Neurotoxicity of Ortho-Phthalates: Recommendations for Critical Policy Reforms to Protect Brain Development in Children

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See also Birnbaum and Bornehag, p. 551.

Robust data from longitudinal birth cohort studies and experimental studies of perinatally exposed animals indicate that exposure to ortho-phthalates can impair brain development and increase risks for learning, attention, and behavioral disorders in childhood. This growing body of evidence, along with known adverse effects on male reproductive tract development, calls for immediate action.

Exposures are ubiquitous; the majority of people are exposed to multiple ortho-phthalates simultaneously. We thus recommend that a class approach be used in assessing health impacts as has been done with other chemical classes. We propose critically needed policy reforms to eliminate ortho-phthalates from products that lead to exposure of pregnant women, women of reproductive age, infants, and children. Specific attention should be focused on reducing exposures among socially vulnerable populations such as communities of color, who frequently experience higher exposures.

Ortho-phthalates are used in a vast array of products and elimination will thus necessitate a multipronged regulatory approach at federal and state levels. The fact that manufacturers and retailers have already voluntarily removed ortho-phthalates from a wide range of products indicates that this goal is feasible. (*Am J Public Health*. 2021;111:687–695. https://doi.org/10.2105/AJPH.2020.306014)

As experts in toxic chemicals and neurodevelopment who are members of Project TENDR (Targeting Environmental Neuro-Development Risks), we have determined that exposure to ortho-phthalates can impair child brain development and increase children's risks for learning, attention, and behavioral disorders. There are robust data from longitudinal birth cohort studies conducted over the last decade that have shown associations between prenatal exposures to ortho-phthalates and attention-deficit hyperactivity disorder (ADHD), other behavioral problems, adverse cognitive development including lower IQ, poorer psychomotor development, and impaired social communication.

This growing body of evidence, along with the known adverse effects on male reproductive tract development of ortho-phthalates, calls for immediate action. Given that general population exposure is ubiquitous and is to a mixture of multiple ortho-phthalates simultaneously, we recommend that assessment of hazard use a class approach, as has been done for a number of other chemical classes. To protect child brain development, ortho-phthalates need to be removed from consumer products that contribute to exposure of pregnant women, women of reproductive age, infants, and children. We summarize the epidemiological evidence on adverse neurodevelopmental effects following prenatal exposure to ortho-phthalates, discuss sources of exposure and what is known about potential mechanisms, and propose urgently needed reforms to substantially reduce exposures to ortho-phthalates over critical periods of child brain development.

WHAT ARE PHTHALATES?

Ortho-phthalates are diesters of phthalic acid and are the predominate

type of phthalate used in commerce. (For simplicity, we will refer to them as phthalates.) They are high-production-volume chemicals used most often as a plasticizer in polyvinyl chloride (PVC) and other plastics. Phthalates are used in numerous consumer products, including food production materials and packaging; medical supplies and coatings of medicines; flooring, wall coverings, and other home materials; and cosmetics and other personal care products.[1] Approximately 4.9 million metric tons are produced annually worldwide (reviewed in Ejaredar et al.[2]). The highest-production phthalates are di-2-ethylhexyl phthalate (DEHP), diisononyl phthalate (DiNP), butylbenzyl phthalate (BBzP), dibutyl phthalates (DBPs), and diethyl phthalate (DEP).[3]

Diet is a particularly important exposure pathway for some phthalates, including DEHP and DiNP.[4] Phthalates have been shown to leach into food from plastic equipment like tubing used in commercial dairy operations, lid gaskets, food preparation gloves, conveyor belts, and food packaging materials.[5] As such, consumption of fast food and other dining-out sources,[5] as well as lipophilic foods such as dairy,[4] can be important dietary sources of phthalate exposures.

Building products containing phthalates, such as vinyl flooring and wall coverings, have a large surface area from which phthalates can migrate into the indoor air and household dust, also resulting in human exposure.[6] Historically, phthalates were added to children's toys, although use of multiple phthalates in toys has been banned by the Consumer Product Safety Commission (CPSC; see the box on page 689).[1,7]

Phthalates including DEP and DBPs are commonly used in cosmetics and other personal care products, and are sometimes used as excipients in medications and supplements (see the box on page 689).[2] For example, DEP and DBPs are used in a wide range of personal care products including nail polish, lotions, fragrances, and hair-styling products.[41] Numerous studies have found correlations between personal care product use and the concentrations of phthalate metabolites in urine.[41] Overall, women have higher exposure to phthalates found in personal care products than men, and Black and Latina women have higher exposure to certain phthalates compared with White women, independent of socioeconomic status.[42] Phthalates are readily transferred from mother to fetus during pregnancy.[2]

US population exposure to phthalates has changed in the last decade.[7] Exposures to di-*n*-butyl phthalate (DnBP), BBzP, and DEHP have declined, while exposures to replacement phthalates such as DiNP and diisobutyl phthalate (DiBP) have increased. The observed temporal trends are likely a reflection of legislative activity and advocacy efforts of nongovernmental organizations, as well as changes by manufacturers and retailers in response to consumer preference (see the box on page 689).[7]

EPIDEMIOLOGICAL EVIDENCE OF NEUROTOXICITY

Historically, most of the health concerns and regulations pertaining to phthalates were motivated by strong toxicological evidence showing adverse antiandrogenic effects on male reproductive tract development.[1] More recently, an increasing number of prospective epidemiological studies have found associations between prenatal exposure to phthalates and adverse neurodevelopment in offspring.[43] A recent systematic review of the human data concluded that prenatal exposure to DEHP, DBPs, DEP, and BBzP has an adverse impact on cognitive and psychomotor development, internalizing and externalizing behaviors, attention, gender-related play behaviors, social responsiveness, and visual spatial abilities of children.[43] As of 2019, there were more than 30 published studies that have measured prenatal exposure to phthalates using validated exposure biomarkers[43–49] or environmental estimates of prenatal exposure[50,51] in longitudinal cohorts assembled from 11 different countries or territories around the globe. Children have been followed for altered neonatal behavior or infant visual recognition memory, cognitive development, behavior, executive function, reciprocal social behavior, gender-related play behaviors, and for symptoms of, or clinical diagnosis with, developmental disabilities including autism and ADHD. Examples of key findings from this extensive literature base are discussed in the following paragraphs.

