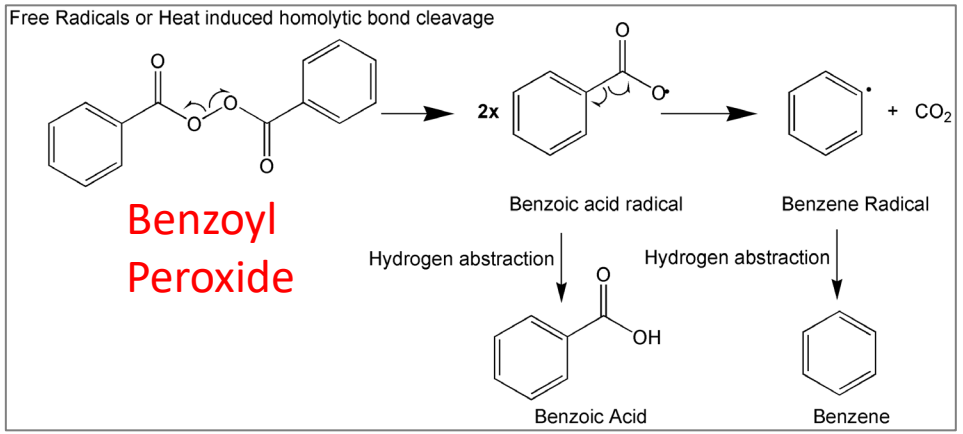
Personal Care Product Safety: The BPO Controversy and Beyond

BPO and Benzene: what do dermatologists do now?



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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Abbvie: Investigator, Consultant
Almirall: Investigator, Consultant
Apogee: Investigator, Consultant
Arcutis: Consultant
Eli Lilly: Consultant
LEO Pharma: Investigator, Consultant
Novartis: Consultant

Ortho Dermatologics: Investigator, Consultant
Palvella: Investigator
Pfizer: Consultant
Sanofi-Regeneron: Consultant
Sun Pharma: Investigator, Consultant
Timber: Investigator
UCB Pharma: Consultant

Dr. Bunick is a Director on the board of the American Acne and Rosacea Society (AARS)

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Multiple skin care products contain the carcinogen benzene:

Timeline of Consumer Product Recalls Due to Benzene Contamination

https://www.valisure.com/valisure-newsroom/timeline-of-consumer-product-recalls-due-to-benzene

Sunscreen ingredients are systemically absorbed

JAMA | Original Investigation

Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

Murali K. Matta, PhD; Jeffry Florian, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Yang Yang, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

INTERVENTIONS Participants were randomized to 1 of 4 sunscreen products, formulated as lotion (n = 12), aerosol spray (n = 12), nonaerosol spray (n = 12), and pump spray (n = 12). Sunscreen product was applied at 2 mg/cm^2 to 75% of body surface area at 0 hours on day 1 and 4 times on day 2 through day 4 at 2-hour intervals, and 34 blood samples were collected over 21 days from each participant.

RESULTS Among 48 randomized participants (mean [SD] age, 38.7 [13.2] years; 24 women [50%]; 23 white [48%], 23 African American [48%], 1 Asian [2%], and 1 of unknown race/ethnicity [2%]), 44 (92%) completed the trial. Geometric mean maximum plasma concentrations of all 6 active ingredients were greater than 0.5 ng/mL, and this threshold was surpassed on day 1 after a single application for all active ingredients. The overall maximum plasma concentrations for each active ingredient for each product formulation are shown in the table. The most common adverse event was rash, which developed in 14 participants.

