

Integrated human PK predictions: Beyond single parameters towards full profile benchmarking



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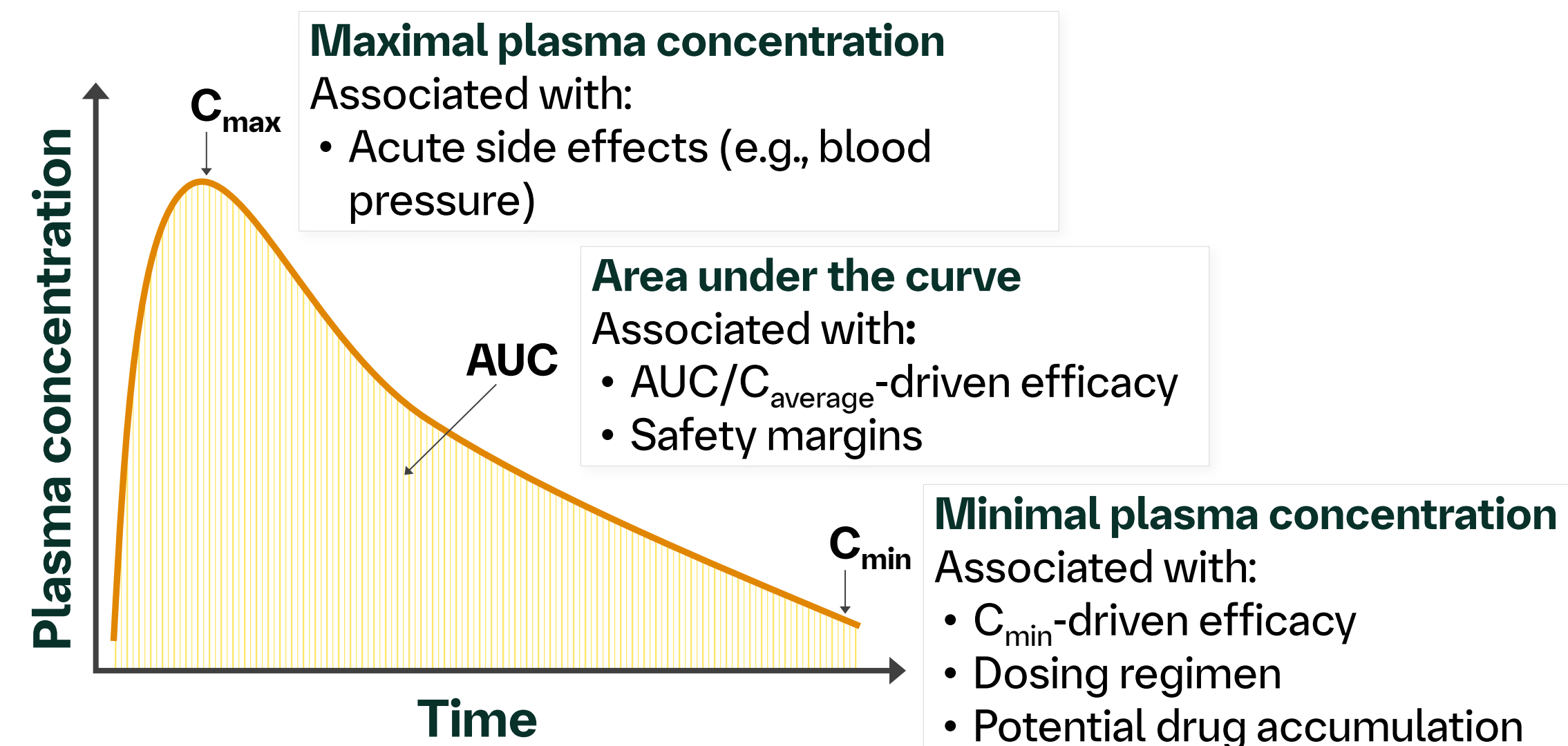
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Human PK prediction