The most consistent pattern across multiple studies is associations with behaviors commonly associated with ADHD (including hyperactivity, aggression/defiance, and emotional reactivity),[43] deficits in executive function,[52,53] or ADHD clinical diagnosis.[54] For example, a 2018 study nested within the Norwegian Mother and Child Cohort leveraged a linkage between this cohort and the Norwegian National Patient Registry, which collects all outpatient diagnoses from specialty clinics. Engel et al. measured second-trimester urinary phthalates and found that children of mothers that fell in the highest quintile of prenatal exposure to DEHP metabolites had almost 3 times the odds of being diagnosed with ADHD as those with mothers in the lowest quintile (odds ratio [OR] = 2.99; 95% confidence interval [CI] = 1.47, 5.49).[54]

Federal Regulatory, Manufacturer, and Retailer Action on Phthalates

I. Federal Regulatory Action

A. US Environmental Protection Agency (EPA)

- Set a drinking water standard for DEHP (6 ppb).[8]
- Listed DEHP and DBP as hazardous air pollutants and as substances on the Toxic Release Inventory that must be reported to EPA if released into any media.[8]
- Listed phthalates as hazardous waste if discarded as commercial chemical products under the Resource Conservation and Recovery Act.[8]
- Recently designated 5 phthalates (DnBP, DiBP, BBzP, DEHP, and DCHP) as high-priority substances for risk evaluation under the Toxic Substances Control Act.[9]

B. US Consumer Product Safety Commission

- Banned 8 ortho-phthalates from use in children's toys and childcare articles: DEHP, DBP, BBzP, DINP, DiBP, DPENP, DHEXP, and DCHP.[10] The regulation is under legal challenge by the National Association of Manufacturers, the American Chemistry Council, and other industry groups.[11]

C. US Food and Drug Administration (FDA)

- Set maximum concentration of DEHP in bottled water at the same concentration that EPA had set in drinking water.[12]
- Issued guidelines (but not regulation) recommending that DBP and DEHP be avoided as excipients in prescription and nonprescription products,[13] advised manufacturers to label medical devices that contain DEHP,[14] and concluded that exposure to DEHP received by some infants from medical device–related sources could be substantially greater than the agency's estimate of the Tolerable Intake.[15]
- Approved use of 28 phthalates as food additives in food contact articles.[16,17] Uses include as plasticizers, binders, coating agents, defoamers, and gasket closures, in materials such as cellophane, paper and paperboard, and plastics.
- Has failed to meet the statutory deadline for final decisions on 3 recently submitted petitions that could substantially reduce dietary exposure to phthalates.[17]
  - o Two were submitted by 11 environmental and public health organizations and requested that FDA strike from its existing regulations its approvals of all 28 phthalates as food additives in food contact articles, as the agency could no longer conclude that such use is safe, as is required by law.[17]
  - o The third petition was submitted by the Flexible Vinyl Alliance and requested that FDA revoke its approval of 24 phthalates that the Alliance claims are no longer used as food additives in food contact applications.[17] The industry petition did not include several approved uses of these phthalates and continued the approval of DEHP, DINP, DCHP, and DIDP as food additives.

II. Examples of Voluntary Action by Retailers and Manufacturers

- Home Depot's safer chemicals policy includes restrictions on phthalates as a class in vinyl flooring and wall-to-wall carpet.[18,19]
- Lowe's, Lumber Liquidators, and Menards have taken action to remove phthalates as a class from vinyl flooring.[19,20]
- Apple has removed phthalates as a class from almost all products.[21]
- Hewlett Packard has removed multiple phthalates from commercial personal computer products and a lesser number from other products.[22]
- IKEA has removed phthalates from a number of its products.[23]
- Mohawk,[24] Tarkett,[24] SC Johnson,[25] and Steelcase[26] have restricted use of phthalates in some products, including household products.
- Ahold Delhaize, the fourth largest grocery chain in the United States (with 2000 stores including Food Lion, Giant Food, Giant/Martin's, Hannaford, and Stop & Shop) recently announced restrictions on phthalates and other chemicals in its own branded products in the following categories: all grocery, baby food and infant formula, and formulated laundry products, as well as personal care, cosmetic, and baby products.[27,28]
- CVS Health,[29] Loblaw,[29] Rite Aid,[30] and Walmart[31] are also reducing the use of phthalates in beauty and personal care products and household products with the goal of elimination.
- Sephora set a goal to reduce high-priority chemicals including 8 phthalates by 50% over the next 3 years.[32,33]
- Panera Bread has replaced vinyl gloves, which must be softened with phthalates or other plasticizers, with safer alternatives such as polyethylene gloves that require no such chemical additives.[33]

III. Examples of Health Care Organization and Medical Supplier Actions

- Dignity Health,[34] Hackensack Meridian Health,[35] and Kaiser Permanente[36] have a stated preference for products made without phthalates.
- Warner Chilcott recently brought a new product to market, Delzicol (mesalamine), which does not contain DBP in the medication coating.[37]

In totality, these examples demonstrate the feasibility of reformulating a vast array of products to remove phthalates. Cited references can help inform steps necessary in selection of safer alternatives when replacing phthalates.[38–40]

Note. BBzP = butylbenzyl phthalate; DBP = dibutyl phthalate; DCHP = dicyclohexl phthalate; DEHP = di-2-ethylhexyl phthalate; DHEXP = di-*n*-hexyl phthalate; DiBP = diisobutyl phthalate; DIDP = di-isodecyl phthalate; DINP = diisononyl phthalate; DnBP = di-*n*-butyl phthalate; DPENP = di-*n*-pentyl phthalate; and ppb = parts per billion.

