



**HAL**  
open science

## Reducing aztreonam/avibactam waste: insights from Monte Carlo simulations

Yeleen Fromage, Hamza Sayadi, Marc Labriffe, Caroline Monchaud, Cyrielle Codde, Jean-Baptiste Woillard

### ► To cite this version:

Yeleen Fromage, Hamza Sayadi, Marc Labriffe, Caroline Monchaud, Cyrielle Codde, et al.. Reducing aztreonam/avibactam waste: insights from Monte Carlo simulations. *Journal of Antimicrobial Chemotherapy*, 2025, <10.1093/jac/dkaf421>. <hal-05414767>

**HAL Id: hal-05414767**

**<https://unilim.hal.science/hal-05414767v1>**

Submitted on 13 Dec 2025

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

1 Reducing aztreonam/avibactam waste: insights from Monte Carlo simulations

2 Yeleen FROMAGE<sup>1</sup>, Hamza SAYADI<sup>2</sup>, Marc LABRIFFE<sup>2,3</sup>, Caroline MONCHAUD<sup>2,3</sup>, Cyrielle

3 CODDE<sup>3,4</sup>, Jean-Baptiste WOILLARD<sup>1,2,3\*</sup>

4 1: Inserm CIC 1435, CHU Dupuytren, Limoges, France

5 2: Department of Pharmacology, Toxicology and Pharmacovigilance, CHU Dupuytren,  
6 Limoges, France.

7 3: Inserm UMR1248, Pharmacology & Transplantation, Univ. Limoges, Limoges, France.

8 4: Infectious and Tropical Diseases Unit, CHU Dupuytren, Limoges, France

9 \* Corresponding author:

10 Jean-Baptiste Woillard

11 Title: PharmD, PhD

12 ORCID: 0000-0003-1695-0695

13 Mail: jean-baptiste.woillard@unilim.fr

14 Address:

15 Univ. Limoges, Inserm U1248 P&T,

16 2 rue du Pr Descottes,

17 F-87000 Limoges, France.

18 Phone: +33 5 55 05 61 40

19 Fax: +33 5 55 05 61 62

20 Running title: Aztreonam/avibactam loading dose optimization

21



23 Synopsis

24 Background: The fixed-dose combination of aztreonam/avibactam is administered with a  
25 loading dose (LD), resulting in systematic drug wastage in patients with preserved renal  
26 function. Whether the LD can be reduced remains unclear.

27 Objectives: To evaluate in silico the pharmacokinetic (PK) and pharmacodynamic (PD)  
28 consequences of reducing the current LD in patients with normal renal function, using a  
29 population PK model and Monte Carlo simulations.

30 Methods: A published two-compartment population PK model was implemented. We  
31 performed 10,000 Monte Carlo simulations of virtual patients with normal renal function  
32 ( $\text{CrCL} > 80 \text{ mL/min}$ ), receiving the standard LD (2g/0.67g over 3 h) or a reduced LD (1.5g/0.5g  
33 over 3 h), followed by standard maintenance doses every 6h. PK metrics ( $C_0$ , AUC) and PTA  
34 were compared between the 2 regimens.

35 Results: Reducing the LD decreased early exposure ( $\text{AUC}_{0-24\text{h}}$ ) from  $1281 \pm 497$  to  $1200 \pm 464$   
36  $\text{mg}\cdot\text{h/L}$  for aztreonam and from  $276 \pm 118$  to  $258 \pm 110 \text{ mg}\cdot\text{h/L}$  for avibactam, but steady-  
37 state  $\text{AUC}_{24-48\text{h}}$  was identical between regimens. PTA differences for intermediate PD  
38 thresholds were modest and transient.

39 Conclusions: Lowering the LD in patients with preserved renal function had only a short-lived  
40 impact on early exposure and did not compromise PK/PD performance. These results  
41 support dose adaptation to reduce unnecessary drug waste.