	Geometric Mean Maximum Plasma Concentration, Coefficient of Variation (%), ng/mL			
	Lotion	Aerosol Spray	Nonaerosol Spray	Pump Spray
Avobenzone	7.1 (73.9)	3.5 (70.9)	3.5 (73.0)	3.3 (47.8)
Oxybenzone	258.1 (53.0)	180.1 (57.3)	Not applicable	Not applicable
Octocrylene	7.8 (87.1)	6.6 (78.1)	6.6 (103.9)	Not applicable
Homosalate	Not applicable	23.1 (68.0)	17.9 (61.7)	13.9 (70.2)
Octisalate	Not applicable	5.1 (81.6)	5.8 (77.4)	4.6 (97.6)
Octinoxate	Not applicable	Not applicable	7.9 (86.5)	5.2 (68.2)

CONCLUSIONS AND RELEVANCE In this study conducted in a clinical pharmacology unit and examining sunscreen application among healthy participants, all 6 of the tested active ingredients administered in 4 different sunscreen formulations were systemically absorbed and had plasma concentrations that surpassed the FDA threshold for potentially waiving some of the additional safety studies for sunscreens. These findings do not indicate that individuals should refrain from the use of sunscreen.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03582215

JAMA. 2020;323(3):256-267. doi:10.1001/jama.2019.20747
Corrected on March 17, 2020.

Titles of articles can be misleading

> J Am Acad Dermatol. 2022 Aug;87(2):440-443. doi: 10.1016/j.jaad.2021.09.003.
Epub 2021 Sep 10.

Sunscreen use is not associated with increased blood concentrations of benzene among adults in the United States: Data from the National Health and Nutrition Examination Survey 2003–2006 and 2009–2018

Michael S Chang [1], Kevin J Moore [1], Nicole Trepanowski [2], Tulay Koru-Sengul [3], Rebecca I Hartman [4]

Severe limitations in sunscreen epidemiology study: Dataset did not include information to make conclusion in their title

Major limitations

Limitations include lack of respondent detail on last application of sunscreen and total daily sunscreen use, unknown timing of blood draws relative to sunscreen use, and lack of urine benzene levels. Additionally, our data set included 2003-2006 and 2009-2018 data, prior to recent reports of benzene found in sunscreen. Further work is necessary to characterize the systemic absorption of benzene due to sunscreens and to identify appropriate quality control measures.

Other sources of benzene

It is possible that other factors may more strongly influence systemic benzene concentrations, including gasoline emissions, second-hand cigarette smoke, chemical products, and occupational exposures.[5] Although quality control screening of sunscreen products is important, addressing other sources of benzene may be more beneficial from a public health standpoint.

Chang MS, Moore KJ, Trepanowski N, Koru-Sengul T, Hartman RI. Sunscreen use is not associated with increased blood concentrations of benzene among adults in the United States: Data from the National Health and Nutrition Examination Survey 2003-2006 and 2009-2018. J Am Acad Dermatol. 2022 Aug;87(2):440-443. doi: 10.1016/j.jaad.2021.09.003. Epub 2021 Sep 10. PMID: 34509542.

Major Policy Changes Ahead:
FDA Cracks Down on Benzene and Formaldehyde

Reformulating Drug Products That Contain Carbomers Manufactured With Benzene

Guidance for Industry

At the time of publication of this guidance, carbomers manufactured with benzene that are used in FDA-regulated drug products may fall under the United States Pharmacopeia-National Formulary (USP-NF) monographs Carbomer 934, Carbomer 934P, Carbomer 940, Carbomer 941, or Carbomer 1342. These monographs permit benzene levels as high as 5,000 parts per million (ppm). In comparison, the USP-NF Carbomer Homopolymer, Carbomer Copolymer, and Carbomer Interpolymer monographs cover carbomers that are manufactured without benzene and limit benzene as an impurity to no more than 2 ppm. To avoid confusion, and because of the safety concerns associated with these unacceptable levels of benzene permitted by these monographs, FDA has asked the USP to remove (or "omit") the Carbomer 934P, Carbomer 940, Carbomer 934, Carbomer 1342, and Carbomer 941 monographs from the USP-NF compendium. FDA is issuing this guidance to help facilitate and expedite the reformulation of drug products that use carbomers manufactured with benzene.