Phthalates, particularly metabolites of DBP and DEHP, have also been associated with more problem behaviors, as estimated by validated inventory-based behavioral rating scales in these largely subclinical populations. For example, Lien et al. reported that third-trimester urinary concentrations of DnBP and DEHP metabolites were associated with more externalizing problems, more delinquent behaviors, and more aggressive behaviors, as measured by the Child

Behavior Checklist, in a population of 8-year-old children in Taiwan.[55] Also using the Child Behavior Checklist and leveraging a US-based multicenter pregnancy cohort enrolled in California, Minnesota, Missouri, and Iowa, Kobrosly et al. reported that third-trimester urinary DiBP metabolites were associated with more inattention, rule-breaking behavior, aggression, and conduct problems.[56] DEHP and BBzP metabolites were also linked with altered behavior that was in some cases sex-specific. Another recent study found an association between prenatal exposure to the sum of low-molecular-weight phthalates (which includes metabolites of DBPs and DEP) and hyperactivity, attention problems, and anxiety at the age of 16 years.[49]

In addition, phthalates have been associated with altered child executive functions using both rater-based and performance-based assessments. Executive functions are higher-order cognitive processes that support goal-directed behaviors and are typically impaired in children with ADHD. Factor-Litvak et al. reported that prenatal DBP metabolites were associated with poorer working memory in a birth cohort enrolled in New York City and administered the Wechsler Intelligence Scale for Children-IV at age 7 years.[53] Engel et al. reported that prenatal metabolites of DBP were associated with poorer working memory on the Behavior Rating Inventory of Executive Function.[52] Factor-Litvak et al. also found that prenatal metabolites of DBPs were associated with a significant linear reduction in child IQ. Overall, child IQ was 7 points lower in the highest versus lowest quartile of DBP exposure. DBP metabolites were also associated with index-specific decrements in processing speed, perceptual reasoning, and verbal comprehension.[53] Maternal urinary concentrations of BBzP metabolites were also associated with reductions in child perceptual reasoning.[53]

It is important to note that the literature is not entirely consistent, particularly among studies that focus on cognitive development during infancy and early childhood. Among these studies, there is often a lack of overlap in the specific metabolites implicated, the gender most affected, or the direction of the relationship. Even among studies of neurobehavior, not all have found associations,[48,49,57,58] and some have found associations primarily with internalizing domains.[59,60] Some of these differences may be attributable in part to differences in the study designs, including the age of the child at testing, the gestational age at urine sample collection, and the instruments used for assessing neurodevelopmental outcomes measures. In addition, early studies of phthalates and neurobehavior summed phthalate metabolites into low- and high-molecular-weight groupings, which makes it difficult to compare results to those reporting findings on individual phthalates, particularly in light of temporal changes of the contribution of specific phthalates to the overall exposure mixture.

Despite these differences, the weight of evidence strongly supports a relationship between certain phthalates and altered neurobehavioral development. This interpretation is additionally supported by the Chronic Hazard Advisory Panel for the CPSC, which concluded that poorer neurodevelopment test scores are generally associated with higher maternal prenatal urinary concentrations of metabolites of DEHP, DBPs, and DEP, and that human exposure to these phthalates should be reduced.[1] Consistent with the systematic review by Zhang et al.,[43] a 2015 review also concluded that prenatal exposures to DEP, BBzP, DEHP, and DBPs were associated with adverse cognitive and behavioral outcomes in children, including lower IQ and problems with attention, hyperactivity, and poorer social communication.[2]

EXPERIMENTAL EVIDENCE OF NEUROTOXICITY

Studies of gestational and early life exposure in animal models, which have mostly focused on DEHP, are generally consistent with the observations from epidemiological studies. The most consistently observed effects include hyperactivity, anxiety and depressive behaviors, and cognitive impairments including impacts on learning and memory.[61] Disruption of the organization and function of the hypothalamic–pituitary–gonadal axis by phthalates known to inhibit fetal testosterone production is also frequently reported.[61] A particularly compelling study showed that rats perinatally (both before and after birth) exposed to a human-relevant phthalate mixture displayed lower cognitive flexibility in a set-shifting task, an outcome that correlated with fewer synapses in the prefrontal cortex.[62] Sensitive windows of exposure span pre- and postnatal life through adolescence[63] including puberty[64–66] and possibly adulthood,[67–70] which is unsurprising given that complex structures including the prefrontal cortex, hippocampus, and cerebellum undergo significant development well into early adulthood.

Consistent with the epidemiological findings, animal outcomes are frequently sex-specific. It is known that many phthalates are antiandrogenic[1] although antiestrogenic effects have also been reported in vitro.[71] It has been hypothesized that the differential effect of phthalates on neurobehavioral

outcome by sex seen in many studies may result from disrupted fetal testosterone production. Critically, unlike rodents in which testosterone is aromatized to estrogen in the developing brain and then acts via estrogen receptors to masculinize the male brain, in genetically male humans testosterone acts primarily via the androgen receptor.[70] Thus, while the phenomenon of sex-specific effects may be conserved across species, specific effects within sex may vary based on taxonomical differences in steroid hormone function. Phthalates can also modulate aromatase activity in the developing brain, which can interfere with estrogen synthesis.[72,73] This is of concern because estrogen plays a critical role in brain plasticity and other developmental refinements,[74] and there is also growing evidence that estrogen synthesis can be extragonadal, including in the brain.[75]

