Phthalate Exposure From Prescription Medications and Breast Cancer Risk

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In the article that accompanies this editorial, Ahern et al¹ used a linkage of Danish registries to evaluate the association between exposure to phthalates via prescription drugs and breast cancer risk. Ahern et al¹ observed a strong association between high cumulative doses of drugs containing dibutyl phthalate (DBP) and breast cancer risk, driven by estrogen receptor–positive cancer, such that women who consumed 10,000 mg or more of DBP experienced a 90% increased risk of estrogen receptor–positive breast cancer as compared with those who were unexposed. No significant associations were observed at lower levels of DBP exposure.

Prior studies conducted on this question observed no association between DBP exposure, as measured by urinary metabolites, and breast cancer risk.^{2–5} Although urinary measures are attractive because they capture exposure from all sources at a given time point, a single urinary measure reflects only relatively recent exposures and would not capture the chronic exposure likely meaningful in the context of breast cancer. To address this concern and given that none of the prior studies were conducted prospectively, a recent study conducted within the Women's Health Initiative used multiple urine samples to assess exposure over time, observing no consistent association for DBP and breast cancer risk.⁵ Although this prospective, longitudinal approach offered an improvement over prior work, it likely did not capture the totality of phthalate exposure over the etiologically relevant time period, given the short half-lives in the body, episodic nature of exposures, and consequent need for multiple urine samples to fully characterize exposure.⁶

In the current study, authors evaluated cumulative exposure resulting from prescription drugs containing phthalates in a large population of 1.12 million women. Unlike prior studies, this approach focuses on one source of exposure—prescription drugs. Despite not accounting for other sources of phthalate exposure, the authors argue that this approach reflects the rank order of exposure because the magnitude of exposure from prescription drugs is much greater than that observed for other sources. This unique approach to exposure assessment applied in the context of the rich data available from the Danish registries offers an exciting alternative approach for assessment of chronic phthalate exposure. Although some

misclassification is possible because of exposure from other sources (such as vinyl flooring in homes or use of personal care products), this approach is believed to identify women with the highest phthalate exposure and offers a clear logistic and cost advantage compared with collecting and analyzing serial urine samples over 10 years of study.

Understanding the potential impact of this work requires that we first assess if findings replicate, particularly in data sets with more thorough adjustment for known breast cancer risk factors, such as body mass index, reproductive factors, and alcohol intake. The authors have taken several steps to reduce the potential for residual confounding; for example, to minimize differences between groups, authors conducted sensitivity analyses evaluating the associations between DBP and breast cancer risk among users of particular drugs contributing much of the DBP exposure (eg, lithium), such that all persons in each of these sensitivity analyses were users of the same drug. In addition, the authors note that they are unaware of any influences on whether a patient would have received a phthalate-containing or phthalate-free formulation of a given drug. However, to further assuage concern about the potential for residual confounding within these active comparator analyses, it would be helpful for future work to address comparability of these groups with regard to severity of disease and a more comprehensive set of patient characteristics (beyond those available in the current study). Although we agree that the strong effect estimates observed are unlikely to be entirely due to confounding, we recognize that there is a tendency for associations to attenuate over time as additional research is conducted. It would also be informative to evaluate whether this association generalizes to a population with a higher baseline level of phthalate exposure, given that there is more stringent regulation of phthalates in personal care products and other consumer goods in the European Union (EU) than in the United States.

If the observed association holds in future studies, the impact of these findings will rest on the exchangeability of these drugs for comparable drugs without phthalates, in terms of both efficacy and safety. The existence of non-phthalate-containing formulations, as demonstrated in this study, seems to suggest the

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availability of alternative options. Understanding the exchangeability of these drugs speaks to the potential for residual confounding within active comparator analyses as well as policy implications and will require that we better understand the indications and contraindications of use, as well as safety of the phthalate-containing versus non-phthalate-containing options. Understanding the influence of common daily exposures to phthalates and their alternatives remains a question of critical public health importance, and in light of the work presented by Ahern et al,¹ phthalates and phthalate alternatives, particularly those with estrogenic activity, likely warrant increased scrutiny. Collectively, this raises the question of whether there are other sources of phthalate exposure that may similarly affect breast cancer risk. As pointed out by the study authors, the magnitude of phthalate exposure via prescription drugs is much greater than that observed for other products; however, the prevalence of use corresponding to other exposures (such as personal care products) is much higher, which could conceivably have potential impact on the population level when compounded over the life course. At this point, it is unclear if these findings may translate to other such exposures.

The global regulatory landscape related to use of phthalates in drugs as well as in consumer and personal care products is complex, with different countries pursuing different tactics to regulate use of DBP and phthalates in general. In 2012, the US Food and Drug Administration (FDA) restricted the use of DBP as an excipient in products regulated by the Center for Drug Evaluation and Research,⁷ and consequently DBP is no longer listed among inactive ingredients used in FDA-approved drug products.⁸ The European Medicines Agency (EMA), which provides regulatory oversight in Denmark, recently set a permitted daily exposure (PDE) of 0.01 mg of DBP/kg body weight/d.⁹ At this PDE, a 63.5 kg woman (approximately 140 lbs) would have to take a prescription containing the PDE of 0.01 mg DBP/kg of body weight every day for more than 43 years to reach the estimated 10,000-mg threshold of cumulative exposure associated with increased breast cancer risk observed in the current study, with the caveat that exposure from other sources might accelerate this timeline. In addition, associations may be affected by duration and timing of exposure, and this PDE may still provide sufficient DBP exposure to cause other adverse health outcomes. Importantly, it should be acknowledged that this threshold is likely not a true threshold but a proxy for high levels of exposure. In the Ahern et al¹ study, exposure groupings are

fairly broad and may obscure potential heterogeneity, and it is possible that an increased risk may be observed at even lower cumulative doses, which could in turn shorten the period by which a person could reach the effective cumulative dose that is associated with increased risk of breast cancer. Regardless, the results of this study provide additional support for the FDA's decision to regulate DBP in prescription drugs, as well as the EMA's decision to limit the PDE.

However, DBP is not consistently regulated in the United States, and this guidance does not extend to dietary supplements, which may be a potential source of exposure to DBP in the US population.¹⁰ Although the US Consumer Product Safety Improvement Act of 2008 restricts the use of DBP in children's toys and other products manufactured specifically for children,¹¹ DBP continues to be commonly used in personal care and consumer products in the United States. In contrast, use of DBP in consumer products is more stringently regulated in the EU, where DBP is legally recognized as a human endocrine disruptor by the European Commission's Registration, Evaluation, Authorization, and Restriction of Chemicals legislation, and has been labeled a substance of very high concern.¹² Use of DBP in children's toys has been restricted in the EU since 1999,¹³ and, unlike in the United States, use of DBP in cosmetics is also banned.¹⁴

As regulations and awareness of phthalates have increased, concentrations of DBP's urinary metabolite, mono-*n*-butyl phthalate, in the population have decreased in the United States and Europe.¹⁵⁻¹⁷ However, environmental monitoring in China suggests that total phthalates in air, soil, and water continue to increase and may contribute to increasing exposures among the general population.¹⁸ Although strides are being made in terms of reducing exposure in some countries, there is likely considerable global heterogeneity in exposure given differing regulatory landscapes.

In conclusion, this is a compelling and innovative article that merits follow-up. Although DBP is already regulated by the FDA and EMA, there is global heterogeneity in the regulation of DBP in prescription drugs, and DBP is not well regulated in consumer goods in the United States. These results raise broad questions about the procarcinogenic potential of high levels of phthalate exposure and more specifically speak to further understanding DBP exposure in relation to breast cancer risk.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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