



A Whole-body Mechanistic Physiologically-based Pharmacokinetic Modeling of Intravenous Iron

Xiaoqing Fan¹, Kangna Cao¹, Raymond S. M. Wong², Xiaoyu Yan^{1*}

¹School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR. ²Division of Hematology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, China SAR

INTRODUCTION

Iron is essential for every cell of the mammalian organism. Iron deficiency, with or without anemia, is frequent worldwide, representing a major public health problem. Intravenous (IV) iron therapy has been used to treat anemia in patients associated with chronic kidney disease (CKD). However, IV iron therapy is known far away from ideal because the quantitative relationship between the pharmacokinetics and biodistribution of IV iron under different iron statuses remains unclear. The unwanted iron accumulation in patients is known to lead to adverse effects, as iron overload produces reactive oxygen species thus leading to toxicity. Optimization of IV iron agent dosage has been identified as a high priority for future research in anemia management for CKD patients[1]. Given the complexity of the PK behavior of IV iron agents, understanding the iron disposition in various tissues (including plasma) post-treatment is crucial for optimizing the dose.

OBJECTIVES

- To develop a whole-body mechanistic physiologically-based pharmacokinetic (PBPK) model to investigate the influence of iron status on body iron-distribution in mice.
- Extrapolation of the mouse PBPK model to rats and humans to examine the utility of the model for predicting the tissue disposition of iron across species.

METHODS

- Data collection:** The PK and biodistribution studies of iron in mice[2], rats[3], and humans[4] were taken from the published literature, which was utilized to build and verify the PBPK model.

