal effectiveness factor. The corresponding erythemal flux in E-vitons can be indexed by stating each value as a per cent of the 308 nm peak. The E-viton index is then plotted against the wavelength to produce

°Amerchol, a unit of CPC International Inc., Edison, N.J. 08817.

†Amerscreen P, a registered trademark of Amerchol, a unit of CPC International Inc., Edison, N.J. U.S. Patent 3,880,992.

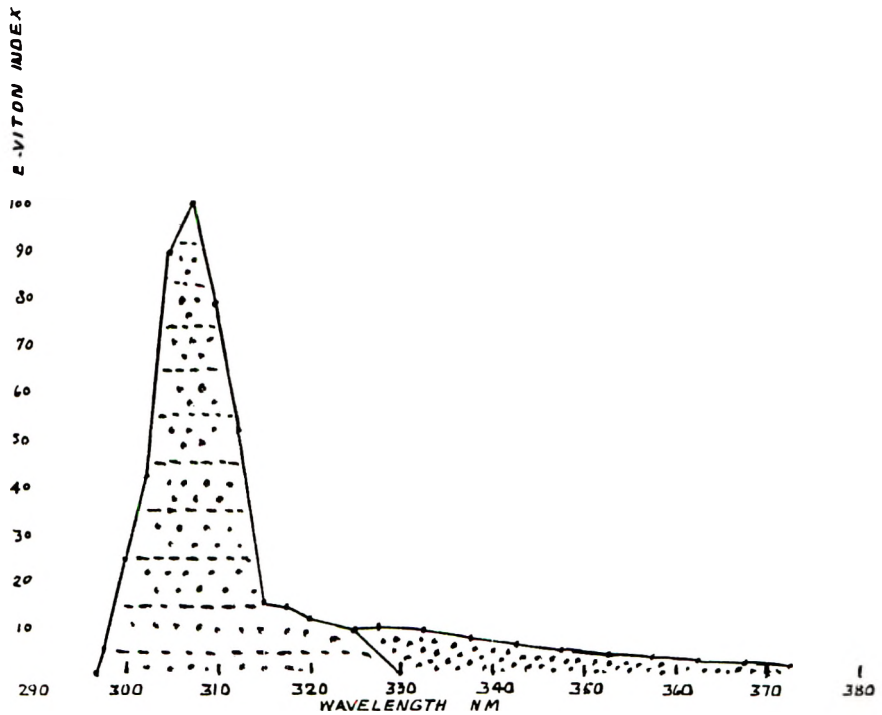


Figure 1. Sunburn and tanning curve: (—) erythemal flux; (●) tanning flux

the familiar sunburn curve (Fig. 1). More than 95 per cent of the total erythemal flux of sunlight occurs at wavelengths below 320 nm. For this reason, the wavelength range from 290 to 320 nm is termed the erythemal or sunburn range. Tanning also takes place in the erythemal range, but does not fall off as rapidly as erythema in the longer wavelengths. Kreps (3) identifies the wavelength range from 320 to 375 nm as the tanning range. Only 24 per cent of tanning actually occurs in this range, with the remaining 76 per cent taking place in the erythemal region. The ideal sunscreen will absorb radiation in the sunburn region (290 to 320 nm), exhibiting maximum absorbance at 308 nm (4) (the wavelength with the greatest burning intensity), and transmit radiation in the tanning region (320 to 375 nm).

The synthesis of propoxylated ethyl p-aminobenzoate and the discovery of its effectiveness as a sunscreen were accomplished in several phases as follows: phase 1, organic synthesis and instrumental evaluation of candidate compounds; phase 2, toxicity testing; and phase 3, performance testing to substantiate efficacy and safety.

The animal tests (except for comedogenicity) were conducted by an inde-

pendent laboratory.* All the clinical and performance studies on humans and the comedogenicity study on rabbits were conducted by another laboratory.†

Experimental

Phase 1—Initial Screening

The first phase of the research program concerned the synthesis of compounds, which were expected to absorb in the optimum uv region. Propoxylated ethyl p-aminobenzoate was selected for further development because it absorbs in the correct uv region and exhibits desirable physical properties. Infrared (ir) spectra, nuclear magnetic resonance (NMR) spectra, and gas chromatographic analysis (GCA) substantiate that propoxylated ethyl p-aminobenzoate is a mixture of 2 moles of N, N-dihydroxypropyl and 1 mole of N-monohydroxypropyl ethyl p-aminobenzoate. NMR spectra show that the hydroxypropyl moiety in the mono- and di-compounds contains both primary and secondary hydroxyls. To further substantiate the actual composition of propoxylated ethyl p-aminobenzoate, pure mono and di hydroxypropyl substituted ethyl p-aminobenzoates were synthesized, analyzed, and reblended in various mole ratios. Ir spectra, NMR spectra, and GCA of a 2 di to 1 mono blend matched propoxylated ethyl p-aminobenzoate exactly. The ir spectra of propoxylated ethyl p-aminobenzoate, N, N-dihydroxypropyl, and N-monohydroxypropyl ethyl p-aminobenzoate are shown in Figs. 2, 3, 4, respectively.

Table I contains the important physical properties, and Table II contains solubility data on propoxylated ethyl p-aminobenzoate.

It should be understood that it is not essential for a compound to exhibit maximum absorbance at 308 nm, but only that the absorption peak be sufficiently broad to encompass the sunburn range of 290 to 320 nm and narrow enough to transmit the tanning range. Figs. 5, 6, 7, 8, 9, and 10 compare propoxylated ethyl p-aminobenzoate absorption with other sunscreens. Propoxylated ethyl p-aminobenzoate exhibits maximum absorbance at 308 to 311 nm, which is the region of the greatest burning intensity, and compares very favorably with the most active sunscreens in use today. It will be noted in Fig. 7 that PABA, which is generally recognized as a very effective screen, has a somewhat less favorable absorption at 310 nm, although it is very active at 290, where comparatively little burning and tanning take place. The comparison with 2-ethoxyethyl-p-methoxycinnamate (Fig. 10) does not tell the whole story until one exposes both compounds to direct sunlight for various periods of time. Fig. 11 shows the dramatic effect of solar energy on the cinnamate with the obvious resulting formation of new compounds. Propoxylated ethyl

*Food and Drug Research Laboratories, Inc., Conshohocken, Penn.
† Ivy Research Laboratories, Inc., Philadelphia, Penn.

