Translational PK M&S for the assessment of duration of contraceptive cover after use of miltefosine for the treatment of visceral leishmaniasis

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DNDi
Drugs for Neglected Diseases *initiative*

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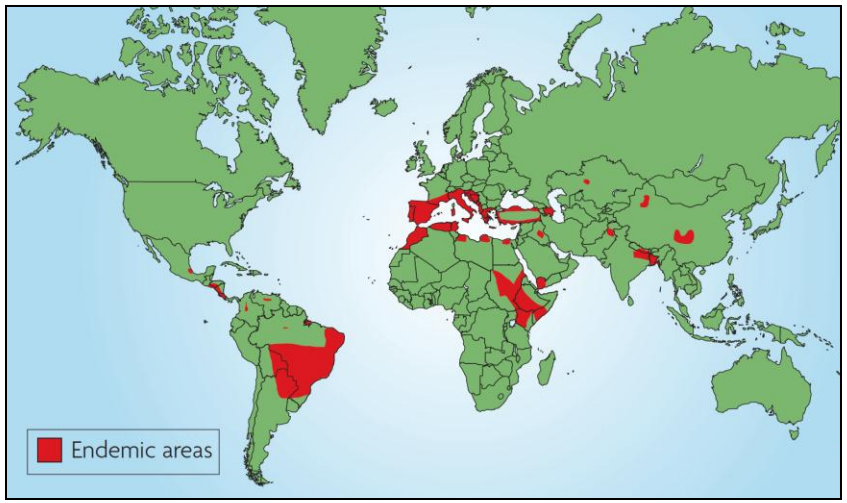
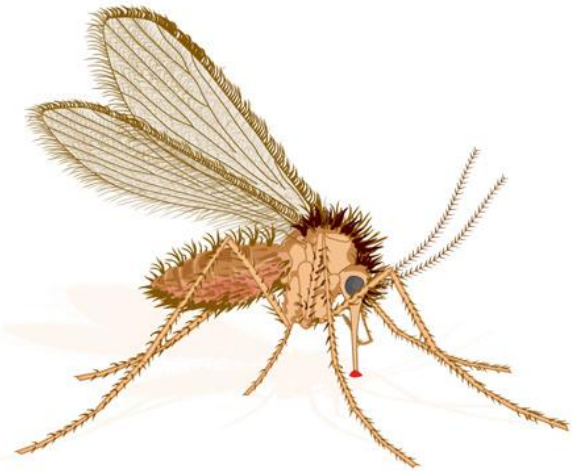
Visceral Leishmaniasis (VL)

- Neglected tropical disease
- Poor rural areas – **India & Sudan**
- Intracellular parasite within macrophages





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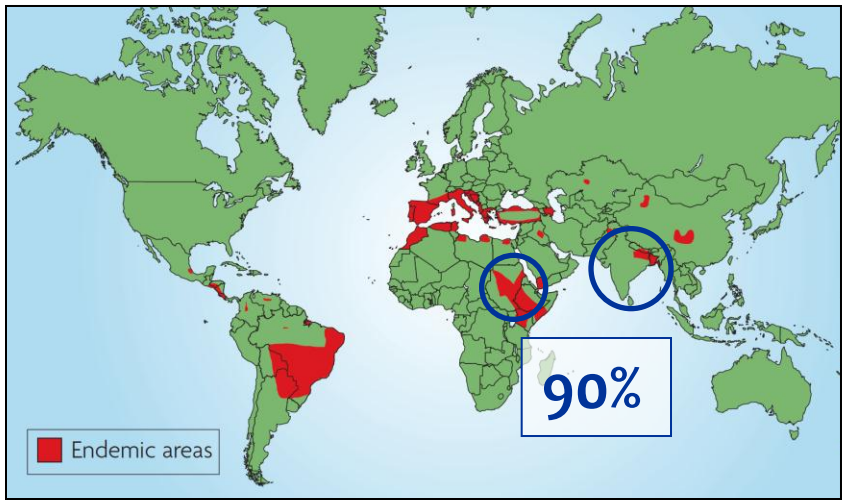

