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Organophosphate Esters: Are These Flame Retardants & Plasticizers affecting Children's Health?

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Abstract

Purpose of Review: Organophosphate esters (OPEs) are applied to a variety of consumer products, primarily as flame retardants and plasticizers. OPEs can leach out of products over time and are consequently prevalent in the environment and frequently detected in human biomonitoring studies. Exposure during pregnancy is of particular concern as OPEs have recently been detected in placenta, suggesting they may be transferred to the developing infant. Also, studies have now shown that children experience higher exposure to several OPEs compared to adults, indicating they may be disproportionately impacted by these compounds. This review summarizes the current literature on reproductive and child health outcomes of OPE exposures and highlights areas for future research.

Recent Findings: Experimental animal studies demonstrate potential for OPEs to adversely impact health and a limited number of epidemiologic studies conducted in adult cohorts suggest that OPEs may interfere with the endocrine system. Neurodevelopment is currently the most well-characterized children's health endpoint, and several studies indicate that prenatal OPE exposures impact both cognitive and behavioral development. Associations have also been reported with reproductive outcomes (e.g., fertilization and pregnancy loss) and with the timing of parturition and preterm birth. Cross-sectional studies also demonstrate associations between OPEs and respiratory health outcomes and measures of adiposity.

Summary: A rapidly expanding body of research demonstrates that OPEs are associated with adverse reproductive health and birth outcomes, asthma and allergic disease, early growth and adiposity, and neurodevelopment. Still, additional research is urgently needed to elucidate the full impact of OPEs on children's health.

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Organophosphate Esters (OPEs) Introduction

In order to comply with U.S. (state and federal) and international flammability regulations, manufacturers of consumer goods, including building materials, furniture, and electronic devices, routinely apply chemical flame retardants to their products (1–3). Until the mid-2000s, a class of brominated flame retardants (BFRs) known as polybrominated diphenyl ethers (PBDEs) were among the most commonly used commercial chemical flame retardants (1–3). Amid concerns of their environmental fate and potential toxicity, however, PBDEs were phased out of production and manufacturers have increasingly used organophosphate esters (OPEs) as alternatives to many BFRs (1–3). As a result, production of OPEs has increased in recent years (3–8). OPEs are applied as "additive" flame retardants (as opposed to "reactive"), meaning they are not chemically bound to their products, and are vulnerable to volatilization and leaching into the environment (4, 6, 7). Although OPEs are perhaps best known for their use as flame retardants in polyurethane foam (6, 7), they are also used as plasticizers, solvents, and in other industrial applications (4, 6, 7, 9), and are applied to electronic devices (10, 11), baby products (12), food packaging (13), recreational equipment (14, 15), and nail polishes (16).

OPE Exposure and Metabolism

Due to their application to a wide variety of consumer products and their capacity to volatilize and leach from these materials, OPEs are present at detectable concentrations in many human environments (4–7, 17–21), including residential housing (2, 17, 19, 21–26), office spaces (17, 19–21, 27, 28), and child care environments (17, 20, 21, 29, 30). In particular, OPEs are frequently detected in indoor air and in the dust of indoor environments (7, 19, 20, 22–24, 26, 30–35); consequently, inhalation and inadvertent ingestion of indoor dust are significant sources of exposure [e.g. (35)], although dermal absorption (14, 15, 36–38), respiration of contaminated air (21, 28, 39), ingestion of contaminated food (32, 40), consumption of contaminated water (41), and other pathways can also contribute to exposure (7, 34).

Inside the body, OPEs are often metabolized to their respective mono- or diesters (34, 42–47) (Figure 1), which are primarily excreted in urine (43, 44, 48), though other metabolic and excretion pathways also exist, such as hydroxylation and conjugation (34, 46, 49). Urinary OPE diester metabolites (and other biological markers of OPE exposure) are consistently detected with high frequencies in biomonitoring surveys and observational studies (21, 22, 24, 25, 32, 33, 50–61), demonstrating widespread exposure to these compounds. Biological half-lives of OPEs are much shorter than PBDEs and are likely on the order of hours to days (43, 44, 48, 62). Studies of intra-individual variability in OPE metabolite concentrations, however, have reported intraclass correlation coefficients (ICCs) for OPEs typically ranging between 0.3 and 0.8, depending on the metabolite, study

population, and time period of interest (55, 63–66). These ICC values indicate moderate reproducibility over time, suggesting exposure is also reasonably consistent over time.

