Enhancing PB(P)K Models for the Female Reproductive Tract: A Framework for Local and Systemic Drug Kinetics

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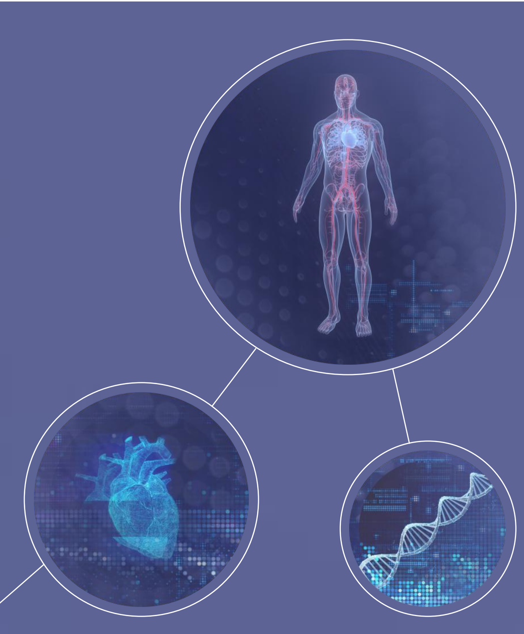

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Intro

Healthcare is advancing, and a deeper understanding of complex physiological systems is crucial for improving treatments. The female reproductive tract (FRT) plays a key role in reproduction and women's health, but is affected by conditions such as infections, endometriosis, and cancer. Nevertheless, the FRT is underrepresented in physiologically-based (pharmaco)kinetic modeling (PB(P)K). A PB(P)K model tailored to the FRT can enhance drug development by predicting tissue and fluid concentrations for both local (e.g., vaginal or uterine) and systemic administration routes. This project aimed to develop and validate a PB(P)K model for levonorgestrel [1], with implementation in the open-source Open Systems Pharmacology (OSP) Suite [2].

Methods

A literature review gathered physiological data to inform model parameters such as specific blood flow and compartment volume for the FRT organs. The FRT model structure was implemented as a MoBi module V12 and can extend any PB(P)K base model available in the OSP Suite [2].

A publicly available levonorgestrel model was extended for the FRT [1]. Levonorgestrel concentration-time profiles were simulated for blood plasma, uterine fluid, and cervical, vaginal, and uterine tissue after oral administration and for an intrauterine device (IUD). Patient data for plasma, myometrium, and endometrium concentration, collected from three studies available in the public domain, were used to validate the model predictions.

Results

The basic PB(P)K model structure was extended for the female reproductive tract (Figure 1). Absorption and distribution parameters governing compound fate in the FRT are partly based on assumptions or numerical optimization. To correctly predict tissue concentrations in the endometrium and myometrium, the diffusion coefficient driving drug uptake from uterine fluid required optimization. The initial value (2.16E-7 cm^2/min), derived from QSAR, was adjusted to approximately 27 times lower than the value estimated based on compound properties (8.03E-9 cm^2/min). Drug release from an IUD was described as: (I) as a zero-order release process and (II) as a Weibull function (Figure 2, Table 1) [3, 4]. Despite the higher deviation on the AUC, a Weibull function improved the prediction of the concentration-time profile. Plasma and uterine tissue concentration predictions for oral and IUD levonorgestrel fall within the 2-fold deviation for the after introducing an additional parameter to account for differences in target availability (Figure 3, Table 2) [5].

