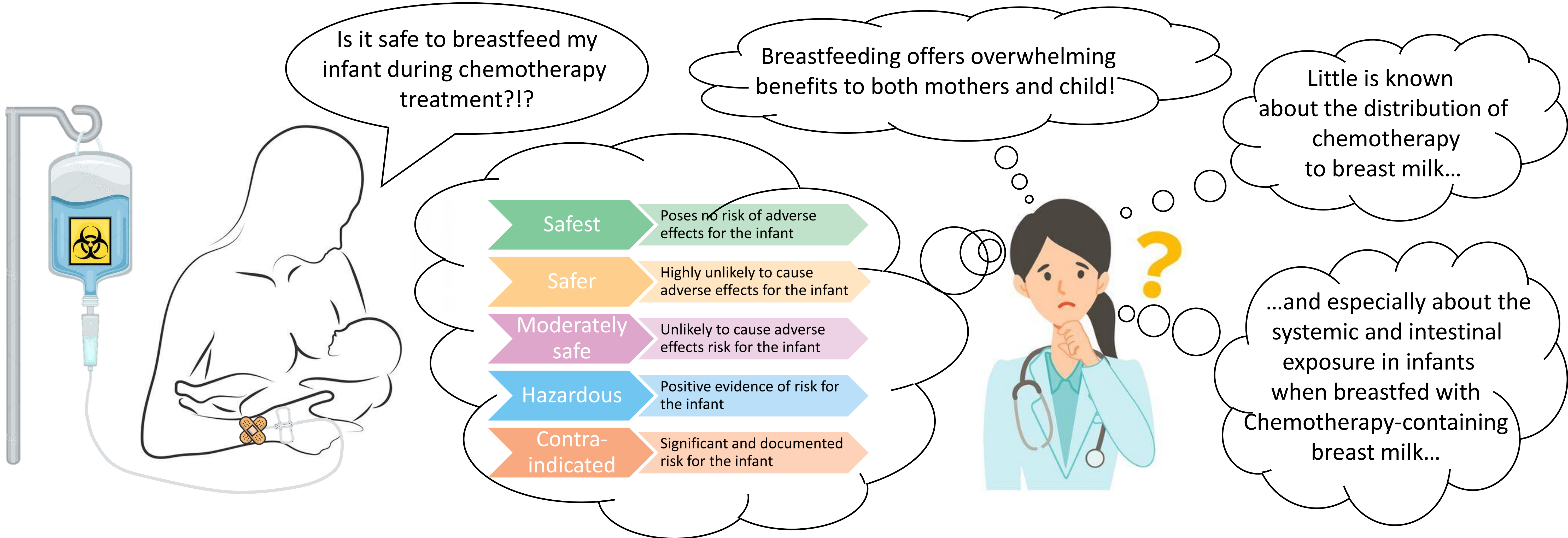


Physiologically based pharmacokinetic (PBPK) model to predict chemotherapy exposure in infants through breastfeeding: paclitaxel as an example

David Damoiseaux¹, Jos H. Beijnen^{1, 3}, Frédéric Amant^{4, 5}, Alwin D.R. Huitema^{1, 6, 7}, Thomas P.C. Dorlo¹

(1) Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands (2) Gynecologic Oncology Department, Amsterdam University Medical Center, Amsterdam, The Netherlands (3) Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands (4) Department of Gynecology, The Netherlands Cancer Institute, Amsterdam, The Netherlands (5) Gynecologic Oncology, UZ Leuven, Belgium (6) Department of Pharmacology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands (7) Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands



Objective

To aid clinicians in making a well-informed decision about possible risks of infant exposure for women that want to breastfeed their infant during chemotherapy.

Methods

- An oral absorption component was added to an available whole-body PBPK model of intravenous paclitaxel in PK-Sim® [1] and paclitaxel concentrations in breast milk after maternal administration of 80 mg/m² (156 mg absolute dose) from a previously published case series were the input for infant breast milk dose calculations [2].
- For safety considerations, we chose to use parameter values derived from a sensitivity analysis associated with the worst-case scenario for the infant, maximizing the predicted area under the concentration-time curve until infinity (AUC_{0-inf}) in plasma.
- Finally, a population of 500 European (ICRP, 2002) infants aged 0 to 1 years were used to predict paclitaxel exposure in plasma and intestinal tissue of infants following feeding of breast milk from paclitaxel-treated mothers.

