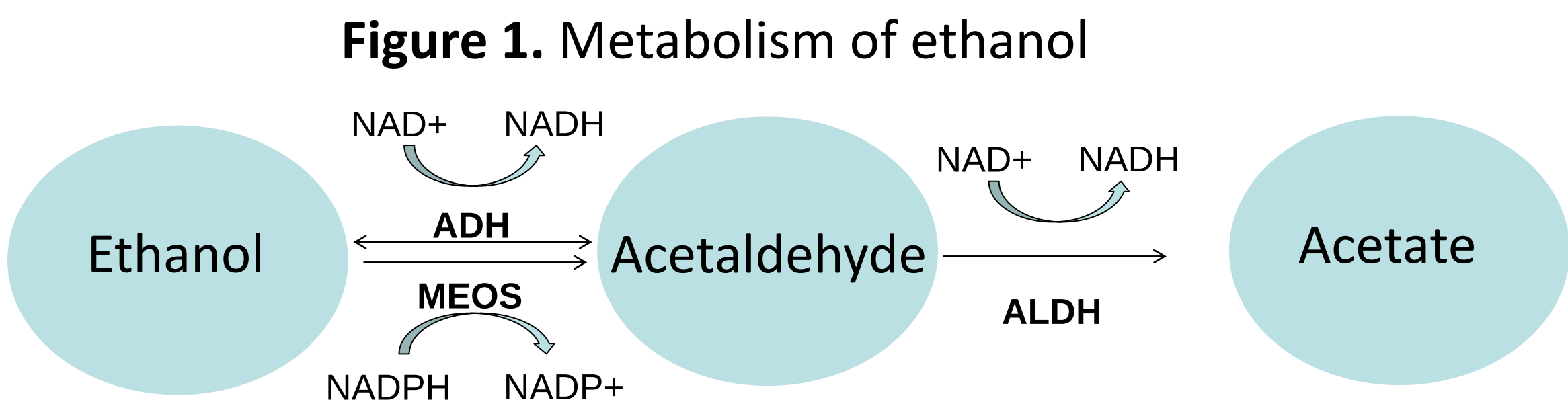


Objective and background

We conducted a cocktail drug-drug interaction study to evaluate the effect of acute ethanol consumption on the most important drug-metabolising cytochrome P450 enzymes, NAT2 and P-glycoprotein. The objective of the present evaluation was to accurately describe internal ethanol exposure in this study.

Primary metabolism of ethanol occurs essentially in the liver and is mainly mediated by a group of alcohol dehydrogenase isoforms, but to a minor extent also by other enzymes including cytochrome P450 CYP2E1. The availability of NAD⁺ limits ethanol oxidation, causing saturating kinetics.



Material and Methods

Subjects: 16 Caucasian healthy volunteers (8 males, 8 females), aged 20 to 52 years old, with a body weight in the range of 54.5 to 97.0 kg.

Study design: Data were obtained from an open-label, single-center, two-way, cross-over study.

In the test period, the initial doses (ml ethanol) were: males, 1.925 * body weight (kg); females, 1.65 * body weight (kg). After 2 hours, the cocktail consisting of omeprazole, tolbutamide, caffeine, dextromethorphan and digoxin was given. Then, the following additional doses of ethanol were given at 4, 8, 12, 16 and 20 h: males, 0.77 * body weight (kg); female, 0.66 * body weight (kg). During the reference period, no alcohol was given, only the cocktail was administered.

Blood alcohol samples were collected at 0 (predose), 1, 4, 5, 8, 13, 16, 26 and 30 h after cocktail dosing and measured by gas chromatography. Breath ethanol concentrations C_B collected at 0, 1, 4, 8, 16 and 30 h after dosing were measured by Draeger breath analyzer Alcotest 7401 plus (Drägerwerk AG, Lübeck, Germany). C_B were assumed to have a linear relationship to blood concentrations C as described by equation 1: C= M * C_B.

Data analysis: Data analysis was performed by the population pharmacokinetic approach using non-linear mixed effects modeling (NONMEM 7.2.0).

Results

Basic model: A one-compartment model with first-order absorption and a Michaelis-Menten elimination pathway was suitable as the basic model and was clearly better than linear or exponential concentration decline (ΔOFV, -9.291). The value of Km could not be estimated and thus was fixed as 0.0821 g/L according to the literature [1].

Covariates analysis: The Stepwise Covariate Model (SCM) implemented backward elimination of covariates was used to analyse covariates. As for covariates, volume of distribution V had a significant relationship with subject body weight (ΔOFV, -152.53), and sex had a small albeit significant effect on maximal elimination capacity VM (ΔOFV, -19.285).

These two covariates were investigated using the following model respectively: $V_{max} = \theta[VM] * (1 + SEX * \theta[Sex \text{ on } V_{max}])$ (0 = Female; 1 = Male); $V = \theta[V] * (weight/71.6) ^ \theta [Weight \text{ on } V]$.