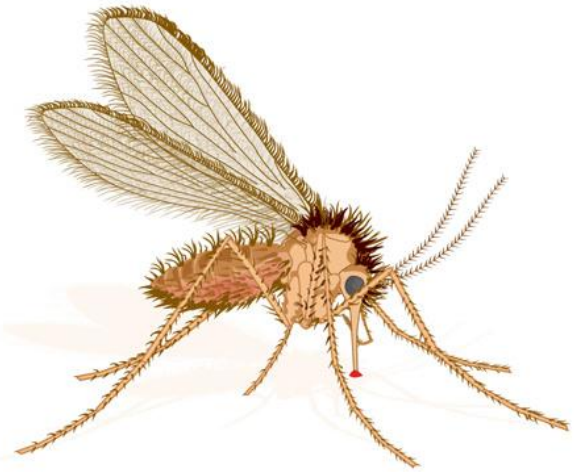

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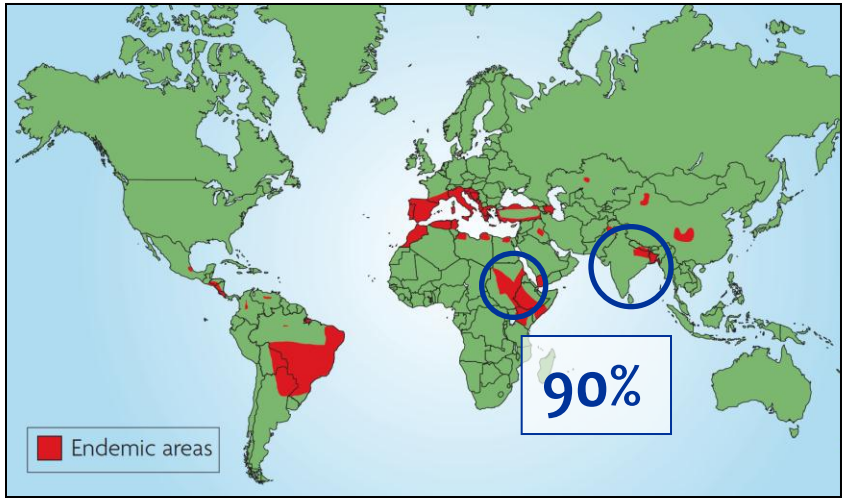
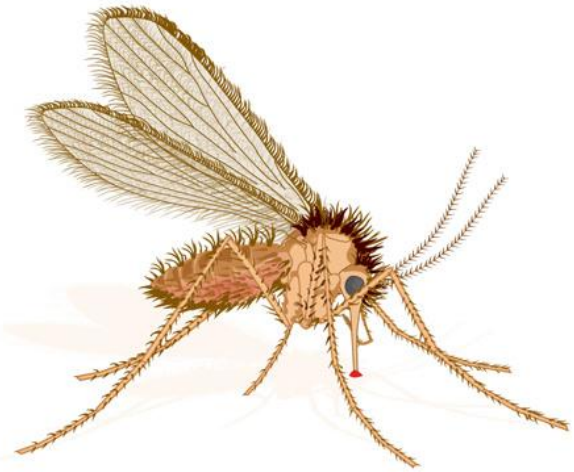


Miltefosine

- Only **oral** drug currently available for VL
- Monotherapy regimen:
  - 2.5 mg/kg for **28 days**
- Extremely **long elimination half-life**
  - **t½:** first **5-7 days** and terminal of **31 days**[1,2]
- **Shorter combination regimens** under development



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Reproductive toxicity of miltefosine

- First-line in India – regional elimination programme
- Toxicity: GI-related & **reproductive toxicity**
- Feto- & embryotoxicity rabbits & rats – **teratogenicity** rats only (≥ 1.2 mg/kg/day for 10 days during gestation)[1]

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- Guidelines: **2 or 3 months post-treatment contraception** for women of child-bearing potential on 28-day regimen[2,3]
- But miltefosine can be detected **until 5 months post-treatment?**[4]

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- But miltefosine can be detected **until 5 months post-treatment?**[4]
- **Ethical dilemma**: Costs & adherence *vs* risk malformation

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Aim & approach

Dose conversion from animal teratogenicity studies (NOAEL)

↓

Human Equivalent Dosage (HED)

↓

Human Equivalent Exposure (HEE)

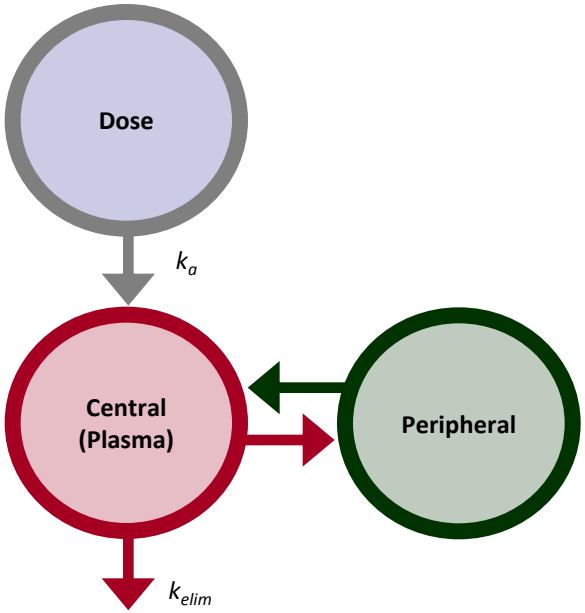
↓

Suggest rational & optimal **durations of post-treatment contraceptive cover**

Population PK model

Developed based on PK data from **Indian children** (9-25 kg), **Indian adults** (25-48 kg) & **European adults** (60-105 kg)[1,2]

Fat-free mass (FFM) & fixed allometric scaling



PK Parameter		Estimate	RSE	BSV
Absorption (k_a)	h^{-1}	0.416	(11.5%)	18.2%
Clearance (CL/*F*)	*L/day*	3.99	(3.5%)	32.1%
Central compart (V_2/*F*)	*L*	40.1	(4.5%)	34.1%
Periph compart (V_3/*F*)	*L*	1.75	(18.3%)	NE
Intercompart. Clearance (Q/*F*)	*L/day*	0.0375	(8.2%)	NE
Residual variability	*%*	34.3	(3.7%)	NE

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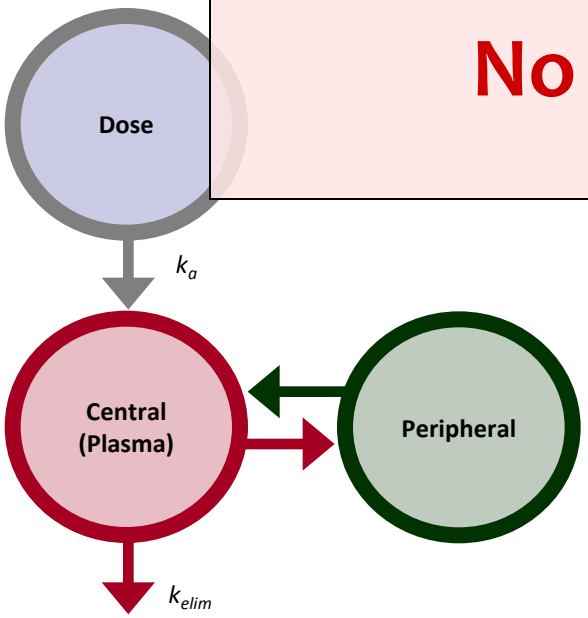
No PK data from females!