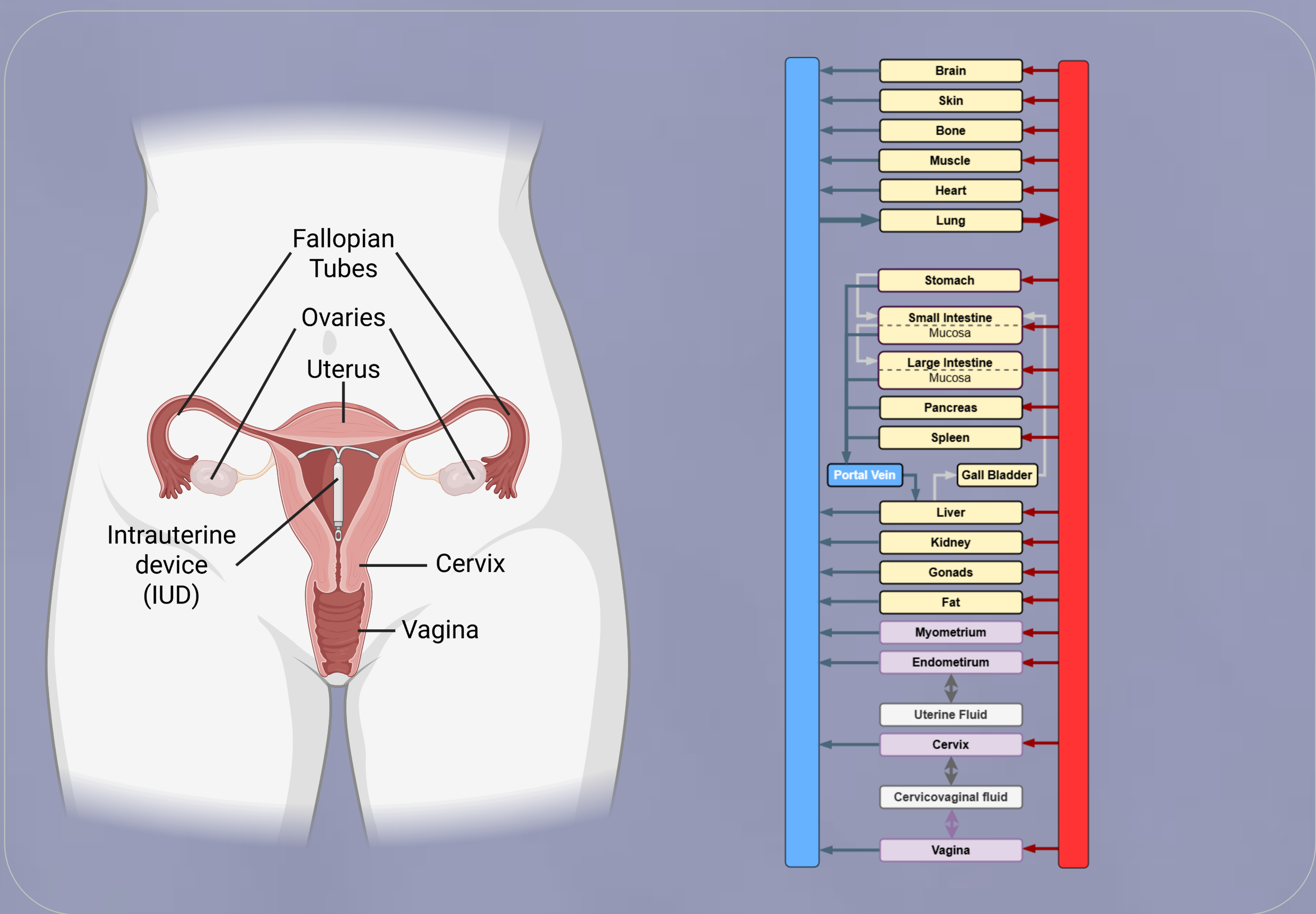

Figure 1: Female reproductive tract (FRT) structure
The female reproductive tract was implemented in the Open Systems Pharmacology (OSP) Suite as an extension module in Mobi V12. Four tissue compartments (cervix, vagina, endometrium, and myometrium) and two fluid compartments (uterine and cervicovaginal fluid) were informed using publicly available data. However, due to the lack of tissue-specific data, the model does not include the ovaries and fallopian tubes. Basic physiologically based (pharmaco)kinetic compartments are shown in yellow, female reproductive tract compartments are in pink, and fluid compartments are in grey. Created in https://BioRender.com

Table 1: Area-under-the-curve (AUC) for plasma after oral administration or intrauterine device (IUD) as zero-order release or Weibull function

	AUC predicted [ng*h/mL]	AUC observed [ng*h/mL]	Fold error	Reference
Oral administration	18.9	20.5	0.92	[1]
Intrauterine device (IUD):		5712.0		[4]
Zero-order release	5004.0		0.87	
Weibull function	3669.6		0.63	

Conclusion

The FRT model accurately predicts levonorgestrel concentrations in plasma and tissues after oral and IUD administration, requiring only minimal parameter adjustments. Ongoing work aims to extend a PB(P)K model for metronidazole to evaluate the FRT module's applicability further. The validated structure will become available to the open-source community in the OPS Suite model library on GitHub. The FRT PB(P)K model has significant potential for drug development and safety assessment in female-specific health areas, including infections, cancer, and reproductive toxicity.

"Women's Health Deserves Better Models — We're building them!"

