Selective removal of sebum components from hair by surfactants

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Synopsis

The detergency of three surfactants, sodium laureth-2-sulfate (SLES-2), ammonium lauryl sulfate (ALS), and sodium octeth-1/deceth-1 sulfate (SODS-1), was measured; variables examined were soil/wash cycles plus sebum component vs total sebum removal. After one soil/wash cycle SLES-2 cleans all sebum components from hair equally well (>90%). ALS is not as good, and SODS-1 is poor for all fractions.

With extended use (ten-cycle data), SLES-2 remains superior for all components (>90% removed), but the behavior of ALS and SODS-1 are substantially different from their one-cycle behaviors. Analysis of tresses washed with ALS under test and simulated use conditions suggests a build-up of fatty acid components on hair; this is interpreted in terms of a hard water ion/fatty acid interaction. Extended use data of SODS-1 show increased removal for all components when compared to the one-cycle data, suggesting either a soil release mechanism or inhibition of soiling.

We hypothesize that a technique that provides a rapid assessment of total sebum removed from hair by a detergent can be used to screen surfactants. However, to model extended use behavior, it is useful to monitor the removal of sebum components.

INTRODUCTION

Effective formulation of hair cleaning products begins with an understanding of the substrate. Perhaps of equal or even greater importance is the type of soil found on the substrate and how it is bound to the fibers. Human hair has a chemical composition, physical properties, and histological structure similar to other keratin fibers. However, the cleaning of hair presents a different, and possibly more difficult, problem because of safety restrictions. The use of fairly low temperatures and short cleaning times adds further restrictions. In comparison, products for cleaning textiles do not have to meet such restrictive criteria.

Soils on human hair can be divided roughly into four groups:
(a) Hair lipid, a fatty material composed mainly of sebum (from sebaceous glands) and lipids (from skin surface cells).
(b) Proteinaceous matter from cell debris and sweat.
(c) Extraneous materials from a polluted environment (soot, hydrocarbons).
(d) Hair product soils, e.g., conditioners, hair sprays, mousses, gels, etc.

The perception of dirty or oily hair is probably attributable to hair lipids. These materials may be sticky and can act like a "cement," causing various particulates to stick to the hair surface.

Sebum production is variable (1). This variation is documented to be seasonal, daily, and due to hormonal activity, with changes from preadolescence, through puberty, and into old age. Compositional changes also occur with both subject age (1), and as the sebum ages (1), after distribution on the hair. Furthermore, evidence exists for the classification of hair sebum into two types: external or surface sebum, and internal sebum (2). External sebum contributions combine with the physical properties of the hair fibers (curliness, diameter) to furnish hair with an oily appearance. It is reasonable to assume that the external sebum, which is easily extractable into lipid solvents, can be shampooed off, while the internal lipid is more difficult to remove. In fact, very strong extraction procedures and enzymatic hydrolysis of hair keratin (2) is needed to remove this material. The exact origin of the internal lipid is under debate, but Koch et al. (2) have provided evidence that most of the components are those found in external lipid. This suggests at least partial origination of these lipids from the sebaceous glands.

Several published papers detail methods for extracting hair lipid (external and internal) both in vitro and in vivo (1-4) and for quantifying the data. There are obvious disadvantages in collecting lipid in vivo by solvent extraction. Gravimetric analysis, because of the small quantities involved even after in vitro extraction, requires sensitive weighing equipment and care.

Several authors have carried out compositional analysis of extracted lipid/sebum. Shaw (5) used gravimetric and spectrophotometric methods to assess total lipid, a fluorimetric technique to determine cholesterol, and thin layer chromatography (tlc) and gas-liquid chromatography (glc) to distinguish between major components of the lipid. Koch (2) determined the total amount and composition of extracted sebum by high pressure liquid chromatography (HPLC). Breuer (6) also reports data for quantifying components of extracted sebum using an HPLC technique. Thompson et al. (7) have described a gas chromatography system for the analysis of sebum components extracted into hexane from hair (in vitro).

This work arose from our use of a modification of the Thompson et al. technique to determine the extent to which a test measuring total sebum removal from wool (by surfactants) was applicable to predicting surfactant performance against sebum, and to investigate certain surfactants of proprietary interest. Thus this work builds upon the published study of Thompson et al. We believe that the knowledge acquired in determining surfactant selectivity for removal (cleaning) of sebum components from hair can provide important guidance for formulating shampoos and other hair cleaning products.

MATERIALS AND METHODS

ARTIFICIAL SEBUM

The artificial sebum used in all experiments was prepared according to the Spangler formula (8) shown in Table I.
**Table I**

Artificial (Spangler) Sebum (8)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic acid</td>
<td>5.0</td>
</tr>
<tr>
<td>Squalene</td>
<td>5.0</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>10.0</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>15.0</td>
</tr>
<tr>
<td>Olive oil</td>
<td>20.0</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5.0</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>5.0</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>10.0</td>
</tr>
<tr>
<td>Paraffin</td>
<td>10.0</td>
</tr>
<tr>
<td>Spermaceti wax</td>
<td>15.0</td>
</tr>
</tbody>
</table>

**HAIR SUBSTRATE**

In all experiments, dark brown, Oriental hair, virgin quality and of 10-inch length was used (DeMeo Brothers, New York). Prior to soiling with sebum, the hair was divided into approximately 3.5-g tresses, washed with 10% TEALS (Standapol T, Henkel) for one minute, rinsed for two minutes under running tap water (105°F), and air dried at room temperature. Tresses were conditioned in a humidity room, 70°F and 60% relative humidity, for 72 hours prior to soiling with sebum. All subsequent weights of hair were made after similar temperature and humidity conditioning.

**SURFACTANTS**

SLES-2 and ALS were obtained from Henkel Corporation (Standapol ES-2 and Standapol A, respectively), and SODS-1 was obtained from VISTA Chemical Company (Alfonic 8,10–20 ether sulfate). The surfactants were used as provided by the manufacturer, with no further purification. Solutions were prepared with deionized water.

**HAIR-SOILING PROCEDURE**

Hair tresses were soiled by suspending a preweighed tress in a solution of sebum in hexane (3.5 g hair/250 ml solution), at the required concentration. After 20 minutes in the sebum solution (with constant stirring), the hair was removed and the solvent allowed to evaporate from the tress at room temperature. After conditioning at 60% relative humidity, the tress was weighed to determine the sebum load. Soiling solutions of 6 and 3 weight percent sebum were used. A 6% solution was used for soiling tresses subsequently washed with 0.01% surfactant (soil/wash condition A) one-cycle experiment. The 3% concentration was used for soiling 1.8-g tresses of the ten-cycle experiment and for soiling tresses washed with 0.1% surfactant (soil/wash condition B). These sebum concentrations produce soiling levels on the tresses of approximately 0.04–0.055 g soil/g hair and 0.03 g soil/g hair, respectively. Hair soiled with the 3% solution is perceived to be “dirty” or “oily” (corresponding to that on heads of consumers who shampoo frequently), whilst tresses soiled in a 6% solution are “very oily,” representing perhaps an extreme in hair oiliness for most Western cultures.
The higher soiling level, however, was most often used in this work as it facilitates the subsequent gc analysis of the sebum.

After the soiled tresses were dry, each was split into two swatches of about 1.7 to 1.8 g each. One of each pair was washed with the appropriate surfactant. The other portion remained unwashed and acted as an internal control. This was necessary to compensate for sample-to-sample variation in soiling levels.

**TEN-CYCLE SOIL/WASH EXPERIMENT**

For the ten-cycle soil/wash experiment, the tresses were split as described above, with one swatch kept as control. The other portion was then washed and dried (described below) and placed in a constant humidity room overnight. The next day these tresses were soiled again with sebum, allowed to dry at room temperature, and placed in the constant humidity room overnight. The following day the tresses were again washed with the appropriate surfactant. This soil/wash cycle was carried out ten times. The order for both soiling and washing procedures was randomized.

**HAIR-CLEANING PROCEDURE**

Cleaning of the soiled tresses was achieved using a bulk process similar to that described in reference 7. The soiled hair tress was suspended in 100 ml of either 0.1% or 0.01% aqueous surfactant at 110°F and agitated (magnetic stirrer) for five minutes. Tresses were then rinsed under running tap water (105°F) for 20 seconds (total rinse volume 500–600 ml). Heat from a hand-held drier was applied for one minute and the drying completed at room temperature. Conditioning in the humidity room followed.

These surfactant concentrations are very low and for SODS-1 are below the cmc. Since oily soil removal occurs through solubilization via micelles, we would expect poor results with this surfactant. In fact, even at concentrations above the cmc, SODS-1 is a poor detergent for removing oily soil. It is included in this study as a negative control.

**EXTRACTION OF SEBUM FROM HAIR**

Before the sebum residues were extracted, all tresses were placed in a forced air draft oven at 55–60°C for four hours. This helped to ensure a uniform moisture content throughout the sample set. About 1 g of hair from each tress was weighed into a vial, 20 ml of hexane added, and the sealed vial shaken on a mechanical shaker for 30 minutes. Hexane was used as the extraction solvent based on data presented in reference 7. These data claim chromatographic profiles of the hexane extract of sebum-soiled tresses to be comparable to profiles of standard sebum/hexane solutions.

After shaking, 15 ml of solution was pipetted from each vial into a previously weighed second vial. The sample was evaporated to dryness (at room temperature) by gently blowing filtered nitrogen over the liquid surface. Subsequently the vials were weighed to estimate total extracted sebum, and the residues analyzed by gas chromatography to determine sebum composition. Sample residues were dissolved in hexane containing internal standard, Eicosane, to a concentration of approximately 6 mg/ml. Sample injection amount was 0.4 microliters. The analyses were performed on a Carlo Erba Mega 5360 High Resolution Capillary Gas Chromatograph fitted with a cold on-column.
injector and a flame ionization detector. The column is a Supelco 60 meter × 0.75 mm i.d. glass column coated with SPB-1 liquid phase to a film thickness of 1.0 microns. Detector temperature was 325°C. GC oven initial temperature was 220°C, held for eight minutes, ramping up to 310°C at 4°C per minute, and holding for 55 minutes. Figure 1 is a typical gas chromatogram of Spangler sebum; we confirmed peak identifications by mass spectrometry. Note that triglycerides are not detected under the column conditions used; previous data indicate that these materials are easily removed by surfactants (7). We intend to modify our chromatographic system to test this conclusion ourselves.

RESULTS AND DISCUSSION

The objective in this work was to determine if surfactants selectively remove sebum components from hair. Tresses were washed in dilute (0.01 to 0.1%) bulk (100 ml) detergent solution rather than attempting to simulate actual shampooing, because Thompson et al. (7) have shown similar results with improved precision by the bulk method.

These low detergent concentrations are used to facilitate analysis of the sebum residues on the hair. If higher concentrations are employed, the recovery and subsequent analysis of the sebaceous residue is not practically feasible because of the very small amount of

![Figure 1. Capillary gas chromatogram of Spangler sebum. 1. Tetradecanoic acid; 2. hexadecanoic acid; 3. n-eicosane (internal standard); 4. 9, 12-octadecadienoic acid; 5. 9-octadecanoic acid; 6. octadecanoic acid; 7. n-docosane; 8. n-tricosane; 9. n-tetracosane; 10. n-pentacosane; 11. n-hexacosane; 12. n-heptacosane; 13. n-octacosane; 14. squalene; 15. n-nonacosane; 16. hexadecyl dodecanoate; 17. n-triacontane; 18. n-hentriacontane; 19. cholesterol; 20. hexadecyl tetradecanoate; 21. n-dotriacontane; 22. n-tritriacontane; 23. hexadecyl hexadecanoate; 24. octadecyl hexadecanoate and hexadecyl octadecanoate; 25. higher molecular weight ester.](image-url)
residue that is recovered. However, experiments in which soiled hair was handwashed using 10% surfactant, simulating actual use conditions, have shown results similar to those reported here for these test conditions (9). These handwashing tests are discussed later in the text.

Five replicates for each of the following three surfactants have been performed:

- SODS-1—Sodium octeth-1/deceth-1 sulfate
- ALS—Ammonium lauryl sulfate
- SLES-2—Sodium laureth-2 sulfate

The surfactants were chosen on the basis of total sebum removal data obtained using a wool substrate as a model keratin (9). Briefly, sebum removal from wool swatches is measured by monitoring the removal of a lipid-soluble dye (coadsorbed with the sebum) using a reflectance technique. These data (Table II) show that the surfactants may be considered as poor (SODS-1), medium-good (ALS), and good (SLES-2). Data are also shown for a second set of soil/wash conditions (B) (0.03 g soil/g hair; 0.1% surfactant); values are averages of three replicates. As evidenced in Table II, values for the total sebum removed are in good agreement for the three experimental conditions (and two substrates) shown. For both A and B conditions, the amount of soil removed from hair is larger or equal to that for a wool substrate. The order of superiority of surfactants is also maintained (agreement with detergency theory), and the wool and hair values are close in magnitude. The total sebum removed under B conditions is larger than for A: as expected, the combination of lower soil loading and higher detergent concentration promotes better cleaning.

The methods used in this work, soil/wash conditions and component identification, have been adapted from work reported in the literature (7). Three cleaning processes were described (7): bulk bath, finger squeeze, and controlled pressure/sponge; the data show that the bulk bath method produces the most uniform results. Therefore, we have used the bulk method to provide as much precision in our experiments as possible and have drawn conclusions by statistical analysis of the data using a p value of 0.05 as the decision criterion. The conclusions in the Thompson paper (7) are based upon the less reproducible controlled pressure/sponge cleaning process.

Thompson et al. (7) evaluated the shampoo detergency of three surfactants commonly used in shampoos: ALS, SLES-2, and AOS (sodium alpha olefin C_{14}-C_{16} sulfonate) against fatty acids, cholesterol, paraffin waxes, wax esters, squalene, and triglycerides. The gc system used in our work did not allow for detection of the triglycerides and all other fractions at the same resolution. The triglycerides have much longer peak reten-

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>% Removed (Cond. A)</th>
<th>% Removed (Cond. B)</th>
<th>% Removed (Wool)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODS-1</td>
<td>40.7 ± 15</td>
<td>56.7 ± 25</td>
<td>35 ± 4</td>
</tr>
<tr>
<td>ALS</td>
<td>72.4 ± 9</td>
<td>97.3 ± 2</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>SLES-2</td>
<td>93.7 ± 3</td>
<td>97.6 ± 2</td>
<td>88 ± 2</td>
</tr>
</tbody>
</table>

Condition A: Hair soiled at 0.04–0.055 g soil/g hair and washed with 0.01% surfactant.
Condition B: Hair soiled at 0.03 g soil/g hair and washed with 0.1% surfactant.
Wool: 3-inch × 4.5-inch wool challis swatch soiled with sebum/lipid-soluble dye soil.

Purchased for the exclusive use of nofirst nolast (unknown)
From: SCC Media Library & Resource Center (library.scconline.org)
tion times, and raising the temperature to speed the elution led to loss of resolution among the other peaks. Since Thompson et al. (7) stated that the triglycerides are easily removed by the three surfactants they used, with no increased build-up at 10 or 20 cycles, we elected to concentrate on the other sebum components.

ONE-CYCLE DATA

The sebum component removal data for tresses were analyzed statistically for seven components, i.e., myristic (C_{14}), palmitic (C_{16}), stearic (C_{18}), and unsaturated (oleic and linoleic) acids (C_{18:21}), cholesterol (CHOL), paraffin waxes (11 fractions combined) (PW), and esters (from spermaceti wax; five fractions combined) (EST).

The total sebum removal data is shown in Table II. As previously stated, these figures correlate well with data acquired using a wool substrate (9) (Table II).

Figure 2 shows results of component removal after one soil/wash cycle (0.01% detergent). The order of removal for the sebum components is similar: ester and paraffin wax removal is the most difficult, and cholesterol the easiest. The only difference is the magnitude of removal that is determined by the nature of the surfactant, i.e., whether it is a good or poor cleaner of lipid soils.

As mentioned, the data show the relative total sebum removal of SLES-2, ALS, and SODS-1 to be similar from hair and wool surfaces, i.e., SLES-2 > ALS > SODS-1. This order confirms that predicted by surfactant theory for oily soil detergency (10). To determine if there is selective removal of components by a surfactant, one way ANOVA
statistics have been performed on these data and removal of individual component groups compared.

The following summarizes the statistical analyses of the sebum component removal by SODS-1, for one soil/wash cycle (95% confidence level). (Component removals are significantly different when components are not underlined by the same line):

<table>
<thead>
<tr>
<th>Least removed</th>
<th>Most removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>EST</td>
<td>PW</td>
</tr>
</tbody>
</table>

These analyses show that this surfactant is most effective in removing the cholesterol component from hair; it is least effective in cleaning off the esters and paraffin waxes.