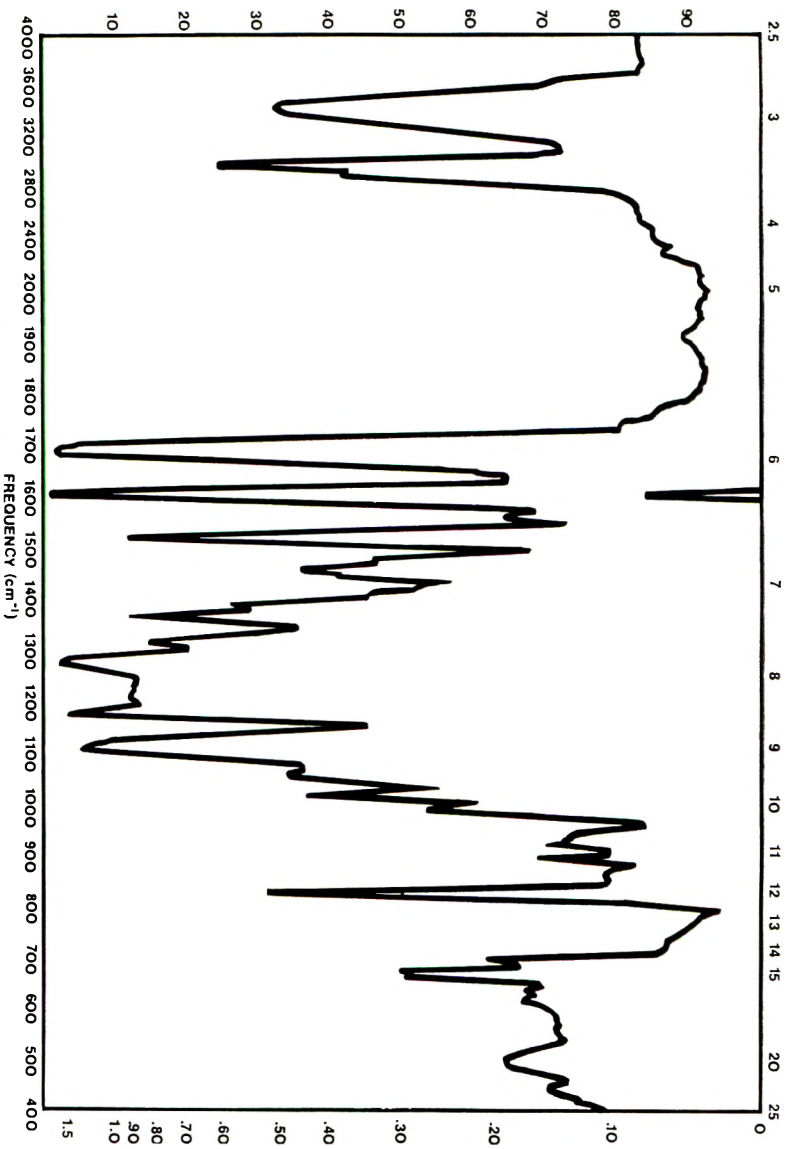


Figure 2. Propoxylated ethyl p-aminobenzoate

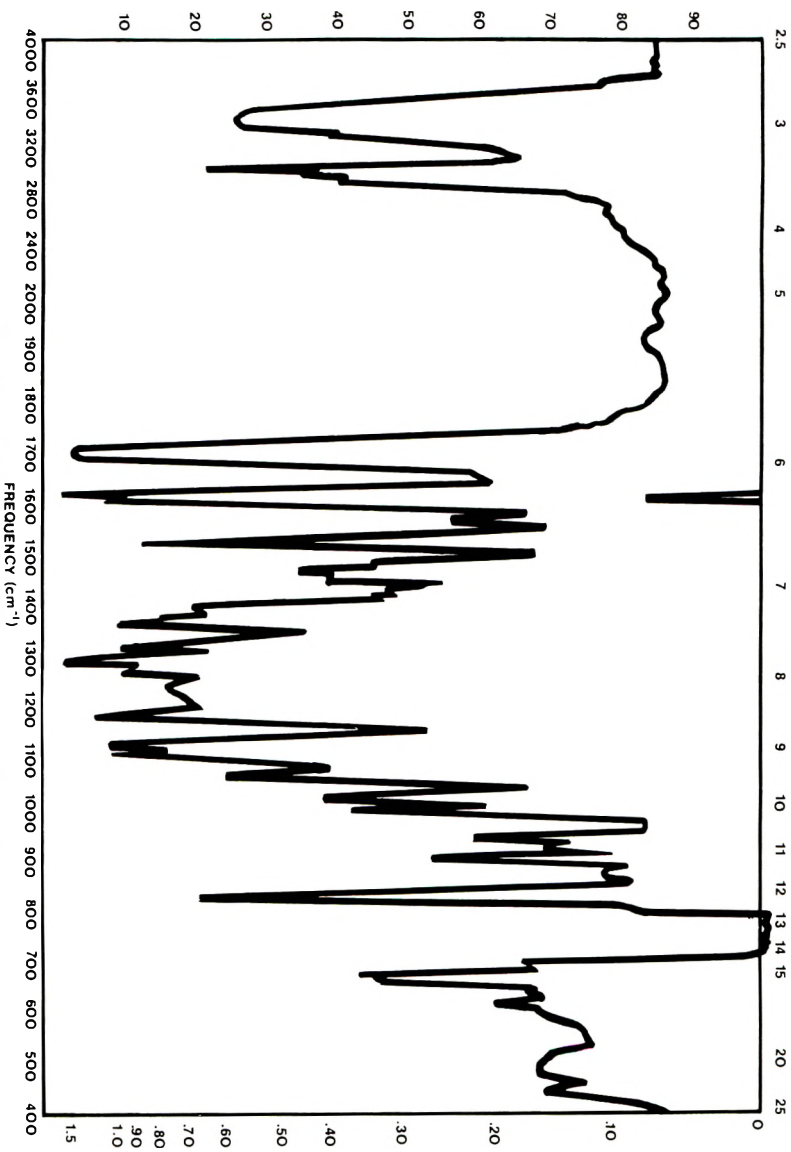


Figure 3. N, N-dihydroxypropyl ethyl p-aminobenzoate

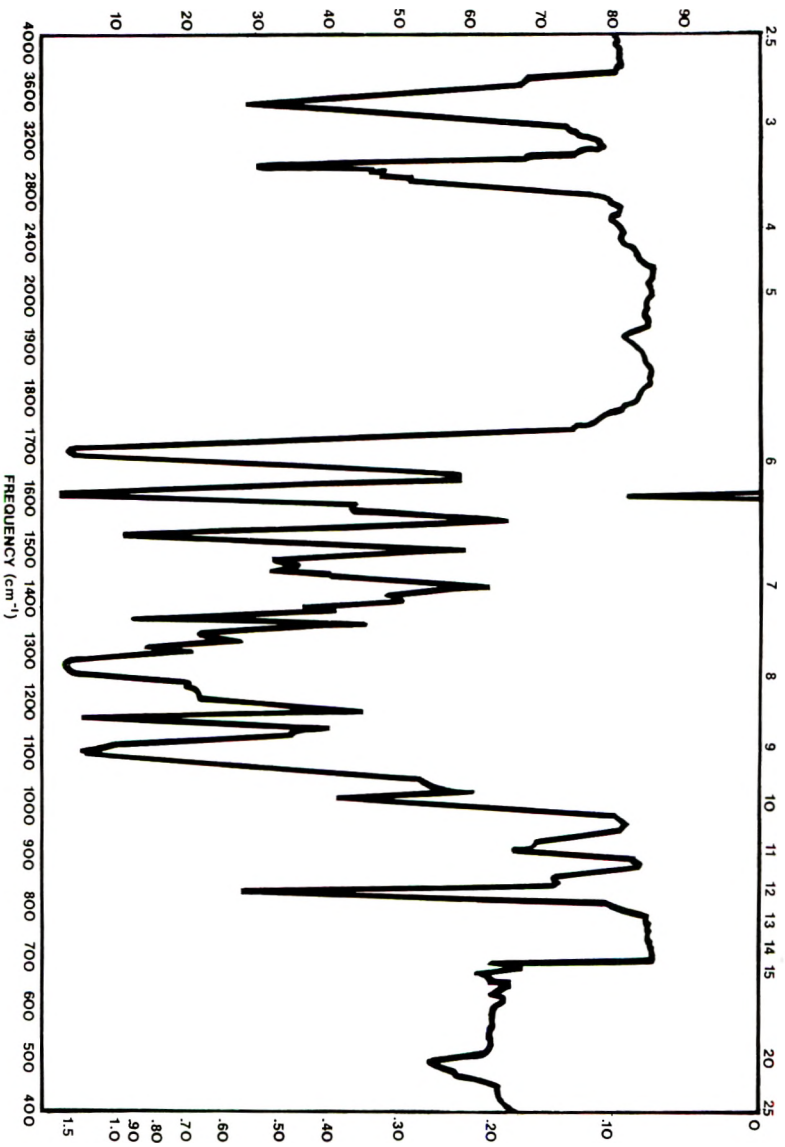


Figure 4. N-monohydroxypropyl ethyl p-aminobenzoate

Table I
Amerscreen P

Properties	
Appearance	Faint yellow semiliquid (crystalizes on aging)
Odor	Practically odorless
Molecular weight	281
uv absorption	Maximum at 308–311 mμ
Acid value	1 Maximum
Hydroxyl value	380–400
Saponification value (4 hours)	190–210
Specific gravity @ 80°C	1.082 nominal
Refractive index @ 60°C	1.5589 nominal
Moisture	0.25 per cent maximum
Ash	0.25 per cent maximum
Microbiological count when packaged	Less than 10/g

Table II
Amerscreen P

Solubility (5 per cent W/W)	