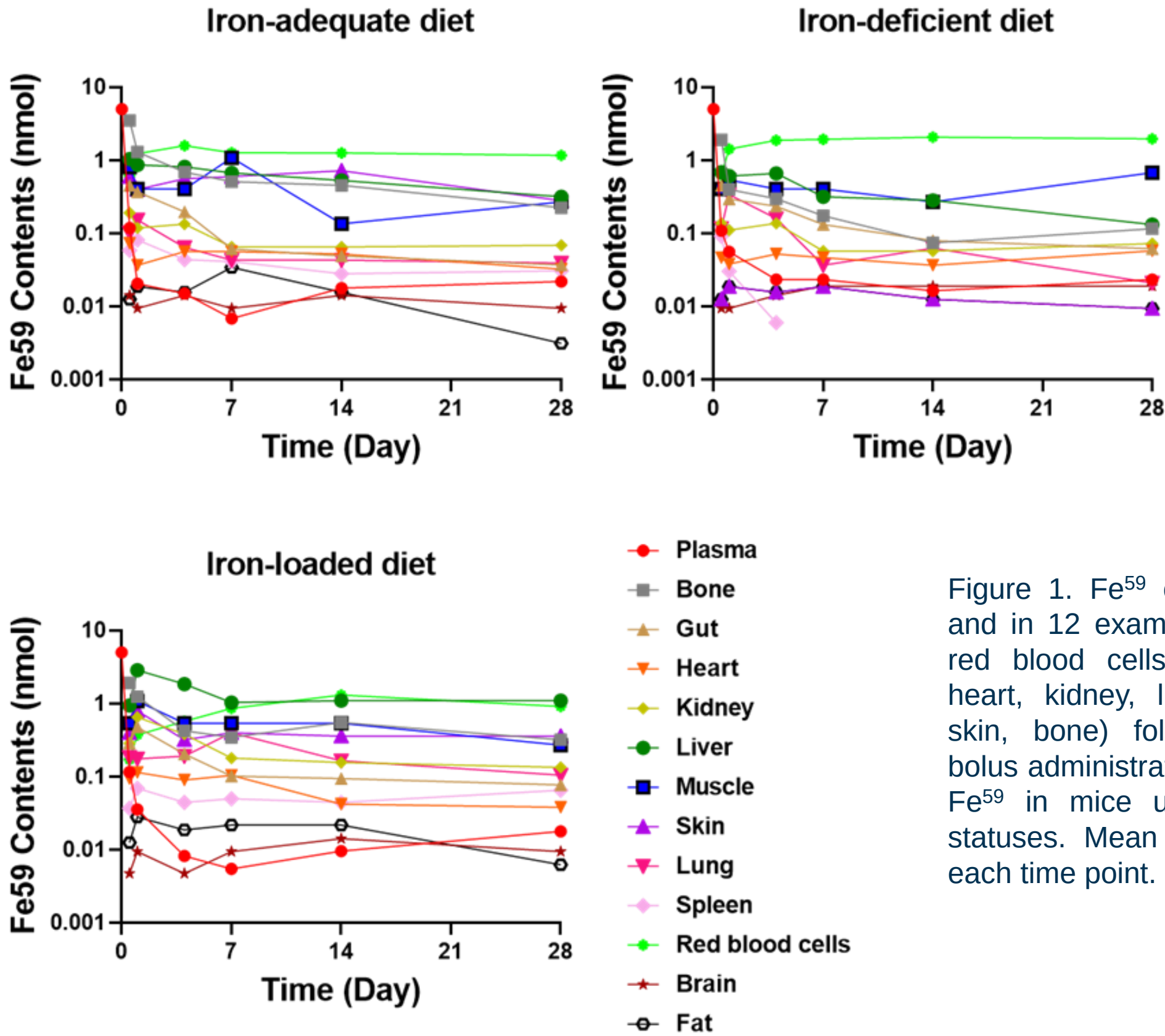


Figure 1. Fe^{59} contents in plasma and in 12 examined tissues (brain, red blood cells, fat, gut, spleen, heart, kidney, liver, lung, muscle, skin, bone) following intravenous bolus administration of $0.02 \mu\text{mol/kg}$ Fe^{59} in mice under different iron statuses. Mean data was used at each time point.

- PBPK Model Development:** The whole body PBPK model in mice was developed with iron distribution data from thirteen organs (Figure 2). Iron concentrations in other organs such as the thymus were not determined and therefore included in the "remainder" compartment.

