

*Alcohol and Alcoholism* publishing standards for animal research

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Dear Prof. P. De Witte,

On behalf of our more than five million members and supporters, I am writing to express concern that *Alcohol and Alcoholism* appears to have published scientifically questionable studies. Two recently published manuscripts, “Hops (*Humulus lupulus*) Content in Beer Modulates Effects of Beer on the Liver After Acute Ingestion in Female Mice” in the September 2016 issue and “Beer Is Less Harmful for the Liver than Plain Ethanol: Studies in Male Mice Using a Binge-Drinking Model” in the May 2015 issue, attempt to make the case that beer or beer ingredients may be less harmful to the liver than hard spirits.

Both studies, conducted by the German Brewing Industry-funded Bergheim group, provide as a rationale that their findings could have consequence for human health, namely liver-related mortality brought on by chronic alcohol abuse, and ask whether or not beer or beer ingredients may be less damaging to the liver than ethanol. However, as opposed to the chronic alcohol abuse cited as a factor in human mortality, mice in these studies are given a single bolus of alcohol in a one-time “binge-drinking” model. While we are thankful that the animals had to endure this unwanted intoxication only once, it is not clear that these experiments address the type of liver damage seen in chronic or even early alcohol-related liver damage.

Motives aside, the results presented further question the applicability of these experiments to human health. This is an important factor, considering that mice do not naturally consume alcohol. In both studies, inducible nitric oxide synthase (iNOS) was elevated in the livers of

ethanol-force-fed mice but not beer-force-fed mice, leading in part to the authors' conclusion that beer may be less harmful to the liver than distilled alcohol.

However, the distribution and regulation of iNOS is different between mice and humans; while some human cells have been shown to express iNOS under severe disease conditions, this expression is more selective and differently controlled than it is in the mouse and is not stimulated by the same variables (Zschaler, Schlorke and Arnhold; Denis). Similarly, cross-species variations in the binding of hepatic transcription factors are substantial, as are transcription factor concentrations, chromatin modifications, and protein interactions (Odom, Dowell and Jacobsen), a point that makes the relevance of hepatic gene expression in these recent studies uncertain as well.

Fundamentally, both of these manuscripts describe ethanol consumption in a species that does not naturally consume it, therefore the hope must be that these experiments will provide insight into the health consequences of human ethanol consumption. Why then, would researchers choose to explore aspects of mouse physiology that are notably unhuman, such as immune activation (Zschaler, Schlorke and Arnhold)? Dr. Elias Zerhouni, former director of the National Institutes of Health, the largest funder of biomedical research in the world, noted in a June 21, 2013 NIH record: "We have moved away from studying human disease in humans. We all drank the Kool-Aid on that one, me included. ... The problem is that it hasn't worked, and it's time we stopped dancing around the problem. ... We need to refocus and adapt

new methodologies for use in humans to understand disease biology in humans.”

Forward-thinking scientists are embracing effective non-animal research methods, including cutting-edge organs-on-chips, which use human tissues and cells to create miniature, functioning human organs to study diseases and treatments. As a respected journal which publishes influential papers using human-relevant data (including many of its most cited and news-worthy articles), we hope that *Alcohol and Alcoholism* will also recognize that non-animal research methodologies are the most promising avenue toward a brighter future for both animal and human health and increase scrutiny of submitted animal studies.

Thank you for your attention to this matter and I look forward to your feedback.

Sincerely,

Emily Trunnell, Ph.D.

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### **Conflicts of Interest Statement**

The author declares no conflict of interest.

### **References**

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