For ALS, sebum component removal is as follows:

<table>
<thead>
<tr>
<th>Least removed</th>
<th>Most removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>EST</td>
<td>PW</td>
</tr>
</tbody>
</table>

Here, the order of removal is the same as SODS-1 but the data (Figure 2) show that ALS removes more of each component than SODS-1 (95% confidence level). The esters and paraffin waxes are clearly more difficult for ALS to remove than the other components, with the exception of the C₁₄ materials. On the other hand, when soiled hair is washed under similar conditions with SLES-2, there are no significant differences in removal among the sebum components (p = 0.05), and SLES-2 removes all components more effectively than either ALS or SODS-1.

Consequently, after one soil/wash cycle (soiling level 0.04–0.055 g/g; 0.01% surfactant), the removal of sebum components by each of the three surfactants tested can effectively be predicted by a value derived for the total sebum removal. SLES-2 is clearly the most effective against all groups of components and SODS-1 the least effective, a confirmation of surfactant theory (10) (Figure 2).

Sebum removal data for hair soiled and washed under a second set of conditions, i.e., 0.03 g sebum/g hair and 0.1% surfactant solution, were also analyzed (9).

The order of component removal for individual surfactants was found to be similar to the order under “A” soil/wash conditions. Additionally, under these conditions of lower soil loading, both ALS and SLES-2 remove all components at >94% levels, approaching the limits of the experiment. Similar to “A” soil/wash conditions, the most difficult fractions to remove are the paraffin waxes and the esters.

Clearly the one-cycle experiments indicate that some sebum components are more difficult to remove, but the same pattern of removal exists for all three surfactants tested. Surfactant theory for oily soil detergency confirms this order (10). Thus, the one-cycle data show that a surfactant with good cleaning power removes all components well, a poor one less well. However, for all surfactants tested, the esters (from spermaceti wax) and the paraffin wax fractions are the most difficult materials to clean from the hair.
TEN-CYCLE DATA AND BUILD-UP OF SOIL

The ten-cycle data (0.01% surfactant) indicate differences relative to the one-cycle data. For the superior lipid soil surfactant SLES-2, there is no change in removal order of the components or in total percent sebum removed (Figure 3). However, there are differences in the ability of SLES-2 to remove different sebum components (p = 0.001). Two distinct groupings of components emerge: the esters and waxes are more difficult to remove than the rest (95% confidence level). These data show some selectivity for SLES-2, but it should be noted that removal of all components is high, i.e., >90%

There are, however, changes in the removal order for both ALS and SODS-1 compared to their one-cycle behaviors (Figures 4 and 5), and the difference between ALS and the latter surfactant has narrowed. For one-cycle the total sebum removal figures are 72.4% and 40.7%, respectively (significantly different at 95% confidence level); for ten cycles they are 65.2% and 59.2% (not significantly different).

The detergency behavior exhibited by the SODS-1 surfactant is as follows (Figure 4 portrays the one- and ten-cycle data for this material). The dominant feature is the large increase in percent removal of the ester and paraffin wax fractions after ten cycles. In fact, all sebum components show increased removal to some extent; for the aforementioned components this increase is substantial. These results may indicate a soil release mechanism is occurring: SODS-1 may be adsorbing onto the hair during subsequent washes, thus preventing further adsorption of certain sebum components. Regardless, the data show that extended use of this surfactant does not induce build-up, but rather enhances removal.

![Figure 3](image-url)  
Figure 3. Removal of sebum components by SLES-2 for one and ten soil/wash cycles.
When data are analyzed (Figure 5) for component residues after ten soil/wash cycles with ALS detergent, there is a decrease in removal for the saturated fatty acid fractions (compared to one-cycle behavior), perhaps indicative of build-up or selective cleaning. The removal of cholesterol, unsaturated acid, ester, and paraffin wax fractions is similar to the one-cycle level.

At the 95% confidence level cholesterol removal is different from the rest (except unsaturated acids); saturated acid fractions remain more readily on the hair. There is distinct evidence of build-up of the saturated fatty acid materials (C₁₄, C₁₆, and C₁₈) on the hair. This build-up is probably due to the interaction between water hardness (Ca²⁺, Mg²⁺ ions), the fatty acids, and ALS. The tap water used in our experiments is 75–80 ppm (as CaCO₃), higher than the 60 ppm reported in reference 7. SLES-2 and SODS-1 do not show this behavior; the ethoxy units apparently aid in preventing this hard water reaction.

In a separate experiment in which 3.5-g hair tresses were successively soiled and hand-washed (ten soil/wash cycles; soil aged overnight between washings), the detergency of 10% ALS and SLES-2 to clean sebum from hair was compared. ESCA data confirmed an increase of calcium ion on the ALS-washed hair as compared to SLES-2 washed tresses. Also, panelists evaluated the ALS-washed tresses to be significantly duller (95% confidence level) than the SLES-2 treated hair. The dulling is presumably a manifestation of the fatty acid residue build-up.

These ALS data affirm that ALS is a good surfactant, although its sebum removal efficacy is less than that for SLES-2. The results are again in accord with surfactant
Figure 5. Removal of sebum components by ALS for one and ten soil/wash cycles.

detergency theory (10). Since these results are for a pure surfactant, more data are necessary to draw any conclusions for extrapolating to shampoos, since other ingredients that alter surfactant properties are used in shampoo formulations.

For one soil/wash cycle, Thompson et al. conclude that the polar materials are more easily cleaned from hair than the non-polar, and that the degree to which the latter are removed is dependent on the surfactant. Our present data are in general agreement with these conclusions; however, our data show that squalene does not build up after ten soil/wash cycles. We also concur that the paraffin waxes are the most difficult materials to remove (along with the spermaceti esters) and that SLES-2 is superior to ALS for cleaning lipid soils.

The Thompson paper indicates the cholesterol fraction to be difficult to remove for one and 20 cycles. For ten cycles there is a dramatic increase from 65% to 85% removal, a value more consistent with our results showing that cholesterol is easily cleaned from hair.

Squalene is present in the sebum used to soil the hair and appears in calibration chromatograms of the sebum. However, after the extraction procedure it is not found in either control or washed tress extracts. The drying and extraction procedures are those reported (7), so it is not clear why no squalene is detected in practically any chromatogram under either of our soil/wash conditions. Preliminary data does indicate some loss of squalene during the low-level heating to provide a uniform moisture content throughout the sample set. This heating may be enough to remove any squalene not cleaned off by the wash surfactant and thus may explain the absence of squalene in
extract chromatograms. One would expect, though, that if squalene is building up, this effect would be evident in our ten-cycle data even if much is vaporized after one cycle. However, there is no evidence of this, and we are at a loss to explain this anomaly between these and the Thompson data for the squalene component.

In summary, our data show that for one soil/wash cycle, surfactants do selectively clean sebum components from hair at low concentrations. But, as a first approximation, the amount of sebum removed is a function of the detergency of the surfactant, and thus the difference between SLES-2 and ALS is primarily a function of the superior detergency of the former [as predicted by surfactant theory (10); SLES-2 has the lower cmc] rather than differences in selective cleaning. The non-polar sebaceous components (paraffin waxes, esters) are more difficult to remove than the more polar ones, but we contend that the overall surfactant detergency is the determining factor. For ten soil/wash cycles, we find that SLES-2 is superior, and a build-up is found on hair washed with ALS under both (a) the model conditions using 0.01% surfactant and bulk washing and (b) realistic conditions using 10% surfactant and handwashing. This we attribute to hard water/fatty acid interactions. We believe that the data of this paper provide sufficient evidence to warrant extended use testing of potential surfactant systems for oily soil detergency in the manner described.

REFERENCES

(9) J. Clarke, Unpublished data.
Comedogenicity and irritancy of commonly used ingredients in skin care products

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Synopsis
A survey, using the rabbit ear, of the comedogenicity and irritancy of several groups of skin care products indicates that many contain follicular and surface epithelial irritating ingredients. These ingredients fall into several chemical classes. Certain generalizations can be deduced by examining the results: (1) medium-chain-length fatty acids are more potent than short- or long-chain fatty acids in producing follicular keratosis, (2) the comedogenicity and irritancy of an organic material can be reduced by combining the molecule with a polar sugar or a heavy metal, (3) increasing the degree of ethoxylation in a molecule tends to reduce the comedogenicity and irritancy of the chemical, and (4) the longer chain lipids, i.e., waxes, appear too large to produce a reaction. By following the guidelines developed in this study, it is possible to formulate nonirritating, noncomedogenic moisturizers, sunscreens, hair pomades, cosmetics, and conditioners.

INTRODUCTION
The possibility of comedogenicity and irritancy of facial skin care products has been well documented (1–3). Because of this work and an increasing public awareness, facial products that are less comedogenic are now becoming available (4). However, other skin care products such as hair conditioners, hair pomades, moisturizers, sunscreens, and even acne treatment products may be a source of cosmetic acne. By taking these products apart, testing their ingredients, and putting them back together and retesting them, an extensive ingredient listing has been created. By studying this list, the cosmetic chemist can begin to be selective in developing formulas for less irritating and less comedogenic products.

The rabbit ear assay has been used since the mid-1950s as a method of measuring follicular keratinization by externally applied compounds (5). The advantage of this rapid screening tool is that it takes only two weeks to develop follicular impactions in the rabbit ear, while it may take six months to develop similar reactions on human skin. The disadvantage of the model is its extreme sensitivity. The fragile, protected epithelium of the inner ear is extremely sensitive. Not everything that irritates this model will also irritate human skin. However, this extensive screening of cosmetic formula-
tions and their ingredients would not have been possible without the use of this animal model. We have now extended the model to include an index of surface skin irritancy as well as of follicular hyperkeratosis.

METHODS

Ingredients are mixed in propylene glycol at a 9 to 1 dilution for testing unless otherwise indicated (10% concentration). A colony of New Zealand albino rabbits that has genetically good ears and is free from mites is used. Three rabbits, weighing two to three kilograms, are used for each assay. Animals are housed singly in suspended cages and fed Purina Rabbit Chow and water ad libitum. Animals are maintained on a 12-hour light and 12-hour dark cycle. A dose of 1 ml of the test material is applied and spread once daily to the entire inner surface of one ear five days per week for two weeks. The opposite untreated ear of each animal serves as an untreated control. Follicular keratosis is judged both macroscopically (visually) and microscopically with a micrometer to measure the width of the follicular keratosis. The macroscopic response is determined by averaging the measurements of the width of six follicles using a Mitutoyo Dial Micrometer (#536-724). A similar microscopic micrometer measurement is obtained by averaging the width of six follicles under a magnification of 430 x after a 6-mm biopsy specimen is fixed in formalin, sectioned at six microns, and stained with hematoxylin-eosin. The results are then combined on a scale of one to five:

Micrometer reading | Grade | Description
--- | --- | ---
0.009 in or less | 0 | No significant increase in follicular keratosis
0.010 in-.014 in | 1 | A moderate increase in follicular keratosis
0.015 in-.019 in | 2 | An extensive increase in follicular keratosis
0.020 in-.025 in | 3 | Epidermal necrosis and slough
0.025 in-.029 in | 4 | No significant increase in follicular keratosis
0.030 in or more | 5 | No irritation

Grade 5 is the presence of large comedones throughout the ear, similar to those induced by the application of our standard "positive" testing agent, isopropyl myristate. As reported in our previous studies, a minimal grade of 0 to 1 is not considered significant. Grade 2 to 3 is borderline. However, a grade of 4 to 5 is uniformly reproducible and considered positive.

The irritancy produced by the repeated application of a chemical or skin care product on the surface epidermis in the rabbit ear is also evaluated on a similar scale of 0 to 5. The grades are summarized as follows:

0 | No irritation
1 | Few scales, no erythema
2 | Diffuse scaling, no erythema
3 | Generalized scaling with erythema
4 | Scaling, erythema, and edema
5 | Epidermal necrosis and slough

To study the effects of different vehicles on comedogenicity and irritancy, several fatty acids and the D&C red pigment #36 are reexamined in different solvents. The fatty...
acids are dissolved in either a volatile solvent or sunflower oil. The D&C red #36 pigment is tested in mineral oil, propylene glycol, polyethylene glycol 400, and pentaeerythritol tetra capra/caprylate.

RESULTS AND DISCUSSION

Cosmetic acne was first reported by French dermatologists in the mid-forties. They reported on brilliantines and hair pomades causing flareups on the temple and forehead facial regions. They attributed the problems to impurities in the brilliantines (6). In 1970, Kligman requested that Gerd Plewig and I examine over 700 men to find some with normal facial skin. Much to our chagrin, the majority had cosmetic acne (7). About 70% showed some evidence of follicular keratoses on the forehead and temples. Occasionally the eruptions were noted on the cheeks down to the jawline area. The lesions were usually noninflammatory, closed comedones. A few lesions developed into small inflammatory papules. However, there were no cases of severe, cystic inflammatory acne. Histologically, the comedones from pomade acne cases were identical to biopsies taken from comedones of classic acne vulgaris patients. In surveying the hair care preparations, we felt that the actual ingredients and not trace contaminants were offenders. Interestingly, very few of the subjects attributed their follicular eruptions to their daily use of a hair pomade. This study stimulated us to examine other skin care products and ingredients.

In 1972 Kligman and Mills reported on acne cosmetica in their survey at the Acne Clinic at the University of Pennsylvania (1). Approximately one third of the adult women had a low-grade, persistent acne in the cheek area, consisting of closed comedones quite similar to those found in pomade acne. This appeared more frequently in women after age twenty and may explain one of the reasons for epidemic adult acne in women in the 1970s and 1980s. In 1976 and 1984, Fulton published results on actual cosmetic lines and on ingredients, and proposed the development of noncomedogenic cosmetics using ingredients that were nonoffenders in the rabbit ear assay (2,3). Several major cosmetic manufacturers have now produced these types of products. However, our screening indicates that work is still needed on many skin care formulations.

It became apparent during our research into potential noncomedogenic ingredients that several hypotheses could be developed: (1) In order for an ingredient to be comedogenic, it must penetrate into the follicle, and (2) once in the follicle, the chemical must produce the follicular reaction of "retention hyperkeratosis" (8). In addition, the overall penetrability of the molecule may be related to (1) the water/oil partition coefficient of the compound (HLB balance) and (2) the relative molecular weight of the ingredient. The ingredient appears to have the most potential if it is fairly soluble in both water and oil (HLB around 10 to 12) and has a range of molecular weight between 200 and 300. The comedogenicity of an ingredient may be reduced by adding a large constituent (i.e., polymers of PEGs), by adding a charged molecule (i.e., sugars), or by adding a heavy metal (i.e., zinc or lithium). This often relates to raising the HLB balance to above 12.

Examples of this concept of water/lipid solubility and molecular weights are apparent in each class of chemicals examined (Table I). Among the lanolins, the classic anhydrous lanolins are not as comedogenic as the moderately ethoxylated derivatives (laneth 10).
### Table I
Ingredients and Their Comedogenicity and Irritancy

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Grade (0–5)</th>
<th>Comedo.</th>
<th>Irrit.</th>
<th>Ingredient</th>
<th>Grade (0–5)</th>
<th>Comedo.</th>
<th>Irrit.</th>
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<td></td>
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<td></td>
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### III. Alcohols, sugars and their derivatives

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<th>Irrit.</th>
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<tr>
<td>Isopropyl alcohol</td>
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<td>0</td>
<td></td>
<td>Isocteryl alcohol</td>
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<td>4</td>
<td></td>
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<tr>
<td>Myristyl alcohol</td>
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<td>2</td>
<td></td>
<td>Cetearyl alcohol</td>
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<tr>
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<td>Oleyl alcohol</td>
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Table I (continued)

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<th>Ingredient</th>
<th>Grade (0–5)</th>
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<td>Irrit. ‡</td>
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<td>Kaolin</td>
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</tr>
<tr>
<td>PVP</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>VI. Oils*</td>
<td></td>
<td>IX. Sterols</td>
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</tr>
<tr>
<td>Cocoa butter</td>
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<td>Cholesterol</td>
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<td>Coconut butter</td>
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<td>Hydrogenated vegetable oil</td>
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(continued)
Table 1 (continued)

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<td>Ethyl ether</td>
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<td>Diethylene glycol</td>
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<td>Tocopherol*</td>
<td>0-3*</td>
<td>0-3*</td>
<td>Ethylene glycol</td>
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<td>0</td>
<td>monomethyl ether</td>
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<td>(EGME)</td>
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<td>Vitamin A palmitate</td>
<td>1-3*</td>
<td>1-3*</td>
<td>Magnesium stearate</td>
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<td>Panthenol</td>
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<td>0</td>
<td>Zinc oxide</td>
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<td>XI. Preservatives and additives</td>
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<td>Zinc stearate</td>
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<td>2</td>
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<tr>
<td>Phenoxyethyl paraben</td>
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<td>0</td>
<td>Amoniomethylpropinate</td>
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<tr>
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<td>Hydantoin</td>
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<td>0</td>
<td>Hydrolyzed animal protein</td>
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<td>Sodium hyaluronate</td>
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</tr>
<tr>
<td>Chondroitin sulfate</td>
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<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precipitated sulfur</td>
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<td>0</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Water-soluble sulfur</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Comedogenicity or ability of test substance to produce follicular hyperkeratosis.
‡ Irritancy or ability of test substance to produce surface epithelial irritation.
* Results depend on source of raw material.
** Parentheses indicate results using “refined” oil.

