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How to scale clearance from adults to children for drugs undergoing hepatic metabolism? Insights from advanced PBPK modelling and simulation

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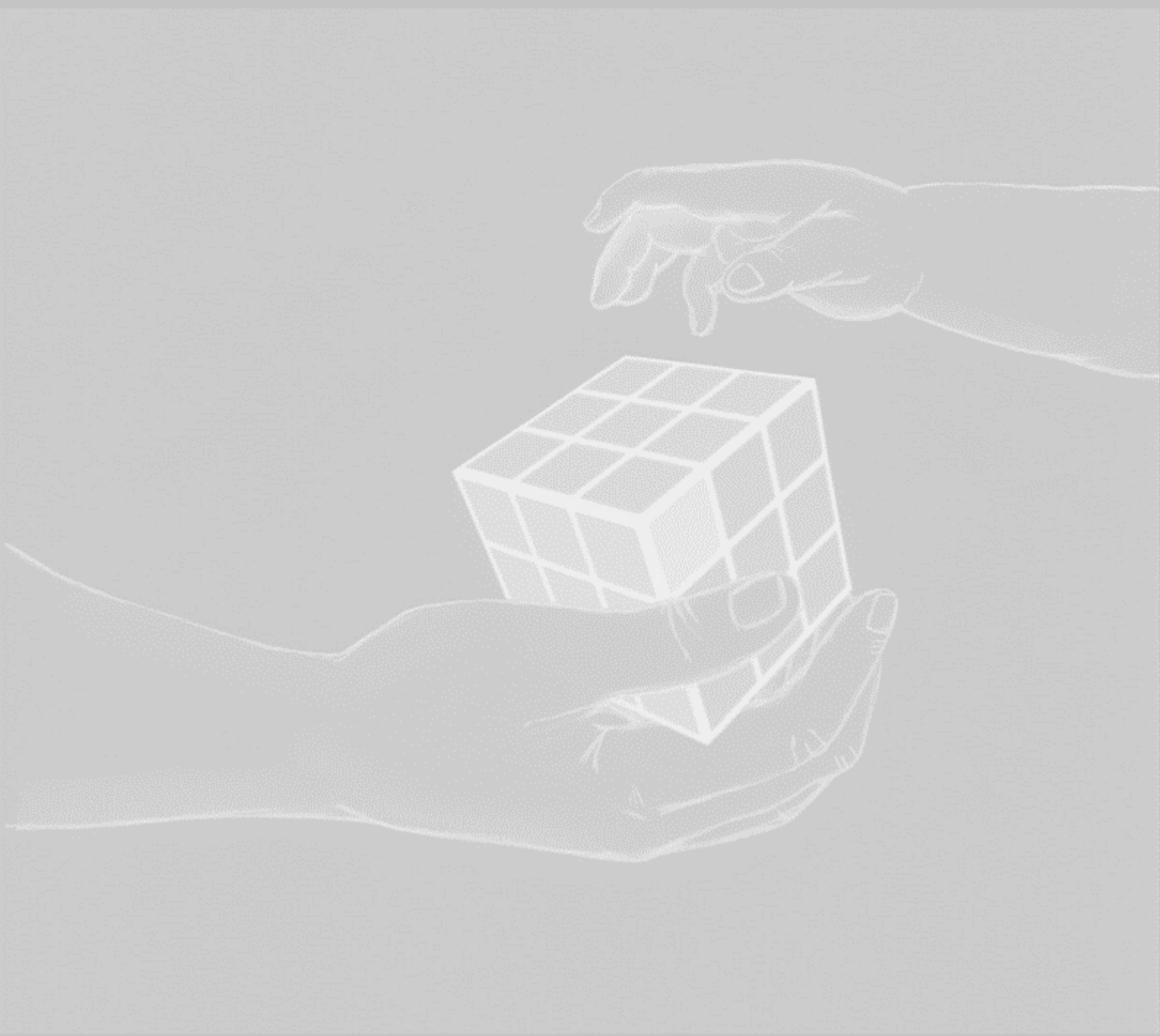
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Appendix