Consistent with findings among the general population, exposure to OPEs among pregnant women occurs with a similar high frequency (22, 52, 53, 55, 56, 63). Though data remain limited, available evidence suggests that maternal-fetal transfer of OPEs may occur. For example, Zhao et al. (67) measured several OPEs and their metabolites in human chorionic villi and deciduae, indicating potential maternal-fetal transfer in early gestation, prior to the development of a mature placenta. Other evidence suggests that placental accumulation and transplacental transfer of OPEs may occur. For example, Ding et al. measured triphenyl phosphate (TPHP) and tris(1,3-dichloroisopropyl)phosphate (TDCIPP) in 86% and 44% (respectively) of placental tissue samples obtained from 50 pregnant women living in China (52). Interestingly, an experimental study by Baldwin et al. (68) observed sex-specific accumulation of TPHP in rat placentas (a potential mechanism for sex-specific effects), but did not observe transfer to pups; a similar study also did not observe gestational transfer of OPEs to rat pups (69).

Higher levels of OPE exposures have been reported for young children and adolescents compared to other age groups (12, 32, 35, 50, 51, 60, 70–73). For example, a pair of investigations of mother-child pairs from California and New Jersey identified higher concentrations of two urinary OPE metabolites (diphenyl phosphate (DPHP), a metabolite of triphenyl phosphate (TPHP); bis(1,3-dichloro-2-propyl) phosphate, a metabolite of tris(1,3-dicholoro-2-propyl) phosphate (TDCIPP)) in children than mothers, including DPHP and BDCIPP concentrations that were 5.9 and 15.0 times greater in children than mothers in the California cohort (50, 51). More recently, Phillips and Hammel at al. (35)reported that urinary metabolites of TDCIPP and isopropylated triarylphosphate esters (ITPs) were universally detected in urine samples from children 3-6 years of age (n=181, collected 2014-2016), and metabolite levels were generally higher than those observed in other temporally and geographically similar cohorts of adults. The four other OPE metabolites assessed in this study were detected in urine samples from greater than 80 percent of children [i.e., mono-tert-butyl phenyl phenyl phosphate (tb-PPP), diphenyl phosphate (DPHP), bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate (BCIPHIPP), and bis(1-chloro-2-isopropyl) phosphate (BCIPP)]. Strong correlations between urinary metabolites and hand wipe samples observed by Phillips and Hammel et al. suggest that elevated hand-to-mouth contact may explain higher levels of exposure experienced by children (35). Additional factors potentially leading to higher levels of OPE exposure for children include the treatment of children’s products with flame retardants or physiological differences between children and adults (12, 74).

Reproductive and Child Health Outcomes

Epidemiologic investigations into the potential health impacts of OPEs have been limited; however, investigations into the potential for OPEs to adversely impact children’s health have increased in recent years (summarized in Table 1). Notably, OPEs have been linked to endocrine disruption in experimental animal and epidemiologic studies (25, 75–86), raising concerns about reproductive toxicity and the health impacts of early-life exposures. Here,

we highlight recent studies which examine the relationship between OPE exposures and reproductive and children's health outcomes and highlight areas for future research.

Reproductive Health

Even prior to birth of the child, there is evidence to suggest that OPE exposure may impact fertilization and conception. In one study, 211 women were recruited from an academic fertility clinic as a part of the Environment and Reproductive Health Study (EARTH)(65) and their exposure to OPEs was assessed by measuring urinary biomarkers. The investigators reported that increases in the sum of three OPE metabolites measured preconception [bis(1,3-dichloroisopropyl) phosphate (BDCIPP), mono-isopropyl phenyl phenyl phosphate (ip-PPP), and DPHP] was associated with decreased rates of successful fertilization, implantation, clinical pregnancy, and live birth (65). In another study of 155 women in the EARTH cohort, preconception urinary DPHP were associated with increased risk of biochemical pregnancy loss as was the molar sum of DPHP, BDCIPP an ip-PPP (87). Consistent with these findings, experimental animal studies also found that OPE exposures decreased egg production, egg quality, hatching and survival among zebrafish and delayed hatching among chicken embryos (77, 78, 86, 88).