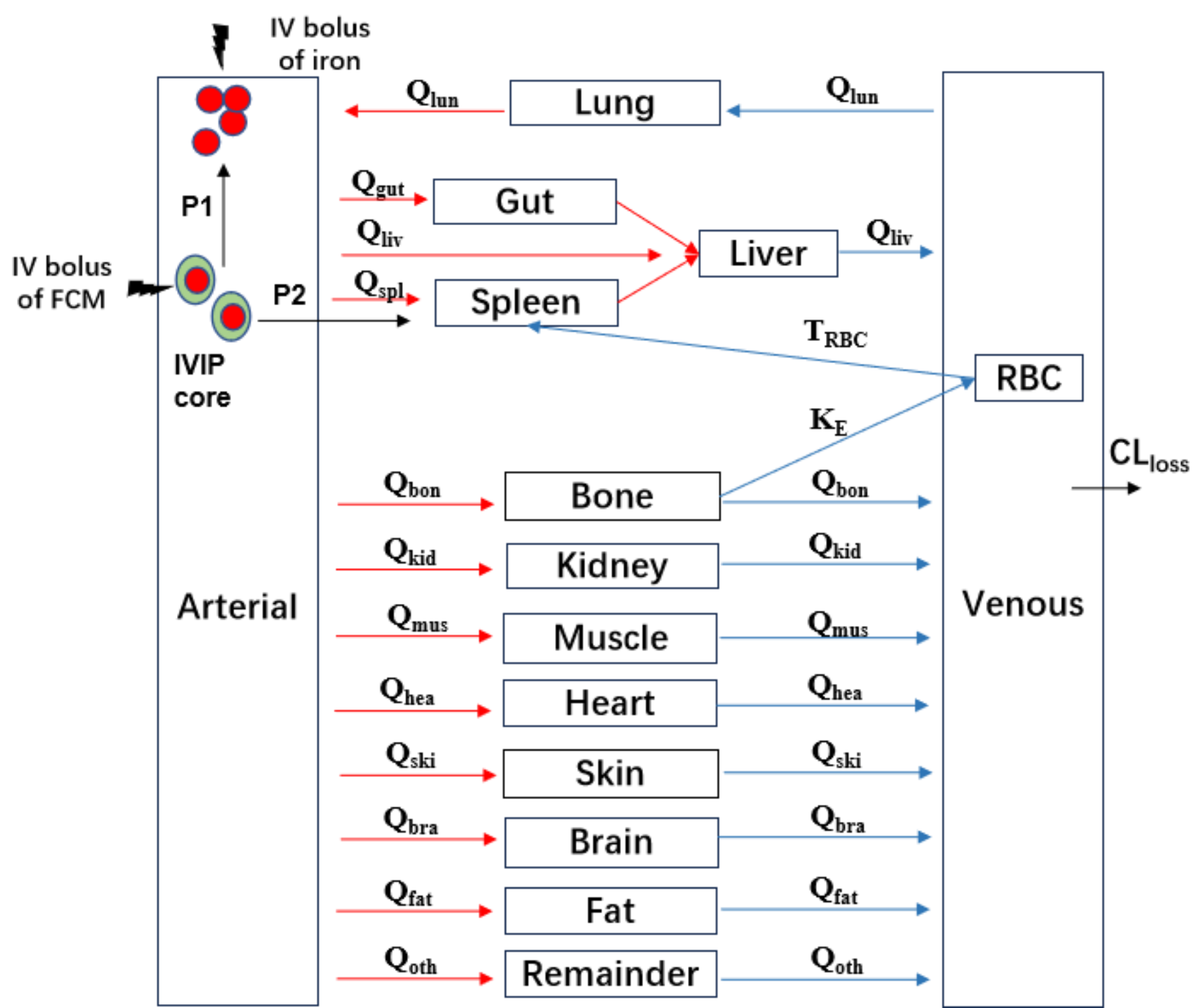


Figure 2. Schematic representation of the PBPK model for IV iron. Q = organ blood flow rate, K_E = production rate of red blood cell (RBC) in the bone compartment by utilizing iron, T_{RBC} = lifespan of RBC, CL_{Loss} = iron unavoidable daily loss rate, FCM = ferric carboxymaltose, IVIP = iron-carbohydrate complex preparation, FCM releases free iron through two pathways, including P1 direct (circulating IVIP-to-plasma) and P2 indirect (IVIP-to-macrophage-to-plasma) iron release.

- Extrapolation from mice to rats and humans:** The model was extrapolated to rats first and then to humans by taking into account the interspecies differences in physiological parameters (body weight, cardiac output, organ volume, and blood flow)[5-7], because there are more data in the rat study[3] compared with the human study[4]. Since the third generation IV iron preparation ferric carboxymaltose (FCM) is an iron-carbohydrate complex preparation (IVIP) that is different from pure iron solution, the model was modified slightly to mimic the P1 direct (circulating IVIP-to-plasma) and P2 indirect (IVIP-to-macrophage-to-plasma) iron release[5]. The organ to plasma partition coefficient K_p for the same type of tissues and the iron unavoidable daily loss rate CL_{Loss} values were assumed to be identical among species. The production rate of red blood cells (RBCs) K_E for humans were scaled from mice to humans using an allometric equation based on the lifespan of RBCs $K_{E(human)} = K_{E(mouse)} \cdot \left(\frac{T_{RBC(human)}}{T_{RBC(mouse)}}\right)^b$. A fixed value of 0.75 was used for the power function b for the allometric relationship.

