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C4ME Supplement

The application of allometric scaling to regulatory toxicology

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Link to YouTube Video:
https://youtu.be/OMsaqJGv5rc

Background

When chemicals pose a threat to human health, a theoretical safe dose for human exposure must be determined. This is the goal of chemical risk assessment in regulatory toxicology. Initially, animal toxicology studies are evaluated. Animal studies provide a means of predicting human toxicities when insufficient human data is available.

Different regulatory bodies use different approaches for inter-species dose extrapolation. This is where uncertainties arise. In our study, the extrapolation process used by the United States (U.S) Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) was compared. The FDA uses allometric scaling for chemical dose extrapolation, whilst the EFSA does not use allometric scaling. Therefore, our study investigated the role of allometry in inter-species dose extrapolation.

Allometry can be defined as adjusting data to allow for differences in body size and function between species. (1) The FDA adjusts chemical doses according to the body surface area, in order to account inter-species differences in metabolic rates. (2) However, drawbacks of allometry are also discussed in the literature. We aimed to discover whether the application of allometry to chemicals tested by the EFSA had the potential to affect regulatory decisions and, hence, determine the applicability of allometry to hazard characterization (dose-response relationship) in regulatory toxicology.

Methods

The Committee on Toxicity (CoT) reviews EFSA toxicity data on chemicals in food, consumer products and the environment. (3) Chemical toxicity data was collected from open source CoT records, available at https://cot.food.gov.uk. Ethical approval was not required since the research project was limited to open source data. A total of 560 papers, from February 2008 to January 2020, were assessed in our study.

The No Observed Adverse Effect Level (NOAEL), animal species used, uncertainty factor, exposure assessment values (mean and 97.5th percentile) were noted for each chemical found in the records. Chemicals were not included in our study if there were insufficient information for analysis. Interestingly, some chemicals had multiple exposure assessment values, as multiple age groups were assessed. Therefore, 43 data points (chemicals with corresponding exposure assessment age groups) were gathered in total.

For each data point, doses were calculated with allometry using the FDA's Maximum Recommended Starting Dose (MRSD) approach, and without allometry using the EFSA's Health Based Guidance Value (HBGV) approach. (2,4) Absolute differences were calculated between doses with and without allometry. Absolute differences were then compared against exposure assessment values to assess if the data points were significant. Ratios were calculated between doses with and without allometric scaling to assess the extent of the dose difference. An alpha of <0.05 was used to determine statistical significance of allometry.

Results

Thirty-nine out of 43 data points had absolute differences greater than the mean exposure assessment values. Only 28 out of 43 data points had 97.5th percentile exposure assessment values quoted in CoT records. Of these 28 data points, 20 had absolute differences greater than the 97.5th percentile exposure assessment values. Overall, 20 data points had absolute difference greater than both the mean and 97.5th exposure assessment values. The absolute differences for the 20 data points ranged from $2.364 \star 10^{\wedge -5}$ to 2.097.

Ratios, between doses with and without allometric scaling, ranged from 1.1 to 12.3. All 43 rations are shown on figure 1. The largest dose decrease after allometry was approximately 92%, and was seen in bisphenol A, diethyphthalate, acetyl-deoxynivalenols and deoxynivalenols. A 9% dose decrease after allometry was seen in both zearalenone (in 4 to 12 month olds) and ochratoxin A (all age groups). However, the absolute difference of zearalenone was greater than both the mean and 97.5th exposure assessment values, wheres the absolute difference of ochratoxin A was not.

The 95% confidence interval of proportion between the total number of data points and significant data points (when compared to the mean exposure assessment values) was 0.779- 0.974.

Discussion

From the 95% confidence interval of proportion calculated, It was evident that a majority of chemicals were affected by allometric scaling in our study. As shown by the data points "zearalenone (in 4 to 12 month olds)" and "ochratoxin A (all age groups)", it was also clear that similar dose decreases can lead to different toxicological outcomes. Therefore, the significance of allometry may not be down to the extent of the dose difference, but the chemical and/or age group itself.

