SKIN

SHORT COMMUNICATION

Percutaneous Penetration: Reliability of Mathematical Models

Anuk Burli, BS[1,2], Rebecca M. Law, MD[1,3], Howard I. Maibach, MD[1]

[1] Department of Dermatology, University of California, San Francisco, San Francisco, CA
[2] University of Rochester School of Medicine and Dentistry, Rochester, NY
[3] Memorial University of Newfoundland School of Pharmacy

In the 300,000 years of homo sapiens evolvement, only in the last century and a half have large numbers of humans been extensively exposed to chemicals via skin exposure. Although we have a global understanding of factors that control percutaneous penetration, experimental human in vivo data for few compounds exist- suggesting the need for QSAR based algorithms to predict flux- based on chemical structure. Several such models exist such as the Potts and Guy Model, the Cleek and Bunge Model and in silico models, but how accurately do they predict the human in vivo available data?[3]. Our recent publications focused on the highest quality in vivo data available for organic compounds and steroids[1,2].

We analyzed in vitro and in vivo percutaneous penetration data for various organic compounds and steroids and calculated in vitro flux based on the most prominent model used by the EPA for percutaneous penetration: Potts and Guy model. We then calculated in vivo flux based on the maximal absorption rate and applied dose. For most chemicals, the flux was over- or underestimated by a factor 10–100. Possible factors for the discrepancy between in vivo and in vitro data include the principle of rubbing and skin washing, which can affect the stratum corneum, a main barrier for skin absorption. Additionally, anatomical variation in penetration exists due to a difference in stratum corneum thickness in different regions of the body. Finally, each subject's age differed and age can affect stratum corneum content.

We also discuss limitations of the Potts and Guy model. The model relies on the variables log Koctanol, saturated aqueous solubility, Kp, and molecular weight, most of which are based on predictive models.

Percutaneous penetration data regarding the use of sunscreens has also been recently studied. Sunscreen percutaneous penetration depends on blood level or urinary excretion. A recent FDA study, involved widespread sunscreen application throughout the body, Matta et al., found fairly high blood levels, indicating that the percutaneous absorption of sunscreen was at a level of concern[4]. However, this research relied on calculating area under the curve. When measuring percutaneous penetrations by this method, it is unclear whether a compound is being excreted or stored systematically in the body. Systematic toxicity based on percutaneous penetration depends on absorption, distribution, metabolism and excretion. By not knowing how all four factors are affected through widespread sunscreen application,

information regarding percutaneous penetration is incomplete.

Percutaneous penetration relies on the different factors mentioned above. However, there is not yet a model that incorporates all these factors in predicting human in vivo percutaneous penetration. There are major public health implications because we are not accurately predicting how much organic compounds in our environment are being percutaneously absorbed through skin. It is necessary for the experimental community to further investigate how best to predict percutaneous penetration, as well as for clinicians who prescribe topical medications to further understand the limitations of current established mathematical models.

Availability of data and material: The data that support the findings of this study are available from the corresponding author, Anuk Burli, upon reasonable request

Conflict of Interest Disclosures**:** None

Funding: None

Corresponding Author:
Anuk Burli
601 Elmwood Avenue
Rochester, New York, 14620
Email: burlianuk@gmail.com

References:

1. Burli A, Law RM, Rodriguez J, Maibach HI, (2020). Organic compounds percutaneous penetration in vivo in man: Relationship to mathematical predictive model. Regul Toxicol Pharmacol.112:104614. doi: 10.1016/j.yrtph.2020.104614.
2. Burli A, Law RM, Maibach HI. Ability of mathematical models to predict human in vivo percutaneous penetration of steroids. Regul Toxicol Pharmacol. 2021 Nov;126:105041. doi: 10.1016/j.yrtph.2021.105041. Epub 2021 Sep 6
3. Cheruvu HS, Liu X, Grice JE, Roberts MS., (2020). Modeling percutaneous absorption for successful drug discovery and development. Expert Opin Drug Discov. 15(10):1181-1198. doi: 10.1080/17460441.2020.1781085.
4. Matta MK, Florian J, Zusterzeel R, et al. Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. *JAMA.* 2020;323(3):256–267. doi:10.1001/jama.2019.20747