42 Introduction

43 Infections caused by multidrug-resistant Gram-negative bacteria are a major public health  
44 threat, particularly those due to carbapenem-resistant Enterobacterales (CRE). Among them,  
45 strains producing metallo- $\beta$ -lactamases (MBLs) such as New Delhi MBLs are of greatest  
46 concern, owing to high mortality rates and a lack of effective therapeutic options.<sup>1,2</sup>  
47 Conventional agents like colistin, tigecycline, or aminoglycosides have limited efficacy and  
48 significant toxicity, and their use is associated with increased mortality in this setting.<sup>3</sup>

49 Aztreonam is a monobactam that remains stable against MBLs but is hydrolyzed by other  $\beta$ -  
50 lactamases such as extended-spectrum  $\beta$ -lactamases, AmpC, and OXA-48-like enzymes.  
51 Avibactam, a  $\beta$ -lactamase inhibitor, restores aztreonam activity against MBL-producing  
52 bacteria by protecting it from co-produced non-MBL  $\beta$ -lactamases. This combination is now  
53 recommended as the treatment of choice for MBL-producing CRE infections by major  
54 infectious diseases societies.<sup>4</sup>

55 A fixed-dose aztreonam-avibactam combination was approved by the European Medicines  
56 Agency in April 2024, but only 1.5/0.5 g vials are available. However, the normorenal  
57 regimen includes a 2/0.67g loading dose over 3 h, then 1.5/0.5g every 6h, leading to  
58 unavoidable wastage.

59 In this context, we aimed to assess whether a reduced loading dose (1.5/0.5g) would be  
60 sufficient to achieve PK/PD targets. Using established population pharmacokinetic models  
61 and Monte Carlo simulations, we explored the impact of standard versus reduced loading  
62 doses in patients with creatinine clearance (CrCL) > 80 mL/min.

63 Materials and methods

64 Pharmacokinetic model

65 A recently published population pharmacokinetic (PopPK) model by Xie et al<sup>5</sup> was  
66 implemented for both drugs. This simultaneous model was developed from a large pooled  
67 dataset including 431 participants for aztreonam and 2,635 participants for avibactam,  
68 encompassing healthy volunteers, renally impaired subjects, and patients enrolled in Phase  
69 II–III clinical trials ensuring a broad and representative patient population. Both drugs were  
70 described by two-compartment models with zero-order infusion and first-order elimination.  
71 Body weight (normalized to 70 kg) was included as a structural covariate on clearance (CL),  
72 central (Vc) and peripheral (Vp) volumes, and intercompartmental clearance (Q), using  
73 classical allometric exponents (0.75 for CL and Q, 1 for Vc and Vp). Time-varying creatinine  
74 clearance (CrCL) influenced CL via a linear function for CrCL  $\geq 80$  mL/min/1.73 m<sup>2</sup> and a  
75 power function for CrCL  $< 80$  mL/min/1.73 m<sup>2</sup>. Additional covariates included ESRD and  
76 dialysis effects on avibactam CL, APACHE II score on avibactam CL, infection-type effects  
77 (cUTI, cIAI, HAP/VAP) on clearance and volumes, and Chinese race on avibactam Vc. Inter-  
78 individual variability (IIV) was included on aztreonam and avibactam CL and Vc, as well as on  
79 avibactam Vp and Q, using exponential random effects. Correlations between aztreonam  
80 and avibactam were modeled via covariance terms on IIVs for CL and Vc, with an OMEGA  
81 block for their variances, and an additional covariance term between avibactam Q and Vp.

82 Model parameters were implemented as published, with residual error terms minimized  
83 (additive and proportional errors set to 0.0001) to focus on IIV and covariate effects, as  
84 previously done.<sup>6</sup>

## 85 Simulations

86 PopPK models were implemented in the *mrgsolve* package in R.<sup>7</sup> Monte Carlo simulations (n  
87 = 10,000) were performed under two dosing scenarios: (i) standard loading dose (2/0.67 g)  
88 followed by 1.5/0.5g every 6h; and (ii) reduced loading dose (1.5/0.5 g) followed by the same  
89 maintenance schedule. We additionally examined the extended loading dose regimen  
90 (500/167mg over 30 min followed by 1,500/500mg over 3h and then the standard  
91 maintenance dose) proposed by Xie *et al*<sup>5</sup> (see Supplemental Material). Simulations focused  
92 on patients with CrCL > 80 mL/min, where the loading dose may cause wastage due to vial  
93 size. Note that the simulated infusion durations were 3 hours in both scenarios. To avoid  
94 extrapolation beyond the validated range of the pharmacokinetic models, simulations were  
95 performed using a truncated normal distribution, restricted to the renal function (CrCL 80–  
96 739 mL/min) and weight (28–190 kg) ranges of the original patient cohorts used to develop  
97 the model. Plasma concentrations were simulated from the first dose to the end of Day 2.  
98 Given the short half-life of aztreonam and avibactam (2–3 h), this time frame was considered  
99 sufficient to observe steady-state attainment and impact on trough concentrations (C<sub>0</sub>).