The higher ethoxylated derivatives with HLBs above 12 are more water-soluble and noncomedogenic and nonirritating (PEG 75 lanolin). Two of the lanolin derivatives studied require special comments: (1) The acetylated lanolin alcohols are both comedogenic and irritating, not because of the acetylated lanolin but because of the cetlyl acetate additive (Figure 1), and (2) PEG 16 lanolin (Solulan 16) is quite comedogenic and irritating, perhaps secondary to the combination of nonlanolin additives: ceteth-16, oleet-16, and steareth-16.

Among the fatty acids and esters a similar analogy is found. The mid-chain-length fatty acids, such as lauric acid and myristic acid and its analogs cause follicle hyperkeratosis. As the molecular weight of the fatty acid becomes larger and the effective charge of the overall molecule is reduced, less follicular reaction is produced. When the fatty acid is esterified with a small- to mid-size alcohol, the combination becomes more potent than the fatty acid itself. The cousins of isopropyl myristate, such as myristyl myristate, isopropyl isostearate, isostearyl neopentanoate, butyl stearate, and decyl oleate, are all comedogenic (Figure 2). Also, when branched-chain fatty acids are used, the derivatives may be more comedogenic. Large molecular weight esters, such as behenyl erucate and cetyl palmitate, are not a problem.
Similar analogies are apparent with the alcohols, ethers, glycols, and sugars. Short-chain alcohols do not cause a reaction. The mid-chain-length alcohols are comedogenic and more irritating than their fatty acid analogs (Figure 3). In the glycol series, as the hydrocarbon component becomes more dominant, the compound is more effective at producing comedones. The pure sugars are noncomedogenic. However, if they are combined with penetrating fatty acids, they may become follicular irritants. Also, if they are combined with another irritant, as in glyceryl stearate (SE), which contains added sodium or potassium stearate, the combination becomes more comedogenic. The increasing addition of polyethylene glycols to the fatty acids increases the HLB balance, reduces the follicular irritancy, and appears to prevent hyperkeratosis. An example is the oleth 3, 5, 10, 20 series (Figure 4).

Among the waxes, the hydrocarbon chains appear too long to penetrate unless the wax is modified, such as in sulfated jojoba oil. In the case of beeswaxes and jojoba oils, some commercial preparations are more comedogenic than others. This suggests more contaminants or irritants in some of the preparations. Emulsifying wax NF may be irritating, depending on the concentration of longer-chain alcohols such as cetearyl alcohol.

Chemicals such as cellulosic polymers, the silicates, and the carbomers used in the pharmaceutical and cosmetic industry to thicken lotions and creams are not usually a problem. The clays, bentonite, and kaolin are also not a problem. Neither is talc.

Clinically, natural oils such as cocoa butter and coconut butter have long been known to cause problems with pomade acne. This is confirmed in the rabbit ear assay. Also,
Figure 2. Ingredient testing in the rabbit ear assay—the macroscopic view of the results from testing isopropyl myristate. Microscopic examination confirmed the comedogenicity seen visually. Note that the ingredient is also an irritant compared to a potential substitute, octyl dodecyl stearoyl stearate.

Hydrogenated vegetable oil (Crisco®) appears to contain residual irritating lipids. Among the natural oils such as sesame oil, avocado oil, and mink oil, the results are improved when a more refined oil is used. However, it seems easier to use safflower oil and sunflower oils, which are naturally less comedogenic. Mineral oil presents a complex problem: some sources are acceptable; others are not.

D&C red colors represent a perplexing mixture of different types of red dyes and pigments. Some are mildly comedogenic; others are not. The common pigments used in powder blushers (D&C red #6, barium lake; D&C red #7, calcium lake; and D&C red #9, barium lake) are relatively noncomedogenic. However, the vehicle is also particularly important for the D&C red colors. A dry compressed powder or powder suspended in an evaporating vehicle such as propylene glycol may be noncomedogenic. The same dye incorporated into a nonevaporating oil can be comedogenic (Table II, Figure 5). Carmine, which is a red dye obtained from insect wings, is noncomedogenic and may be used as a substitute. The iron oxides, chromium hydroxide, and titanium dioxide are not a problem.

The silicones and sterols do not appear to be a problem. Among the vitamins, tocopherol is a follicular irritant. Tocopherol has been advocated by the layman for years to increase wound healing and reduce scar formation. However, it should not be used on acne-prone skin because of its potential to produce follicular hyperkeratosis. The derivative, tocopheryl acetate, is noncomedogenic, and research needs to be done to see if it is an acceptable substitute.
As for the miscellaneous items, the usual sunscreen active ingredients are noncomedogenic. Among chemical solvents, acetone, ether, and EGME are not problems, but xylene is comedogenic and an irritant. When metallic bases, such as lithium, magnesium, and zinc stearate, are added to the fatty acids, the metal appears to prevent the comedogenic reaction. Among bases, triethanolamine is more comedogenic than aminomethylpropanolamine. The classic formulation of a cold cream often involves a salt bridge between stearic acid and triethanolamine. In testing different ratios [4:1, 1:1, 1:4] of stearic acid to triethanolamine (stearic acid:TEA) in a cold cream base, all combinations were found to be comedogenic.

The influence of the vehicle or solvent on the comedogenicity and irritancy of a chemical appears quite significant. For example, the use of rapidly evaporating vehicles such as acetone or ether reduces the comedogenicity of fatty acids when compared to the results obtained with sunflower oil, a nonvolatile vehicle (Table III). The effects on irritancy are reversed. Fatty acids are less irritating when delivered in a nonvolatile vehicle. As with the fatty acids, the vehicle or carrier for the D&C red pigment is extremely important. Whereas the D&C red color may be noncomedogenic in volatile propylene glycol, it may be more comedogenic in mineral oil. Possible alternatives for mineral oil, such as pentaerythritol tetra capra/caprylate and polyethylene glycol 400, also reduce the comedogenicity of the red color (Table II). We have chosen propylene glycol as the routine diluent for these studies, as it gradually evaporates and leaves a concentrate of the raw material to be tested. Also, lot after lot of propylene glycol has proven to be nonirritating and noncomedogenic.
Figure 4. Oleth-3 compared to oleic acid. The initial additions of ethylene glycols to potentially comedogenic and irritating ingredients appear to increase this propensity. Further additions of ethylene glycols, such as oleth-10 and oleth-20, tend to reduce reactions.

Some ingredient combinations—for example, the combination of glyceryl stearate with potassium stearate (available commercially as glyceryl stearate S.E.) and also the combination of D&C red #36 and mineral oil—appear more comedogenic than the individual compounds themselves. These synergistic reactions need to be studied further.
Table II
Comedogenicity of D&C Red #36 Dye in Different Vehicles

<table>
<thead>
<tr>
<th></th>
<th>Grade (0–5)</th>
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<tr>
<td></td>
<td>Comedo.</td>
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<tr>
<td>D&amp;C red #36 in mineral oil</td>
<td>3</td>
</tr>
<tr>
<td>D&amp;C red #35 in pentaerythritol tetra capra/caprylate</td>
<td>2</td>
</tr>
<tr>
<td>D&amp;C #36 in propylene glycol</td>
<td>1</td>
</tr>
<tr>
<td>D&amp;C red #36 in PEG 400</td>
<td>0</td>
</tr>
</tbody>
</table>

The opposite is also possible. For example, the combination produced by the ingredient D&C red #36 and the vehicle polyethylene glycol is less comedogenic than D&C red #36 when incorporated into other vehicles. The cosmetic chemist may be able to take advantage of these findings in the future to custom design noncomedogenic products.

SUMMARY

These studies indicate that skin care preparations that are nonirritating and noncomedogenic can be made. Nonreactive ingredients can be used to make elegant products, and borderline ingredients can be combined with other ingredients to reduce the reactions to acceptable levels. In spite of these guidelines, new formulations must always be examined with the rabbit ear assay before the cosmetic chemist can be assured that his ideas work.

Figure 5. The comedogenicity of D&C red #36 when incorporated into two different vehicles. The vehicle may increase or decrease an ingredient's ability to produce follicular hyperkeratosis.
Table III
Effects of the Solvent on Comedogenicity and/or Irritancy of Fatty Acids

<table>
<thead>
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<th>Fatty acids</th>
<th>Organic solvent*</th>
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<td>Irrit. (0-5)</td>
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<td>Comedo. (0-5)</td>
<td>Irrit. (0-5)</td>
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<td>Capric acid</td>
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* Ethyl ether or acetone.

The rabbit ear assay remains important to the rapid evaluation of new ingredients and the cosmetic chemist’s formulations. Both the visual and microscopic evaluations of the rabbit ear need to be done simultaneously (9). Materials found to be noncomedogenic in the rabbit assay appear to be noncomedogenic in the human model (10). Whether highly comedogenic ingredients in the rabbit ear assay are always comedogenic in humans still remains uncertain. Currently, it is more prudent to avoid these offenders.

The major offenders, such as isopropyl myristate, acetylated lanolin alcohol, and lauric acid derivatives such as laureth-4, should be used with caution in skin care products. We are not convinced of the statement that lower concentrations of these compounds can be safely used with no comedogenic consequences (11). Human skin studies have been used to give that statement credence, but the back skin of human volunteers is relatively insensitive (7). However, when the rabbit ear assay is positive but the human back skin results are negative after only eight weeks’ exposure, the results from the rabbit ear assay should not be dismissed. The reaction may take longer or the back skin may not be the ideal testing surface.

An additional “bonus” of the rabbit ear assay is detection of the potential of an ingredient or finished product to produce an epithelial irritant reaction. It is easy to keep track of the surface irritancy while doing the follicular studies. The stratum corneum of the rabbit ear is very thin and undeveloped. This results in an extreme sensitivity of the skin to exposure to irritants. If this test finding is confirmed by others, we may find it unnecessary to use the Draize rabbit dermal irritancy test.

This paper is meant to be a survey of the ingredients used in skin care and hair care products. The survey is not at all definitive but simply designed to stimulate research, so that new noncomedogenic products will become available for those of us with acne-prone complexions. This subject has recently received an excellent review by the American Academy of Dermatology Invitational Symposium on Comedogenicity (12).

REFERENCES


Development of a novel hybrid powder formulated to quench body odor

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Synopsis

Olfactory and instrumental analyses show that short-chain fatty acids contribute to both foot and axillary malodors.

The mechanism of choice to quench short-chain fatty acid malodors was to convert volatile short-chain fatty acids into their corresponding nonvolatile odorless metallic salts. Several metal-containing candidates were evaluated by means of headspace gas chromatography (HS-GC) for their ability to efficiently quench short-chain fatty acids. Zinc oxide was found most suitable for this purpose. Despite its strong deodorizing power, due to its aggregating ability, shortcomings such as clogging of aerosols and rough texture are unavoidable when formulating zinc oxide into deodorant products of various forms. By forming a hybrid powder in which zinc oxide is uniformly covered on the surface of a spherical resin such as nylon, these shortcomings were overcome without sacrificing any deodorizing power.

Body odor quenchers formulated with this hybrid powder were more efficacious than conventional antiperspirants and deodorants on both foot and axillary odor.

INTRODUCTION

Regardless of sex, age, or race, people have always been sensitive in trying to eliminate offensive body odors as much as possible. To fulfill such demands, countless products by various manufacturers have appeared in the marketplace. Human body odors result from interactions between secretions of eccrine, sebaceous, and apocrine glands, and resident bacteria. Several approaches have been made to control body odors, out of which the antiperspirants and antimicrobials have been most successful. Antiperspirants inhibit perspiration by means of aluminum salts, and antimicrobials inhibit odor-forming bacteria. Nevertheless, such ingredients are intended to prevent the generation of body odors and generally have little effect in reducing malodor once formed.

Body odors have been investigated in terms of chemical compound constituents by dermatologists and analytical chemists, but little is still known as to which chemical compounds are responsible for the malodor for specific body sites. We have recently...
reported that short-chain fatty acids contribute considerably to both foot and axillary odor (1). Especially in the case of foot odor, isovaleric acid was found to be the key odor component responsible for the malodor. As for axillary odor, a particular key odor component remains yet to be identified, although short-chain fatty acids of comparatively long carbon chain (>C6) seem to comprise a considerable portion of the malodor. It is well known that the method of choice in eliminating short-chain fatty acid malodors is to convert volatile short-chain fatty acids into their corresponding odorless nonvolatile fatty acid metallic salts.

In this study, ingredients capable of converting short-chain fatty acids into their metallic salts were investigated by headspace gas chromatography (HS-GC). Furthermore, deodorant products formulated with such ingredients, which hopefully will not only prevent but also act directly upon malodor already formed, were compared with conventional products for their ability to efficiently quench foot and axillary odor.

EXPERIMENTAL

HEADSPACE GC ANALYSIS FOR EVALUATING QUENCHING ACTIVES

Equilibrium headspace gas chromatography was employed to assess the ability of various compounds to efficiently quench short-chain fatty acids. HS-GC is unique in that only the vaporized portion of the sample is introduced into the GC. The method permits analysis of volatile chemicals without having to introduce the total sample matrix into the GC. The sample matrix may well contain nonvolatile compounds that are neither amenable nor desirable for GC operation. Isovaleric acid was chosen to represent the short-chain fatty acids since it was found to be the key odor component of foot odor and also because of its extremely low olfactory threshold level (2). Quantitative comparison among the candidates should easily be made since the concentration of isovaleric acid in the vapor phase should be directly proportional to the GC peak area obtained.

Approximately 80 mg of the candidate was accurately weighed in a glass vial especially designed for the headspace gas chromatograph, to which one ml of 0.5% isovaleric acid aqueous solution was added. The vial was tightly closed and placed inside an ultrasonic generator for five minutes for sample dispersion. It was then placed inside an oven maintained at 60øC for 60 minutes to allow isovaleric acid vapor to equilibrate in the headspace of the vial prior to analysis.

The vial was introduced into a Perkin Elmer SIGMA 3B headspace gas chromatograph equipped with a flame ionization detector and a three-foot glass column packed with 10% FFAP. The HS-GC was operated at a column temperature of 150øC isothermally. The headspace of the vial was automatically pressurized for four minutes, after which it was forced into the carrier gas flow. The GC peaks were recorded and the peak area was calculated in arbitrary units using a Hewlett Packard HP 3380A integrator. For each candidate, three consecutive GC runs were acquired, and the mean peak area was employed for the calculation explained later on. To check the stability of the GC, the standard isovaleric acid aqueous solution was measured once in every five sample runs.

Each candidate was evaluated by calculating a value expressed as "isovaleric acid consumption/mg ingredient." An example of how to calculate the isovaleric acid consump-
Figure 1. Calculation of iso-valeric acid consumption values. Upon addition of a quenching ingredient, the GC peak area of the standard iso-valeric acid solution decreases.

The calculation value is shown in Figure 1. The larger the value, the greater the efficacy of the ingredient to quench iso-valeric acid odor.

CONFIRMATION OF THE QUENCHING MECHANISM BY FT-IR

Fatty acids in the free form and metallic salt form are readily distinguishable by Fourier transform infrared spectrophotometry (FT-IR), since they exhibit characteristic absorption bands at different wave numbers. Therefore, the speculated quenching mechanism in which volatile short-chain fatty acids are converted into metallic salts was confirmed by FT-IR. To a mixed aqueous solution (0.1%) of propionic, iso-valeric, and caproic acids, resembling that of a sweaty body malodor, zinc oxide was gradually added until excess zinc oxide started to precipitate. The excess zinc oxide was filtered, and the filtrate was evaporated to dryness in vacuum. An FT-IR spectrum of the resulting residue in the form of a KBr tablet was acquired using a Biorad Qualimatic FT-IR, scanning a range of 4000 to 400 cm\(^{-1}\).

FORMATION OF A ZINC OXIDE/NYLON HYBRID POWDER

Although zinc oxide is a widely used cosmetic ingredient, it possesses a couple of unfavorable shortcomings that derive from its aggregating property. Even though some commercially available zinc oxides are claimed to be as small as 0.1 \(\mu\)m in particle size, they readily cohere to form massive lumps, as shown in Figure 2. This is said to be due to the electrostatic behavior of zinc oxide, and can thus easily lead to clogging of aerosol...
products. It also has a fairly rough texture, which may feel uncomfortable when applied to sensitive skin. The whiteness of zinc oxide is often considered too vivid in contrast to skin color and may be emphasized when applied to exposed parts of the body. To overcome such shortcomings, we attempted to form a composite or “hybrid” powder,

**Table I**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formula 1</th>
<th>Formula 2</th>
<th>Formula 3</th>
<th>Formula 4</th>
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<td>0</td>
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<td>30</td>
</tr>
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<td>50</td>
<td>35</td>
<td>50</td>
</tr>
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<td>15</td>
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</tr>
<tr>
<td>ZnO</td>
<td>30</td>
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<td>S. microbeads</td>
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</tr>
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</table>

The content of each ingredient in the powder is shown in weight percent.