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Anthropometric data

- Collected at MSF hospital in Bihar, India
- Total of **2247 VL patients**

465 females of child-bearing potential (12-45 yrs)

Parameter	Median value (IQR)
Age (years)	25 (16–31)
Weight (kg)	38 (34–42)
Height (cm)	148 (144–152)
Body mass index (kg/m^2)	17.3 (15.8–18.8)
Fat-free body mass (kg)	27.1 (24.6–29.5)

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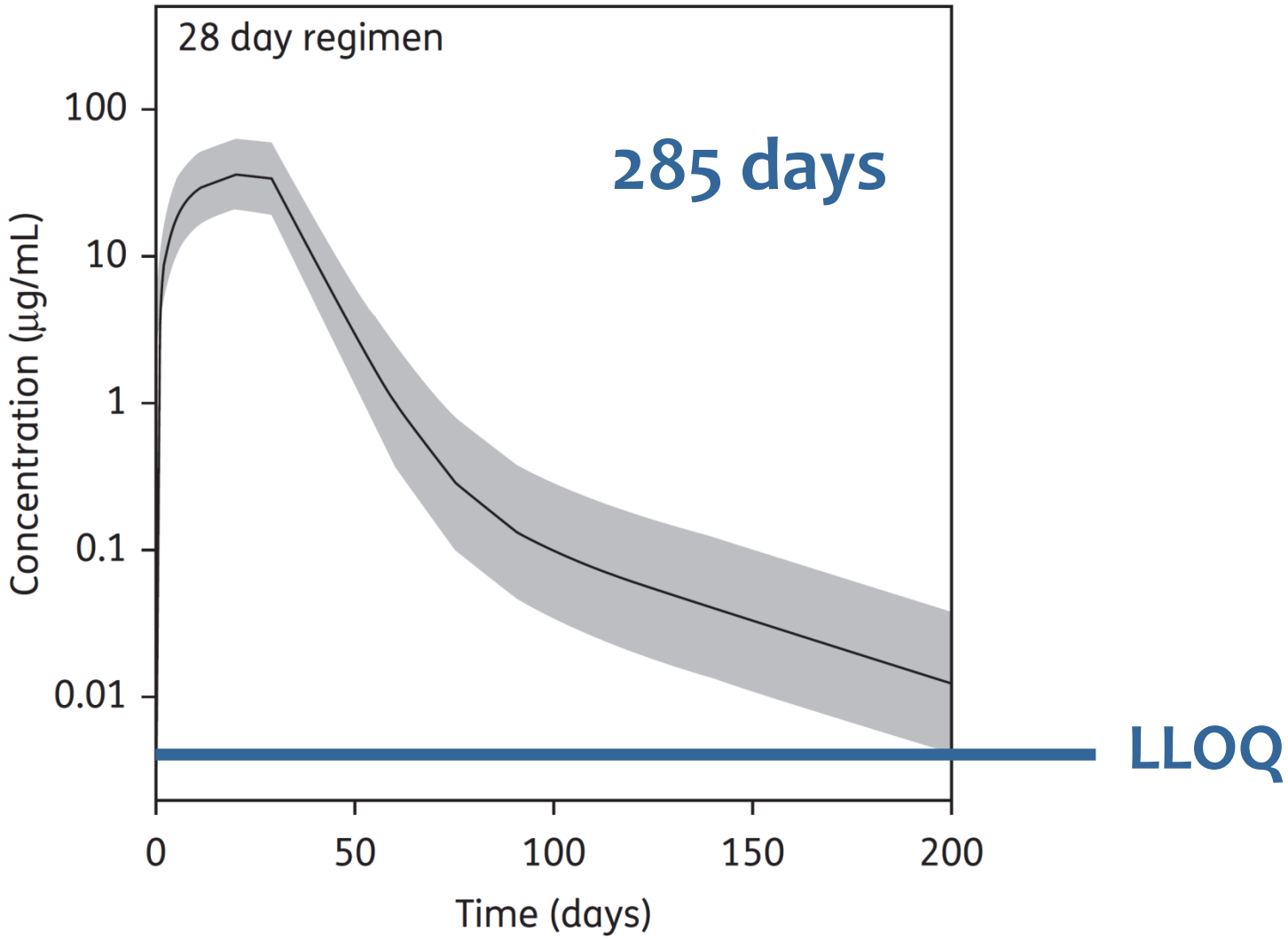
Monte Carlo PK simulations for Indian females