OPEs have also been implicated in male fecundity and reproductive health in experimental and epidemiologic studies (25, 78, 89–93). For example, exposure to OPEs, particularly when considering mixtures, was associated with aberrant DNA methylation at imprinted genes in sperm (n=67 men). Although differences in methylation with OPE exposure were small in this study, successful fertilization with a sperm cell that is aberrantly methylated may present detrimental consequences for offspring (90). Among men recruited from a fertility clinic (n=50), TDCIPP and TPHP in residential house dust were inversely associated with sperm concentration and motility (25). More recently, larger-scale research in the EARTH study participants using urinary exposure biomarkers did not support findings of an association between OPE exposure and semen parameters (92) but did find associations between urinary BDCIPP concentrations measured preconception and reduced fertilization (93)(n=220 and 201, respectively).

Past research in the EARTH study participants suggests that, in comparisons with female partners, male partner exposure appeared less relevant to adverse pregnancy outcomes (65, 93); however, it is important to note that available evidence relating OPE exposures to reproductive health has been limited to fertility treatment cohorts which may limit the generalizability of these findings to the general population.

Gestational Length and Infant Size at Birth

Adverse birth outcomes, including premature birth and low birthweight, represent the leading causes of neonatal mortality in developed countries, and while most babies survive, those born too early or too small are at increased risk of chronic health conditions throughout their lifetimes (94). Experimental studies in animals suggest that exposure to OPEs may affect early-life growth and development (77, 82, 84, 86, 95–99). For example, chicken embryos exposed to TDCIPP were observed to have a 7% decrease in weight at

hatching (86), and prenatal exposure to TDCIPP has been shown to increase the number of visibly small rat pups (i.e., runt pups) and significantly impacted weight gain through weaning (84). Gestational duration and potential impacts of OPEs on preterm birth risk have not been investigated in toxicological studies, due in part to the tightly controlled timing of parturition in most animal species.

Epidemiologic evidence for impacts on birth outcomes is limited to two studies. In a small study (n=14 term infants) of pregnant women from Shanghai, China, no associations were observed between birth weight and urinary DPHP measured in second trimester urine samples (median DPHP 1.1 ng/mL; BDCIPP assessed but detected infrequently) (53). Among a subset of women in the Pregnancy Infection and Nutrition Study (PIN), we recently reported sex-specific associations between OPEs assessed in second-trimester urine samples and birth outcomes (n=349). Women with the highest ip-PPP and BDCIPP concentrations in urine delivered girls earlier and were more likely to deliver preterm infants than women with lower exposure levels. Among males, maternal ip-PPP was associated with decreased odds of preterm birth and DPHP was suggestively associated with longer gestational age (100). Similar associations were observed with birthweight, but associations were attenuated when accounting for gestational age. Sex-specific impacts on gestational age are particularly interesting in the context of Baldwin et al. (68) which reported sex-specific accumulation of TPHP in rat placentas. Though not yet evaluated in human cohorts, it is possible that sex-specific accumulation of OPEs in the placenta is impacting placental function and as a result, the timing of parturition.

Physical Growth and Adiposity

Evidence linking OPE exposure with impacts on growth and adiposity is largely derived from *in vitro* and experimental animal studies. For example, four OPEs (i.e., TDCIPP, TCIPP, TPHP and TCEP) were positively correlated with triglyceride accumulation in a cell culture (3T3-L1) commonly use to investigate adipogenesis (i.e., fat cell development) (85). Furthermore, isopropylated triphenyl phosphate (ip-TPP) exposure was associated with increased total and HDL cholesterol, increased fructosamine (suggestive of hyperglycemia), and hypertrophy and neutral lipid accumulation in the adrenal gland in exposed rats (101). Further, perinatal exposure to Firemaster® 550, a flame retardant mixture containing OPEs [TPHP and isopropylated triaryl phosphates (ITPs)] and brominated compounds (2-ethylhexyl-2,3,4,5-tetrabromobenzoate and bis(2-ethylhexyl)-2,3,4,5-tetrabromophthalate) was associated with rapid weight gain in rat pups and obesity in adult rats (95).