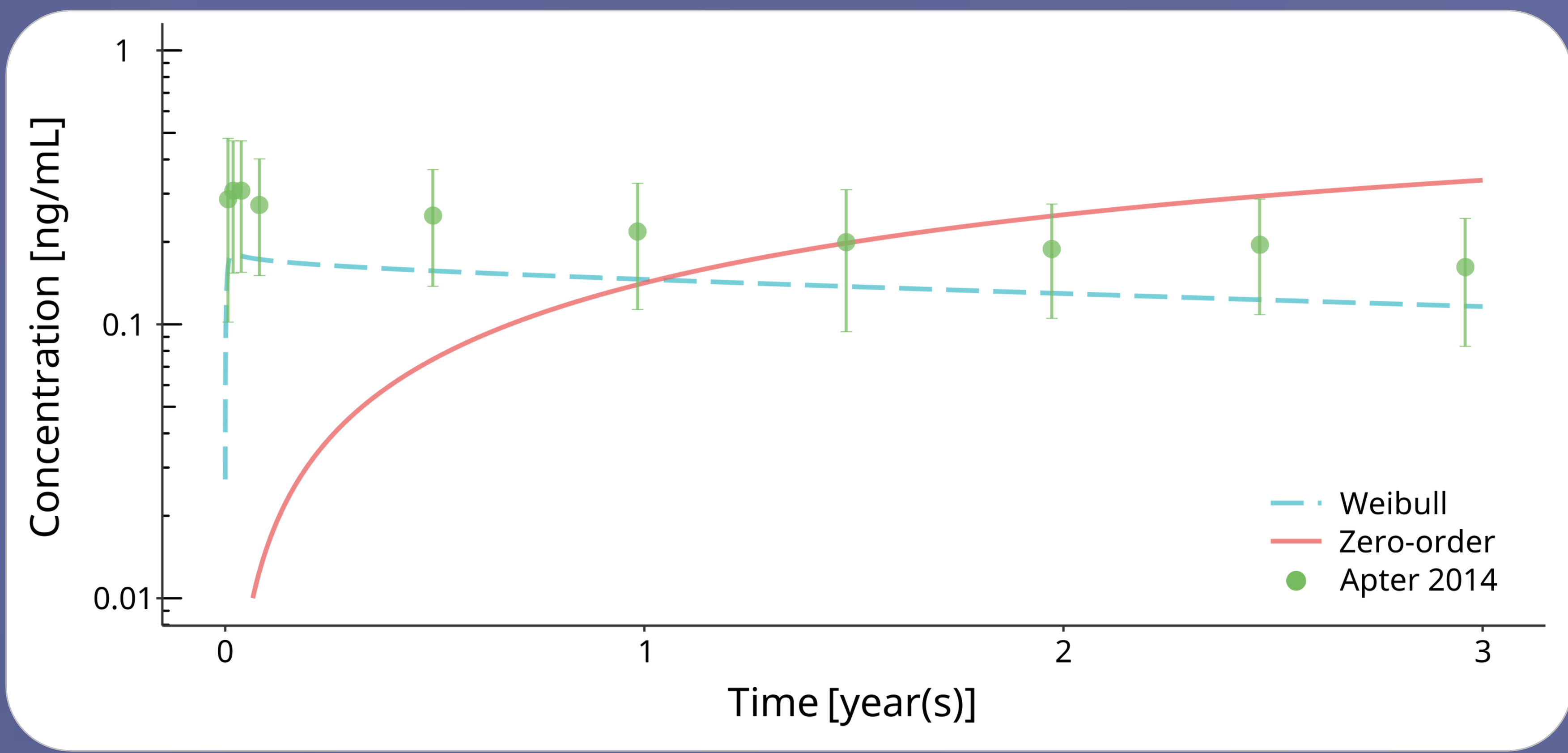

Figure 2: Comparison of drug release from an intrauterine device (IUD) as zero-order release or Weibull function
Predicted plasma concentrations for IUD administration implemented as a zero-order release process (red) or a Weibull function (blue). Both options were parametrized with *in vivo* release rate data spanning 8 years [3]. Observed plasma (mean ± SD) concentrations are shown in green [4].