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which consists of a spherical nylon as the core powder, the surface of which is uniformly covered with fine-particled zinc oxide. To 80 parts of nylon 12 powder (average particle size 6.6 μm, Nikko Rica Corp.), 20 parts of zinc oxide (average particle size 0.1 μm, Sakai Kagaku Kogyo) were added and mixed together in a Henschel mixer (Mitsui Miike Machinery Co., Ltd., Model 10B) for five minutes. The mixture was placed inside a tumbling mill (Retsch, Model S2) charged with alumina balls (0.8–30 mm i.d.), where it was mixed and compressed for 30 to 60 minutes.

EFFICACY OF QUENCHERS FORMULATED WITH HYBRID POWDER ON FOOT ODOR

Efficacy of body odor quenchers in the form of aerosols was assessed. Four quenchers, whose powder parts formulae are shown in Table I, were prepared for the assessment. Our panel consisted of six subjects (six men, 20 to 30 years old) with fairly strong foot odor, all from our laboratory. For each formula the assessment was carried out in the following manner.

First of all, the six subjects self-evaluated their right and left feet, based on a five-step foot odor intensity: 0, no foot odor; 1, faint foot odor; 2, medium foot odor; 3, strong foot odor; 4, extremely strong foot odor.

After evaluation, the quencher was applied to the foot possessing the stronger foot odor, and the other foot was left untreated. The quencher was always applied only on the former foot during the assessment, and the latter was left as control. The quencher was applied twice a day for two days. Foot odor was self-evaluated just before applying the quencher. An example of such an assessment procedure is shown in Figure 3. As shown

8/9 9:00  selection of foot for applying the quencher
          (olfactory evaluation)

     first application

8/9 13:00 olfactory evaluation

     second application

8/10 9:00 olfactory evaluation

     third application

8/10 13:00 olfactory evaluation

     fourth application

8/10 16:00 olfactory evaluation

Figure 3. Assessment procedure for body odor quenchers on foot odor. The assessment lasts for two days during which four applications and five evaluations are accomplished.

Purchased for the exclusive use of nofirst nolast (unknown)
From: SCC Media Library & Resource Center (library.scconline.org)
in the figure, foot odor was evaluated five times during an assessment. During the two days, the subjects were allowed to bathe but not permitted to use soaps or deodorants of any kind. The same assessment was carried out on all four formulae.

EFFICACY OF QUENCHERS FORMULATED WITH HYBRID POWDER ON AXILLARY ODOR

Efficacy of quenchers formulated with hybrid powder was assessed on axillary odor as well. A panel of 20 patients (three men, 17 women, average age 30), suffering from strong axillary odor, was selected from hospitals and universities in Japan. Double-blind trials were made on body odor quencher A (a conventional formula containing aluminum chlorhydrate as active ingredient + hybrid powder, equivalent to formula 2) and body odor quencher B (a conventional formula containing only aluminum chlorhydrate as active ingredient, equivalent to formula 4). Trained olfactory assessors evaluated the efficacy of A and B as listed below:

- Efficacy of A >> efficacy of B
- Efficacy of A > efficacy of B
- Efficacy of A = efficacy of B
- Efficacy of A < efficacy of B
- Efficacy of A << efficacy of B

Quencher A was applied to the right axilla and B to the left, or vice versa. The quenchers were applied twice a day, once in the morning and once in the afternoon, for seven consecutive days during which the patients could bathe, but the usage of neither soaps nor deodorants was permitted. The axillae of the patients were evaluated by the assessors on the seventh day. The identity of A and B was kept blind to both the patient and the assessor, and only the supervisor who finally collected the results could distinguish the two formulae.

RESULTS AND DISCUSSION

HEADSPACE GC ANALYSIS FOR EVALUATING QUENCHING ACTIVES

If we keep in mind the quenching mechanism we are proposing here, the candidates under investigation should contain metallic elements, preferably with a mild alkaline effect, and needless to mention, must be safe on human skin. Several possible candidates to fulfill the above demands were analyzed by headspace GC. Isovaleric acid consumption values of the candidates are illustrated in Figure 4. Fine-particled zinc oxide was found to be most efficacious, followed by hydroxy apatite, known as a peptide adsorber. The most widely used antiperspirant ingredient, aluminum chlorhydrate, was superior compared to talc, which showed almost no effect at all, but was significantly ineffective in comparison with zinc oxide. The quenching mechanism of zinc oxide can be estimated as shown below:

\[ 2C_4H_9COOH + ZnO \rightarrow (C_4H_9COO)_2Zn + H_2O \]

CONFIRMATION OF THE QUENCHING MECHANISM BY FT-IR

The FT-IR spectrum of zinc oxide-treated short-chain fatty acid aqueous solution is shown in Figure 5. The strong absorption band observed near 1600 cm\(^{-1}\) can be as-
signed as the carboxylate anion of short-chain fatty acid zinc salt. The absence of an absorption at 1700 cm$^{-1}$, which should be observed in the presence of free fatty acids, convinced us that the expected reaction as shown below was actually proceeding:

$$2\text{RCOOH} + \text{ZnO} \rightarrow (\text{RCOO})_2\text{Zn} + \text{H}_2\text{O}$$

(R: alkyl group)

Figure 4. Isovaleric acid consumption values of various ingredients. The larger the value, the greater the efficacy of the ingredient to quench isovaleric acid odor.
FORMATION OF A ZINC OXIDE/NYLON HYBRID POWDER

As can easily be predicted from the microscopic photograph shown in Figure 6, spherical nylon powder has a smooth texture. A photograph of a composite or a hybrid powder of zinc oxide and nylon powder is shown in Figure 7. A uniform layer of zinc oxide is clearly observed around the nylon core powder. Some attractive characteristics of the hybrid powder, in comparison with zinc oxide alone, are summarized below.

1. Increases the surface area of zinc oxide
2. Improves the rough texture of zinc oxide
3. Prevents aggregation of zinc oxide
4. The specific gravity of the hybrid powder is controllable
5. Improves the transparency of zinc oxide

By forming a hybrid powder, the surface area of zinc oxide should increase considerably, and hence it should react faster with short-chain fatty acids. The texture of zinc oxide was improved so much that it was indistinguishable from nylon powder alone. Since zinc oxide is uniformly wrapped around nylon powder, the particle size of the hybrid powder should be almost identical with that of nylon powder. This should prevent the clogging of aerosols considerably. As mentioned above, the specific gravity of the hybrid powder can be controlled by changing the amount of zinc oxide to be coated on top of the nylon powder. The optimum amount to form a single layer was found to be

Figure 5. FT-IR spectrum of zinc oxide-treated short-chain fatty acids. The strong absorption band around 1600 cm\(^{-1}\) is assigned as the carboxylate anion of short-chain fatty acid zinc salt. The absence of an absorption band at 1700 cm\(^{-1}\) shows that no free short-chain fatty acids are present.
around 20%. Amounts above 20% would overload the nylon surface, which consequently would result in rough texture, and amounts below 20% would leave some portions of the surface naked. When applied to the skin, the hybrid powder was more transparent than zinc oxide alone.

**EFFICACY OF QUENCHERS FORMULATED WITH HYBRID POWDER ON FOOT ODOR**

Odor assessment results of formulae 1 and 4 are shown in Figure 8 and Figure 9, respectively. The horizontal axis is taken as the time in hours after the first application. The vertical axis is taken as the mean foot odor intensity self-evaluated by the subjects. Out of the four formulae, formula 1 was the most efficacious, due to the high content of zinc oxide, but its texture was the worst, and several aerosols were clogged by it. The efficacy of formula 4, i.e., a conventional formula with no zinc oxide, was the lowest. Formula 2, containing 30% of hybrid powder, was comparable in efficacy to formula 1 but with a better texture. Formula 3 was found to be more effective than formula 4 but
not as much as formula 2, due to the amount of hybrid powder. No aerosol clogging was reported for formulae 2, 3, and 4. Consequently, the formula of choice is formula 2.

Figure 7. Photomicrograph of hybrid powder. A uniform layer of zinc oxide on the surface of nylon powder is observed.

Figure 8. Odor assessment result of formula 1 on foot odor. Foot odor of the applied foot is suppressed in comparison with that of the control foot.
Efficacy of Quenchers Formulated with Hybrid Powder on Axillary Odor

The results of the double-blind trials are shown in Table II. The total number of subjects was 18, since two subjects resigned during the assessment. Hybrid powder containing quencher A showed a statistically significant deodorant effect over quencher B, a conventional formula. Hybrid powder-formulated quenchers were proven to be efficacious not only on foot odor but also on axillary odor.

Conclusions

Short-chain fatty acids have been identified not only in the foot and the axilla but also in other sites of the human body such as the vagina (3), hair and scalp (4), and physio-

Table II
Double-Blind Assessment Results of Quenchers A and B

<table>
<thead>
<tr>
<th>Comparison of efficacy</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A ≫ B</td>
<td>4</td>
</tr>
<tr>
<td>A &gt; B</td>
<td>8</td>
</tr>
<tr>
<td>A = B</td>
<td>1</td>
</tr>
<tr>
<td>A &lt; B</td>
<td>4</td>
</tr>
<tr>
<td>A ≪ B</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
</tr>
</tbody>
</table>

Wilcoxon sign-rank test evaluation: $U_o = 1.7328$; $P_o = 0.0831$. **

Figure 9. Odor assessment result of formula 4 on foot odor. Foot odor of the applied foot is only slightly suppressed in comparison with that of the control foot.
logical fluids (5). Along with low-molecular-weight compounds containing nitrogen and sulfur, short-chain fatty acids seem to comprise a considerable portion of human body malodors.

The best method to efficiently eliminate short-chain fatty acids was considered to be through chemical reaction converting them into their corresponding odorless metallic salts. Out of the several chosen candidates, zinc oxide was found to be most suitable. Taking into account the several shortcomings that zinc oxide possesses, we have developed a hybrid powder consisting of a spherical nylon resin as the core whose surface is uniformly covered with fine particles of zinc oxide. This hybrid powder overcomes zinc oxide's drawbacks, especially those encountered upon formulating it into deodorant products, without sacrificing any of its deodorizing power. The body odor quenchers formulated with hybrid powder were assessed on subjects with strong foot and axillary odor, and were found to be more efficacious in eliminating malodors as compared with conventional antiperspirants and deodorants.

The hybrid powder body odor quencher is a novel deodorizer that theoretically not only prevents the generation of body malodor as conventional products do, but also chemically "quenches" body malodor once formed from short-chain fatty acids. This concept is applicable to body odors from regions other than the foot and axilla, provided that the key odor components are short-chain fatty acids.

REFERENCES

Synergism of preservative system components:
Use of the survival curve slope method to demonstrate anti-Pseudomonas synergy of methyl paraben and acrylic acid homopolymer/copolymers in vitro


Received July 2, 1989.

Synopsis
The survival curve slope method allows determination of synergy in multicomponent systems when the slope (i.e., rate of death of the population of test organisms) is a larger negative number than the sum of the slopes of each of the components. This method was used to demonstrate anti-Pseudomonas synergy of methyl paraben (MP) and acrylic acid homopolymer/copolymers in vitro.

Preservative efficacy testing of nonionic lotions containing 0.2% MP and 0.2% acrylic acid homopolymer/copolymers revealed anti-Pseudomonas synergy against P. aeruginosa, P. putida, P. fluorescens, and P. stutzeri. Addition of 0.1% CaCl₂ to the lotion caused significant increases in D-values and eliminated the anti-Pseudomonas synergy.

Similar patterns of synergy were observed in lotions containing 0.2% MP and 0.2% carbomer 934, 941 or acrylates/C10-30 alkyl acrylate cross polymer (1342) and in tap water containing 0.2% MP and 0.01% Na₂EDTA. The anti-Pseudomonas synergy observed with MP and neutralized acrylic acid homopolymer/copolymers is probably related to chelation of divalent metal ions and similar to permeabilization synergy reported for preservative action by EDTA.

INTRODUCTION
Preservative efficacy testing is performed to determine the type and minimum effective concentrations of preservatives required for products to meet acceptance criteria (1). Testing is needed for each product because the physicochemical composition of a formula may enhance or reduce the antimicrobial effectiveness of preservatives.

When designing the preservative system of a product (2,3), it is desirable to select compounds that enhance the antibacterial action of the preservative system. Synergism is observed when the effect produced by the combination of components is greater than the sum of the effects of each component taken separately. Synergy of antimicrobial preservatives has been reported by several workers (4–7).

*Current Address: Neutrogena Corporation, 5755 West 96th Street, Los Angeles, CA 90045.
During testing with the linear regression method (8), we noticed that *Pseudomonas aeruginosa* was inactivated more rapidly in nonionic emulsion systems containing carbomer 941 than in products that did not contain this material. By thoroughly studying this system, we developed a method of demonstrating synergy of preservative system components that uses the rates of inactivation of test organisms determined by the linear regression method.

The most desirable outcome of testing antimicrobial preservatives for synergy is finding the combination that will allow the use of fewer and/or reduced concentrations of preservatives in consumer products. The use of a preservative system that has synergistic action is of practical significance because it may help reduce the cost of the product and the irritation or sensitization potential of the formula.

**EXPERIMENTAL**

**TEST ORGANISMS**

The strains of *Pseudomonas* used in this study were received directly from the American Type Culture Collection (ATCC) and consisted of *P. aeruginosa* ATCC strains 9027, 9721, 10145, and 27853; *P. cepacia* ATCC strains 13945 and 25416; *P. fluorescens* ATCC 13525; *P. putida* (Biotype A) ATCC 12633; *P. stutzeri* ATCC 17588; and *Pseudomonas* sp. 9230. *P. aeruginosa* 9027 routinely is used in antimicrobial preservative testing (1), and *P. aeruginosa* 27853 is a standardized strain for antibiotic susceptibility testing. Multiple strains of species of *P. aeruginosa* and *P. cepacia* were available, and consequently, *P. aeruginosa* 9027 and *P. cepacia* 13945 were used unless other strains are indicated. *Bacillus cereus* ATCC 11778 was obtained directly from the ATCC. *E. coli* ATCC 8739 was obtained from Hill Top Biolabs, Inc. *Staphylococcus aureus* ATCC 6538 (FDA 209 strain) and *Bacillus* sp. were taken from the Jergens culture collection. The cultures were maintained by weekly transfer on Tryptic Soy Agar (TSA). All test organisms were grown on TSA with 0.07% lecithin and 0.5% Tween 80 (TSALT) in 150-mm Petri dishes for 24 hr prior to use in preservative efficacy testing. *S. aureus*, *E. coli*, *Bacillus* sp., and *B. cereus* were incubated at 37°C. All *Pseudomonas* test organisms were incubated at 30°C for 24 hr in preparation for preservative efficacy testing. All Petri dishes prepared from samples for determination of aerobic plate counts (APCs) were incubated for 48 hr at 37°C (except for those prepared from samples challenged with both *P. cepacia* strains and *P. fluorescens*, which were incubated for 48 hr at 30°C).

**TEST SAMPLES**

The test samples used in this study included a nonionic o/w lotion (Table I). The lotion was prepared as follows: Parts A, B, and C were heated to 70°C. Part A was added to part C with continuous mixing. Part B was added after 5 min, and mixing was continued as the batch was cooled to ambient temperature. This lotion was selected for studying the effects of emulsion pH, [polyacrylic acid resin (934 or 941) or acrylic acid copolymer (1342), B.F. Goodrich] neutralizing agent [TEA 99% or 85% (Dow Chemical), TEA 99% (Union Carbide), or NaOH], and CaCl₂, on antimicrobial activity. The pH readings were adjusted to the stated value (± 0.1 pH unit).
Table I
Nonionic Lotion Formula

<table>
<thead>
<tr>
<th>Part</th>
<th>Formula components</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Mineral oil</td>
<td>7.50</td>
</tr>
<tr>
<td></td>
<td>Glyceryl stearate and PEG 100 stearate</td>
<td>3.50</td>
</tr>
<tr>
<td>B</td>
<td>Water</td>
<td>30.00</td>
</tr>
<tr>
<td></td>
<td>Acrylic acid homopolymer/copolymer</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>TEA 99%*</td>
<td>0.30</td>
</tr>
<tr>
<td>C</td>
<td>Methyl paraben</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Water</td>
<td>58.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.00</td>
</tr>
</tbody>
</table>

* pH of lotion adjusted to pH 7.0 (± 0.1) by addition of TEA.

A batch of nonionic lotion was prepared and brought up to 99.9% of the final weight by the addition of water after cooling. Approximately 60 min before use in preservative efficacy testing, the lotion with 0.1% CaCl₂ was prepared by adding 0.5 g CaCl₂ to 499.5 g of the lotion base, with several minutes of mixing. The control was prepared by adding 0.1% filter-sterilized deionized water to the remainder of the batch of lotion, with mixing. The pH of the lotion with 0.1% CaCl₂ was pH 5.7 and had a water-thin viscosity. The pH of the control lotion was pH 6.8, and the viscosity of this lotion was not changed noticeably by the addition of water.

