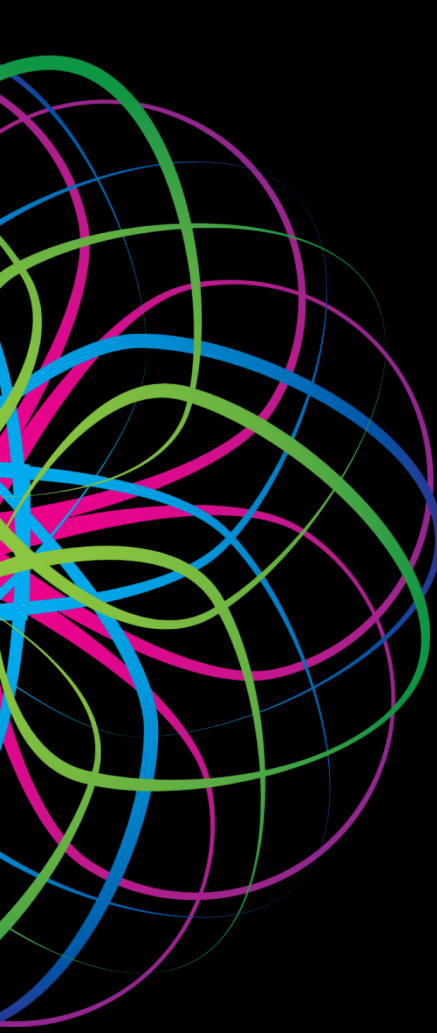




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INTRODUCTION

Modeling relatively uninformative or limited data could benefit from making use of existing knowledge about the described system. Information from literature or previous models might stabilize and improve models by the prior subroutine in NONMEM. The aim of the present study is to evaluate the prior subroutine and its use in aiding model development in such a setting.

METHODS

PK models for THC were developed using NONMEM[®] 7.2. Four datasets were used totaling to 84 subjects (18 female), with a mean age of 22y and BMI of 22.4 kg/m²; a cross-over study with a single dose (9mg pulmonary (IP) and 4.55mg intravenous (IV))^[1], two multiple dose studies (2, 4, 6mg / 2, 6, 6mg IP, 1.5h interval)^[2,3] and a single dose study (5, 6.5 or 8mg oral (PO) of Namisol[®])^[4]. This pooled dataset was used to build the *integrative model*. The *prior model* was based on the 2, 6, 6mg IP study alone (22 subjects), and used results from a model based on the other three studies as a prior. To evaluate performance of the prior subroutine, results of the integrative and prior model were compared.