We also tried to use Free-fat Mass (FFM) as covariate and found no significant further improvement of the model, probably because the subjects in our clinic trial all had body normal weight within a narrow range.

Integration of breath ethanol concentrations: Although the data were obtained both from blood and breath ethanol concentrations, they were integrated well with the introduction of equation 1.

Table 1. Population pharmacokinetics parameters estimates in the base and final models, and a 1000 replicate bootstrap

Parameter	Model, mean (RSE%)	bootstrap, mean (95% CI)
Max. elimination rate Vmax (g/h)	6.99 (4%)	6.99 (6.5-7.56)
Effect of sex on Vmax	0.402 (18%)	0.4019(0.258- 0.543)
Concentr. at 50% VM, Km (g/L)	0.0821 FIX	0.0821
Volume of distribution V (L)	31.6 (3%)	31.64 (29.7-34.1)
Effect of weight on V	1.35 (11%)	1.35 (1.07-1.65)
First-order absorption from gut KA (h ⁻¹)	1.4 (8%)	1.39 (1.23-1.64)
plasma/breath conc. ratio M	1860 (2%)	1856 (1780-1940)
IIV Vmax	0.0101 (27%)	0.0101 (0.0038 -0.0143)
IIV KA	0.0341(38%)	0.0341 (0.00789-0.0595)
Additive Error (g/l)	0.00644 (21%)	0.00644 (0.00395-0.00912)