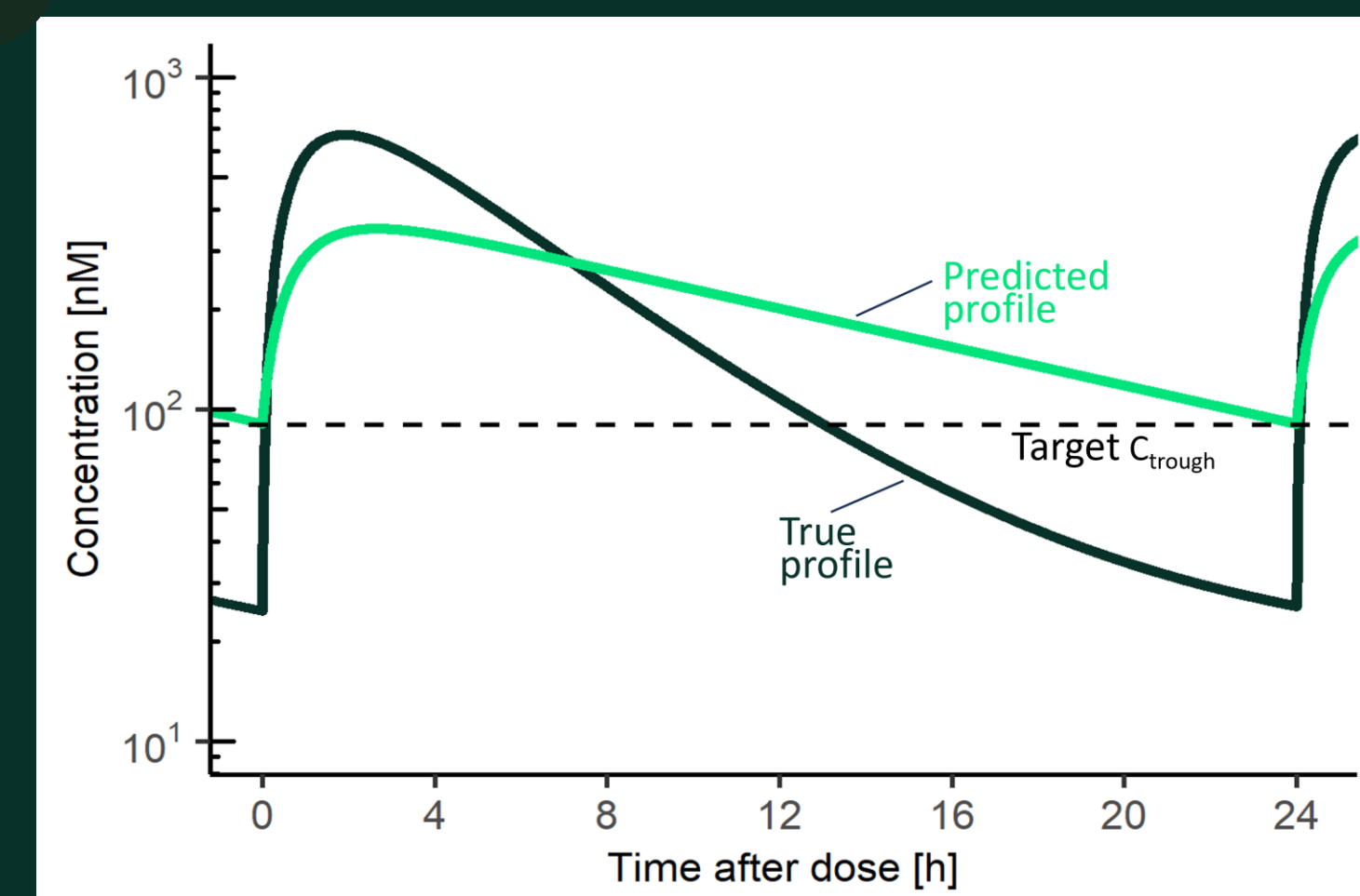
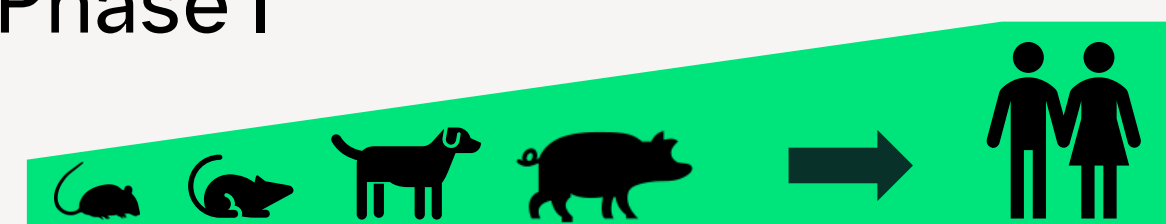


