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Journal of the Society of Cosmetic Chemists

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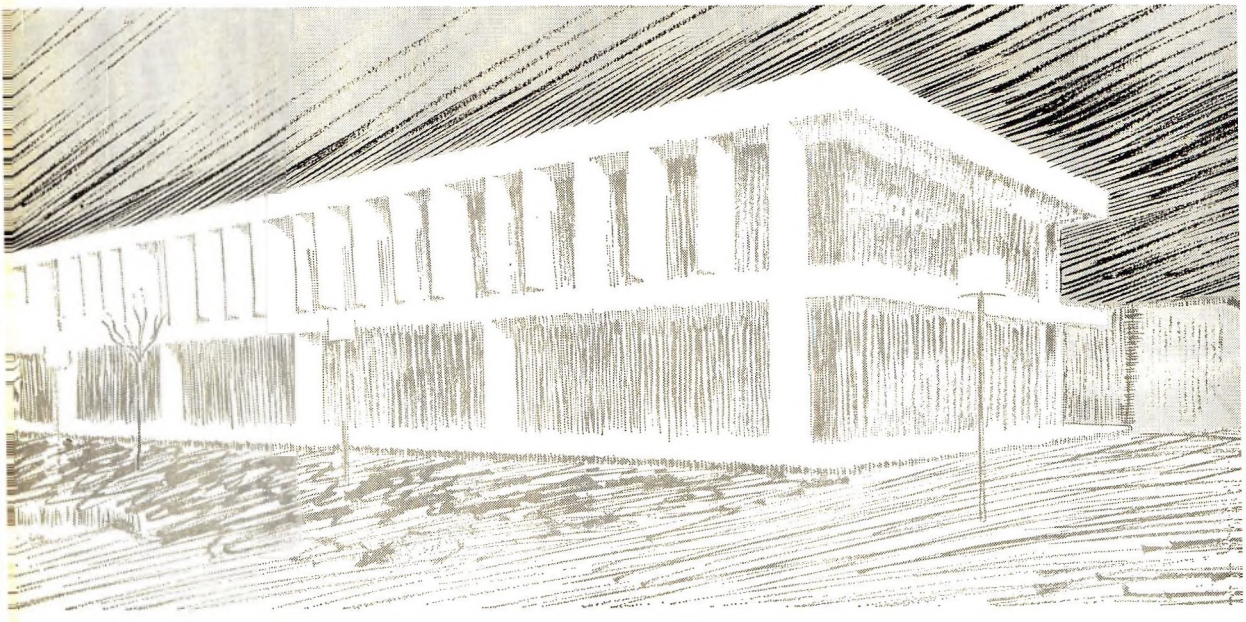

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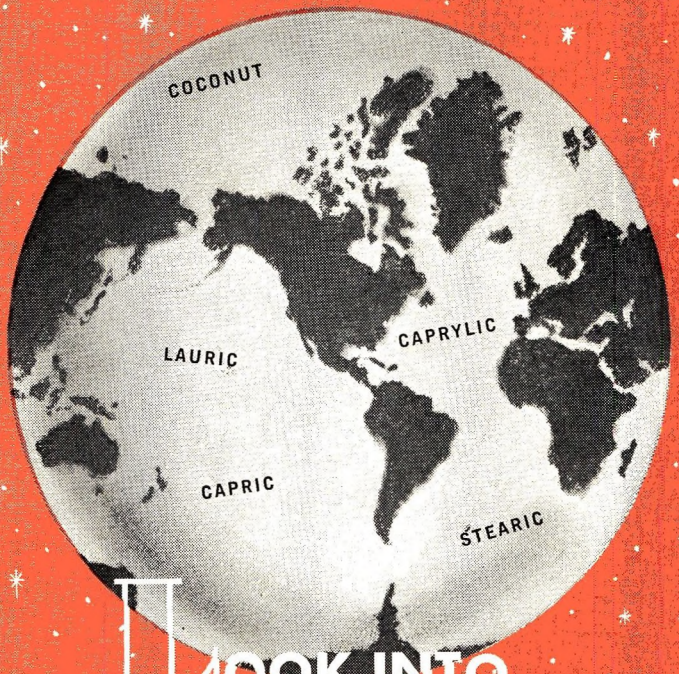

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SYNOPSES FOR CARD INDEXES

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.

Skin moisturizers. I. Methods for measuring water regain, mechanical properties, and transepidermal moisture loss of statum corneum: Martin M. Rieger and Donald E. Deem. *Journal of the Society of Cosmetic Chemists* **25,** 239 (May 1974)

Synopsis—Four parameters for assessing the interaction between human stratum corneum and water are described. Two methodologies, elastic modulus and stress relaxation, for determining the mechanical properties of stratum corneum have been utilized. It is shown that both of these parameters depend on the moisture content of the stratum corneum, i.e., the ambient relative humidity. The rate of water vapor absorption by human stratum corneum, the third parameter examined, is a function of the ambient relative humidity. Surprisingly, the equilibrium moisture content of stratum corneum at humidities below approximately 80% appears to be essentially the same for unextracted stratum corneum and for stratum corneum extracted with lipid solvent. The fourth parameter, the rate of water vapor transmission through stratum corneum *in vitro,* is a linear function of the ambient relative humidity and has been shown to be markedly affected by changes in temperature.

Skin moisturizers. II. The effects of cosmetic ingredients on human stratum corneum: Martin M. Rieger and Donald E. Deem. *Journal of the Society of Cosmetic Chemists* **25,** 253 (May 1974)

Synopsis—The four parameters described in Part I of this study, i.e., elastic modulus, relaxation function, water absorption, and water vapor transmission, have been used to study the effect of typical cosmetic ingredients on human stratum corneum. The elastic modulus and the stress relaxation modulus are useful measures of the ability of various cosmetic materials to alter the viscoelastic behavior of stratum corneum. It has been demonstrated that typical cosmetic humectants increase the rate of transepidermal water loss *in vitro,* and an attempt is made to explain this phenomenon.

Photochemistry of sunscreens. II. The photochemistry of methyl-p-dimethylaminobenzoate: C. D. M. Ten Berge and C. H. P. Bruins. *Journal of the Society of Cosmetic Chemists* **25,** 263 (May 1974)

Synopsis—The isolation and identification of another two photochemical reaction products of methyl-*p*-dimethylaminobenzoate are described. Ultraviolet irradiation of this compound in 1,4-dioxane in the presence of oxygen yielded also methyl *p*-*N*-formylaminobenzoate and methyl-*p*-aminobenzoate. Isolation was achieved by means of gas chromatography. The two products were identified by comparison of the ir, nmr, and mass spectra of the isolated and synthesized substances. For methyl *p*-(*N*-formyl-*N*-methyl) aminobenzoate, mentioned in a previous communication, a new synthesis is described.

Current perspectives on aerosol toxicity: Charles O'Connor Ward. *Journal of the Society of Cosmetic Chemists* **25,** 271 (May 1974)

Synopsis—The toxicity of cosmetic, household, or personal product aerosols is primarily the result of either deliberate abuse or allergic reactions to one or more of the ingredients. Hair sprays, antiperspirants, deodorants, and feminine hygiene sprays, among others, have been reported to produce toxic reactions in some users. A review of the published experimental and clinical data does not substantiate the contention that, when used as directed, they are hazardous. It is true, for instance, that the fluorocarbon propellants, in experimental situations, can sensitize the myocardium to catecholamine-induced arrhythmias and thus produce a situation detrimental to the user, but not in the amounts to which the consumer is ordinarily exposed. The differences between toxicity, the inherent ability to produce undesirable alterations in biological tissue, and hazard, the likelihood that toxicity will occur, may explain the case for aerosol products. The potential for toxicity of properly packaged cosmetic, household, and personal product aerosols is present; the hazard is small under conditions of normal use.

Testing for inhalation toxicity: William R. Troy. *Journal of the Society of Cosmetic Chemists* **25,** 283 (May 1974)

Synopsis—The purpose of this review is to outline some of the fundamental considerations involved in testing for inhalation safety of cosmetic products. Apart from design of the exposure system and selection of test animals, factors such as environmental controls, proper dose levels, and signs of toxicity to watch for are of prime importance when conducting such studies.

A discussion of three areas of concern with regard to the inhalation safety of cosmetic aerosols is also included. The questions of hair spray "storage disease," possible aspiration of spray talc, and allegations of cardiotoxicity of aerosol propellants are treated with regard to experimental activity in these areas and what, if anything, has been proven to date by these investigations.

J. Soc. Cosmet. Chem., **25**, 239–252 (May 1974)

Skin Moisturizers. I. Methods for Measuring Water Regain, Mechanical Properties, and Transepidermal Moisture Loss of Stratum Corneum

MARTIN M. RIEGER, Ph.D., and DONALD E. DEEM, M.S.*

Synopsis—Four parameters for assessing the interaction between human STRATUM CORNEUM and WATER are described. Two methodologies, ELASTIC MODULUS and STRESS RELAXATION, for determining the MECHANICAL PROPERTIES of stratum corneum have been utilized. It is shown that both of these parameters depend on the moisture content of the stratum corneum, i.e., the ambient relative humidity. The rate of WATER VAPOR ABSORPTION by human stratum corneum, the third parameter examined, is a function of the ambient relative humidity. Surprisingly, the equilibrium moisture content of stratum corneum at humidities below approximately 80% appears to be essentially the same for unextracted stratum corneum and for stratum corneum extracted with lipid solvents. The fourth parameter, the rate of WATER VAPOR TRANSMISSION through stratum corneum *in vitro*, is a linear function of the ambient relative humidity and has been shown to be markedly affected by changes in temperature.

Introduction

Since Blank's observation in 1952 (1), that the water content of skin is responsible for its softness, the properties of epidermis as a function of its moisture content and of the presence of "natural" and extraneous moisturizers have been studied extensively by cosmetic chemists and dermatologists.

The subject of transepidermal moisture loss *in vivo* under various ambient conditions of humidity, temperature, and air flow has been studied by several investigators. Of particular interest is a paper by Grice *et al.*, who indicated that the relationship between transepidermal water loss and ambient relative humidity *in vivo* is not linear (2). This is not in accord with the data by Wildnauer *et al.*, who suggested that the relationship between mechanical properties and relative humidity is linear (3).

*Warner-Lambert Research Institute, 170 Tabor Rd., Morris Plains, N.J. 07950.

The relationship between the mechanical properties of stratum corneum and its moisture content has been studied by several techniques (4–6). Much of this work has been conducted on stratum corneum obtained from guinea pig foot pads or human callus. It was pointed out by Kligman that the stratum corneum of guinea pigs allows water to pass three times as fast as human abdominal stratum corneum (7). He also states that "the specialization of the horny layer of the palms and soles is so unique as to require separate status." These tissues contain lower quantities of the water-soluble substances present in abdominal skin and are more permeable to water; data from callus will not "accurately apply to the membranous horny layer." A considerable body of work on the mechanical properties of human skin *in vivo* is not pertinent because it deals primarily with the mechanical properties of the dermis which presumably is not touched by normal cosmetic treatments. Water vapor transmission experiments *in vivo* are made difficult by sweating unless this is repressed by vasoconstricting drugs. As a result, well-controlled experimentation *in vivo* is very difficult.

Substrate variability and the noted complications of *in vivo* studies make it attractive to study mechanical and water-holding properties of human stratum corneum *in vitro*. This study has been designed to study and to compare techniques suitable for measuring the interaction of stratum corneum with water. Part II of this work deals with the effect of a variety of typical cosmetic ingredients in order to establish a rationale for their use in skin treatment preparations.

Theoretical Treatments and Experimental Procedures

Mechanical Properties

Elastic Modulus

When a viscoelastic strip of material of length l and cross sectional area A is subjected to a normal tensile force (f), the stress (σ) is $\frac{f}{A}$, and the strain (ϵ) is the fractional increase in length, $\Delta l/l$. Below the yield point, Young's modulus of elasticity (E) is the ratio of σ/ϵ, i.e., the slope of the load-elongation curve. Since A of the stratum corneum is not constant and is very difficult to measure at all points, it was decided to use the parameter AxE (eq 1) and assume that strips taken from the same specimen of stratum corneum have approximately the same cross-sectional area. It was, therefore, necessary to determine AxE of an untreated control for each specimen of stratum corneum in order to compare the effect of a given treatment.

$$A \times E = \frac{fl}{\Delta l} \tag{1}$$

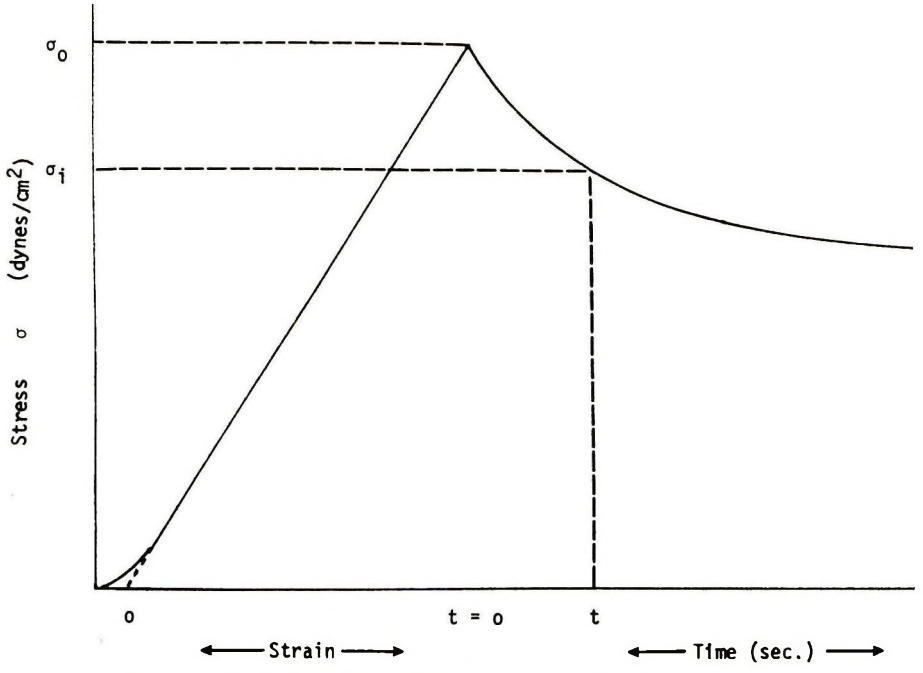

Figure 1. Typical loading and relaxation curve for stratum corneum

Relaxation Function

When an elastic material is strained (to strain ϵ, Fig. 1) by stressing (to load σ_0), the value of σ will decay as a function of time (t) if the strain ϵ is kept constant. The relaxation modulus $E_r(t)$ at any time t can then be computed by dividing the stress (σ_i) at time t_i by the strain ϵ at $t = 0$ (Fig. 1). At $t = 0$, $E_r(t)$ equals Young's modulus as long as the material has not been strained beyond its yield point. Wall *et al.* used the stress relaxation spectrum, $H(\ln\tau)$, to describe the "multiple mechanical relaxation phenomena" in human hair (8). They plotted the derivative of the relaxation modulus with respect to the logarithm of time:

$$H(\ln\tau) = \frac{d(E_r(t))}{d\ln\tau} \tag{2}$$

Since the primary interest here is the effect of moisture on the behavior of stratum corneum, the cross-sectional area was included in the relaxation function. Since a plot of log $AxE_r(t)$ *vs.* log t is essentially linear between 1 and 10^4 sec, the slope of this line is the only value required to describe the effect of a given moisture condition or cosmetic treatment on the stratum corneum.

The linear behavior described above is typical of amorphous polymers of high molecular weight below their glass transition temperatures (9). The

response to the external stress consists primarily of local adjustments since the chain backbone configuration is essentially immobilized.

Technique

A model TM Instron Tensile Tester®* was used for measuring both elastic moduli and relaxation spectra. The rate of travel of the cross head was 2.54 mm/min, which was equivalent to an extension of about 10–15%/min. (The sample length varied between 17 and 25 mm.)

Strips of stratum corneum, 0.5 cm wide by approximately 3.5 cm long, were attached to Bakelite®† tabs with a commercial epoxy cement or Duco®‡ cement. The length of each strip (between tabs) was measured to the nearest 0.01 mm with a cathetometer.§ The samples were stored at the desired relative humidity (RH) for at least 24 hours and then suspended in a cylinder (diameter, 7 cm; length, 15 cm) mounted on the Instron. Air at the same RH was passed through the chamber for 20 min at which time the samples were extended to a load of 4.0 g.

Some obvious minor modifications of the above procedure were required for those stratum corneum strips which were extended under deionized water or test solutions.

Water Absorption

A Cahn RG Electrobalance®// was used to measure moisture absorption by stratum corneum or of cosmetic materials applied to samples of stratum corneum or to glass filter paper. The Electrobalance was fitted with an *X*-*Y* recorder¶ which has an input range of 0.1 mg/2.54 cm, while the graph can be read to 0.002 mg. Equilibrium weights can be estimated to 0.001 mg using a null system. The balance was also fitted with a cube-shaped plastic chamber (7.5 cm on each side) into which air of controlled humidity was blown at a rate of 1200 ml/min. The determination of equilibrium water content was made immediately after stopping the air flow so that air currents would not affect the reading. Equilibration occurs quite rapidly due to the moving air stream (absence of an unstirred layer and the small size of the sample). Attainment of equilibrium was evidenced by constancy of weight for 4 to 5 hours.