Aqueous samples of 0.2% MP, 0.01% Na₂EDTA, 0.2% MP + 0.01% Na₂EDTA, and deionized water (control) were prepared for sterilization time (ST) determinations and were filter-sterilized by passing 5-ml aliquots of each solution through a 0.45-μm filter in a Sweeny-type filter holder. Similarly, aliquots of stock solutions of phenoxyethanol (P) and Nipastat (N), which is a 50:15:10:20 mixture of methyl-, ethyl-, propyl-, and butyl-paraben, were added to sterile saline to give final concentrations of 0, 0.1, 0.5, and 1.0% P, and 0, 0.005, 0.01, 0.05, and 0.10% N.

TEST PROCEDURES

Preservative efficacy tests were performed using saline suspensions from surface growth of each test organism after incubation for 24 hr on TSALT, as described above. A loopful of growth was suspended in 5 ml of saline to give about 10⁷ organisms/ml, and 0.1 ml of the saline suspension of each test organism was added to separate 50-ml portions of each test sample in a 100-ml screw-capped bottle. Samples were taken at designated times; APCs were performed using Letheen Broth with 0.01% (v/v) Triton X-100 diluent and TSALT as the recovery system; the Petri dishes were incubated at 37°C for all test organisms (except for both P. cepacia strains and P. fluorescens, which were incubated at 30°C); and D-values were determined by taking the negative reciprocal of the slope of the survivor curve for each test organism in each test sample, as described in an earlier report (8). All tests were performed at least in duplicate, unless otherwise stated.
A modified preservative efficacy test was used to determine sterilization times (STs) for the test organisms in aqueous samples. The inocula were prepared as above and added to solutions of MP, Na₂EDTA, MP + Na₂EDTA, and deionized water (control). The contents of the tubes were mixed using a Vortex Genie Mixer, and samples were taken at 0, 2, 4, 24, and 48 hr by inserting a sterile swab into the liquid in each tube. A separate Petri dish containing TSALT was streaked with each swab. The Petri dishes were incubated for 48 hr at 30° or 37°C, depending on the test organism, as described above. The Petri dishes were examined for growth of the test organisms, and the ST was determined to be the first time at which test organisms were not recovered from the test solution.

The ST and the concentration of organisms in the inoculum were used to calculate the slope of the survivor curve, correcting for the volume change that occurs when the inoculum is added to the test system. In these studies, the concentration of organisms in test tube samples was 1/100th the concentration in the inoculum because 0.1 ml was added to 10-ml solution in each test tube. D-values were determined by taking the negative reciprocal of the slope of each survivor curve (8). Where no endpoint was reached in the ST experiments, because the test organisms were still alive at 48 hr, the minimum possible ST (MPST) was used. The MPST was defined as a time longer than the last time at which test organisms were recovered (i.e., >48 hr). The MPST and the concentration of the organisms in the inoculum were used to construct a virtual survival curve. The maximum possible slope (MPSlope) of the virtual survivor curve and the corresponding minimum possible D-value (MPD-value) were calculated.

Synergism was observed when the slope of the survivor curve obtained with the combined components was a larger negative number than the sum of the slopes (or MPSlopes) for each of the components determined separately.

Duplicate samples of tap water; tap water containing 0.01% Na₂EDTA, adjusted to pH 7.0 by the addition of one drop of TEA; and deionized water were tested for water hardness by the method of Betz Laboratories (9).

A 0.1% 1342 dispersion was prepared by slowly adding 0.1 g 1342 to 99.9 g tap water with vigorous agitation. This dispersion was stirred for 2 hr at room temperature to allow hydration of the 1342. The beakers containing tap water and the 1342 dispersion were covered with aluminum foil and were allowed to stand, undisturbed, at room temperature for 3 days. The dispersion settled to about ⅓ of the liquid level in the beaker after this period. The water layer was decanted to give 1342-treated tap water. Duplicate samples of tap water, 1342-treated tap water, and freshly drawn deionized water were assayed for hardness (9).

Mean D-values and standard deviation (s) were calculated. Statistically significant differences between mean D-values of duplicate experiments were determined by a two-
The survivor curves for *P. aeruginosa* in 0.2% MP adjusted to pH 7.0 with TEA or NaOH, with and without 0.2% 1342, are shown in Figure 1. The system with 1342, MP, and TEA inactivated *P. aeruginosa* so quickly that the APC was 600/ml immediately after inoculation. No organisms were recovered at 2 hr or thereafter in this system. The estimated D-value for *P. aeruginosa* was <0.006 hr, based on the APC of the inoculum and the APC immediately after inoculation. This is indicated by the dashed line in the figure. The system containing MP and 1342 neutralized with NaOH had an initial APC of 4.3 × 10⁵/ml and a D-value of 0.9 hr. Linear regression analysis gave an estimated ST of slightly greater than 5 hr. Solutions of MP and 0.16% NaOH or 0.6% TEA (the amounts of these bases required to adjust the pH to 7.0) did not kill *P. aeruginosa* during the 24-hr test period. This initial experiment was performed once using duplicate Petri dishes.

The results in Table II show the preservative efficacy test results of the nonionic lotion challenged with *S. aureus*, *B. cereus*, *E. coli*, and different species of *Pseudomonas*. Most species of *Pseudomonas* were inactivated rapidly, with D-values of ≤1.1 hr. The preservative system was much less effective against *S. aureus*, *B. cereus*, and *E. coli* than against most species of *Pseudomonas* tested. *Pseudomonas* sp., *P. cepacia* 13945, and *P. cepacia* 25416 were more resistant than the other pseudomonads to the anti-*Pseudomonas* action.
Table II
Preservative Efficacy Test Results Obtained With Nonionic Lotion Containing 0.2% MP and 0.2% 1342 Challenged With S. aureus, B. cereus, E. coli, and Several Different Species of Pseudomonas

<table>
<thead>
<tr>
<th>Test organism</th>
<th>D-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. aeruginosa 9027</td>
<td>0.9 (0.3)</td>
</tr>
<tr>
<td>P. aeruginosa 10145</td>
<td>1.1 (0.1)</td>
</tr>
<tr>
<td>P. cepacia 13945</td>
<td>24* (4)</td>
</tr>
<tr>
<td>P. cepacia 25416</td>
<td>11* (0)</td>
</tr>
<tr>
<td>P. fluorescens 13525</td>
<td>1.1 (0.9)</td>
</tr>
<tr>
<td>P. putida 12633</td>
<td>1.0 (0.6)</td>
</tr>
<tr>
<td>P. stutzeri 17588</td>
<td>0.5 (0)</td>
</tr>
<tr>
<td>Pseudomonas sp. 9230</td>
<td>9.3 (0.9)</td>
</tr>
<tr>
<td>S. aureus 6538</td>
<td>26* (0)</td>
</tr>
<tr>
<td>B. cereus 11778</td>
<td>7.2 (0.4)</td>
</tr>
<tr>
<td>E. coli 8739</td>
<td>78* (28)</td>
</tr>
</tbody>
</table>

Table values are mean D-values in hours, with the standard deviations in parentheses. * D-values over 10 hr were rounded to the nearest whole number.

of the preservative system, as indicated by the larger D-values obtained with these organisms.

The D-values and slopes of the survivor curves obtained with P. aeruginosa, P. cepacia, P. fluorescens, and P. putida in the nonionic lotion with MP; with 934, 941, or 1342 and no MP; and with MP and 934, 941, or 1342 are presented in Table III. All lotions were adjusted to pH 7.0 with TEA. The D-values were much smaller (i.e., the rates of death of the test organisms were much faster) in all lotions containing 934, 941, or 1342 with MP than in lotions containing only MP or acrylic acid homopolymer/copolymer. The dramatic anti-Pseudomonas effect obtained with MP + 934, in comparison with MP or 934, is illustrated in Figure 2.

In this work, a synergistic effect in multicomponent preservative systems was defined as one in which the slope (i.e., rate of death of the population of test organisms) was a larger negative number in the presence of two or more agents than the sum of the slopes in the presence of each agent by itself. Thus, a synergistic effect was obtained when the slope in the presence of the MP and acrylic acid homopolymer/copolymer was a larger negative number than the sum of the slopes in the presence of MP (without 934, 941, or 1342) and 934, 941, or 1342 (without MP). The test systems that produced synergistic anti-Pseudomonas activity are indicated by an asterisk in Table III. All test systems, except the 1342/MP system challenged with P. cepacia, exhibited synergistic antibacterial activity. The antibacterial action of MP and 1342 for P. cepacia was additive in this test lotion.

The results of preservative efficacy testing of the nonionic lotion containing 0.2% 1342 and 0.2% MP, with and without 0.1% CaCl₂, are shown in Table IV. The addition of CaCl₂ to the lotion significantly increased the D-values and eliminated the anti-Pseudomonas synergy for P. aeruginosa, P. fluorescens, and P. putida. The CaCl₂ significantly decreased the D-values for P. cepacia (Table IV). No attempt was made to demonstrate synergy or antagonism in the experiments done with CaCl₂ test systems.

Addition of CaCl₂ to the lotion decreased the viscosity to a water-thin consistency and decreased the pH from 6.8 to 5.7, but no phase separation was apparent during the

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Table III
Synergism of MP and Polyacrylic Acid Homopolymer/Copolymer: Preservative Efficacy Test Results in Nonionic Lotion Containing 0.2% MP; 0.2% 934, 941, or 1342; and 0.2% MP + 0.2% 934, 941, or 1342, Challenged With P. aeruginosa 9027, P. cepacia 13945, P. fluorescens 13525, and P. putida 12633

934 Test system:

<table>
<thead>
<tr>
<th>Test organism</th>
<th>MP</th>
<th>934</th>
<th>MP + 934</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D-value</td>
<td>Slope</td>
<td>D-value</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>6.3</td>
<td>-0.16</td>
<td>25</td>
</tr>
<tr>
<td>P. cepacia</td>
<td>52</td>
<td>-0.02</td>
<td>35</td>
</tr>
<tr>
<td>P. fluorescens</td>
<td>31</td>
<td>-0.03</td>
<td>64</td>
</tr>
<tr>
<td>P. putida</td>
<td>34</td>
<td>-0.03</td>
<td>9.3</td>
</tr>
</tbody>
</table>

941 Test system:

<table>
<thead>
<tr>
<th>Test organism</th>
<th>MP</th>
<th>941</th>
<th>MP + 941</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D-value</td>
<td>Slope</td>
<td>D-value</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>6.3</td>
<td>-0.16</td>
<td>390</td>
</tr>
<tr>
<td>P. cepacia</td>
<td>52</td>
<td>-0.02</td>
<td>45</td>
</tr>
<tr>
<td>P. fluorescens</td>
<td>31</td>
<td>-0.03</td>
<td>400</td>
</tr>
<tr>
<td>P. putida</td>
<td>34</td>
<td>-0.03</td>
<td>8</td>
</tr>
</tbody>
</table>

1342 Test system:

<table>
<thead>
<tr>
<th>Test organism</th>
<th>MP</th>
<th>1342</th>
<th>MP + 1342</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D-value</td>
<td>Slope</td>
<td>D-value</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>6.3</td>
<td>-0.16</td>
<td>60</td>
</tr>
<tr>
<td>P. cepacia</td>
<td>52</td>
<td>-0.02</td>
<td>48</td>
</tr>
<tr>
<td>P. fluorescens</td>
<td>31</td>
<td>-0.05</td>
<td>110</td>
</tr>
<tr>
<td>P. putida</td>
<td>34</td>
<td>-0.05</td>
<td>16</td>
</tr>
</tbody>
</table>

Table values are D-values in hours and the corresponding slopes of the survivor curves in hours⁻¹.
* Synergistic anti-Pseudomonas activity is indicated by a larger negative slope with MP + acrylic acid derivative than with the sum of slopes obtained with MP and polyacrylic acid homopolymer/copolymer.

course of the preservative testing. A 0.1% solution of unneutralized 1342 in tap water had moderate chelating ability. The mean hardness of duplicate tap water samples was 109 (s = 0.71) ppm as CaCO₃, and the mean hardness of duplicate 0.1% 1342 solutions was 75 (s = 1.5) ppm as CaCO₃. These means were significantly different (p < 0.01).

The STs of the test organisms in MP, Na₂EDTA, and MP + Na₂EDTA solutions were determined. The 0.2% MP solutions were not rapidly bacteriocidal because all test organisms (including S. aureus and E. coli) were viable at 24 hr. P. cepacia 13945 and P. putida were not recovered at 48 hr (Table V). Similarly, all but two of the pseudomonad test organisms were recovered from the Na₂EDTA solutions at 48 hr. In contrast, the combination of 0.01% Na₂EDTA + 0.2% MP showed marked anti-Pseudomonas action, because all test organisms, except P. cepacia 13945 and 25416 and Pseudomonas sp. 9230, had STs <4 hr. P. cepacia 13945 was the only pseudomonad recovered at the 24-hr sampling. S. aureus and E. coli had STs >48 hr. These results parallel the results obtained in Table II, in which both P. cepacia strains and Pseudomonas sp. were found to
Figure 2. Comparison of D-values for *P. aeruginosa* 9027, *P. cepacia* 13945, *P. fluorescens* 13525, and *P. putida* 12633, determined by preservative efficacy testing of the nonionic lotion containing 0.2% MP, 0.2% 934, or both 0.2% MP and 0.2% 934.

be much more resistant to the preservative system of the lotion containing 0.2% MP + 0.2% 1342. Even though the *P. stutzeri* inoculum contained $1.7 \times 10^7$/ml, this organism was not recovered from the initial sampling in the MP + Na$_2$EDTA solution. Similarly, *P. stutzeri* was inactivated more rapidly than all other test organisms in the lotion containing MP + 1342 (Table II). Hardness analyses of tap water, tap water containing 0.01% Na$_2$EDTA, and deionized water gave mean hardness values of 137 (s = 5.0), 109 (s = 1.4), and 20 (s = 14) ppm CaCO$_3$, respectively. These means were significantly different ($p < 0.05$).

The STs obtained in Table V were used to calculate survivor curve slopes and D-values and to demonstrate synergy for all *Pseudomonas* test organisms in 0.1% MP + 0.01% Na$_2$EDTA solutions, except for *P. cepacia* 13945 (Table VI). It was possible to calculate a slope and D-value where STs were known, as in the case for *P. cepacia* 13945 in 0.2%

Table IV

<table>
<thead>
<tr>
<th>Test organism</th>
<th>Lotion</th>
<th>Lotion with CaCl$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em></td>
<td>1.8 (0.8)</td>
<td>10* (0)</td>
</tr>
<tr>
<td><em>P. cepacia</em></td>
<td>90* (16)</td>
<td>13* (0.7)</td>
</tr>
<tr>
<td><em>P. fluorescens</em></td>
<td>2.0 (0.07)</td>
<td>8.5 (0.4)</td>
</tr>
<tr>
<td><em>P. putida</em></td>
<td>2.2 (0.28)</td>
<td>11* (1.0)</td>
</tr>
</tbody>
</table>

Table values are mean D-values from duplicate experiments, with standard deviations in parentheses.

* D-values over 10 hr were rounded to the nearest whole number.

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From: SCC Media Library & Resource Center (library.scconline.org)
Table V
Determination of Sterilization Times of Several *Pseudomonas* Species in MP, Na₂EDTA, and MP + Na₂EDTA Solutions

<table>
<thead>
<tr>
<th>0.2% MP solutions:</th>
<th>Test organism</th>
<th>0 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>24 hr</th>
<th>48 hr</th>
<th>ST</th>
<th>MPST</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em> 9027</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 27853</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 9721</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 10145</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. cepacia</em> 13945</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td><em>P. cepacia</em> 25416</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td><em>P. fluorescens</em> 13525</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+[2]</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. putida</em> 12633</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td><em>P. putida</em> 17588</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td><em>P. stutzeri</em> 9230</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td><em>S. aureus</em> 6538</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td><em>E. coli</em> 8739</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>48</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>0.01% Na₂EDTA solutions:</th>
<th>Test organism</th>
<th>0 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>24 hr</th>
<th>48 hr</th>
<th>ST</th>
<th>MPST</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em> 9027</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 27853</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 9721</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 10145</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. cepacia</em> 13945</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. cepacia</em> 25416</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. fluorescens</em> 13525</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. putida</em> 12633</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. putida</em> 17588</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. stutzeri</em> 9230</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>S. aureus</em> 6538</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>E. coli</em> 8739</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>0.2% MP + 0.01% Na₂EDTA solution:</th>
<th>Test organism</th>
<th>0 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>24 hr</th>
<th>48 hr</th>
<th>ST</th>
<th>MPST</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em> 9027</td>
<td>+</td>
<td>+</td>
<td>[s]</td>
<td>—</td>
<td>—</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 27853</td>
<td>+</td>
<td>+</td>
<td>[s]</td>
<td>+</td>
<td>[2]</td>
<td>—</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 9721</td>
<td>+</td>
<td>+</td>
<td>[s]</td>
<td>—</td>
<td>—</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 10145</td>
<td>+</td>
<td>+</td>
<td>[1]</td>
<td>—</td>
<td>—</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>P. cepacia</em> 13945</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td><em>P. cepacia</em> 25416</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>P. fluorescens</em> 13525</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>P. putida</em> 12633</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>P. putida</em> 17588</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.1*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp. 9230</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td><em>S. aureus</em> 6538</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td><em>E. coli</em> 8739</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>24</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deionized water (control):</th>
<th>Test organism</th>
<th>0 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>24 hr</th>
<th>48 hr</th>
<th>ST</th>
<th>MPST</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em> 9027</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 27853</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 9721</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 10145</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>&gt;48</td>
</tr>
</tbody>
</table>

Purchased for the exclusive use of nofirst nolast (unknown)
From: SCC Media Library & Resource Center (library.scconline.org)
Table V (Continued)

Deionized water (control):

<table>
<thead>
<tr>
<th>Test organism</th>
<th>0 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>24 hr</th>
<th>48 hr</th>
<th>ST</th>
<th>MPST</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. cepacia</em> 13945</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. cepacia</em> 25416</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. fluorescens</em> 13525</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. putida</em> 12633</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>P. stutzeri</em> 17588</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>&gt;48</td>
</tr>
<tr>
<td>Pseudomonas sp. 9230</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>S. aureus</em> 6538</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>&gt;48</td>
</tr>
<tr>
<td><em>E. coli</em> 8739</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>&gt;48</td>
</tr>
</tbody>
</table>

Explanation of symbols: +, growth on TSALT; --, no growth on TSALT; numbers in brackets (i.e., [1] and [2]) indicate the number of colonies growing on TSALT; [s] is used to designate scant growth (i.e., 8–15 colonies growing on TSALT). ST, sterilization time in hr. MPST, minimum possible sterilization time in hr.