Dec 2023

FDA proposes ban on hair-straightening products containing formaldehyde

Proposal comes after study showing 50% increase in risk of uterine cancer for users of straighteners, who are frequently Black women

A 2022 lawsuit targeted L'Oréal over its hair-straightening products. Photograph: Kehinde Akinbo/Alamy

Proposed Ban April 2024

Regulatory concerns about benzene in skin care products:

Understanding the concept of "conditional limit"

FDA U.S. FOOD & DRUG ADMINISTRATION

Table 1. – Class 1 Solvents in Pharmaceutical Products (Solvents That Should Be Avoided)

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1,500	Environmental hazard

"Solvents in Class 1 (Table 1) should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect.

However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified."

Stability testing is a regulatory requirement:

It is not intended to copy consumer use/"real-world”

•Stability testing is not intended to copy consumer use/"real-world," it's intended to evaluate the full, 3-year product "life cycle" in a condensed fashion

•3-year stability at RT = 169 days at 50C (122F).
Ref: https://pkgcompliance.com/resource/accelerated-aging-calculator/

•It is a regulatory requirement (Ref: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-technical-guides/expiration-dating-and-stability-testing-human-drug-products)

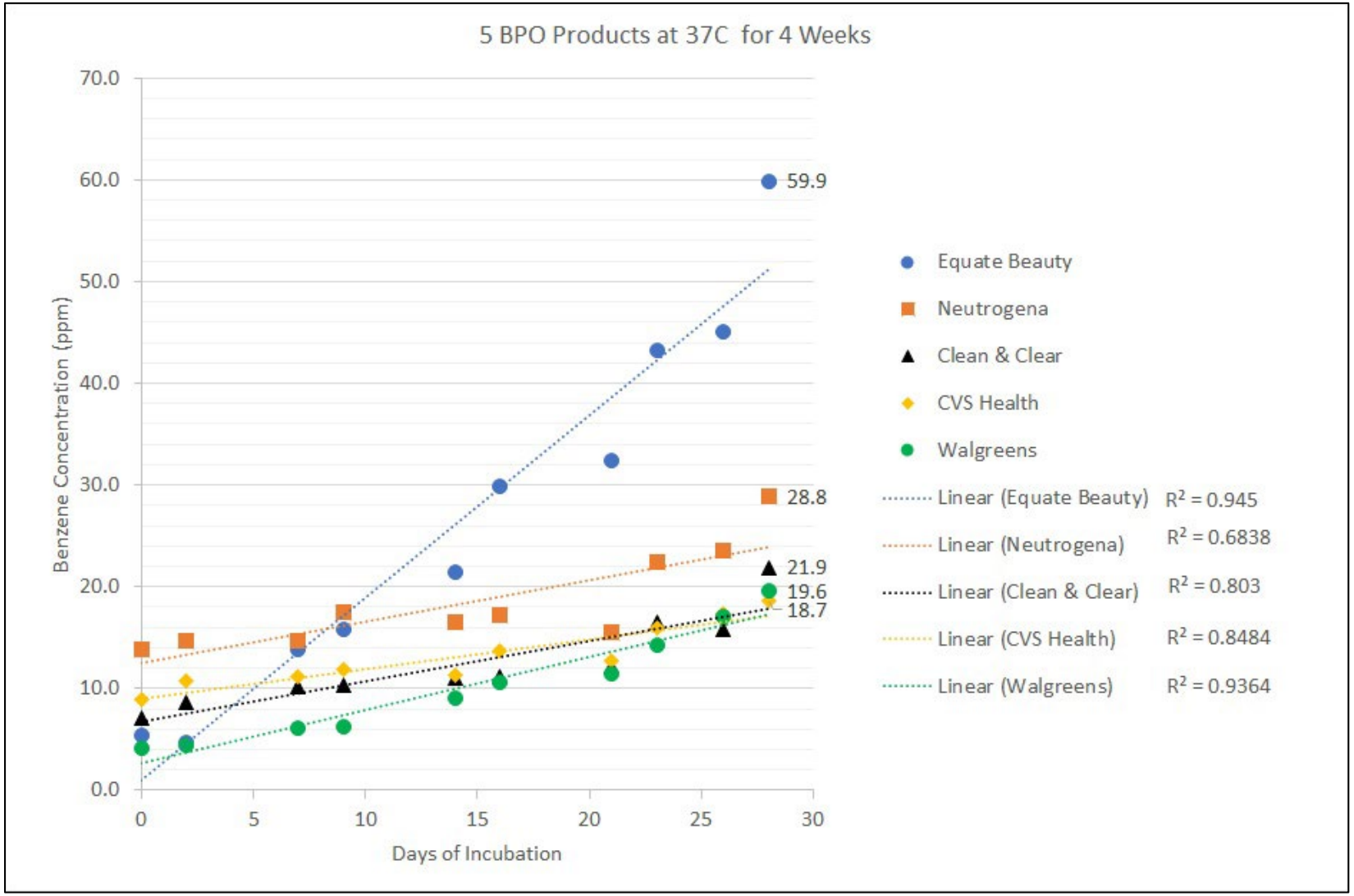
- "Stability studies should be conducted on product stored under normal storage conditions or, preferably, under exaggerated conditions."