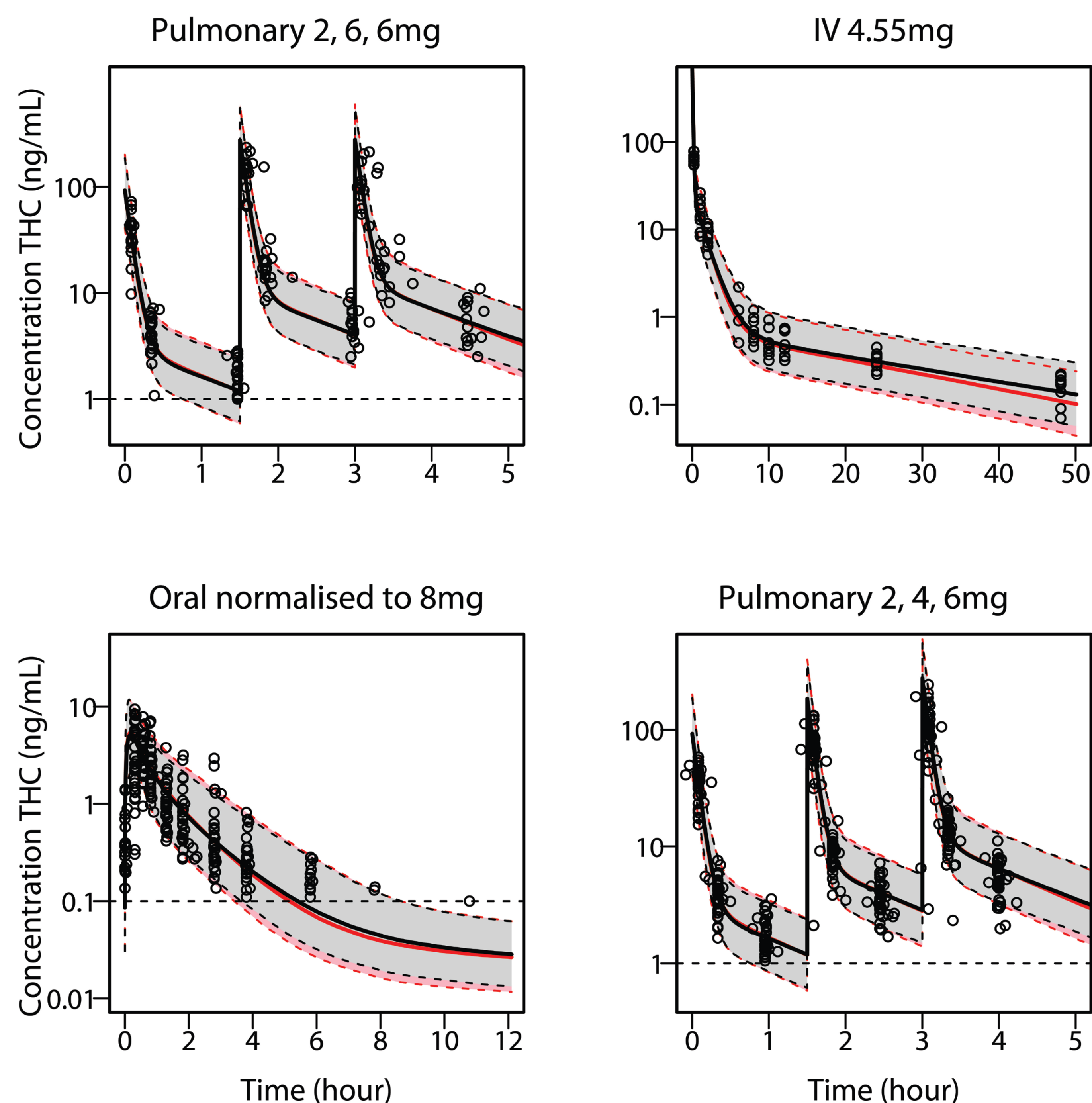


Figure 1: Integrative and Prior Visual Predictive Checks. Black circles, observations; Solid line, typical predicted concentration; Shaded area, 95% prediction interval; Black, integrative model; Red, prior model; Dotted line, LOQ.