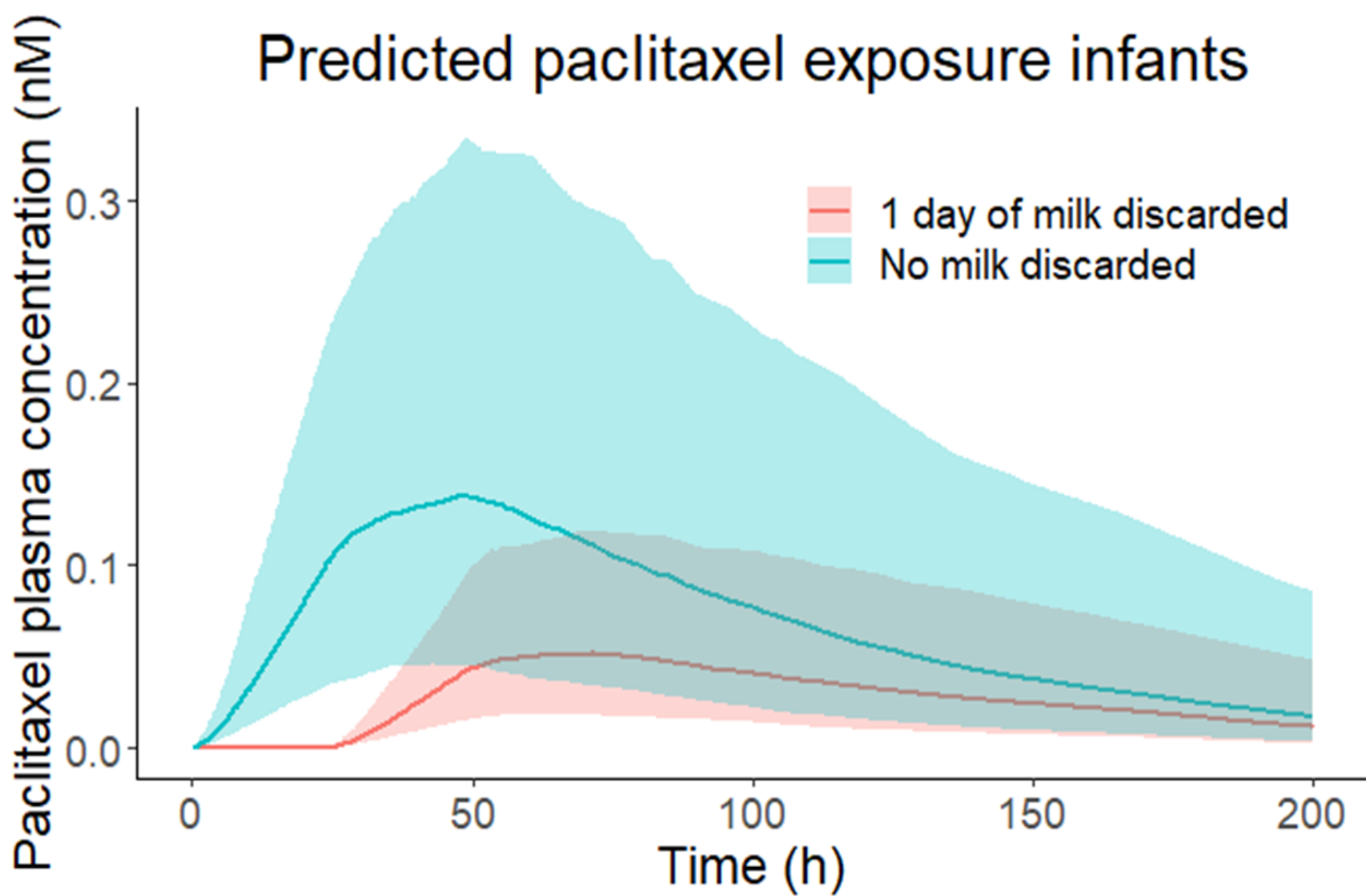


Figure 2: Median and 90% confidence interval of paclitaxel plasma exposure in infants predicted for breastfeeding during the entire cycle and with discarding the breast milk of the first day after maternal administration.