- Software:** NONMEM7.5 FOCEI

REFERENCES

[1] Kidney Int Rep. 2021;6(9):2381-2391. [2] Toxicology. 2007;241(1-2):19-32.
[3] Eur J Pharm Biopharm. 2022;174:56-76. [4] Arzneimittelforschung. 2010;60(6a):362-72.
[5] Pharm Res. 1993;10(7):1093-5. [6] Toxicol Ind Health. 1997;13(4):407-84.
[7] J Pharm Sci. 2012;101(3):1221-41. [8] Haematologica. 2021;106(11):2885-2896.

Corresponding Author: Xiaoyu Yan, PhD, xiaoyuyan@cuhk.edu.hk

RESULTS

- The model fits the literature data in mice well.

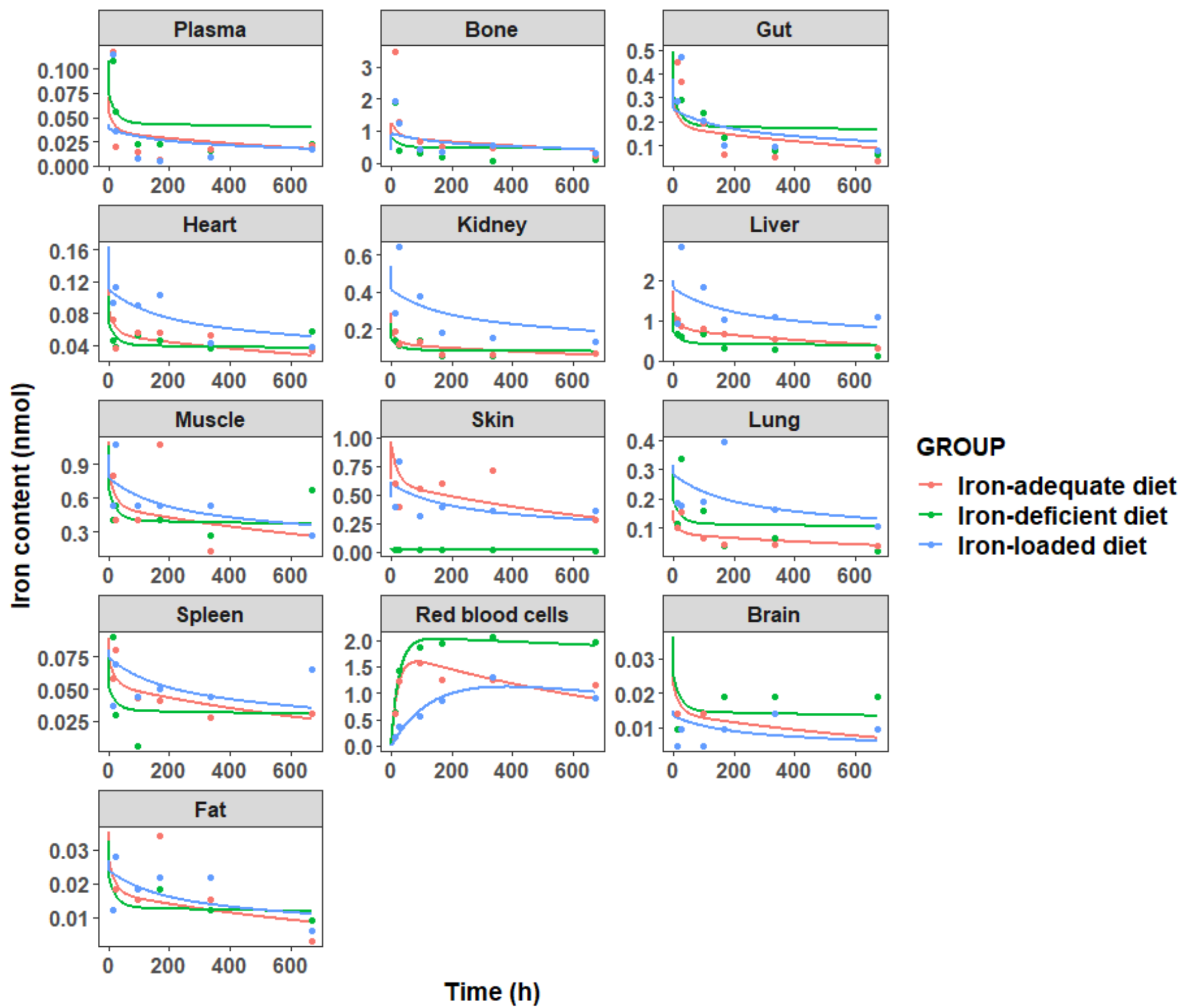


Figure 3. Observed (dots) and predicted (lines) iron concentrations in plasma and various organs/tissues in mice. Each dot represents the mean of the observations digitized from the literature[2].

Organs	Parameters (Unit)	PBPK estimated (RSE%)		
		Iron-deficient diet	Iron-adequate diet	Iron-loaded diet
Plasma	K_{out} (nmol/L/h)	0.1518 (19.35)	1.607 (0.326)	1.163 (0.079)
Brain	$K_{P_{bra}}$	0.7862 (29.68)	1.062 (0.341)	0.9134 (0.082)