*Instron Corp., Canton, Mass.
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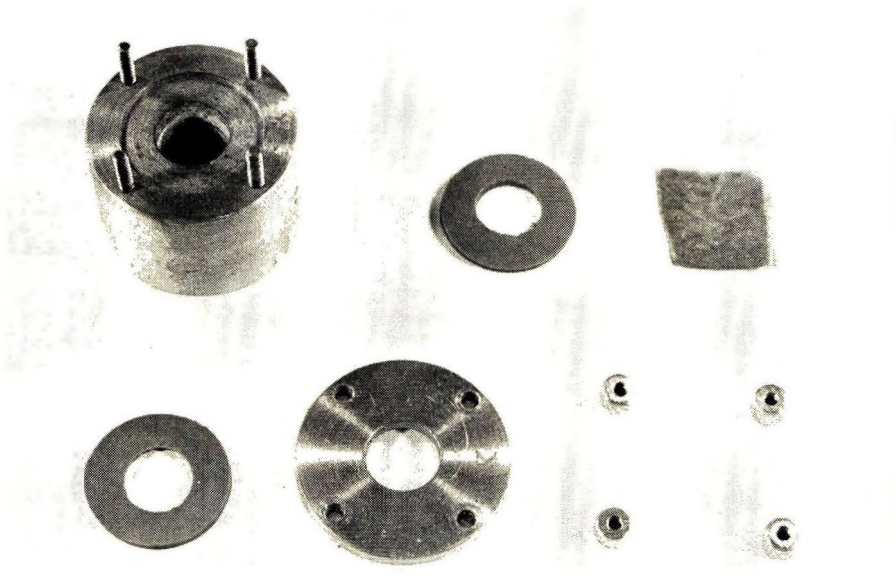

Figure 2. Construction of water vapor transmission cell. Top row, left to right: body of cell, lower silicone gasket, stratum corneum. Bottom row, left to right: upper silicone gasket, top plate, closure nuts)

Water Vapor Transmission

Cells for measuring the rate of diffusion of water vapor through stratum corneum were constructed of cylindrical aluminum stock (3.7 cm in diameter x 2.2 cm high) into which was drilled a 1.5-cm deep hole having a diameter of 1.3 cm (Fig. 2). This depression has a capacity of approximately 2 ml. An aluminum top provided with a 1.3-cm hole could be attached to the lower chamber with four bolts. The stratum corneum was placed between two silicone rubber gaskets which were then placed between the chamber and the top. The bolts were attached "finger tight" in order not to deform the silicone gasket. After mounting the stratum corneum on a cell containing 0.3 ml of water, the cell was placed into a chamber containing a constant RH solution or exposed to a stream of humidified air. The cell was weighed every 24 hours until the rate of water loss became constant.

Initial rates of transepidermal water loss are fairly high, and up to 4 days may be required to reach a steady rate. Only those rates were utilized in this study which remained constant for 2 to 3 days after the initial equilibration. Whenever long periods of time were required for testing at several humidities, the sample was examined for signs of mold growth or stretching of the epidermis due to the "vacuum" formed inside the cell as water leaves the cell. The loss of water was computed as mg/cm^2/hr.

Humidity Control

In order to obtain dry air (0% RH), the air was first passed through reagent grade sulfuric acid and then magnesium perchlorate* since it has been reported that calcium chloride will permit passage of up to 160 ppm of water in a gas stream (10). In experiments in which constant humidity solutions were used, the saturated solutions of several salts were employed (11).

When an air stream of constant humidity was required for several days, the use of saturated salt solutions is inconvenient due to blockage of the gas dispersion tube by crystallization. Therefore, the apparatus described by Smith (12) was used. This apparatus consists of a proportioning valve and saturators to mix controlled quantities of wet and dry air to obtain a given humidity. The equipment is capable of accurately supplying air at any RH between 0 and 100% in 5% RH steps over a wide range of temperatures.

Materials

Unless otherwise indicated, C.P. reagents were employed throughout. Postmortem abdominal skin was immediately frozen in dry ice. Within 72 hours, the samples were heated in a water bath to 52° ± 2°C, and the stratum corneum was peeled from the dermis as described by Kligman and Christopher (13). The separated stratum corneum was washed in several changes of distilled water and gently picked up on a piece of stainless steel wire mesh. The stratum corneum was air-dried, removed from the screen, and stored over magnesium perchlorate. When extracted stratum corneum was required, it was extracted according to the procedure of Blank (14), i.e., 24 hours in pyridine at room temperature followed by 1-hour extraction with water at room temperature.

Results and Discussion

Mechanical Properties

In order to avoid experimental artifacts and to conserve material it was decided to determine whether the stratum corneum is elastically isotropic or anisotropic like the dermis. The values of the quantity AxE for stratum corneum extended under water at room temperature were $1.79 \pm 0.12 \times 10^4$ dynes and $1.90 \pm 0.18 \times 10^4$ dynes, respectively, for strips (8 in each direction) cut at right angles to each other. The results indicate that the stratum corneum may be considered isotropic. Adjacent strips of stratum corneum usually have AxE values within ± 5% but occasionally vary by as much as 30–40%

As expected, the elastic modulus of human stratum corneum was found to be a function of the ambient RH. The results of Fig. 3 confirm those of many other investigators and show that stratum corneum becomes "softer" when

*Anhydrone®, J. T. Baker Chemical Co., Philadelphia, N.J.

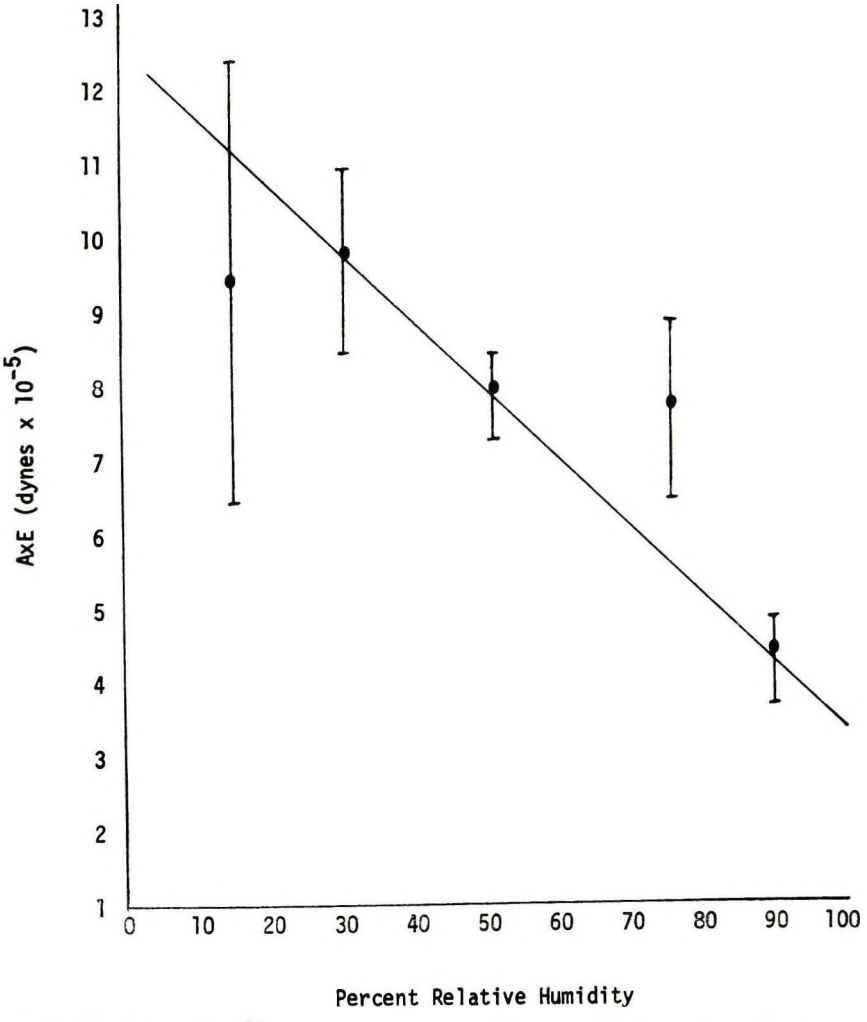

Figure 3. Elastic modulus of stratum corneum as a function of relative humidity (vertical bars refer to average deviation)

the RH increases. The average deviations noted in these experiments are quite high. In fact, the large deviation at 15% RH suggests that relatively dry stratum corneum cannot respond as a homogeneous material. Goodman and Wolf (15) also have noted large standard deviations of *in vivo* water transmission data at low RH's. At higher RH's, the higher moisture content tends to make the stratum corneum act in a more homogeneous way, thus lowering the average deviation. The relationship between modulus and RH has been presented in linear form, although Parks and Baddiel (16) have indicated that this relationship is nonlinear above 60% RH. It is noted in passing that different specimens of stratum corneum yield "lines" having different slopes.

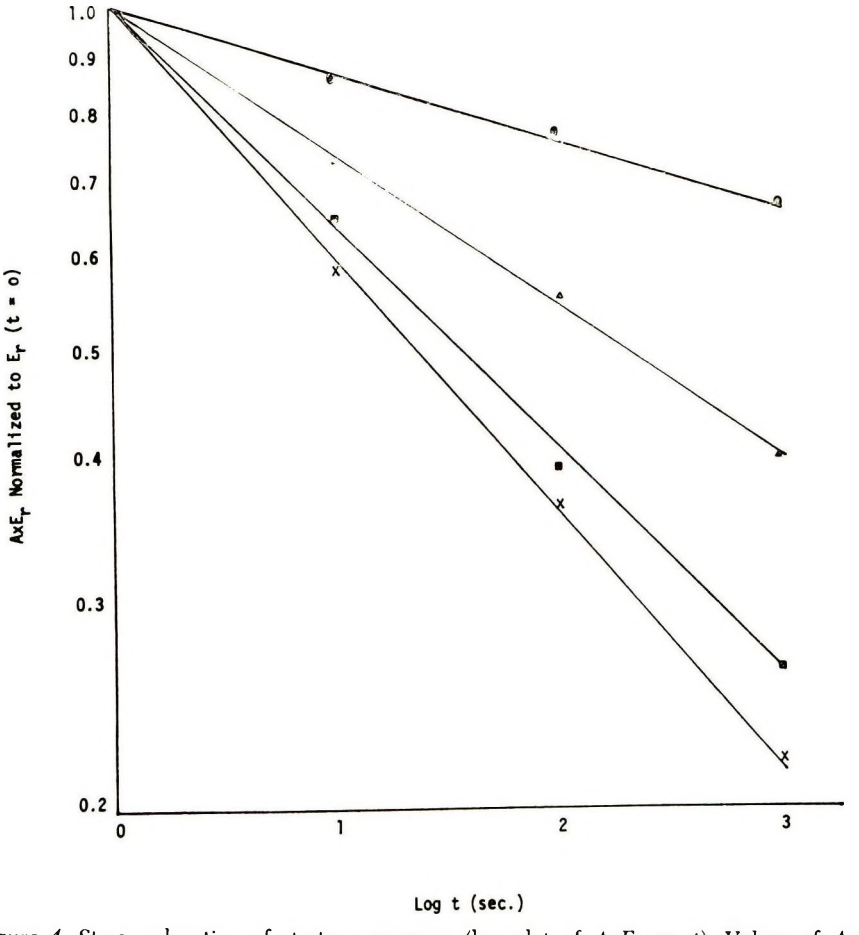

Figure 4. Stress relaxation of stratum corneum (log plot of AxE_r *vs.* t). Values of AxE_r at any time are divided by AxE_r at time zero

● = 0% RH ■ = 76% RH
◗ = 31% RH X = 100% RH

The stress relaxation experiments were conducted on samples of stratum corneum in humidified air. In preliminary experiments, it was found that for strains between 0.01 and 0.10 the relaxation spectra were essentially identical. Therefore, the samples were stressed to a constant stress (4.0 g) rather than a constant strain, since stress is instrumentally more easily controlled.

At the start it was necessary to demonstrate that the slopes of the lines resulting from a plot of log AxE_r *vs.* log t depend on the humidity of the air. Figure 4 shows that the plots are linear and that their slopes are functions of humidity. It is possible to estimate the errors of the slopes by comparing the slopes resulting from stress relaxation experiments on adjacent pieces of stratum corneum at the same RH. These errors are compared to those obtained by

Table I
Average Deviation of Mechanical Measurements

% RH	$A \times E$		Slope $[H(\ln\tau)]$	
	Value	Av. Dev.	Value	Av. Dev.
100 (4)[a]	215	± 35	−0.173	±0.039
76 (4)	280	± 29	−0.164	±0.031
31 (5)	393	±100	−0.0938	±0.004
0 (4)	534	±121	−0.0528	±0.002

[a]Figure in parentheses refers to number of samples tested at each RH.

merely determining the value of AxE for adjacent pieces of stratum corneum at the same RH (Fig. 3). This comparison, shown in Table I, indicates that AxE values are most precise at high RH, while the slope of the stress relaxation function is most precise at low RH's. Accordingly, the stress relaxation function is the preferred measurement under relatively dry conditions.

Water Absorption

The rate of water absorption by strips of unextracted stratum corneum dried over concentrated H_2SO_4 and then exposed to different RH's is shown in Fig. 5. In agreement with other investigators, the *rate* of regain was found to be dependent on RH and on the presence of "natural moisturizers." In the examples studied here at high RH (93%), the difference in absorption rates up to about 30 min between the extracted and unextracted stratum corneum is unexpectedly low. Most investigators who have studied the differences in moisture absorption of extracted and unextracted "keratinized" tissue record *equilibrium* moisture absorption. Singer and Vinson (17) record equilibrium moisture contents (at 80% RH) for normal neonatal rat corneum and callus of about 50% and of about 20–30% after solvent + H_2O extraction. The equilibrium moisture contents at RH's up to 80% obtained in this study of unextracted human stratum corneum are much lower and are only marginally dependent on extraction (with pyridine and water). The results are recorded in Table II and were so unexpected that the problem was studied on three specimens of stratum corneum. In all cases, the moisture absorption was determined on a small piece of stratum corneum and was then redetermined on the identical piece after extraction. The weight loss due to extraction generally ranged between 25 and 30%. It is not possible to offer a definitive explanation for the discrepancy of the data obtained here and those reported by other investigators (14). It is noted that the data of Fox *et al.* (18) are close to those found here, and that the significant differences between extracted and unextracted cornified epithelial tissue observed by other investigators occur at RH's > 80%. Such high humidities were usually avoided here because it was difficult to maintain high humidities for the long periods required for equilibration (up to 8–10 hours) at ambient temperature without condensation.

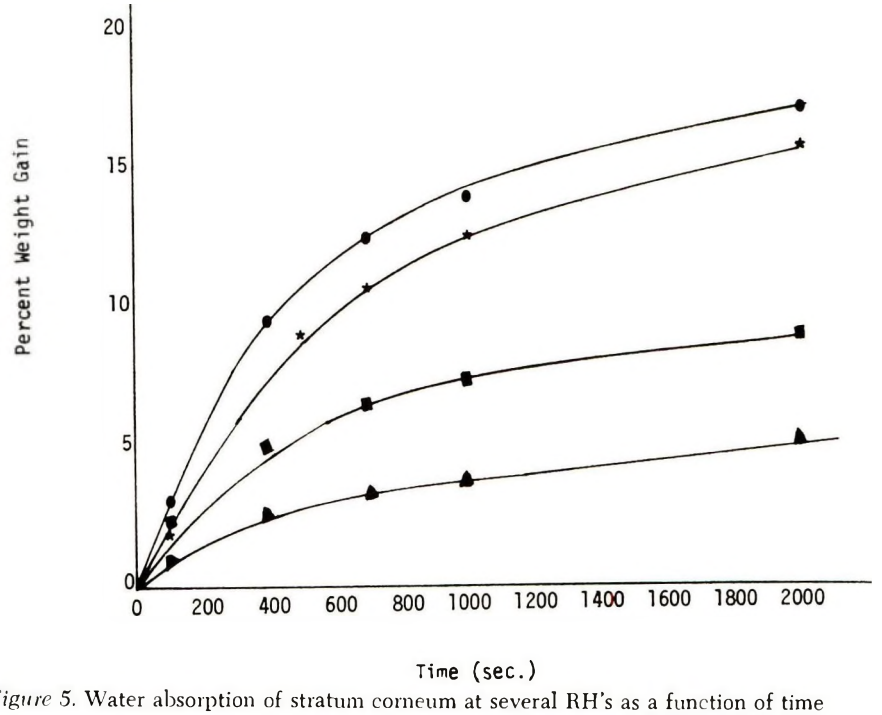

Figure 5. Water absorption of stratum corneum at several RH's as a function of time

—●—●—●— 93% RH unextracted
—°—°—°— 93% RH extracted
—■—■—■— 60% RH unextracted
—▶—▶—▶— 30% RH extracted

Table II
Equilibrium Moisture Content of Human Stratum Corneum

Sample	% RH	% Water Absorbed by Dry Stratum Corneum[a]	
		Unextracted	Extracted
A	31	5.4[b] (4.9-6.0)	5.3[e] (3.9-6.2)
A	76	11.4[b] (10.8-12.1)	13.3[e] (12.5-14.1)
B	31	9.3[c] (8.5-10.3)	6.5[d] (5.8-7.3)
B	76	13.1[d] (12.0-14.2)	14.1[d] (12.8-15.0)
C	5	2.5	2.5
C	15	4.0	**5.0**
C	31	4.0	**5.1**
C	35	6.5	7.0
C	50	8.6[c] (7.9-9.3)	9.9[e] (9.0-11.0)
C	75	14.5[c] (13.8-15.1)	15.8[e] (14.2-17.4)
C	90	21.9[e] (21.8-22.1)	**22.5**[e] (20.4-24.5)

[a]Figures in parentheses are ranges.
[b]Average of 5 determinations.
[c]Average of 3 determinations.
[d]Average of 4 determinations.
[e]Average of 2 determinations.

Water Vapor Transmission

The results of *in vitro* transepidermal water losses through untreated stratum corneum at 21 ± 1.5°C against a dry atmosphere ($CaCl_2$) show wide variations depending on the stratum corneum specimen. When water vapor is in contact with the stratum corneum inside the cell, the average rate is about 0.25 mg cm^{-2} hr^{-1}. When water contacts the stratum corneum, the average transepidermal water loss rises to about 0.30 mg cm^{-2} hr^{-1}. These values are fairly close to each other and are in accord with normally accepted values of transepidermal moisture loss obtained *in vivo* (19).

Extraction of stratum corneum, first with pyridine and then with water, increases the rate of transepidermal moisture loss from about 0.2 to as much as 1.6 mg cm^{-2} hr^{-1}. This is a clear indication that the extractables (primarily lipids) present in the stratum corneum contribute significantly to slowing down the moisture loss from dermal and epidermal tissue by evaporation.