The hippocampus and, consequently, aspects of neural plasticity, cognitive flexibility, anxiety-like behavior, learning, and memory, are thought to be particularly vulnerable to phthalates. For example, male mice prenatally exposed to DEHP had evidence of oxidative stress, neuronal loss, and neuroinflammation in the hippocampus as adults, along with elevated anxiety behavior and impaired recognition memory.[76,77] Similarly, male rats perinatally exposed to DEHP had impaired dendritic complexity in the hippocampus, particularly in CA1 pyramidal neurons.[78]

A recent review of the phthalate literature discussed several additional potential mechanisms to explain the epidemiological and animal toxicity literature.[3] Disruption of thyroid hormone pathways is one potential mechanism of interest, given that thyroid hormone is essential for brain development. There is also evidence of altered ion homeostasis including calcium signaling, peroxisome proliferator-activated receptors activation, and lipid metabolism, particularly in the hippocampus.

In summary, multiple longitudinal studies of human prenatal phthalate exposure have found evidence of altered neurobehavioral development. These findings are of concern especially in light of the supporting evidence from experimental studies and a growing understanding of the mechanisms whereby phthalates may adversely affect fetal brain development. Given the widespread exposures to phthalates, including among women and children, and the limited existing US regulations, none of which focus on pregnant women, health-protective regulatory actions are required to eliminate these potentially harmful exposures.

RECOMMENDATIONS FOR SENSIBLE POLICY REFORMS

Mounting evidence on the impacts of phthalates on children's brain development compels meaningful actions to eliminate exposure for women of reproductive age, pregnant women, infants, and children. As discussed, human exposure to phthalates ranges from foods to building materials to medical products, pharmaceuticals, cosmetics, and other personal care products. Therefore, reducing human exposure necessitates a multipronged approach through regulations at the federal and state levels, as well as through voluntary action on the part of retailers and manufacturers.

To date, federal regulation of phthalates in the United States has been minimal with several exceptions, including restrictions on 8 phthalates in children's toys and childcare articles (see the box on page 689). We strongly urge both federal and state agencies to move rapidly to eliminate phthalate use. Specific attention should be focused on reducing exposures among socially vulnerable populations such as communities of color, who frequently experience higher exposures.[42] States should not wait for the federal government to act, as state action can galvanize federal regulation. It is encouraging that voluntary action on the part of manufacturers, retailers, and health care organizations has removed phthalates from a wide range of products (see the box on page 689). Consumer pressure is critical to motivate additional manufacturers and retailers to act, as well as to encourage federal and state regulation.

We recommend that the evaluation of hazards of phthalates use a class approach as has been done for other classes of chemicals (e.g., organophosphate pesticides, dioxin-like compounds) and as has recently been recommended by a National Academy of Sciences report on organohalogen flame retardants.[79,80] This approach is appropriate given that general population exposure is to mixtures of phthalates, coupled with the fact that phthalates have similarities in chemical structures, metabolism, and biological activity, including disruption of multiple endocrine systems, and have common health outcomes, including adverse effects on child neurodevelopment and male reproductive tract development, as well as other adverse effects.

Following are 5 critical recommendations for reducing phthalate exposures:

1. to reduce dietary exposure,
2. to reduce exposure from medical supplies and medication,

3 to reduce exposure from personal care products and other household products,
4 to reduce exposure from a broad range of other products including building materials, and
5 to reduce risk of regrettable substitution.

Dietary

The US Food and Drug Administration (FDA) must remove from its existing regulations its approvals of all 28 phthalates for use in food packaging and other materials that come in contact with food. There is no longer any basis for the agency to conclude that there is "reasonable certainty of no harm" from these uses, which is the legal standard for safety of food contact materials under the federal Food, Drug, and Cosmetic Act (see 21 CFR [updated September 19, 2019]), which governs FDA's actions. All of the phthalates that have been associated with adverse child neurodevelopment, discussed previously, are currently approved by FDA for food contact use.

Until the FDA takes action to protect the food supply from phthalates, the food industry, including producers, processors, retailers, and restaurant chains, should investigate, identify, and remove sources of phthalates from their food products.

Medical Supplies and Medication

The use of phthalates in medications and medical devices also falls under FDA jurisdiction. While FDA has published guidelines to address many of these sources (see the box on page 689), the agency must promulgate regulations to eliminate their uses.

Personal Care and Other Household Products

Authority to regulate phthalates in cosmetics (which are defined broadly to include many personal care products) also falls under FDA jurisdiction. However, the agency's authority is much less comprehensive and health protective than its authority to ensure the safety of food or drugs. This needs to be rectified by congressional action.

The CPSC has authority to ensure the safety of consumer products and is to be commended for eliminating a number of phthalates from children's toys. However, the agency must also take action to prohibit the sale of other phthalate-containing products that fall under its jurisdiction.

In addition to federal action, elimination of phthalates from personal care and household products requires action on the part of states, manufacturers, and retailers.

Personal care and household products must be labeled if they contain phthalates so consumers can make informed decisions to avoid these substances if desired.

Building Materials and Other Products

The US Environmental Protection Agency (EPA) must use its authority under the Toxic Substances Control Act (TSCA; 15 USC Ch 53 [2016]) to regulate phthalates. EPA has recently embarked on a multiyear process for evaluating the risk of several phthalates under TSCA. The agency must broaden this effort using a class approach in assessing health impacts. Furthermore, EPA should aggressively exercise its authority to regulate the manufacture, import, processing, distribution in commerce, disposal, and known and reasonably foreseeable uses of phthalates.

