

# Physiologically Based Pharmacokinetic Modelling of Topically Applied Propylparaben - a Widely Used Topical Excipient - with a Novel Skin Metabolism Framework

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## Experimentally scaled skin metabolism enables dermal PBPK prediction of propylparaben across *in vitro* permeation testing and *in vivo* studies

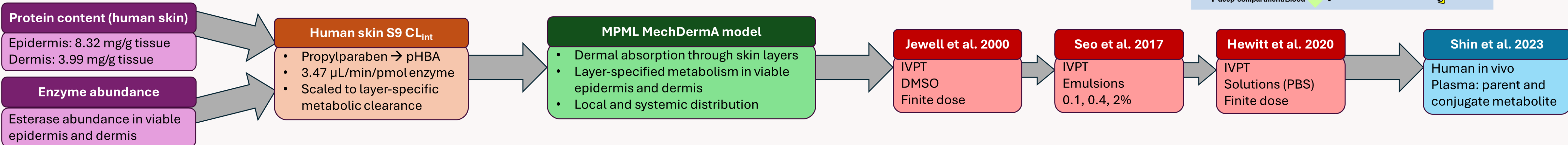
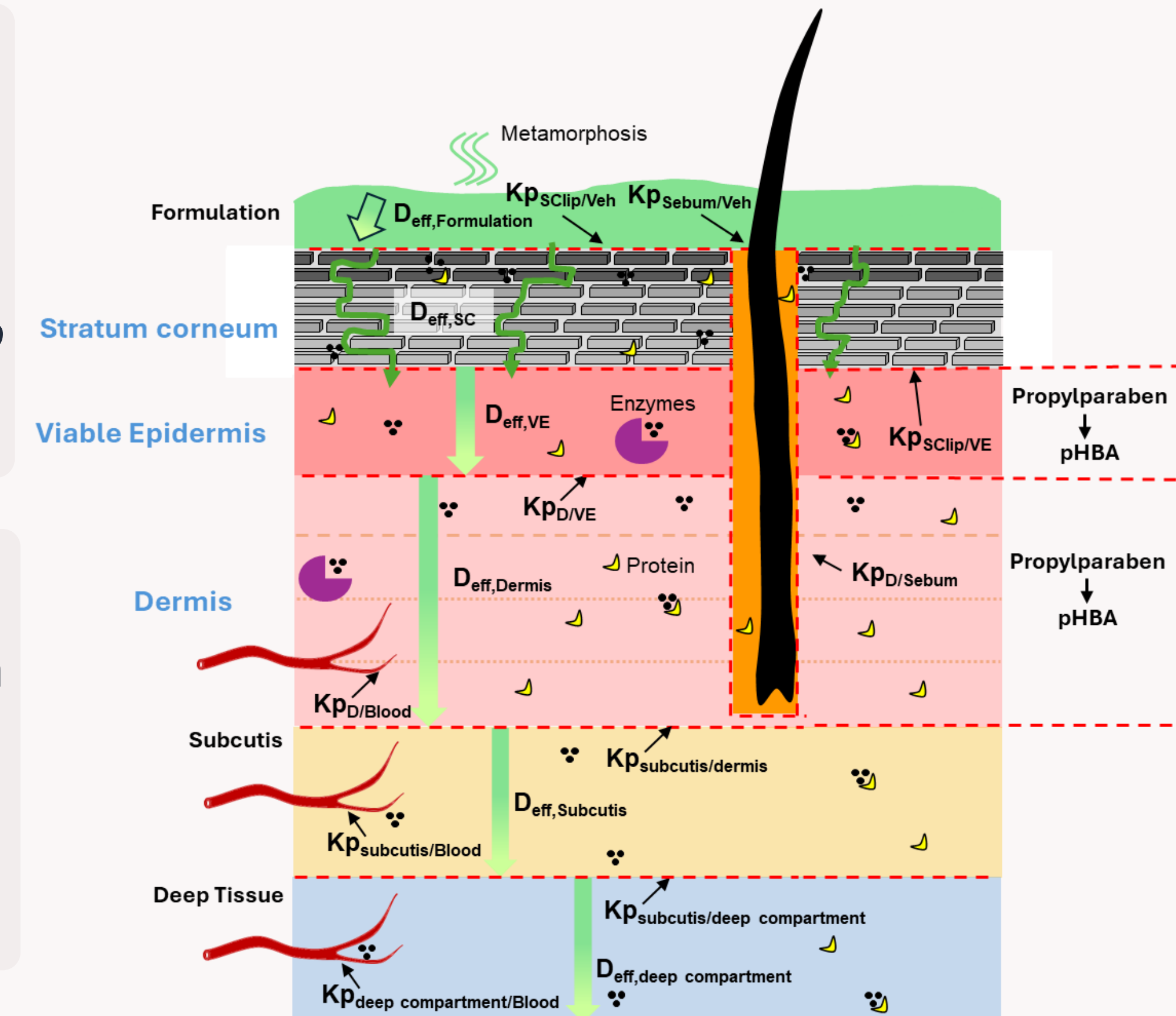
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### Background and Objective