On theoretical grounds and intuitively one would expect that the transepidermal water loss from a cell of the type described here depends on the RH to which the cell is exposed, i.e., the driving force for diffusion is the chemical potential gradient. That this is the case has been shown here because the plot of water vapor transmission rate *vs.* RH (Fig. 6) is linear with a slope of -1.95×10^3 mg cm^{-2} hr^{-1}/% RH. These results are different from those reported by Grice *et al.* (2), who indicated that a plot of water vapor transmission *vs.* RH yields a curve showing a maximum between 25 and 50% RH (Fig. 6). It was at first thought that this difference might be due to the fact that an unstirred layer in the system used here was responsible for the discrepancy. However, when the results were repeated under a stream of air (1200 ml/min) aimed at the exposed surface of the stratum corneum, the results were essentially unchanged. It appears, therefore, that the results of the *in vitro* experimentation conducted here conform to the *in vivo* data reported by Goodman and Wolf (15), whose results yield linear plots although the slope of their line has a value of -4.5×10^3 mg cm^{-2} hr^{-1}/% RH.

The effect of temperature on the permeability of stratum corneum or any membrane follows the Arrhenius equation (20). Thus, a plot of the logarithm of permeability *vs.* $\frac{1}{T}$ is linear and has a slope of $-\frac{E_p}{2.303R}$, where E_p is the activation energy of permeation.

The experimentally measured flux, J, is related to permeability (P) *via* eq 3,

$$J = P \Delta C \tag{3}$$

where ΔC = the difference in the concentration of the water on the internal side of the membrane and the external side (moles l^{-1}).

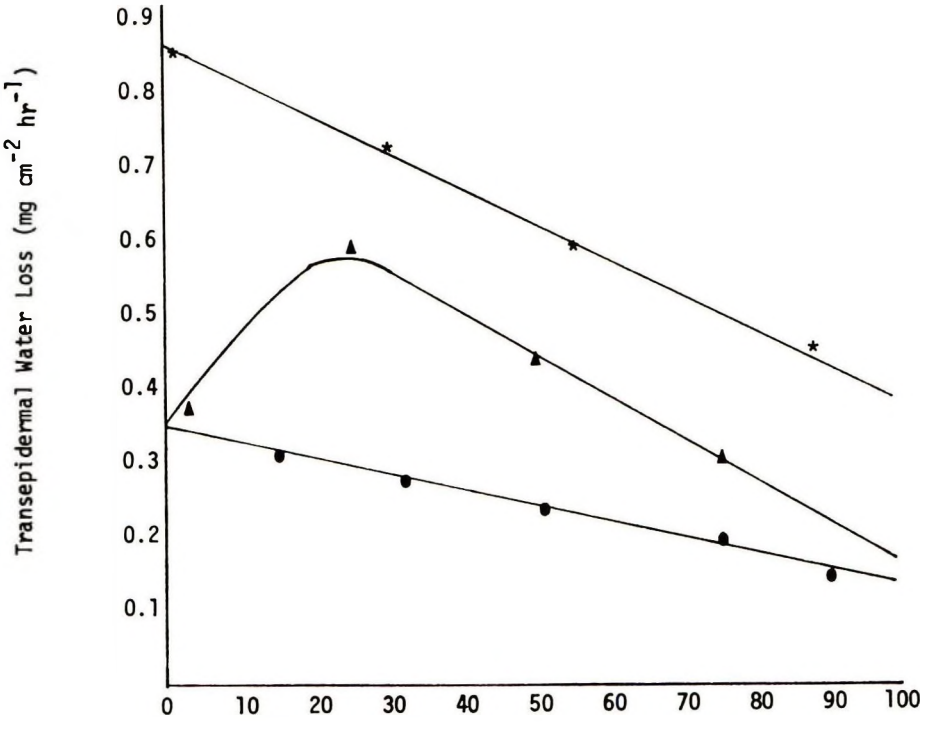

Figure 6. Transepidermal water loss vs. relative humidity

—°—°—°— Goodman and Wolf (15)
—▶—▶—▶— Grice *et al.* (2)
—●—●—●— present paper

Thus it is possible to plot log J against $\frac{1}{T}$ (Fig. 7) and compute E_p. The value for E_p for fully hydrated stratum codneum cited by Scheuplein and Blank (21) is 13-16 kcal mole^{-1}. The clearly expotential temperature dependence of water vapor permeability is proof of transmission by diffusion. Transmission by random kinetic motion through a capillary would be expected to be proportional to $T^{1/2}$ (22). A more comprehensive discussion of the factors involved in diffusion of water through stratum corneum has been given by Berube and Berdick (23).

Conclusions

1. The mechanical properties of human stratum corneum, as measured by the elastic modulus or by stress relaxation, are dependent on the moisture content of the stratum corneum.

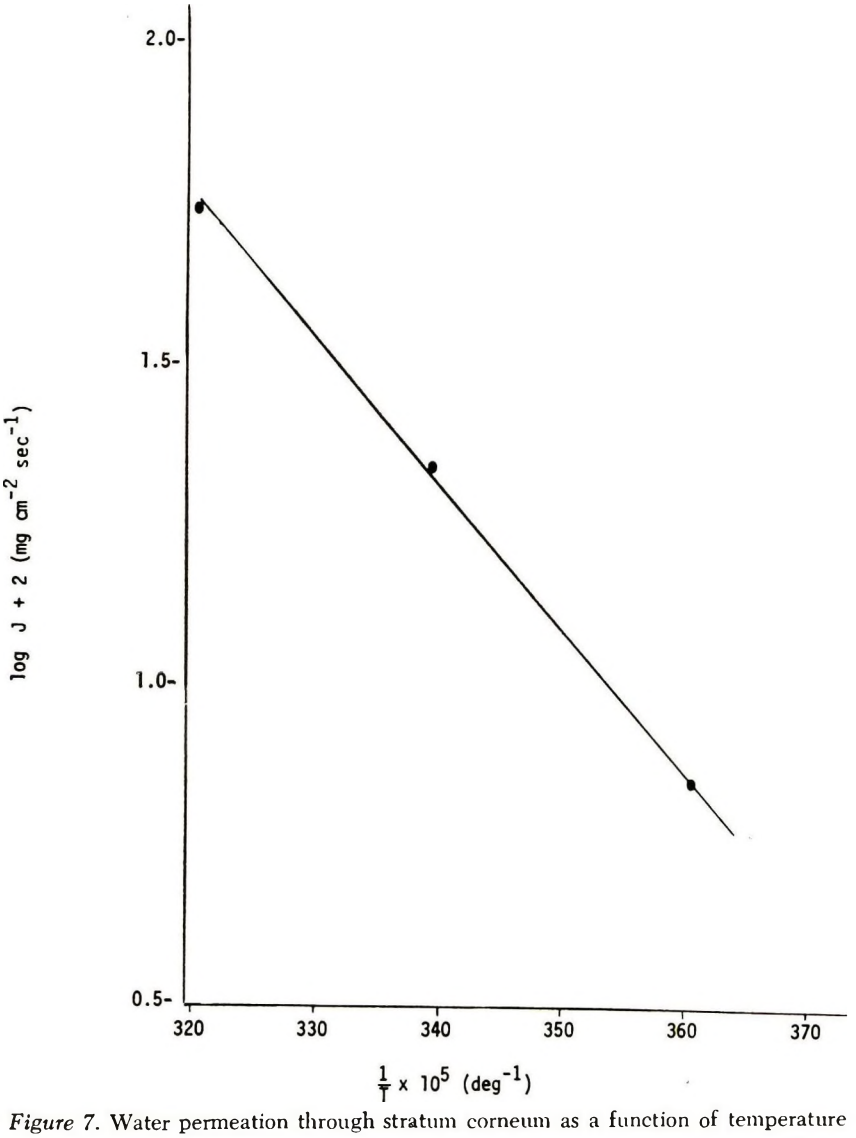

Figure 7. Water permeation through stratum corneum as a function of temperature

2. The rate of water vapor absorption of human stratum corneum depends on the relative humidity. The equilibrium water content of extracted and unextracted human stratum corneum at humidities below about 80% is essentially the same.

3. The rate of water vapor transmission through human stratum corneum *in vitro* is a linear function of the ambient relative humidity. This rate is markedly decreased by a reduction in temperature.

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Skin Moisturizers. II. The Effects of Cosmetic Ingredients on Human Stratum Corneum

MARTIN M. RIEGER, Ph.D., and DONALD E. DEEM, M.S.*

Synopsis—The four parameters described in Part I of this study, i.e., elastic modulus, relaxation function, water absorption, and water vapor transmission, have been used to study the effect of typical COSMETIC INGREDIENTS on human STRATUM CORNEUM. The elastic modulus and the stress relaxation modulus are useful measures of the ability of various cosmetic materials to alter the VISCOELASTIC BEHAVIOR of stratum corneum. It has been demonstrated that typical cosmetic HUMECTANTS increase the rate of transepidermal water loss *in vitro*, and an attempt is made to explain this phenomenon.

Introduction

A variety of humectants and of occlusive lipids has been used for many years to improve human skin and to protect it against damage, even though the principles underlying these approaches to skin treatment were not clearly understood. Blank showed in 1952 how important water is to the well-being of human skin and, in effect, established a rational basis for these time honored methods for skin conditioning (1). In his very thoughtful review, Chudzikowski comments on the undesirability of highly occlusive barriers because they have a tendency to lead to edema; he also rejects the traditional treatment of dry skin with humectants because they will absorb moisture not only from the air but also from the skin (2). It is apparent, therefore, that the cosmetic benefits of either treatment are debatable and that basic knowledge on how skin moisturizers work is lacking.

In the first part of this study, *in vitro* methods for determining the response of human stratum corneum to moisture were developed. It is the purpose of this second part to describe the influence of common cosmetic moisturizers on the properties of stratum corneum.

*Warner-Lambert Research Institute, 170 Tabor Rd., Morris Plains, N.J. 07950.

Experimental Procedures

The techniques are those described in Part I (3) with minor modifications if required. Generally, strips of stratum corneum (with the attached tabs) were immersed for one hour into the test material or solution. Thereafter the strip was floated onto a stainless steel wire mesh, drained, and carefully blotted. The strip was then air-dried and placed into the appropriate relative humidity chamber for at least 24 hours before testing. Sometimes, the test substance was applied to the stratum corneum with a cotton swab. Any excess was carefully blotted off before the stratum corneum was conditioned.

For the determination of water sorption by humectants, 50% aqueous solutions of the humectants were applied to small preweighed pieces of Gelman Type A glass filter paper. After conditioning at 0% RH, the weight of humectant was determined and the weight gain at a given RH was based on this "dry" weight. The glass filter paper was shown to absorb less than 1% of water at 90% RH, and this sorption was generally neglected.

Results and Discussion

Mechanical Properties

Many cosmetic materials are reported to soften skin and to act as emollients. It was expected, therefore, that these materials would exert some influence on the mechanical properties of stratum corneum. Of particular interest is glycerol which is widely used by cosmetic formulators as a humectant and skin moisturizer. It is generally recognized (2) that glycerol is hygroscopic and will absorb water until it reaches equilibrium with the ambient RH. Glycerol has been employed for many years to "heal" chapped skin, and this effect is attributed to its ability to hold water in contact with the skin.

Values of the modulus AxE obtained at 22°C on strips of stratum corneum immersed in mixtures of glycerol and water are summarized in the curve shown in Fig. 1. The experimentally obtained values of AxE are normalized by dividing them by AxE of the same strip of stratum corneum immersed in distilled water to yield the plotted value of E_n. The results indicate that glycerol does not increase the elasticity of stratum corneum by itself but actually stiffens the stratum corneum at concentrations above about 30%, possibly by removing stratum corneum–hydrating water. These results are in accord with Blank's findings that water is the only plasticizer of horny material (4).

It was considered possible that the interaction of the stratum corneum/glycerol/water system under investigation was temperature sensitive. In order to study this aspect, the effect of temperature on the value of AxE was first determined by extending strips of stratum corneum, taken from the same specimen, under water maintained at various temperatures between 2° and

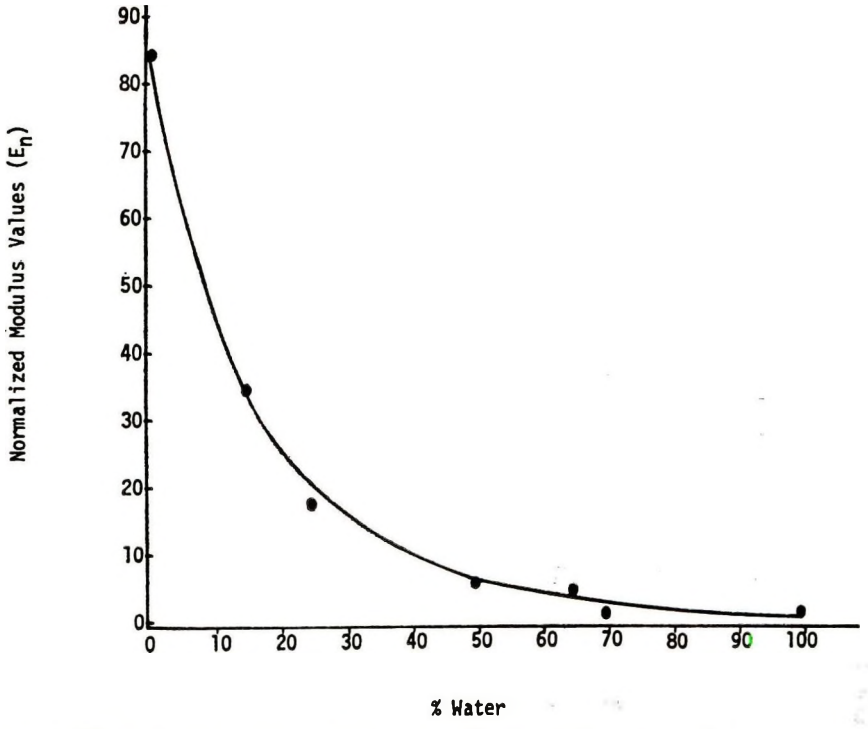

Figure 1. Effect of water concentration on normalized modulus values of stratum corneum (extended in glycerol/water mixtures at 22°C)

37°C. The values were divided by the value of *AxE* at 37°C under water, and the results are included in Fig. 2. It is apparent that the extensibility of human stratum corneum under the conditions of this experiment (immersed in water) shows very little change between 37°C and about 5°C. Middleton and Allen (5) also observed only a modest change in extensibility of guinea pig foot pad stratum corneum between about 20° and 40°C under different experimental conditions (in air of RH between 60 and 80%). Below about 5°C, stratum corneum appears to be stiffer, i.e., harder to stretch.

Figure 2 also includes the results of stretching in a solution of 1:1 water: glycerol (wt/wt) and a solution of 6*M* potassium iodide. The plotted data points were obtained by dividing the *AxE* values by the *AxE* values found at 37°C in the respective solutions. Glycerol was selected as a typical humectant, while potassium iodide (6*M*) is known to break the structure of water (6). In view of the similarity of the results, it is likely that the effect of glycerol is due to the breaking of the water structure in the stratum corneum; this might reduce hydration of the protein and make the stratum corneum stiffer or more difficult to stretch at temperatures below 18°C. The temperature dependence of stratum corneum elasticity observed here is probably too low

Table I

Elastic Modulus and Relaxation Function of Treated Stratum Corneum

Material	Elastic Modulus			Relaxation Modulus		
	Control $E_o xA$	Treated $E_o xA$	Effect of Treatment[a]	Control[b] $\left(\frac{\log E_o xA}{\log t}\right)$	Treated[b] $\left(\frac{\log E_o xA}{\log t}\right)$	Effect of Treatment[c]
0.1*N* NaOH	2085 ± 25	689 ± 180	++	0.040	0.040	o
0.1*N* HCl	2085 ± 25	751 ± 231	++	0.040	0.040	o
4% glycerol	826 ± 40	798 ± 42	o	0.043	0.072	+
50% glycerol	320 ± 42	230 ± 15	(+)	0.029[d]	Curved	
100% glycerol	320 ± 42	254 ± 27	(+)	0.029[d]	Curved	
50% propylene glycol	621 ± 16	500 ± 35	(+)	0.043	0.076	+
4% sodium pyrrolidone carboxylate	732 ± 82	88 ± 27	++	0.038	0.101	++
Light technical mineral oil	411 ± 35	524 ± 12	(−)	0.054	0.035	−
4% glucose glutamate	401 ± 5	416 ± 42	o	0.105	0.274	++
4% sorbitol	961 ± 196	632 ± 105	+	0.054	0.070	−
20% urea	409 ± 89	361 ± 55	o	0.053	0.098	−
4% Lanexol AWS®[e]	2363 ± 301	1098 ± 361	+	0.032	0.032	o
Safflower oil	783 ± 174	922 ± 99	(−)	0.037	0.028	(−)
2% iodoacetic acid	1544 ± 260	1062 ± 158	+	0.043	0.041	o
4% glycine	1544 ± 260	1406 ± 170	o	0.043	0.049	o
4% PEI 18® (pH 8)[f]	1584 ± 81	786 ± 58	+	0.122	0.047	−
4% sodium lactate	848 ± 141	357 ± 57	+	0.057	0.065	o
4% potassium iodide	1584 ± 260	633 ± 99	+	0.122	0.191	+

[a] ++ = much more elastic; + = more elastic; − = less elastic; o = no change; (±) = marginal effect.

[b] The recorded values have an average error of about ± 4%.

[c] ++ = much faster relaxation; + = faster relaxation; − = slower relaxation; o = no change; (±) marginal effect.

[d] Large deviation after 100 sec.

[e] An ethoxylated lanolin manufactured by Croda, Inc., New York, N.Y.

[f] A polyethyleneimine manufactured by Dow Chemical Co., Midland, Mich.