Studies of adults and pregnant women have generally shown positive associations between measures of adiposity and OPE exposure (56, 65, 102). The epidemiologic literature includes a single cross-sectional evaluation of OPEs and children’s adiposity. Boyle et al. (102) reported that among children in the National Health and Nutrition Examination Survey (2013-2014 cycle), OPEs were associated with indicators of adiposity; however, the direction of the association differed by compound. Urinary di-n-butyl phosphate (DBUP) concentrations, for example, were inversely associated with the prevalence odds of obesity as well as body mass index z-scores. Conversely, urinary bis(2-chloroethyl) phosphate (BCEP) concentrations were suggestively associated with increased prevalence odds of

being overweight, and similar relationships were observed with BMI z-scores and waist circumference (102). As noted by Boyle et al., these findings may be due to reverse causality. For example, if obese individuals consume more OPE-contaminated foods or spend more time in contact with OPE-containing furniture than lean individuals, higher levels of OPEs could be expected in overweight individuals. Although few studies have evaluated food as a source of OPE exposure, diets high in fresh foods have been associated with lower OPE metabolite concentrations in adults (63, 103), and OPEs have been reported in a greater proportion of packaged foods (89%) than non-processed foods (11%) (104).

Asthma and Allergy

Few studies have assessed OPE impacts on children's immune and allergic outcomes, though allergic dermatitis has been reported following exposure (105–107). In a cross-sectional study evaluating allergic symptoms (i.e., rhinoconjunctivitis, wheeze, and eczema) among Japanese school children (n=128), TDCIPP in house dust was associated with eczema (108). Rhinoconjunctivitis and having at least one allergy symptom was more frequently observed among children who had the highest quartile of TCIPP urinary metabolites compared to the lowest quartile. Greater concentrations of metabolites of tris(2-butoxyethyl) phosphate (TBOEP) and TDCIPP were also observed to be associated with eczema and at least one allergy symptom. Previous work in Japan (n=516, including children and adults) found significant and positive associations between TCIPP and TDCIPP in house floor dust and the prevalence of atopic dermatitis (109). Tributyl phosphate (TBP) in both floor and multi-surface dust samples were also associated with asthma and allergic rhinitis. A matched case-control study conducted in Sweden evaluated asthma among 220 children at either 4 or 8 years of age with OPEs measured in mattress dust. Maternal mattress dust collected when children were 2 months of age was higher in TPHP and meta, meta, para-tricresyl phosphate (mmp-TMPP) for children that did not develop asthma (110). In addition, a null result was observed in the U.S. between OPEs measured in settled and HVAC filter dust and the severity of childhood asthma among 54 children (average age 10 years) (111). Overall, there is some suggestion that OPE exposure could be related to children's allergy symptoms; however, more thorough evaluations are needed to determine if a relationship exists between OPEs and asthma. Possible differences in findings in the current literature could be due to the use of household dust as an indicator of exposure in many studies. While the home environment and household dust are likely sources of exposure, it is worth noting that these measures do not capture information about other microenvironments (i.e., the car, other areas of the home, the workplace or school, etc.) which may be important contributors to exposure.

Neurodevelopment

The links between organophosphate pesticides and children's neurodevelopment have hastened the development of experimental models investigating behavioral impacts of OPE exposures. Experimental evidence has focused on OPE exposures and behavioral changes in model organisms (112–116), specifically zebrafish, which are proving to be useful model organisms for neurodevelopmental toxicity screening (117, 118). For example, Oliveri et al. (115) reported that zebrafish exposed to TDCIPP in early life exhibited elevated locomotor

activity and reduced predator escape behavior in adulthood, relative to controls. Similarly, Noyes et al. reported neurodevelopmental defects in embryonic zebrafish exposed to several OPEs (114).

Three prospective epidemiologic studies and one cross-sectional study evaluated the neurodevelopmental impacts of OPE levels in the U.S. over the past two decades (119–121) (122). Lipscomb et al. (122) studied the sum of OPE concentrations measured in passive silicone wristband samplers worn by Oregon preschool children in relation to the children's scores on the Social Skills Improvement Rating Scale, a teacher-rated social behavior assessment (n=72). Higher OPE concentrations in the passive samplers were associated with poorer performance on the Responsibility subscales and Externalizing subscales. However, the cross-sectional nature of this study limits causal inference.

