U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

FDA Sunscreen Study: Totality of the Data

Jeffry Florian, Ph.D.
Division of Applied Regulatory Science
Office of Clinical Pharmacology
OTS/CDER/OMTP/FDA

Disclaimer

- **The opinions expressed in this presentation are the presenter's and do not necessarily reflect the official views of the United States Food and Drug Administration (FDA).**

Overview

- Background
- Lessons learned from FDA sunscreen studies
- Areas of ongoing learning
- Summary

Background

- FDA published a proposed rule in February 2019
  - update regulatory requirements for certain sunscreen ingredients
- A key data gap for these active sunscreen ingredients is understanding whether, and to what extent, the ingredient is absorbed into the body after topical application
- Many questions around how this information gap could be addressed
- FDA conducted two **PILOT** studies to gather initial data on the systemic absorption
  - a maximal usage trial following maximal usage trial guidance
  - a study evaluating exposure after a single application and a longer duration

FDA Sunscreen Studies

Study 1:

Notable design elements:

- 4 products / 6 subjects
- Multiple applications per day
- Sample plasma out to Day 7

Clinical Study: [NCT03582215]

Study 2:

Notable design elements:

- 4 products / 12 subjects
- Single application Day 1
  - Multiple applications Day 2, 3, and 4
- Sample skin (Day 14) and plasma (Day 21)

Trials Successfully Conducted

JAMA | Preliminary Communication

Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

Murali K. Matta, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Jeffry Florian, 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

JAMA | Original Investigation

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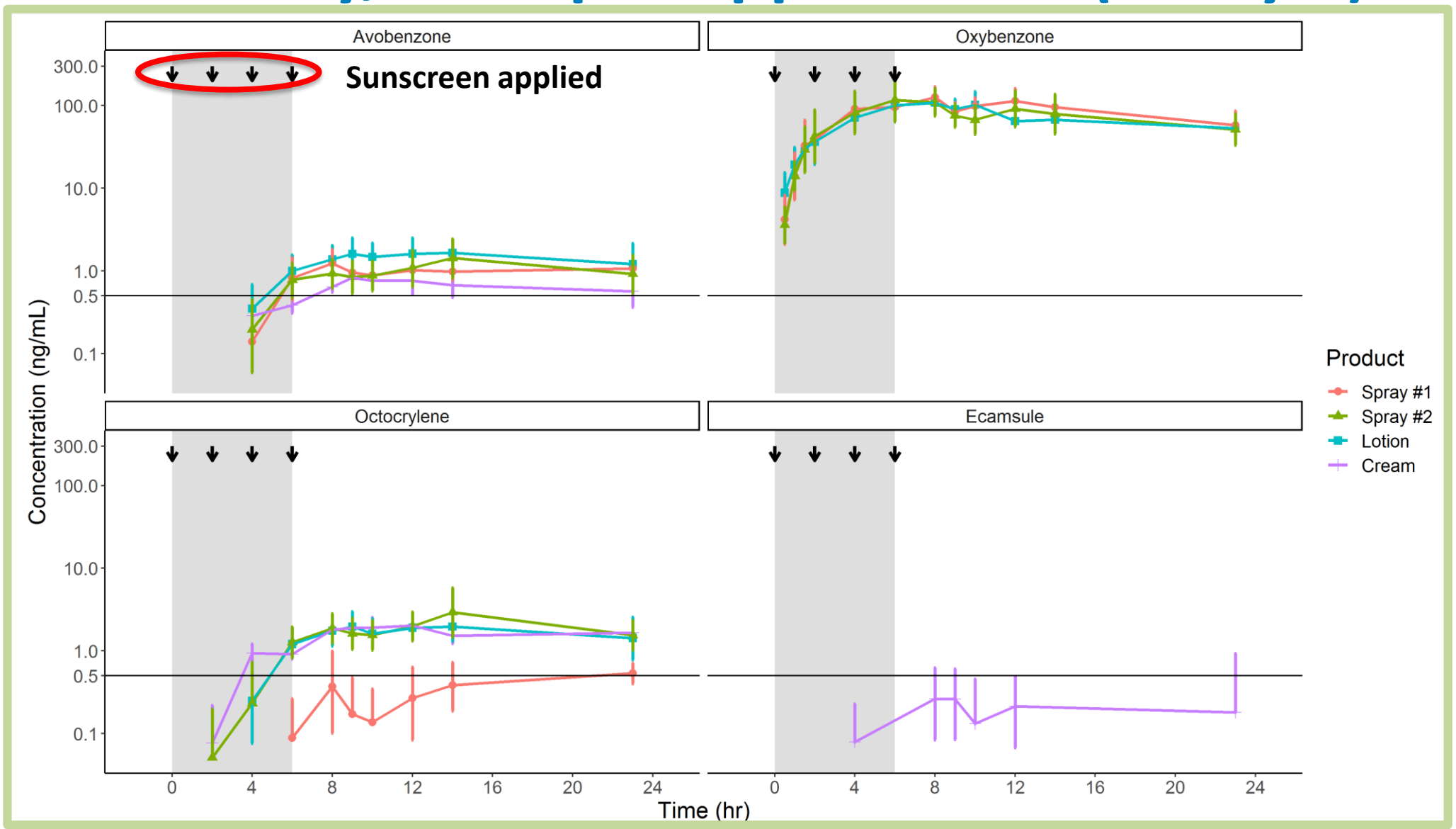
Clinical Study: NCT03582215