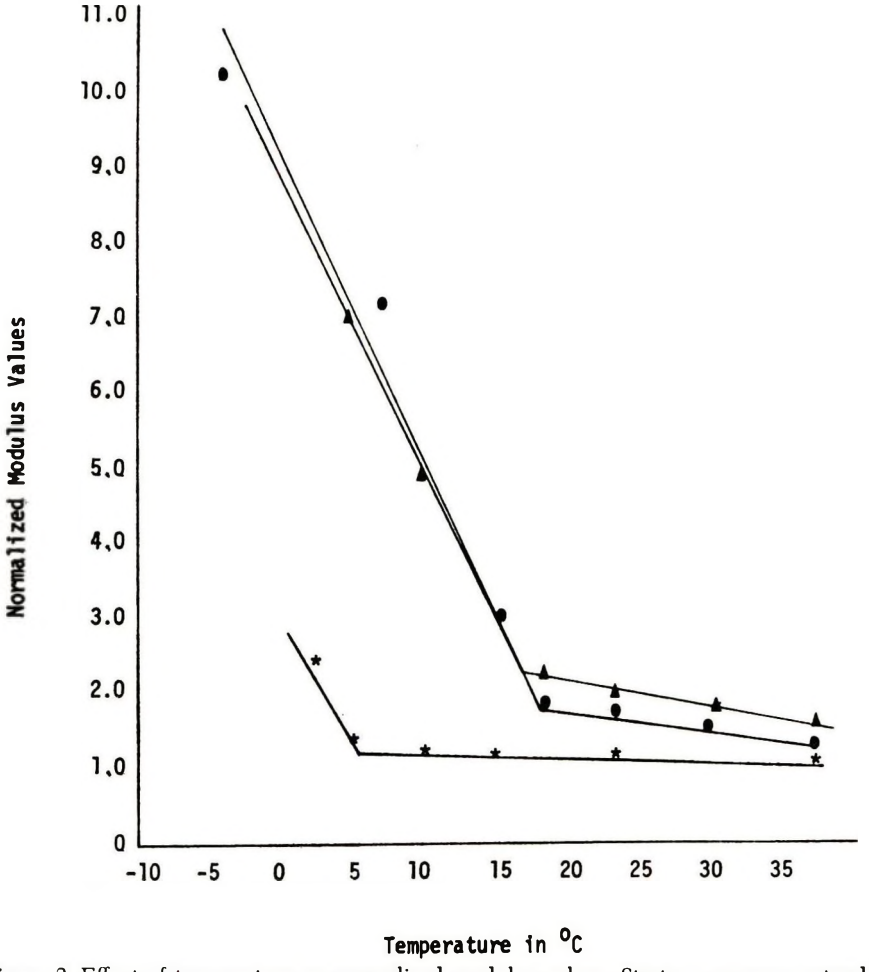

Figure 2. Effect of temperature on normalized modulus values. Stratum corneum extended under solution and normalized to the value for water at 37°C

—●—●—●—glycerol:water (1:1)

—°—°—°—water

—▶—▶—▶—6*M* potassium iodide

to exert any influence on chapping or related skin disorders, since the temperature of the face and hands does not reach 18°C until the air temperature drops to about −12°C [extrapolated from data of Phelps and Vold (7)]. However, the temperature of the lower extremities can reach 18°C at an ambient temperature as high as 19°C (8).

The effects of a variety of cosmetic ingredients and of a few chemical treatments on the physical properties of stratum corneum at 31% RH are summarized in Table I. In examining these data, it must be remembered that only horizontal comparisons are possible since the "control" and "treated" samples

are from the same stratum corneum specimen. A comparison within the various columns may lead to erroneous conclusions. A decrease in the elastic modulus below that of the control (recorded as +) is indicative of an increase in the elasticity of the stratum corneum. In the case of the stress relaxation modulus, an increase in the value over that of the control (recorded as +) describes the skin's ability to relieve a strain by viscoelastic response. The wide variations in the values for the controls are due to the fact that different specimens of epidermis were used, but this in no way reduces the value of the data. Each value recorded in Table I represents an average of 4 to 6 determinations on the same specimen of human epidermis. Treatment with either acid or base increases the elasticity of the stratum corneum substantially but does not appreciably alter its ability to relieve stress. Generally, the elastic and the stress relaxation moduli results after treatment parallel each other. Particularly noticeable is the remarkable "plasticizing" effect of dilute solutions of sodium pyrrolidone carboxylate and of sodium lactate. It is believed that the influence of cosmetic ingredients on the mechanical performance of stratum corneum correlates directly with their beneficial effect in skin preparations.

Moisture Absorption

The equilibrium moisture absorption of several important cosmetic moisturizers on glass filter cloth was studied after equilibration at several relative humidities. The data in Table II show that sodium pyrrolidone carboxylate and sodium lactate are capable of holding relatively large quantities of water even at intermediate relative humidities, i.e. between 50 and 70% RH. It proved impossible to conduct similar experimentation with propylene glycol because of its unexpectedly high volatility. Data for stratum corneum and some hydrophobic materials are included merely as a matter of orientation.

In view of the large effect of glycerin on the mechanical behavior of stratum corneum as a function of temperature (Fig. 2), it was considered conceivable that there is a specific interaction between glycerin, stratum corneum, and water which may increase the water-holding properties of stratum corneum. Similarly, the high hygroscopicity of sodium pyrrolidone carboxylate makes it possible that it too might impart some special water-holding properties to stratum corneum. In order to determine whether any such interactions occur, the isothermal absorptions of water by combinations of known weights of unextracted stratum corneum and glycerol or sodium pyrrolidone carboxylate were determined. The results shown in Table III clearly show that water absorption by stratum corneum is merely additive to that by the humectant. In other words, the moisture absorption by stratum corneum treated with a humectant is the sum of the absorptions of the individual components, with no evidence for any synergistic effects. These results are in agreement with the data reported by Fox *et al.* (9).

Table II
Equilibrium Moisture Absorption

Material	% Water Absorbed at 31% RH	52% RH	76% RH	90% RH
Stratum corneum	7	9	13	22
Glycerol	11	26	67	240
Sodium lactate	19	40	104	...
Sodium pyrrolidone carboxylate	17	45	210	...
Mineral oil	0.2	0.4	0.9	...
Safflower oil	0.2	0.5	1.0	...

Table III
Weight Gain (Water Content) of Stratum Corneum and Stratum Corneum Plus Humectant

Sample	Initial Weight[a] (mg)	Amount of Water (mg) after Equilibration at 35% RH	75% RH
Stratum corneum	3.816	0.226	0.530
Glycerol[b]	3.058	0.339	2.058
Stratum corneum + glycerol			
Experimental	6.874	0.572	2.575
Calculated	...	0.565	2.588
Stratum corneum	3.784	0.183	0.515
Sodium pyrrolidone carboxylate[c]	3.468	0.720	3.488
Stratum corneum + sodium pyrrolidone carboxylate			
Experimental	7.252	0.892	3.892
Calculated	...	0.903	4.003

[a]At equilibrium with air at 0% RH.
[b]U.S.P.
[c]Applied from a 50% solution.

Water Vapor Transmission

The loss of moisture from the skin to the atmosphere is a continuous process, and excessive loss at low humidity and low temperatures is generally associated with skin dryness and chapping. It seemed particularly important to determine how cosmetic ingredients applied to stratum corneum might alter this tissue's ability to "transpire" water to an essentially dry atmosphere. Some typical *in vitro* water vapor transmission rates through stratum corneum are summarized in Table IV. This table also includes some common cosmetic humectants, some occlusive lipid materials, and Lotion #78. This last preparation, which is Formula 78 described by Barnett (10), was employed here because it was also studied *in vivo* by Berube *et al.* (11).

Table IV
In Vitro Water Vapor Transmission through Stratum Corneum

Material	Rate (mg cm^{-2} hr^{-1})		Ratio
	Untreated	Treated	(Treated/Untreated)
25% glycerol	0.264	0.518	1.96
4% sodium lactate	0.294	0.372	1.27
4% sodium pyrrolidone carboxylate	0.142	0.227	1.60
4% propylene glycol	0.223	0.267	1.20
Light tech. mineral oil	0.274	0.205	0.75
Safflower oil	0.309	0.281	0.91
Lotion 78[a]	0.335	0.181	0.54

[a]Formula 78 from Barnett (10).

The results obtained here are only directional in view of several experimental uncertainties: Experimentally, stratum corneum was first equilibrated in the diffusion cell against 0% humidity to yield an "untreated" rate. The material of interest was then applied to the exposed stratum corneum surface with the aid of a cotton swab. An effort was made to remove excess material while maintaining a continuous film, but there is no quantitation of the amount of substance actually remaining on the stratum corneum. The "treated" rate recorded in Table IV is the rate resulting after complete equilibration of the treated stratum corneum against the dry environment. As expected, lipid materials reduce water vapor transmission, whereas humectants cause a marked increase. The results with Lotion #78 confirm the *in vivo* data of Berube *et al.* who found that heavy application of this preparation was required to produce the occlusive effect (11). It is particularly noted that the small amount of sodium pyrrolidone carboxylate remaining on the stratum corneum after applying a 4% aqueous solution still causes a very large increase in the rate of water vapor transmission. These results clearly confirm the earlier data presented by Powers and Fox (12) that humectants increase transepidermal moisture loss.

Traditionally, humectants, such as glycerol, have been used for "improving dryness of skin and chapping." Published controlled clinical data attesting to the utility of humectants are missing, although the authors have access to a monadic clinical in-use study suggesting strongly that a preparation containing a high concentration of glycerol without any occlusive properties alleviates the dryness/chapping syndrome (13). It is difficult to reconcile the evidently beneficial effects of glycerol with its ability to increase transepidermal water loss. Only a very tentative hypothesis is offered here: Stratum corneum is commonly thought of as a homogeneous layer of cornified epithelial cells. The assumption is probably incorrect, since the outer portion of the stratum corneum may have suffered some damage due to wear and tear and the dissolution of lipid- and water-soluble constituents. As a result, the outer

barrier to the evaporation of water from stratum corneum is not the top of the stratum corneum but lies somewhere between the topmost and innermost cellular layers of the stratum corneum. Glycerol is known not to penetrate stratum corneum appreciably and presumably its application will result in the formation of a layer at or near the top of this epidermal structure. By virtue of its hygroscopicity, glycerol will unquestionably attract water from the lower layers of the stratum corneum whenever ambient humidity conditions preclude absorption from the air. This will result in continuous migration of water molecules through all layers of stratum corneum towards the glycerol layer which, in turn, readily loses water to the atmosphere. The benefits derived from the application of glycerol then reside in its ability to move the evaporative layer of skin moisture from somewhere in the center of the stratum corneum to the very top of the stratum corneum.

Conclusions

1. The stress relaxation modulus and the elastic modulus are sensitive measures of the ability of various cosmetic treatments to affect the viscoelastic behavior of stratum corneum.

2. The water-holding capacity of a system comprising a humectant and stratum corneum is the sum of the component parts. No synergistic effect could be demonstrated.

3. The application of typical cosmetic humectants to the exposed side of the stratum corneum increases the rate of transepidermal water loss.

4. A model to explain the beneficial effects of a moisturizer on the surface of the stratum corneum is proposed.

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J. Soc. Cosmet. Chem., **25**, 263–269 (May 1974)

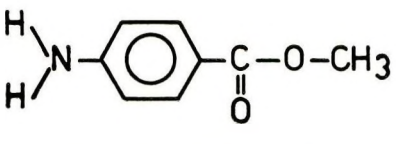
Die Photochemie von Sonnenschutzmitteln

II. Über die Photochemie von Methyl-p-dimethylaminobenzoat

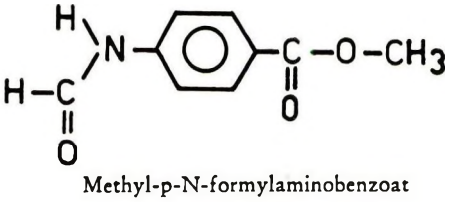
C. D. M. TEN BERGE* und C. H. P. BRUINS*

Synopsis—**Photochemistry of sunscreens. II. The photochemistry of methyl-p-dimethylaminobenzoate.**—The isolation and identification of another two photochemical reaction products of METHYL-p-DIMETHYLAMINOBENZOATE are described. ULTRAVIOLET IRRADIATION of this compound in 1,4-dioxane in the presence of oxygen yielded also METHYL-p-N-FORMYLAMINOBENZOATE and METHYL-p-AMINOBENZOATE. Isolation was achieved by means of gas chromatography. The two products were identified by comparison of the IR, NMR, and mass spectra of the isolated and synthesized substances. For METHYL-p-(N-FORMYL-N-METHYL)-AMINOBENZOATE, mentioned in a previous communication, a new synthesis is described.

Vor kurzem berichteten wir über die Photochemie von Methyl-p-dimethylaminobenzoat (1). Wir fanden vor allem, daß bei UV-Bestrahlung von Methyl-p-dimethylaminobenzoat in sauerstoffgesättigtem 1,4-Dioxan zwei photochemische Reaktionsprodukte entstehen, nämlich Methyl-p-N-methylaminobenzoat und Methyl-p-(N-formyl-N-methyl)-aminobenzoat (1). Weitere Untersuchungen haben gezeigt, daß noch weiter zwei Produkte nachzuweisen sind, Methyl-p-aminobenzoat und Methyl-p-N-formyl-aminobenzoat (s. Formelbilder). Das Gas-Chromatogramm zeigt außerdem einen kleinen



Methyl-p-aminobenzoat



Methyl-p-N-formylaminobenzoat

* Laboratorium voor Farmaceutische en Analytische Chemie der Rijksuniversiteit, Dir. Prof. Dr. J. S. Faber, Antonius Deusinglaan 2, Groningen/Nederland.

Peak 3, doch konnten wir die entsprechende Substanz nicht identifizieren. Die neuen Versuche fanden unter genau denselben Reaktionsbedingungen statt, wie für die Isolierung von Methyl-p-N-methylaminobenzoat und Methyl-p-(N-formyl-N-methyl)-aminobenzoat angegeben wurde. Nun gelang auch die Isolierung der zwei genannten Reaktionsprodukte gas-chromatographisch, deren Identifizierung durch Vergleich der IR-, NMR- und Massenspektren der isolierten und synthetisierten Substanzen erfolgte.

In Zusammenhang mit unseren Untersuchungen erscheint die Arbeit von Reisch und Niemeyer wichtig (2). Diese Autoren fanden, daß durch UV-Bestrahlung von Äthyl-p-aminobenzoat in Äthanol u. a. ein über die Aminogruppe verkettetes Oxidationsprodukt entsteht, an dem zwei Moleküle Äthyl-p-aminobenzoat beteiligt sind. Diese Autoren betonen, daß sie die Bestrahlungen nicht in Inertgas-Atmosphäre durchgeführt haben, so daß die Bildung der Oxidationsprodukte zum Teil durch die Einwirkung von Luftsauerstoff erklärt werden kann.

Trotz der Tatsache, daß unsere Untersuchungen unter anderen Reaktionsbedingungen durchgeführt sind, ist es interessant, daß in beiden Fällen nur die aromatische Aminogruppe photochemisch reaktionsfähig ist und die Estergruppe zunächst nicht angegriffen wird.

Als Ergänzung dieser Arbeit haben wir eine neue Synthese des Methyl-p-(N-methyl-N-formyl)aminobenzoat beschrieben (1). Wegen der Carcinogenität von Diazomethan haben wir eine Synthese mittels Methyl-p-N-methylaminobenzoat und n-Butylformiat durchgeführt.

Beschreibung der Versuche

Massen-Spektrometrie: Typ MS 9 (AEI); NMR-Spektrometrie: Typ A 60 (Varian), Tetramethylsilan als innerer Standard; IR-Spektrometrie: Beckman IR-33; Elementaranalysen wurden von der Mikroanalytischen Abteilung**) des Chemischen Institutes der Reichsuniversität Groningen ausgeführt.

Synthese von Methyl-p-aminobenzoat

Eine Lösung von 27,4 g (0,2 M) p-Aminobenzoesäure (USP XVIII) in 600 ml Methanol (Merck) wurde mit 20 ml konz. Schwefelsäure (Merck) vermischt. Das Gemisch wurde 23 Stunden unter Rückfluß gekocht, dann das Methanol abdestilliert. Der Rückstand wurde unter Rühren in eine Lösung von 40 g Natriumhydroxid in 200 ml Wasser, dem Eis zugesetzt war, gegossen. Der Ester wurde abfiltriert, mit Wasser gewaschen und aus Äthanol/Wasser umkristallisiert. Die farblosen Kristalle wurden bei 90° C getrocknet.

**) Leiter: W. M. Hazenberg

F. 112—113° C. Ausbeute: 23,7 Methyl-p-aminobenzoat. Die IR-, NMR- und Massenspektren bestätigten die Struktur dieser Verbindung.

$C_8H_9NO_2$ (151,2)	Ber.:	C 63,56	H 6,00	N 9,27
	Gef.:	C 63,59	H 5,87	N 9,49

Synthese von Methyl-p-N-formylaminobenzoat

Als Richtschnur für die Synthese diesr Verbindung diente die Vorschrift von Moffat et al. (3). Statt Äthylformiat wurde n-Butylformiat verwendet.

n-Butylformiat wurde wie folgt hergestellt: 760 ml Ameisensäure (E. Merck, 98—100 %) wurden mit 920 ml Butanol-1 (Merck) vermischt und 24 Stunden unter Rückfluß erhitzt. Nach Abkühlen auf Raumtemperatur wurde mit 100 ml gesättigter NaCl-Lösung und weiter mit 4 Portionen von je 50 ml der gleichen Lösung ausgeschüttet, nachher mit 100 ml gesättigter $NaHCO_3$-Lösung, der in kleinen Portionen festes Natriumhydrogencarbonat zugefügt wurde, bis keine CO_2-Entwicklung mehr stattfand. Schließlich wurde zweimal mit je 100 ml gesättigter NaCl-Lösung ausgeschüttelt. Das Reaktionsprodukt wurde über Al_2O_3 [Aluminiumoxid aktiv neutral, Aktivitätsstufe 1, für die Säulenchromatographie (Merck); Säulenhöhe 12 cm, Durchmesser 4½ cm] getrocknet. Das getrocknete Produkt wurde mit 150 ml Benzoylchlorid (Merck) versetzt, 4 Stunden unter Rückfluß erhitzt und destilliert, wobei das zugesetzte Benzoylchlorid und die enstandenen Produkte zurückblieben. Der rohe Ester wurde mit 100 ml gesättigter NaCl-Lösung und danach mit 100 ml gesättigter $NaHCO_3$-Lösung ausgeschüttelt, der festes Natriumhydrogencarbonat zugefügt wurde, bis keine CO_2-Entwicklung mehr stattfand. Nachher wurde noch zweimal mit je 100 ml gesättigter NaCl-Lösung ausgeschüttelt, über Al_2O_3 [Aluminiumoxid aktiv neutral, Aktivitätsstufe 1, für die Säulenchromatographie (Merck); Säulenhöhe 12 cm, Durchmesser 4½ cm] getrocknet und destilliert (Vilgreux-Fraktionieraufsatz; 40 cm). Kp. 108—109° C. Ausbeute: 560 g n-Butylformiat.

