Dr Kevin Healy

School of Natural Sciences

Zoology Building

Trinity College

Dublin 2, Ireland

healyke@tcd.ie

Tel: + 353 85 155 7282

28 April 2017

Dear Editor,

Please consider our manuscript entitled “Snake venom potency and volume are driven by metabolism, dimensionality and prey characteristics” for publication as a research article in *Proceedings of the National Academy of Sciences.*

People have long been fascinated by venomous snakes because of their ability to cause death and harm. Venom is also of interest to medical researchers due to both human physiological responses and potential as a source for new drugs. Despite our interests, little is known about the evolutionary drivers of snake venom despite the potential to explain vast differences in toxicity, (e.g. inland taipan can kill 100,000’s of prey while the marbled sea snake holds minuscule amounts of weak venom). However, a major barrier allowing a consistent comparative approach of venom is the difficulty of comparing potencies where measures are based on very different lab (model) species many of which are unrelated to the snake’s natural prey. We overcome this by taking a novel approach by accounting for the evolutionary distance between the model species and the types of species naturally in their diet.

Using this approach, we find that potency is greater in model species closely related to natural prey – indicating that venom is adapted to incapacitate common prey. Examining patterns in the venom yield a species possess, we also find that yield varies in a manner consistent with size-related changes in metabolic rate, rather than that predicted by the scaling of snake and prey body mass. Finally, we show that increased habitat dimensionality, a previously neglected factor in venom evolution, reduces the amount of venom a species possesses.

These findings have novel implications for our understanding of not only the evolution and ecology of venom in snakes, but also for other venomous groups and predator trait evolution in general. Our results not only resolve a long standing debate within the field of venom evolution relating to the overkill versus prey-specific hypotheses, but also provides novel findings regarding the role of predator body size, prey size and habitat dimensionality in venom evolution.

We think our paper will make an excellent fit for PNAS due to its general appeal to both the public and research fields ranging from the biomolecular sciences to ecology and evolution. Our paper also reflects similar papers on venom evolution and macroecological patterns published in PNAS (1, 2)

We look forward to hearing from you in due course

Kevin Healy, on behalf of my co-authors

The manuscript contains 41,983 characters including spaces in the main text, and four figures. Using the online page estimation tool our paper requires 6 pages. None of the material has been published or is under consideration elsewhere.

**Suggested Referees**

Dr Bryan Fry,

School of Biological Sciences,

Faculty of Science [bgfry@uq.edu.au](mailto:bgfry@uq.edu.au)

Dr Nicholas Casewell,

Liverpool School of Tropical Medicine, [nicholas.casewell@lstmed.ac.uk](mailto:nicholas.casewell@lstmed.ac.uk)

Dr Ulrich Brose,

Friedrich Schiller University Jena [ulrich.brose@idiv.de](mailto:ulrich.brose@idiv.de)

**References**

1. Vonk FJ*, et al.* (2013) The king cobra genome reveals dynamic gene evolution and adaptation in the snake venom system. *Proceedings of the National Academy of Sciences* 110(51):20651-20656.

2. Kodric-Brown A, Sibly RM, & Brown JH (2006) The allometry of ornaments and weapons. *Proceedings of the National Academy of Sciences* 103(23):8733-8738.