# Quantitative prediction of human oral bioavailability from animal bioavailability data: Comprehensive analysis of literature data

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## Introduction

Understanding of the oral bioavailability (F) of a new drug candidate is a key factor in the development process, and also from a regulatory perspective. The use of F values in preclinical species for predicting F in humans has long been debated. However, previously published reports on this issue have been limited in study size without a rigorous inclusion criteria, hence containing ambiguous data.

## Aims

The objective of this study was to conduct a comprehensive analysis of F values in humans and corresponding values in preclinical animal species with a view to determine any correlations, and if such correlations can be used for prediction purposes.

## Methods

Data from previous comparisons [1,2] were re-evaluated, with original references obtained wherever possible to ensure integrity of the data. The dataset was then extended using a published database of human F values [3] and literature searches for corresponding animal data. Species considered were mouse, rat, dog and non-human primates (NHP).

Due to the complex nature of bioavailability data a rigorous inclusion criteria (**Table 1**) were applied to ensure a high quality dataset. These criteria were based on an understanding of the issues that can affect estimation of F values.

**Table 1.** Inclusion criteria for bioavailability studies.

| |
|---|
| **1. Oral and intravenous data should be established in the same group.** |
| **2. Species should fall under category of Mouse, Rat, Dog or Non-Human Primate.** |
| **3. AUC should be calculated to infinity or absorption phase should be complete.** |
| **4. Original study data must be included when possible.** |

For compounds with more than one bioavailability study available, the weighted mean for the oral bioavailability was calculated.

Linear regression was applied for oral bioavailability in animal species and human and the coefficient of determination ($R^2$) and the slope and intercept were determined for each species and for the whole dataset. Prediction intervals, calculated by prediction of F in human from F in animal, and the concordance correlation coefficient (ccc) were calculated as a measure of the predictive power of the model.

## Results & Discussion

An extended dataset of 184 compounds was assembled where F values were available for human alongside corresponding value at least in one other animal species of interest. The correlations between human and animal F values were weak (combined dataset or stratified by each species). The results of the linear regression, including coefficient of determination ($R^2$), confidence intervals (CI) are shown in **Table 2**.

**Table 2.** Results of linear regression

| Species | N | Slope | 95 % CI (slope) | Intercept | ccc | $R^2$ | p Value |
|---|---|---|---|---|---|---|---|
| All | 318 | 0.55 | 0.47 - 0.64 | 33.1 | 0.55 | 0.34 | <0.001 |
| Mouse | 30 | 0.51 | 0.18 - 0.83 | 39.5 | 0.44 | 0.25 | <0.005 |
| Rat | 122 | 0.54 | 0.39 - 0.70 | 35.8 | 0.47 | 0.29 | <0.001 |
| Dog | 125 | 0.58 | 0.45 - 0.71 | 26.4 | 0.61 | 0.37 | <0.001 |
| NHP | 41 | 0.69 | 0.55 - 0.83 | 32.9 | 0.70 | 0.69 | <0.001 |

While an $R^2$ value of 0.69 in NHP suggests a reasonable correlation, the resulting wide prediction intervals (PI) (**Figures 1 & 2**) show a lack of predictive power for human bioavailability for the general dataset and each species, including NHP.

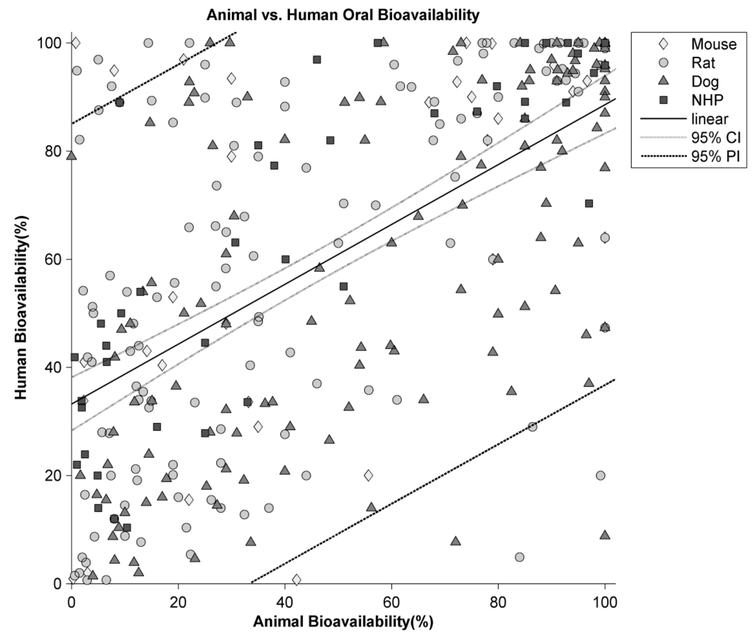


**Figure 1.** Plot of the linear regression analysis for the general dataset, animal versus human oral bioavailability. Diamonds are for mouse, circles for rat, and triangles for dog and squares for non-human primates (NHP).Solid black line represents the mean regression line,