400 ml frisch hergestelltes Formiat wurde mit 8 g Methyl-p-aminobenzoat gemischt, wobei eine trübe Lösung entstand. Die Mischung wurde 24 Stunden unter Rückfluß erhitzt und nachher im Vakuum eingeengt. Dem Rückstand wurden 300 ml Wasser zugesetzt. Es wurde mit 4 N Salzsäure angesäuert. Die Lösung wurde 30 min bei Raumtemperatur gerührt, der Kristallbrei abgesaugt, mit Wasser gewaschen, aus Äthanol/Wasser (Aktivkohle) umkristallisiert und im Vakuumexsikkator über konz. Schwefelsäure getrocknet: Farblose, glänzende Kristalle, F. 124° C.

Ausbeute: 4,8 g Methyl-p-N-formylaminobenzoat.

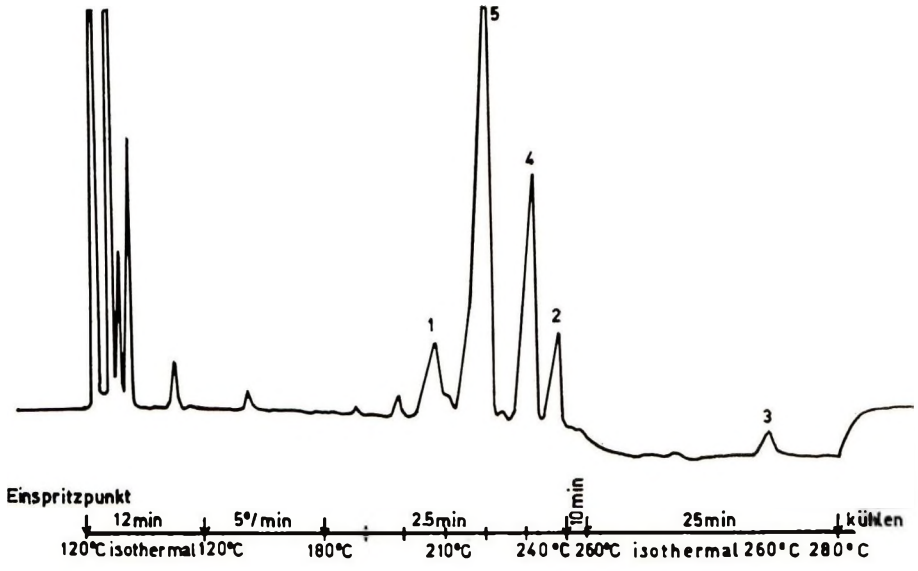


Abbildung 1

Gas-Chromatogramm der Reaktionsprodukte (nach 48 Stunden Bestrahlung) an einer SE 30-Säule (20 %) (s. Text). 1 Methyl-p-aminobenzoat, 2 Methyl-p-N-formylaminobenzoat, 3 unbekannt (s. Text), 4 Methyl-p-(N-formyl-N-methyl)-aminobenzoat, 5 Methyl-p-N-methyl-aminobenzoat.

IR: siehe *Abb.* 2.

NMR ($CDCl_3$): δ 3,9 [S] 3H, (CH_3 an O); 7,5—8,1, 4H (aromat); 8,44 [S] 1H, (formyl); 8,9 [S] 1H, (H an N).

$C_9H_9NO_3$ (179,2)	Ber.: C 60,33	H 5,06	N 7,82	O 26,79
	Gef.: C 60,54	H 5,12	N 7,94	O 26,86

Synthese von Methyl-p-(N-formyl-N-methyl)-aminobenzoat

Eine Lösung von 7 g Methyl-p-N-methylaminobenzoat (5) in 350 ml frisch hergestellten n-Butylformiats (s. Vorschrift) wurde 68 Stunden unter Rückfluß auf Siedetemperatur erhitzt. Nach Einengen im Vakuum wurden 300 ml Wasser zugefügt und die Lösung mit 4 N Salzsäure bis pH ca. 3 angesäuert. Dann wurde 30 min bei Raumtemperatur gerührt. Die weiße Substanz (kleine Kristalle) wurde abfiltriert, mit Wasser gewaschen, aus Äthanol/Wasser umkristallisiert und im Vakuumexsikkator über konz. Schwefelsäure getrocknet. F. 99° C. Ausbeute: 4,8 g Methyl-p-(N-formyl-N-methyl)-aminobenzoat.

Das IR-Spetrum war mit dem für die Substanz schon beschriebenen identisch.

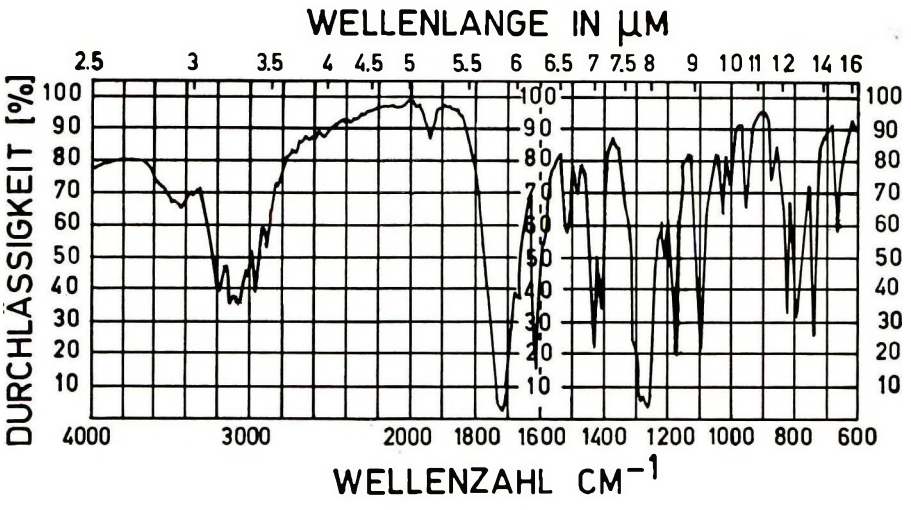


Abbildung 2

IR-Spektrum von Methyl-p-N-formylaminobenzoat (Konzentration 2 mg; 300 mhg KBr).

Isolierung der Photoreaktionsprodukte

Die Bestrahlung erfolgt nach der Vorschrift von ten Berge et al. (2). Eine Lösung von 4 g Methyl-p-dimethylaminobenzoat in 400 ml 1,4-Dioxan wurde in beschriebener Weise 48 Stunden bestrahlt. Hierauf wurde die braungelb gewordene Lösung bei einer Wassertemperatur von 30° C im Vakuum auf 10 ml eingeengt. Diese Lösung wurde zur Isolierung der den Peaks 1, 2, 3 und 4 (Abb. 1) entsprechenden Substanzen verwendet.

Zu diesem Zwecke wurde ein Becker Multigraph Research Gas-Chromatograph Type 409 benutzt, aber nun mit einen „Effluent splitter with component trap, Becker Delft N. V. (Detektorkapillare 0,25 mm innerer Durchmesser; Ausgangsrohr zum Auffangen der Substanzen 1 mm innerer Durchmesser), H_2-Flammenionisationsdetektor, Edelstahl-Trennsäule (4,75 mm innerer Durchmesser) von 2 m und Chromsorb W.A.W., Korngröße 80/100 mesh als Trägermaterial. Einspritzblocktemperatur: 300° C; Detektorblocktemperatur: 330° C; Temperaturprogramm: 120° C Anfangstemperatur, bei dieser Temperatur 12 min konstant, 5°/min bis 180° C, 2,5°/min bis 240° C, 10°/min bis 260° C, bei dieser Temperatur 25 min konstant. Stationäre Phase: SE-30-20 %, Trägergas: N_2. Gasströmungsgeschwindigkeit: 60 ml/min. Probenmenge: 40 µl. Es wurde so lange chromatographiert, bis ausreichend Substanz für die verschiedenen Analysen erhalten worden war. Diese Mengen betrugen: Peak 1:46 g; Peak 2:21 mg; Peak 3:12 mg und Peak 4:82 mg. Die

erhaltenen Substanzen wurden in Aceton aufgelöst und zur Reinheitskontrolle in eine SE-30-Trennsäule eingespritzt. Substanzen entsprechend den Peaks 3 und 4 wurden genügend rein befunden. Die Lösung entsprechend Peak 3 wurde eingeengt und sehr gut im Vakuum bei 100° C getrocknet. Es blieb ein dunkelbraunes Öl zurück, das hart und transparent wurde: Kristalle entstanden nicht. Das Massenspektrum dieser Verbindung zeigte eine Molekülion (M^+) von $\frac{m}{e}$ 263.
Die weiteren spektrometrischen Daten (NMR, MS, IR) erlauben keine Auskünfte über die Molekülstruktur.

Die Peaks 1 und 2 erwiesen sich als nicht genügend rein. Daher wurde eine gas-chromatographische Reinigung durchgeführt. Es wurde eine 2m-Edelstahl-Trennsäule (4,75 mm innerer Durchmesser) mit Chromosorb G.A.W.-DMCS, Korngröße 80/10 mesh als Trägermaterial und Apiezon-L-3 % als stationäre Phase benutzt.

Nur die Substanz entsprechend Peak 2 wurde nach 20 min bei 200° C (isothermal) gewonnen. Sie wurde in etwa 200 µl Dioxan gelöst in und in 3 Portionen auf die beschriebenen Apiezon-L-Trennsäule gebracht. Es wurde der vorgenannte Gas-Chromatograph benutzt, ausgestattet mit dem beschriebenen „Splitter" und einem H_2-Flammenionisationsdetektor. Einspritzblocktemperatur: 300° C; Detektorblocktemperatur: 330° C. 200° C isothermal. Trägergas: N_2. Gasströmungsgeschwindigkeit: 50 ml/min. Probenmenge: etwa 60 µl. Aufgefangen wurden etwa 14 mg Substanz.

Nach Übertragen mittels Dioxan in ein Reagenzgläschen und Trocknen im Vakuum wurde ein IR-Spektrum aufgenommen, das sich als identisch mit dem des synthetisierten Methyl-p-N-formylaminobenzoates erwies.

Die Substanz entsprechend Peak 1 wurde weiter verarbeitet: sie wurde in 0,5 ml Dioxan aufgelöst und auf eine Trennsäule mit folgenden Merkmalen gebracht: 2m-Edelstahl (Innendurchmesser 4,75 mm); Trägermaterial: Chromosorb W.A.W.-DMCS, Korngröße 80/100 mesh; Stationäre Phase: Apiezon-M-15 %. Benutzt wurde der vorgenannte Gas-Chromatograph, ausgestattet mit dem beschriebenen „Splitter" und einem H_2-Flammenionisationsdetektor. Einspritzblocktemperatur: 275° C; Detektorblocktemperatur: 275° C. 180° C isothermal. Trägergas: N_2. Gasströmungsgeschwindigkeit: 60 ml/min. Probenmenge: 100 µl. Die erhaltene Substanz wurde mit ein wenig Aceton (p. a. Merck) in ein Reagenzgläschen übergeführt, eingeengt und im Exsikkator getrocknet. Es wurden 25 mg farblose Kristalle erhalten. Das IR-Spektrum erwies sich als identisch mit dem des synthetisierten Methyl-p-aminobenzoats.

ZUSAMMENFASSUNG

Isolierung und Identifizierung zweier weiterer Photoreaktionsprodukte des Methyl-p-dimethylaminobenzoats werden beschrieben. Die Ultraviolettbestrahlung dieser Verbindung in 1,4-Dioxan in Gegenwart von Sauerstoff liefert auch Methyl-p-N-formylaminobenzoat und Methyl-p-aminobenzoat. Die Isolierung erfolgte gas-chromatographisch. Beide Produkte wurden durch Vergleich der IR-, NMR- und Massenspektren der isolierten und synthetisierten Substanzen identifiziert. Für das in einer früheren Mitteilung behandelte Methyl-p-(N-formyl-N-methyl)-aminobenzoat wird eine neue Synthese angegeben.

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SOCIETY OF COSMETIC CHEMISTS

ANNUAL SCIENTIFIC MEETING

December 2-3, 1974

The program will include the following topics:
Dandruff, Dr. Albert Kligman, Moderator
Product Stability, Warren Hintz, Moderator
Scientific Approach to Cosmetic Efficacy, Carl Felger, Moderator
New Technology in Product Development, Bob Hutchison, Moderator

Special Education Session

Measuring and Improving Creativity, Joe Kratochvil, Moderator

AMERICANA HOTEL

New York, New York

J. Soc. Cosmet. Chem., **25**, 271–281 (May 1974)

Current Perspectives on Aerosol Toxicity

CHARLES O'CONNOR WARD, Ph.D.*

Presented May 4, 1973, Seminar, Cincinnati, Ohio

Synopsis—The TOXICITY of cosmetic, household, or personal product AEROSOLS is primarily the result of either deliberate abuse or allergic reactions to one or more of the ingredients. Hair sprays, antiperspirants, deodorants, and feminine hygiene sprays, among others, have been reported to produce toxic reactions in some users. A review of the published experimental and clinical data does not substantiate the contention that, when used as directed, they are hazardous. It is true, for instance, that the fluorocarbon PROPELLANTS, in experimental situations, can sensitize the myocardium to catecholamine-induced arrhythmias and thus produce a situation detrimental to the user, but not in the amounts to which the consumer is ordinarily exposed. The differences between toxicity, the inherent ability to produce undesirable alterations in biological tissue, and HAZARD, the likelihood that toxicity will occur, may explain the case for aerosol products. The potential for toxicity of properly packaged cosmetic, household, and personal product aerosols is present; the hazard is small under conditions of normal use.

Introduction

As with any other type of packaging or delivery system for cosmetics, drugs, or household products, aerosols have characteristics that are uniquely their own. In general, they are safe, convenient, easy to manipulate, and, for the most part, economical to use. In addition to these advantages, however, this particular method of packaging and delivery is somewhat harder to control once the contents have been liberated from the container. Foams, paints, and cosmetic powders are easily seen and handled; but many drug and liquid cosmetic formulations, such as deodorants and hair sprays, are hard to see once released and often the respect that other aerosol products are given by the consumer is not accorded these items.

Individuals often have a difficult time relating to a substance that, because of its small particle size, is difficult to see; thus, the potential hazards, including warning labels, are often ignored. This can be illustrated in the case of a

*St. John's University, College of Pharmacy and Allied Health Professions, Jamaica, N.Y. 11439.

hypothetical man who sprays an entire can of an aerosol insecticide into a small room and then, without opening any windows, goes to sleep in the room; rising later he finds manifestations of a contact allergy. Yet he probably would not have treated a can of gasoline that way, despite the relatively innocuous nature of the chemicals in the can of gasoline.

Types of Aerosol Toxicity

Toxic reactions to aerosols have been reported in the literature for several categories of products: cosmetics, such as hair sprays (1–3) and deodorants (1, 4, 5); perfumes (6); personal products such as feminine hygiene deodorant sprays (7, 8); and household products, such as spray paints (9), insecticides (10), aerosolized vegetable oils (11), and room deodorizers (5, 9). Medicinal aerosols have also been reported to produce some of the same toxic effects, but they will not be discussed in this paper. The types of toxicity reported can be broken down into two main categories, those due to the propellants and those due to the active or inert ingredients in the formulations.

Propellant toxicity can result either from the refrigerant properties of the propellants (freezing of tissues or local anesthesia) or from the chemical nature of the propellants and the biological responses they elicit (12).

Many of the reported cases of aerosol toxicity are likely due to toxic reactions to the active or inert ingredients in the formulation, rather than to the propellants. Allergic reactions are among the more common forms of toxic responses to cosmetic aerosols. It has been estimated that approximately 10% of the population as a whole has some type of allergic disease (6) or has suffered an allergic response to some foreign substance during their lifetime; and it is a well-accepted medical fact that people who are allergic to one substance, or have an allergic disease such as asthma or hay fever, are prone to be allergic to other products as well—especially upon repeated exposure.

The incidence of persons allergic to cosmetic products, on the other hand, is probably between 2 and 3%, when verified by a patch test (6). In the data compiled by one cosmetic company who markets a broad range of products, only 448 reactions were reported in 114 million units sold (6). In an earlier reference, the incidence of allergic skin reactions to lanolin was 1.14% in an unscreened sample of users. (Lanolin is widely used in cosmetic formulations for its unique emollient and emulsification properties.) On the other hand, when a controlled sample with no history of allergic skin disease was tested, no allergic reactions to lanolin were reported (13). Recent refinements and improvements in the purification of the lanolin used in cosmetic products have eliminated lanolin allergy as a significant problem. Reactions to perfume oils, a ubiquitous ingredient in cosmetic aerosol products, are almost entirely due to an allergic or hypersensitive response, rather than due to primary irritation (6). There are more than 5000 odiferous substances in general use

today as perfumes. Most cosmetics contain approximately 0.5% perfume oil; colognes about 4%; and perfumes up to 20%. Each of these perfume substances may contain up to 50 different chemical ingredients, so the task of identifying the cause of an allergic response is, at best, a difficult one (6).

Photosensitization is a type of allergic response and has been reported for a number of essential oils, such as neroli, pettigrain, cedarwood, lavender, and bergamot (6, 14). In addition, dermatitis has been reported following the use of oil of bergamot. Chlorophyll, traces of copper, and psoralens, all found in oil of bergamot, are suspected of being the cause of the allergies. Aging of the oil reduces its sensitizing propensity (6). Even once the allergy-causing ingredient has been found, the problem of cross-sensitivity may arise. Persons allergic to oil of citronella, for example, are also often allergic to lemon oil (15).

A partial solution to the problem of allergy to perfume oils may have been found with the marketing, by a number of companies, of a group of chemically-reproducible perfume substances which have been patch tested to prove a low incidence of allergic responses (16). Hypoallergenic cosmetics may be another solution. These are a group of cosmetic products, marketed by a few companies, which are specifically for the use of individuals hypersensitive to many cosmetics. The raw materials for these products are selected on the basis of a reported low incidence of allergic responses (6).