Bone	$K_{P_{bon}}$	3.364 (15.38)	7.526 (0.387)	7.609 (0.10)
Fat	$K_{P_{fat}}$	0.1311 (24.61)	0.2522 (0.343)	0.3214 (0.081)
Gut	$K_{P_{gut}}$	3.879 (25.45)	5.23 (0.35)	6.853 (0.080)
Heart	$K_{P_{hea}}$	7.065 (23.78)	13.51 (0.347)	25.39 (0.082)
Kidney	$K_{P_{kid}}$	4.663 (25.49)	9.012 (0.346)	28.51 (0.080)
Liver	$K_{P_{liv}}$	3.55 (25.81)	9.14 (0.345)	19.46 (0.075)
Lung	$K_{P_{lun}}$	13.68 (25.56)	13.39 (0.351)	44.46 (0.083)
Muscle	$K_{P_{mus}}$	0.9418 (24.91)	1.726 (0.332)	2.351 (0.079)
Red blood cells	K_E (nmol/L/h)	0.3175 (1.097)	0.2175 (0.086)	0.03881 (0.025)
Spleen	T_{RBC} (h)	44.37 (14.28)	34.33 (0.062)	197.5 (0.011)
Skin	$K_{P_{ski}}$	0.07313 (27.69)	4.547 (0.358)	4.175 (0.08)
Remainders	$K_{P_{rem}}$	7.392 (22.1)	16 (0.343)	23.5 (0.08)
		2.979 (23.09)	2.36E-10 (5.20)	4.00E-9 (22.57)

Table 1. Estimated parameters in the mouse PBPK model together with their relative standard errors (RSE).

- Extrapolation of the PBPK model from mice to rats successfully.