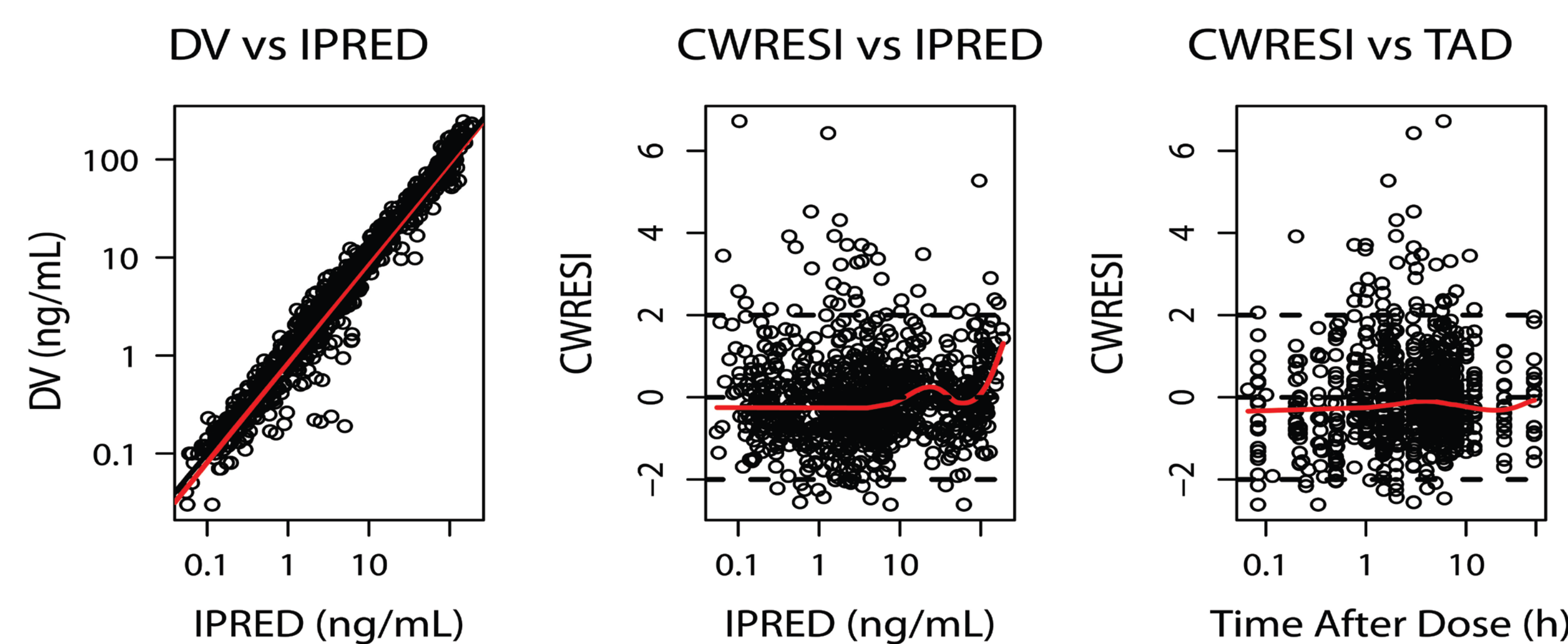
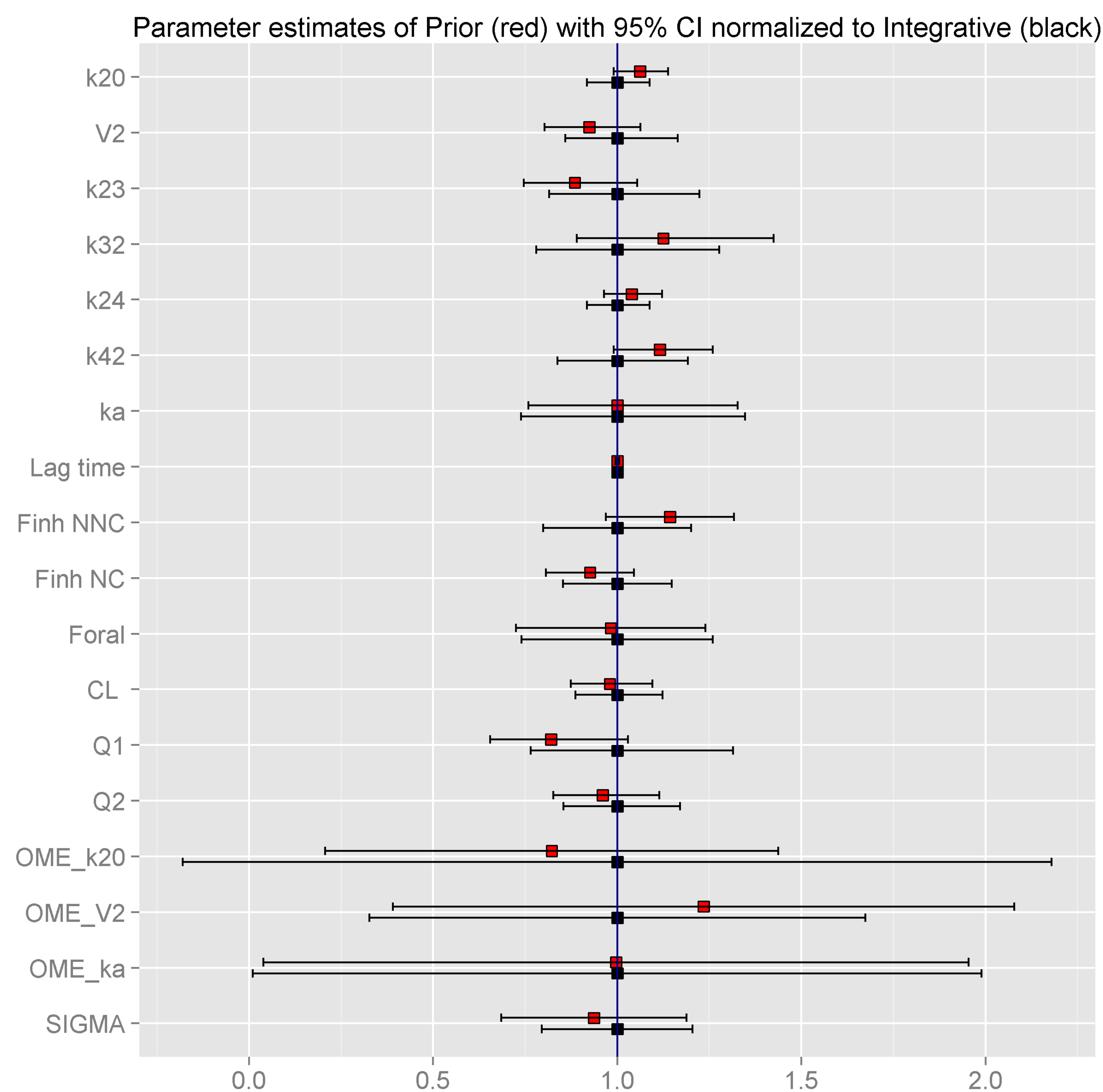