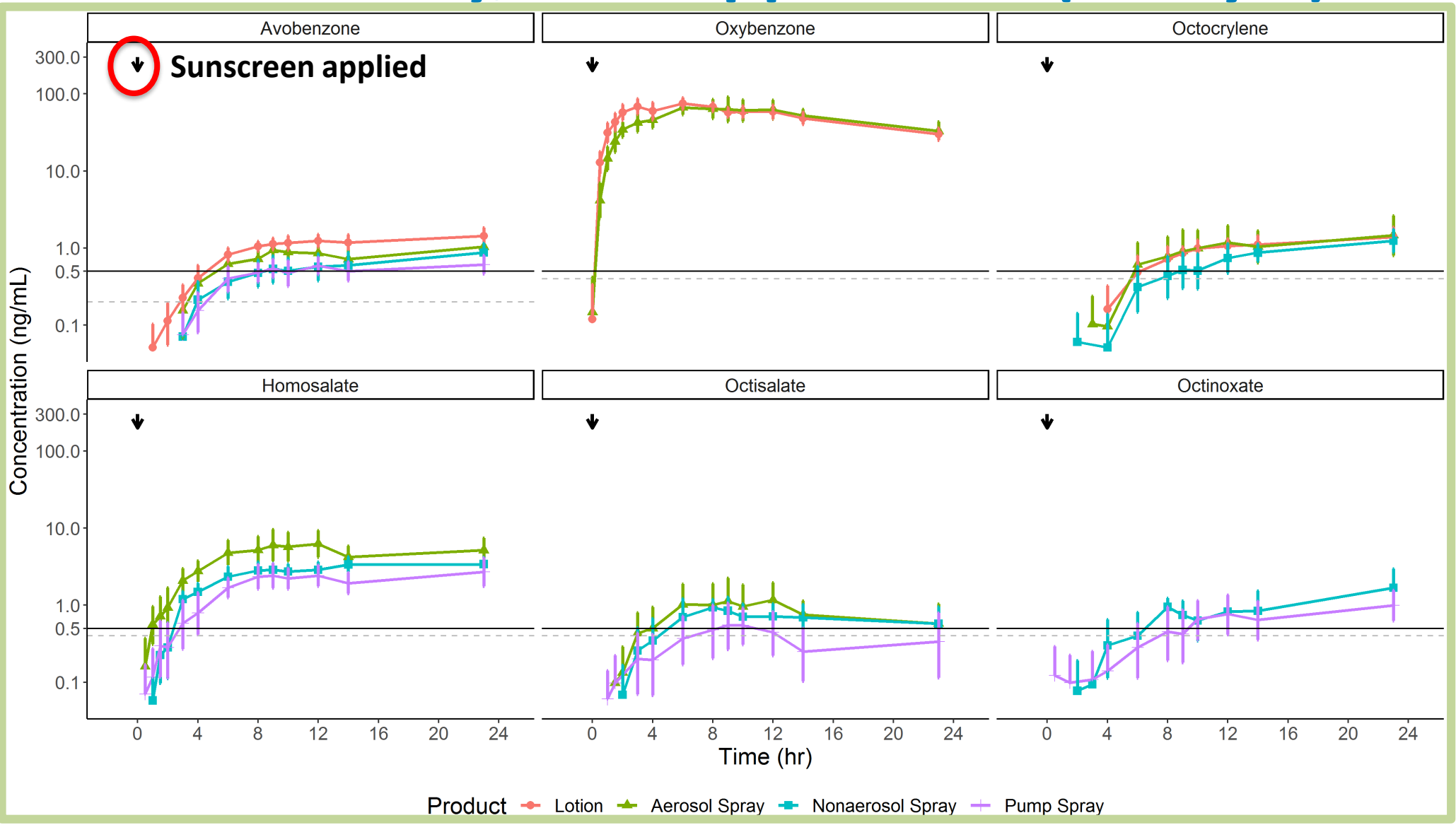
Active Ingredients Are Absorbed and Can Be Detected

Geometric Mean (ng/mL)		
	Study 1	**Study 2**
Avobenzone	1.8-4.3	3.3-7.1
Oxybenzone	169-210	180-258
Octocrylene	2.9-7.8	6.6-7.8
Homosalate	40.3	13.9-23.1
Octisalate	10.0	4.6-5.8
Ecamsule	1.5	-
Octinoxate	-	5.2-7.9