Stability testing conditions can overlap with real-world:
BPO breaks down into benzene at skin temperature (~37C (98.6F))

- However, stability testing conditions can overlap with real-world

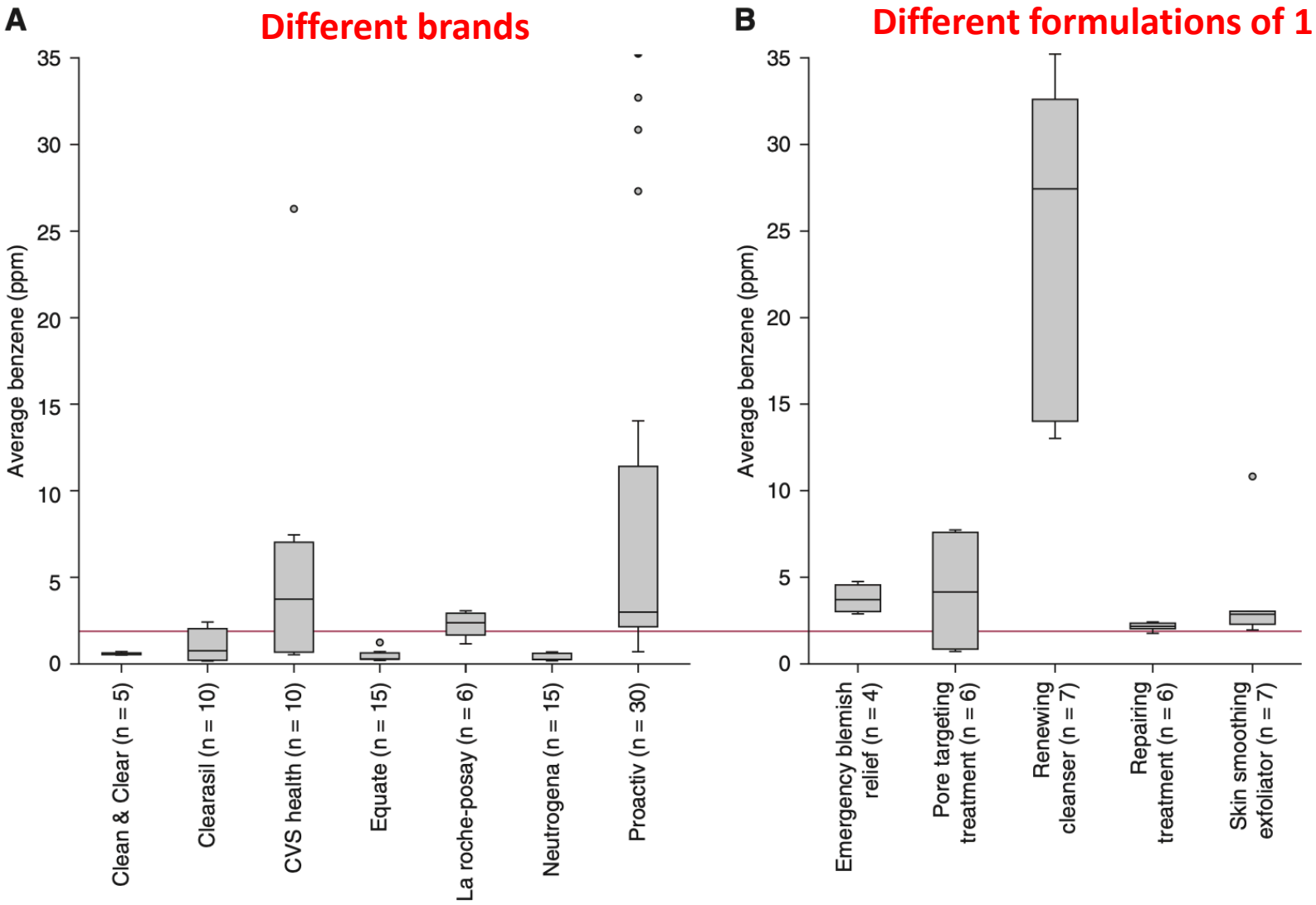
- Of 5 products at 37C, "Day 0"/RT values: 1 product >10ppm, 5 products >2ppm