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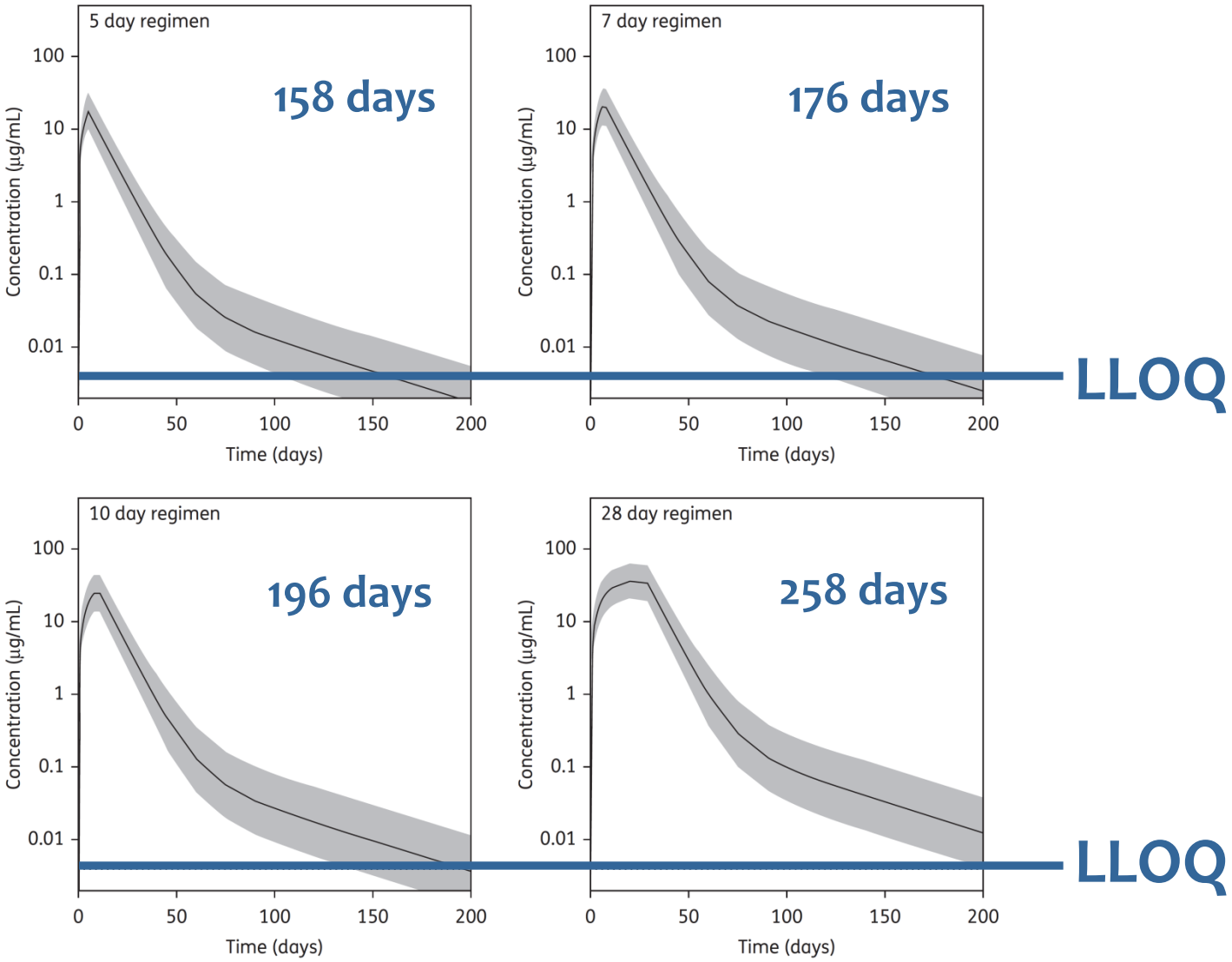

Dose conversion: animal to human

- Rat reproductive **NOAEL**: 0.6 mg/kg for 10 days[1]
- BSA normalisation[2,3] & total dose

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Dose conversion: animal to human

- Rat reproductive **NOAEL**: 0.6 mg/kg for 10 days[1]
- BSA normalisation[2,3] & total dose
- **Human equivalent dose** (HED):

  0.6 mg/kg for 10 days in rat = 6 mg/kg total in rat = 36 mg/m^2 in rat = **45 mg total HED**

[1] Sindermann et al, TRSTMH (2003) [2] Reagan-Shaw et al, FASEB J (2008) [3] FDA Oncology Tools: Dose calculator (2011)

Dose conversion: reproductive safety threshold exposure limit

- Monte Carlo simulations of **HED** in 465 Indian female VL patients:
  - **Median $AUC_{0-\infty}$ (90% PI):** 245 µg·day/mL (140 – 467)
- Species-specific **sensitivity** to reproductive toxity?

[1] EPA Guidelines Developmental Toxicity (1991) [2] FDA Guidance First-in-human dose (2005) [3] Dourson et al, Regul Toxicol Pharmacol (1996)