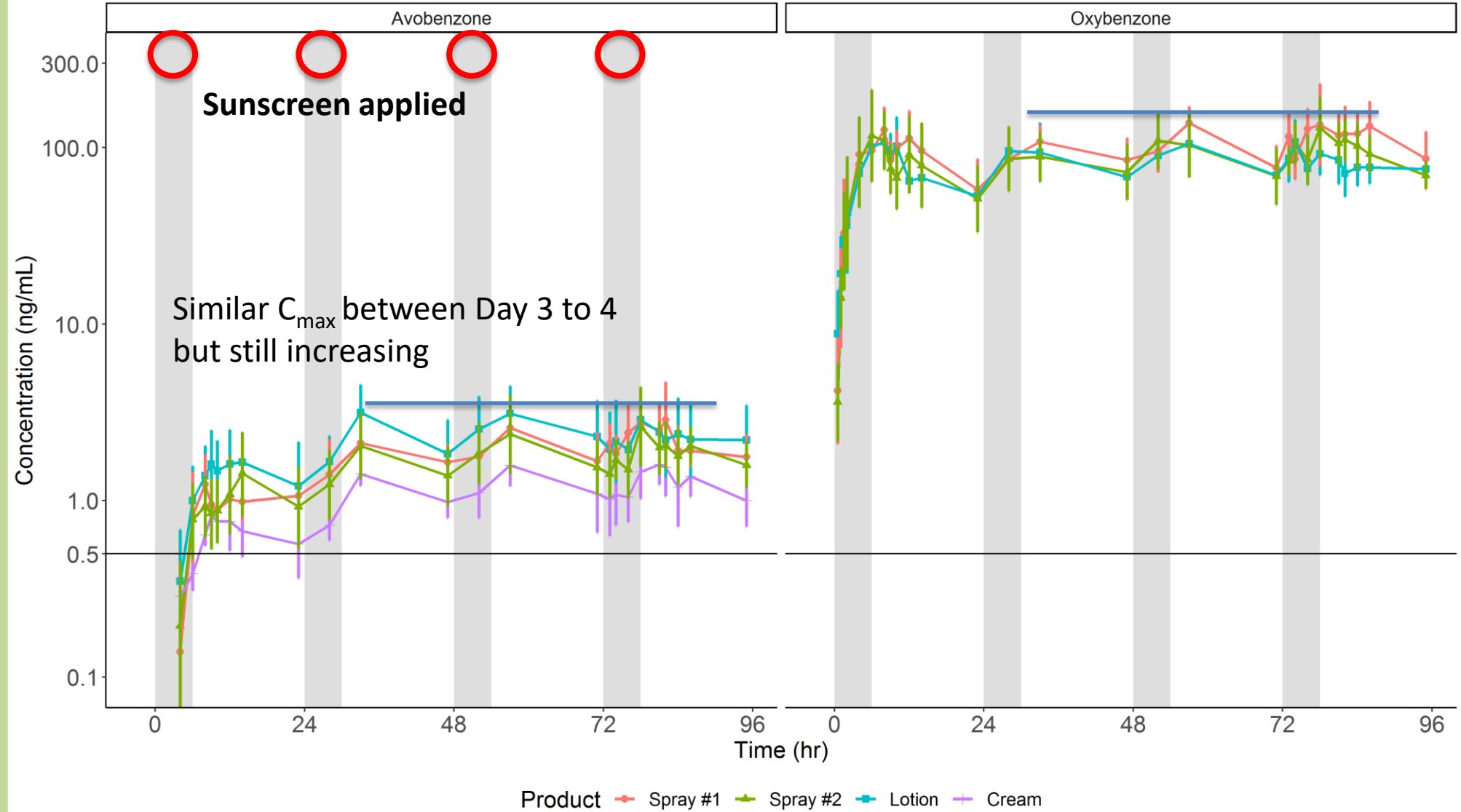
Active Ingredients Were Absorbed After One Day, Multiple Applications (Study 1)