Ethanol (95 per cent)	S[a]
Ethanol (70 per cent)	S
Ethanol (50 per cent)	S
Isopropyl alcohol	S
Propylene glycol	S
Ethanol, propylene glycol, water (50/20/30)	S
Ethanol, glycerine, water (50/20/30)	S
Castor oil	S
Corn oil	S (2.5 per cent)
Isopropyl myristate	S (2.5 per cent)
Solulan 98	S
Solulan PB-10	S
Glycerine	I[b]
Mineral oil, 70 viscosity	I
Water	I

[a] S stands for soluble.
[b] I stands for insoluble.

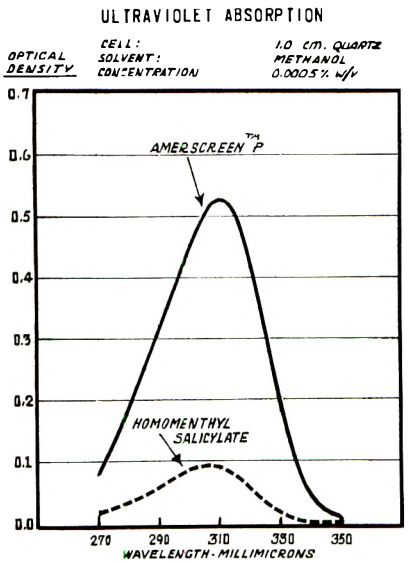
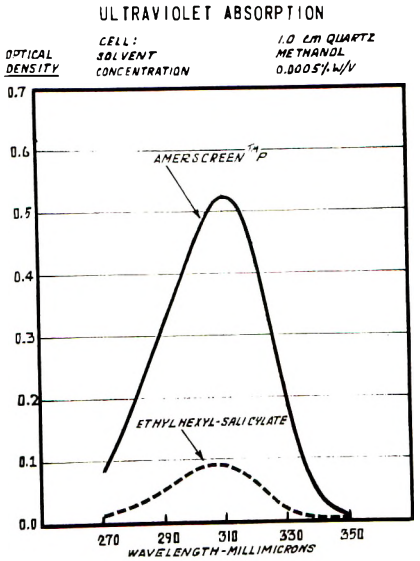


Figure 5.



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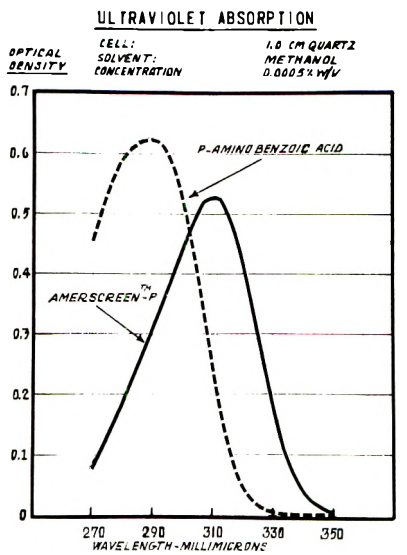

Figure 7.

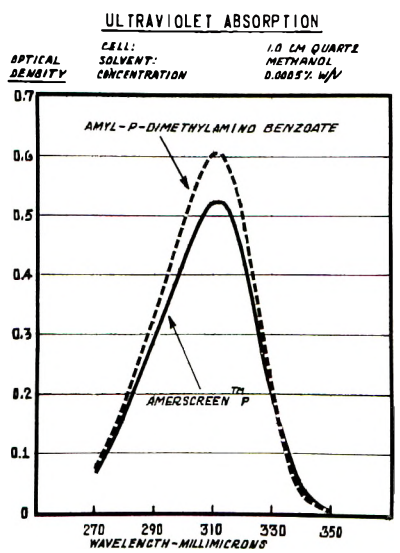

Figure 8.

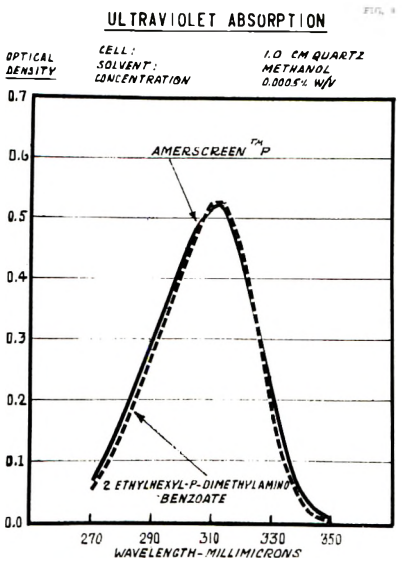

Figure 9.

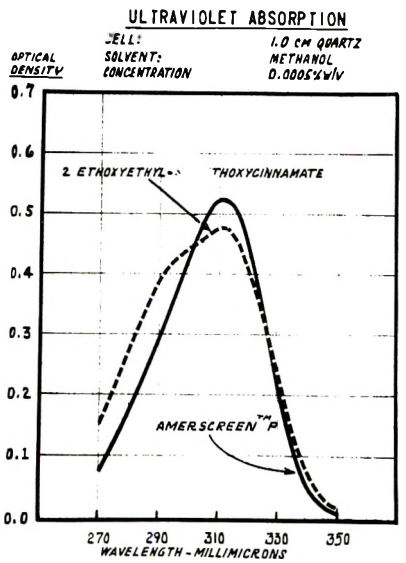

Figure 10.

