Cosmeceuticals: A Review of the Scientific Evidence

Molly Wanner, MD/MBA
I have the following relevant financial relationship with a commercial interest to disclose:

Scientific Advisory Board, Nu Skin
Grand funding, Solta
Investment, Clarity Cosmetics
What Is a Cosmeceutical?
Drugs: Mitigate, prevent, or treat disease. Affect body structure.

Cosmetic: A product intended to improve appearance with NO effect on structure and function of skin
“Cosmeceuticals” = Cosmetic
6 out of 10 people believe that over the counter products are regulated

Federal Food, Drug and Cosmetic Act (1938)

- Ingredients in cosmetics and personal care products are **NOT** obliged to FDA standard regulatory practices (with exception of food color additives)
- FDA prohibits adulterated or misbranded products

(b) If it consists in whole or in part of any filthy, putrid, or decomposed substance.
Cosmetics Are Not Regulated

What does this mean?

• FDA cannot require companies to submit pre-marketing safety data
• FDA cannot require companies to report any side effects of products reported by consumers
• Instead, monitoring is performed by the Personal Care Products Counsel

*Sponsored by cosmetics industry*
Savvy Consumers Started Asking Questions

Are my products safe?
Do my products work?
Are My Products Safe?

The Clean Cosmetics movement

The search for “non toxic” products
“Clean” Cosmetics: The “Bad” List

Methylisothiazolinone (MI), methylchloroisothiazolinone (MCI), Vitamin A derivatives, fragrance mix, phenoxyethanol, petroleum distillates, formaldehydes, triclosan and triclocarban, toluene, resorcinol, petroleum distillates, butylated hydroxyanisole (BHA), boric acid and sodium borate, phthalates, placenta extract, parabens, phenoxyethanol, PEGs and ceteareth (1,4-dioxane), formaldehydes, coal tar ingredients (including aminophenol, diaminobenzene and phenylenediamine), petroleum distillates, placenta extract
What Is Toxic?

• Toxicity depends on dosage (concentration and absorption)
• There is too much of a good thing.
  – Fat soluble vitamins A, D, E, K are stored
  – Chronic excessive supplementation can lead to coma or death
• “Natural” ≠ non toxic
  – Poison Ivy is “natural”
“Clean” Cosmetics: Let’s See the Science

Commonly avoided chemicals grouped into three categories: irritants/allergens, potential endocrine disruptors, potential carcinogens

PubMed Search performed for chemicals in each above category, with attention to:

- Type of study/study subjects (human data available?)
- Dose (relevant to routine exposure?)
- Route of administration (topical?)

Arrived at a “shortlist” of chemicals that may be worth avoiding

Dr. Neera Nathan
Clean Cosmetics
3 Categories of “Bad” Ingredients

- Carcinogens
- Allergens
- Irritants
- Endocrine Disruptors
Allergens and Irritants
Commonly avoided in “Clean” products

• Formaldehyde
• Fragrance
• Methylisothiazizone (MI)
• Methylchloroisothiazolione (MCI)
• Phenoxyethanol
• Petroleum distillates
• Vitamin A
Allergens and Irritants

What does the science back up avoiding?

- Formaldehyde – hair straightener
- Fragrance
- Methylisothiazione (MI) - preservative
- Methylchloroisothiazolinone (MCI) - preservative
- Phenoxyethanol
- Petroleum distillates
- Vitamin A

Allergens of the year
Allergens and Irritants

What can stay in the cosmetic bag?

• Formaldehyde
• Fragrance
• Methylisothiazalone (MI)
• Methylchloroisothiazoline (MCI)
• Phenoxyethanol
• Petroleum distillates
• Vitamin A
Endocrine Disruptors

Imitate hormones & interfere with normal signaling of chemical messengers
DES (Diethylstilbestrol)

*Endocrine disruptor in Medical History*

- Synthetic estrogen given orally to women in 1940s to 1970s to prevent miscarriage

- Linked to clear cell adenocarcinoma of the vagina and cervix in daughters of women who received this medication
Endocrine Disruptors
What does the science back up avoiding?