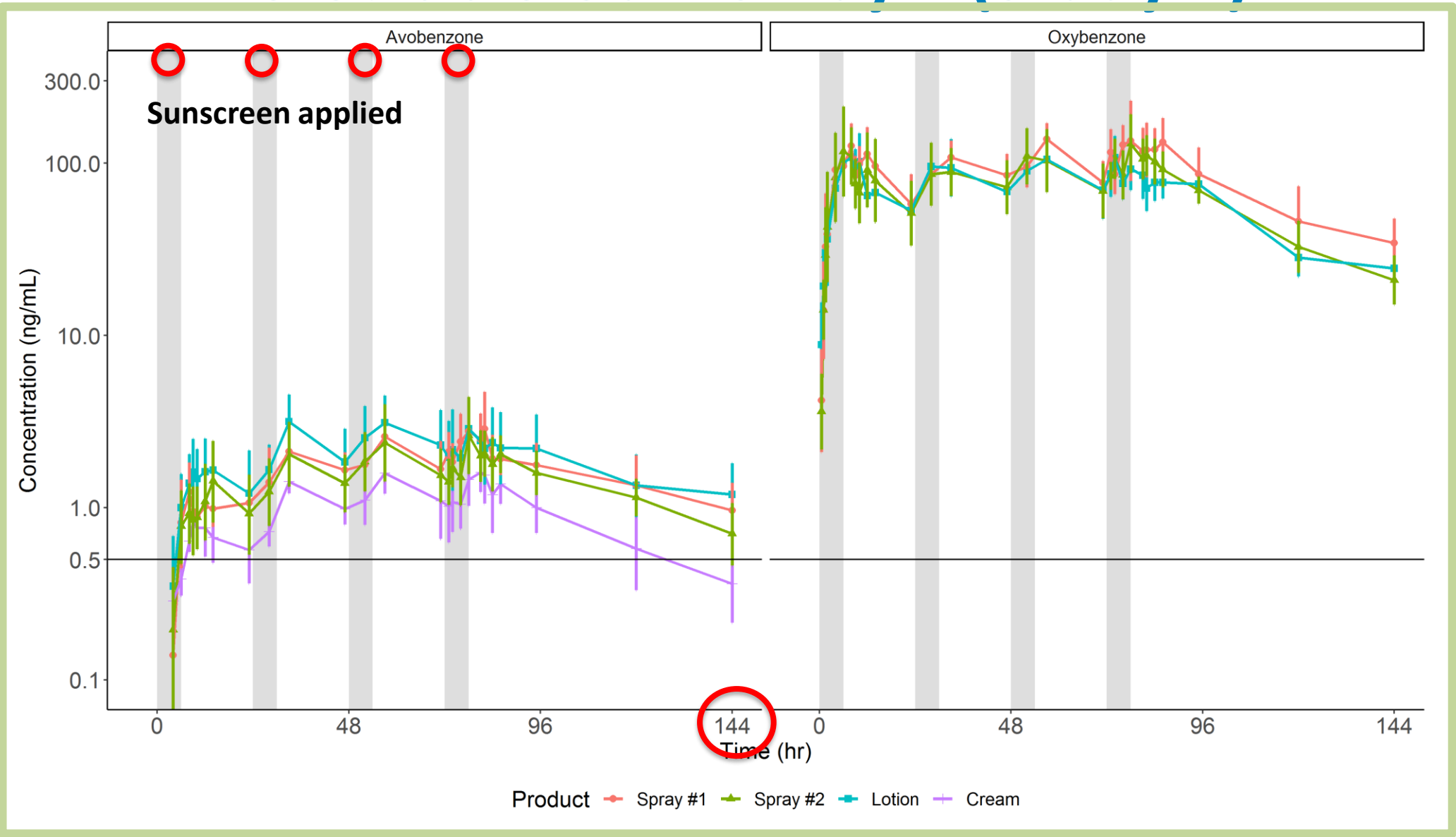
Active Ingredients Absorbed After One Day, One Application (Study 2)