Dose conversion: reproductive safety threshold exposure limit

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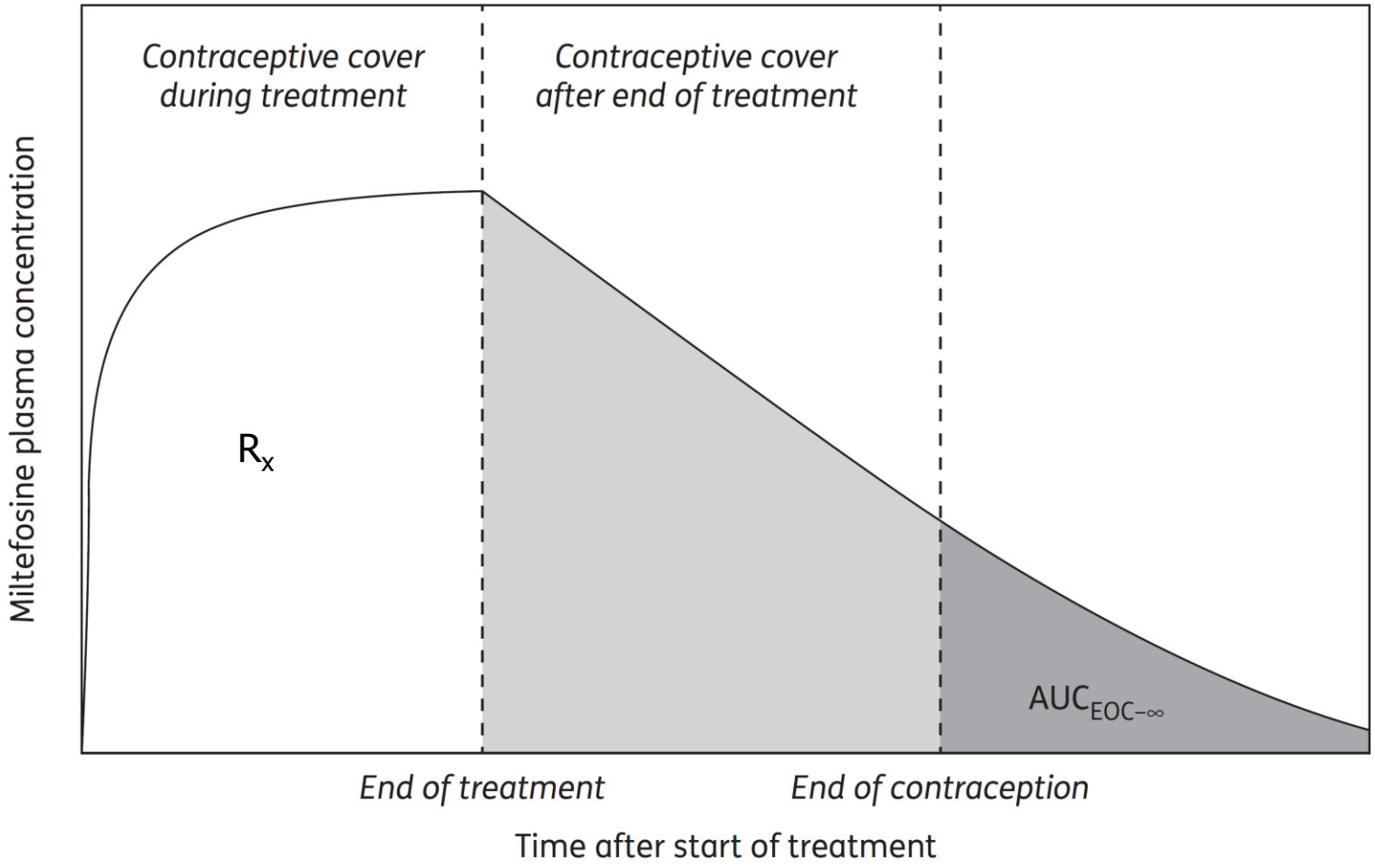
  - **Median $AUC_{0-\infty}$ (90% PI):** 245 µg·day/mL (140 – 467)
- Species-specific **sensitivity** to reproductive toxity?
- Animal-to-human **safety factor of 10**[1,2,3]