Median AUC _{inf} (nM)	Compared to AUC _{inf} on treatment	Median C _{max} (nM)	Compared to C _{max} on treatment	Compartment	Discarded milk
14.9 ± 18.3	0.15%	0.14 ± 0.09	0.03-0.12%	Systemic	No
17160 ± 6441	-	28.4 ± 13.7	-	Small intestine	No
2162 ± 1613	-	225 ± 52.8	-	Large intestine	No
6.2 ± 7.5	0.06%	0.06 ± 0.04	0.01-0.05%	Systemic	1 st day
6707 ± 2532	-	11.5 ± 11.2	-	Small intestine	1 st day
857 ± 1221	-	86.4 ± 20.2	-	Large intestine	1 st day

Table 1: The median (± standard deviation) predicted AUC_{inf} and C_{max} of paclitaxel in plasma, small and large intestines of an infant after administration of paclitaxel containing breast milk and their percentages of the AUC_{inf} and C_{max} observed in paclitaxel treatment. Both AUC_{inf} and C_{max} with and without discarding the first day of breast milk after maternal administration of paclitaxel

Results

- Parameter values resulting in the highest AUC_{0-inf} of plasma paclitaxel: +10% for lipophilicity, +200% for the specific intestinal permeability, 12 breastfeeding's per day, administration with fatty food and the Rodgers & Rowland calculation method for the partition coefficients (figure 1).
- In table 1 and figure 2 predicted paclitaxel exposures in infants are presented.
- In vitro* studies report paclitaxel IC₅₀s of 2.5 nM after 24-hour paclitaxel exposure for different cell lines [3]. Systemic C_{max}, simulated with the worst-case scenario parameters, did not exceed the reported IC₅₀s. In contrast, intestinal C_{max} did exceed the reported IC₅₀s.