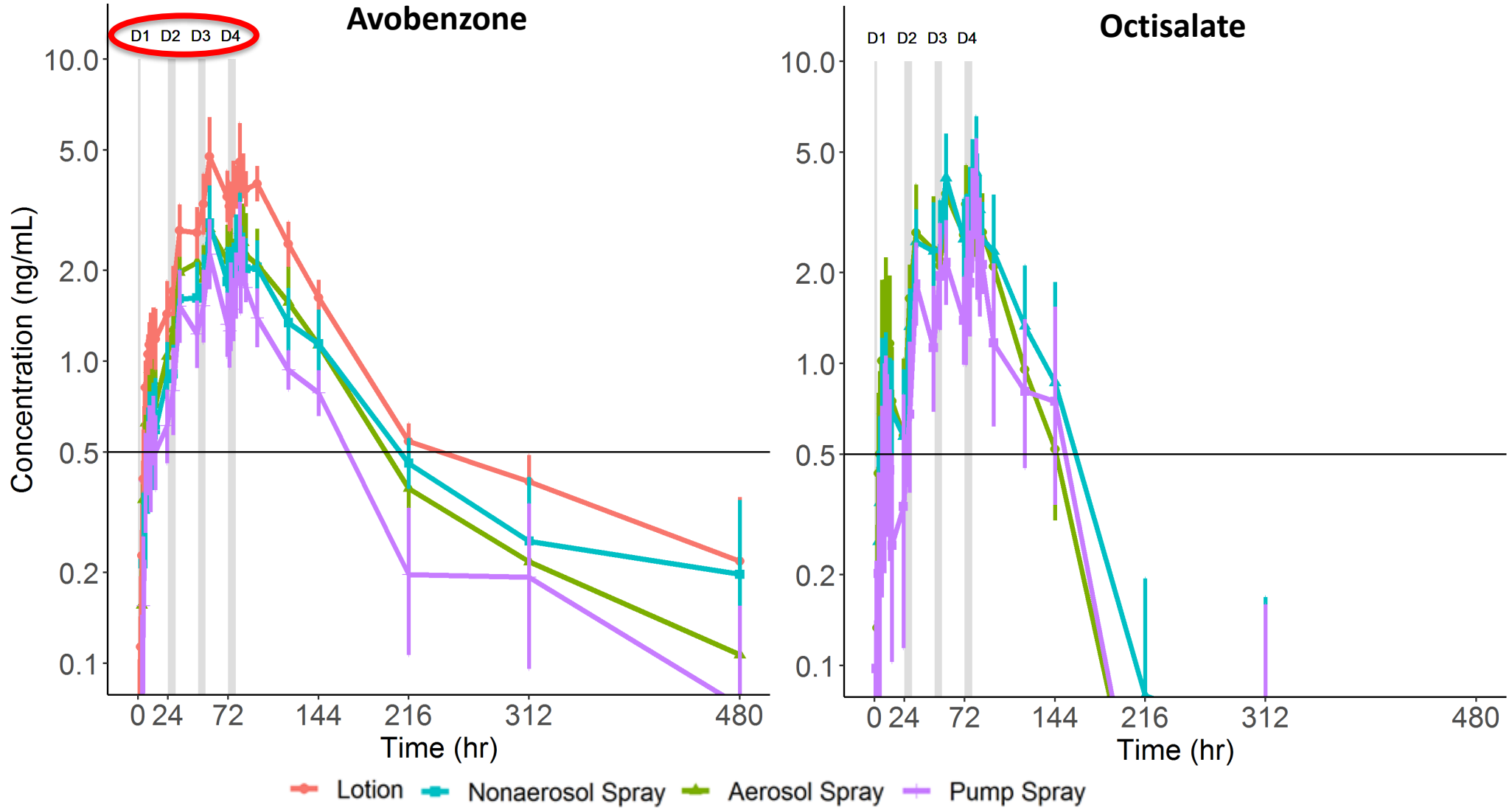
Active Ingredients Accumulate With Repeat Administration (Study 1)



Active Ingredients Were Detectable Out to Day 7 (Study 1)



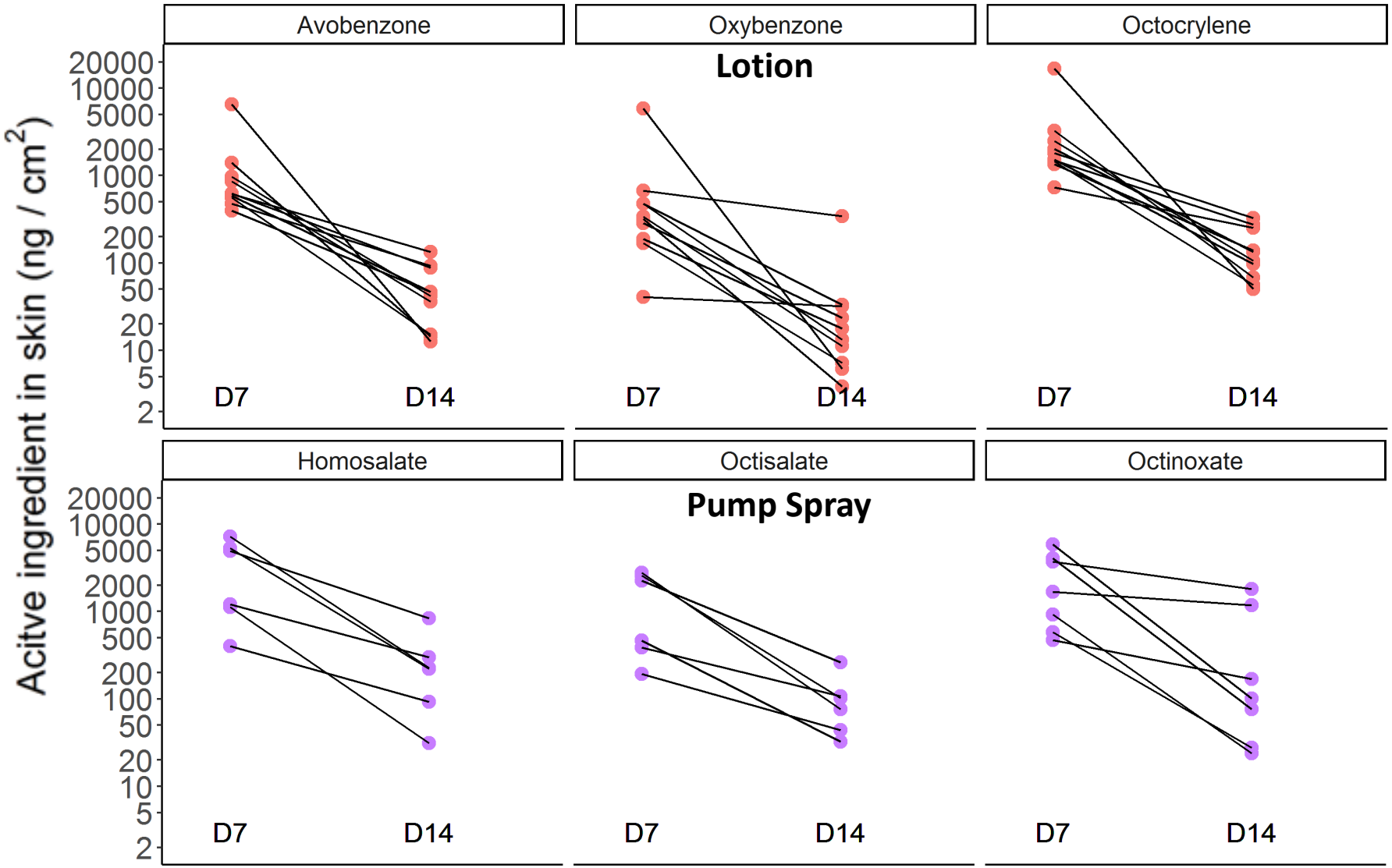
Some Active Ingredients Were Detectable Out to Day 21 (Study 2)