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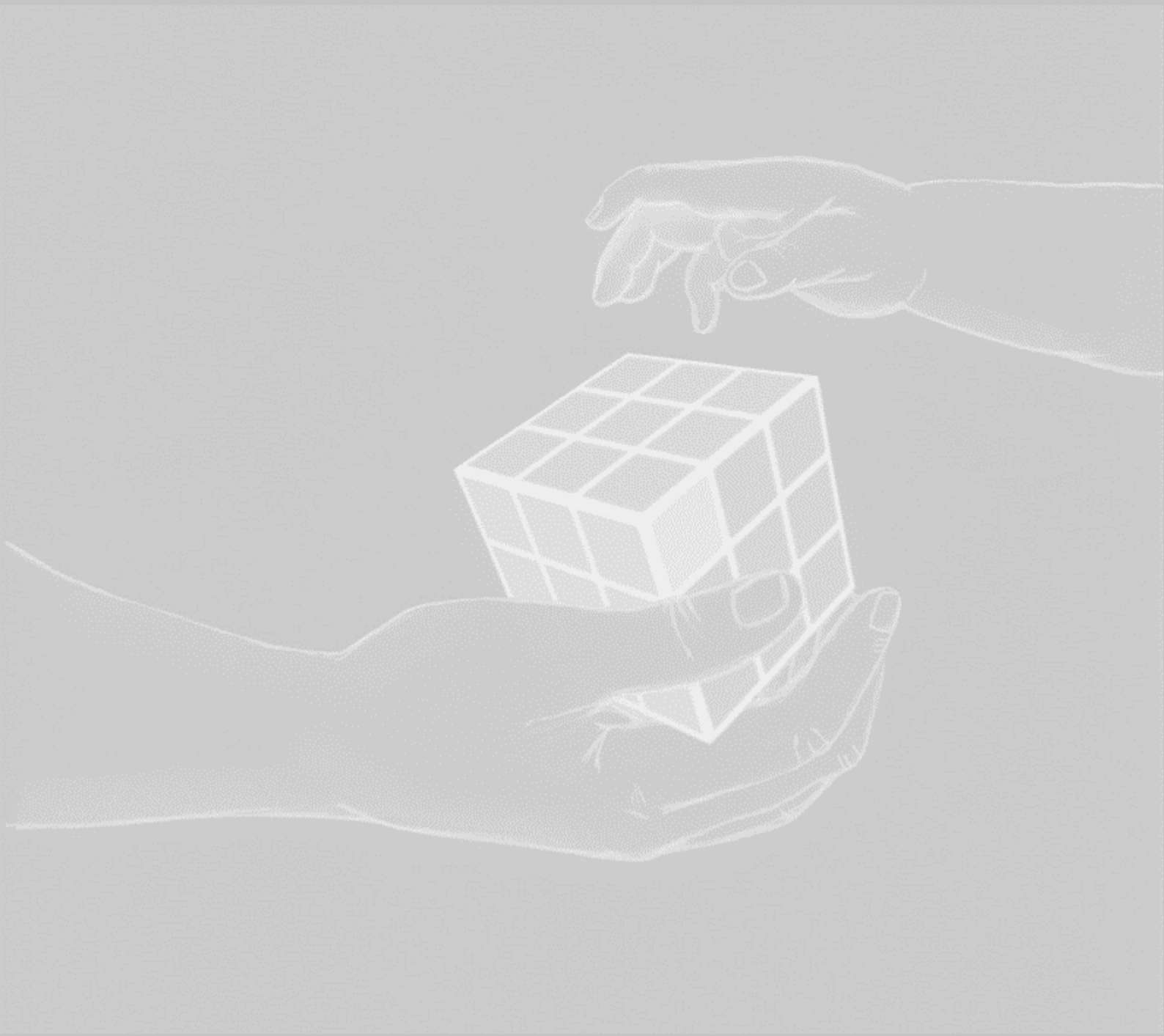
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Appendix