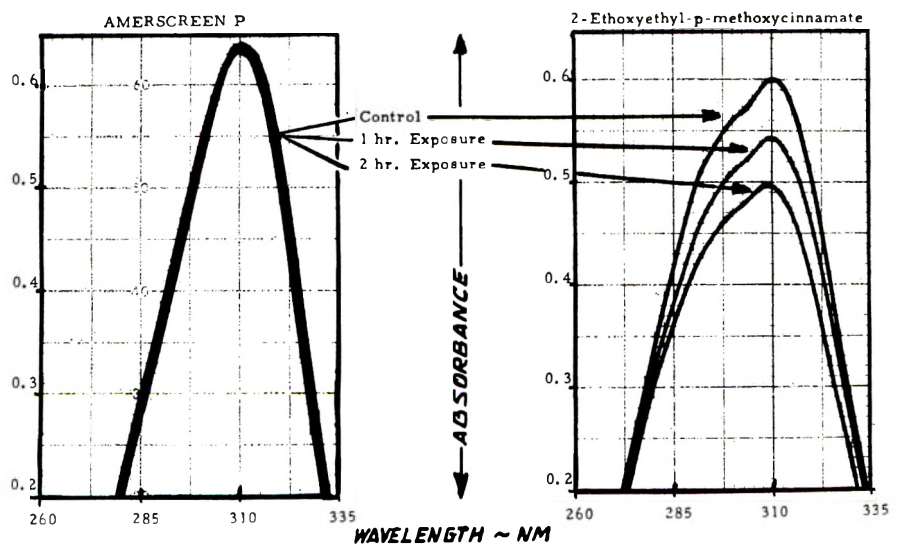

Figure 11. Stability of Amerscreen P and 2-ethoxyethyl-p-methoxycinnamate. 0.5 per cent methanolic solutions exposed to direct sunlight uv curves on 0.5 per cent solutions in 0.0025 cm cell

p-aminobenzoate remains unchanged when treated under similar conditions.

Figure 12 is a plot of erythemal transmission versus concentration using an 0.0025 cm quartz cuvette, which approximates a use application. A 1 per cent concentration of propoxylated ethyl p-aminobenzoate in methanol transmits only 1 per cent of the erythemic radiation (290 to 320 nm integrated) by this procedure.

Figure 13 is a plot of tanning wavelength transmission versus concentration again using the 0.0025 cm quartz cuvette. A 1 percent concentration of propoxylated ethyl p-aminobenzoate in methanol permits transmission of 68 per cent of the desirable tanning rays (320 to 375 nm integrated), while cutting 99 per cent of the undesirable erythemic rays.

Cumpelik (5) has developed a simple analytical procedure to evaluate sunscreens. Per cent transmittance is determined for several concentrations at wavelength increments from 2900 to 3750 Å. Each wavelength is weighted by its erythemal effectiveness factor and the erythemal and tanning fluxes integrated over the wavelength range to determine the total per cent of erythemal and tanning transmission. A plot of concentration versus both erythemal and tanning transmission can be used as a guide to sunscreen concentration. Erythemal and tanning transmission curves were developed for propoxylated ethyl p-aminobenzoate following Cumpelik's procedure. These are presented in Fig. 14.

Phase 2—Toxicity and Safety

Propoxylated ethyl p-aminobenzoate was selected for further testing to determine its toxicity and safety in use. With the need for proof of safety uppermost in mind, we elected to undertake a rather extensive testing program. At each step of phase 2, the candidate compound could have been eliminated, forcing a return to the phase 1 screening program.

Animal Studies

The first step was to determine acute oral toxicity. We tested 100 per cent propoxylated ethyl p-aminobenzoate on 5 groups of albino rats consisting of 5 male and 5 female rats in each group of Sherman-Wistar strain. The acute oral LD_{50} is 13.3 ml/kg. For comparison, the LD_{50} of benzocaine is calculated to be 10.9 ml/kg (6) and of PABA 6 ml/kg.

Five per cent propoxylated ethyl p-aminobenzoate in Carbowax ointment was then tested for primary skin and eye irritation. This concentration, which represents about five times the normal recommended level in most suntan formulations, was selected to exaggerate the test. No cases of skin and eye irritation were noted on 6 albino rabbits.

Comedogenicity of 5 per cent propoxylated ethyl p-aminobenzoate was evaluated by applying the agent daily to the external ear canal of 3 rabbits for 3 weeks. No sign of comedones or irritation was observed.