Multiple Day Terminal Half-life – Skin Depot?

Terminal Half-life (hr)		
	Study 1	**Study 2**
Avobenzone	33-55	24-31
Oxybenzone	48-79	79
Octocrylene	43-84	48-79
Homosalate	41	47-78
Octisalate	26	54-77
Octinoxate	-	51-157

Tape Stripping Results – Likely Skin Depot



Lessons Learned/Remaining Questions

We Now Know

- Studies are feasible to conduct
- Active ingredients
  - are absorbed
  - can be measured
  - accumulate with repeat application
  - remains in system for extended period of time
- Skin serving as a depot

Remaining Questions – Safety

- Conducted studies do not answer questions about safety *but*

JAMA publications

CONCLUSIONS AND RELEVANCE In this preliminary study involving healthy volunteers, application of 4 commercially available sunscreens under maximal use conditions resulted in plasma concentrations that exceeded the threshold established by the FDA for potentially waiving some nonclinical toxicology studies for sunscreens. The systemic absorption of sunscreen ingredients sup
significance of these findir
from the use of sunscreen.

CONCLUSIONS AND RELE
examining sunscreen ap
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.

JCO Oncology Practice[1]

Interpreting the Findings and the Need for More Data

The fact that the sunscreen active ingredients are absorbed systemically does not mean they are unsafe. Rather, this
the safety of
ime.[8]