Regrettable Substitution

Assessment to identify safer alternatives to phthalates must consider adverse effects to human health and the environment as well as societal impacts along with performance and costs.[80] This is critical given the potential for regrettable substitution and the availability of lower-hazard alternatives (see the box on page 689 for resources on approaches for selecting safer alternatives). No phthalate should be used as a substitute for another phthalate, as has already been done with DiNP for DEHP. In addition, PVC plastics should be replaced with safer materials that do not require plasticizers. The substitution of safer alternatives for phthalates is critical given the risk these chemicals pose to child brain development.

CONCLUSION

Substantial evidence links exposure to phthalates with increased risks for child learning, attention, and behavioral problems. We therefore recommend that phthalates be eliminated from products that may lead to exposure of women of reproductive age, pregnant women, infants, and children. As discussed, this will necessitate a multipronged approach through regulations at the federal and state levels, as well as through voluntary action on the part of retailers and manufacturers. However, given that manufacturers have already successfully

removed phthalates from a wide range of products, including food, medicine and medical supplies, personal care products, and other household and building materials (see the box on page 689), we believe the goal of phthalate elimination is achievable. AJPH

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REFERENCES

1. *Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Bethesda, MD: US Consumer Product Safety Commision; 2014.
2. Ejaredar M, Nyanza EC, Ten Eycke K, Dewey D. Phthalate exposure and childrens neurodevelopment: a systematic review. *Environ Res*. 2015;142:51–60. https://doi.org/10.1016/j.envres.2015.06.014
3. Miodovnik A, Edwards A, Bellinger DC, Hauser R. Developmental neurotoxicity of ortho-phthalate diesters: review of human and experimental evidence. *Neurotoxicology*. 2014;41:112–122. https://doi.org/10.1016/j.neuro.2014.01.007
4. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health*. 2014;13(1):43. https://doi.org/10.1186/1476-069X-13-43
5. Zota AR, Phillips CA, Mitro SD. Recent fast food consumption and bisphenol A and phthalates exposures among the US population in NHANES, 2003–2010. *Environ Health Perspect*. 2016;124(10):1521–1528. https://doi.org/10.1289/ehp.1510803
6. Mitro SD, Dodson RE, Singla V, et al. Consumer product chemicals in indoor dust: a quantitative meta-analysis of US studies. *Environ Sci Technol*. 2016;50(19):10661–10672. https://doi.org/10.1021/acs.est.6b02023
7. Zota AR, Calafat AM, Woodruff TJ. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001–2010. *Environ Health Perspect*. 2014;122(3):235–241. https://doi.org/10.1289/ehp.1306681
8. US Environmental Protection Agency. Phthalates action plan. Available at: https://www.epa.gov/sites/production/files/2015-09/documents/phthalates_actionplan_revised_2012-03-14.pdf. Accessed November 30, 2020.
9. Environmental Protection Agency. Final scopes of the risk evaluations to be conducted for twenty chemical substances under the Toxic Substances Control Act; notice of availability. *Fed Regist*. 2020; 85:55281–55283. Available at: https://www.federalregister.gov/documents/2020/09/04/2020-19671/final-scopes-of-the-risk-evaluations-to-be-conducted-for-twenty-chemical-substances-under-the-toxic. Accessed November 27, 2020.
10. Consumer Products Safety Commission. Prohibition of children's toys and child care articles containing specified phthalates. *Fed Regist*. 2017; 82:49938–49982. Available at: https://www.federalregister.gov/documents/2017/10/27/2017-23267/prohibition-of-childrens-toys-and-child-care-articles-containing-specified-phthalates. Accessed November 27, 2020.
11. *Texas Association of Manufacturers, Texas Chemical Council, Texas Association of Business, National Association of Manufacturers and American Chemistry Council, Petitioners v. United States Consumer Product Safety Commission, Respondent*, Case No. 17-60836 (on petition for review of a final rule of the Consumer Product Safety Commission; 5th Cir Ct App; 2018). Available at: http://documents.nam.org/law/amicusbriefs/2018/TXAssnofMfrs_v_CPSC_5Cir_Reply_120318.pdfw. Accessed November 25, 2020.
12. US Food and Drug Administration. Beverages: bottled water quality standard; establishing an allowable level for di(2-ethylhexyl)phthalate. *Fed Regist*. 2011;76:64810–64813. Available at: https://www.federalregister.gov/documents/2011/10/19/2011-26707/beverages-bottled-water-quality-standard-establishing-an-allowable-level-for-di2-ethylhexylphthalate#p-. Accessed November 25, 2020.
13. US Food and Drug Administration. Guidance for industry on limiting the use of certain phthalates as excipients in Center for Drug Evaluation and Research-regulated products. *Fed Regist*. 2012; 77:72869–72870. Available at: https://www.federalregister.gov/documents/2012/12/06/2012-29461/guidance-for-industry-on-limiting-the-use-of-certain-phthalates-as-excipients-in-center-for-drug. Accessed November 27, 2020.
14. US Food and Drug Administration. Medical devices; draft guidance; medical devices made with polyvinylchloride using the plasticizer di-(2-ethylhexyl) phthalate. *Fed Regist*. 2002;67:57026–57027.Available at: https://www.federalregister.gov/documents/2002/09/06/02-22687/medical-devices-draft-guidance-medical-devices-made-with-polyvinylchloride-using-the-plasticizer. Accessed November 27, 2020.
15. Center for Devices and Radiological Health, US Food and Drug Administration. Safety assessment of di(2-ethylhexyl)phthalate (DEHP) released from PVC medical devices. Available at: https://www.fda.gov/media/114001/download. Accessed November 27, 2020.
16. US Food and Drug Administration. Breast Cancer Fund, Center for Environmental Health, Center for Food Safety, Center for Science in the Public Interest, Clean Water Action, Consumer Federation of America, Earthjustice, Environmental Defense Fund, Improving Kids' Environment, Learning Disabilities Association of America, and Natural Resources Defense Council filing of food additive petition. *Fed Regist*. 2016;81:31877–31879. Available at: https://www.federalregister.gov/documents/2016/05/20/2016-11866/breast-cancer-fund-center-for-environmental-health-center-for-food-safety-center-for-science-in-the. Accessed November 27, 2020.
17. Neltner T. How and when will FDA rule on ortho-phthalates in food? It's anyone's guess. Environmental Defense Fund. January 29, 2019. Available at: http://blogs.edf.org/health/?s=phthalates+in+food+&searchsubmit=Find. Accessed November 27, 2020.
18. Abrams R. Home Depot says it will phase out chemical used in vinyl flooring. *New York Times*. April 22, 2015. Available at: https://www.nytimes.com/2015/04/23/business/home-depot-says-it-will-phase-out-chemical-used-in-vinyl-flooring.html. Accessed November 27, 2020.