Among the prospective studies, Castorina et al. (121) investigated three OPE metabolites measured in maternal prenatal urine and offspring's performance on three psychometric assessments administered at 7 years of age to children in California (n's from 248 to 282). The authors reported that higher concentrations of DPHP (as well as ΣOPEs, including DPHP, BDCIPP, and ip-PPP) in prenatal urine were associated with worse scores on the Wechsler Intelligence Scale for Children (WISC-IV), (particularly the Working Memory scale), and that higher concentrations of ip-PPP were associated with higher scores on the Behavior Assessment System for Children (BASC-2) Hyperactivity scale, suggesting more hyperactive behaviors. While this work has a number of strengths, it is important to note that mothers in this study were enrolled between 1999 and 2000, prior to the PBDE phase-out and subsequent increase in OPE usage; therefore, OPE exposure levels in this cohort may not reflect exposures post-PBDE phase-out, particularly for more recently introduced compounds, which are likely to be higher.

Among participants of the PIN study in North Carolina (2005-2008), concentrations of OPE metabolites in prenatal urine were associated with both cognitive and behavioral development at 2-3 years of age (n from 149 to 227) (119, 120). Specifically, higher ip-PPP concentrations were associated with poorer performance on two cognitive assessments: the Mullen Scales of Early Learning (MSEL) and the MacArthur-Bates Communicative Development Inventories (MB-CDI) (120). Higher BDCIPP concentrations were associated with more withdrawal and attention problems among children and higher DPHP concentrations were associated with greater hyperactivity and attention problems (assessed using the BASC-2) (119).

In summary, the limited body of available epidemiologic evidence suggests early-life exposures to OPEs, like exposure to their PBDE predecessors, may be associated with cognitive and behavioral effects, though these studies are not without their limitations. Reproduction of their results in other study populations, with repeated measures of OPE exposure are necessary to make stronger inference about the potential cognitive and behavioral effects of early-life OPE exposures and to identify periods of developmental susceptibility.

Conclusions and Recommendations

The past decade has seen an explosion of research investigating OPE exposures, with numerous studies demonstrating near ubiquitous detection of OPEs in various microenvironments and in human populations world-wide. In contrast, epidemiologic studies investigating potential health impacts remain limited in number; however, the available evidence suggests that OPEs may be affecting children's health. Neurodevelopment and asthma are perhaps the most well characterized adverse health outcomes, but the few available studies have notable limitations. Importantly, prior studies have been relatively small and have been limited in their capacity to investigate potential sex-specific impacts, and many have also been limited by cross-sectional designs, which precludes assessment of temporal ordering between exposure and outcome. Though most past studies have evaluated TPHP and TDCIPP metabolites, other OPEs investigated vary between studies making it difficult to assess consistency. In addition, past studies have relied heavily on urinary exposure biomarkers, which may be problematic given the rapid metabolism of OPEs. Although some research suggests moderate reliability of biomarkers over time [e.g. (24, 55, 63, 64, 66)], relying on a single spot urine measurement to capture long term exposure is likely to result in substantial exposure misclassification. External exposure monitoring (e.g. silicone wristbands or hand wipes) may be useful complementary measures of exposure in future studies (35, 71, 123).

Despite recent efforts, there remain important areas of children's health that have not been evaluated with respect to early-life OPE exposure. Of particular importance, perinatal exposure has not been assessed with respect to metabolic disorders (e.g. the development of obesity, diabetes, etc.). Given that childhood obesity is a risk factor for a multitude of adverse health outcomes throughout the life course and animal models suggest endocrine disrupting properties may impact growth, research in this area is urgently needed. Although experimental and epidemiologic studies of adults demonstrate impacts on endocrine function, there are no data evaluating OPE exposures and children's endocrine function, to our knowledge. While we find these novel areas of research to be particularly compelling for understanding the potential risks of early OPE exposure, additional studies evaluating all children's health outcomes are urgently needed. Much of the work that has been done investigating reproductive and children's health outcomes associated with OPE exposure thus far has been limited to a few cohorts (EARTH and PIN), and replication is essential. Also of importance in moving the field forward, researchers should consider possible patterns of co-exposure to other toxicants and the potential for interaction between contaminants in impacting children's growth, development and health. Given that OPEs are also used as plasticizers, similar to phthalates, it may be particularly interesting to look at co-exposures to these two groups. For example, we recently reported correlation between biomarkers of exposure to OPEs and phthalates in young children in the U.S. (124). Thus, it may be important to consider exposure to phthalates when evaluating health impacts of OPE exposures.

