Reviewer's report

Title: Human Physiologically Based Pharmacokinetic Model for Propofol

Version: 2 Date: 5 October 2004

Reviewer: Richard Neil Upton

General

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The revised manuscript is a significant improvement, and the decision to remove the clinical implications material is appropriate considering the level of validation of the model. The new material on propofol kinetics and obesity is a useful addition to the literature.

1. The model is highly dependent on the presence of variable lung sequestration after a bolus but not an infusion. The authors have quoted the data of He et al. to support this, but I think their analysis falls into a common and long standing misconception with the analysis of dual indicator of lung kinetics. I tried to address this in a review at one point (Upton RN, Doolette DJ. Kinetic aspects of drug disposition in the lungs. Clin Exp Pharmacol Physiol 26: 381-391 (1999)). In brief, this review showed via modelling that the passage of a drug (with a mean transit time of less than 1 min and no sequestration) through the lungs can appear to have a retention (sequestration) of 66% when compared to a vascular indicator. This apparent sequestration is simply artefact to due to the study design. I don't expect the authors to change their point of view, but I think they should actively pursue evidence for this lung sequestration of propofol. My own analysis of Fig. 1 from the He paper via first-pass modelling suggests that only 10% of the propofol dose is unaccounted for.

2. The unusual method used for curve-fitting remains unjustified and unreferenced. The authors claim that the "weighted residual method" is a common statistical technique for fitting data, particularly in X-ray crystallography. However, when the phrase "weighted residual method" is entered into Google, only 5 hits are returned. When "weighted least squares" is entered, there are 35,900 hits. If something other than "weighted least squares" is used for curve-fitting, it needs to be justified and referenced.

3. The lack of standard errors for the parameter estimates, and correlation between the parameters values, means that the model building process falls short of accepted modelling practice. It is possible to achieve good fits of data with parameter values that are highly correlated or undetermined (that is, they are not a unique solution to the problem). I find it strange that the authors have avoided using the standard least squares curve-fitting routines in Maple that could easily return these values via a Hessian matrix, but went for their poorly documented "weighted residual method".

4. The symbols and abbreviations used remain non-standard.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

Unchanged from earlier review