Commonly avoided in “Clean” products
- Triclosan and triclocarbon
- Parabens
- Phthalates
- Toluene
- Resorcinol
- Petroleum
- Butylated hydroxyanisole
- Boric acid and sodium borate
- Placenta extract
- Phenoxyethanol

More research is needed.
More Research Is Needed

Toxicity depends on concentration and absorption

• Most studies performed in vitro and in animals

• In animal studies, ingredients studied at high doses, orally or subcutaneously

• In human studies, source is unclear, not specifically topical, conflicting studies
Endocrine Disruptors

- **Parabens** – preservative, antimicrobial
- **Phthalates** – softener in shampoos and nail polish
- **Triclosan and triclocarbon** – antimicrobial in toothpaste and deodorant

- Universal
- Many sources
- Absorbed through skin
- Animal studies
- Difficult to link to topicals
- No definitive link to human disease
**Parabens**

*Preservative in cosmetics, moisturizers, shampoos, food additives, food packaging, pharmaceuticals*

- Penetrate skin. 99% rapidly metabolized in skin to weaker metabolite.

- Weak estrogen
  - 4 most common parabens 10,000 less potent than estradiol

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Fransway AF et al. Parabens: Contact (Non)allergen of the year. Dermatitis 2018.
Final amended report of safety assessment of methylparaben, ethylparaben, propylparaben, isopropylparaben, and benzylparaben as used in cosmetic products. Inter J Toxicology 2008; 27: 1-82.
In Vivo Studies of Parabens Conflict

*Are parabens endocrine disruptors?*

- 338 children in farmworking community
- Increased urinary levels of methylparaben associated with shift (1.3-1.5 months) in pubarche (pubic hair appearance) and <1 month (menarche)

- 1239 girls in NYC, Cincinnati, San Francisco: No impact on puberty
- Human studies: no impact on semen quality or sperm DNA

Phthalate “Tha-leit”

Enhance flexibility of plastic (“plasticizers”), food wrappers, flooring, medical devices, toys, lacquers, varnish, personal care products

- Phthalates can be absorbed through the skin
  - Baby lotion in infants < 8 months & powder > 8 months
- Not all phthalates are alike
  - In personal care products, diethyl phthalate (DEP) most common in US
  - DEP does not have hormonal activity
  - Long side chain phthalates have weak hormone activity at high doses

Janjua NR. Urinary excretion of phthalates and parabens after repeated whole-body topical application in humans. Int J andrology 2008; 31: 118-130.
Phthalate Endocrine disruption potential?

- Inverse association of concentration with breast development (Wolff)
- Possible association of DEHP on male genitalia (Swan)
- No association in pubertal timing in girls or boys (Harley)


Long side chain
Weak hormone activity
High doses impact rat fertility
Triclosan
Antibacterial and antifungal deodorants, toothpaste, clothing, household items

- Animal studies show dose dependent impact on thyroid
  - Rat study: Dose dependent decrease of T4 with oral triclosan

- RCT of 132 subjects and 0.3% triclosan in toothpaste – no impact on thyroid

- Human studies conflict

Potential Carcinogens

Commonly avoided in “Clean” products

- Formaldehyde
- Coal tar ingredients
- Petroleum
- 1-4 dioxane
- Placenta extract
Potential Carcinogens
What does the science back up avoiding?

**Formaldehyde**

- Linked to cancer in animals and humans in high doses including topical occupational exposure
- Labeled a known carcinogen by NIH National Toxicology Program

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25,619 workers in the formaldehyde industry: link between formaldehyde and nasopharyngeal cancer

Potential Carcinogens

What can we leave in the bag?

- Coal Tar
- Formaldehyde
- 1,4 dioxane
- Petroleum distillates
- Placenta extract
Coal Tar

Potential Carcinogens

What can we leave in the bag?

- Industrial use linked to cancer—“chimney sweeps”
- Cohort study of 13,200 patients did not increase risk of malignancies

No Increased Risk of Cancer after Coal Tar Treatment in Patients with Psoriasis or Eczema

Judith H.J. Roelofszen1,2, Kajja K.H. Abels1,3, Ursula T.H. Oldenhof1, Peter-Jan Coenraads4, Hans A. Allomade5, Peter C.M. van de Kerkhof5, Peter G.M. van der Valk5 and Lambertus A.L.M. Kiemenej1,2,6

Coal tar is an effective treatment for psoriasis and eczema, but it contains several carcinogenic compounds. Occupational and animal studies have shown an increased risk of cancer after exposure to coal tar. Many dermatologists have abandoned this treatment for safety reasons, although the risk of cancer after coal tar in dermatological practice is unclear. This large cohort study included 13,200 patients with psoriasis and eczema. Information on skin disease and treatment, risk factors, and cancer occurrence was retrieved from medical files, questionnaires, and medical registries. Proportional hazards regression was used to evaluate differences in cancer risk by treatment modality. Patients treated with coal tar were compared with a reference category of patients treated with dermatocorticosteroids (assumed to carry no increased cancer risk). The median exposure to coal tar ointments was 6 months (range 1-400 months). Coal tar did not increase the risk of non-skin malignancies (hazard ratio (HR) 0.92; 95% confidence interval (CI) 0.78-1.09), or the risk of skin cancer (HR 1.09; 95% CI 0.69-1.70). This study has sufficient power to show that coal tar treatment is not associated with an increased risk of cancer. These results indicate that coal tar can be maintained as a safe treatment in dermatological practice.