## 100 PK/PD targets

101 The bactericidal activity of aztreonam is time-dependent. While a target of 60% of the dosing  
102 interval with free drug concentrations above the MIC (fT>MIC) is often considered sufficient,  
103 we adopted a more conservative target of 100% fT>MIC based on evidence suggesting that  
104 more aggressive targets are associated with better clinical outcomes in critically ill and septic  
105 patients.<sup>8</sup> This higher target also provides a safety margin to account for variability in MIC  
106 determination and tissue penetration. We aimed for free drug concentrations 4 to 8 times  
107 the MIC. Considering the 56% protein binding of aztreonam in normorenal patients,<sup>9</sup> this  
108 corresponds to total concentrations of 8 to 16 × MIC. Using the EUCAST susceptibility

109 breakpoint of  $\leq 8$  mg/L,<sup>10,11</sup> the resulting PK/PD target range for total drug concentrations is 2  
110 to 128 mg/L. For comparison, an analysis using the conventional target of 60% fT > MIC was  
111 also performed and is provided in the Supplemental Material.

112 For avibactam, free concentrations  $\geq 2.5$  mg/L for  $\geq 50\%$  of the dosing interval were used as  
113 efficacy thresholds.<sup>12</sup>

114 PTA were calculated across the MIC range following the first three maintenance doses to  
115 evaluate the impact of reducing the LD.

## 116 Results / Discussion

117 Given the scarcity of clinical TDM data, model performance was evaluated based on the  
118 limited published pharmacokinetic metrics available.<sup>5,11,13-15</sup> For aztreonam, prior data in  
119 normorenal subjects reported median  $C_0$  of 18.4 mg/L (range: 7.9–24.6),  $C_{max}$  of 17.6 - 78  
120 mg/L, and  $AUC_{0-24h}$  of 833–1372 mg·h/L. Our simulations yielded median  $C_0$  (Q1-Q3) of 9.4  
121 (4.4–17.4) mg/L, median  $C_{max}$  (Q1-Q3) of 22.2 (13.4–33.8) mg/L, and mean  $AUC_{0-24h} \pm sd$  of  
122  $1091 \pm 450$  mg·h/L consistent with literature. For avibactam, reported values of  $C_{max}$  range  
123 from 7.05 to 12.1 mg/L and  $AUC_{0-24h}$  from 161 to 175.5 mg·h/L. In our simulations,  $C_{max}$   
124 (median [Q1–Q3]) was lower (4.3 [2.4–7.0] mg/L) but  $AUC_{0-24h}$  was comparable ( $234 \pm 105$   
125 mg·h/L), supporting adequate model plausibility.

126 As shown in Table 1, reducing the loading dose led to lower early plasma concentrations,  
127 especially at 2.9 h (first  $C_0$ ): aztreonam median (Q1-Q3)  $C_0$  decreased from 29.9 (19.4–41.7)  
128 mg/L to 22.4 (14.6–31.3) mg/L; median avibactam (Q1-Q3)  $C_0$  from 5.2 (3.2–8.1) mg/L to 4.1  
129 (2.4–6.1) mg/L. This difference faded from 14.9 h, with median levels converging from the  
130 second maintenance dose onward.

131 For aztreonam, PTA assessed at trough concentrations after the 1<sup>st</sup> and 2<sup>nd</sup> maintenance  
132 doses showed similar target attainment across regimens (Figure 1A-1C). For low thresholds  
133 (e.g., 2 mg/L), both regimens achieved >90% PTA at all time points. For intermediate  
134 thresholds (10–25 mg/L), a slight early advantage was observed with the loading dose (e.g.,  
135 56.1% versus 53.9% at 10 mg/L at 1<sup>st</sup> maintenance dose C0). At higher thresholds (>40 mg/L),  
136 PTA decreased consistently regardless of loading dose or sampling time. Reducing the  
137 loading dose from 2 g to 1.5 g transiently delayed target attainment at C0 after the 1<sup>st</sup>  
138 maintenance dose across concentrations ranging from 10 to 50 mg/L. This difference was no  
139 longer observed at C0 after the 2<sup>nd</sup> maintenance dose, as shown in Figure 1C. Full PTA results  
140 for aztreonam, considering both 100% and 60% of the dosing interval, are provided in Tables  
141 S2 and S3, respectively and for avibactam in Table S4. For avibactam (Figure 1B-1D), both  
142 regimens achieved 90% PTA for the pharmacodynamic target of maintaining concentrations  
143  $\geq 2.5$  mg/L for  $\geq 50\%$  of the dosing interval, confirming the absence of impact from loading  
144 dose reduction. These results are consistent with the time-dependent PK/PD profile of these  
145 antibiotics, where transient reductions in C<sub>max</sub> from a lower loading dose are not expected  
146 to impact overall clinical efficacy, given that steady-state concentrations and target  
147 attainment are rapidly restored after the first maintenance dose. We also simulated the  
148 alternative extended loading dose strategy proposed by Xie et al. <sup>5</sup>, which yielded similar  
149 conclusions (see Supplemental Material, Table S1).