- 3-year stability at RT = 415 days at 37C (98.6F)



Kucera K, Zenzola N, Hudspeth A, Dubnicka M, Hinz W, Bunick CG, Dabestani A, Light DY. Benzoyl Peroxide Drug Products Form Benzene. Environ Health Perspect. 2024 Mar;132(3):37702.

Follow up study of 111 BPO over-the-counter products at room temperature show 1/3 of all BPO products on store shelf exceed FDA's 2 ppm conditional benzene limit



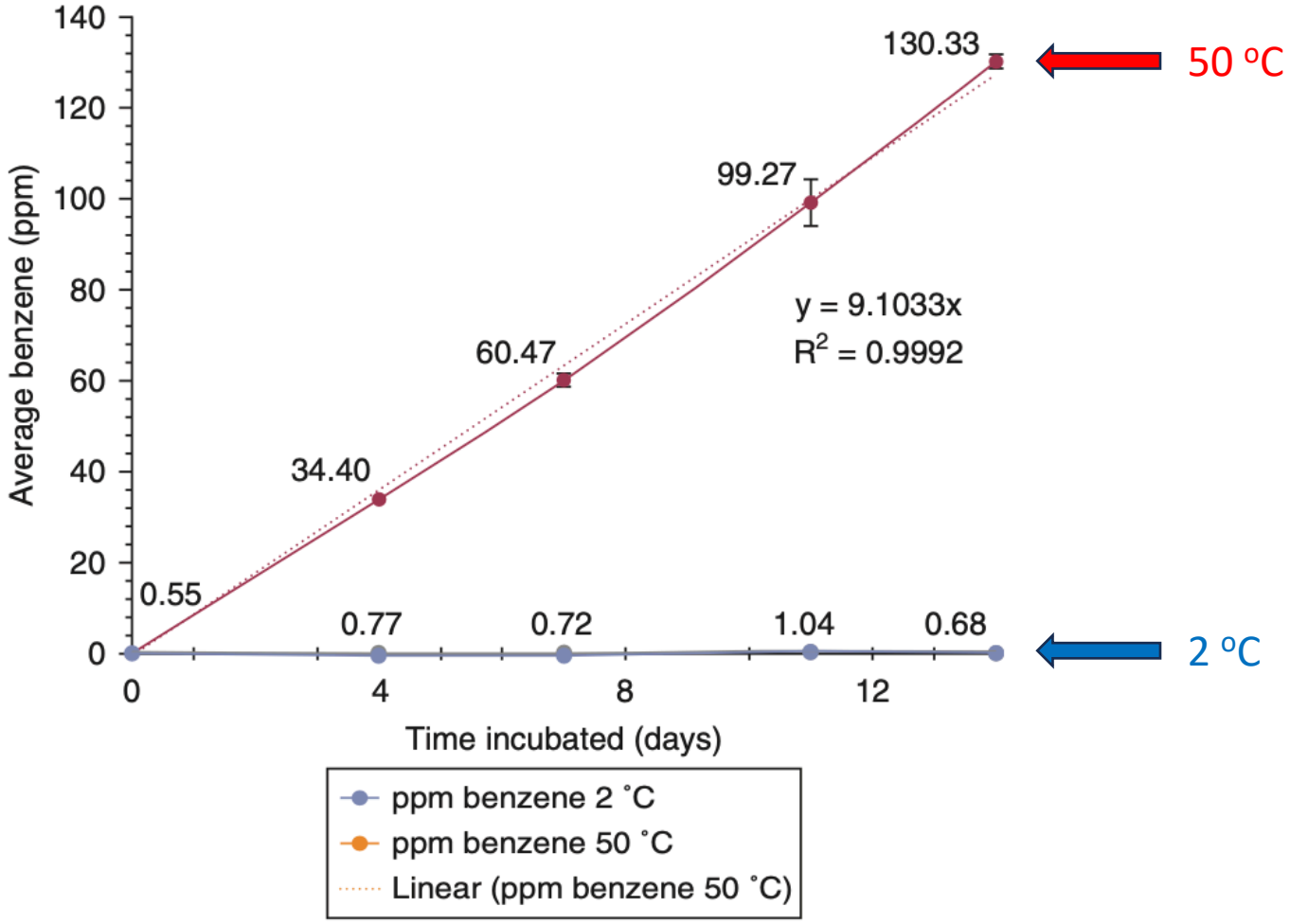
- 111 BPO products sourced from 6 states across United States
- 34% of OTC BPO drug products exceeded the FDA's conditional limit

FDA conditional limit: 2 ppm

Kucera K, Zenzola N, Hudspeth A, Dubnicka M, Hinz W, Bunick CG, Girardi M, Dabestani A, Light DY. Evaluation of Benzene Presence and Formation in Benzoyl Peroxide Drug Products. J Invest Dermatol. 2024 Oct 7:S0022-202X(24)02155-9.

Cold temperature reduces BPO degradation into Benzene

Encapsulated BPO drug product



Kucera K, Zenzola N, Hudspeth A, Dubnicka M, Hinz W, Bunick CG, Girardi M, Dabestani A, Light DY. Evaluation of Benzene Presence and Formation in Benzoyl Peroxide Drug Products. J Invest Dermatol. 2024 Oct 7:S0022-202X(24)02155-9.

What do Dermatologists Do Now?

1. All prior BPO containing products subjected to hot showers, cars, or other heated environments should be discarded.
2. All expired benzoyl peroxide products should be discarded.
3. For those physicians and patients who wish to continue using benzoyl peroxide products, consider storing them at 4C, or refrigerator temperature. This will not necessarily eliminate the risk of benzene, but should slow any temperature-dependent degradation of benzoyl peroxide.
4. Replace your benzoyl peroxide product regularly, such as every 10-12 weeks to avoid long-term accumulation of benzene.
5. Industry and pharmacy should consider "cold chain" 4C storage throughout the entire lifecycle of benzoyl peroxide products: from manufacturer, to pharmacy/shelf, to patient/consumer homes.
6. As further information and guidance comes, we as a dermatology community can move forward with what is always in the best interest of our patients.