Phthalates Should Be Regulated as a Class to Protect the Brains of Our Children

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See also Engel et al., p. 687.

Phthalates are a ubiquitous, high-volume class of synthetic chemicals often used in plastics to make them soft and pliable. They have been used in medical products, toys, vinyl flooring, food containers, paint, cleaning products, cosmetics, and more. Because they are not covalently bound to the matrix, they can leak and migrate to the surrounding environment into dust, food, and liquids. They are semivolatile, so they can also be found in the air. Consequently, humans are constantly exposed to phthalate esters in food as well as household air and dust through inhalation, ingestion, and dermal absorption. Phthalates are rapidly metabolized, and their metabolites are routinely detected worldwide in human urine. Phthalates have been associated with a plethora of adverse health effects: endocrine disruption, reproductive effects, both demasculinization and feminization, behavioral effects, asthma, obesity, diabetes, immunotoxicity, and cancer.[1]

In this issue of *AJPH*, Engel et al. (p. 687) urgently call for reducing phthalate exposure and regulating phthalates to protect our children's developing brains. Their article provides solid and sound scientific evidence from population-based epidemiology studies supported by extensive evidence from animal models and mechanistic studies that early life exposure to ortho-phthalates increases the risk of impaired neurodevelopment and sexual development. They argue that a class approach is needed for assessing health impacts to eliminate phthalates as a chemical group in consumer products. The call to treat these compounds as a class is not new. The National Academy of Sciences called for a cumulative approach to phthalate risk assessment more than 12 years ago,[2] and the Consumer Product Safety Commission supported this in 2014.[3]

Because phthalates are used in so many commonly used products, the general population is simultaneously exposed to multiple phthalates in complex mixtures. This raises concerns because most chemical risk assessment is based on a compound-by-compound approach, failing to consider that exposure is never one compound at a time. The need for cumulative assessment is based on a growing body of studies demonstrating that exposure to mixtures of phthalates may pose a health risk. A recent study from Sweden measured 26 chemicals, including phthalates, in the first trimester urine or blood of pregnant women; the researchers found that the presence of these chemicals was associated with Wechsler Intelligence Scale for Children–IV IQ scores of the women's children at age seven years.[4] The study clearly showed that exposure to this contamination of chemicals included eight phthalates above the level of detection in the urine of all 2300 pregnant women in the study. Of concern was that IQ scores of boys were 1.9 points (95% confidence interval = −3.6, −0.2) lower for an interquartile-range change in the mixture index of 10 chemicals of concern. Two phthalates, diethyl phthalate and butyl benzyl phthalate (BBzP), were found among these 10 chemicals of concern.

Another recent study used a novel approach for chemical mixture risk assessment by linking observational human studies with experimental animal tests.[5] A combined exposure of four phthalates—di butyl phthalate, BBzP, diethyl hexyl phthalate (DEHP), and diisononyl phthalate (DiNP)—in early pregnancy was associated with a shorter anogenital distance in boys at aged 22 months. A mixture of these four phthalates was further tested in an in vivo animal model using a ratio and doses relevant for human exposure to estimate a dose–response relationship

and to determine a point of departure, which was used to calculate a reference dose. This experimental reference dose was compared with human exposure to conduct a mixture risk assessment. The mixture approach showed that 13% of the pregnant women were at risk for having a child with a shorter anogenital distance; by contrast, only 1.6% of the pregnant women were considered at risk when the four phthalates were evaluated in isolation in a traditional compound-by-compound strategy.

Results from recent studies on mixture exposures therefore indicates that risks may have been underestimated with the current risk-assessment approach, even when individually all chemicals are below their guideline values. Understanding this is highly relevant for phthalates because biomonitoring data have clearly shown that different phthalates are routinely found to coexist in complex mixtures.

The problem with unfortunate substitution is another concern stressed by Engel et al., whereby chemicals of concern in products are replaced with related chemicals about which very little is known. Older, clearly toxic phthalates such as DEHP and BBzP have been replaced by DiNP and diisobutyl phthalate. Recent findings have found that these replacements also impose health risks because many of the phthalate products stay in use for many years or decades (e.g., PVC [polyvinyl chloride] flooring exposure will continue throughout the product's lifecycle, even though the phthalate additive has been removed from production). This also reinforces the need for a class approach and safe substitutions.

Finally, we find it reasonable to focus on both neuro- and sexual development because there may be shared biological mechanisms that can explain how exposure to phthalates causes these adverse effects, as Engel et al. describe. We agree that negative developmental effects on cognition and behavior are adverse health effects, as they lead to irreversible consequences for learning, social behavior, motor skills, and more throughout life. The impact of adverse early life phthalate exposure on sexual development is also associated with adverse reproductive effects later in life.

The use of phthalates in many types of products and consumer goods has led to environmental contamination and human exposure, with evidence of adverse health effects in the general population. Because phthalates are present in complex mixtures, it is imperative that all federal and state agencies in the United States and abroad take a cumulative approach to assessing their risk. And because phthalates constitute a structurally related group of chemicals, they should be assessed as a class and one should not be substituted for another. Finally, substitution of chemicals that have been found to be harmful must be done very carefully. Given that safe alternatives have been found, phthalates should be banned from production and use. AJPH

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CONFLICTS OF INTEREST

Neither author has any conflicts of interest to disclose.

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