150 This study has several limitations. First, the currently available PopPK model for  
151 aztreonam/avibactam is based on a limited dataset and not fully built from infected patient  
152 populations; its reliability could be further strengthened by future independent model  
153 development. Second, our analysis focused solely on plasma concentrations and PK/PD  
154 indices, without accounting for tissue distribution or clinical outcomes. Third, the protein

155 binding of aztreonam is known to be variable, with reported free fractions ranging from 42%  
156 to 62% depending on the study population and methodology. This variability represents a  
157 source of uncertainty in our results, as it influences the translation of total plasma  
158 concentrations to the pharmacologically active free concentrations. Finally, and obviously,  
159 clinical validation is needed before applying reduced loading doses in practice.

160 Our simulations indicate that reducing the aztreonam/avibactam loading dose slightly lowers  
161 early exposure but does not affect steady-state PK or PTA. Differences in target attainment  
162 were minor and resolved within 24 h. These findings support the potential for dose  
163 reduction to limit waste without compromising pharmacological performance. In a context  
164 of increasing medical and economic constraints, this modest but consistent cost reduction—  
165 approximately €270 per patient—may justify re-evaluating loading dose strategies to limit  
166 waste without compromising efficacy. Moreover, using fractions of the full dose may  
167 increase the risk of medication errors during preparation and contribute to ecological impact  
168 from discarded solutions. Future studies could evaluate other dosing strategies, such as a  
169 1.35/0.45g loading dose in severe renal impairment or a 0.75/0.25g maintenance dose in  
170 moderate renal impairment.

171

172 Acknowledgements

173 None.

174 Funding

175 This study was carried out as part of our routine work.

176 Transparency declarations

177 None to declare.

178

179 References

- 180 1. Bhatnagar A, Boyd S, Sabour S, *et al.* Aztreonam-Avibactam Susceptibility Testing Program  
181 for Metallo-Beta-Lactamase-Producing Enterobacterales in the Antibiotic Resistance  
182 Laboratory Network, March 2019 to December 2020. *Antimicrobial Agents and*  
183 *Chemotherapy* 2021; **65**: 10.1128/aac.00486-21.
- 184 2. Mojica MF, Rossi M-A, Vila AJ, Bonomo RA. The urgent need for metallo- $\beta$ -lactamase  
185 inhibitors: an unattended global threat. *The Lancet Infectious Diseases* 2022; **22**: e28–34.
- 186 3. Isler B, Aslan AT, Akova M, Harris P, Paterson DL. Treatment strategies for OXA-48-like and  
187 NDM producing *Klebsiella pneumoniae* infections. *Expert Rev Anti Infect Ther* 2022; **20**:  
188 1389–400.
- 189 4. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases  
190 Society of America Guidance on the Treatment of Extended-Spectrum  $\beta$ -lactamase  
191 Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and  
192 *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. *aeruginosa*). *Clinical*  
193 *Infectious Diseases* 2021; **72**: e169–83.
- 194 5. Xie R, Rogers H, Chow JW, Soto E, Raber SR. Population  
195 pharmacokinetic/pharmacodynamic modeling to optimize aztreonam-avibactam dose  
196 regimens for adult patients. *Antimicrob Agents Chemother* 2025; **69**: e0195024.
- 197 6. Labriffe M, Woillard J-B, Debord J, Marquet P. Machine learning algorithms to estimate  
198 everolimus exposure trained on simulated and patient pharmacokinetic profiles. *CPT*  
199 *Pharmacometrics Syst Pharmacol* 2022; **11**: 1018–28.
- 200 7. Elmokadem A, Riggs MM, Baron KT. Quantitative Systems Pharmacology and  
201 Physiologically-Based Pharmacokinetic Modeling With mrgsolve: A Hands-On Tutorial.  
202 *CPT Pharmacometrics Syst Pharmacol* 2019; **8**: 883–93.
- 203 8. Guilhaumou R, Benaboud S, Bennis Y, *et al.* Optimization of the treatment with beta-  
204 lactam antibiotics in critically ill patients-guidelines from the French Society of  
205 Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique-  
206 SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société  
207 Française d’Anesthésie et Réanimation-SFAR). *Crit Care* 2019; **23**: 104.
- 208 9. Swabb EA. Review of the clinical pharmacology of the monobactam antibiotic aztreonam.  
209 *The American Journal of Medicine* 1985; **78**: 11–8.
- 210 10. Harris H, Tao L, Jacobs EB, *et al.* Multicenter Evaluation of an MIC-Based Aztreonam and  
211 Ceftazidime-Avibactam Broth Disk Elution Test. *J Clin Microbiol* 2023; **61**: e0164722.
- 212 11. Cornely OA, Cisneros JM, Torre-Cisneros J, *et al.* Pharmacokinetics and safety of  
213 aztreonam/avibactam for the treatment of complicated intra-abdominal infections in  
214 hospitalized adults: results from the REJUVENATE study. *J Antimicrob Chemother* 2020;  
215 **75**: 618–27.