Curriculum Vitae

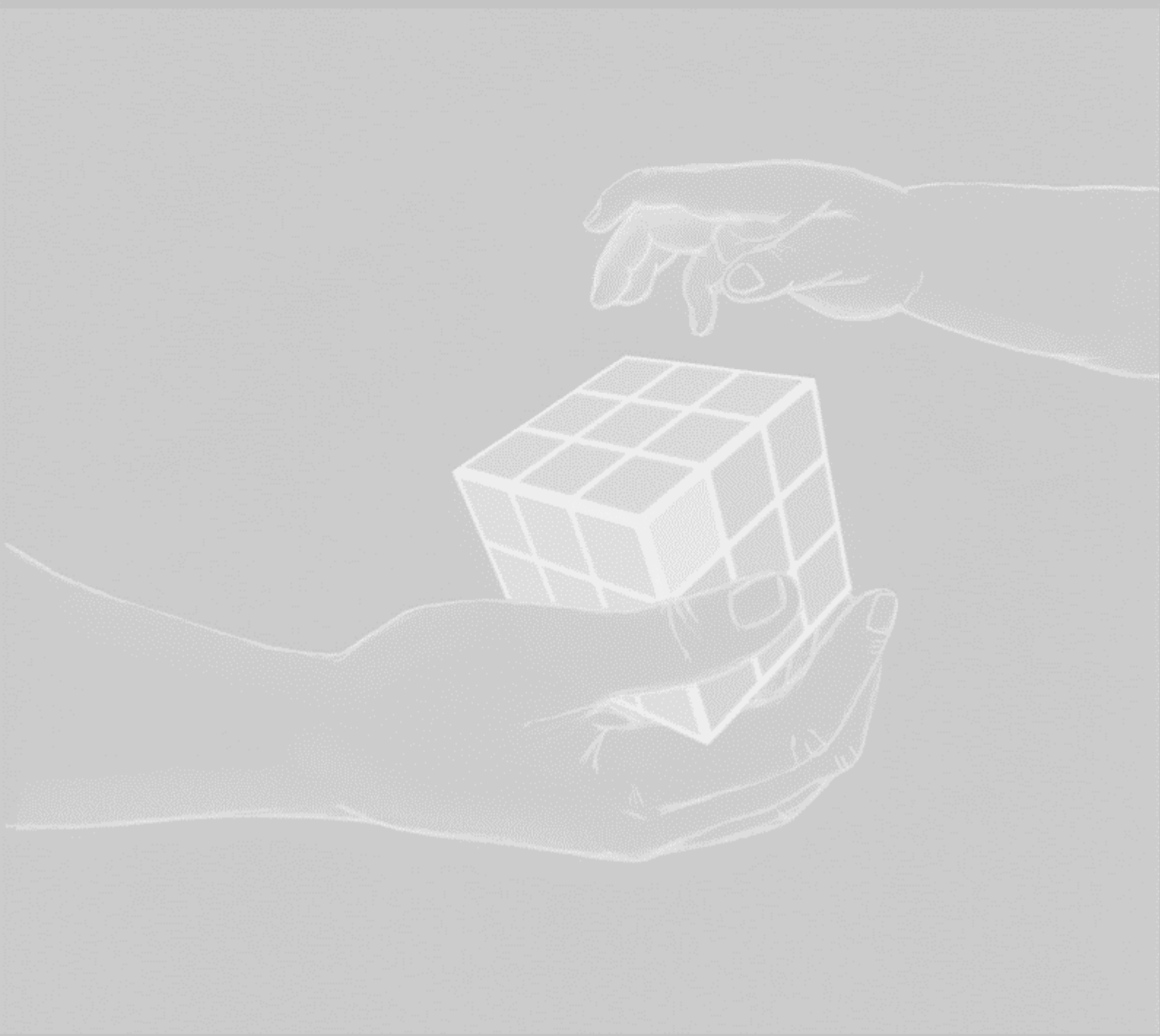


Curriculum Vitae Elisa Calvier

Elisa Calvier was born on the 23rd of September 1987, in Montélimar, France. She completed her A levels in 2005 at Alain Borne secondary school in Montélimar, before studying pharmaceutical sciences and graduating with a PharmD in 2014 at the University of Montpellier I, France. She specialized in pharmacometrics through an MSc in pharmacokinetics at the faculty of pharmacy of Paris Descartes University in 2013 as well as internships in the pharmacokinetic department of the faculty of pharmacy of Montpellier, in the Modelling and Simulation group of Sanofi Montpellier, and in the pharmacometrics group of Uppsala University. In 2013, she started her PhD research at Leiden Academic Centre for Drug Research at Leiden University under the supervision of Professor Catherijne Knibbe, Professor Dick Tibboel and Doctor Elke Krekels. Her research aimed at expediting and ensuring the systematic accuracy of clearance scaling from adults to paediatric patients, with a special focus on drugs undergoing hepatic metabolism, which resulted in this thesis. This research was funded by the Vidi Grant of Catherijne Knibbe, a grant from the NWO, the Netherlands Organisation for Scientific Research. In 2018 she started to work as a pharmacometrician in the Modelling and Simulation group of Sanofi Montpellier.

Appendix

List of publications



List of publications

Publications related to this thesis

Calvier, E. A. M., Krekels, E. H. J., Johnson, T. N., Rostami-Hodjegan, A., Tibboel, D. *et al.* Scaling drug clearance from adults to the young children for drugs undergoing hepatic metabolism: Striving for a simple solution. *The AAPS journal*, 2018. [Manuscript under revision]

Krekels, E. H. J.*, **Calvier, E. A. M.***, Van der Graaf, P. H. & Knibbe, C. A. J. Children are not small adults, but can we treat them as such? *CPT Pharmacometrics Syst. Pharmacol.* (2018). [Accepted for publication]