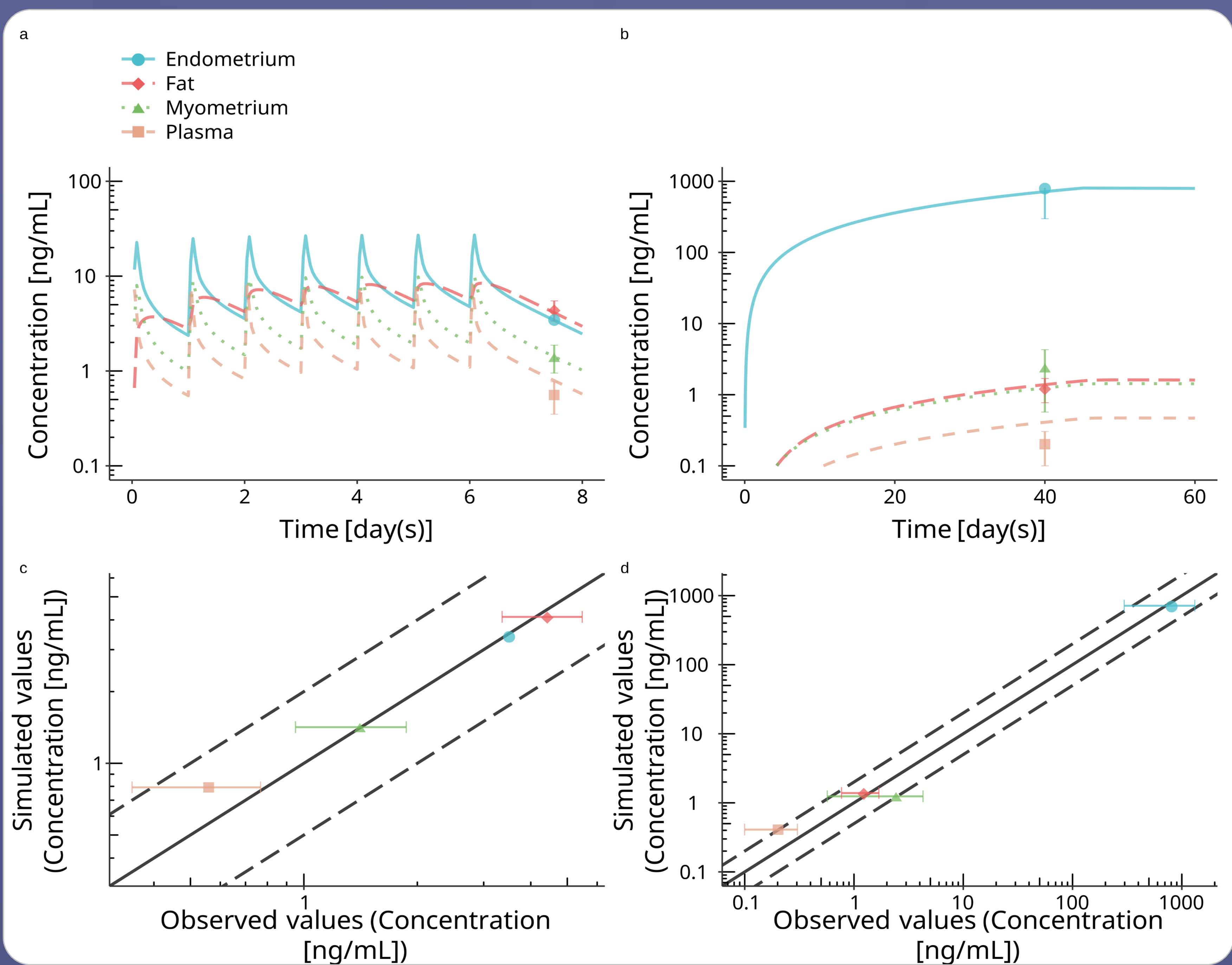

Figure 3: Plasma, fat, and uterine concentrations for oral and intrauterine (IUD) administration of levonorgestrel
Lines represent predicted concentration in endometrium (blue), fat (red), myometrium (green), and plasma (orange) for oral (a) and IUD (b) administration. Simulated versus observed data are shown for oral (c) and IUD (d) administration, with the line representing unity and dotted lines representing a 2-fold prediction error. Observed concentrations (mean ± SD) are shown for endometrium (circle), fat (diamond), myometrium (triangle) and plasma (square) [5].

Table 2: Plasma and uterine concentrations for oral and intrauterine (IUD) administration of levonorgestrel [5]

Tissue	Oral administration		Intrauterine device (IUD)	
	Predicted	Observed	Predicted	Observed
Plasma	1.79E-3 µmol/L	2.54E-3µmol/L	6.47E-3 µmol/L	0.02 µmol/L
Myometrium	8.09E-3 µmol/L	4.00E-3 µmol/L	3.94E-3 µmol/L	7.77E-3 µmol/L
Endometrium	0.01 µmol/L	0.01 µmol/L	2.24 µmol/L	2.48 µmol/L

References

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Modeling Scaling Coding

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