- Parabens are widely used preservatives in topical pharmaceutical and cosmetic products.
- Propylparaben (PP) is hydrolysed in skin to p-hydroxybenzoic acid (pHBA).
- Skin metabolism in PBPK models is generally not present or not mechanistically represented.
- Objective:** Develop and verify a dermal PBPK model with skin layer-specific metabolism across *in vitro* permeation testing (IVPT) and *in vivo* datasets.

### Methods

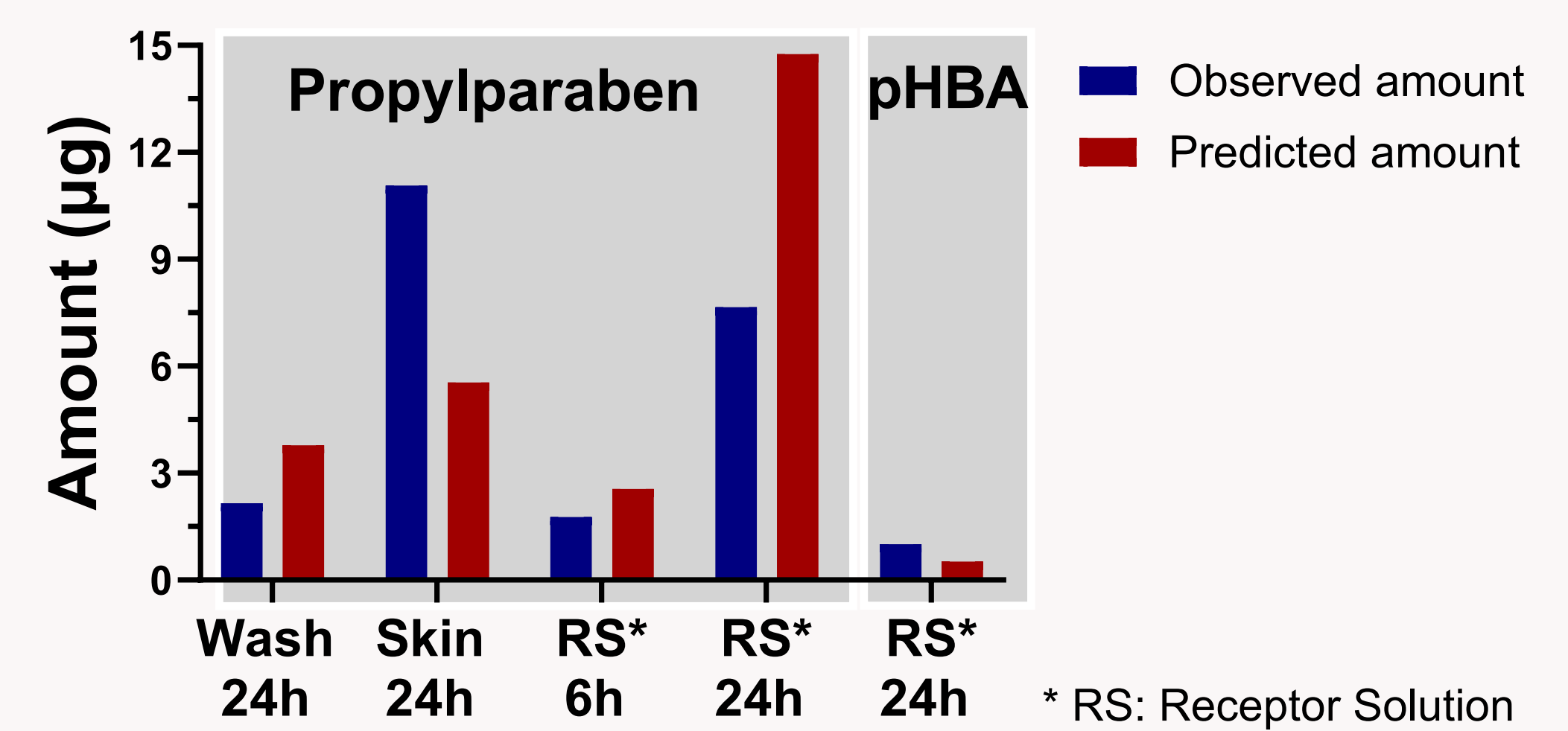
- Quantified protein content and esterase abundance in epidermis and dermis from 17 human skin samples<sup>1,2</sup>.
- Scaled human skin S9 intrinsic clearance<sup>3</sup> for propylparaben hydrolysis to layer-specific skin metabolism.
- Implemented metabolism in Simcyp MPML MechDerma (Version 24).
- Optimised corneocyte permeability to Jewell *et al.*<sup>4</sup>, then verified against independent datasets.