- 216 12. Singh R, Kim A, Tanudra MA, *et al.* Pharmacokinetics/pharmacodynamics of a  $\beta$ -lactam  
217 and  $\beta$ -lactamase inhibitor combination: a novel approach for aztreonam/avibactam. *J*  
218 *Antimicrob Chemother* 2015; **70**: 2618–26.
- 219 13. Das S, Riccobene T, Carrothers TJ, *et al.* Dose selection for aztreonam-avibactam,  
220 including adjustments for renal impairment, for Phase IIa and Phase III evaluation. *Eur J*  
221 *Clin Pharmacol* 2024; **80**: 529–43.
- 222 14. Anon. emblaveo-epar-product-information\_en.pdf. Available at:  
223 [https://www.ema.europa.eu/en/documents/product-information/emblaveo-epar-](https://www.ema.europa.eu/en/documents/product-information/emblaveo-epar-product-information_en.pdf)  
224 [product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/emblaveo-epar-product-information_en.pdf). Accessed June 23, 2025.
- 225 15. Hölsken O, Sponheuer K, Weber F, *et al.* First Clinical Application of Aztreonam-  
226 Avibactam in Treating Carbapenem-Resistant Enterobacterales: Insights from  
227 Therapeutic Drug Monitoring and Pharmacokinetic Simulations. *J Pers Med* 2024; **14**:  
228 1135.
- 229 16. Anon. v\_14.0\_Breakpoint\_Tables.pdf. Available at:  
230 [https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Breakpoint\\_tables/v\\_](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_14.0_Breakpoint_Tables.pdf)  
231 [14.0\\_Breakpoint\\_Tables.pdf](https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_14.0_Breakpoint_Tables.pdf). Accessed January 18, 2024.

232

233

234 Table

235 Table 1. Evolution of trough concentrations over the initial 48 hours.

Time (h)	Aztreonam		Avibactam		236	Actu
	Actual	Reduced	Actual	Reduced	237	al
	dose scheme	dose scheme	dose scheme	dose scheme	238	dosi
	Median (Q1-Q3) concentrations (mg/L)				239	ng
2.9	29.9 (19.4-41.7)	22.4 (14.6-31.3)	5.5 (3.2-8.1)	4.1 (2.4-6.1)	240	sche
8.9	8.6 (3.5-17.7)	8.1 (3.3-16.2)	1.9 (0.8-3.8)	1.7 (0.8-3.5)	241	me:
14.9	6.9 (2.9-14.5)	6.9 (2.9-14.3)	1.5 (0.7-3.2)	1.5 (0.7-3.1)	242	stan
20.9	6.6 (2.9-13.8)	6.6 (2.9-13.8)	1.5 (0.7-3.0)	1.5 (0.7-3.0)	243	dard
26.9	6.7 (2.9-13.9)	6.7 (2.9-13.9)	1.5 (0.7-3.1)	1.5 (0.7-3.1)	244	loadi
32.9	6.8 (3-13.9)	6.8 (3-13.9)	1.5 (0.6-3.0)	1.5 (0.6-3.0)	245	ng
38.9	6.6 (2.8-13.9)	6.6 (2.8-13.9)	1.5 (0.6-3.0)	1.4 (0.6-3.0)	246	dose
44.9	6.7 (2.9-14.1)	6.7 (2.9-14.1)	1.5 (0.6-3.0)	1.5 (0.6-3.0)	247	(2g/0
					248	.67g)

249 followed by 1.5g/0.5g every 6h.

