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CLARITY-BPA Program in Rats: Is It Translatable to Humans?

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The Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) program was the most comprehensive study to date examining a full range of health effects of varying bisphenol A (BPA) exposure in rats. The major concern of the CLARITY-BPA program that has not previously been discussed is whether exposing rats to varying doses to BPA is translatable to humans, even at the "typical" exposure ranges for humans. This perspective will provide evidence that the vast majority of pharmaceutical drug development and other trials in animals have not been replicated in human randomized studies. Similarly, to truly understand whether BPA exposure affects human health, clinical trials are needed to examine BPA administration in humans in controlled settings.

Freeform/Key Words: bisphenol A, diabetes, CLARITY, obesity, oral consumption

Bisphenol A (BPA), a high-volume chemical used to produce polycarbonate plastics and epoxy resins, has been used in consumer products for >50 years. BPA has attracted national media attention and consumer interest, because human exposure is widespread, with detectable urine levels in 92% of the US population. The Food and Drug Administration (FDA), with a mission of protecting public health, has been involved in BPA research for years. The American Chemical Board and federal agencies internationally have insisted that low-dose exposure to BPA is safe. However, a striking discrepancy was found in the results, such that academic researchers consistently showed that low-dose BPA exposure in mice and rats had negative health consequences but federal researchers did not find similar effects. To address this discrepancy, in 2012, the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) program was initiated and remains the most comprehensive study to date examining a full range of health effects of various BPA exposures in rats [1].

The program, with a cost of ~$34 million, was a collaborative effort by the National Institute of Environmental Health, National Toxicology Program, US FDA, and 14 academic scientific researchers. In February 2018, before the core report was available and before the academic researchers had been consulted, the initial FDA press release by Steven Ostroff, MD, Deputy Commissioner for Foods and Veterinary Medicine, stated "Overall, the study found minimal effects for the BPA-dosed groups of rodents…our initial review supports our determination that currently authorized uses of BPA continue to be safe for consumers" [2]. This press release was highly debatable, as Frederick Vom Saal [3] persuasively addressed fatal flaws in the study design and outcome measures, raising questions about the results and the FDA press release. However, a major concern of the CLARITY-BPA program and FDA press release that has not previously been discussed is whether exposing rats to varying doses

Abbreviations: BPA, bisphenol A; CLARITY-BPA, Consortium Linking Academic and Regulatory Insights on BPA Toxicity; EPA, Environmental Protection Agency; FDA, Food and Drug Administration.

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of BPA is translatable to humans, even at the "typical" exposure ranges for humans. Clearly, animal research is necessary to lay the foundation and discover the potential mechanisms of BPA exposure. However, humans are anatomically and physiologically vastly more complex than rats, mice, or other animals.

The research data have consistently shown that studies using rats and mice might not necessarily be translatable to humans. For example, animal work is essential for pharmaceutical drug development and toxicity; however, for drug approval to occur, randomized trials are required in humans. The vast majority of these drug development and other trials (≥67%) in animals have not been replicated in human randomized studies. Based on these and other studies, Richard Klausner, MD, former director of the National Cancer Institute, stated to the Los Angeles Times "The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades—and it simply didn't work in humans" [4]. Another example is the discovery of the hormone leptin. In 1994, Jeffrey Freidman discovered and characterized the hormone leptin in obese mice. Studies of mice have consistently shown that leptin administration reduces obesity [5]. Thus, this single hormone, secreted from adipose cells, was widely viewed as the biological link to obesity with the potential to positively affect widespread human health. However, the so-called antiobesity hormone leptin has had no real effect on reducing obesity in humans. Leptin administration in humans does not lower weight or obesity in nondeficient adults [5], and leptin is now considered an antienergy-deficit hormone. Finally, diethylstilbestrol, a synthetic estrogen used in human medicine to prevent miscarriages and as a cancer treatment, initially had minimal effects in chickens [6]. In the 1970s, diethylstilbestrol use during pregnancy was found to be related to vaginal cancer in the children of women who had been given the chemical during pregnancy. Subsequently, the FDA banned diethylstilbestrol use during pregnancy. Thus, some caution is warranted when trying to extrapolate animal findings to humans.