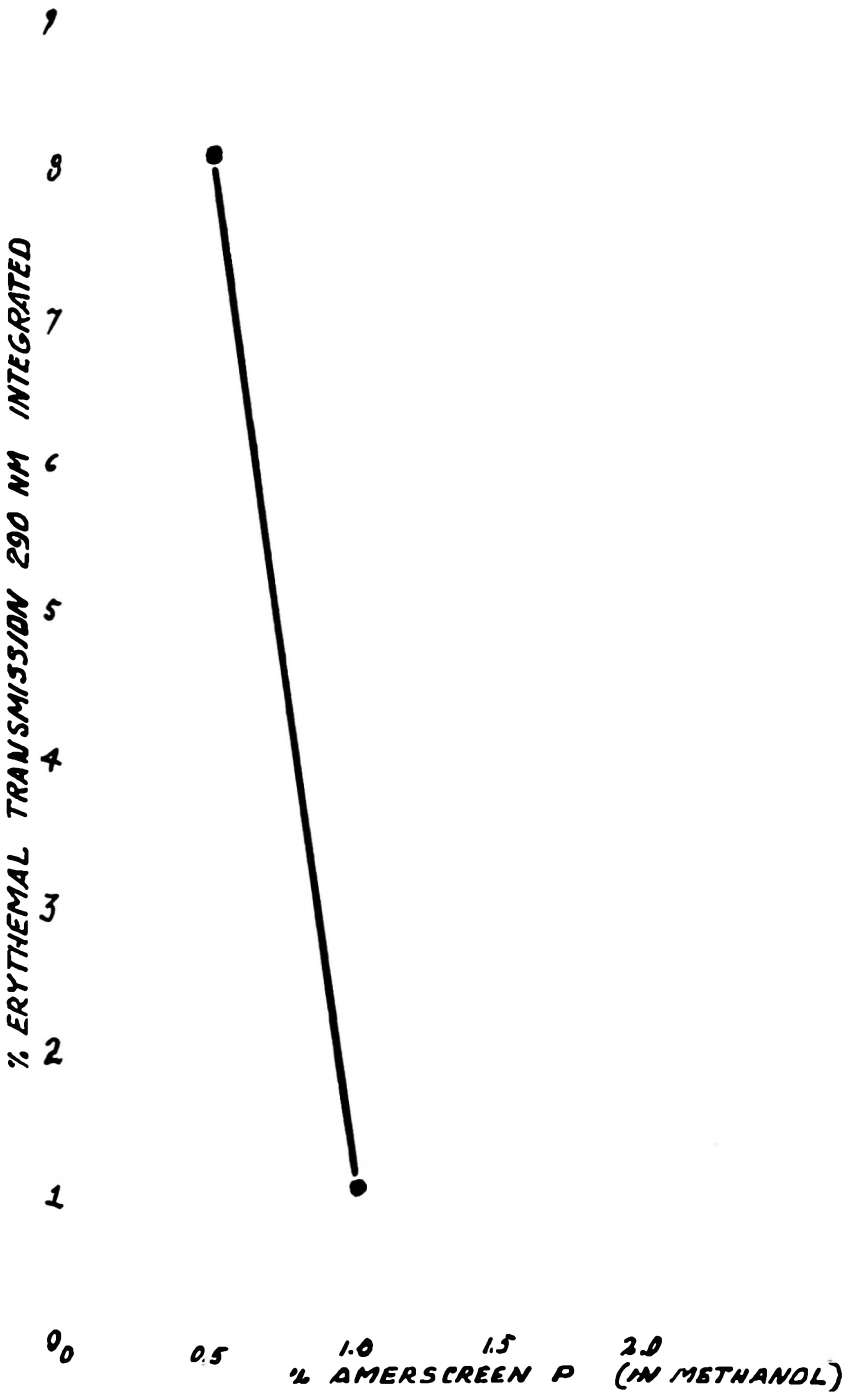

Figure 12. Erythemal transmission Amerscreen P. Cell 0.0025 cm quartz

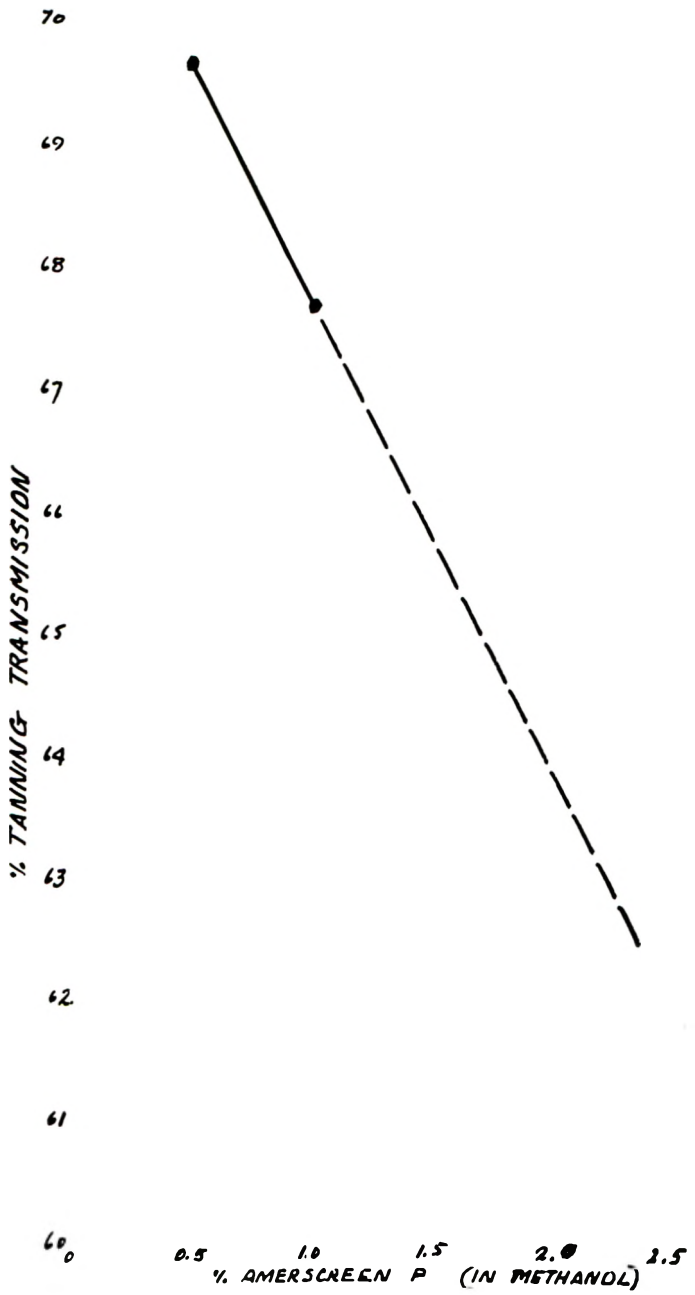

Figure 13. Tanning transmission Amerscreen P. Cell 0.0025 cm quartz

Clinical Studies on Humans

The clinical studies of toxicity and safety on humans employed, as was the case in the animal studies, a 5 per cent concentration of propoxylated ethyl p-aminobenzoate. This was considered to represent approximately five times the normal use concentration as is shown in the table below.

5 Per cent Propoxylated Ethyl p-Aminobenzoate Lotion

Amerscreen® P°	5.0 per cent
Alcohol SDA-40	20.0
Amerchol® L-500°	3.0
Isopropyl Lanolate	1.0
Polyoxyl 40 Stearate	2.0
Propylene Glycol Monostearate	3.0
Carbopol® 934†	0.5
Triethanolamine, 10 per cent solution	5.0
Water	60.5

Erythema was rated according to the following code: (0) no reaction; (1) barely perceptible erythema; (2) easily recognized erythema; (3) deep redness and swelling. A summary of the important findings and methods used follows.

(1) *Photoxicity:* No instance of phototoxicity was observed in the 10 healthy adult male volunteers who served as subjects for this test. Two-tenths ml of the test material was applied occlusively to duplicate 2 cm^2 normal and stripped skin sites on the upper backs of the subjects. Each stripped site received 6 minimal erythemal doses (MED) of Xenon‡ solar-simulating radiation filtered through window glass. The normal site was similarly exposed to the same dose of long-uv after 24 hours of occlusion. Observations were made at 1-, 3-, and 24-hour intervals after irradiation.

(2) *Facial Stinging and Burning:* No instance of facial stinging and burning was observed when a 5 per cent concentration of propoxylated ethyl p-aminobenzoate was applied liberally to the face of 15 healthy adult male volunteers. The subjects were placed in an environmental chamber for 30 min at 115°F with 50 per cent relative humidity. Subjects were checked at 5-, 10-, and 30-min intervals for stinging or burning and irritation. All subjects were then checked 24 hours later.

(3) *Primary Dermal Irritation:* No instance of primary dermal irritation on normal and stripped skin was observed on 10 healthy Caucasian adult male volunteers treated with 5 per cent propoxylated ethyl p-aminobenzoate lotion. There was an occasional transient minimal response on stripped skin, which is

° Amerchol, Edison, N.J.
† B. F. Goodrich Chemical Co., Akron, Ohio.
‡Macbeth Sales Corp., Newburgh, N.Y. 12553.

