

# WB-PBPK Population Modeling to Simulate the Influence of Weight and Age on the PK of a combined Oral Contraceptive Containing Drospirenone and Ethinylestradiol

C. Becker(1), K. Coboeken(1), L. Kuepfer(1), J. Lippert(1), R. Nubbemeyer(2), H. Blode(2)

(1) Bayer Technology Services GmbH, Competence Centre Systems Biology, D-51368 Leverkusen, Germany;  
(2) Bayer Schering Pharma AG, D-13342 Berlin, Germany

## Introduction

Obesity has reached epidemic proportions. WHO's latest projections indicate that in 2005 approximately 1.6 billion adults were overweight.<sup>1</sup> The body fat fraction is an important determinant of the PK and can become the dominant factor for highly lipophilic compounds such as steroids.

## Objective

This study aimed to use a WB-PBPK model to investigate the influence of age and weight on the PK to be expected after administration of a fixed dose combination of ethinylestradiol (EE) and drospirenone (DRSP) in a combined oral contraceptive (COC).

## Methods

Physiology-based pharmacokinetic (PBPK) modeling is used to describe EE and DRSP concentration-time profiles using known physiological parameters (body and organ weights, blood flows, tissue composition etc.) included in the software PK-Sim®.<sup>2,3</sup>

The simulated plasma concentration-time profiles were validated using observed data from 48 women.<sup>4-6</sup>

The PK-Pop module of PK-Sim® (Bayer Technology Services GmbH) was used to build virtual populations as described in Willmann et al.<sup>7</sup> BMI/Age classifications were based on the Third National Health and Nutrition Examination Survey (NHANES III)<sup>8</sup> and the definition of overweight and obesity in the CDC US Growth Charts.<sup>9</sup>

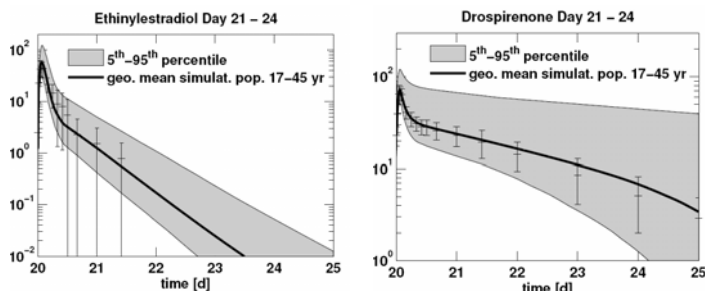
Age Group	BMI and obesity definitions	
12.5 – 13.5 years	Normal weight	10. to 85. percentile
13.5 – 14.5 years	Overweight	85. percentile to 95. percentile
14.5 – 15.5 years	Obesity	95. percentile to 97. percentile
15.5 – 16.5 years	Severe	97. percentile to 99. percentile, but at least a BMI of 40
16.5 – 17.5 years		
17.5 – 45.0 years		

Steady state (SS), i.e. day 15 – 24, PK parameters (AUC,  $C_{trough}$ ,  $t_{1/2}$ ) and concentration time profiles of DRSP and EE were compared between the different virtual populations.

## Results

The WB-PBPK model matched the experimentally measured concentration-time profiles and derived PK parameters in the validation population<sup>4-6</sup> comprising women with slight underweight to slight overweight very well, as shown in Figure 1.

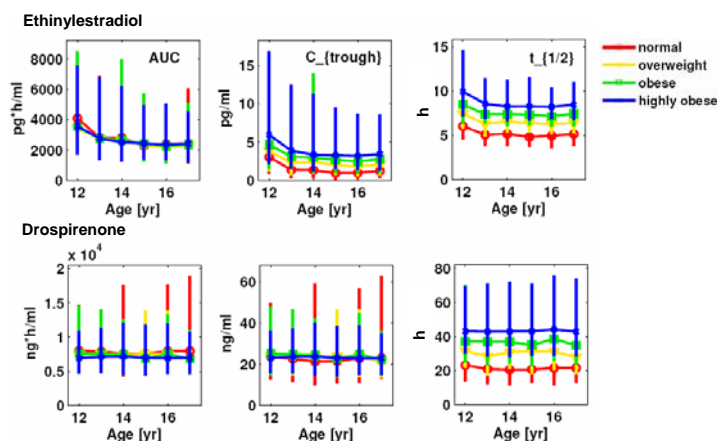
Figure 1. Validation of the PBPK Models for DRSP and EE.<sup>4-6</sup>



The deviation between the simulated and observed values in the elimination phase can be explained by the fact that concentrations below the lower limit of quantification were set to zero. Therefore the mean plasma concentrations are artificially low.

As illustrated in Figure 2, age-related differences of PK parameters were not observed for DRSP and EE in women >14 yrs. Plasma AUC and  $C_{trough}$  were simulated to be similar for both compounds at SS across the different BMI groups. In silico, a decrease in the EE and DRSP  $C_{max}$  to  $C_{trough}$  ratio was observed in the obese compared to the normal weight population. Nevertheless, a prospective post-marketing surveillance study found DRSP/EE containing COCs to be equally effective in obese and non-obese populations.<sup>10</sup>

Figure 2. Comparison of steady state PK parameters within the female populations of different BMI



## Conclusion

The WB-PBPK population modeling approach provided an excellent description of the experimental data. Our analysis complements the classic population PK approach since we could mechanistically study the influence of co-factors like age or BMI. The possibility to predict tissue concentrations enables model-based PK/PD predictions for populations of interest not covered by available clinical data.

## References

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