Key task during drug discovery and drug development



Impact

- Defines the human dose together with target exposure
- Selection of clinical candidates
- Basis for safety window assessments and early clinical development plan
- Relevant for development of initial human formulations to support Phase I



PK profiles generated with a 1-compartment (predicted) vs. 2-compartment (true) PK models with identical CL, V_{ss} , F, and k_a .

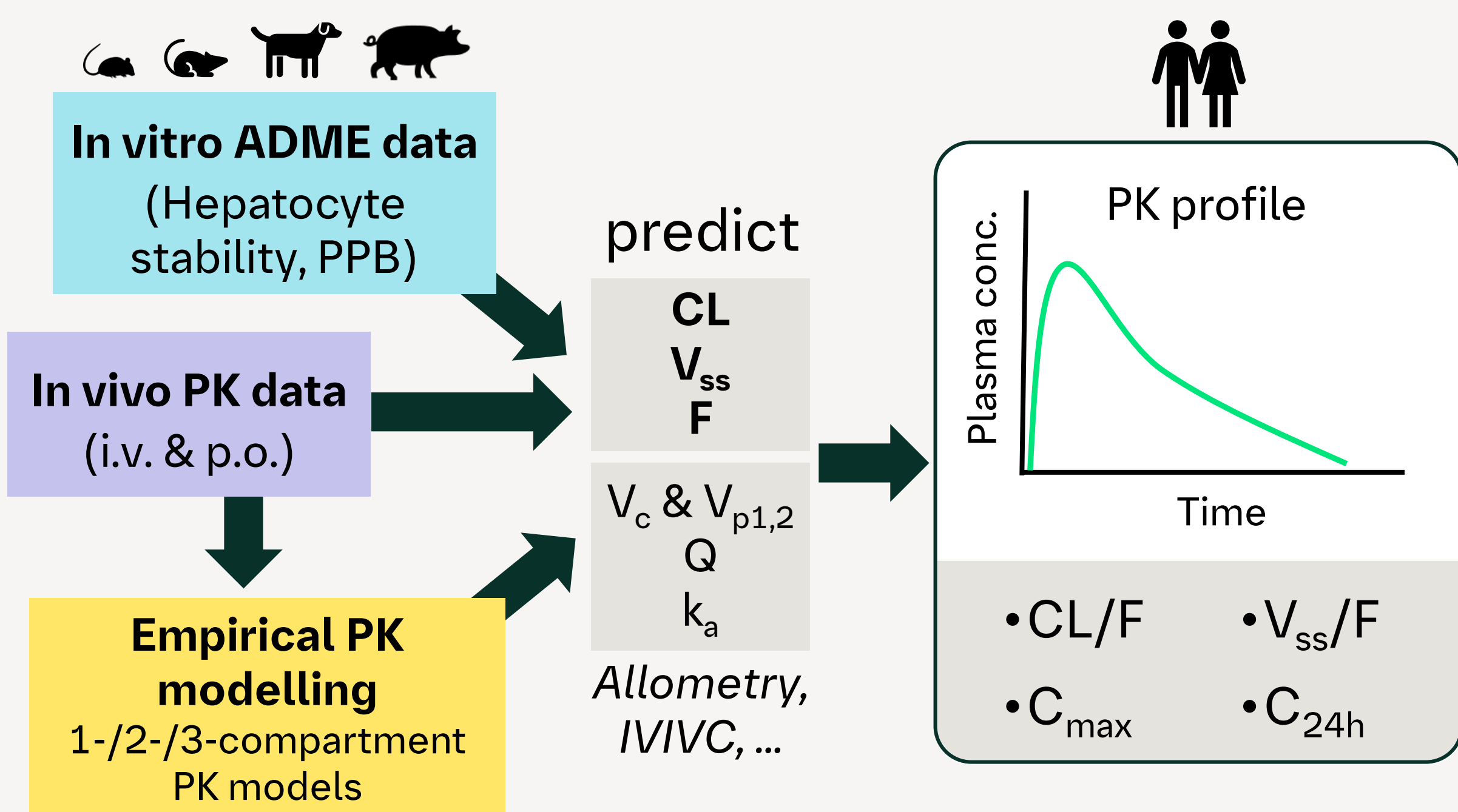
- Most published evaluations focus on single PK parameters (CL, V_{ss} , MRT) and key points of the PK profile (AUC, C_{max})
- Few evaluations exist for C_{min} (C_{24h}) or the shape of the PK profile
- Without a full concentration-time profile important PK characteristics such as C_{max} , t_{max} , and C_{min} cannot be evaluated