* P. stutzeri was not recovered, so ST was set at 0.1 hr because this is the approximate time required for setting up the series of samples after inoculation.

APC of the saline suspensions inocula:

- *P. aeruginosa* 9027 = 1.1 \times 10^7/ml.
- *P. aeruginosa* 9721 = 1.8 \times 10^7/ml.
- *P. aeruginosa* 27853 = 1.5 \times 10^7/ml.
- *P. aeruginosa* 10145 = 2.0 \times 10^7/ml.
- *P. cepacia* 13945 = 1.7 \times 10^7/ml.
- *P. cepacia* 25416 = 9.9 \times 10^6/ml.
- *P. fluorescens* 13525 = 1.6 \times 10^7/ml.
- *P. putida* 12633 = 1.6 \times 10^7/ml.
- *P. stutzeri* 17588 = 1.7 \times 10^7/ml.
- Pseudomonas sp. 9230 = 6.3 \times 10^6/ml.
- *S. aureus* 6538 = 6.3 \times 10^6/ml.
- *E. coli* 8739 = 6.3 \times 10^6/ml.

MP. It was not possible to calculate STs, slopes, and D-values when the organisms were recovered at 48 hr (i.e., ST >48 hr), as for all strains of *P. aeruginosa* in MP or Na₂EDTA. Nevertheless, the survivor curve slope method may be used to determine synergy when the experimentally determined rate of death (slope) is a larger negative number than the sum of the MPSlopes of each of the components. Use of MPSlopes in determining synergy is discussed in greater detail below. No synergy was observed for *S. aureus* or *E. coli* in these experiments.

The results in Table VII show the growth response of *P. aeruginosa* 9027 on TSALT after exposure to various combinations of P and/or N in saline. As one reviews the growth responses of *P. aeruginosa* following exposure to various combinations of P and N, it is apparent that several of the combinations killed the population of *P. aeruginosa* faster than the same concentrations of either N or P used alone. The test organism was not recovered from test systems containing 0.1% N (except for one tube containing both 1% P and 0.1% N, in which one colony developed on TSALT at the 0 hr sampling). *P. aeruginosa* grew on TSALT streaked with 0.1% N; consequently, preservative carryover was not responsible for the lack of growth on TSALT in systems containing the highest concentration of N. Synergy was observed when the slope of the survivor curve was a larger negative number than the sum of the slopes (or MPSlopes) for the components. The systems in which synergism was observed are marked with an asterisk (Table VIII).
Table VI

Use of STs and MPSTs to Determine Antimicrobial Synergy for Several Species of *Pseudomonas* in 0.2% MP, 0.01% Na$_2$EDTA, and 0.2% MP + 0.01% Na$_2$EDTA (data from Table V)

<table>
<thead>
<tr>
<th>Test organism</th>
<th>ST</th>
<th>MPST</th>
<th>D-value</th>
<th>MPD-value</th>
<th>Slope</th>
<th>MPSlope</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0.2% MP solution:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>P. aeruginosa</em> 9027</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.5</td>
<td></td>
<td>&lt;−0.105</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 27853</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.3</td>
<td></td>
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</tr>
<tr>
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<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.1</td>
<td></td>
<td>&lt;−0.110</td>
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<tr>
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<td>48</td>
<td></td>
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<td>−0.109</td>
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<tr>
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<td>&lt;−0.104</td>
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<td>&gt;48</td>
<td></td>
<td>&gt;9.2</td>
<td></td>
<td>&lt;−0.108</td>
</tr>
<tr>
<td><em>P. putida</em> 12633</td>
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<td></td>
<td>9.2</td>
<td></td>
<td></td>
<td>−0.108</td>
</tr>
<tr>
<td><em>P. stutzeri</em> 17588</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.2</td>
<td></td>
<td>&lt;−0.109</td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp. 9230</td>
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<td>&gt;48</td>
<td></td>
<td>&gt;10</td>
<td></td>
<td>&lt;−0.100</td>
</tr>
<tr>
<td><em>S. aureus</em> 6538</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.3</td>
<td></td>
<td>&lt;−0.107</td>
</tr>
<tr>
<td><em>E. coli</em> 8739</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;10</td>
<td></td>
<td>&lt;−0.100</td>
</tr>
<tr>
<td><strong>0.01% Na$_2$EDTA solution:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 9027</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.5</td>
<td></td>
<td>&lt;−0.105</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 27853</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.3</td>
<td></td>
<td>&lt;−0.108</td>
</tr>
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<td>&gt;48</td>
<td></td>
<td>&gt;9.1</td>
<td></td>
<td>&lt;−0.109</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 10145</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.1</td>
<td></td>
<td>&lt;−0.110</td>
</tr>
<tr>
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<td>48</td>
<td></td>
<td>9.2</td>
<td></td>
<td></td>
<td>−0.109</td>
</tr>
<tr>
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<td></td>
<td>&gt;9.6</td>
<td></td>
<td>&lt;−0.104</td>
</tr>
<tr>
<td><em>P. fluorescens</em> 13525</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.2</td>
<td></td>
<td>&lt;−0.108</td>
</tr>
<tr>
<td><em>P. putida</em> 12633</td>
<td>48</td>
<td></td>
<td>9.2</td>
<td></td>
<td></td>
<td>−0.108</td>
</tr>
<tr>
<td><em>P. stutzeri</em> 17588</td>
<td>24</td>
<td></td>
<td>4.6</td>
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<td></td>
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<td></td>
<td>&gt;10</td>
<td></td>
<td>&lt;−0.100</td>
</tr>
<tr>
<td><em>S. aureus</em> 6538</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.3</td>
<td></td>
<td>&lt;−0.107</td>
</tr>
<tr>
<td><em>E. coli</em> 8739</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;10</td>
<td></td>
<td>&lt;−0.100</td>
</tr>
<tr>
<td><strong>0.2% MP + 0.01% Na$_2$EDTA solution:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 9027</td>
<td>4</td>
<td></td>
<td>0.8</td>
<td></td>
<td></td>
<td>−1.260*</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 27853</td>
<td>4</td>
<td></td>
<td>0.8</td>
<td></td>
<td></td>
<td>−1.294*</td>
</tr>
<tr>
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<td></td>
<td>4.6</td>
<td></td>
<td></td>
<td>−0.219*</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> 10145</td>
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<td></td>
<td>0.8</td>
<td></td>
<td></td>
<td>−1.325*</td>
</tr>
<tr>
<td><em>P. cepacia</em> 13945</td>
<td>48</td>
<td></td>
<td>9.2</td>
<td></td>
<td></td>
<td>−0.109</td>
</tr>
<tr>
<td><em>P. cepacia</em> 25416</td>
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<td></td>
<td>0.4</td>
<td></td>
<td></td>
<td>−2.498*</td>
</tr>
<tr>
<td><em>P. fluorescens</em> 13525</td>
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<td></td>
<td>0.5</td>
<td></td>
<td></td>
<td>−2.102*</td>
</tr>
<tr>
<td><em>P. putida</em> 12633</td>
<td>2</td>
<td></td>
<td>0.4</td>
<td></td>
<td></td>
<td>−2.602*</td>
</tr>
<tr>
<td><em>P. stutzeri</em> 17588</td>
<td>0.1</td>
<td></td>
<td>&gt;0.02</td>
<td></td>
<td></td>
<td>&lt;−52.304*</td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp. 9230</td>
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<td></td>
<td>5.0</td>
<td></td>
<td></td>
<td>−0.200</td>
</tr>
<tr>
<td><em>S. aureus</em> 6538</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;9.3</td>
<td></td>
<td>&lt;−0.107</td>
</tr>
<tr>
<td><em>E. coli</em> 8739</td>
<td></td>
<td>&gt;48</td>
<td></td>
<td>&gt;10</td>
<td></td>
<td>&lt;−0.100</td>
</tr>
</tbody>
</table>

Explanation of symbols: ST, sterilization time in hr; MPST, minimum possible sterilization time in hr; D-value, D-value in hr; MPD-value, minimum possible D-value in hr; Slope, slope of the survivor curve, in hr$^{-1}$; MPSlope, maximum possible slope of the virtual survivor curve, in hr$^{-1}$.

* Synergy observed, because the slope of the survivor curve was a larger negative number than the sum of the slopes (or MPSlopes) for the same concentrations of MP and Na$_2$EDTA taken separately.

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### Table VII

Determination of Sterilization Times for *P. aeruginosa* 9027 in Saline Containing 0 to 1.0% Phenoxyethanol and 0 to 0.10% Nipastat

<table>
<thead>
<tr>
<th>Preservative</th>
<th>0 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>24 hr</th>
<th>48 hr</th>
<th>ST</th>
<th>MPST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline control</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>0.1% P</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>0.5% P</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>1.0% P</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>48</td>
<td>---</td>
</tr>
<tr>
<td>0.005% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>0.01% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>0.05% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>0.10% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>2</td>
<td>---</td>
</tr>
<tr>
<td>0.1% P + 0.005% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>0.1% P + 0.01% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>0.1% P + 0.05% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>2</td>
<td>---</td>
</tr>
<tr>
<td>0.1% P + 0.10% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>0.1*</td>
<td>---</td>
</tr>
<tr>
<td>0.5% P + 0.005% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>---</td>
<td>&gt;48</td>
</tr>
<tr>
<td>0.5% P + 0.01% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>24</td>
<td>---</td>
</tr>
<tr>
<td>0.5% P + 0.05% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>2</td>
<td>---</td>
</tr>
<tr>
<td>0.5% P + 0.10% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>0.1*</td>
<td>---</td>
</tr>
<tr>
<td>1.0% P + 0.005% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>4</td>
<td>---</td>
</tr>
<tr>
<td>1.0% P + 0.01% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>4</td>
<td>---</td>
</tr>
<tr>
<td>1.0% P + 0.05% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>nd**</td>
<td>4</td>
</tr>
<tr>
<td>1.0% P + 0.10% N</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>+/+</td>
<td>2</td>
<td>---</td>
</tr>
</tbody>
</table>

Table symbols represent growth of *P. aeruginosa* on one (+/-), on both (+/+), or neither (-/-) TSALT plates inoculated from duplicate tubes containing the indicated concentrations of phenoxyethanol (P) or Nipastat (N). Tubes with P and/or N were incubated at room temperature for the times indicated. ST, sterilization time in hr; MPST, minimum possible sterilization time in hr.

* Although *P. aeruginosa* was not recovered in these samples, the ST was set at 0.1 hr because this is the approximate time required for setting up the series of samples after inoculation.

** nd, not done.

The *P. aeruginosa* inoculum APC = 1.7 × 10^7/ml.

### DISCUSSION

This work was initiated when it was realized that the preservative system in adequately preserved nonionic emulsion systems was inactivating *P. aeruginosa* much more rapidly than the other test organisms customarily used in preservative efficacy testing (8). All of these emulsions contained MP. The parabens are known to be active against a wide range of gram-positive bacteria and fungi, but they are less active against gram-negative bacteria, especially the pseudomonads (12). Although 0.2% MP did not kill *P. aeruginosa* in 24 hr, combinations of MP and 1342 caused rapid killing of this test organism (Figure 1). The nonionic lotion with 0.2% MP (Table I) was selected for investigating the cause of this rapid inactivation of *P. aeruginosa* observed in our laboratory.

*Pseudomonas* has been particularly troublesome for the cosmetic and pharmaceutical industries. *P. aeruginosa, P. cepacia, P. fluorescens, P. putida,* and *P. stutzeri* can survive and grow in deionized water, and they have been isolated from contaminated cosmetics (13—15). *P. aeruginosa* has been recovered from contaminated mascaras and has caused...
### Table VIII
Use of STs and MPSTs to Determine Antimicrobial Synergy for *P. aeruginosa* 9027 in 0 to 1.0% Phenoxyethanol and 0 to 0.10% Nipastat (data from Table VII)

<table>
<thead>
<tr>
<th>Preservative</th>
<th>ST</th>
<th>MPST</th>
<th>D-value</th>
<th>MPD-value</th>
<th>Slope</th>
<th>MPSlope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline control</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>0.1% P</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>0.5% P</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>1.0% P</td>
<td>48</td>
<td>—</td>
<td>6.6</td>
<td>—</td>
<td>−0.151</td>
<td>—</td>
</tr>
<tr>
<td>0.005% N</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>0.01% N</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>0.05% N</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>0.10% N</td>
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<td>—</td>
<td>0.3</td>
<td>—</td>
<td>−3.615</td>
<td>—</td>
</tr>
<tr>
<td>0.1% P + 0.005% N</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>0.1% P + 0.01% N</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>0.1% P + 0.05% N</td>
<td>2</td>
<td>—</td>
<td>0.3</td>
<td>—</td>
<td>−3.615*</td>
<td>—</td>
</tr>
<tr>
<td>0.1% P + 0.10% N</td>
<td>0.1</td>
<td>—</td>
<td>0.01</td>
<td>—</td>
<td>−72.304*</td>
<td>—</td>
</tr>
<tr>
<td>0.5% P + 0.005% N</td>
<td>—</td>
<td>&gt;48</td>
<td>—</td>
<td>&gt;6.6</td>
<td>—</td>
<td>&lt; −0.151</td>
</tr>
<tr>
<td>0.5% P + 0.01% N</td>
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<td>—</td>
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<tr>
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<td>—</td>
<td>0.3</td>
<td>—</td>
<td>−3.615*</td>
<td>—</td>
</tr>
<tr>
<td>0.5% P + 0.10% N</td>
<td>0.1</td>
<td>—</td>
<td>0.01</td>
<td>—</td>
<td>−72.304*</td>
<td>—</td>
</tr>
<tr>
<td>1.0% P + 0.005% N</td>
<td>4</td>
<td>—</td>
<td>0.6</td>
<td>—</td>
<td>−1.808*</td>
<td>—</td>
</tr>
<tr>
<td>1.0% P + 0.01% N</td>
<td>4</td>
<td>—</td>
<td>0.6</td>
<td>—</td>
<td>−1.808*</td>
<td>—</td>
</tr>
<tr>
<td>1.0% P + 0.05% N</td>
<td>4</td>
<td>—</td>
<td>0.6</td>
<td>—</td>
<td>−1.808*</td>
<td>—</td>
</tr>
<tr>
<td>1.0% P + 0.10% N</td>
<td>2</td>
<td>—</td>
<td>0.3</td>
<td>—</td>
<td>−3.615</td>
<td>—</td>
</tr>
</tbody>
</table>

Explanation of symbols: ST, sterilization time in hr; MPST, minimum possible sterilization time in hr; D-value, D-value in hr; MPD-value, minimum possible D-value in hr; Slope, slope of the survivor curve, in hr⁻¹; MPSlope, maximum possible slope of the virtual survivor curve, in hr⁻¹.

* Synergy observed, because the slope of the survivor curve was a larger negative number than the sum of the slopes (or MPSlopes) for the same concentrations of P and N taken separately.

Corneal ulcers (16,17). This organism produces several virulence factors that are believed to contribute to its multifactorial pathogenicity and complicate the clinical course of infections (18–23).

*P. cepacia* has considerable physiological versatility and has broad resistance to antibiotics (24,25). *P. cepacia* 13945 was selected for detailed investigation in this work because, generally, it was more resistant than the other pseudomonads in our culture collection to preservative systems containing MP and acrylic acid homopolymer/copolymer. *P. fluorescens* and *P. putida* were selected for detailed studies here because they are nutritionally versatile and are able to grow on a wide variety of substrates (24,26).