### Results

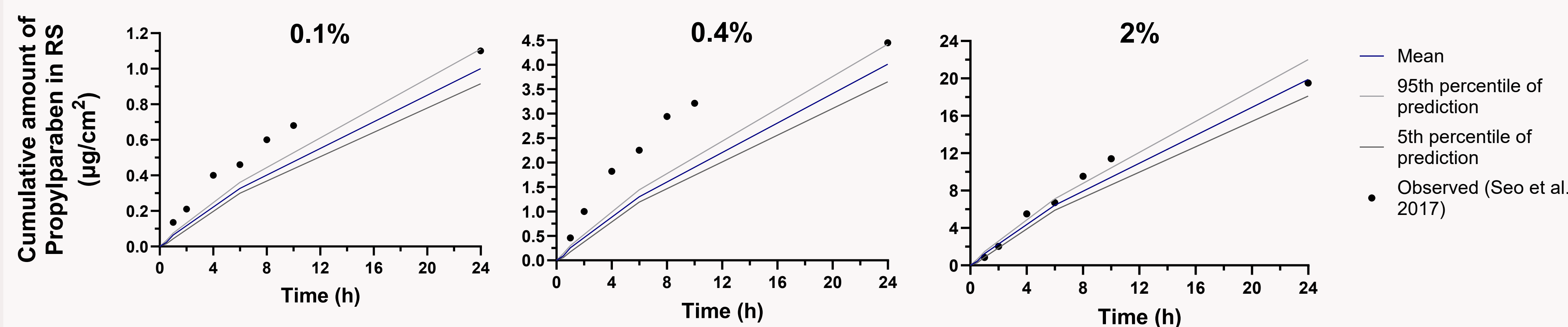
For the Jewell *et al.*<sup>4</sup> dataset, simulated wash, skin, and receptor solution amounts of propylparaben, together with receptor solution amount of pHBA, were within two-fold of observed values. The model recovered both parent disposition and metabolite formation after dermal application.

The only absorption parameter adjusted was the corneocyte membrane permeability: optimised from the default  $1.0 \cdot 10^{-5}$  cm/h to  $1.9 \cdot 10^{-6}$  cm/h.