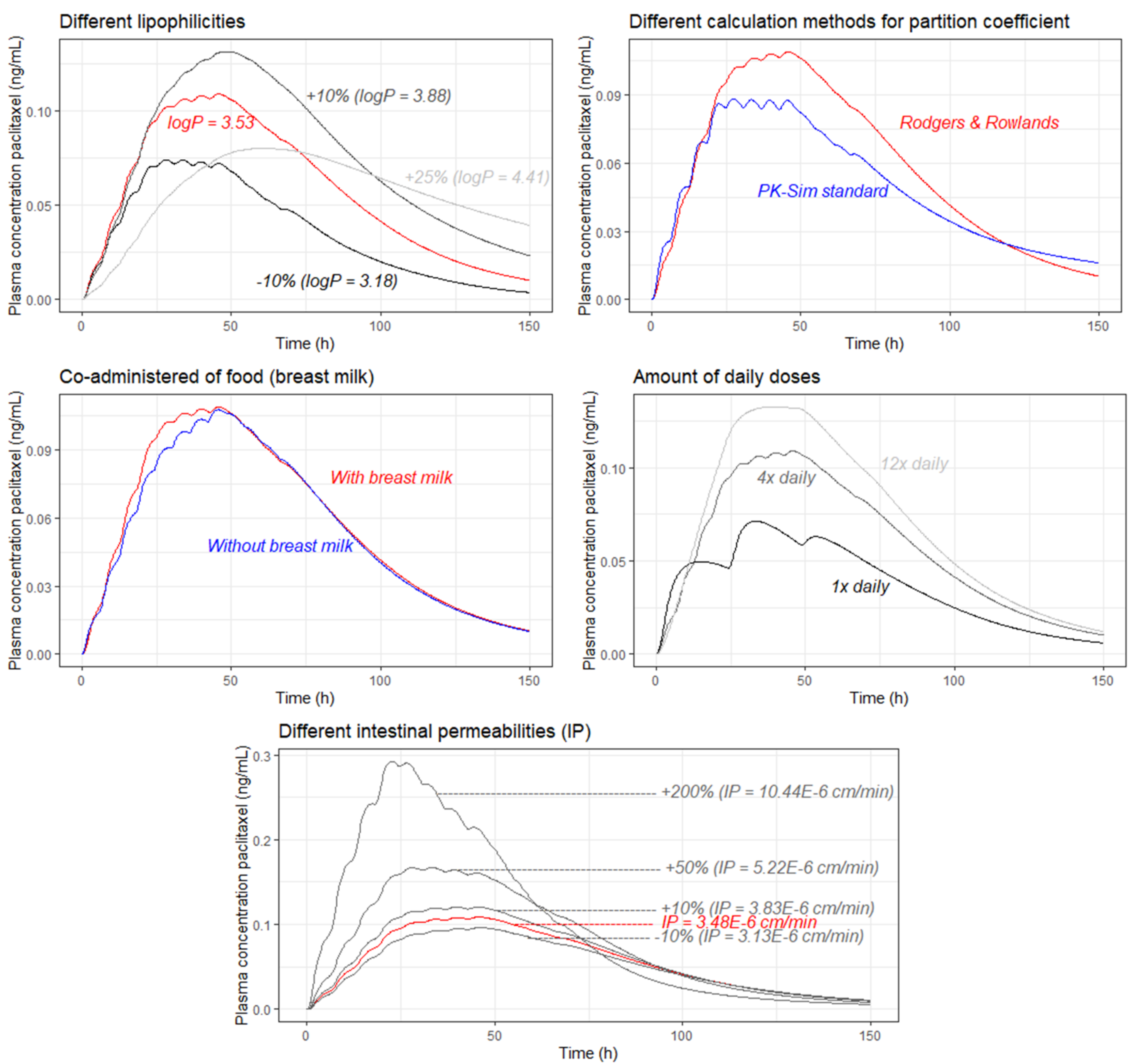


Figure 1: The sensitivity analysis results for each evaluated parameter. Tested parameter values were 3.53 (optimized value from IV model), -10%, +10% and +25% for lipophilicity; 3.48 × 10⁻⁶ cm/min (theoretical value calculated by PK-Sim®), -10%, +10%, +50% and +200% for the specific intestinal permeability; 1, 4 and 12 times daily for the number of daily doses; administration with and without fatty food; and standard PK-Sim and Rodgers & Rowland calculation methods for partition coefficients.

Conclusion

- Systemic exposure in infants after oral administration of breast milk containing chemotherapy is negligible with a predicted systemic median C_{max} 18-fold lower than the *in vitro* IC₅₀ associated with cytotoxic effects, in contrast to intestinal C_{max} that exceeded the reported IC₅₀s possibly resulting in local adverse events.
- Exposure can be reduced by another 60% when the first day of breast milk after maternal administration is discarded.
- Furthermore, no mutagenic effect has been identified for paclitaxel suggesting there is no risk for mutations that permanently alter the infants DNA [4]



Contact information:
Name: David Damoiseaux
E-mail: d.damoiseaux@nki.nl

Acknowledgments:

Presentation of this poster and participation in the 30th PAGE meeting was made possible thanks to a PAGE scholarship. Financial support was based on predefined criteria and the merit of each application was assessed by a selection committee

References:

- Open Systems Pharmacology GitHub repository. <https://github.com/Open-Systems-Pharmacology/Paclitaxel-Model/tree/94dc8185a543d2f7740239a92c32436e520d073b>.
- Damoiseaux D, Calpe S, Rosing H, Beijnen JH, Huitema ADR, Lok C, Dorlo TPC, Amant F. Presence of 5 chemotherapeutic drugs in breast milk as a guide for the safe use of chemotherapy during breastfeeding: results from a case series. Clin Pharmacol Ther. 2022 Apr 29. doi: 10.1002/cpt.2626. Epub ahead of print. PMID: 35486426.
- Liebmann, J.E., et al., Cytotoxic studies of paclitaxel (Taxol) in human tumour cell lines. Br J Cancer, 1993. 68(6): p. 1104-9.
- Szikriszt, B., et al., A comprehensive survey of the mutagenic impact of common cancer cytotoxics. Genome Biol, 2016. 17: p. 99.