Changes in regulations surrounding the use of flame retardants in building materials, electronics and furniture could impact the use of flame retardants moving forward, and subsequently result in reductions in the use of these chemicals. However, OPEs are

environmentally persistent in indoor environments, and exposure will continue for many years to come. To date, there has been very little research evaluating methods to reduce individual exposure. Several studies have assessed handwashing, which has been related to reduced exposure to other flame retardants and indoor contaminants, but estimated OPE exposure reductions have been small and not statistically significant in children's cohorts (12, 35). A recent cross-over study demonstrated that house cleaning and hand washing led to decreased OPE urinary metabolites in adult mothers, but similar relationships were not assessed among their children (125). Given the environmental ubiquity of OPE, research evaluating possible interventions to reduce exposure is urgently needed.

Though they have been in commerce for decades, data suggest that the use of OPEs increased in the early 2000s as other brominated flame retardants were phased-out due to toxicity concerns. At that time, OPEs were largely thought to be safer because they are less persistent in the human body than their predecessors. However, as an increasing number of studies suggest ubiquitous detection in human samples and possible health impacts, the safety of OPEs should be rigorously investigated and their potential as a regrettable substitution should be scrutinized.

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Using silicone wristbands to assess exposure cross-sectionally, children with higher ΣOPFR were rated as having less responsible behavior and more externalizing behavior problems.

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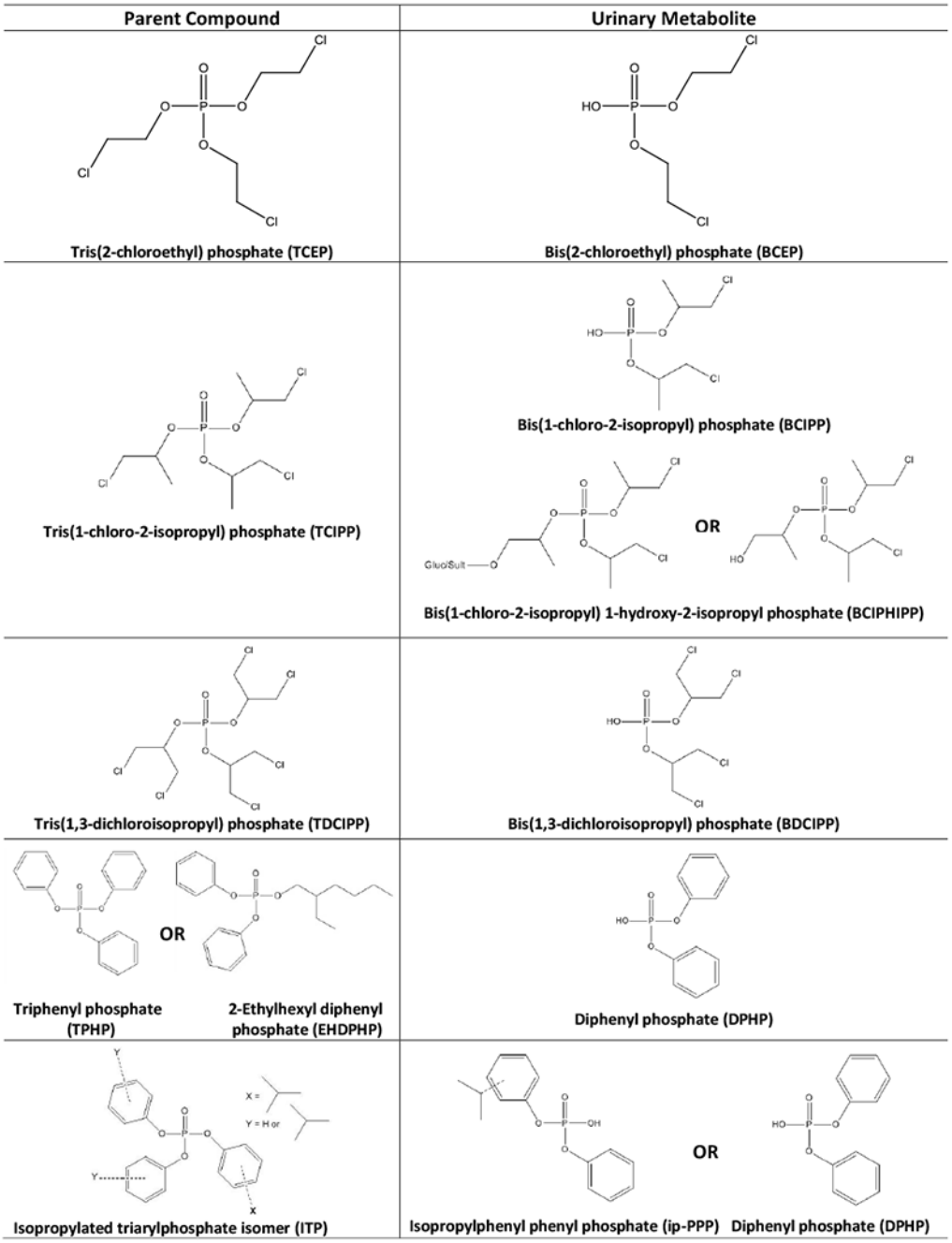