Figure 2: Diagnostic plots integrative model; red line, regression (left) or LOESS line (middle and right) through the observations.

RESULTS

The three-compartment integrative model accurately describes the pooled data. The prior model with the same structural model results in comparable parameter estimates and uncertainties, despite the absence of any information on the oral absorption or the terminal phase of THC in the dataset. The same structural model did not result in convergence when the prior was omitted. An additional benefit was that the prior model had a 17x shorter run time.



CONCLUSIONS

The prior subroutine can be used to supplement information that is missing from raw data. Modeling results were shown to be similar to an integrative approach. The prior subroutine can therefore aid model development and speed up the process.

^[1] Klumpers LE, Cole DM, Khalili-Mahani N, Soeter RP, Te Beek ET, Rombouts SA et al. Manipulating brain connectivity with delta(9)-tetrahydrocannabinol: a pharmacological resting state fMRI study. Neuroimage 2012; 63:1701-1711.

^[2] Kleinloog D, Liem-Moolenaar M, Jacobs G, Klaassen E, de KM, Hijman R et al. Does olanzapine inhibit the psychomimetic effects of Delta(9)-tetrahydrocannabinol? J Psychopharmacol 2012; 26:1307-1316.

^[3] Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Single dose kinetics of deuterium labelled delta 1-tetrahydrocannabinol in heavy and light cannabis users. Biomed Mass Spectrom 1982; 9:6-10.

^[4] Klumpers LE, Beumer TL, van Hasselt JG, Liplaa A, Karger LB, Kleinloog HD et al. Novel Delta(9) -tetrahydrocannabinol formulation Namisol(R) has beneficial pharmacokinetics and promising pharmacodynamic effects. Br J Clin Pharmacol 2012; 74(1): 42-53