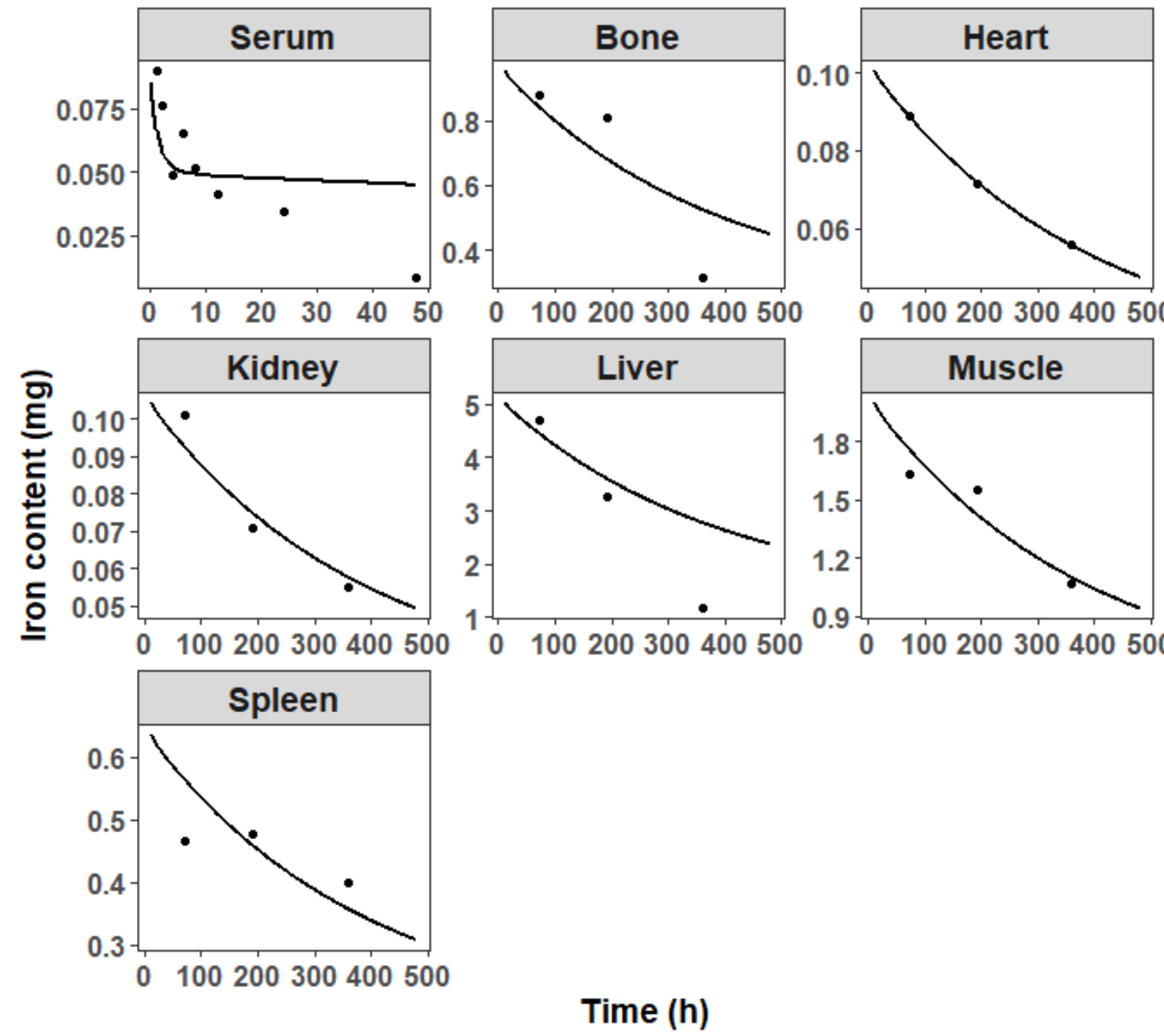


Figure 4. Observed (dots) and predicted (lines) iron concentrations in plasma and various organs/tissues in rats. Each dot represents the mean of the observations digitized from the literature[3].

- The simulated serum iron concentrations were in good agreement with the observed values in patients with IDA following IV dose regimens of FCM.