The pyrethrins, found in many insecticide aerosols, may also cause a variety of allergic manifestations in susceptible individuals; erythema, rash, loss of feeling in exposed parts of the skin, and diminished vision have all been reported (10).

Another type of toxicity, though less important, that may result from the active or inert ingredients in many cosmetic aerosols, is primary irritation of the skin (17). This is not an allergic response but rather is a result of the caustic nature of certain ingredients in the formulation. Calcium thioglycolate is a primary irritant found in many aerosol foam depilitories (6). Antiperspirants often contain salts of zinc, zirconium, or aluminum which can cause primary irritation (6). Ocular irritation from dandruff shampoos has been reported (18, 19), probably as a result of certain zinc salts.

Effect of Aerosols on Anatomy and Physiology of the Skin and Respiratory System

The underlying cause of many of the toxic reactions resulting from the use of cosmetic and household aerosols seems to be the result of an alteration in the basic anatomy and/or physiology of the skin and respiratory systems. The type of alteration produced depends, to a degree, on the product in question and the area of the body it comes in contact with. Alterations in skin pH are thought to be the basis for the primary irritation produced by the depilitories in foam aerosols. Preparations containing calcium thioglycolate, for example,

usually have a pH of about 12, while the normal pH of the skin is between 4 and 6 (6). The metallic salts of zinc, aluminum, and zirconium used in aerosol antiperspirants may cause superficial skin infections because they produce narrowing of the ducts of sweat glands which may give rise to apocrine sweat gland occlusion and a true hydradentitis (6, 18).

The refrigerant action of propellants in personal or household aerosols can produce cooling or freezing of the sensitive corneal (5) or vaginal (7) tissues if they are used improperly. Many facets of skin metabolism, including cellular respiration, can be altered by some cosmetic aerosols (20). The propellants have been reported to sensitize the myocardium to arrhythmias caused by anoxia and catecholamines (21), although there is no definitive evidence that this type of cardiac toxicity can result from normal use of any aerosol product (22, 23). The interruption of the normal bacterial flora of several body orifices was formerly a potential problem with vaginal deodorant sprays containing antibacterial agents (24). It is known that once the normal flora of the vagina or rectum is altered (as with tetracycline therapy), an abnormal overgrowth of yeasts and fungi (usual symbionts in these areas) may cause pruritis (25) and/or other bacterial infections. Since most vaginal sprays no longer contain antibacterial chemicals, this problem has essentially ceased to exist. Keratitis, due to a foreign body reaction of the skin, has been reported in response to the presence of materials from several household aerosols that have, in effect, been driven into the skin by the force of the spray (5). An increased formation of pulmonary edema fluid and lipid pneumonia has been reported following a foreign body response to the inhalation of oil droplets from an aerosol containing a vegetable oil (11). Edema fluid is an ideal medium for the growth of pathogens, resulting in aspiration pneumonia. A slight reduction in specific airway conductance, posing no clinical danger, has been reported following the inhalation of several bronchodilator aerosols. The bronchoconstriction reported, which was less than that caused by smoking a cigarette, was attributed to the aerosol propellant and/or the surfactant chemicals (sorbitol trioleate and soya lecithin) contained in the two bronchodilator aerosols evaluated (26).

Propellant Toxicity and Abuse

The controversy regarding the toxicity of aerosol products, in general, and the propellant chemicals they contain, in particular, began several years ago with the publication in the lay press of several deaths due to "sniffing," especially by teen-agers, of the vapors from a wide variety of aerosol products (27). The practice involved the deliberate, deep inhalation of the concentrated vapors, usually from a balloon or paper bag (28).

These reports of aerosol abuse brought the toxic potential of the various propellants to the attention of the aerosol industry. The toxicity of the propellants can be divided into three major categories: toxicity due to the refrig-

erant action of the propellants (12), which may cause reflex airway obstruction, especially of the larynx, and tissue damage to the delicate mucous membranes of the vulva (7) and eye (29); decomposition into phosgene when the vapors come into contact with an open flame (30); and finally, systemic toxicity, chiefly referrable to the cardiovascular system (21, 22). It is this latter type of toxicity which has been accorded so much unwarranted publicity by the press.

The problem of teen-age abuse of aerosols is one over which the aerosol industry has little control, other than to update the warnings printed on the aerosol cans. The Inter-Industry Committee on Aerosol Use has established the Aerosol Education Bureau (31) to administer a safety campaign which is designed to warn teen-agers of the potential lethal consequences of abusing aerosolized products.

Soon after the controversy regarding the deaths from aerosol "sniffing" began, Taylor and Harris (21) reported that the exposure of mice to several propellants, followed by asphyxia in a plastic bag, produced sensitization of the myocardium to hypoxia, resulting in arrhythmias such as sinus bradycardia, atrioventricular block, and T wave depression. They used these experiments to postulate that the sudden deaths that followed aerosol abuse by teen-agers could be the result of a toxic action of the propellants used in almost all aerosol packages, as well as to provide a basis for warning against the possible hazards to frequent users of a variety of aerosol products. It is well known, and has been for some time, that high concentrations of many propellants frequently used by aerosol manufacturers can produce a wide variety of toxic effects. Ataxia, tremors, liver, and kidney damage are among some of the more common findings (32, 33). But these experimental results in animals, especially at the high concentrations studied, bear little or no relationship to the lower concentrations to which the consumer of aerosol products is exposed (28). Also, there is lack of general agreement as to the accuracy of the data on aerosol toxicity when it is extrapolated from animal studies to humans (22, 34).

Following several reports by Taylor and Harris on the cardiac toxicity of aerosol propellants, other investigators attempted to reproduce their findings, with little success. McClure, in 1972, failed to produce significant changes in the heart rate or electrocardiogram of anesthetized mice after the administration of several propellants in aerosol form, followed by asphyxia (35). In general, he found that the cardiovascular effects produced by propellant exposure were similar to the cardiovascular effects of asphyxia alone. McClure was also unable to confirm similar findings reported by Taylor and Harris in dogs (21). Egle *et al.* (23) also attempted to repeat the results of Taylor and Harris. They exposed mice to several propellants, either alone or with nitrogen-induced asphyxia, and reported no augmentation of the asphyxia-induced bradycardia or atrioventricular block by the several fluorocarbon propellants

studied. In all, four groups of investigators have failed to repeat the findings reported by Taylor and Harris (22).

On the other hand, many investigators have reported the safety of the fluorocarbon propellants in concentrations generally produced following normal use. McClure (35) reported no effect on heart rate, blood pressure, and electrocardiogram in dogs following the intratracheal administration of an epinephrine aerosol. Azar *et al.* (36) were unable to produce arrhythmias in anoxic and hypercapnic dogs following repeated exposure to several commercial aerosols. Others were unable to produce significant electrocardiographic changes in several patients, ill with a variety of bronchopulmonary disorders, following the repeated inhalation of Propellant 11 and Propellant 12 (27).

There is little question that the various propellants can, when administered in high concentrations over a prolonged exposure period, produce cardiac arrhythmias. Flowers and Horan (37) exposed anesthetized dogs to several commercial aerosols in high concentrations; their data showed bradycardia and ventricular arrhythmias in many of the dogs thus treated. Reinhardt *et al.*, in 1971, reported that the inhalation of high concentrations did, in fact, sensitize dogs to catecholamine-induced cardiac arrhythmias (28). In addition, the propellants also produced questionable sensitization to endogenously-released catecholamines resulting from audiogenic stimuli (28). The conditions described in these experiments, as well as many others, do postulate a mechanism for the sudden deaths resulting from aerosol abuse, but in no way pertain to the safety of the thousands of commercially available aerosol products currently in use today, assuming reasonable use of such products.

Toxicity of Cosmetic and Personal Product Aerosols

Antiperspirants and Deodorants

These have been reported to cause granulomas of the axilla (38), which are probably linked to a hypersensitivity to the zirconium, aluminum, or other heavy metal salts used in these preparations (12). While the few reported cases to date have resulted from using either lotion or stick deodorants, similar reactions may possibly occur in allergic individuals using aerosol deodorants or antiperspirants containing these chemicals.

Other toxic reactions reported to be associated with the use of antiperspirant/deodorant aerosols include: pulmonary granulomatosis (1), epithelial keratinization of the eye (9), and clogging of the sweat glands with subsequent infection (18). There have not been enough reported cases in any of these incidents to establish a definite cause-effect relationship.

Aerosol deodorants have been reported to produce "flashback" reactions in users of hallucinogenic drugs, such as mescaline and LSD. Two such

cases have been reported in teen-agers (4); and either Propellant 12 or a mixture of Propellant 11 and Propellant 12 has been implicated, although not conclusively.

Feminine Hygiene Deodorant Sprays

Such products have been reported to be no better than frequent bathing to keep the vaginal area free from unpleasant odors (24, 39). Despite this, they have caught on in popularity and are sold widely, probably because many women believe they need them, despite the opinion of some gynecologists to the contrary (40). There are certain formulation differences between vaginal and underarm deodorants, i.e., vaginal deodorants commonly have less alcohol and less perfume—in order to reduce the possibility of irritating the tender vaginal mucous membranes (41). Irritation is more likely to occur with vaginal than underarm deodorants because the user is more likely to spray the can longer, in that the spray is quite dry and there is little apparent residue. Also, the delivery rates of vaginal deodorants are likely to be higher than underarm deodorants because they are often packaged under substantially higher pressure. Propellant 12 is often used to reduce chilling (41).

The Food and Drug Administration has reported that reactions to the vaginal spray deodorants are usually due to one or more of the following: injuries resulting from the high pressure of the propellants; primary irritation from the alcohol, antibacterial chemical, or perfume; the rapid chilling effects of the propellants on the delicate mucous membranes or skin in this area; allergies to the antibacterial chemicals or perfumes (40). Women users have reported irritation of the skin or mucous membranes, vulvitis, weeping dermatitis, chemical burns, and various hypersensitivity reactions, such as pruritis, burning, and edema (7, 40). Some of the special anatomical features of the vaginal area that make it more susceptible to deodorant sprays include the apocrine sweat glands, the thin horny stratum, and the special bacterial flora of the vaginal mucous membranes (24).

Hair Sprays

Hair sprays have been implicated, in a cause-effect relationship, with the development of pulmonary granulomatosis (3) and blood dyscrasias (2) in chronic users of such products, possibly due to a hypersensitivity reaction. The resinous ingredients contained in these products have been reported to be the noxious agents. In several reported cases, radiographic examination of the chest showed infiltration of the lung field in users of hair sprays which cleared when the usage of these products was discontinued (3). However, several attempts to duplicate these human findings in rats (42), guinea pigs (43), and dogs (44), exposed to commercial hair spray preparations for as long as two years, failed to demonstrate any pulmonary pathology that could be attributed

to exposure to these products. The PAS-staining biopsy material, reported by Bergmann *et al.* (3) to indicate the presence of hair spray resins, was also found in the control animals (44). Furthermore, hematologic studies of dogs exposed to commercial hair sprays for up to 2 years (44) failed to demonstrate the blood dyscrasias (aplastic anemia, thrombocytopenia, and leukopenia) reported as being compiled from the AMA Department of Drugs Registry on Adverse Drug Reactions by DeNosaquo (2).

Further evidence of the safety of commercial hair sprays has been reported in two separate studies of hairdressers in Great Britain. In the first, John (45) studied 146 hairdressers, both men and women, who used hair sprays for between 3 and 5 years. Radiographic examination of these hairdressers, from 14 different salons, failed to demonstrate any pulmonary abnormalities. In a similar study by McLaughlin *et al.* (46), an X-ray survey of 505 hairdressers in Great Britain was reported. The hair sprays included both shellac-based sprays and sprays containing polyvinylpyrrolidone (PVP). In all groups a significant number of hairdressers had used the sprays for more than 6 years. No abnormal X-ray appearances, suggesting the presence of pulmonary granulomatosis (thesaurosis), were reported, despite the fact that the majority of particles in both types of hair sprays had a diameter of less than 1 μ and were thus capable of being inhaled. In a study of the particle sizes of hair sprays manufactured in the United States, at least 50% of the hair spray particles had a diameter of 35 μ or greater (47), which is larger than the size that is capable of penetrating the lungs to a significant extent. Further studies by Larson (47) also attest to the safety of commercial hair sprays. In this study, no differences in midexpiratory flow rate, measured spirometrically, were found between users of hair sprays and nonusers, in a controlled population of female college students. While the controversy over the safety of hair sprays continues, the bulk of scientific evidence at present indicates that earlier concerns over their safety is unfounded.

Toxicity of Household Aerosols

Because of the diverse nature of the products in this category, and the large number of users in all age groups, the toxicity of these products is of major interest to both the consumer and the aerosol industry. Other than the toxicity of the ingredients in a specific preparation, some of the factors contributing to the toxicity of the household aerosols include the pattern produced by aerosol spray (5) and the cooling action of the propellants (12). If the spray pattern of a product is not well controlled, particles intended for application in one place may well penetrate into the eye or impact on the skin. The impaction of particles from these products, because of the relatively high pressure exerted at release, may cause aerosol particles, that would otherwise be harmless, to penetrate the surface of the skin or the cornea of the eye, thus

making removal of the material difficult and increasing the likelihood of foreign body tissue reactions (5, 9). Spray keratitis, such as that just described, has been reported for hair sprays, insecticides, paint sprays, and deodorants (5, 9). Furthermore, the cooling and drying action of the propellants and/or solvents in a product may aid in the penetration of aerosol particles into the eye (5).

Predicting the toxicity of household aerosols in humans, as a result of screening studies in animals, is not easily accomplished. The anatomy and physiology of the respiratory structures in lower animals is different from man (34); also, diseased humans will often respond differently to a product than will healthy laboratory species. Another problem is the design of a suitable exposure chamber; assuming that the environment can contribute to the potential hazards of a household aerosol product, there is little equivalency between the exposure chambers commonly used in the testing laboratories to evaluate the potential toxicity of aerosol products and the actual rooms that humans live in when using such products (34). In general, though, despite the millions of units of household aerosol products consumed each year in this country, few toxic reactions are reported and, of those that are reported, approximately half are probably due to consumer error in following the instructions for use printed on the package.

Toxicity and Hypersensitivity

Toxicity is a function of a chemical compound and its reaction with biological tissues and can usually, but not always, be predicted from animal studies. It is the responsibility of the manufacturer of cosmetic and household aerosols to market products with a low order of toxicity; in general, this responsibility has been adequately accomplished. Hypersensitivity, or allergic, responses only occur in a small percentage of users of aerosolized products and, in general, cannot be adequately predicted from animal investigation. It is known, however, that persons with certain allergic diseases and/or a hereditary tendency towards respiratory and skin diseases may be more likely to elicit allergic reactions to many types of products commonly used in the home, including aerosols. There is little a manufacturer can do to reduce such adverse reactions to commercial aerosols, except to use ingredients which have been shown, through years of use or extensive laboratory and clinical testing, to produce a low incidence of hypersensitivity reactions. Other suggestions to reduce the incidence of aerosol-related allergy would be: pooling of reported allergic responses to products and ingredients; clinical testing on a wider scale to determine ingredients causing allergic responses; and limited marketing of new cosmetic or household aerosols, containing new ingredients, until the allergy profile is well established.

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Testing for Inhalation Toxicity

WILLIAM R. TROY, M.S.*

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Synopsis—The purpose of this review is to outline some of the fundamental considerations involved in testing for INHALATION SAFETY of COSMETIC PRODUCTS. Apart from design of the exposure system and selection of test animals, factors such as environmental controls, proper dose levels, and signs of TOXICITY to watch for are of prime importance when conducting such studies.

A discussion of three areas of concern with regard to the inhalation safety of cosmetic AEROSOLS is also included. The questions of hair spray "storage disease," possible aspiration of spray talc, and allegations of cardiotoxicity of aerosol propellants are treated with regard to experimental activity in these areas and what, if anything, has been proven to date by these investigations.

Introduction

Investigations in inhalation toxicity present some rather unique problems. Unlike most other cosmetic products, aerosols are afforded practically immediate access to the systemic circulation by virtue of their being inhaled into the highly vascular lungs. For this reason, the potential for toxicity for such products is greater than for formulations that are routinely applied to the skin such as flowing make-ups or body lotions. In addition to the possibility of systemic toxicity, there may also be localized adverse effects on the organs of the respiratory system by inhaled toxicants. Naturally, not even the slightest hint of either type of adverse effect would be acceptable for any cosmetic aerosol.

The following review has a twofold intention: first, to outline some of the equipment used in inhalation toxicology, parameters measured, and conditions necessary for proper investigation; and second, a discussion of the recent literature in the area of cosmetic aerosol toxicology.

*Avon Products, Inc., Suffern, N.Y. 10901.

Inhalation Methodology

Systems

The first factor to be considered with regard to the design of an inhalation experiment is the design of the exposure system. Many considerations, including the number and species of animals to be used, space available, nature of the sample, etc., are involved in the selection of equipment for this type of toxicity testing. There are two basic types of inhalation exposure (and several variables of these): head-only and whole-body exposure. In the former type of experiment, the animal may be in an enclosure which is external to the actual chamber; only its head protrudes into the chamber and is exposed to the test material. This approach finds frequent use in noncosmetic areas where the possibility of oral ingestion of the test material should be separated from the inhalation route of entry; oral intake of the material can occur quite easily if the whole animal is exposed and goes through the normal routine of preening its fur which has been saturated with an aerosolized product. A modification of the head-only type of exposure is one in which the aerosol is delivered through a face-mask which has been fitted to the animal; an antiasthma preparation was recently reported as having been tested in this manner (1).

The whole-body method of exposure probably best approximates the types of contact with which we must deal in the use of cosmetic aerosols. In exposing the entire animal to an aerosolized material, of course, it must be understood that in addition to conducting an experiment in inhalation toxicology, we are also performing qualitative tests in eye irritation, oral toxicity, and dermal toxicity since all of these organ systems are being exposed to the aerosol in addition to the lungs. It makes good sense, then, to fully investigate the potential for toxicity on these other organ systems before investing time and effort in an inhalation study.

Many different chamber designs have been suggested since the original plexiglass box used by Draize (2). In one type, the axis of orientation is horizontal and the test material is introduced on one side, while the chamber is evacuated on the other side. In a second type, the axis is vertical and sample movement is from top to bottom. The latter seems to be more popular and is generally used in conjunction with a chamber whose body is basically cubical and tapers towards the top and bottom.