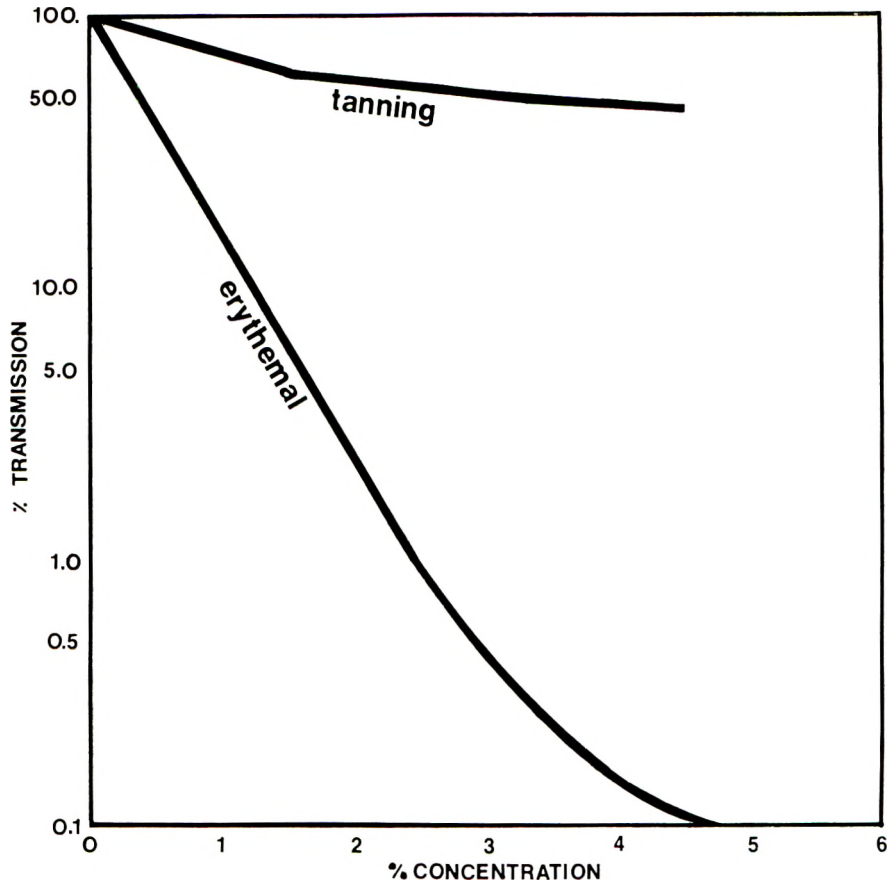

Figure 14. Propoxylated ethyl p-aminobenzoate erythemal and tanning transmission versus concentration

considered of no significance in this test. These results are shown in Table III. Propoxylated ethyl p-aminobenzoate compared favorably with two commercial products when all three were tested simultaneously. Three sites on the volar part of the right arm were stripped to the glistening layer by repeated application of clear tape. The volar part of the left arm was used for normal skin. Each of the test materials was applied once daily for 10 days under occlusion to the arms of the subjects. Clinical evaluations were made daily, using a 0 to 4 scale. The method is that developed by Klingman and Wooding (7).

(4) *Maximization Testing of Sensitizing Potential* (8): No instance of contact sensitization was noted on 25 healthy adult male volunteers.

Table III
Results

Subject Number	Initials	Stripped Skin Study Day 1	2	3	4	5	6	7	8	9	10
1	K.G.	0	0	0	0	1	0	0	0	0	0
2	L.L.	0	0	1	1	1	0	0	0	0	0
3	M.W.	0	1	1	0	0	0	0	0	0	0
4	C.J.	0	0	0	0	0	0	0	0	0	0
5	L.C.	0	1	1	0	0	0	0	0	0	0
6	M.R.	0	0	1	1	0	0	0	0	0	0
7	C.O.	0	0	0	0	0	0	0	0	0	0
8	E.S.	0	0	0	0	0	0	0	0	0	0
9	J.C.	0	0	0	1	1	1	0	0	0	0
10	J.R.	0	0	0	1	1	0	0	0	0	0

[a]Material: 5 per cent Amerscreen P lotion.

Table IV
Irritancy

Subject Numbers	Initials	Subtotal Inunction for 21 days Day Number 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	L.L.	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	0	1	1	0	0
2	E.S.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	T.S.	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	1	0	1	0
4	M.M.	0	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	1	0	0
5	G.S.	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	1	0
6	J.C.	0	0	0	0	0	0	0	0	1	0	0	1	1	1	0	0	0	1	0	0	0
7	M.R.	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	1
8	C.O.	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0	0
9	T.O.	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0
10	J.D.	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0
11	M.W.	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
12	K.G.	0	0	0	0	0	0	1	0	0	1	1	0	1	0	0	1	0	0	0	1	0
13	C.J.	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
14	L.C.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1
15	J.R.	0	0	0	0	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	0	0
16	R.J.	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
17	J.F.	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
18	L.J.	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	1	0	0
19	R.H.	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	H.P.	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0

Table V
The Irritancy and Safety of Topically Applied 5 per cent Amerscreen P Lotion

DATE Subject #1, LL.	Day 0 8-6-73	Day 22 8-28-73
Hematology		
Hemoglobin—GM per cent 11.5—18.0 GM per cent	14.3	13.3
Hematocrit—VOL per cent 34-52 per cent	42	40
WBC/MM³ 4,000-11,850	4,719	4,049
Platelets/MM³ 150,000-475,000/MM³	Adequate	Adequate
Reticulocytes—per cent 0.4-1.2 per cent	0.5	0.6
Differential (per cent)		
Neutrophils (polys) 25-70	53	66
Lymphocytes 21-56	45	34
Monocytes 2-8	0	0
Eosinophils 0-7	2	0
Basophils 0-2	0	0
Bands 0-11	0	0
Urinalysis		
S.G. 1.003-1.035	1.024	1.020
Albumin <30 MG per cent (< 1+)	negative	negative
Sugar Negative (0.1 per cent)	negative	negative
WBC/HPF 6/HPF average	4-8	2-3
RBC/HPF 3/HPF average	0	0
Casts LPF 4/LPF average	0	0
Epith	few	few
Bacteria	0	0
Crystals	0	0
Mucus Threads	0	0
Chemistry		
Chosesterol MG per cent 260 MG per cent	—	—
Bun MGM per cent 7-20 MG per cent	10	12
Fbs MGM per cent 60-100 MG per cent	80	82
Uric acid MGM per cent 3.0-7.0 MG per cent	—	—
Sgot U <40 Sigma units	32	35

Pretesting—The 5 per cent propoxylated ethyl p-aminobenzoate lotion was pretested on 5 subjects in order to determine whether sodium lauryl sulfate pretreatment was required. A patch of the material was applied to normal sites on the backs for 48 hours under occlusion. No subject had any irritation and it was decided to use sodium lauryl sulfate (SLS) pretreatment in the test.

(5) *Subtotal Topical Application for Irritancy and Toxicity:* Repeated massive application of 5 per cent propoxylated ethyl p-aminobenzoate lotion on 20 healthy adult male volunteers substantiates that propoxylated ethyl p-aminobenzoate has a very low level of irritancy and toxicity. The lotion was liberally applied to the entire area of the chest, back, shoulders, and face once

daily for 21 days. Clinical examinations were made daily. Results are shown in Table IV. Extensive blood and urine chemical and microscopic studies were done before and after the experiment. All laboratory tests were normal before and after 21 days. Results are shown in Table V for a typical patient.

Propoxylated ethyl p-aminobenzoate emerged from phases 1 and 2 as a sunscreen candidate, which absorbs in the correct uv region and is safe to use. The final and all-important step of this investigation is devoted to performance testing and stability.

Phase 3—Performance and Stability

MED

The response of normal human skin to sunlight is a function of the total E-viton units reaching the skin and the length of exposure to the sun's rays. Approximately 20 min exposure during the midday period of 10:00 am to 2:00 pm in midsummer is required to produce minimum perceptible erythema at 40° latitude. This amount of radiation is called one MED. Suntan lotions are used to permit longer exposure to the sun's rays. A sunscreen rating of 10 MED means that the first perceptible erythema is not observed until exposure to 10 times the radiation, which would produce mild erythema on untreated skin. In more practical terms, a 10 MED rating will protect against mild erythema for 3 hours and 20 min.

Many factors are involved in the actual effectiveness of a sunscreen. Riegelman and Penna (9) have shown that the effectiveness of a sunscreen is greatly influenced by the nature of the solvent in which it has been dissolved. Other factors such as film thickness absorption into the skin, and substantivity after bathing lead to the conclusion that only actual testing on human skin can be used to determine performance of a sunscreen.