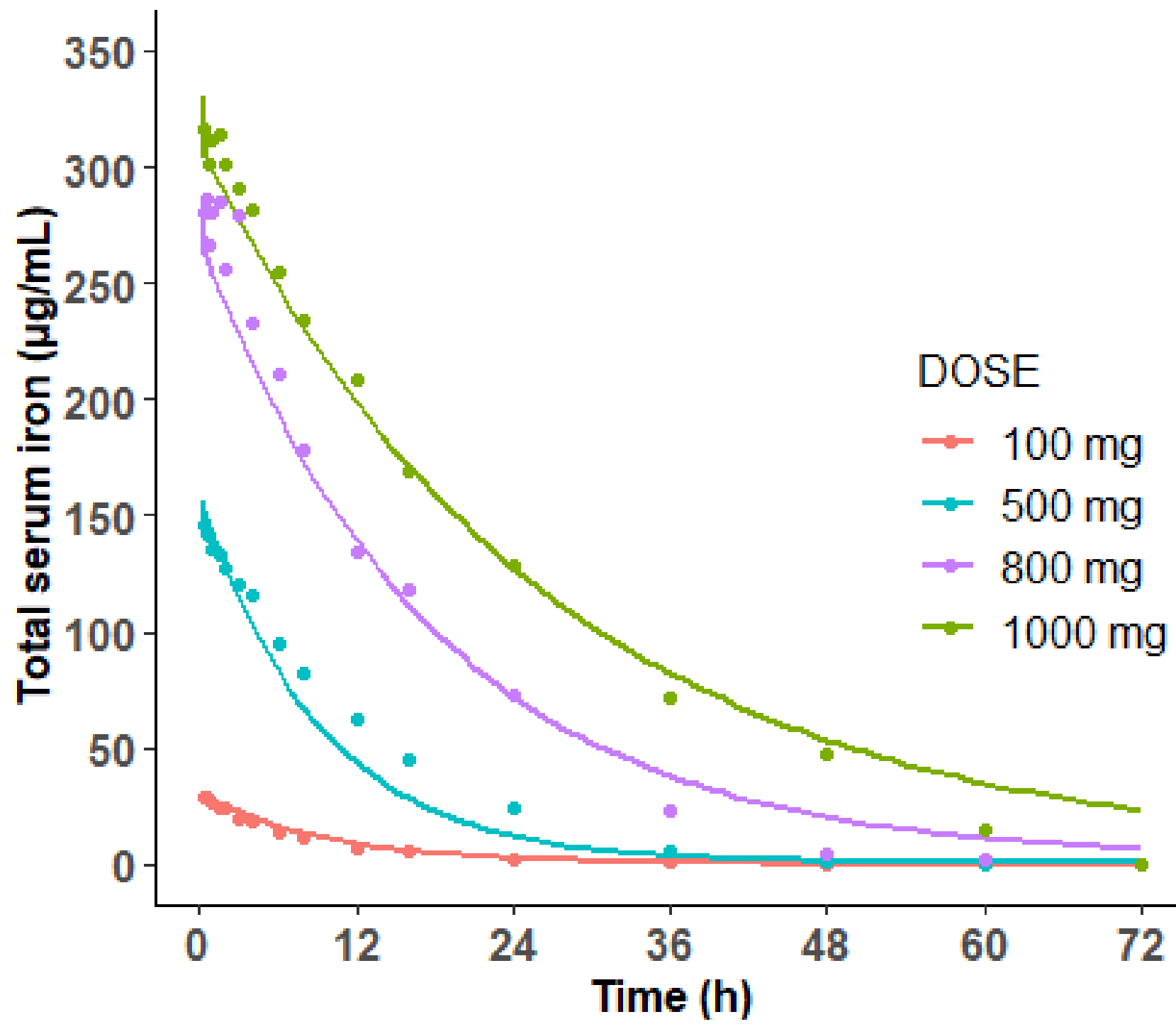


Figure 5. Observed (dots) and predicted (lines) iron concentrations in serum in humans. Each dot represents the mean of the observations digitized from the literature[25]. Solid lines are the fit predictions based on the proposed PBPK model.

CONCLUSIONS

- A translational whole body PBPK model was developed, which is capable of describing the iron concentration-time profiles in plasma and various target tissues after receiving pure iron and FCM, as evidenced by reproducing the observed PK data.
- The PBPK model provides mechanistic insights regarding the mechanism of action of iron, which may have clinical applications in the efficacy and safety assessment of iron therapy.