19. Schade M. Home Depot and Lowe's eliminating toxic phthalate flooring. Safer Chemicals, Healthy Families. May 21, 2015. Available at: https://saferchemicals.org/2015/05/21/home-depot-and-lowes-eliminating-toxic-phthalates-in-flooring. Accessed November 30, 2020.
20. Miller G, Belliveau M, Schade M, Walsh B. Success! – Home improvement retailers follow through on commitments to remove phthalates from flooring. Safer Chemicals, Healthy Families. June 27, 2019. Available at: https://saferchemicals.org/2019/06/27/success-home-improvement-retailers-follow-through-on-commitments-to-remove-phthalates-from-flooring. Accessed November 30, 2020.
21. Apple. Environmental Responsibility Report 2019 Progress Report, covering fiscal year 2018. Available at: https://www.apple.com/environment/pdf/Apple_Environmental_Responsibility_Report_2019.pdf. Accessed November 30, 2020.
22. Hewlett Packard. HP green chemistry timeline. June 2019. Available at: http://h20195.www2.hp.com/v2/GetDocument.aspx?docname=c06048911. Accessed November 30, 2020.
23. IKEA of Sweden AB. Specification chemical compounds and substances. 2016. Available at: https://www.ikea.com/us/en/files/pdf/2a/0f/2a0f5e67/ikea_restricted_substance_list.pdf. Accessed November 30, 2020.
24. Vallette J. The end is near for phthalate plasticizers. Healthy Building Network. July 9, 2015. Available at: https://healthybuilding.net/blog/196-the-end-is-near-for-phthalate-plasticizers. Accessed November 30,2020.
25. Goodman S. S. C. Johnson to cleanse phthalates from their household products. *Scientific American*. March 13, 2009. Available at: https://www.scientificamerican.com/article/johnson-halts-phthalates. Accessed November 30, 2020.
26. Steelcase. Product environmental profile. June 2017. Available at: https://www.steelcase.com/content/uploads/sites/10/2015/09/2017_sc_emea_ology_pep_en.pdf. Accessed November 30, 2020.
27. Ahold Delhaize USA. Ahold Delhaize USA brands announce commitment to sustainable chemistry, transparent products and packaging. *GlobeNewswire*. September 19, 2019. Available at: https://www.globenewswire.com/news-release/2019/09/19/1918074/0/en/Ahold-Delhaize-USA-Brands-Announce-Commitment-to-Sustainable-Chemistry-Transparent-Products-and-Packaging.html. Accessed November 30, 2020.
28. Safer Chemicals, Healthy Families. Grocer Ahold Delhaize to restrict toxic chemicals in food packaging and beauty products. September 19, 2019. Available at: https://saferchemicals.org/2019/09/19/grocer-ahold-delhaize-to-restrict-toxic-chemicals-in-food-packaging-and-beauty-products. Accessed November 30, 2020.
29. Safer Chemicals, Healthy Families. 2018 who's minding the store? A report card on retailer actions to eliminate toxic chemicals. Available at: https://retailerreportcard.com/wp-content/uploads/2018/11/retailerreportcard.com_2018_report_card.pdf. Accessed November 30, 2020.
30. Rite Aid Pharmacy. Chemical policy. Updated November 17, 2019. Available at: https://www.riteaid.com/corporate/chemical-policy. Accessed November 30, 2020.
31. Franklin K. Walmart releases high priority chemical list. Substances include formaldehyde, parabens, triclosan, NPEs, phthalates. Chemical Watch. July 21, 2016. Available at: https://chemicalwatch.com/48724/walmart-releases-high-priority-chemical-list. Accessed November 30, 2020.
32. Sephora. Public chemicals policy. July 2019. Available at: https://www.sephorastands.com/wp-content/uploads/Sephora-Public-Chemicals-Policy-2019.pdf. Accessed November 30, 2020.
33. Mind the Store. Ranking retailers on toxic chemicals. Key findings. 2019. Available at: https://retailerreportcard.com/2019/11/key-findings-2019. Accessed November 30, 2020.
34. Wenger R. Healthy chemicals, healthy patients—why health care needs federal chemicals reform. Dignity Health. Available at: https://www.cleanproduction.org/images/ee_images/uploads/resources/dignity_health_factsheet.pdf. Accessed November 30, 2020.
35. Hackensack Meridian Health Purchasing Department. HMH Sustainable Procurement Policy Procedure No. MM-52.0 Revised January 15, 2018. Edison, NJ: Hackensack Meridian Health; 2018.
36. Lent T. Kaiser Permanente kicks PVC & phthalates out of medical equipment. Healthy Building Network. January 20, 2012. Available at: https://healthybuilding.net/blog/353-kaiser-permanente-kicks-pvc-phthalates-out-of-medical-equipment. Accessed November 30, 2020.
37. Center for Drug Evaluation and Research. Application number 204412Orig1s000. Summary review for regulatory action. February 1, 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204412Orig1s000SumR.pdf. Accessed November 30, 2020.