Evaluate prediction quality of the in-house human PK prediction process

PK Prediction Framework

Evaluation based on 40 NCEs from the Boehringer Ingelheim pipeline with available clinical and preclinical PK data



Prediction methodology chosen based on compound characteristics.

Evaluation of prediction quality

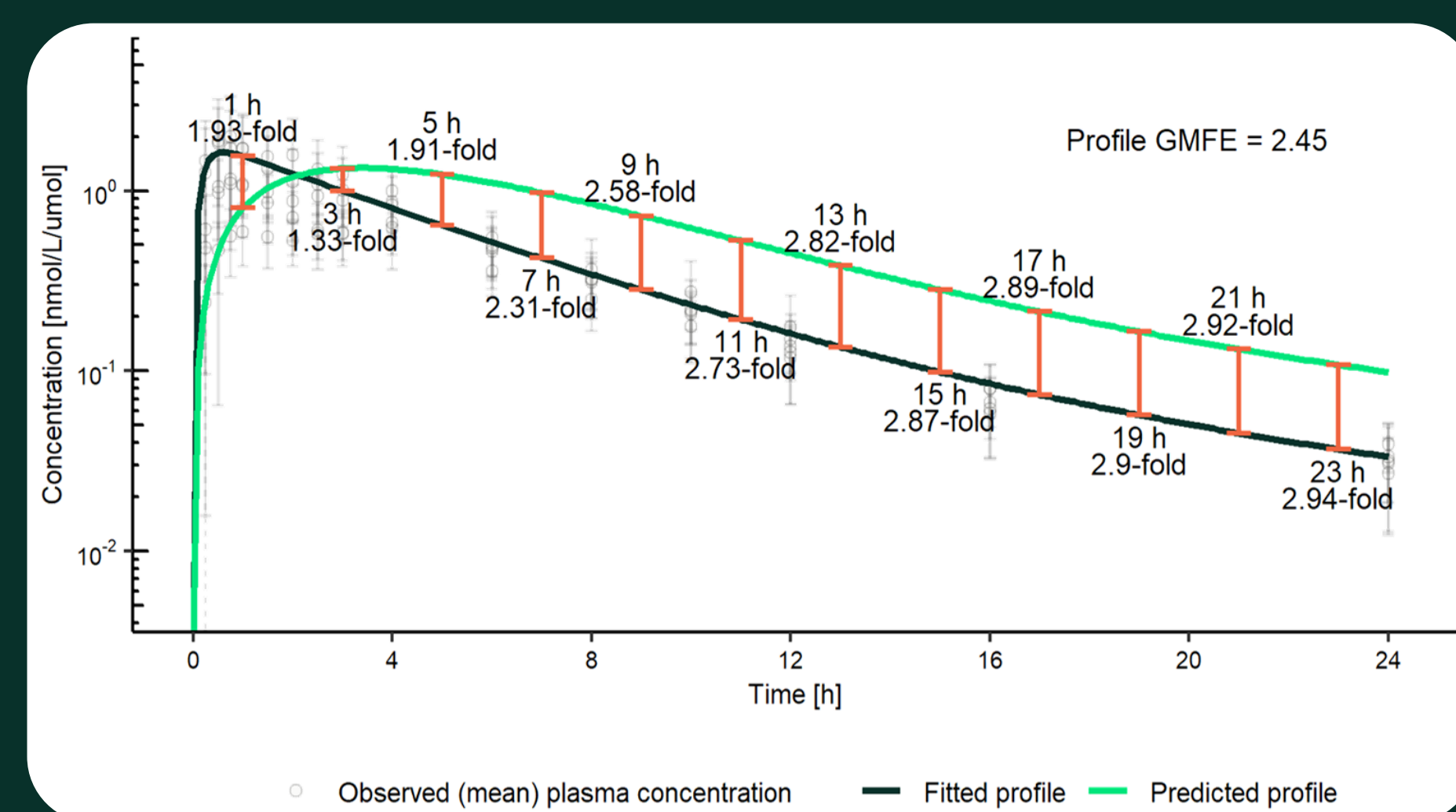
The absolute fold-error (FE) was calculated as the main metric for comparison between observed (obs) and predicted (pred) metrics for each compound (i):

$$FE = \frac{pred_i}{obs_i}, \text{ if } pred_i > obs_i \quad \left| \quad FE = \frac{obs_i}{pred_i}, \text{ if } obs_i > pred_i$$