Allusion was made to the introduction and distribution of sample. Again, there are two basic approaches available. In the so-called "static chamber" system, the dose of material is introduced into the chamber atmosphere, the system is sealed, and the animals breathe only the air which is present in the chamber. In the "dynamic" system, the gas or suspended liquid is introduced into a stream of air which is continuously sweeping through the chamber at a constant rate. With proper chamber design, good distribution of the aerosol is almost assured if the airflow is rapid enough.

No matter what type of exposure chamber is used, size is very important. This does not mean that a big chamber is better than a small chamber, or *vice versa*. The essential point is that the volume which the animals occupy within the chamber should be small in relation to total chamber volume; a generally accepted figure for animal volume is around 5% (3). In such a situation, especially in a long-term study, the inhaled doses are more easily standardized than if a large portion of the chamber volume is removed with each inspiration. This chamber-to-animal volume ratio is even more critical if a static exposure system is being used, because here the available oxygen is being used up and not replaced.

Animal Selection

It cannot be stated that, for example, "the rat is the animal of choice for inhalation studies." All species are obviously quite different and may react differently to the material being tested. Whatever animals are chosen, the species best suited to the particular experiment should be used. This means that the way in which the animal metabolizes the test material, for example, should be taken into account. The vital capacity of each species should also be a part of the calculation of dose.

Chamber Environment

As in the animal colony, the conditions of temperature and humidity within the inhalation chamber should be standardized—usually at 25°C and 50% relative humidity. Needless to say, there must be a sufficient level of oxygen for the animals to breathe, and there must be an efficient method of removal of expired CO_2 from the chamber. In a static system, these factors limit the length of time that the animals can be exposed.

The homogeneous distribution of gases or suspended liquids within the inhalation chamber is also of critical importance. This is affected by several factors; among them, method of generation of the aerosol, rate of airflow, and chamber geometry. Also to be taken into consideration is the equilibration time, that is, how long it will take the test material to attain a constant level within the chamber. If this is significant, then the overall duration of the experiment must be modified accordingly.

The duration of the experiment is variable and depends on the type of material to be tested and the intended dose level. A commonly used exposure time in a dynamic system is 4 hours per day. As mentioned above, this would be practically impossible in a static chamber, unless the chamber-to-animal volume ratio were extremely large. While the animals are in the chamber, there should be facilities for monitoring the concentration and, if desirable, the particle size of the test material in the experimental atmosphere; gas-liquid chromatography, infrared, and standard wet chemistry can be performed for analytical purposes. The techniques for particle sizing are many

and varied. They range from simple collection on a glass slide, followed by visual classification, to the sophisticated technique of laser holography. Again, the method of choice is the one that gives the investigator the information he wants within the realistic limitations of his experiment.

Length of Study

The overall duration of the experiment can be acute, subacute, or chronic. As in other types of toxicological investigation, the acute study is conducted to enable us to get an idea of the toxic potential of the material in question in relation to other materials. This is normally referred to as the LD_{50}—the amount of test material which will kill 50% of the population to which it is administered in one dose. In inhalation toxicology this value is called the LC_{50}, C representing the concentration of the material in air, and it is usually expressed with relation to time in terms of *ppm*, *mg/l.*, or mg/m^3. It should now be clear that it is even more important to know chamber and animal volume so that the nominal dose of inhaled material can be calculated.

In most cases, when dealing with cosmetic aerosols, the LC_{50} is difficult if not impossible to calculate because the airborne concentration of material which might produce death in the animals is impractically high. For this reason, the procedure of selecting some fractional multiple of the LC_{50} to use for the subacute study is inappropriate. Instead, the test material may be aerosolized at a nominal chamber concentration of 20–200 mg/m^3, the precise dose being left to the investigator's judgment and experience, and his understanding of how the product is intended to be used.

Chronic studies, which may run for 2 years, have rarely been used in the area of cosmetic inhalation toxicology. In the future, however, some emphasis may shift toward this variety of test, particularly with reference to the investigation of raw materials and aerosol propellants. Larger species of animals such as dogs or monkeys are many times preferred for such testing.

Observations

Throughout any inhalation experiment, the animals should be observed carefully and regularly for any visible signs of toxicity such as changes in behavior, physical appearance, locomotor activity, etc. In addition, before a subacute or chronic study is initiated, while it is in progress, and after its completion, the animals should be weighed and a record kept of their food consumption.

At the termination of the experiment blood samples are taken from the animals and the standard hematological parameters are examined; serum enzyme levels and other clinical tests are also performed. After sacrifice, tissues from the various organ systems are removed and fixed for histological sectioning. The histopathological findings can then be added to the gross observa-

tions at autopsy, and to the blood data, to get a picture of the effect of the test material.

Special Measurements

Besides histological examination of tissue sections, another parameter which may be of interest to the inhalation toxicologist is the observation of the mucociliary activity of the respiratory system. This activity is one of the ways that the lungs are protected from the deposition of foreign material. Basically, the cells lining the trachea, larynx, and upper airways have special modifications called cilia which are microfine, whisker-like projections from the free surfaces of these cells. These cilia have an inherent, rhythmic beat, whose total activity produces a wave-like motion directed towards the pharynx. In addition to the ciliated cells, interspersed among the latter are the so-called goblet cells which secrete a mucous substance. This mucous forms a blanket overlying the cilia so that fine inhaled particles may become entrapped in the mucous and removed from the respiratory system by movement of the blanket layer *via* the underlying cilia.

It is known that certain inhaled materials impede this mucociliary streaming, and some actually paralyze it. To determine whether it is still operating effectively, a fresh tracheal preparation taken from an animal that has been exposed to the suspect material can be examined. Usually, pollen grains or synthetic microspheres are placed on the tracheal membrane, and their progress between two fixed points is observed under a microscope. Another method for monitoring mucociliary function involves administration of an aerosol containing radiolabelled particles to an animal (usually of large size). The movement of these particles back up the airways is then monitored by scintillation detectors and their rate of clearance is determined.

If the inhaled particle escapes the mucociliary system and actually gains access to the alveoli of the lungs, it is confronted with a second system which is concerned with entrapment and removal of foreign matter. There is present in the interalveolar walls a specialized cell called the septal cell whose job it is to act like the policeman for the alveolus. In performing this function, termed phagocytosis, projections of the septal cytoplasm surround the particle, and then join, enclosing it within a vacuole. Soon after this, such a cell becomes detached from the alveolar wall. In this free state it is commonly referred to as an alveolar macrophage; it still participates in phagocytic activity, and it also appears to be capable of ameboid movement. It is by way of this movement that the macrophage reaches the ciliated lining of the airways through which it is carried toward the nasopharynx, where it enters and is swallowed.

The possibility exists that the septal cells too may be adversely affected by aerosol inhalation. The most common derangement might be a simple over-

loading of the system—that is, too much foreign material entering the alveoli for the septal cells to handle efficiently. In such cases, foreign particles may penetrate the alveolar membrane or otherwise enter the interstitium. In this case, the particle is transported to a satellite lymph node whose purpose it is to drain the lung tissue. From there, it may then enter the blood stream. Another alternative is that the particle or group of particles may not be cleared by the lung at all, but rather be sequestered in the lung tissue and walled off by reactive fibrous tissue formation; this is referred to as pneumoconiosis. This pathological condition may be entirely benign and have no real long-term adverse effect on the individual, or, on the other hand, it may lead to a slowly developing, steady deterioration of lung function.

A third system in the lungs which may suffer toxicological effects of aerosol inhalation is the pulmonary surfactant. It is this biochemical substance (thought to be a mixture of lipid, protein, and possibly carbohydrate) which is responsible for evening out large differences in alveolar surface forces due to differences in their size during respiration. If it were not for the presence of this substance, the alveoli would tend to collapse, and each breath would become increasingly more difficult. Impairment of the pulmonary surfactant, through inhalation toxicity, then, would have obvious consequences. The surfactant is also related to the alveolar clearance mechanisms in that movement of the septal cell out of the alveolus and up into the airways actually occurs in the surfactant bathing these surfaces. Measurements of the surface tension of pulmonary washings has been used to study this parameter.

Problems in Cosmetic Aerosol Toxicology

Inhalation Toxicity of Hair Sprays

The first area for this discussion of some of the problems that have arisen in the field of cosmetic aerosol toxicology will be the allegations concerning the use of hair sprays. These questions have been around for almost as long as aerosolized hair sprays have been in existence, but, as will be seen, extensive animal testing and human clinical observations have failed thus far to prove any of the charges.

In 1958, Bergmann published a paper (4) in which he described certain findings in X-rays of the lungs of two female patients. In addition to darkened areas of the lungs (indicating fibrous tissue formation), he biopsied the lymph nodes associated with drainage from the lung and found a large number of granules which reacted positively with the Periodic Acid–Schiff histological stain. As a result of his findings, Bergmann concluded that he had uncovered a new clinicopathologic entity, which he called "pulmonary thesaurosis."

Within a year, a second paper appeared (5) describing another young woman with similar findings; the diagnosis of thesaurosis was also made here. And again, 2 years later, a fourth case was reported and similarly diagnosed

(6). In 1962, Bergmann published a second paper (7) in which he offered 12 further cases which he had diagnosed as pulmonary thesaurosis resulting from inhalation of hair spray. As with his previous paper, however, his case was built around the presence of PAS-positive granules in the lung and lymph tissue which he took to be evidence of polyvinylpyrrolidone resin from the hair spray.

In the meantime, several reports were published on the efforts to induce thesaurosis-like changes in the lungs of animals (2, 8–11). It was found that, indeed, PAS-positive granules could be demonstrated in the lung tissue after exposure to hair spray by inhalation, but that they were present to an equal extent in both treated and control animals. In addition, an *in vitro* procedure for staining the PVP resin with PAS yielded a negative result (9). As for the tissue changes, a study was performed in which rats were exposed to aerosolized PVP for 8 hours a day, 5 days a week, for one month (11). The concentration used, 146 mg/m^3, is equivalent to discharging a typical 13-ounce can of hair spray continuously for about 1½ minutes in a room measuring 8 x 8 x 8 feet, and then maintaining that level for the duration of the test. Histological examination of the lungs was carried out immediately following the study, and at 1, 3, 4, and 6 months after completion. Lung tissue from the animals sacrificed immediately and at one month showed no structural changes. At 3 months, mild peribronchial lymphoid hyperplasia or fibroplasia was seen. In none of these sections was PAS-positive material found. At 4 months, however, PAS-positive particles were seen in the peribronchial lymphatics, and also at 6 months. At no time were any inflammatory changes seen in the lungs, nor did the authors feel that the PAS-positive reaction was due to the staining of PVP itself, but was probably some material coating the particles. The fact that PVP could be identified in the lung tissue by chemical analysis following this extremely high level of inhaled resin, but that nothing suggesting granulomatous lung disease was seen at autopsy up to 6 months after completion of the study, is perhaps the most important finding here.

At this point, then, the state of knowledge on this problem was that the diagnosis of pulmonary thesaurosis in humans hinged on the demonstration of PAS-positive granules (which, incidentally, were found in lung tissue taken from persons who had never been exposed to hair spray) (12). In addition, the signs seen in humans could not be reproduced in animals, even by heroic means. Since animal studies alone, however, could not really exclude the possibility that this might be a phenomenon unique to humans, several investigators decided to undertake surveys involving human subjects. It was anticipated that if such a thing as hair spray thesaurosis could be produced in humans, it would certainly be seen to a much greater extent in a group that had been subjected to high concentrations of the suspected agent for long periods of time; professional hairdressers seemed ideally suited to this purpose. During the period 1963–72, over 2200 such hairdressers, the ma-

jority of whom were female, were examined by 10 different investigators utilizing chest X-ray (13–22); the reports came from England, France, Germany, and the U.S., and conclude unequivocally that no symptoms such as were seen by Bergmann *et al.*, and which could be diagnosed as pulmonary thesaurosis, had been seen in any of the subjects. Notably, however, one case of a lung disorder called sarcoidosis was uncovered in a group of 114 in the U.S. (19), and a second diagnosis of sarcoidosis made from a group of 596 in France (20). Because of many diagnostic similarities between sarcoidosis and the proposed thesaurosis, many investigators began to have doubts as to whether the two were distinct clinical entities.

During the same period that the hairdressers were being surveyed, solitary cases diagnosed as hair spray thesauresis continued to be reported (15, 22–24). More care appears to have been taken in the diagnosis of some of these later cases (9 in number), sarcoidosis having been specifically eliminated in a few of them. So while there is no real evidence to date to link the use of hair sprays to harmful effects on the lungs, the possibility continues to be suggested. It therefore remains the responsibility of industry to continue a program of investigation to settle the issue for once and all. The ultimate question will not be whether thesaurosis or sarcoidosis is the proper diagnosis, but whether these are real, pathological effects on lung tissue as a result of the inhalation of hair sprays.

Spray Powders

Another cosmetic product which has received attention as a potential inhalation hazard is talc. The most common toxicological consequence of misuse of this material seems to be accidental aspiration of large quantities which choke off the airways and overwhelm clearance mechanisms (25–27); this occurs most frequently in young children.

Recently, there was a brief uproar surrounding asbestos contamination of the talcs being used in cosmetics. The concern which followed the original report arose because certain forms of asbestos have been implicated in the production of cancer in man and animals; the insidious nature of the carcinogenesis, in that it takes up to 20 years to manifest itself, was the main motivation for the initial reaction. However, upon closer investigation of the problem, it was found that the asbestos forms that are implicated in carcinogenesis (chrysotile, amosite, crocidolite, and anthophylite) were not present in the talcs used for cosmetics. Another variety, tremolite, for which there is no evidence of carcinogenic hazard, was identified as being present at concentrations of less than 5%.

Even though carcinogenicity does not seem to be a potential problem, then, as far as the talcs are concerned, they should still be subjected to rigorous inhalation testing the same as other aerosolized products.

Propellant Toxicity

Possibly the most sensitive problem currently concerning aerosols and their safety is the question of propellant toxicity. An attempt will be made here to briefly recap some of the inhalation toxicity testing that has been done on the propellants, and then to discuss the recent reports which charge that they are unsafe.

More than 30 years ago, the Underwriters Laboratories designed inhalation studies using guinea pigs which exposed them to the Freon®* propellants for different lengths of time. The result was a classification, based on the relative inhalation toxicity of these and other materials, that was divided into 8 groups. For purposes of this discussion, the most significant facts to come out of this rating were that Propellant 11 was put into the same category as carbon dioxide, and that Propellants 12 and 114 were two categories removed from this and classified as less toxic than CO_2.

More recent animal studies (28) have reported that when a concentration of 0.08% dichlorodifluoromethane (Propellant 12) is breathed for 8 hours a day, 5 days a week, for a total of 30 exposures, or when it is breathed continuously around the clock for 90 days, some liver damage appears to result in guinea pigs, but not in rats, rabbits, dogs, or monkeys. To put this into perspective, this is approximately the level of P-12 that would be present in an 8 x 8 x 8-foot bathroom if the entire contents of a standard can of aerosol deodorant were discharged in that room (an effort requiring about 4¼ minutes of continuous spraying).

Similar experiments (29) using trichlorofluoromethane (P-11) at 0.1% for a continuous 90-day exposure, or at 1.0% for the 8-hour a day, 30-day regimen, demonstrated no organ changes, and only very minor deviations in certain biochemical parameters in dogs; no effects were seen in rats, guinea pigs, or monkeys. Several other investigators support these findings (2, 30–32). It can be concluded, therefore, that these compounds are practically inert with regard to toxicity when they are dispensed in an aerosol product in a normal fashion, or even when used to excess, for the purpose for which they were designed.

During the late 1960's, however, it began to become apparent that products containing these propellants were being used for something other than their intended purpose. In 1970, Bass (33) reported on this phenomenon; increasing numbers of young people were inhaling volatile hydrocarbons for the sensation of "high" that they produced. Between 1966 and 1969 a tremendous upsurge in this unique form of abuse was noted. The mechanism is rather simple: the contents of an aerosol are discharged into a plastic or paper bag, and the volatilized, concentrated propellants are then inhaled. Bass also noted,

*E. I. du Pont de Nemours & Co., Inc., Wilmington, Del. 19898.

however, a large increase in the number of sudden deaths immediately following inhalation; in many of these cases, some exertion or stress had directly preceded the death. Reasoning that most of these people were oxygen-deficient as a result of confining their breathing to the contents of the bag, and realizing that, as has been known for many years, halogenated hydrocarbons will sensitize the heart to the effects of epinephrine, he hypothesized that the stressful activity had resulted in the endogenous release of epinephrine in the victim, and that sensitization by the fluorinated hydrocarbon propellants had resulted in a fatal cardiac arrhythmia.

Also during the 1960's, an epidemic of sudden deaths among asthma-sufferers who used aerosolized bronchodilators was noted (34). This large increase in the death rate seemed to be confined, however, to England and Wales, Ireland, Scotland, New Zealand, and Australia and reached a peak around 1967, after which the rate declined.

Putting these two phenomena together, Taylor and Harris published a paper (35) in 1970 in which they presented experiments that purported to support their theory that the asthma deaths had resulted from cardiac toxicity induced by the propellants in the victims' nebulizers. Since its publication, debate has continued on the errors in design and conclusions of this study, but unfortunately, the damage has been done to the confidence of the asthma patient in his medication and to the general confidence of the consumer in aerosolized products. One major fault in these experiments was that the mice that were used were administered one puff from an antiasthma nebulizer, discharged directly into their nose and mouth. The normal volume of air inspired by a mouse varies from 0.20–0.25 ml, so that the 6.5 ml of propellant gas delivered by the nebulizer assured that the animal would breathe 100% propellant for the three inspirations which it was allowed. The normal volume of air inspired by a human is about 450 ml, approximately 1800 times that of the mouse, so that the propellants would normally be inhaled by a human at a concentration of about 1% of the inspired air in the initial breath.