250 Reduced dosing scheme: reduced loading dose (1.5g/0.5g) followed by 1.5g/0.5g every 6h.

251

252

253

254

255

256

257

258

259

260 Figure

261 Figure 1. Early probability of target attainment over the first 24 hours, covering the first two  
262 maintenance doses.

263 A : PTA for aztreonam at C0 following the first maintenance dose

264 B : PTA for avibactam at 50% of the dosing interval following the first maintenance dose

265 C : PTA for aztreonam at C0 following the second maintenance dose

266 D: PTA for avibactam at 50% of the dosing interval following the second maintenance dose

267 The blue shaded area represents the PK/PD target range for a typical *Klebsiella pneumoniae*  
268 isolate with an ECOFF MIC of 0.5 mg/L <sup>16</sup>, corresponding to an aztreonam target of 4 mg/L  
269 (8×MIC) to 8 mg/L (16×MIC). For avibactam, the PK/PD target was defined as a concentration  
270 >2.5 mg/L for at least 50% of the dosing interval.

271 As the PD target for avibactam corresponds to maintaining concentrations above the  
272 threshold for at least 50% of the dosing interval, the PTA timepoints selected differed from  
273 those of aztreonam, which requires sustained exposure above the target concentration for  
274 100% of the interval. For aztreonam, PTA is shown up to the 64 mg/L threshold; full results  
275 for 100% and 60% ft>MIC are provided in Tables S2 and S3.

276

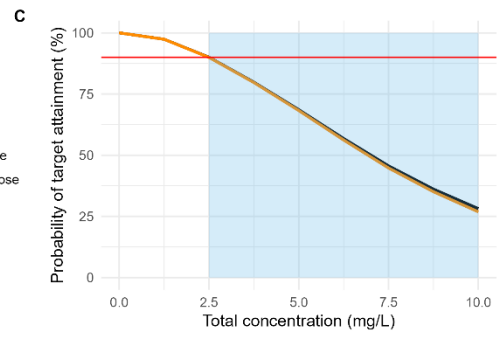
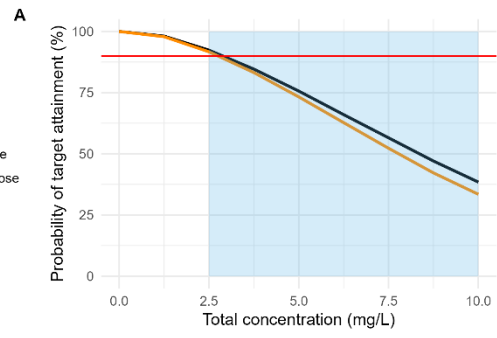
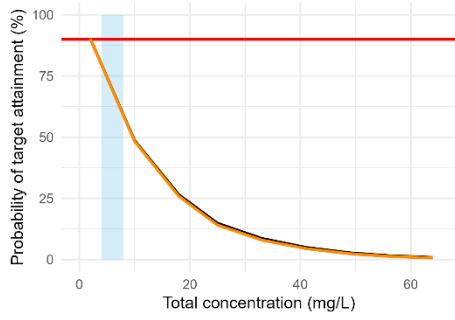
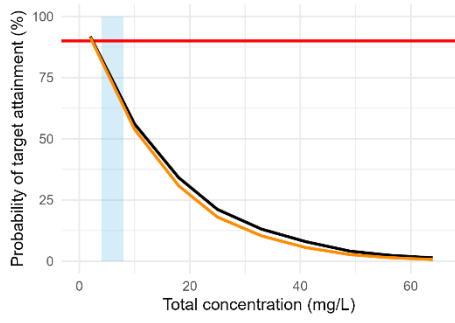
277

278

279

280

281



282

283

284

285

286

287

288

289

290

291

292

293

294

295