Fig. 2 Goodness of fit plots

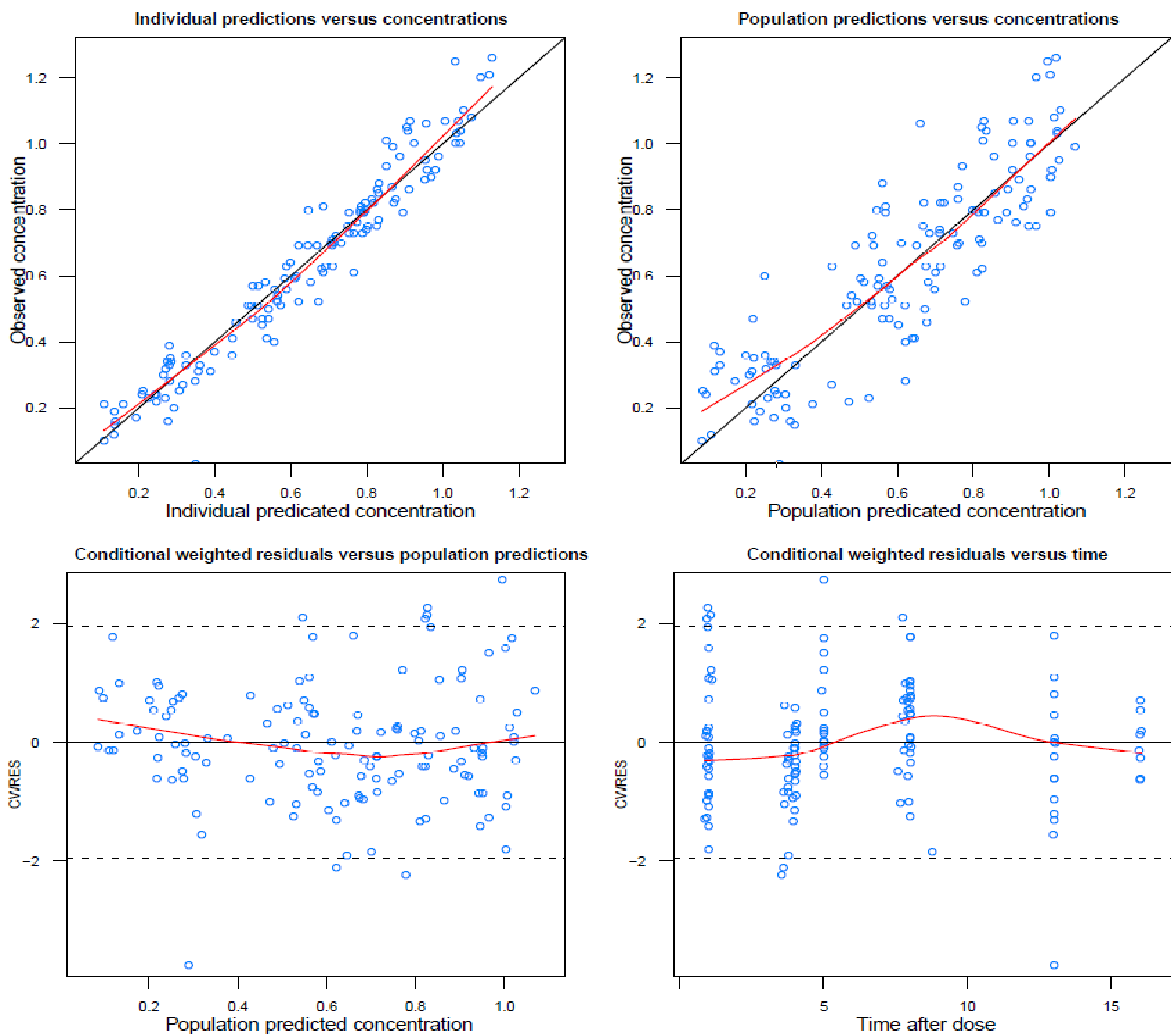
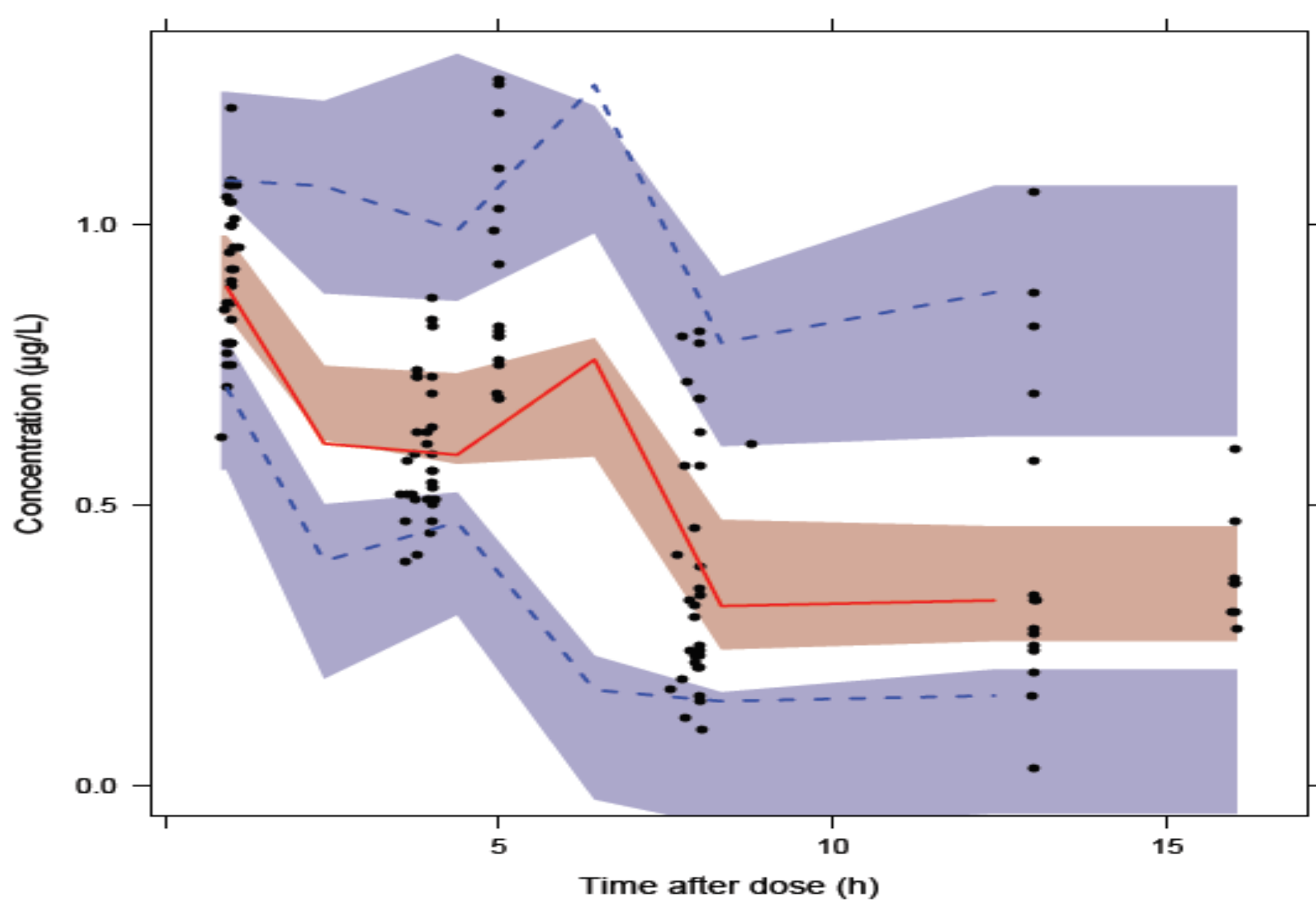


Fig. 3 Visual predictive check plot of the final model



Conclusion

Despite the involvement of multiple enzymes, a simple model was suitable to describe internal ethanol exposure. Results are in accordance with published data.

Reference

[1] Wilkinson PK, Sedman AJ, Sakmar E, Earhart RH, Weldler DJ, Wagner JG. Blood ethanol concentrations during and following constant-rate intravenous infusion of alcohol. Clin Pharmacol Therap 19, 1975. 213-223.