In addition to this, the head of the animal was thrust into a tightly-fitting plastic bag after exposure to the nebulizer until cardiac abnormalities appeared on the electrocardiograph. The purpose of this bag was to simulate the lack of air which asthmatics may suffer before using the nebulizer. Taylor and Harris reported serious cardiac arrhythmias following propellant plus asphyxia, but none following asphyxia alone of up to 4 minutes. Investigations by 5 different laboratories (36–40) have been unable to duplicate these results and have found that the asphyxia component alone is sufficient to induce serious changes in cardiac rhythm. In a recent answer to his critics, Harris (41) now contends that the asphyxia originally described as being induced by ". . . a form-fitting plastic bag wrapped tightly around the nostrils and mouth . . ." (35) was actually only partial asphyxia. It is for this reason, he states, that his asphyxia alone did not result in arrhythmias.

In addition to all of this, it has been shown that the blood half-life of P-11 is between 0.3 and 1.5 min, while the maximum blood concentration measured after two consecutive puffs from a nebulizer was 2.6 μg/ml (42). It is known that at least 10 times this level is required to cause cardiac sensitization in nonanesthetized dogs when challenged with intravenous epinephrine (43, 44).

We can safely conclude, then, that the propellants were not the culprits in the increase in asthma deaths. Just as a point of information, it has been reported (45) that this increase coincided with an increase in sales of one brand of nebulizer which contained 5 times the concentration of isoproterenol as was present in the other brands; in addition, this more potent formula was not licensed for sale in this country, but was sold in the countries which experienced the epidemic of sudden asthma deaths. The myocardium of the dog has been shown to be particularly sensitive to isoproterenol when arterial oxygen tension is low (46), as would be the case in a severe attack of asthma.

Although the aerosol propellants were not implicated after all in these deaths, there is still a great deal of concern over their safety as a result of the findings of several investigations which may have been stimulated by the original, unfounded charges. One of the first such studies which supplied critical data on this problem was conducted by Reinhardt and his group (47). Briefly stated, they found that conscious dogs breathing a minimum of 0.35% P-11, or about 10 times as much P-12, experienced serious cardiac arrhythmias when challenged with an intravenous injection of epinephrine; the concentration of epinephrine approximated the amount thought to be released under conditions of stress. Additionally, they found that when the animal breathed 80% P-11 for 30 sec, and was then frightened by a loud noise to stimulate endogenous epinephrine release, serious disturbances in heart rhythm could be produced in some of the dogs. Using barbiturate-anesthetized dogs, Flowers and Horan (48) have reported similar findings when the animals breathed the propellant gases from a plastic bag and were also given oxygen supplementation to prevent anoxia.

A second study by Taylor *et al.* (49), better planned than the first, subjected monkeys to inhalation through an endotracheal tube of an air mixture containing 30% P-12 and 9% P-114. They reported several different types of arrhythmias in response, without the use of injected epinephrine. Further work has also been done by Reinhardt's group (50). Using conscious beagle dogs which were running on a treadmill, they exposed the animals to atmospheres containing P-11, P-12, or P-114. Up to 1.0% P-11 produced no cardiac arrhythmias. At a level of 5.0% P-114, and 10.0% P-12, ventricular arrhythmias were produced in one of the dogs.

For purposes of comparison, to return again to the calculation for propellant released by total discharge of a can of deodorant, we find that even the lowest level of P-12 which had an adverse effect on the heart in the above ex-

periments (i.e., 10.0%) is about 100 times higher than the total amount of P-12 available in such a can when discharged into an 8 x 8 x 8-foot room, and the effective level of P-11 is at least 10 times that available. Use conditions for this aerosol deodorant would mean about 10–15 sec (at most) of propellant discharge, producing a 0.005% concentration of P-12 in this room. Multiple use of several different aerosol products would not even begin to generate propellant levels such as are necessary for, or even close to, producing cardiac arrhythmias.

It has been known for more than 60 years that halogenated hydrocarbons, such as chloroform, are capable of sensitizing the heart to epinephrine. Originally intended for use as refrigerants, and then utilized in aerosol devices, the fluorinated hydrocarbons were carefully tested for their toxic effects after inhalation of concentrations that were thought to be far in excess of any possible perversions of use. As it turns out, however, it was not contemplated that they would be sprayed into a bag and then inhaled at a concentration of upwards of 80%. Abuse of this type is impossible to control and difficult to prevent. However, it must be kept in mind that this is an unintended misuse of the product, practiced by an extremely small percentage of the people who use aerosols. Fortunately, it appears that this fad may have run its course (or that the word may have spread about the inherent dangers), because the frequency of reports in the literature has declined greatly since the peak in 1969–71.

We must admit, then, that as our aerosol products are made today, there is a possibility for abuse. However, there is absolutely no evidence yet to show that the fluorinated hydrocarbon propellants, at levels that would be encountered during normal, or even exaggerated, use, have any deleterious effects on the user of a cosmetic aerosol. The cosmetic industry, through the CTFA and CSMA, has taken a very responsible position on the issue of propellant toxicity and has commissioned several studies into the effects of these propellants on both animals and humans. In addition, they have instituted an educational program in which school-age children are shown a film dealing with the dangers in propellant abuse.

While the last word has yet to be spoken on the ultimate safety of the aerosol propellants, this author hopes that when it is, it will be based on scientific evidence and not on purely emotional considerations. The difference between conditions of use and those of gross abuse are great, and must be taken into account when any statements are made about propellant safety.

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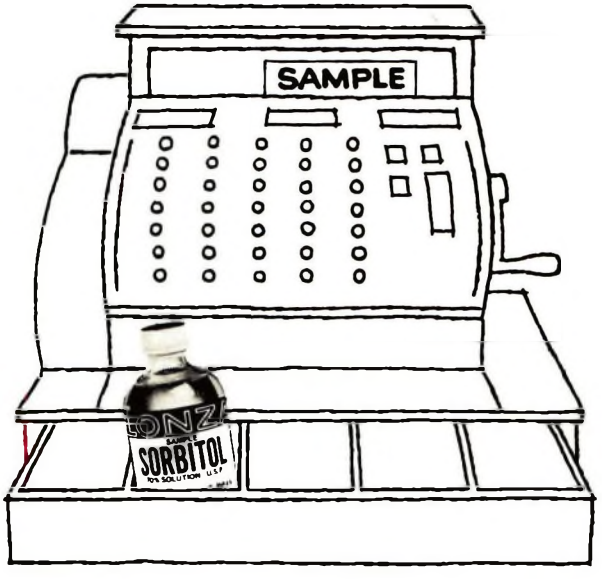

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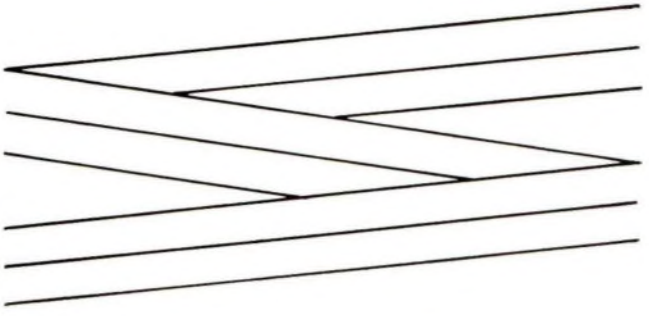

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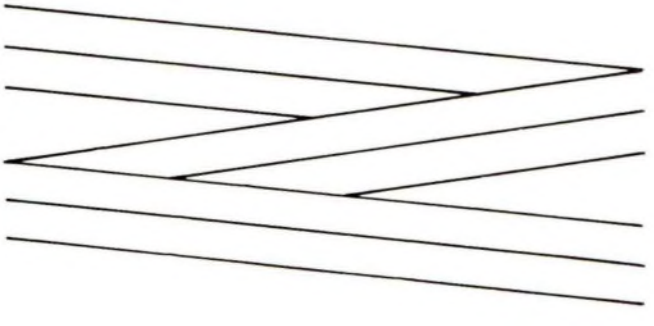

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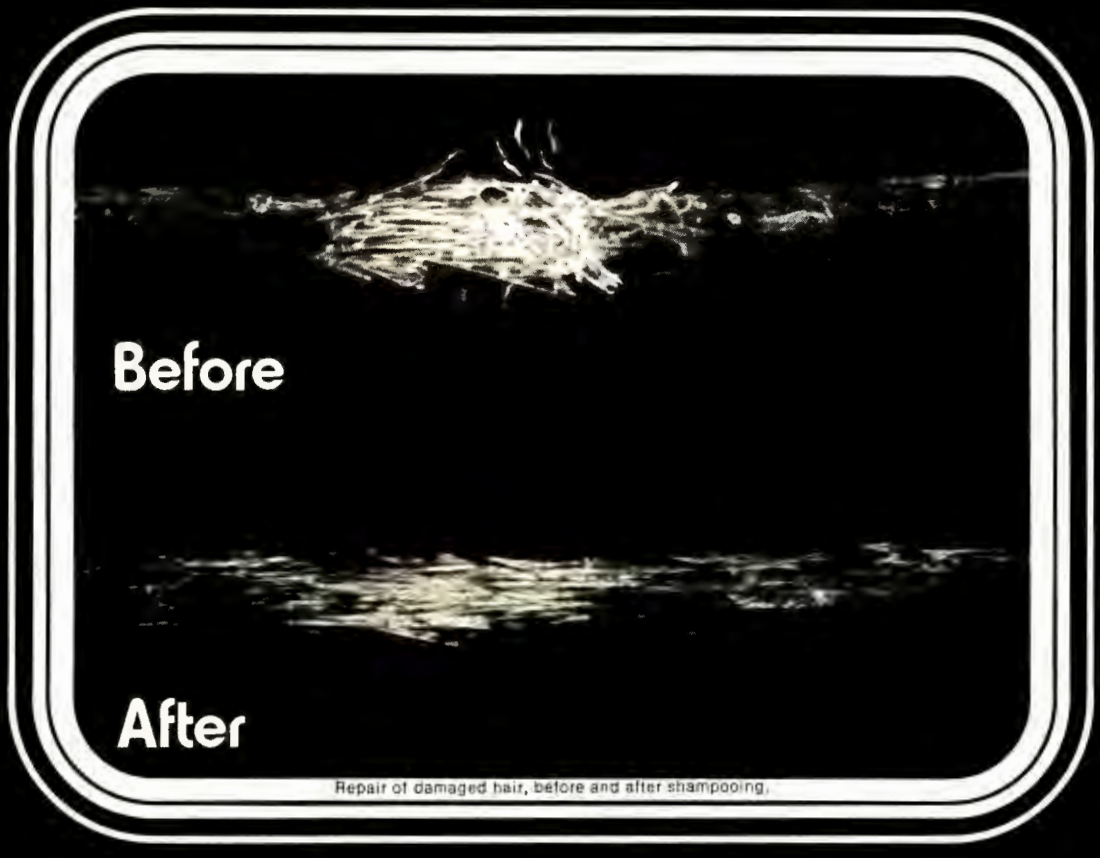

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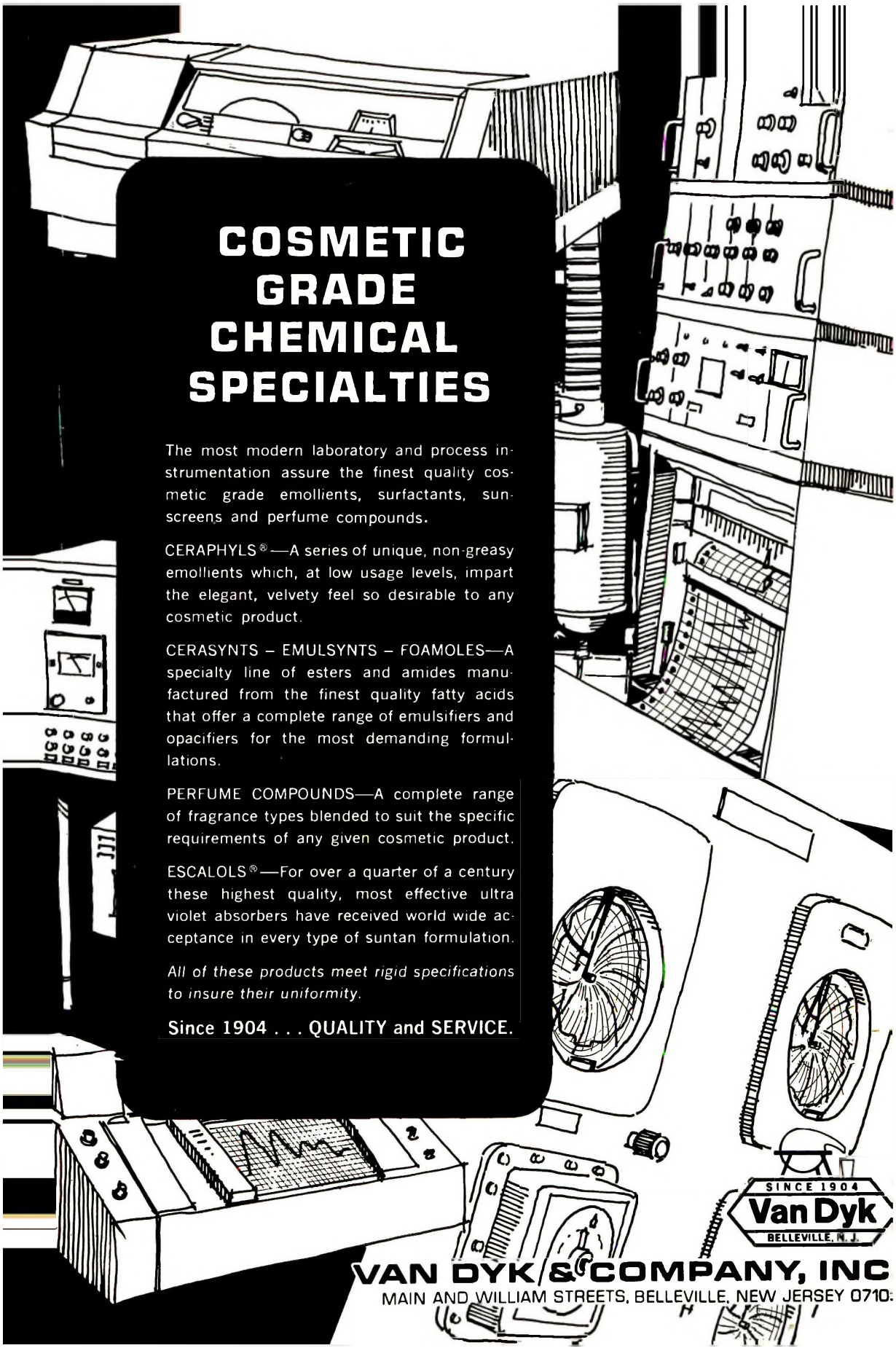

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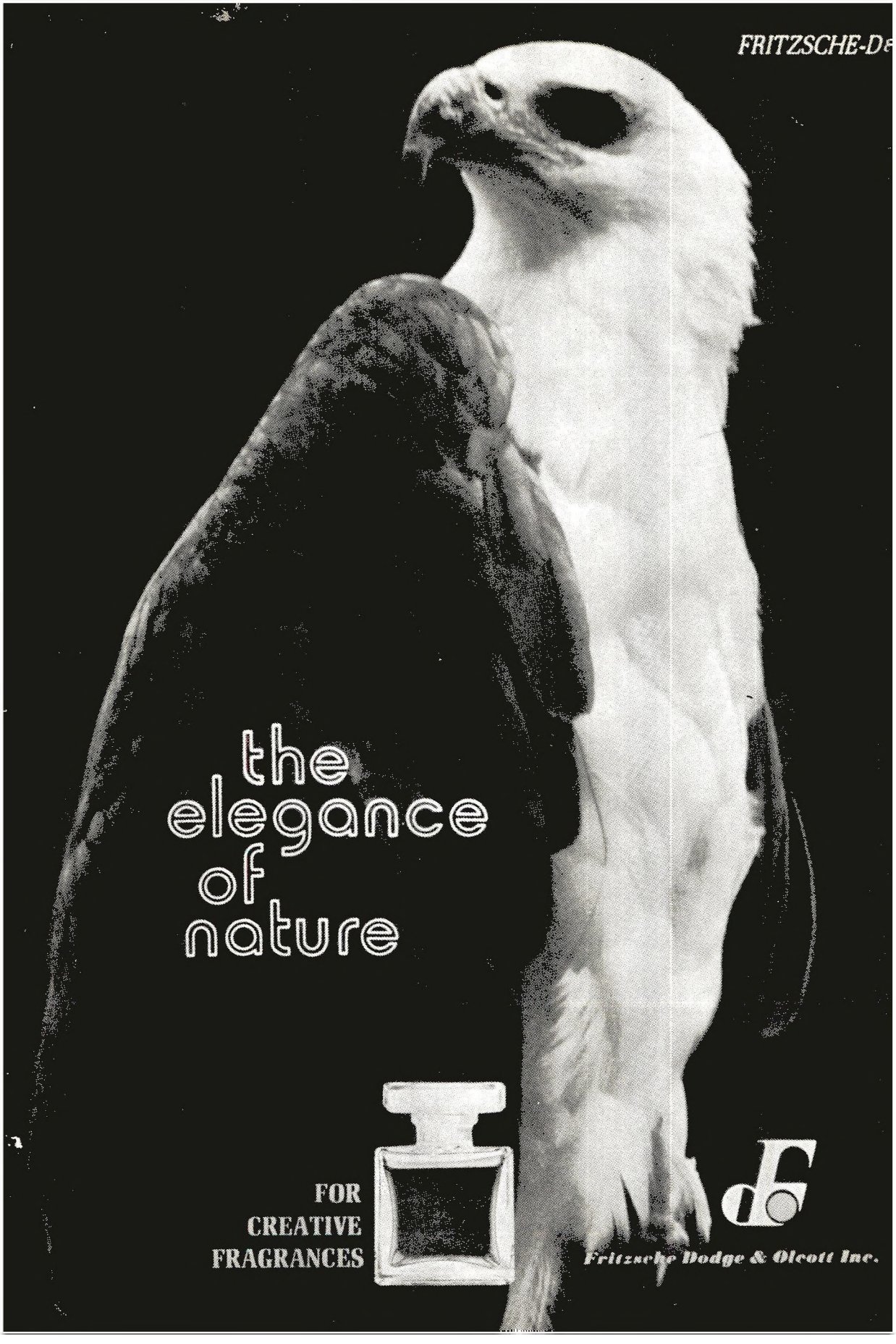
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