Published evidence by Schneider et al., also support the use of allometry in toxicological risk assessment. (5) However, based on our study alone, it is difficult to conclude that allometric scaling alone could affect regulatory decisions. This is because our study contains some limitations and gaps in knowledge. For instance, only 43 data points were included in our study. Therefore, larger and in-depth studies are required to validate our findings. In the future, it may also be worth investigating intrinsic chemical properties, such as lipophilicity, to understand which chemicals are affected by allometry. In addition, physiologically-based toxicokinetic modelling could be utilised to identify the accuracy of allometry in future studies. (6)

It is also important to note that allometry disregards many inter-species variation, such as genetic polymorphisms affecting species' toxicokinetics and toxicodynamics. (7) Therefore, allometry may not be reliable on its own. It may be that allometry should be used in combination with advancements in computational toxicology. This includes mathematically-modelled uncertainty factors or use of toxicogenomic data in animal studies. (8, 9)

Lessons Learnt

Since allometric scaling is a concept dating back to 1930s, many papers had been published. Therefore, it was necessary to systematically evaluate older and recent publications. Formulating questions after reading the literature helped me conduct more focused database searches and keep up with advancements in inter-species dose extrapolation.

This data analysis project also involved evaluating many CoT papers. Hence, effective time management was of upmost importance. Setting myself deadlines every week and making daily "to-do" lists helped me keep up with the workload. Some mistakes were made when recording chemical data on Microsoft Excel, which helped me realise the importance of proof reading with each data entry. Overall, this project challenged my critical thinking and organisational skills.

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Figures

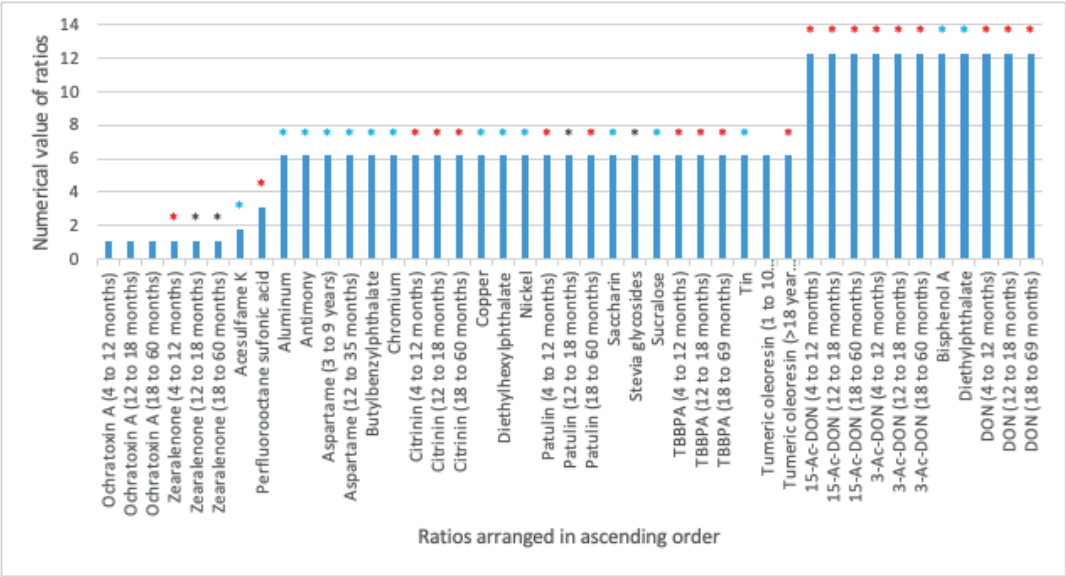

Figure 1: Graph showing the ratios arranged in ascending order. *The ratios for 43 data points range from 1.1 to 12.3. Six data points had ratios of 1.1, one data point had a ratio of 1.8, one data point had a ratio of 3.1, 24 data points had ratios of 6.2, and 11 data points had ratios of 12.3. Data points with absolute differences greater than both the mean and 97.5th percentile exposure assessment values are denoted as *. Data points with absolute differences greater than the mean exposure assessment values, and those with no reported 97.5th percentile exposure assessment values are denoted as *. Data points with absolute differences greater than only the mean exposure assessment values are denoted as *. Data points with absolute differences not greater than both the mean and 97.5th percentile exposure assessment values have no asterisks. DON= Deoxynivalenol; TBBPA= Tetrabromobisphenol A*

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