*Journal of Investigative Dermatology* (2011) 139, 943-952 doi:10.1038/jid.2011.218; published online 17 December 2010
Potential Carcinogens

What can we leave in the bag?

- Coal Tar
- Formaldehyde
- 1,4 dioxane
- Petroleum Distillates?
- Placenta extract

No symbol over Formaldehyde.
Potential Carcinogens

What can we leave in the bag?

- CRUDE petroleum on the skin of 50 mice increased skin cancer
- Cosmetics have highly refined petroleum distillates
  - Poly aromatic hydrocarbons are not present (known carcinogen)
- 4 Human studies: petrolatum stays in superficial skin due to size

Petry T et al. Review of data on the dermal penetration of mineral oils and waxes used in cosmetic applications. Tox Letters 2017; 280: 70-78.
Potential Carcinogens

*What can we leave in the bag?*

- Coal Tar
- Formaldehyde
- Placenta extract
- Refined Petroleum
- 1,4 dioxane

More data
Do My Products Work?

Are my products safe?

Do my products work?
Common Cosmeceuticals

- Vitamins A, B, C
- Growth Factors
- Peptides
- Sugars
### Table 15E.3 Summary of cosmeceuticals and their potential uses.

<table>
<thead>
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<th>Active Ingredient</th>
<th>In vitro studies</th>
<th>Animal studies</th>
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<td>Miller et al. 2006 [237]</td>
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</table>

**Conclusion**

Do My Products Work?

Absorbed?  Biologic effect?  Clinical effect?

Yes
Absorbed?
Concentration and Molecular Weight Influences Absorption

Absorption (J) = Permeability coefficient * Concentration

(Partition coefficient*Diffusion coefficient/Length of path of diffusion)

<500 dalton

Non ionized
Non polar

pH

drophilic – lipophobic balance
Can Vitamin A be absorbed through the skin?

DOES MY PRODUCT WORK?
Vitamin A: Tretinoin Is Our Gold Standard for Photoaging

- 6 double blind, controlled studies
- 2 largest trials
  - 619 subjects
  - Followed for 6 months
  - 86% had global improvement vs 44% control

OTC Vitamin A: Retinaldehyde Induces Retinoic Acid Activity in Humans More Than Retinol

Retinol

Retinaldehyde (Retinal)

All transretinoic acid (Tretinoin)


Vitamin A – Retinaldehyde Reduces Fine Lines

- 125 subjects, retinaldehyde 0.05 vs tretinoin 0.05 vs placebo

- Silicone replicas of crows feet

- Improvement of photoaging

Retinol Reduces Fine Lines

- Retinol 0.4% (36 subjects): -1.64 point improvement wrinkles vs control on 9 pt scale (statistically significant)

- Concentration in cosmeceuticals can be as low as 0.08%

My Approach to Vitamin A

- Retinaldehyde when can not tolerate tretinoin

- Concentration matters
Does My Product Work?

Vitamin B3

Nicotinic acid

Vitamin B3

Niacin

Nicotinamide / Niacinamide

Inositol hexanicotinate
Vitamin B3

- Precursors of NAD(H) and NADP(H) enzymes – oxidative metabolism
- +ceramides and keratinocyte differentiation
Can Vitamin B3 Be Absorbed Through the Skin?
ABSORPTION OF SOME ORGANIC COMPOUNDS THROUGH THE SKIN IN MAN*

ROBERT J. FELDMANN, M.D. AND HOWARD I. MAIBACH, M.D.

ABSTRACT

We studied the percutaneous penetration of 21 organic chemicals. The experimental method consisted of the application of the chemical to the human forearm and quantitating its penetration through the skin by its appearance in urine.

There was a great diversity in the ability of the chemicals to penetrate human skin. Compounds such as hippuric acid, nicotinic acid, and nitrobenzene support the generally held view of the excellent chemical barrier properties for them.