The first step in determining actual performance on human skin involved the development of prototype formulations. Lotions, creams, oils, lip balms, and lipsticks have been prepared. Since this paper is aimed only at discussing the efficacy and safety considerations involved in the introduction of a new therapeutically active chemical raw material to the cosmetic industry, it suffices to say here that a complete range of formulations can be conveniently made.

Protective Index (PI)

The PI (10) is a numerical rating for sunscreen effectiveness. It is the ratio of radiation required to produce mild erythema on treated versus untreated skin. PI's were determined for various propoxylated ethyl p-aminobenzoate formulations and are presented in Table VI. These values of 20 to 70 MED are far in excess of the protection required.

Concentration Effect

Under controlled laboratory conditions 6 healthy adult male volunteers

Table VI
Protective Index

Sample	Description	Protective Index
T27-78-3	Amerscreen P 2 per cent in alcohol glycerine water	20
T27-78-4	Amerscreen P 5 per cent in alcohol glycerine water	30
T25-268-2	Amerscreen P 5 per cent in Carbopol lotion base	60
T32-64-2	Amerscreen P 5 per cent in Carbowax base	70
T32-56-1	Amerscreen P 5 per cent in oil base	20

were exposed to 20, 40, and 60 times the radiation necessary to produce mild erythema on untreated skin (20, 40, and 60 MED). The 1.0 and 2.5 per cent propoxylated ethyl p-aminobenzoate lotions are modifications of the 5.0 per cent propoxylated ethyl p-aminobenzoate lotion previously described, with water replacing propoxylated ethyl p-aminobenzoate in the formula. Fifty μg of lotion were applied to 1 sq in. of skin and observed versus untreated skin as a control. A Xenon lamp was used as the radiation source. Only barely perceptible erythema was observed at the highest radiation dose with the 1.0 per cent propoxylated ethyl p-aminobenzoate concentration.

Substantivity after Bathing

To determine whether propoxylated ethyl p-aminobenzoate formulations would still be effective after bathing, 50 μg of lotion were applied tol sq in. test area on the forearms of 6 healthy adult male volunteers. The volunteers immersed their forearms in an agitated water bath thermostatically controlled at 37°C. After 10 min immersion the subjects were exposed to 6 MED. Results of this immersion test are tabulated in Table VII and indicate that propoxylated ethyl p-aminobenzoate formulations will provide a fair degree of protection even after bathing, but concentrations higher than 1 per cent are recommended for complete protection after bathing.

Heat Stability

To determine heat stability of propoxylated ethyl p-aminobenzoate, a closed jar of 100 per cent propoxylated ethyl p-aminobenzoate was held at 105°C for 62 hours. The jar was opened periodically and samples removed to determine changes in uv absorption, chemical composition, color, and odor. Very slight yellowing was detected; however, the heated sample was still within normal batch-to-batch variation, and uv absorption, composition, and odor were unchanged.

Staining of Fabrics

Propoxylated ethyl p-aminobenzoate formulations were tested for staining of cotton and 80/20 cotton-nylon blends. Hydroalcohol and oil preparations containing 2.5 and 5.0 per cent propoxylated ethyl p-aminobenzoate were ap-

Table VII
Amerscreen P; Immersion Effect

	1 per cent Amerscreen P Lotion Radiation (MEDS)	2.5 per cent Amerscreen P Lotion Radiation (MEDS)	5.0 per cent Amerscreen P Lotion Radiation (MEDS)
Subject	6	6	6
1	2	1	1
2	2	1	0
3	1	1	0
4	2	1	1
5	1	0	0
6	2	2	1
Control	3+	3+	3+

plied to the fabrics and exposed to direct sunlight for 5 hours. All formulations produced slight yellowing, which was easily and completely removed by mild laundering, while PABA formulations produced a permanent deep yellow stain. Results are shown in Table VIII.

Field Trials

Each formula type must be evaluated under actual use conditions to prove efficacy in both sunburn prevention and suntan formation. Field trials were conducted with the following sunscreen butter formulas as is shown in the following table.

Amerscreen P°	1.0%	2.0%
Solulan® PB-20°	40.0	40.0
Isopropyl palmitate	43.0	42.0
Candelilla wax	12.0	12.0
Carnauba wax	4.0	4.0
Perfume and preservative	q.s.	q.s.

Sunscreen butter is prepared by dissolving propoxylated ethyl p-aminobenzoate in Solulan PB-20 with slight heating. The remaining ingredients are added and the mixture heated to 85°C while it is mixed slowly until it is clear and uniform. Mixing is continued while it is cooled to 35°C, and the formula is then homogenized.

The formulas were packaged in tubes and distributed over an 18-month period to more than 25 subjects. The formulas were used in the Swiss Alps at 3000 m and on the beaches of the Bahamas, Southern Florida, New Jersey, and Long Island. No special precautions were taken for initial exposure. All

° Amerchol, Edison, N.J. 08817.

Table VIII
Staining[a] Tests Cotton Cloth

	Original Cloth	Initial Stain	5 Hours Exposure	Mild Laundering
5 per cent Amerscreen P lotion	0	1	2	0
2.5 per cent Amerscreen P lotion	0	1	2	0
5 per cent PABA lotion	0	2	2	2
2.5 per cent PABA lotion	0	2	2	2
80 Cotton/20 Nylon Cloth				
5 per cent Amerscreen P lotion	0	1	2	0
2.5 per cent Amerscreen P lotion	0	1	2	0
5 per cent PABA lotion	0	2	2	2
2.5 per cent PABA lotion	0	2	2	2

[a]Stain rating: (0) no stain, (1) clear oil stain, (2) light yellow oil stain, (3) amber oil stain.

subjects reported that they developed a deep tan after 1 to 2 weeks use. No cases of sunburn were noted. The subjects were not able to distinguish between the formulas with 1 and 2 per cent propoxylated ethyl p-aminobenzoate. Both concentrations were equally effective in preventing sunburn while suntan developed. In addition, informal field trials were conducted with lotions, creams, and oils. All reports substantiate the laboratory and clinical findings that 1 per cent propoxylated ethyl p-aminobenzoate is effective in preventing burning while tanning develops.

Summary

Steps involved in the development of a new sunscreen, propoxylated ethyl p-aminobenzoate, were described. The various procedures required to substantiate efficacy and prove safety were presented in detail. It is clear that the introduction into the market today of a new functional raw material is neither simple nor inexpensive. It should be obvious that the manufacturer of cosmetic raw materials must be just as involved as the cosmetic manufacturer in the current trend toward proving safety and efficacy before a consumer product is put on the market.

Acknowledgment

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Society of Cosmetic Chemists Medal Award to Dr. Murray Berdick

The Society of Cosmetic Chemists presented its highest honor for 1975 to Dr. Murray Berdick, Director of Regulatory Affairs with Chesebrough-Pond's Inc., Trumbull Industrial Park, Trumbull, Conn.

The Medal Award was presented to Dr. Berdick in recognition of the many contributions he has made over the years to the Cosmetic and Toiletries industry and to the Society of Cosmetic Chemists organization in particular.

The formal presentation was made at the December 1, 1975 luncheon during the Society of Cosmetic Chemists' Annual Scientific Meeting by Mr. Stephen Hoch, 1975 Society of Cosmetic Chemists' President. Dr. E. G. McDonough, a long-time colleague of Dr. Berdick, acted as Eulogist. A dinner-dance in honor of Dr. and Mrs. Berdick was held at the Americana Hotel in the evening of December 1, 1975.