Evaluation of plasma concentration-time profiles

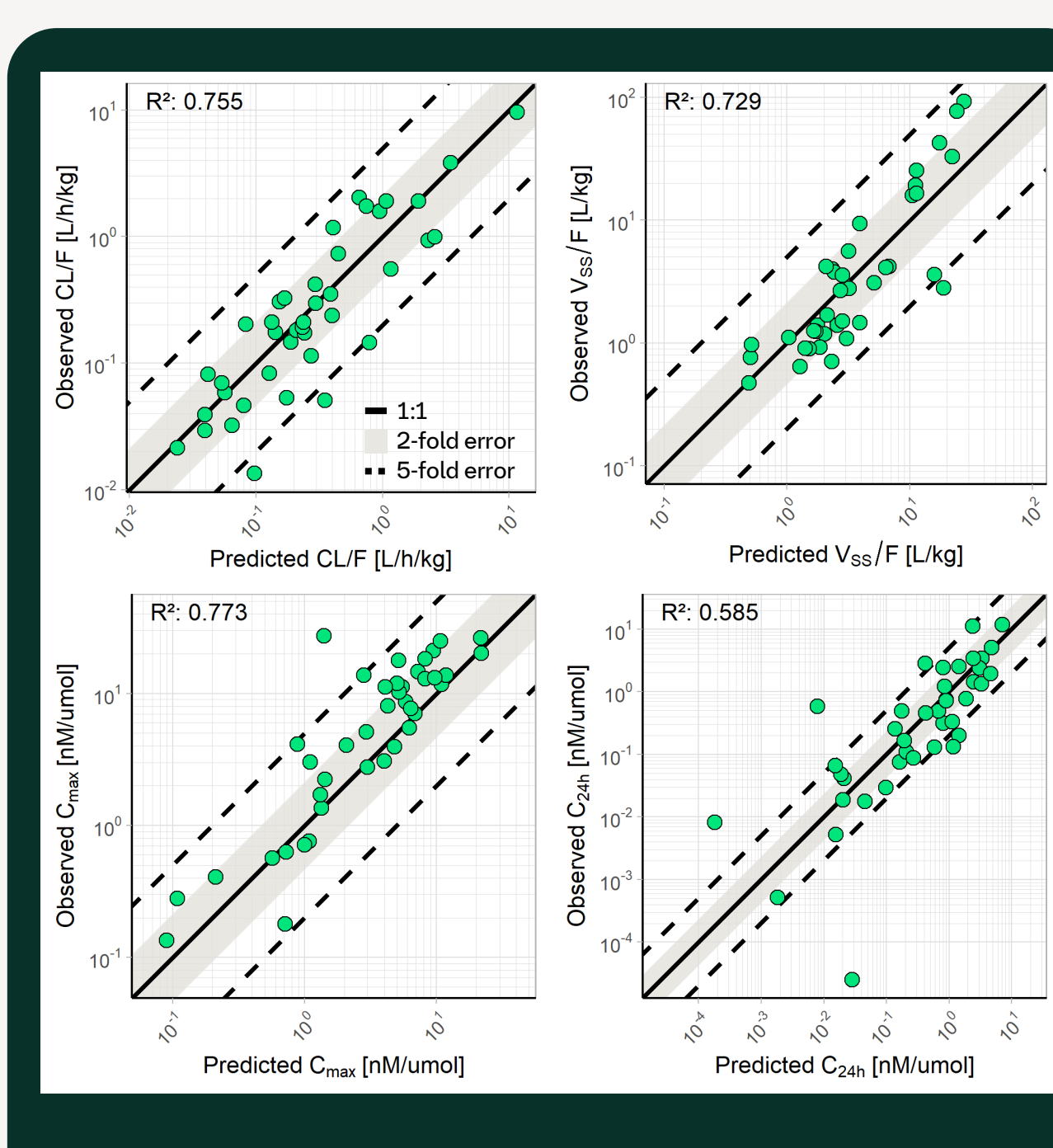
Geometric mean fold error (GMFE) was used as metric to evaluate the agreement between predicted and fitted profile. Concentrations from fitted and predicted profiles are compared over 24 h with an interval of six minutes.

$$GMFE = 10^{\frac{1}{n} \times \sum_i \log \left(\frac{conc_{predicted} i}{conc_{fitted} i} \right)}$$



Example calculation method of a PK profile GMFE using an interval of 2 hours instead of six minutes.