38. Association for the Advancement of Alternatives Assessment. Other resources. University of Massachusetts Lowell. Available at: http://saferalternatives.org/resources/alternatives-assessment-resources. Accessed November 30, 2020.
39. Green Screen. More about GreenScreen® for safer chemicals. Available at: https://www.greenscreenchemicals.org/learn/full-greenscreen-method. Accessed November 30, 2020.
40. National Academy of Sciences, Engineering, and Medicine. Alternative assessment for chemicals to inform government and industry decision-making. A framework to guide selection of chemical alternatives. 2014. Available at: https://www.nationalacademies.org/our-work/alternatives-assessment-for-chemicals-to-inform-government-and-industry-decision-making. Accessed November 30, 2020.
41. Berger KP, Kogut KR, Bradman A, et al. Personal care product use as a predictor of urinary concentrations of certain phthalates, parabens, and phenols in the HERMOSA study. *J Expo Sci Environ Epidemiol*. 2019;29(1):21–32. https://doi.org/10.1038/s41370-017-0003-z
42. Zota AR, Shamasunder B. The environmental injustice of beauty: framing chemical exposures from beauty products as a health disparities concern. *Am J Obstet Gynecol*. 2017;217(4):418.e1–418.e6. https://doi.org/10.1016/j.ajog.2017.07.020
43. Zhang Q, Chen XZ, Huang X, Wang M, Wu J. The association between prenatal exposure to phthalates and cognition and neurobehavior of children—evidence from birth cohorts. *Neurotoxicology*. 2019;73:199–212. https://doi.org/10.1016/j.neuro.2019.04.007
44. Bornehag CG, Lindh C, Reichenberg A, et al. Association of prenatal phthalate exposure with language development in early childhood. *JAMA Pediatr*. 2018;172(12):1169–1176. https://doi.org/10.1001/jamapediatrics.2018.3115
45. Jankowska A, Polanska K, Hanke W, et al. Prenatal and early postnatal phthalate exposure and child neurodevelopment at age of 7 years—Polish Mother and Child Cohort. *Environ Res*. 2019;177:108626. https://doi.org/10.1016/j.envres.2019.108626
46. Percy Z, Xu Y, Sucharew H, et al. Gestational exposure to phthalates and gender-related play behaviors in 8-year-old children: an observational study. *Environ Health*. 2016;15(1):87. https://doi.org/10.1186/s12940-016-0171-7
47. Qian X, Li J, Xu S, et al. Prenatal exposure to phthalates and neurocognitive development in children at two years of age. *Environ Int*. 2019;131:105023. https://doi.org/10.1016/j.envint.2019.105023
48. Shin HM, Schmidt RJ, Tancredi D, et al. Prenatal exposure to phthalates and autism spectrum disorder in the MARBLES study. *Environ Health*. 2018;17(1):85. https://doi.org/10.1186/s12940-018-0428-4
49. Hyland C, Mora AM, Kogut K, et al. Prenatal exposure to phthalates and neurodevelopment in the CHAMACOS cohort. *Environ Health Perspect*. 2019;127(10):107010. https://doi.org/10.1289/EHP5165
50. Larsson M, Weiss B, Janson S, Sundell J, Bornehag CG. Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6–8 years of age. *Neurotoxicology*. 2009;30(5):822–831. https://doi.org/10.1016/j.neuro.2009.01.011
51. Philippat C, Bennett DH, Krakowiak P, Rose M, Hwang HM, Hertz-Picciotto I. Phthalate concentrations in house dust in relation to autism spectrum disorder and developmental delay in the CHildhood Autism Risks from Genetics and the Environment (CHARGE) study. *Environ Health*. 2015;14(1):56. https://doi.org/10.1186/s12940-015-0024-9
52. Engel SM, Miodovnik A, Canfield RL, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect*. 2010;118(4):565–571. https://doi.org/10.1289/ehp.0901470
53. Factor-Litvak P, Insel B, Calafat AM, et al. Persistent associations between maternal prenatal exposure to phthalates on child IQ at age 7 years. *PLoS One*. 2014;9(12):e114003. https://doi.org/10.1371/journal.pone.0114003
54. Engel SM, Villanger GD, Nethery RC, et al. Prenatal phthalates, maternal thyroid function, and risk of attention-deficit hyperactivity disorder in the Norwegian Mother and Child Cohort. *Environ Health Perspect*. 2018;126(5):057004. https://doi.org/10.1289/EHP2358
55. Lien YJ, Ku HY, Su PH, et al. Prenatal exposure to phthalate esters and behavioral syndromes in children at 8 years of age: Taiwan Maternal and Infant Cohort Study. *Environ Health Perspect*. 2015;123(1):95–100. https://doi.org/10.1289/ehp.1307154
56. Kobrosly RW, Evans S, Miodovnik A, et al. Prenatal phthalate exposures and neurobehavioral development scores in boys and girls at 6–10 years of age. *Environ Health Perspect*. 2014;122(5):521–528. https://doi.org/10.1289/ehp.1307063
57. Braun JM, Kalkbrenner AE, Just AC, et al. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic

behaviors in 4- and 5-year-old children: the HOME study. *Environ Health Perspect*. 2014;122(5):513–520. https://doi.org/10.1289/ehp.1307261

58. Gascon M, Valvi D, Forns J, et al. Prenatal exposure to phthalates and neuropsychological development during childhood. *Int J Hyg Environ Health*. 2015;218(6):550–558. https://doi.org/10.1016/j.ijheh.2015.05.006
59. Philippat C, Nakiwala D, Calafat AM, et al. Prenatal exposure to nonpersistent endocrine disruptors and behavior in boys at 3 and 5 years. *Environ Health Perspect*. 2017;125(9):097014. https://doi.org/10.1289/EHP1314
60. Whyatt RM, Liu X, Rauh VA, et al. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. *Environ Health Perspect*. 2012;120(2):290–295. https://doi.org/10.1289/ehp.1103705
61. Gore AC, Krishnan K, Reilly MP. Endocrine-disrupting chemicals: effects on neuroendocrine systems and the neurobiology of social behavior. *Horm Behav*. 2019;111:7–22. https://doi.org/10.1016/j.yhbeh.2018.11.006
62. Kougias DG, Sellinger EP, Willing J, Juraska JM. Perinatal exposure to an environmentally relevant mixture of phthalates results in a lower number of neurons and synapses in the medial prefrontal cortex and decreased cognitive flexibility in adult male and female rats. *J Neurosci*. 2018;38(31):6864–6872. https://doi.org/10.1523/JNEUROSCI.0607-18.2018
63. Holahan MR, Smith CA. Phthalates and neurotoxic effects on hippocampal network plasticity. *Neurotoxicology*. 2015;48:21–34. https://doi.org/10.1016/j.neuro.2015.02.008
64. Wang R, Xu X, Zhu Q. Pubertal exposure to di-(2-ethylhexyl) phthalate influences social behavior and dopamine receptor D2 of adult female mice. *Chemosphere*. 2016;144:1771–1779. https://doi.org/10.1016/j.chemosphere.2015.10.062
65. Wang R, Xu X, Weng H, Yan S, Sun Y. Effects of early pubertal exposure to di-(2-ethylhexyl) phthalate on social behavior of mice. *Horm Behav*. 2016;80:117–124. https://doi.org/10.1016/j.yhbeh.2016.01.012
66. Holahan MR, Smith CA, Luu BE, Storey KB. Preadolescent phthalate (DEHP) exposure is associated with elevated locomotor activity and reward-related behavior and a reduced number of tyrosine hydroxylase positive neurons in post-adolescent male and female rats. *Toxicol Sci*. 2018;165(2):512–530. https://doi.org/10.1093/toxsci/kfy171
67. Ma N, Liu S, Gao P, Cao P, Xu H. Effect of diisobutyl phthalate on learning and memory behavior and apoptosis of hippocampus cells in mice [in Chinese]. *Wei Sheng Yan Jiu*. 2013;42(1):57–60.
68. Min A, Liu F, Yang X, Chen M. Benzyl butyl phthalate exposure impairs learning and memory and attenuates neurotransmission and CREB phosphorylation in mice. *Food Chem Toxicol*. 2014;71:81–89. https://doi.org/10.1016/j.fct.2014.05.021
69. Ma N, Wang X, Gao P, Xu H. Effects of DiBP on the cAMP/PKA-CREB-BDNF signaling pathway of hippocampus in mice [in Chinese]. *Wei Sheng Yan Jiu*. 2013;42(3):405–409.
70. Wallen K. Hormonal influences on sexually differentiated behavior in nonhuman primates. *Front Neuroendocrinol*. 2005;26(1):7–26. https://doi.org/10.1016/j.yfrne.2005.02.001
71. Czernych R, Chraniuk M, Zagozdzon P, Wolska L. Characterization of estrogenic and androgenic activity of phthalates by the XenoScreen YES/YAS in vitro assay. *Environ Toxicol Pharmacol*. 2017;53:95–104. https://doi.org/10.1016/j.etap.2017.05.010
72. Andrade AJ, Grande SW, Talsness CE, Grote K, Chahoud I. A dose–response study following in utero and lactational exposure to di-(2-ethylhexyl)-phthalate (DEHP): non-monotonic dose–response and low dose effects on rat brain aromatase activity. *Toxicology*. 2006;227(3):185–192. https://doi.org/10.1016/j.tox.2006.07.022
73. Bonefeld-Jørgensen EC, Long M, Hofmeister MV, Vinggaard AM. Endocrine-disrupting potential of bisphenol A, bisphenol A dimethacrylate, 4-n-nonylphenol, and 4-n-octylphenol in vitro: new data and a brief review. *Environ Health Perspect*. 2007;115(suppl 1):69–76. https://doi.org/10.1289/ehp.9368
74. McCarthy MM. Estradiol and the developing brain. *Physiol Rev*. 2008;88(1):91–124. https://doi.org/10.1152/physrev.00010.2007
75. Diotel N, Charlier TD, Lefebvre d'Hellencourt C, et al. Steroid transport, local synthesis, and signaling within the brain: roles in neurogenesis, neuroprotection, and sexual behaviors. *Front Neurosci*. 2018;12:84. https://doi.org/10.3389/fnins.2018.00084
76. Barakat R, Lin PC, Park CJ, et al. Corrigendum to "Prenatal exposure to DEHP induces neuronal degeneration and neurobehavioral abnormalities in adult male mice."*Toxicol Sci.* 2018;164(2):645. https://doi.org/10.1093/toxsci/kfy165
77. Barakat R, Lin PC, Park CJ, et al. Prenatal exposure to DEHP induces neuronal degeneration and neurobehavioral abnormalities in adult male mice. *Toxicol Sci*. 2018;164(2):439–452. https://doi.org/10.1093/toxsci/kfy103
78. You M, Dong J, Fu Y, et al. Exposure to di-(2-ethylhexyl) phthalate during perinatal period gender-specifically impairs the dendritic growth of pyramidal neurons in rat offspring. *Front Neurosci*. 2018;12:444. https://doi.org/10.3389/fnins.2018.00444
79. Committee on the Health Risks of Phthalates. *Phthalates and Cumulative Risk Assessment—The Tasks Ahead*. Washington, DC: National Research Council of the National Academies; 2008.
80. Committee on the Design and Evaluation of Safer Chemical Substitutions. *A Framework to Guide Selection of Chemical Alternatives*. Washington, DC: National Research Council; 2014.