Closely related compounds showed great differences in penetration. Benzoic acid was absorbed at 200 times the amount of its glycine conjugate—hippuric acid. Nicotinic acid barely penetrated; 10% of its amide, nicotinamide, penetrated. This suggests that molecules may be tailored to decrease or increase penetration as needed for the most suitable biological function.
Vitamin B3 Improves Skin Barrier Function

Placebo

5% myristyl nicotinate (nicotinic acid derivative)

- Increases skin thickness
- Promotes epidermal differentiation
- Decreases TEWL

Vitamin B3: 4-5% Niacinamide Improves Acne, Photoaging, and Melasma

- **Acne**
  - 80 subjects
  - Improved, not as much as 1% clindamycin

- **Photoaging**
  - 50 subjects
  - 5% reduction in wrinkles vs control

- **Melasma**
  - 27 subjects
  - 44% improved on niacinamide vs 55% hydroquinone
Reduction in the appearance of facial hyperpigmentation after use of moisturizers with a combination of topical niacinamide and N-acetyl glucosamine: results of a randomized, double-blind, vehicle-controlled trial

A.B. Kimball, J.R. Kaczvinsky,* J. Li,* L.R. Robinson,* P.J. Matts,† C.A. Berge,* K. Miyamoto* and D.L. Bissett*

Harvard Medical School, Boston, MA 02114, U.S.A.
*The Procter & Gamble Company, Cincinnati, OH, U.S.A.
†The Procter & Gamble Company, Egham, Surrey, U.K.

Reduced brown spots
My Approach to Vitamin B3

Moisturizer or spray for Acne

Sensitive skin and photoaging

4% concentration, pH 4-7
Antioxidant

Vitamin C

Collagen
Can Vitamin C be absorbed through the skin?

DOES MY PRODUCT WORK?
Vitamin C Absorption Maximized at Concentration of 20% and pH Less Than 3.5

Ferulic Acid Stabilizes Vitamin C

Ferulic Acid Stabilizes a Solution of Vitamins C and E and Doubles its Photoprotection of Skin

Fu-Hsiung Lin,* Jing-Yi Lin,† Ravindra D. Gupta,* Joshua A. Tournas,* James A. Burch,* M. Angelica Selim,* Nancy A. Monteiro-Riviere,† James M. Grichnik,* Jan Zielinski,§ and Sheldon R. Pinnell*

*Duke University Medical Center, Durham, North Carolina, USA; †Chang Gung Memorial Hospital, Taipei, Taiwan; §North Carolina State University, Raleigh, North Carolina, USA; ‡Zielinski Research, San Diego, California, USA.

Ferulic acid is a potent ubiquitous plant antioxidant. Its incorporation into a topical solution of 15% L-ascorbic acid and 1% α-tocopherol improved chemical stability of the vitamins (C + E) and doubled photoprotection to solar-simulated irradiation of skin from 4-fold to approximately 8-fold as measured by both erythema and sunburn cell formation. Inhibition of apoptosis was associated with reduced induction of caspase-3 and caspase-7. This antioxidant formulation efficiently reduced thymine dimer formation. This combination of pure natural low molecular weight antioxidants provides meaningful synergistic protection against oxidative stress in skin and should be useful for protection against photoaging and skin cancer.

Key words: antioxidant/ferulic acid/photoprotection/vitamin C/vitamin E

J Investig Dermatol 129:826–832, 2005

— After 2 months, 0% of L-ascorbic acid remained
— >90% L-ascorbic acid present at 2 months when formulated with Ferulic acid

Concentration Matters for Collagen Stimulation

Increase collagen
15% Vit C increased collagen I and III in skin biopsies by 20%-25% (p<0.06)

5% Vitamin C no effect in skin biopsies

Vitamin C Is Photoprotective

Increases sun protection


Clinical Studies:
Vitamin C and Photoaging

• 3 studies, 10-20 subjects, 1 RCT

• Improvement statistically significant, but variable

My Approach to Vitamin C

- Photoprotective effects morning
- Dark bottle, small opening
- Ideal pH 3.5 (sting) > not for sensitive skin
- Concentration in 10-15% range
- Formulation with ferulic acid may be helpful
<table>
<thead>
<tr>
<th>Should I Use This Product?</th>
<th>What does the science support?</th>
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<tbody>
<tr>
<td><strong>NO</strong></td>
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<tr>
<td>• Formaldehyde</td>
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<tr>
<td>• Fragrance</td>
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<tr>
<td>• Methylisothiazione (MI)</td>
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<td>• Methylchloroisothiazoli none (MCI)</td>
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<tr>
<td><strong>YES</strong></td>
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