Results to date do not alter benefit/risk of sunscreen use

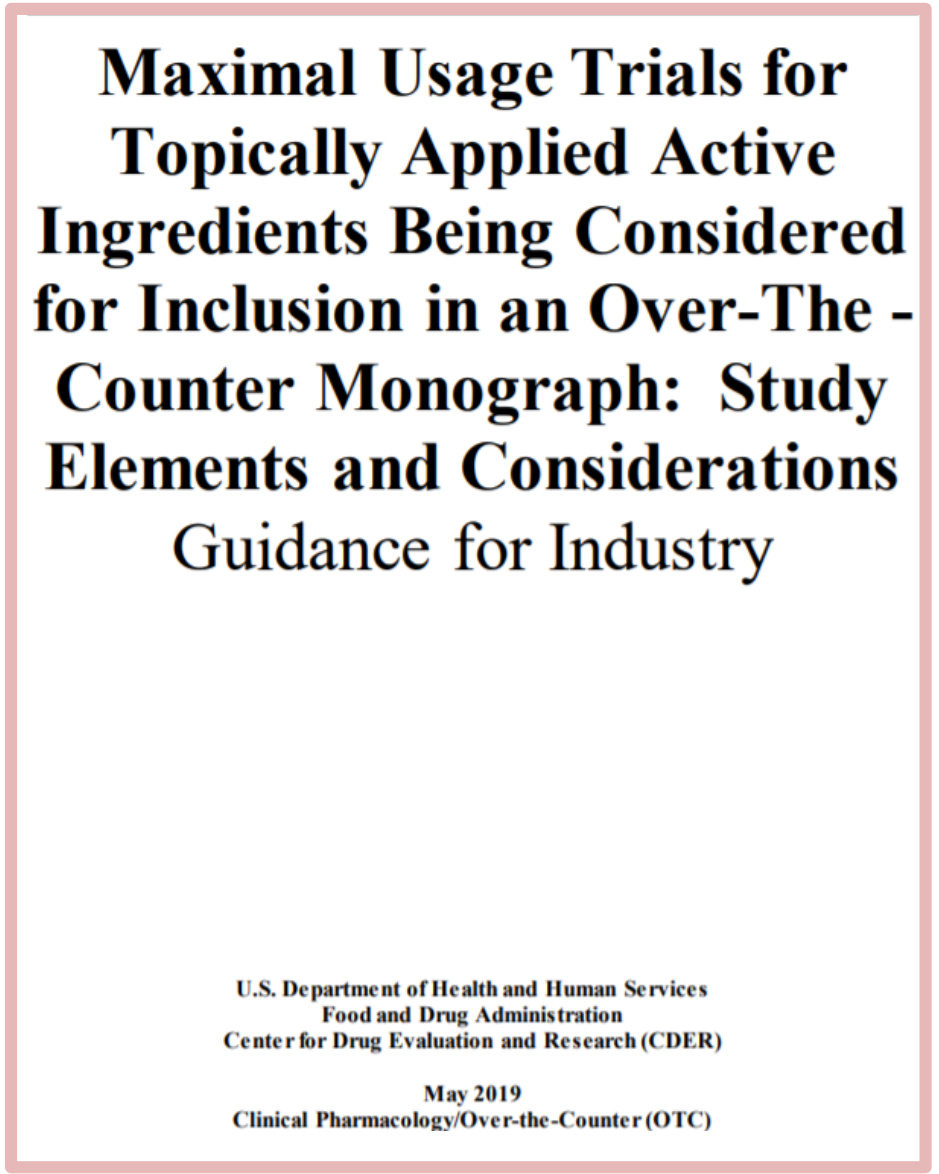
e sunscreen active ingredients may be absorbed. However, the fact that an ingredient is absorbed through the skin and into the body does not mean that the ingredient is unsafe, nor does the FDA seeking further information indicate such. Rather, this finding calls for further industry testing to determine the safety and effect of systemic exposure of sunscreen ingredients, especially with chronic use."

[1]DG Strauss and TM Michele, 2020 – JCO Oncology Practice
[2]https://www.fda.gov/news-events/fda-voices/shedding-new-light-sunscreen-absorption
[3]https://www.fda.gov/news-events/fda-brief/fda-brief-fda-announces-results-second-sunscreen-absorption-study

Remaining Questions – Study Design

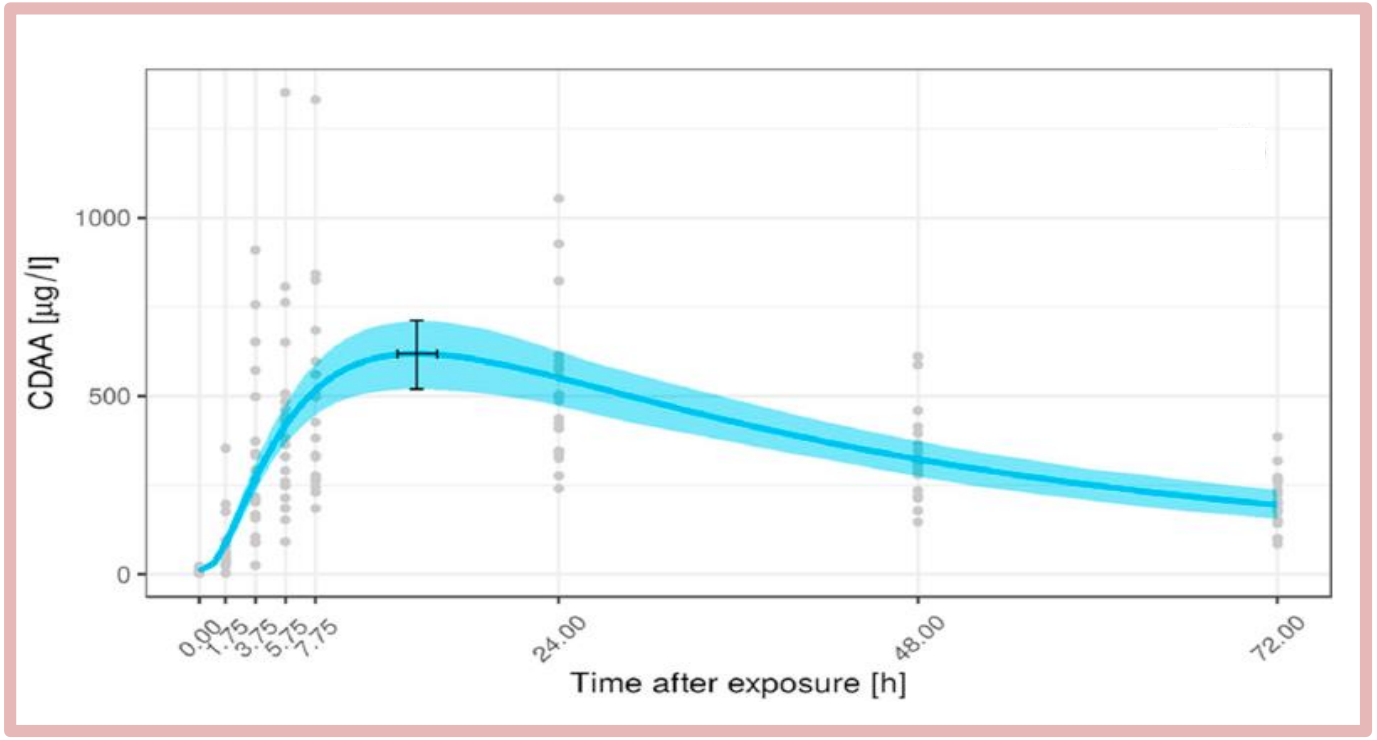
- Substantial information learned from both FDA studies *but*
- Different designs may be needed for different products
  - number of subjects
  - length of study
  - amount applied
  - population