Dr. Berdick was chairman of the Society of Cosmetic Chemists' Annual Meeting in 1972, and is a past chairman of the SCC Literature Award Committee. Since 1971, he has been chairman of the Inter-Industry Color Technical Committee. Active in the Cosmetic, Toiletry and Fragrance Association (CTFA), he is past chairman of the CTFA Scientific Advisory Committee, past chairman of the CTFA-FDA Scientific Liaison Group, and is currently chairman of the CTFA Color Additive Committee.

He is a Fellow of the American Institute of Chemists, Fellow of the Society of Cosmetic Chemists, a Fellow of AAAS, and a member of Sigma Xi, Phi Lambda Upsilon, Sigma Tau, Society for Investigative Dermatology, American Chemical Society, and Society of Chemical Industry. He is author of over 30 papers on a variety of scientific, technical and regulatory subjects and holds a number of U.S. and foreign patents.

Left to right: Martin M. Rieger, Medal Award Chairman; Murray Berdick, Ph.D., Medal Awardee; Everett G. McDonough, Ph.D., Medal Award Eulogist; and Stephen G. Hoch, 1975 SCC President

Society of Cosmetic Chemist Literature Award Presented to Dr. Donald L. Opdyke

The 1974 Society of Cosmetic Chemists Literature Award was presented to Donald L. Opdyke Ph.D., President of the Research Institute for Fragrance Materials Inc., at the Society's Annual Scientific Meeting on December 2, 1975, held at the Americana Hotel in New York City.

Formal presentation of the award was made to Dr. Opdyke by Mr. Stephen Hoch, 1975 Society of Cosmetic Chemists President, during luncheon ceremonies on December 2nd. The award consists of a scroll and an honorarium of $1,500.

Dr. Opdyke earned his Ph.D. from Washington University School of Medicine in St. Louis, specializing in anatomy and histology, and served as an instructor in anatomy, histology, and neuroanatomy until 1952.

In 1952, Dr. Opdyke joined the Procter & Gamble Company, where he supervised studies in toxicity. He came to Revlon in 1963, where he was Director of Pharmacological Research and supervisor of a variety of departments prior to being named Director of Basic Research in 1967.

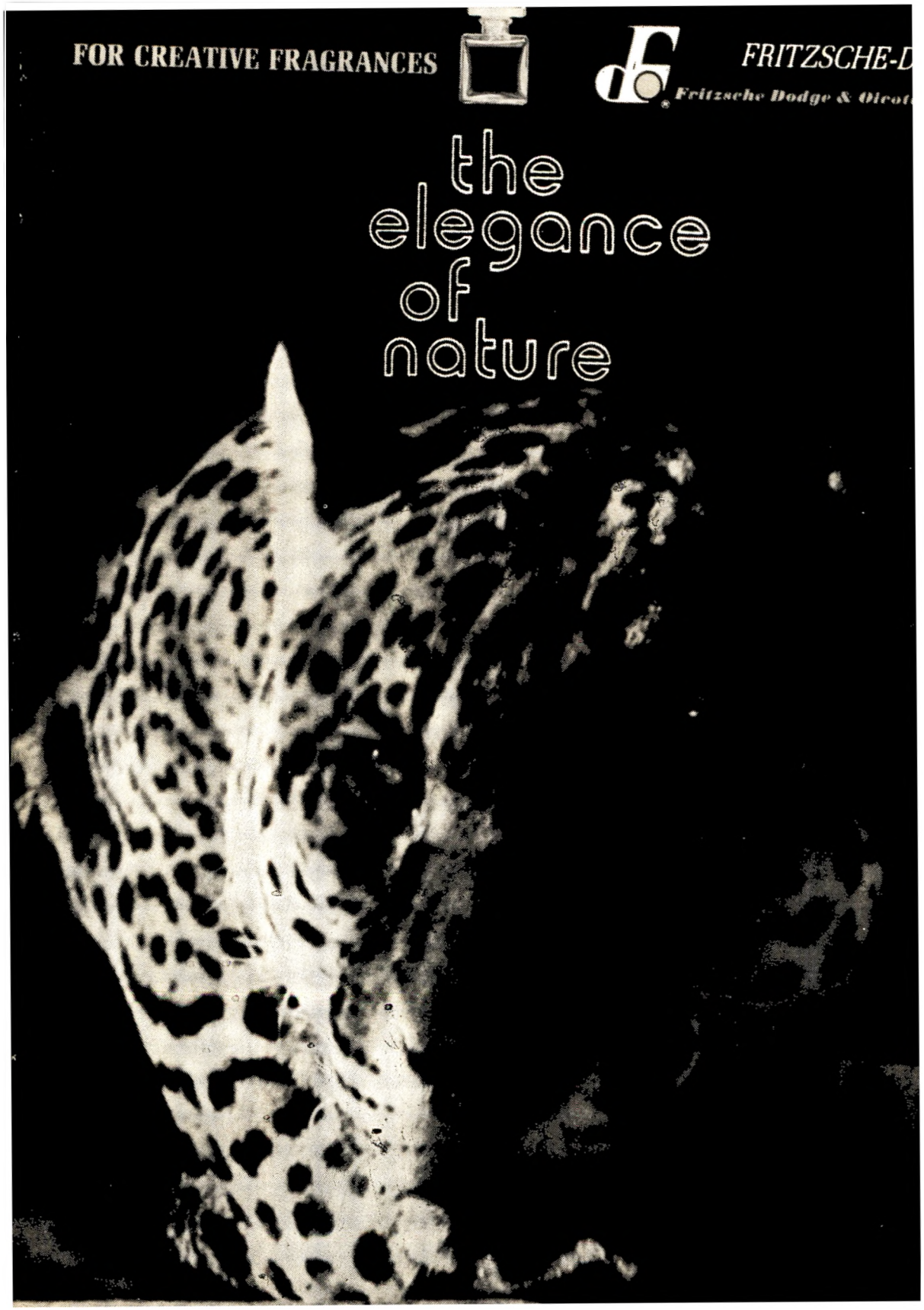
His own research work has been widely published in the *Journal of Investigative Dermatology*, *Toxicology and Applied Pharmacology*, the *British Medical Journal*, and the *Anatomical Record*.

Left to right: Joseph Gubernick, Chairman, Literature Review/Award; Donald L. Opdyke, Ph.D., Literature Award Recipient; and Stephen G. Hoch, 1975 SCC President

Society of Cosmetic Chemists 1975 Merit Award Presentation

The 1975 Society of Cosmetic Chemists Merit Award was presented to Paul Thau, Section Head, Toiletries Products Development, Warner-Lambert Co., Morris Plains, New Jersey, at the December 2nd luncheon during the Society's Annual Scientific Meeting in New York City. The award was given to Mr. Thau in recognition of his many years of outstanding service to the Society. Mr. Thau has been active in the SCC for many years, having served the New York Chapter as Treasurer (1969) and Chairman (1971). His National activities have included responsibilities as Councilor (1972) and Director (1973). He is currently serving the Society as National Treasurer.

Left to right: Stephen G. Hoch, 1975 SCC President; Paul Thau, Merit Awardee; and George A. Fioto, Merit Award Chairman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