When the lotion was prepared using 0.2% 1342 and 0.2% MP, preservative efficacy testing revealed significant antibacterial activity against most test cultures of *Pseudomonas* (Table II). All fluorescent pseudomonads [*P. aeruginosa, P. fluorescens, P. putida* and *P. stutzeri* (24)] were inactivated rapidly, with D-values ≲1.1 hr. Both *P. cepacia* strains were inactivated more slowly in the preservative system than were the fluorescent pseudomonads. The reasons for the resistance of strains 13945 and 25416 are not known; however, *P. cepacia* is nutritionally versatile and accumulates poly-beta-hydroxybutyrate (PHB) as a carbon reserve (24,27,28). These physiological characteristics may enable *P. cepacia* to be more difficult to inactivate in test systems containing chelating agents and MP than are the fluorescent pseudomonads.
We speculate that PHB may be a classical chelating agent, in the sense described by Marshall et al. (29). Intracellular accumulation of PHB by *P. cepacia* (24) may enable this species to retain divalent metal ions as a PHB chelate, which could provide an internal reservoir that may help prevent loss of metal ions to exogenous chelators. This would enable *P. cepacia* to resist more effectively the destabilization caused by external chelating agents (7) than do the fluorescent pseudomonads, which do not accumulate PHB (24). Definitive studies are needed to confirm this.

The data in Table II show that the preservative system in this lotion was less effective for *S. aureus*, *B. cereus*, and *E. coli* than it was for many of the *Pseudomonas* test cultures. The percentage of sporulation of *Bacillus* sp. was 30–50% at 24 hr (8); however, *B. cereus* produced only a few visible spores in a microscopic field (1000×) when 24-hr TSALT cultures were suspended, stained, and examined microscopically. Experience with *Bacillus* sp. and *B. cereus* 11778 revealed that these organisms produce few (if any) preservative system-resistant spores during 24-hr growth on TSALT at 37°C. These organisms were used to determine the effects of preservative systems on vegetative bacilli.

The data in Table III illustrate anti-*Pseudomonas* synergy because the rate of inactivation (i.e., slope of the survivor curve) of each population of test organisms in MP + 934, 941, or 1342 was a larger negative number than the sum of the rates (slopes) of inactivation in MP and each acrylic acid homopolymer/copolymer taken separately. *P. cepacia* showed an additive effect in lotion containing MP + 1342.

The effect of nonionic lotion pH on the results of preservative efficacy testing with *P. aeruginosa*, *P. cepacia*, *P. fluorescens*, and *P. putida* was determined in lotions adjusted to pH 6–9 by adding varying amounts of TEA. No consistent effect of lotion pH on antibacterial activity with these four test organisms was observed. The antibacterial effect of MP is reported to increase with decreasing pH below the pKa of MP (pH 8.17) (30). *P. cepacia* was inactivated more slowly than the other pseudomonads in lotions adjusted to pH 6–9.

Incorporation of ≥0.1% 934, 941, or 1342 into the nonionic lotion produced a marked decrease in the D-values for *P. aeruginosa*, *P. cepacia*, *P. fluorescens*, and *P. putida*, compared to the D-values obtained in lotions containing no 934, 941, or 1342. We were unable to demonstrate a consistent relationship between the acrylic acid homopolymer/copolymer concentration, from 0.1–0.4%, and the observed rates of death of the test organisms. It is possible that the maximum synergistic action was obtained at ≤0.1% polycrylic acid/acrylic acid copolymer so that higher concentrations produced no further increase in anti-*Pseudomonas* activity.

The addition of 0.1% CaCl₂ to the nonionic lotion containing 0.2% 1342 and 0.2% MP produced significant increases in the D-values for the fluorescent pseudomonads (*P. aeruginosa*, *P. fluorescens*, and *P. putida*) and eliminated the anti-*Pseudomonas* synergy. The opposite effect was observed with *P. cepacia*, because addition of 0.1% CaCl₂ produced a significant decrease in D-values for this organism (Table IV). The inhibitory effects of CaCl₂ on *P. cepacia* may have been due primarily to the decrease in the pH of this lotion caused by the addition of CaCl₂, compared to the control. *P. cepacia* was the only test organism that did not show synergistic anti-*Pseudomonas* activity in the presence of 1342 and MP (Table III). These results reflect the physiological diversity of different species of *Pseudomonas*. 

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Analyses of tap water and 1342-treated tap water indicated that exposure of the water to the 1342 caused a significant decrease in hardness, expressed as ppm CaCO₃. This suggests that 1342 is capable of chelating Ca²⁺ ions. The 0.1% 1342 and 0.01% Na₂EDTA reduced water hardness by similar amounts. This suggests that these compounds have similar chelating abilities for the Ca²⁺ ions.

The ST study revealed little antibacterial activity by either MP or Na₂EDTA alone (Table V). Rapid killing occurred in the presence of MP + Na₂EDTA because no viable organisms were recovered at 4 hr in most test systems. The test organisms found to be more persistent in these tests were, in general, more persistent in lotions containing 1342 and MP (Table II). In some cases, it is believed that differences in results between these two tables may be attributed to differences in APCs of the inocula.

The STs and MPSTs in Table V were used to calculate the slopes and D-values (or MPSlopes and MPD-values) in Table VI. Survivor curve slopes may be determined when the STs and initial inocula of the test organisms are known. For example, P. aeruginosa 9027 had an ST of 4 hr in MP + Na₂EDTA, and the APC in the sample was 1.1 × 10⁷/ml. Here, the D-value and slope were 0.8 hr and −1.26 hr⁻¹, respectively. Where STs are not known (i.e., ST >48 hr), the MPD-values and corresponding MPSlopes may be estimated from a virtual survivor curve constructed using the APC of the inoculum and the MPST, as explained above. Here, the MPD-value for P. aeruginosa 9027 in MP was calculated to be >9.5 hr and the MPSlope was <−0.105 hr⁻¹. This slope is the negative reciprocal of the MPD-value and represents the fastest possible rate of death of this organism in this test system. If P. aeruginosa were being killed at a faster rate, then no organisms would have been recovered at the last sampling (i.e., at 48 hr). The MPSlope for P. aeruginosa 9027 in Na₂ EDTA was estimated similarly to be <-0.105 hr⁻¹. Synergy was observed here, because the slope for the system containing MP + Na₂EDTA (-1.26 hr⁻¹) was a larger negative number than the sum of the MPSlopes for MP and for Na₂EDTA (-0.210 hr⁻¹). This procedure was used for each test organism shown in Table VI. The MP + Na₂EDTA system had synergistic anti-Pseudomonas activity for all pseudomonads, except for P. cepacia 13945. The MPD-values for different strains of P. aeruginosa were slightly different due to the slightly different concentrations of organisms in the inocula (Table VI). The estimated STs for S. aureus and E. coli were >48 hr in all test systems; consequently, it was not possible to establish synergy for these organisms in this experiment.

Numerous workers have reported the enhancement of preservative action by EDTA (3,7,31–34). The potentiating by EDTA is believed to be due to permeabilization synergy, in which one antimicrobial agent (EDTA) assists the passage of the other antimicrobial through the cell wall or membrane (7). We propose that the anti-Pseudomonas synergy observed with 934, 941, or 1342 and MP is due, at least in part, to chelation of divalent metal ions and that it is similar to permeabilization synergy reported for the potentiation of preservative action by EDTA (7). Results in support of this are the demonstration that 1342 has chelation activity, the elimination of the synergism observed with the fluorescent pseudomonads by the addition of 0.1% CaCl₂ (Table IV), and the similarities in the survival patterns of the various pseudomonads in nonionic lotions with polyacrylic acid or acrylic acid copolymer/MP systems (Table II) and in Na₂EDTA/MP solutions (Table V).

Similar patterns of inactivation were observed in both aqueous and nonionic emulsion
systems. This suggests that the observed synergy is not due to the nonionic emulsions studied here. The effect of 934, 941, or 1342 and MP on the inactivation of *Pseudomonas* was not tested in anionic or cationic emulsion systems or in various surfactant systems such as anionic shampoos and liquid soaps. The reason for this is that 1342 emulsion systems are sensitive to electrolytes, which cause loss of emulsion stability (35).

Adair *et al.* (36) reported that *P. aeruginosa* 9027 underwent lysis following metabolism of di- or tricarboxylic acids and sodium lauryl sulfate, and that lysis was not due to chelation. It is evident that the mechanism reported by these workers is not the same as the mechanism observed in the current work.

The antibacterial synergy of MP and acrylic acid homopolymer/copolymers against most *Pseudomonas* test cultures was not observed with *E. coli* 8739. This gram-negative organism was not inactivated rapidly in nonionic emulsions containing MP and 1342 or in solutions containing MP + Na₂EDTA (Tables II, V, and VI). These findings suggest a mechanism of action that is relatively specific for pseudomonads and not other gram-negative bacteria; however, testing with other strains of *E. coli* and other gram-negative organisms is necessary to confirm this.

The survivor curve slope method of determining synergy of preservative systems has application to both current experimental findings and to data presented in the literature. Application of this method to the ST data of Richards and Hardie (37) revealed synergism for fentichlor/phenylethanol combinations against *E. coli* and *Proteus vulgaris* at 0.0015% or 0.0050% fentichlor + 0.4% phenylethanol, and with 0.0050% fentichlor + 0.4% phenylethanol against *P. aeruginosa*. The survivor curve slope method revealed increased antibacterial activity against *S. aureus*; however, this effect was not synergistic. Our use of the survivor curve slope method corroborated the findings of Richards and Hardie.

The survivor curve slope method of determining synergy was applied to the D-values for *S. aureus*, in various combinations of preservatives in saline, reported by Akers *et al.* (38). Slopes of the survival curves were determined by taking the negative reciprocal of the D-values reported by these workers, and these slopes were used to determine whether mixtures of two preservatives exhibited synergy. Although these workers did not attempt to determine synergy, application of the survival curve slope method to their data for linear analysis of preservatives in saline solutions revealed that systems containing 0.2% phenol + 0.3% m-cresol, 0.2% phenol + 0.2% m-cresol, and 0.2% MP + 1.0% benzyl alcohol exhibited synergy. Akers *et al.* ranked the efficacy of these preservative systems in the top half of the systems tested against *S. aureus*.

The survivor curve slope method was used to study synergy in a system reported by Boehm to be synergistic (4). He reported that 0.25% P and 0.09% N were synergistic against *P. pyocyanea*. Since we did not have the same strain as in Boehm's experiments, it was decided to "bracket" the concentrations of P and N used in Boehm's studies. The results in Table VII show the growth response observed with *P. aeruginosa* 9027 in 0 to 1% P and/or 0 to 0.1% N. The STs and MPSTs in Table VII were used to calculate the slopes, MPSlopes, D-values, and MPD-values in Table VIII. Our findings show synergy for concentrations that bracket the synergistic combination reported by Boehm.

The use of kinetic parameters—the slopes of survivor curves obtained by use of the linear regression method—to demonstrate anti-*Pseudomonas* synergy of MP and acrylic acid homopolymer/copolymers *in vitro* has not been reported previously. The survivor
curve slope method may be used to determine synergy when STs are known for the test organisms in systems containing combined preservative system components and in which the inoculum level is known. Isobolograms (5,7,39) are not needed when using this method.

We propose that the synergy with acrylic acid homopolymer/copolymers and MP is due, at least in part, to the chelation of divalent metal ions by the homopolymer/copolymers and that it is similar to the potentiation of preservative action by EDTA. No synergy was demonstrated in systems challenged with \textit{E. coli}, \textit{S. aureus}, and \textit{B. cereus}, which suggests that the synergy was specific for the pseudomonads. In general, \textit{P. cepacia} was inactivated more slowly than the fluorescent pseudomonads in test systems containing acrylic acid homopolymer/copolymers and MP. It is possible that the primary benefit from the polyacrylic acid/acrylic acid copolymer synergy with MP may be obtained in systems in which EDTA cannot be used or in systems with low ionic strength. Experiments were not performed to determine whether acrylic acid homopolymer/copolymers exert a synergistic effect on MP/EDTA systems, or whether EDTA exerts a potentiating effect on MP/acrylic acid homopolymer/copolymers.

Additional experiments are required to define the range of synergy of MP and other paraben esters with these homopolymer/copolymers and to characterize the mechanism of this synergy with certainty.

ACKNOWLEDGMENTS

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Skin stripping as a potential method to determine in vivo cutaneous metabolism of topically applied drugs


Received August 25, 1989.

Synopsis

By chromatographing an extract of the tapes obtained in a skin stripping procedure, cutaneous metabolism of compounds after topical administration may be observable, provided that outward transdermal migration occurs. This method may be helpful, especially in situations where no differentiation between cutaneous and systemic metabolism can be made due to the experimental design or the very low systemic concentrations. Through use of this methodology, it can be assessed that the penetration enhancer for percutaneous absorption, Azone®, is only present as the parent compound in the stratum corneum, whereas the anti-acne agent Cyoctol undergoes cutaneous biotransformation during skin passage.

INTRODUCTION

In recent years there has been a renewed and growing interest in dermal and transdermal drug delivery. This route opens new possibilities for systemic therapy, especially for drugs with short biological half-lives due to extensive first-pass metabolism in the liver. Compounds, however, may also be metabolized in the skin before reaching the systemic circulation (1,2), thereby reducing their bioavailability.

For this reason, the cutaneous metabolism of these compounds should be studied and compared to already available systemic biotransformation data. If cutaneous metabolism occurs, additional investigations may be required to determine the pharmacological profile of the dermally formed metabolites.

A simple method to establish in vivo cutaneous metabolism of topically applied agents was developed and will be discussed on the basis of two compounds currently under investigation in our laboratories, Azone® and Cyoctol. Both compounds are to exert their action in human skin, Azone as a penetration enhancer for percutaneous absorp-
tion (3) and Cyoctol, an anti-androgen (4), as an anti-acne drug. In order to be able to follow the metabolic processes, tracer amounts of $^{14}$C-labeled compounds were used. The structure of the compounds and the position of the labels is given in Figure 1.

**MATERIALS AND METHODS**

**MATERIALS**

$^{14}$C-labeled Azone, 1-dodecylazacycloheptan-2-one ([1-$^{14}$C]-dodecyl), and Cyoctol, 6-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-3-one ([$^{14}$C]-carbonyl), were kindly supplied by Nelson Research, Irvine, California, and Chantal Pharmaceutical Corporation, Los Angeles, California, respectively. The radiochemical purity was determined by isocratic high-performance liquid chromatography (HPLC) to be at least 95.3 and 97.0%, respectively, using the system described below. All other materials were HPLC grade and obtained commercially.

**METHODS**

*Study performance.* In separate studies Azone and Cyoctol were applied to a 24-cm² area on the volar aspect of the forearm of healthy human volunteers and left in place under occlusion for 12 and 8 hours, respectively. Azone was dosed in a therapeutic formulation (100 mg) to three volunteers at a concentration of 1.6%, containing tritium-labeled...
beled triamcinolone acetonide as well, at a concentration of 0.05%. Cyoctol was dosed to four volunteers in an aqueous alcohol solution (ethanol (96%)/bidistilled water 75/25) at a concentration of 1.5%. Study conditions have been reported in full detail elsewhere (5,6). Skin samples were obtained at 1, 20, and 44 hours (Azone) or 1, 23, and 45 hours (Cyoctol) after removal of the dose by the skin stripping method described below.

Skin stripping. Skin stripping was done by means of commercial translucent cellophane tape of 9-mm width, made by 3M Company (Leiden, The Netherlands). Strips of ca. 6 cm in length were affixed and removed sequentially from the same transverse portion of the treatment site. At each stripping, the tape was firmly rubbed in place to achieve thorough adherence and then removed after about three seconds. The stripping procedure was complete when the area started to become glistening and the tape no longer adhered to the skin when applied, or when it became painful to the volunteer. Maximally 28 strips were applied.

All strips from one procedure were combined in a glass container, and 60 ml of methanol was added. The container was vigorously shaken for 16 hours to allow full extraction of drug-related material. The chemical stability in methanol of both compounds is at least several years. As it is impossible to spike tapes, the efficiency of extraction of radioactive material from the tapes cannot be given. At the end of the extraction period, however, the sticky layer of the tape had completely dissolved in the scintillation cocktail.

The extracts were evaporated to dryness under vacuum, and the residue was redissolved in methanol/phosphate buffer 0.01 M, pH 6.8 (85/15 v/v) (Azone), or in methanol (Cyoctol). After redissolution, the samples were filtered through a 0.45-μm filter. A 50-μl aliquot of the filtrate was injected into the HPLC system described below. The efficacy of the analytical procedure was checked. When a methanol solution containing tapes was spiked with 14C-Azone or 14C-Cyoctol and assayed identically, the recovery proved to be 94.7 ± 1.2 and 96.3 ± 2.4 (mean ± S.D.), respectively.

