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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 articles in *Proceedings of the National Academy of Sciences of the United States of America.*

Snake venom has fascinated humanity due to its ability to cause death and harm. It features across many cultures and is of interest to researchers due to both the medical consequences of snakebites ([1](#_ENREF_1)) and its potential as a source for new drugs ([2](#_ENREF_2)). Even at the subconscious level, snake venoms potential danger is likely to be an innate fear found in all humans ([3](#_ENREF_3)).

However, despite the level of interest in snake venom and its evolution ([4](#_ENREF_4), [5](#_ENREF_5)) little is known regarding why some venoms are so lethal and why other are effectively harmless. For example, the Inland taipan can kill 100,000’s of prey while the marbled sea snake can no longer deliver its minuscule amounts of weak venom ([6](#_ENREF_6)). Comparative approaches typically allow for the drivers of such differences to be identified however a major barrier to such a comparative analysis of venom is the difficulty of comparing potencies of venoms that are measures on lab species which are not found in their diet. Here, we overcome this barrier by using the novel approach of including the evolutionary distance between a species diet and the model used to measure its venoms potency.

This approach not only allows us to conducted a comparative analysis across all the major groups of venomous snakes but also allowes us to show that snake venom in general has evolved to be more potent towards prey species. This finding settles a long standing debate on whether prey-specific venoms are the rule rather than the exception ([2](#_ENREF_2), [7-11](#_ENREF_7)).

We also show that metabolic rate, and not predatory-prey body size scaling, is the primarily driver of venom quantity, a result that will contribute to the ongoing debate of the ecological importance of the energetic cost of venoms. Finally, we also show that habitat dimensionality, a previously neglected factor that may affect predatory trait evolution, reduces the amount of venom available in 3-dimensional habitats.

These findings are both highly significant and novel with implications for our understanding of not only venom evolution in snakes and other groups but also for predator trait evolution in general. We not only resolve a long standing debate within the field of venom evolution but also provide novel findings regarding the effects of body size and habitat dimensionality on the ability of a predatory trait to kill prey. Our approach will also open up the possibility of similar comparative analysis in other venomous groups.

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 ([5](#_ENREF_5), [12](#_ENREF_12)).

We look forward to hearing from you in due course

Kevin Healy, on behalf of my co-authors

The manuscript contains xxx words in the main text, and we estimate the paper will require 6 pages. None of the material has been published or is under consideration elsewhere.

**Suggested Referees**

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We could go for the metabolic people such as Jim Brown?

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