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Dear Dr. Yaegashi:

Thank you in advance for your time and consideration. I'm writing on behalf of People for the Ethical Treatment of Animals U.S.—PETA entities have more than 9 million members and supporters globally—to share some disturbing information about an animal study conducted at the Graduate School of Medicine of the Tohoku University School of Medicine and funded by Ajinomoto Co.

**Based on the information below, this study should not have been approved by Tohoku University's internal governing body. We respectfully ask that you investigate this matter, reconsider accepting funds from Ajinomoto Co., and prohibit similar studies from being carried out at your school.**

The study, titled “Oral Histidine Intake Improves Working Memory Through the Activation of Histaminergic Nervous System in Mice,” was coauthored by six individuals, all affiliated with the Graduate School of Medicine of the Tohoku University School of Medicine.<sup>1</sup> The experimenters inserted a cannula into the brains of mice, filled their cages with water for 48 hours in order to force the animals to become sleep-deprived and fatigued due to water-floor stress, injected histidine and other substances into their brains, forced them to go through a maze, and then killed and dissected them. The experimenters also inserted a cannula into the brains of rats, starved them, force-fed them L-histidine, and then killed and dissected them.

These experiments were extremely stressful and cruel because the mice were still conscious when subjected to sleep deprivation. The water in their cages prevented their natural grooming behavior and nesting behavior, which are important for their well-being.<sup>2</sup> The water also increased the mice's heat loss and exacerbated their cold stress, which is known to occur at standard laboratory housing temperature, such as the  $23 \pm 1^\circ \text{C}$  used in this study.<sup>3</sup>

Furthermore, this research was unnecessary because L-histidine is commonly available as a

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<sup>1</sup>Nakamura T, Naganuma F, Kudomi U, Roh S, Yanai K, Yoshikawa T. Oral histidine intake improves working memory through the activation of histaminergic nervous system in mice. *Biochem Biophys Res Commun.* 2022;609:141-148. doi:10.1016/j.bbrc.2022.04.016

<sup>2</sup>Bailoo JD, Murphy E, Boada-Saña M, et al. Effects of cage enrichment on behavior, welfare and outcome variability in female mice. *Front Behav Neurosci.* 2018;12:232. doi:10.3389/fnbeh.2018.00232

<sup>3</sup>Vialard F, Olivier M. Thermoneutrality and immunity: How does cold stress affect disease? *Front Immunol.* 2020;11:588387. doi:10.3389/fimmu.2020.588387

supplement for humans<sup>4</sup> and numerous clinical studies on L-histidine have already been published.<sup>5</sup> Researchers could have conducted a study using human volunteers. Alternatively, advanced *in vitro* and computational models—which are widely used for investigating the mechanisms of how foods affect human health—could have been employed.

This experiment on animals violated the 3Rs principle (replacement, reduction, and refinement). In addition, Article 41 of Japan’s Act on Welfare and Management of Animals states, “[C]onsideration shall be given to the appropriate use of such animals by such means as using alternative methods to that of the use of animals as much as possible.”<sup>6</sup> This directive corresponds with “replacement” in the 3Rs principle. Because the study could have been conducted on human volunteers or used other animal-free methods, it was in apparent violation of the 3Rs principle and the Act. Other Japanese regulations also do not require tests on animals in order to substantiate health claims for foods and ingredients,<sup>7</sup> which is relevant because L-histidine was examined in the study as a health-promoting food ingredient.

The latest World Animal Protection ranking for Japan in the Animal Protection Index is E (on a scale of A to G, in which A is the best), and the portion regarding laws that apply to animals used for experiments is also E.<sup>8</sup> In Japan—unlike in some other countries—following the guidelines for the welfare of animals used in experiments is largely voluntary. Therefore, individual governing entities have more responsibility to uphold the standards. As the dean of the Graduate School of Medicine of the Tohoku University School of Medicine and the chair of its Animal Experiment Facility Steering Committee, you have the responsibility to ensure that studies on animals conducted at your school follow international best practices.

May I please hear from you by October 15, 2022, regarding this important matter? You can contact me at [FrancesC@peta.org](mailto:FrancesC@peta.org). Thank you.

Sincerely yours,



Frances Cheng, Ph.D.  
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<sup>4</sup>Google shopping search results for “[l-histidine supplement](#)”

<sup>5</sup>Thalacker-Mercer AE, Gheller ME. Benefits and adverse effects of histidine supplementation. *J Nutr.* 2020;150(Suppl 1):2588S-2592S. doi:10.1093/jn/nxaa229

<sup>6</sup>Act on Welfare and Management of Animals (Act No. 105 of October 1, 1973). Last revised May 30, 2014. Accessed April 21, 2022. [aigo\\_kanri\\_1973\\_105\\_en.pdf \(env.go.jp\)](#)

<sup>7</sup>PETA. (Communication with CAA.) July 22, 2020. Accessed April 21, 2022. [20200722-CAA-to-PETA.pdf](#)

<sup>8</sup>World Animal Protection. Animal Protection Index (API) 2020 Japan: Ranking E. March 4, 2020. Accessed April 21, 2022. [api\\_2020 - japan.pdf \(worldanimalprotection.org\)](#)