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Getting the Lay of the Land: Human and Animal Evidence on Environmental Chemicals and Autism

Wendee Nicole

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Autism spectrum disorder (ASD)—a neurobehavioral condition with multiple levels of expression and severity—touches the lives of many individuals and their families. In the United States alone, ASD diagnoses have risen from 1 in 150 in 2002 to 1 in 59 in 2014.[1] Estimated costs for medical care, lost parental work time, and special education range from $11.5 billion to $60.9 billion.[1] Although the reasons for this climb are not completely understood, "the increase in the prevalence of autism in such a short span of time is certainly alarming," says Katherine Pelch, senior scientist at the Endocrine Disruption Exchange. Pelch is lead author of a new scoping review on autism and environmental chemicals published in *Environmental Health Perspectives*.[2]

The review comprehensively combs the literature for both human and animal studies looking at ASD and early-life environmental exposures—the most vulnerable window of time for the developing brain. The authors' goal was to identify gaps in the research, propose specific exposures for systematic review with respect to ASD, and recommend future research priorities.

With the help of machine learning technology, Pelch and colleagues searched PubMed for studies on chemical exposures that occurred at or before 2 months of age in humans and a comparable period in rodents (at or before 14 days of age). ASD is clinically diagnosed with three main criteria: persistent difficulties with social communication and interaction, repetitive behavior patterns or restricted interests, and the presence of symptoms in early childhood.[3] The review authors used all epidemiological studies that reported an outcome of ASD, no matter the diagnostic tool used in the original study.

Because there are no universally accepted guidelines as to what constitutes an animal model of ASD, the authors selected rodent behaviors that have previously[4,5,6] been deemed analogous to diagnostic behaviors observed in humans. Animal studies were selected if they measured at least one reciprocal social communication behavior or one repetitive behavior—even if the study did not set out to observe autistic behaviors.

After screening 21,603 unique studies, the authors identified 46 experimental rodent studies, 54 epidemiological studies, and

Future studies would benefit from rigorous reporting of how autism diagnoses are made. But there's a catch. Autism diagnostic tools make assumptions about what constitutes neurotypical behavior, and sometimes those assumptions are based on the norms of relatively affluent European-American populations.[7] That can limit these tools' usefulness in diagnosing children from other cultures and socioeconomic groups. Image: © iStockphoto/junce.

50 reviews that met their criteria for inclusion. "One thing that surprised me is how many reviews we found—fifty—though there have only been a hundred primary studies published on the topic," says Pelch. "This was particularly surprising given how many of the chemicals have only been investigated [in relation to ASD] in one or two studies each." None of the systematic reviews or meta-analyses they reviewed included animal data.

The review papers covered 152 environmental exposures. The exposures most commonly examined in humans were nonspecific air pollution, particulate matter, mercury, and lead; in animals, they were chlorpyrifos, mercury, and lead. The authors specifically recommended that researchers conduct systematic reviews on lead, chlorpyrifos, and polychlorinated biphenyls in association with ASD, a recommendation based partly on the fact that several relevant articles have been published on each of these substances. They also cited the need for greater geographical diversity in epidemiological research, because studies were heavily skewed towards the United States, California in particular.

The authors suggested that future studies be more precise in reporting the ASD diagnostic techniques that are used—an important piece of information that was lacking in many of the studies reviewed. They also pointed out that various exposure measures differ in the extent to which they can be linked to a specific time period of exposure or chemical. Finally, noting that many chemicals were studied in only animals or only humans, they recommended harmonizing the chemicals studied in both groups, perhaps basing targeted animal studies on chemicals of potential concern identified in epidemiological research. For many topics in environmental health, Pelch says, we must combine the best of both study types.

Aisha Dickerson, an assistant professor in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health, who was not involved in the project, believes the new review is an important contribution to the body of literature on environmental risk factors for ASD. But she is also concerned that a few of the suggestions could exclude certain cultures, races, and socioeconomic groups from future research.

"One of the more concerning suggestions for epidemiological studies was the recommendation that researchers use the most rigorous autism diagnostic methods," says Dickerson. "These are not only relatively expensive but also time-consuming and not always culturally appropriate." For example, she explains, some items on the Autism Diagnostic Observation Schedules assess deficits based on culture-specific activities like birthday parties. Thus, they are biased toward behaviors considered normal in Western society. "As such, they are not often suitable for research in low- and middle-income countries or, for that matter, underserved populations within the U.S.," Dickerson says.

Likewise, the use of personal monitoring systems and repeated measurements can be difficult in disadvantaged communities. This is partly due to these communities' limited access to research facilities and the discomfort of wearing personal monitors in, for instance, physically taxing work environments.

Kristen Lyall, an assistant professor at the A.J. Drexel Autism Institute at Drexel University, who also was not involved in this study, comments, "What strikes me about this article is its impressive scope, detailed figures, and interactive content via the Tableau tables provided in the data supplement." Tableau, a novel analytics platform, creates interactive visualizations of data that are typically more intuitive for readers to interpret and digest, compared with traditional tables or figures.

"It's rare for an article of this type to place such high focus on animal studies in addition to human studies, and I'm a little cautious about interpreting animal model results with the same weight as human studies," Lyall adds. "Ultimately, I think we need more large-scale epidemiological analyses of these chemicals to better understand key associations—including potential combined effects—in humans."

Wendee Nicole has written for *Discover*, *Scientific American*, and other publications.

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