- **Final human threshold exposure limit: 24.5 µg·day/mL**

[1] EPA Guidelines Developmental Toxicity (1991) [2] FDA Guidance First-in-human dose (2005) [3] Dourson et al, Regul Toxicol Pharmacol (1996)

Post-treatment contraceptive cover of 1, 2, 3 and 4 months



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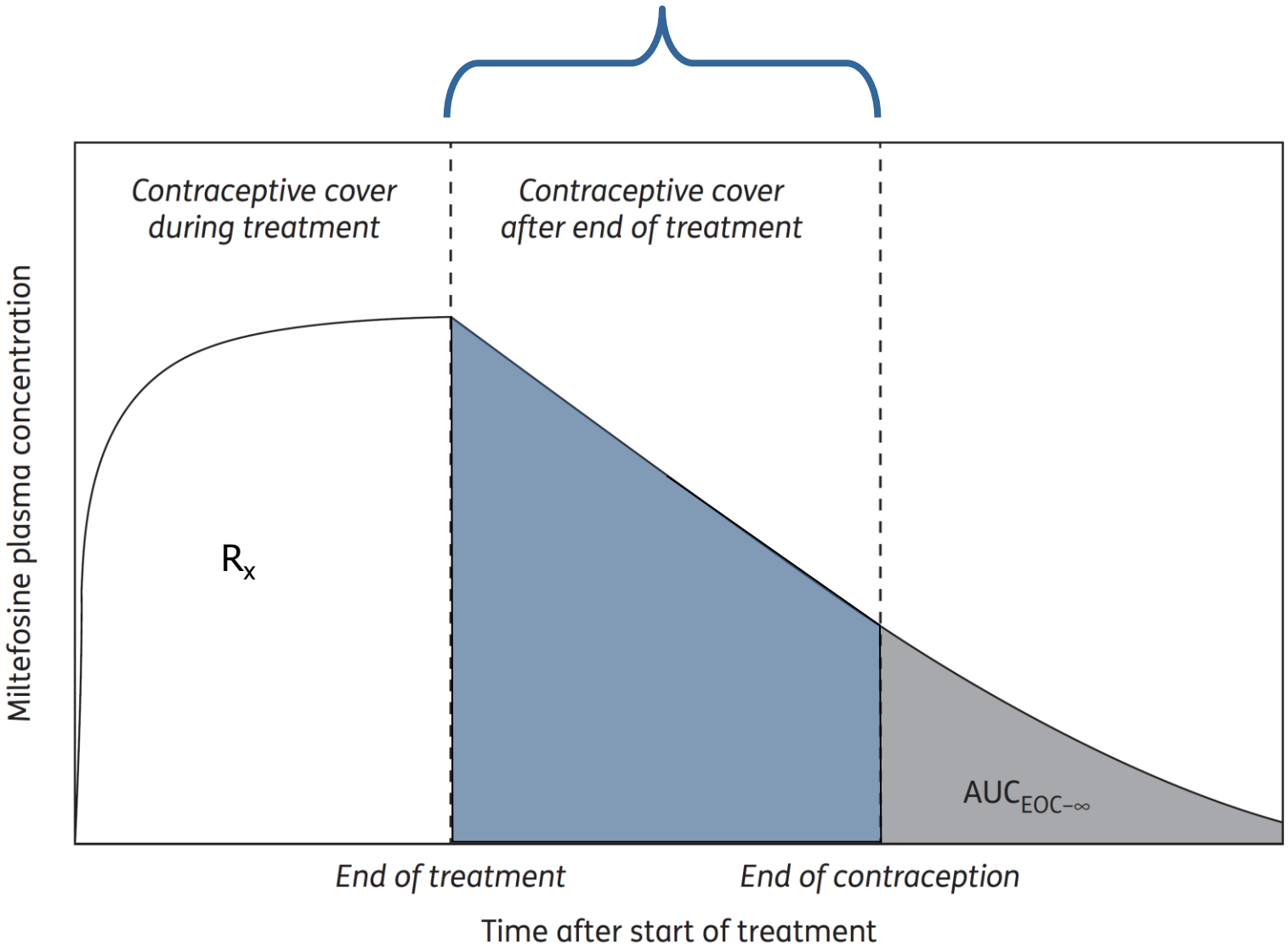