Results

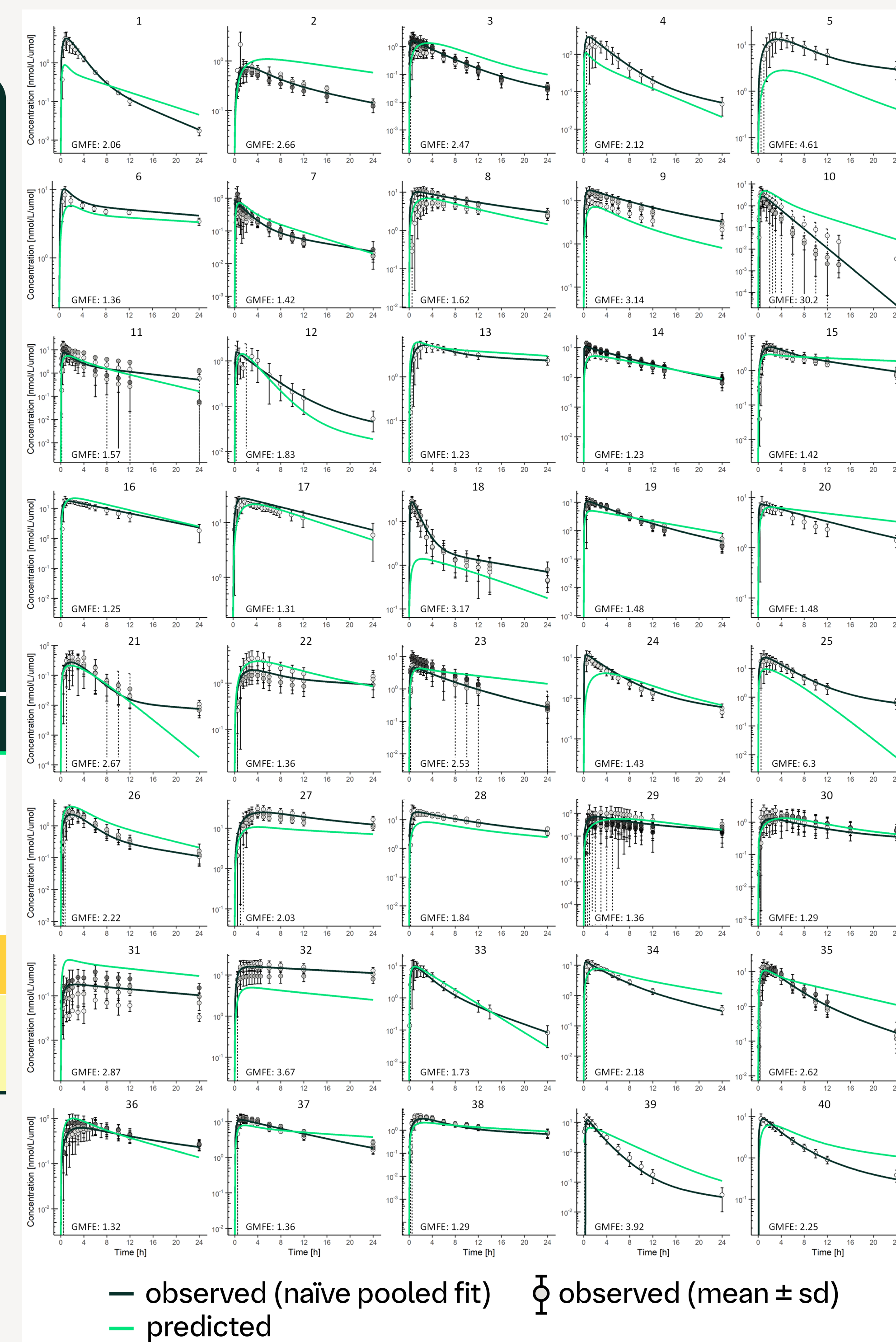


	AFE	MFE	Bias	FE < 2
CL/F	2.04	1.60	1.14	67.5%
V _{ss} /F	1.97	1.70	1.08	70.0%
C _{max}	2.33	1.59	1.03	65.0%
C _{24h}	33.4	2.45	1.19	42.5%
Profile GMFE	2.85	1.84		52.5%

AFE: Average absolute fold error across all compounds

MFE: Median absolute fold error across all compounds

Bias of 1 signifies no systematic bias



Conclusion

- The use of mechanism-based compound-specific predictions enabled accurate prediction of human PK, including the full plasma concentration–time profile, typically within a two-fold error margin.
- Prediction quality was competitive with published benchmarks and superior to published in vitro- or in silico-based approaches.
- This approach underscores the importance of comprehensive evaluation beyond single PK parameters for the accurate prediction of human pharmacokinetics.

Literature

Himstedt, et al. "Beyond CL and V_{ss} : a comprehensive approach to human pharmacokinetic predictions." *Drug Discovery Today* (2024): 104238. <https://doi.org/10.1016/j.drudis.2024.104238>

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