- Considerations in implementing a Master Protocol for sunscreens will be presented this afternoon



Remaining Questions – Metabolite Exposure

- Potential for metabolites to be absorbed
  - Similar or even greater exposure than parent compound



- Separate study quantified metabolite exposures
- 20 healthy volunteers
- Analytes
  - 2-cyano-3,3-diphenylacrylic acid (CDAA)
    - octocrylene metabolite
- Additional information is needed

Hiller et al, 2019 *Environmental International*

Summary

- FDA completed two **PILOT** clinical studies on sunscreen absorption
- Studies demonstrated all active ingredients from seven products
  - were absorbed, accumulated with repeat administration, and could be detected in circulations for an extended period of time
- When designing your own studies, the design may vary by product
  - FDA encourages conversations before beginning pilot studies

- **The fact than an ingredient is absorbed through the skin and into the body does not mean that the ingredient is unsafe**

Acknowledgements

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Jian Wang, PhD
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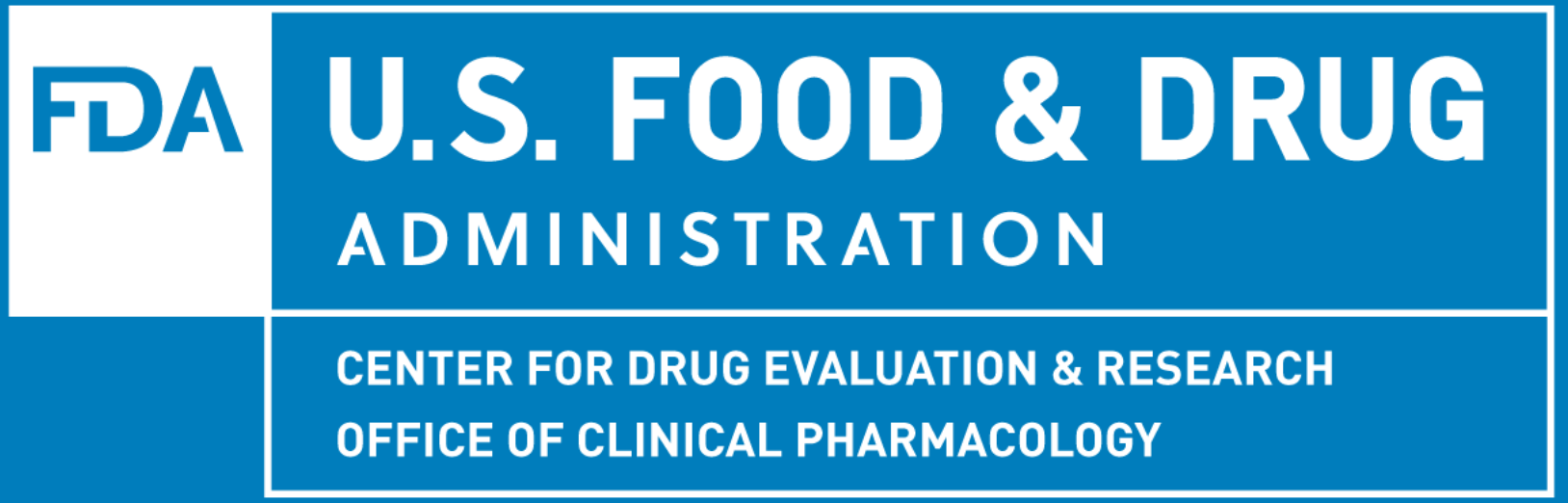
THANK YOU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