Author response to Kingston's comment on "An Increase in Dietary Supplement Exposures Reported to US Poison Control Centers"

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We thank Drs. Kingston, Wong, and Khan for their comments but disagree with a number of their statements.

Although our study analyzed exposures that are included in the broad NPDS category "dietary supplements/herbals/homeopathic," this is not a limitation of the study, and contrary to their assertion, the Ma huang/ephedra information is both relevant and critical to report. Ma huang/ephedra is an important example of a dietary supplement category that was recognized by the FDA to pose an unreasonable risk of illness or injury. This FDA action prompted a ban on these products. We believe it is both appropriate and important to use a large national database such as NPDS to monitor the effects of this FDA action, with information from before and after the ban. Both the rate of exposures and the number of serious outcomes from Ma huang/ephedra products dropped significantly following the ban. As discussed in our paper, this provides evidence of the effectiveness of FDA regulatory actions in protecting consumers.

Data from Table 1 of our study demonstrate that approximately one third of exposures resulted in a minor or no effect [1]. This was reassuring to find. However, because of the significant increase in the number of exposures over the

13 years of the study, it is important to take a "deeper dive." We evaluated subcategories of products, which might mirror the Ma huang/ephedra group experience, with potentially higher risk of injury but not previously reported because they are obscured by other, more benign, outcomes. Data on these product subcategories, such as yohimbe and energy products that have higher proportions of adverse medical outcomes, are reported in our study.

Medical outcomes were reported both individually (no effect, minor effect, moderate effect, major effect, and death) and collectively combined into a "serious outcomes" category of moderate effect, major effect, and death. Their assertion that this misleads readers to equate these serious outcomes as life-threatening brings their own bias to the interpretation of our choice of words. We, however, clearly define these categories in the methods section to avoid misinterpretation. Additionally, the data reported in Table 1 show that > 37,000 patients were evaluated in a health care facility, including > 4500 patients who were admitted for medical treatment, which supports that there are, in fact, serious outcomes associated with these products.

Their concern about inclusion of incidents coded as death requires a response. Fatalities reported to NPDS go through a separate multi-level review process prior to inclusion in the database. The review includes (1) case review at the reporting poison center, often including autopsy results and post-mortem toxicology results along with preparation of a fatality abstract by the center, (2) peer review at the AAPCC level, and (3) final review by the AAPCC fatality committee chair. Only after completing this multi-level review does a case remain as a fatality in the NPDS database. While reports of fatalities were relatively low, they clearly merit reporting.

Their comments regarding the use of sales data as the denominator is a point of view commonly proposed by the industry. As described in the methods section, we reported

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frequencies and population-based rates of exposure, which are accepted public health epidemiologic metrics. We noted that both the number and rate of exposures were rising. Use of sales data as a denominator, as they suggest, reflects a mindset that exposures are expected to go up as sales increase. This is a troubling viewpoint because exposures and the adverse medical outcomes of those exposures should not be regarded as the expected price of doing business. We strongly urge a public health approach to this public health issue and call on the FDA to strengthen its regulatory oversight as described in our article.

Compliance with Ethical Standards

Conflicts of Interest None

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References

1. Rao N, Spiller HA, Hodges NL, et al. An increase in dietary supplement exposures reported to US poison control centers. *J Med Toxicol.* 2017;13(3):227–237.