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The survey at the foot of this page assessed the effect of various formulations on how effective they are in helping those with comedogenic problems (blackheads on the skin) and the irritation such compounds cause. Ratings are given for each.

The nearer to 0, the better the result. A 5 rating is a warning indication of potential problems.

Synopsis
An assessment of how rabbit ears can be used in formulations can be used to help resolve or minimise blackheads in the skin and side by side with how irritable these solutions are found to be. We have classified these chemicals into classes in order to help draw conclusions.

- Medium chain length fatty acids.
- Combination with polar sugar.
- Increasing ethoxylation
- Longer chain waxes.

The results can be used to formulate new products to be used by the general public.

INTRODUCTION
The possible association of comedogenicity and irritancy of facial skin care products are already well reported (1-3). Because of this work and 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, moisturisers, sunscreens, and even acne treatment products, may be a source of cosmetic acne.
We have analysed all these products and their ingredients for testing purposes and formed an extensive list. Analysing this list, a qualified chemist will find the results very helpful in creating new products.
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The detailed investigation of this approach is to offer an alternative treatment for skincare as recommended by Healthline.com and used in typical clinics such as Ai Beauty Clinic for skin treatments in London.

The rabbit ear assay has been used since the mid-1950s as a method of measuring follicular keratinisation 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 mode 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.

JOURNAL OF THE SOCIETY OF COSMETIC CHEMISTS
However, this extensive screening of cosmetic formulations and their ingredients would not have been possible without the use of this animal model. We have developed the model to include an index of surface skin irritancy as well as 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 have ears in a healthy condition were used. The rabbits were well-fed, and our substances were applied to their ears over a two-week period.

The opposite untreated ear of each animal serves as an untreated control. Follicular keratosis is judged macroscopically (visually) and microscopically with a micrometre 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 micrometre measurement is obtained by averaging the width of six strands under a magnification of 430 x after a 6-mm biopsy specimen is fixed in

formalin, sectioned at six microns, and stained with toxylin-eosin. The results are then combined on a scale of one to five:

Micrometer reading	Grade	
0.009 in or less	0	No significant increase in follicular keratosis
0.010 in—.014 in	1	
0.015 in—.019 in	2	A moderate increase in follicular keratosis
0.020 in—.025 in	3	
0.025 in—.029 in	4	An extensive increase in follicular keratosis
0.030 in or more	5	

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 is produced by applying a chemical or skin care product on the ear on a similar scale.

0 No irritation at all.
1 Few scales, no sign of erythema
2 Diffuse scaling, no sign of erythema
3 Generalised scaling with some erythema
4 Scaling, erythema, and edema
5 Epidermal necrosis and slough

To study the effects of different vehicles on comedogenicity and irritancy, we tested several fatty acids and the D&C red pigment #36 was re-examined in different solvents.

COMEDOGENICITY

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 pentaerythrital 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 hair pomade. This study stimulated us to examine other skin care products and ingredients.

In 1972 Kligman and Mills reported on acne cosmetics 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 the epidemic of adult acne in women in the 1970s and 1980s. In 1976 and 1984, Fulton published results on actual cosmetic lines and ingredients and proposed the development of non-comedogenic 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 non-comedogenic 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.

The higher ethoxylated derivatives with HLBs above 12 are more

water soluble, noncomedogenic and non-irritating (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 cetyl acetate additive (Figure 1), and (2) PEG 16 lanolin (Solulan 16) is quite comedogenic and irritating, perhaps secondary to the combination of non-lanolin additives: ceteth-16, oleth-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 their analogues cause follicle hyperkeratosis. When the molecular weight of the fatty acid becomes larger, and the effective charge of the overall molecule is reduced, the 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 biphenyl erucate and cetyl palmitate, are not a problem.

Survey results

Ingredients	Comedogenic	Irritancy
Acetylated lanolin	0	0
Acetylated lanolin alcohol	4	2
Anhydrous lanolin 0-1* 0	0	0
Lanolin alcohol	0	0
Lanolin oil	0	0
PEG 16 lanolin	4	3
Caprylic acid	1	3
Capric acid	2	2
Lauric acid	4	1
Myristic acid	3	0
Palmitic acid	2	0
Eicosanoic acid	2	0
Cytel acetate	4	2
Decyl oleate	3	0

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