Regarding BPA, human exposure is extensive, and observational and cross-sectional studies have consistently showed that BPA exposure is related to negative health consequences. BPA has been identified as contributing to obesity and has been linked to cardiovascular disease in adults. The National Health and Nutrition Examination Survey, Nurses' Health Study II, and other cross-sectional data have shown associations between urinary BPA concentrations and type 2 diabetes, prediabetes, insulin resistance, and elevated hemoglobin A1c levels. Thus, the chronic influence of BPA exposure has currently only been observed through epidemiological studies, and the most important adverse effects of BPA appear to be caused by longer term low-dose exposure.

To truly understand whether BPA exposure affects human health, BPA must be administered to humans. As peculiar as this might seem, numerous studies have already administered BPA to humans in a controlled setting, with no reported gastrointestinal side effects or unintended participant harms. Several well-controlled pharmacokinetic studies have orally administered BPA at doses from 20 to 100 μg/kg body weight to humans. Recently, two clinical experimental studies examined the effects of orally administered BPA on the indexes of glucose metabolism. BPA was administered at the US Environmental Protection Agency (EPA) safe dose of 50 μg/kg body weight and the European Food Safety Authority recommended dose of 4 μg/kg body weight to adults [7]. The results indicated that a single administration of BPA at the US EPA safe dose had an immediate effect on lowering glucose, insulin, and C-peptide concentrations in response to an oral glucose tolerance test. These results have been supported by another experimental study showing that a single administration of BPA at the US EPA safe dose suppressed insulin and C-peptide concentrations in response to glucose infusion [8]. Several conclusions can be drawn from these human studies. First, BPA administration in humans is feasible, with no reported gastrointestinal distress or unintended participant harm. Second, BPA administration at the US EPA safe dose, surprisingly, had an immediate effect on lowering the indices of glucose metabolism, suggesting that BPA has an effect on the gastrointestinal absorption of glucose, hepatic glucose production, pancreatic insulin secretion, and/or insulin sensitivity. Finally, the results from these human studies have laid the foundation for future clinical

experimental trials to test the direct effects of longer term orally administered BPA on human health. Our laboratory is currently studying whether 4 days of orally administered BPA has an effect on the pathogenesis of diabetes using the reference standard measures, including hepatic glucose production and muscle insulin sensitivity via euglycemic hyperinsulinemic clamp technique with stable glucose isotope infusion (ClinicalTrials.gov Identifier, NCT03771066).

Given the lack of translation of animal data to human relevance, the CLARITY-BPA program results in rats and the FDA press release that BPA is safe might not be translatable to human exposure and potential negative health effects. However, the program has laid the groundwork for future human experiment studies. To fully understand whether different doses of BPA affect human health, well-controlled clinical trials are required, similar to pharmaceutical drug trials.

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References and Notes

1. Schug TT, Heindel JJ, Camacho L, Delclos KB, Howard P, Johnson AF, Aungst J, Keefe D, Newbold R, Walker NJ, Thomas Zoeller R, Bucher JR. A new approach to synergize academic and guideline-compliant research: the CLARITY-BPA research program. *Reprod Toxicol.* 2013;**40**:35–40.
2. Ostroff MDS. National Toxicology Program draft report on bisphenol A. 2018. Available at: www.fda.gov/newsevents/newsroom/pressannouncements/ucm598100.htm. Accessed 1 Apil 2019.
3. Vom Saal FS. Flaws in design, execution and interpretation limit CLARITY-BPA's value for risk assessments of bisphenol A [published online ahead of print 27 December 2018]. *Basic Clin Pharmacol Toxicol.* doi: 10.1111/bcpt.13195.
4. Maugh T II. Cancer Drugs Face Long Road From Mice to Men. 1998. Available at: www.latimes.com/archives/la-xpm-1998-may-06-mn-46795-story.html. Accessed 1 April 2019.
5. Farr OM, Gavrieli A, Mantzoros CS. Leptin applications in 2015: what have we learned about leptin and obesity? *Curr Opin Endocrinol Diabetes Obes.* 2015;**22**(5):353–359.
6. Raun AP, Preston RL. History of Diethylstilbestrol Use in Cattle. Champaign, IL: American Society of Animal Science; 2002.
7. Hagobian TA, Bird A, Stanelle S, Williams D, Schaffner A, Phelan S. Pilot study on the effect of orally administered bisphenol A on glucose and insulin response in nonobese adults. *J Endocr Soc.* 2019;**3**(3):643–654.
8. Stahlhut RW, Peterson J, Taylor JA, Nadal A, Dyer JA, vom Saal FS. Experimental BPA exposure and glucose-stimulated insulin response in adult men and women. *J Endocr Soc.* 2018;**2**:1173–1185.