Metabolic profiling. Extracts of the dosages and the tapes were analyzed in an HPLC-system consisting of two Waters M510 HPLC-pumps (Millipore, Etten-Leur, The Netherlands), controlled by an Adalab® data acquisition/control system (Interactive Microwave, State College, Pennsylvania). Isocratic elution with methanol/phosphate buffer 0.01 M, pH 6.8 (85/15 v/v) was performed when analyzing the extracts of the dosage and the tapes containing 14C-Azone-derived radioactivity. In the case of 14C-Cyoctol-derived radioactivity, a linear gradient from 100% phosphate buffer 0.01 M, pH 6.8, to 100% methanol in 20 minutes followed by a methanol flush of 10 minutes was performed. In both cases the flow rate was 1.0 ml/min. Effluent fractions of 0.5 minutes were collected in polyethylene scintillation vials and vigorously shaken with 3 ml of the scintillation cocktail RiaLuma (Lumac, Landgraaf, The Netherlands). The samples were counted on a Packard Minaxi B4450 Liquid Scintillation Spectrometer (Packard Technologies, Irvine, California) for five minutes or a statistical accuracy of 0.5%.

RESULTS AND DISCUSSION

The chromatograms of the radioactivity in the dosages and the tape extracts are shown in Figures 2 and 3 for Azone and Cyoctol, respectively. The relative contribution of the peaks to the total eluted amount of radioactivity is given in Table I.
The metabolic profile of the $^{14}$C-Azone-derived radioactivity in the tape extract obtained from the stripping procedure at one hour after removal of the dose showed only the parent compound, except for a minor amount of radioactivity in the front. Tritiated triamcinolone acetonide was co-administered with the carbon-14-labeled Azone and was present in the tape extracts in large amounts relative to the amount of carbon-14 radioactivity (5). As the tritiated drug eluted at two minutes, the small peak at the
SKIN STRIPPING TO DETERMINE METABOLISM

Figure 3. Radiochromatograms of 14C-Cyoctol-derived radioactivity in the dosage (A) and the tape extracts at 1 (B), 23 (C), and 45 hours (D) after removal of the dose.

front most likely originated from the tritiated drug. It should be noted in this regard that even though liquid scintillation counters have programs to correct for spillovers when 14C and 3H isotopes are counted simultaneously, such programs may not be able to adequately correct if the amounts of 14C isotopes present are rather small in comparison to the amounts of 3H isotopes. Radiochromatograms at 20 and 44 hours showed similar profiles, yet at much lower quantities, due to the rapid disappearance of Azone from the stratum corneum (5). Levels of radioactivity were therefore close to the baseline, and this makes the assessment of the percentual contribution of individual peaks meaningless. Nevertheless, all profiles were basically the same at the three collection times, and it can therefore be concluded that only unchanged Azone is present in the stratum corneum.

With Cyoctol, the situation appears to be quite different. At one hour after removal of the dose, some metabolites can be detected in small amounts, but the majority of the radioactivity is still present as the parent compound (see Figures 3A and 3B). Table I shows that, as time goes by, the relative contribution of Cyoctol (peak 4), decreases, whereas that of the metabolites increases. At 45 hours after removal of the dose, only about 35% of the radioactivity in the stratum corneum is present as unchanged Cyoctol.
### Table I

Relative Contribution of Individual Compounds as a Percentage of the Total Eluted Amount of \(^{14}\text{C}-\text{Azone (A; n = 3) or }^{14}\text{C}-\text{Cyoctol (C; n = 4)}\) Derived Radioactivity (mean ± SD)

<table>
<thead>
<tr>
<th>Test compound</th>
<th>Peak number(^1)</th>
<th>Dosage</th>
<th>Relative contribution (%) in tape extracts at hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azone</td>
<td></td>
<td></td>
<td>1 (A + C) 20 (A) or 23 (C) 44 (A) or 45 (C)</td>
</tr>
<tr>
<td>1</td>
<td>95.4 ± 1.8</td>
<td>94.0 ± 3.8</td>
<td>N.D.(^2) 17.5 ± 3.9 N.D.(^2)</td>
</tr>
<tr>
<td>1</td>
<td>1.4 ± 0.9</td>
<td>9.7 ± 5.0</td>
<td>15.7 ± 1.7</td>
</tr>
<tr>
<td>2</td>
<td>4.0 ± 2.6</td>
<td>12.2 ± 4.2</td>
<td>5.9 ± 1.6</td>
</tr>
<tr>
<td>3</td>
<td>4.0 ± 3.1</td>
<td>8.3 ± 7.0</td>
<td>35.4 ± 13.4</td>
</tr>
<tr>
<td>4</td>
<td>93.9 ± 1.4</td>
<td>78.3 ± 16.8</td>
<td>49.5 ± 19.7 14.2 ± 10.0</td>
</tr>
<tr>
<td>5</td>
<td>6.6 ± 7.6</td>
<td>9.2 ± 5.8</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) The numbers correspond to those in Figures 2 and 3.

\(^2\) N.D. = not determined.

The possibility of chemical degradation of Cyoctol during the sample work-up could be excluded by having the parent compound undergoing the same sample processing. No compounds other than Cyoctol could be detected.

These findings indicate that only unchanged Azone is present in the tape extracts, while in the case of Cyoctol, both the parent compound and its metabolites can be found. The stratum corneum, however, is a layer of dead cells, assumed to be devoid of metabolic activity, as opposed to the underlying viable epidermis and dermis where skin metabolism may take place (1). Bioconversion of Cyoctol, therefore, conceivably occurred in one of these layers. Yet, stripping removes only two thirds of the stratum corneum (7) and cannot have removed part of the viable epidermis. The presence of metabolites in the stratum corneum can be explained by assuming outward migration of the metabolites formed in the viable epidermis and/or dermis. Outward migration has been described for compounds following oral administration (8,9), but recently could be established following dermal application as well in the case of Cyoctol (6,10). Although the majority of the metabolites formed in the viable epidermis will move inwards into the body, favored by a more aqueous environment and systemic removal, a concentration gradient will also exist towards the stratum corneum. As a result of that, the stripping technique will usually underestimate the extent of metabolism. In the case of Cyoctol, for instance, De Zeeuw et al. showed that this drug was completely metabolized during skin passage to a more nonpolar metabolite, corresponding to peak 5 in Figure 1 (10).

A good indication as to cutaneous metabolism can be obtained from the metabolic profiles of the ipsi- and contralateral plasma samples (11). However, it is sometimes impossible to apply the latter methodology, for example, when dosing on areas such as the back, abdomen, or forehead. Moreover, the levels of radioactivity in the ipsi- and contralateral plasma samples have to be relatively high to obtain reliable metabolic profiles. This presents severe difficulties with drugs that have low dermal absorption such as Azone (5,12,13).

The skin stripping methodology does not have these disadvantages and thus seems to be an interesting, simple, and noninvasive alternative to assess in vivo cutaneous metabolism, provided that sufficient outward migration of metabolites occurs. The technique
should be considered as a potential method to determine whether metabolism can take place rather than providing quantitative information on the extent of cutaneous metabolism.

ACKNOWLEDGMENTS

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REFERENCES


This 964-page volume of formulations consists of three parts: subject index, formulations—making procedures, and raw materials—trade names. It contains more than 1,800 cosmetic formulations based on information obtained from more than 150 different suppliers, whose addresses are listed in the last section of the book.

In most cases the formula source is provided, and in many but not all cases, a brief making procedure is described. Each formulation is identified by its end use. The formulations—making procedure section is divided into 14 different product classes: antiperspirants and deodorants, baby products, bath and shower products, beauty aids, creams, fragrances and perfumes, hair care products, insect repellants, lotions, shampoos, shaving products, soaps, suncare products, and miscellaneous. Each section contains a large number of different types of formulations; for example, the shampoo section contains more than 100 different types of shampoo formulas.

To those beginning in cosmetics and toiletry formulation, this book could be exceedingly useful. Even to those with several years experience, it is a useful reference source, and it offers convenience, since this single volume can be used to replace large file cabinets of supplier formula information.

The only drawbacks that this book offers are the steep price and, in some cases, the rather limited information provided on making procedures. Of course, the price is only a drawback to those on a strict budget. The limited making procedure information could present problems for the beginning cosmetics formulator, but it is certainly adequate for the experienced formulator.

Cosmetic and Toiletry Formulations can be a useful and valuable addition to the libraries of those involved in cosmetics formulation. — CLARENCE R. ROBBINS

—Colgate Palmolive Co.
Abstracts

The Annual Scientific Meeting and Seminars of the Society of Cosmetic Chemists are important venues for informing the participants about the state of the art and recent technical advances in the field of Cosmetic Science. To provide broader dissemination of that information, the Publications Committee has decided to publish abstracts of the technical presentations made at these Meetings and Seminars in the Journal.—The Editor.

Society of Cosmetic Chemists
Annual Seminar
May 10–11, 1990
San Francisco Hilton on Hilton Square
San Francisco

Program arranged by the Society’s Committee on Scientific Affairs
Anne Wolven-Garrett (A.M. Wolven, Inc.), Chair, 1990

SESSION A
INTERACTION BETWEEN RAW MATERIAL SUPPLIERS AND FORMULATORS

Optimizing the formulator-supplier relationship
Peter J. Kaufmann, Almay, Inc., 1501 Williamsboro St., Oxford, NC 27565

The relationship between the cosmetic chemist and the raw material supplier, will be examined emphasizing ways to optimize the productivity of both. Current trends in the cosmetic and related industries will be examined, forming the basis for suggestions on improving the partnership between chemists and raw material suppliers in the development of new personal care products.

Technical interactions between supplier and customer
Duane G. Krzysik, Dow Corning Corporation, 2200 W. Salzburg Rd., Midland, MI 48686

It is the purpose of this paper to touch on current interactions between suppliers of specialty chemicals and their customers, mainly product development chemists. We will then discuss some of the apparent difficulties of this relationship and suggest possible alternatives that will help make both the supplier and the customer more successful.

Gaining and maintaining a competitive edge will be a key factor to success in the 1990s. Competition will be tough not only for the supplier but also for the customer. Consumers at every level are becoming more educated, and with that education comes increased expectations.

To meet these expectations, significant advancements will be made in cosmetic science as well as in related fields such as dermatology. This will require more complex interactions and development between suppliers and customers. It is this interaction, however, that will be a key factor in new product development, commercialization, and, ultimately, market success.

A Realistic toxicological profile for new cosmetic ingredients
Howard I. Maibach, M.D., Department of Dermatology, University of California Medical Center, San Francisco

When exciting new cosmetic ingredients are being introduced into the consumer skin and hair care market, both the supplier and the cosmetic manufacturer want to be sure that consumers using their new product can realize the benefits of the product with minimal risk. Early evaluation of individual ingredients based on experience and testing, where required, will prevent unexpected and expensive problems late in the product development process. New materials can be evaluated first by comparing chemical structure with known classes of irritants and sensitizers. These comparisons will help the cosmetic product developer and the supplier to determine together whether minimal or extensive toxicological testing is desirable. Once the final proto-
type product has been selected, a series of skin toxicological tests are available; however, the selection of a reasonable combination of tests will depend on product use: skin care or hair care, single use or continuous use, probable site of application, probable misuse, intended function, and experience with similar products in the same category.

SESSION B
REGULATORY ISSUES IN THE 1990S

New and Existing raw materials—A regulatory minefield
Joel E. Rogelberg, Lonza, Inc., 1717 Route 208, Fairlawn, NJ 07410

The 1980s brought with it a new set of ground rules concerning the protection of our environment. The strong thrust of new regulations in the 80s challenged American industry to respond rapidly, while maintaining its position in highly competitive markets.

While regulatory pressures gain in strength, the number of companies that are willing and able to adapt has withered. This is a reflection of global consolidation and the financial impact compliance requires.

The author will examine some of the dangers and opportunities for the 90s based on the manufacture of specialty biocides. Included will be a focus on specialty biocides and the associated regulatory issues. Topics of discussion are:

- Acceptance of a preservative system for worldwide use
- Handling of hazardous basis raw materials and by-products
- Biodegradability
- Preservative safety testing
- Consumer needs vs. environmental requirements
- Negotiating with regulatory agencies

SESSION C
FRAGRANCE SCIENCE AND TECHNOLOGY

The biology of olfaction: Focus on an odorant-binding protein
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The molecular basis of olfaction is poorly understood. Odorants must travel from air through the nasal mucosa to reach olfactory receptor cells located in the olfactory epithelium. To understand these processes, we studied the binding of radioactive odorants to homogenates of the cow or rat nose. We identified an odorant-binding protein (OBP) that is present in many species including humans. OBP is a small, soluble protein that is synthesized in the lateral nasal gland. It is secreted from that gland into nasal mucus in high concentration. The pure protein can bind odorants of various structural classes including terpenes, aromatics, musks, and aldehydes. We cloned the gene for rat OBP. Analysis of the protein sequence indicates that OBP is homologous to a family of transport proteins, such as the retinol-binding protein that carries vitamin A to the eye. We propose that OBP is a carrier protein for odorants, delivering them to olfactory neurons within the nose.

The effects of odor administration on performance and stress in a sustained attention task
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Based on some data from EEG recording and subjective reports, we expected the administration of certain fragrances to enhance performance and/or reduce stress in a sustained attention (vigilance) task. Subjects were asked to detect the occurrence of a visual signal that was infrequently and aperiodically presented on a video screen, temporally interspersed among similar patterns. In experiment 1, subjects received a 30-second burst of either of two fragrances, peppermint or muguet, or plain air. Both fragrances had been judged pleasant in a pilot study; peppermint had been judged alerting, muguet relaxing. Subjects in both fragrance conditions showed superior performance accuracy to those in the plain-air condition. No effects on self-reported stress were found. In experiment 2, only peppermint was used, along with a plain-air and a no-air control. Subjects in the peppermint condition did better than the control subjects and also reported less stress. The exact mechanism for these effects has yet to be identified.

Fragrance use and social interaction
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This study investigated the relationship between individuals' use of personal fragrances and their social interactions. Subjects maintained a social interaction diary for three weeks. The diaries provided detailed summaries of the quality and quantity of subjects' social contacts, including subjects' beliefs about others' awareness of their fragrances and how pleasant their fragrances were to others. Subjects' perceptions of how often others were aware of their fragrances were unrelated to quality and quantity of their social interactions. Subjects' estimates of how pleasing their fragrances were to others were unre-
lated to the quantity of their interactions. However, these estimates were closely related to the quality of social interactions. The more pleasant subjects thought their fragrances were to others the more satisfaction and intimacy they found in social interaction and the more confident they felt in interaction. The results were similar for men and women. The data suggests that fragrances should be studied as social psychological phenomena in addition to being considered as olfactory stimuli.

SESSION D
PATHWAYS OF SKIN PENETRATION

Biophysical evaluation of the skin’s barrier function
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The stratum corneum (SC) is the morphologically unique outer layer of the skin that acts as the primary barrier in terrestrial mammals to water loss and the uptake of toxic substances. The techniques of differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) spectroscopy have been used to evaluate the biophysical properties of the SC. These techniques provide information on both SC protein and lipid structure that can then be correlated with permeability measurements. Results show that temperature-induced changes in water permeability through SC are remarkably similar to data obtained with lipid bilayers. Spectral results show that changes in the lipid acyl chain conformation are highly correlated with water permeability. Taken together, these results strongly support the role of SC lipids in barrier function. Furthermore, they provide a mechanistic interpretation of permeant transport that is independent of pore formation. Finally, if the lipid biophysics of water transport through SC and lipid bilayers are mechanistically similar, why do the absolute rates differ by over 1000-fold? The answer may be found in the unique morphology of the SC, where corneocyte “bricks” may serve to increase the tortuosity of water transport.

Polar pathway, transepidermal water loss, and moisturization
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The stratum corneum has traditionally been envisioned as a lipophilic barrier to skin penetration, and this viewpoint is in accord with most measurements. However, the slow but finite permeation of polar solutes through the skin, including water itself, suggests that there may be a special pathway for such molecules. The nature of this pathway has not been definitively identified, but several suggestions have been put forth. One is that polar molecules are transported via the shunts, such as the hair follicles and sweat gland ducts. Another notion is that spaces between polar head groups of the neutral intercellular lipids of the stratum corneum line up to permit water and other polar molecules to pass between the cells. Higuchi’s pore model accounts mathematically for much data, but does not identify the location of the “pores.” In recent experiments on simultaneous lidocaine and water transport through excised, dermatomed human skin, the enhancement of water penetration by surfactants was proportional to lidocaine enhancement. These data suggest that water is not restricted to the polar pathway in the presence of agents that perturb the intercellular lipids.

Iontophoresis and sonophoresis—Skin penetration through appendageal pathways?
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Conventional delivery of active materials into and through the skin is based on the driving force of a concentration gradient from the active in a topical formulation to a lower concentration in the dermis. Iontophoresis actively delivers substances across the skin by employing electrical potential energy, while sonophoresis invokes ultrasonic waves to enhance the transport of actives across the skin. Unlike passive diffusion, active transfer of charged and neutral molecules across the skin changes the relative contribution of proposed hydrophobic, hydrophilic, and appendageal pathways of penetration. As the cosmetic industry moves towards treatment of skin aging and reversal, rather than concealment, of skin blemishes and discoloration, greater specificity of the area and delivered dose of cosmeceuticals will be needed to normalize different skin conditions.
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