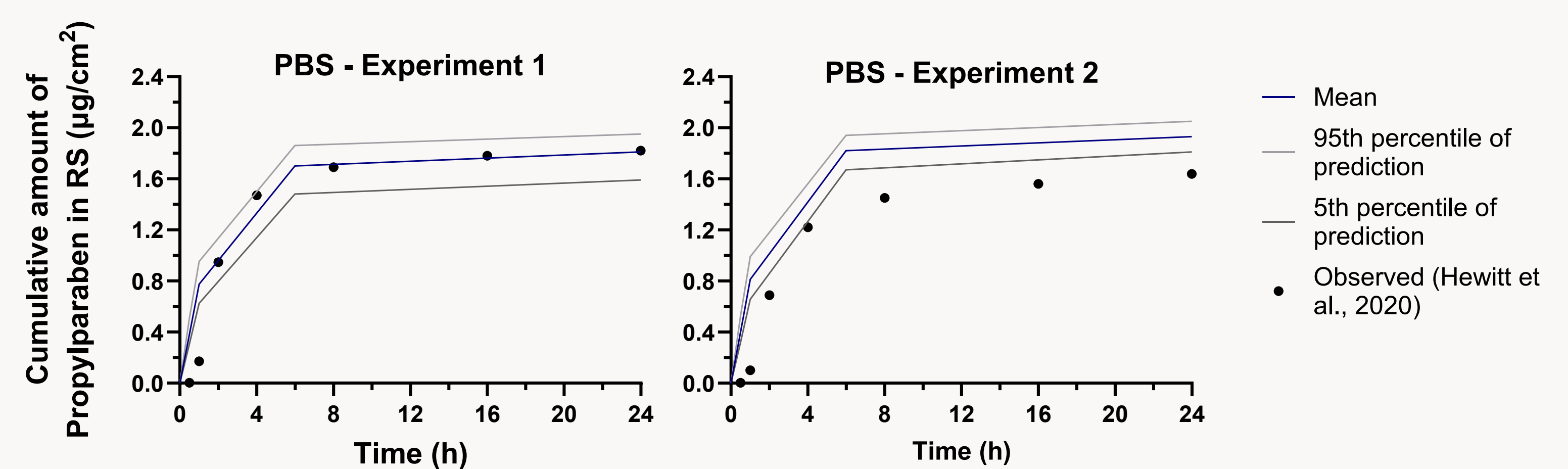


For the Seo *et al.*<sup>5</sup> study, the same model captured receptor profiles across the 0.1%, 0.4%, and 2% cream formulations. The stratum corneum (SC) lipid: vehicle partition coefficient was optimised as an effective parameter to account for the unknown vehicle composition.

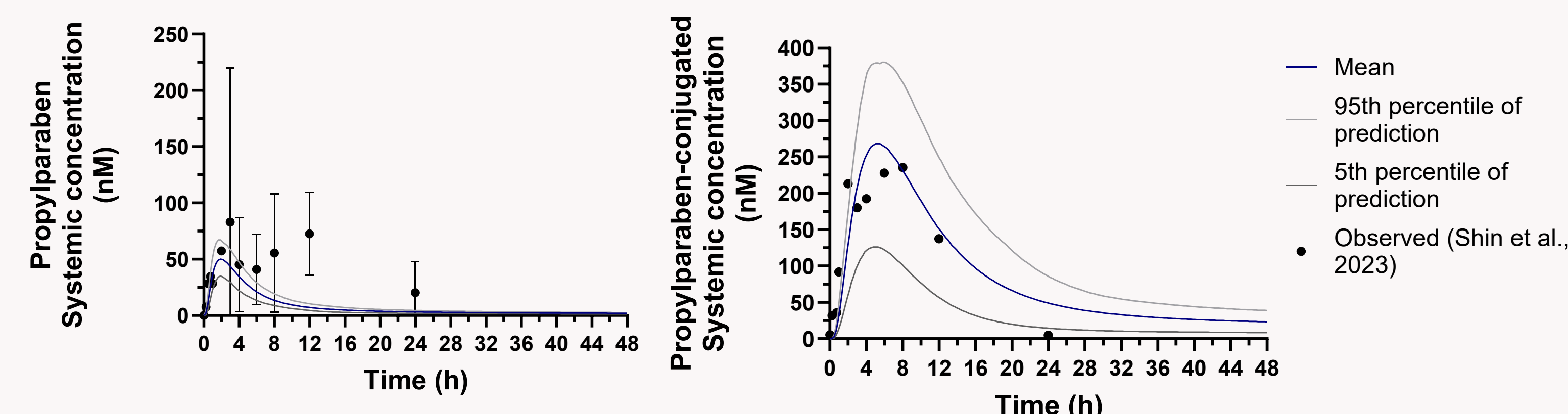
Predicted/observed ratios for the 24 h cumulative receptor amount were 0.91, 0.90, and 1.02, respectively, demonstrating good agreement across formulation strengths.



For the Hewitt *et al.*<sup>6</sup> datasets using PBS as a vehicle, the model reproduced receptor solution exposure well, with 24 h predicted/observed ratios of 0.99 and 1.14. However, SC amounts were overpredicted (P/O 149.9 and 18.6), whereas viable epidermis (P/O 0.69 and 0.36) and dermis amounts (P/O 0.08 and 0.05) were underpredicted.



In Shin *et al.*'s<sup>7</sup> human dermal PK study, the model reproduced the overall time course of systemic exposure. Predicted plasma concentrations for parent propylparaben and its conjugated metabolite were largely within the simulated population range, and predicted  $C_{max}$  and  $T_{max}$  were within two-fold of observations.



### Conclusion

- A dermal PBPK model with experimentally derived, layer-specific skin metabolism described propylparaben disposition across IVPT and human *in vivo* datasets.
- The model predicted parent and metabolite *in vitro* permeation and clinical systemic concentration profiles.
- Disabling skin metabolism caused small differences, consistent with metabolism acting as a modest sink under the conditions of the studies.
- These results support the use of mechanistic skin metabolism in dermal PBPK modelling for quantitative risk assessment.

### References

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