Calvier, E. A. M., Nguyen, T. T., Johnson, T. N., Rostami-Hodjegan, A., Tibboel, D. *et al.* Can population modelling principles be used to identify key PBPK parameters for paediatric clearance predictions? An innovative application of optimal design theory. *Pharm. Res.* **35**, 209 (2018).

Calvier, E. A. M., Krekels, E. H. J., Yu, H., Väitalo, P. A. J., Johnson, T. N. *et al.* Drugs being eliminated via the same pathway will not always require similar pediatric dose adjustments. *CPT Pharmacometrics Syst. Pharmacol.* **7**, 175–185 (2018).

Calvier, E. A. M., Krekels, E. H. J., Väitalo, P. A. J., Rostami-Hodjegan, A., Tibboel, D. *et al.* Allometric scaling of clearance in paediatric patients: When does the magic of 0.75 fade? *Clin. Pharmacokinet.* **56**, 273–285 (2017).

Publications unrelated to this thesis

Goulooze, S. C., Völler, S., Väitalo, P. A. J., **Calvier, E. A. M.**, Aarons, L. *et al.* The influence of normalization weight in population pharmacokinetic covariate models. *Clin. Pharmacokinet.* 1–8 (2018). doi:10.1007/s40262-018-0652-7

Mian, P., Knibbe, C. A. J., **Calvier, E. A. M.**, Tibboel, D. & Allegaert, K. Intravenous paracetamol dosing guidelines for pain management in (pre)term neonates using the paediatric study decision tree. *Curr. Pharm. Des.* **23**, 5839–5849 (2017).

Valkenburg, A. J., **Calvier, E. A. M.**, van Dijk, M., Krekels, E. H. J., O'Hare, B. P. *et al.* Pharmacodynamics and pharmacokinetics of morphine after cardiac surgery in children with and without Down syndrome. *Pediatr. Crit. Care Med.* **17**, 930–938 (2016).

Brussee, J. M., **Calvier, E. A. M.**, Krekels, E. H. J., Väitalo, P. A. J., Tibboel, D. *et al.* Children in clinical trials: towards evidence-based pediatric pharmacotherapy using pharmacokinetic-pharmacodynamic modeling. *Expert Rev. Clin. Pharmacol.* **9**, 1235–44 (2016).

Van Donge, T. & **Calvier, E. A. M.** Physiologically-based pharmacokinetic predictions of lorazepam paediatric clearance. *Student Undergrad. Res. E-journal* **1**, (2015).

*Both authors contributed equally