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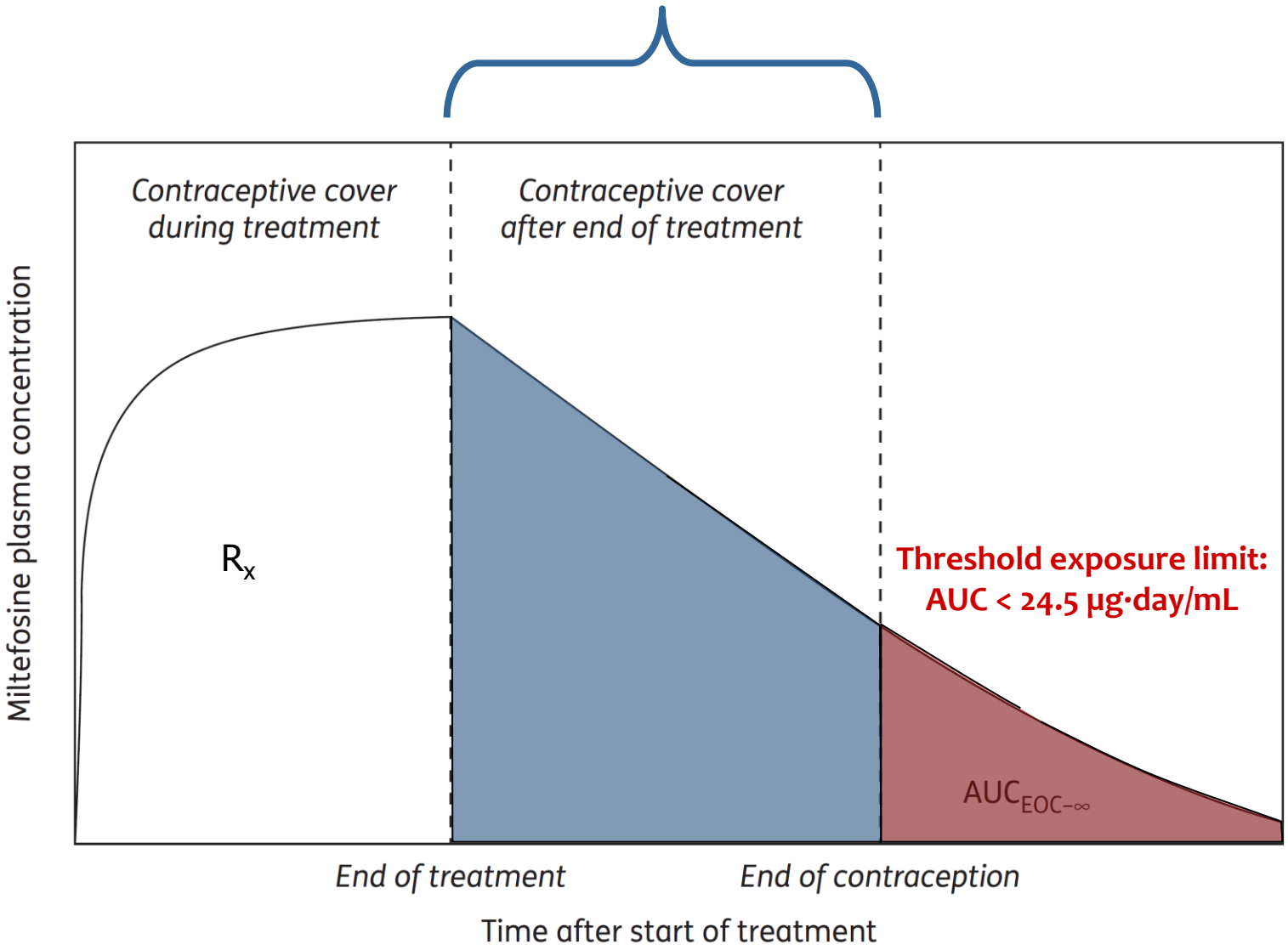
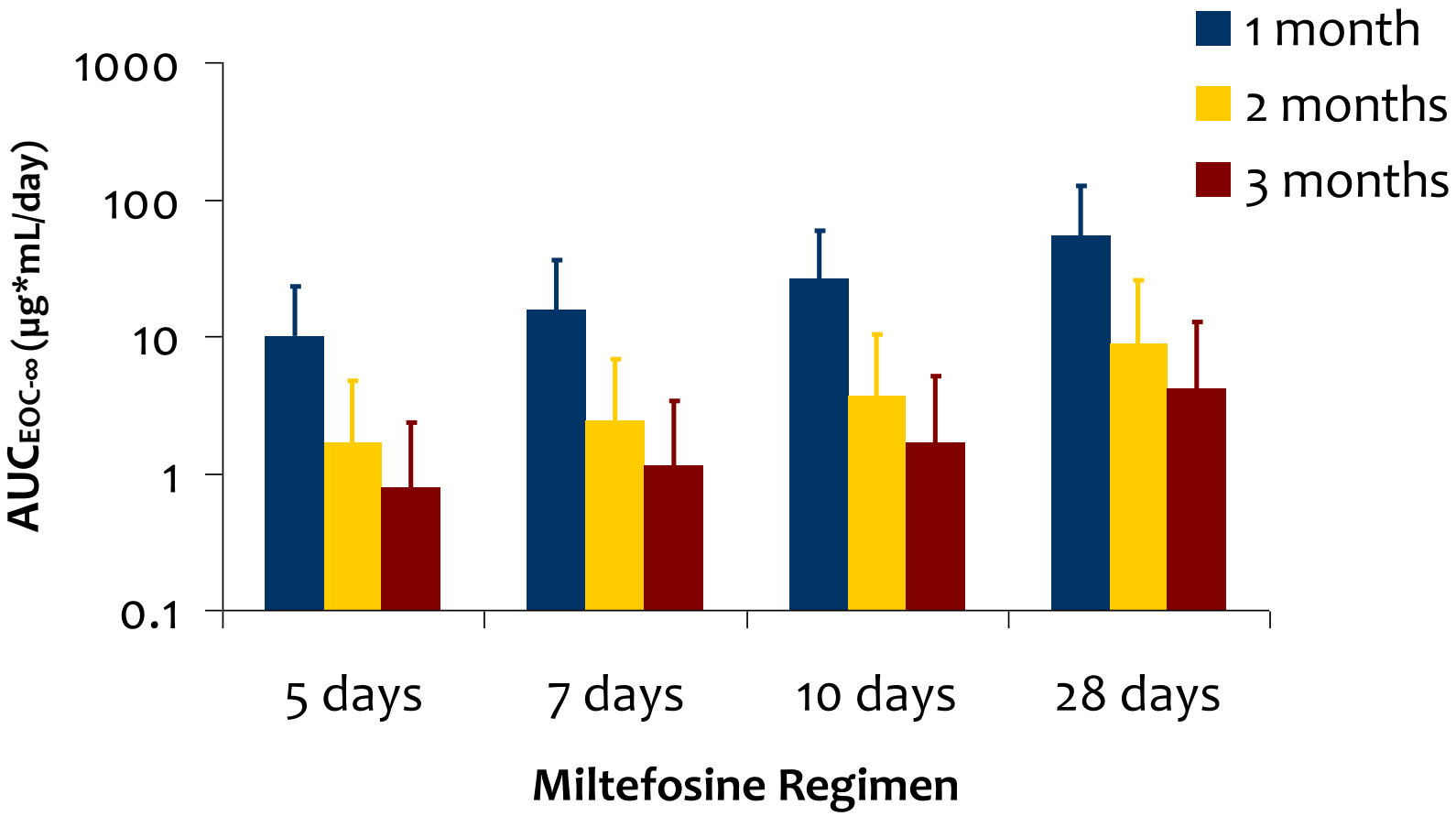