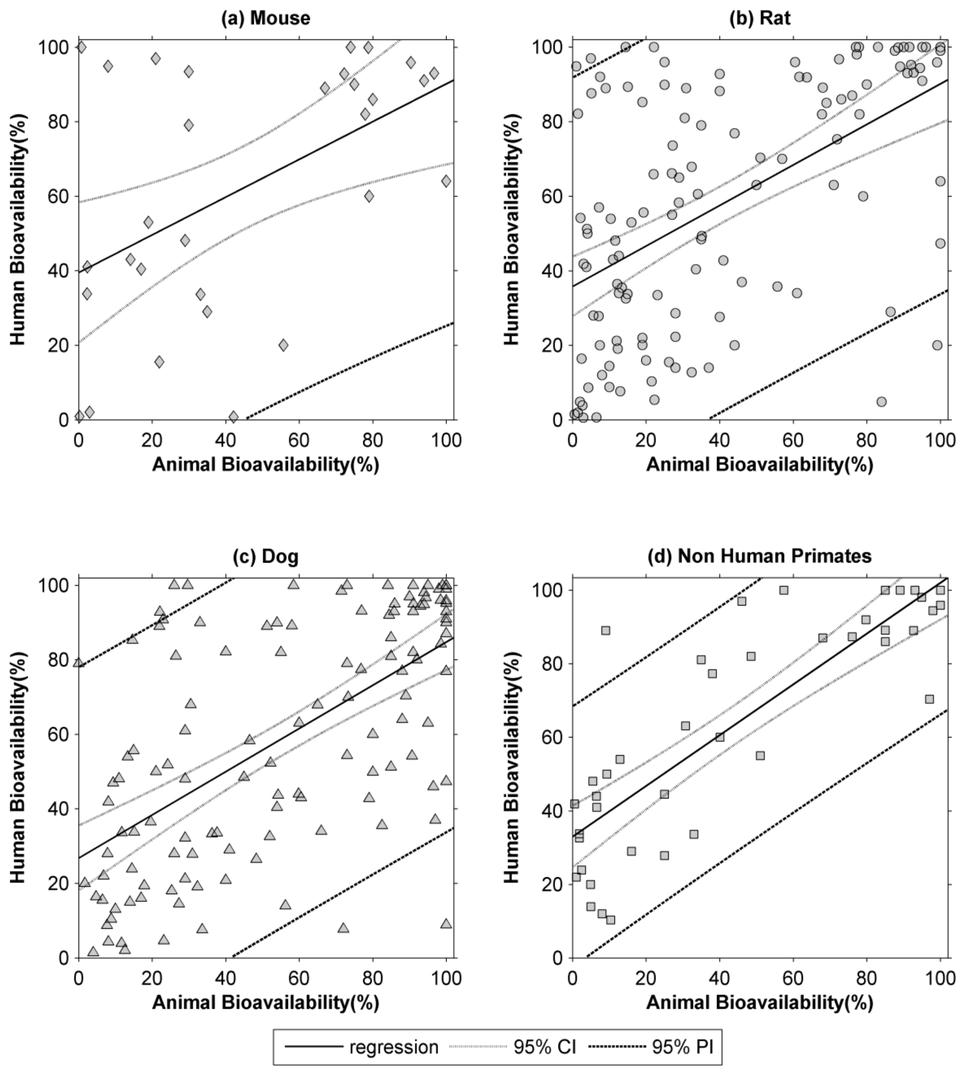


**Figure 2.** Plot of the linear regression analysis for each species.

## Conclusions

An extended dataset, with inclusion criteria to verify the integrity of the data, highlights the difficulties in using animal data to quantitatively predict human bioavailability.

Due to the lack of predictive power, it is suggested that, although the relationships may be useful for qualitative decision making (high/low bioavailability), more mechanistic models resulting from an understanding of interspecies differences concerning physiology, metabolism and transport, are required for quantitative predictions of F values.

## References

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