Simulations: Exposure post-EOC

Monte Carlo simulations *n = 465 females (500x)*



PI: prediction interval; EOC: end of contraception

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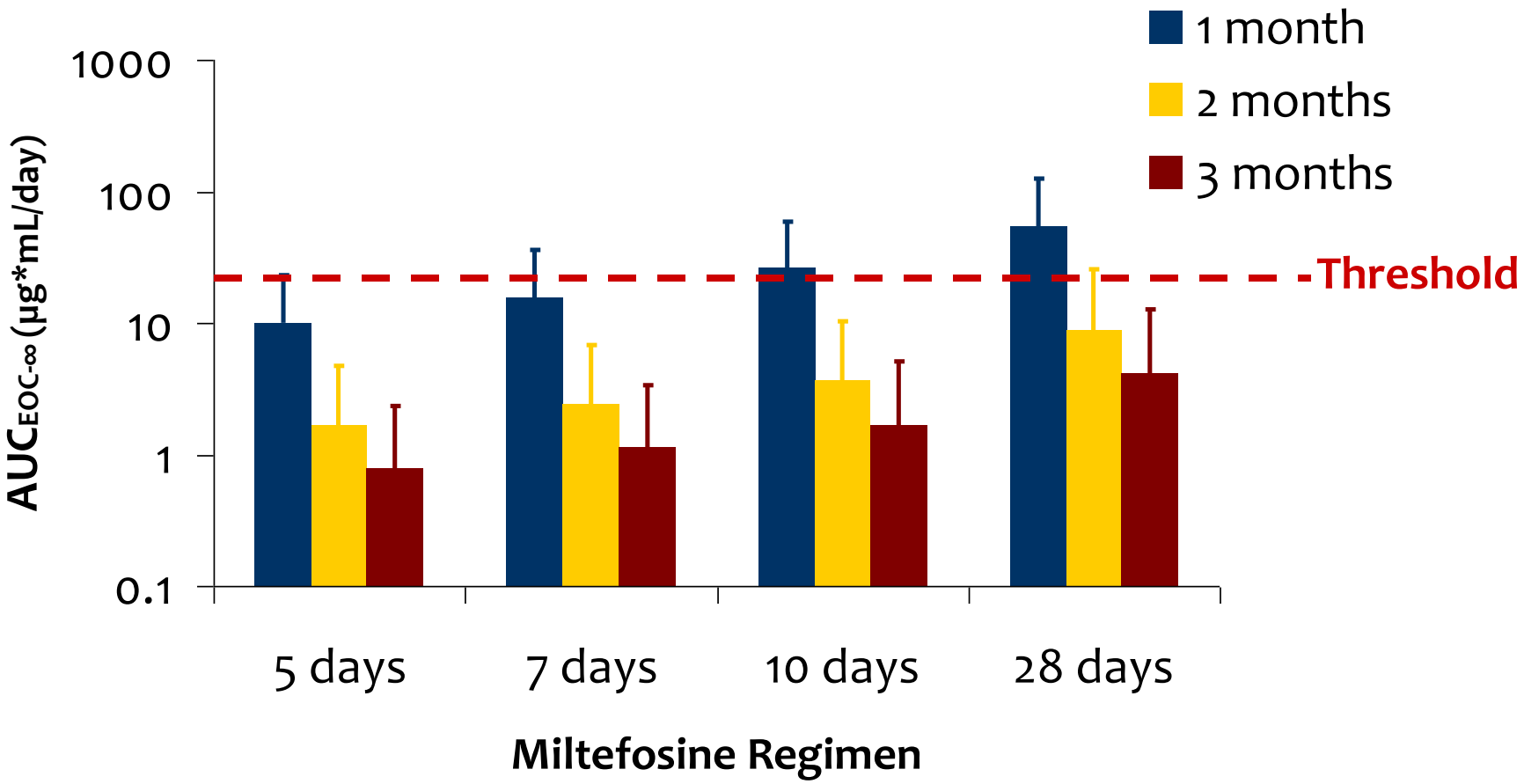

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Simulations: Probability

Comparison to the exposure threshold limit:

	Probability of exposure above the reproductive safety threshold exposure limit for the indicated number of months on contraception after EOT			
Miltefosine regimen	1 month	2 months	3 months	4 months
5 days	**4.3%**	<0.1%	<0.1%	<0.1%
7 days	**18.2%**	<0.1%	<0.1%	<0.1%
10 days	**54.6%**	0.198%	<0.1%	<0.1%
28 days	**93.6%**	**5.42%**	**0.581%**	<0.1%

EOT, end of therapy.

Interpretation

- Incidence of **congenital malformation (CM)**
  - India: 0.2-3.6% - limited evidence[1]
  - Europe: **2.44%**[2]
- Approx 1/10th of CM due to environmental factors[3]
- Probability of exposure above chosen threshold should be less than CM-incidence due to environmental factors

  < 1/10th of 2.44%

[1] Swain et al, Indian pediatrics (1994) [2] EURO-PERISTAT, European perinatal health report (2008) [3] European Surveillance of Congenital Anomalies (EUROCAT). Special Report: A Review of Environmental Risk Factors for Congenital Anomalies (2004)

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Longer than current guidelines,
but shorter than approach based on LLOQ (>5 months)

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Discussion:
Teratogenic risk management

Other examples:

- *Isotretinoïn*
  - Endogenous levels Vit A
- *Ribavirin*
  - Turnover-time erythrocytes (site accumulation)
- *Leflunomide*
  - Based on undetectability (LLOQ!)[1]

Concentration-effect relationship?

[1] Brent RL. *Teratology* (2001)

Discussion:
Limitations of our study

- Reproductive tox studies in small set of animals
- Animal-to-human dose conversion
  - Similar PK in animals (mouse, rat, dog, human)
  - Distribution into cell membranes
  - No evidence interspecies metabolic differences

→ **Animal-to-human safety factor (10x)**

Conclusion

- **M&S**:
  → Simulate PK in a **unique & vulnerable population**
  →Non-parametric probability estimations with full variability
- **More rational teratogenic risk management**
- **Contraceptive cover recommendations:**
  - 4 months for miltefosine monotherapy (e.g. oral or intra-uterine)
  - 2 months for shorter combination regimens (e.g. depot medroxyprogesterone acetate)

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Nines Lima

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Sakib Bursa, Avinash Sadashivaiah, Gaurab Mitra, Marta Gonzalez, Mattia Novella and Bjorn Nissen

Paper

The full paper describing the work presented here was recently accepted for publication in *Journal of Antimicrobial Chemotherapy*:

Dorlo et al. Translational pharmacokinetic modelling and simulation for the assessment of duration of contraceptive use after treatment with miltefosine. ***J. Antimicrob. Chemother.*** *(2012) doi: 10.1093/jac/dks164*

http://jac.oxfordjournals.org/content/early/2012/05/10/jac.dks164
http://dx.doi.org/10.1093/jac/dks164