Figure 1:
Select organophosphate esters and their urinary metabolites.

Table 1:

Epidemiologic studies investigating OPE exposures and impacts on reproductive and children's health.

	Study Sample	Location	Study Design	Exposure Metric	Year of Sampling	Outcomes	Summary Findings
Reproductive Health							
Meeker et al. 2010	50 male partners in an infertile couple	Massachusetts, USA	cross-sectional	house dust	1999-2003	semen quality: concentration, motility and morphology; serum hormones: FSH, LH, inhibin B, SHBG, testosterone, free androgen index, free T4, total T3, and TSH	TDCPP associated with decline in free thyroxine and increase in prolactin; TPP was associated positively associated with prolactin and inversely associated with sperm concentration
Soubry et al. 2017	67 men in the TIEGER Study	North Carolina, USA	cross-sectional	urine	2012-2013	Sperm: differentially methylated regions (DMRs) of imprinted genes	OPES were associated with a higher fraction of aberrantly methylated sperm cells
Carignan et al. 2017	211 women in the EARTH Study	Massachusetts, USA	prospective IVF cohort	preconception urine	2005-2015	IVF outcomes: successful fertilization, implantation, clinical pregnancy and live birth	inverse associations between the sum of three OPE metabolites (BDCIPP, ip-PPP and DPHP) and proportions of fertilization, implantation, clinical pregnancy and live birth
Carignan et al. 2018	201 couples in the EARTH Study	Massachusetts, USA	prospective IVF cohort	preconception urine	2005-2015	IVF outcomes: successful fertilization, implantation, clinical pregnancy and live birth	male partner urinary BDCIPP was associated with reduced fertilization
Ingle et al. 2018	220 men in the EARTH Study	Massachusetts, USA	prospective IVF cohort	preconception urine	2005-2015	sperm count, concentration, motility, and morphology	odds of having a low sperm count decreased with increasing BDCIPP concentrations; other associations were weak and inconsistent
Messerlian et al. 2018	155 women with 179 pregnancies	Massachusetts, USA	prospective IVF cohort	preconception urine	2005-2015	pregnancy loss	preconception DPHP and the molar sum of OPEs associated with elevated risk of biochemical pregnancy loss
Birth Outcomes							
Feng et al. 2016	23 pregnant women (14 delivering term infants)	Shanghai, China	prospective pregnancy cohort	prenatal urine	2015	miscarriages, neonatal birthweight, gestational diabetes	no reported associations
Hoffman et al. 2018	349 women in the PIN Study	North Carolina, USA	prospective pregnancy cohort	prenatal urine	2002-2005	birth weight, gestational age, and birthweight for gestational age from medical records	Females: ip-PPP and BDCIPP inversely related to gestational age and odds of preterm birth Males: ip-PPP associated with decreased odds of preterm birth and DPHP suggestively associated with longer gestational age
Physical Growth and Adiposity							

	Study Sample	Location	Study Design	Exposure Metric	Year of Sampling	Outcomes	Summary Findings
Boyle et al. 2019	784 children age 6-19 years from NHANES	USA	cross-sectional	urine	2013-2014	obesity, body mass index, and waist circumference	inverse associations between DBUP and the prevalence odds of being obese, lower BMI z-scores and WC; BCEP was associated with increased prevalence odds of being overweight vs. normal weight among children
Asthma and Allergy							
Araki et al. 2013	516 all ages (126 children)	Japan	cross-sectional	house dust	2006	report of medical treatment for bronchial asthma, atopic dermatitis, allergic rhinitis, or allergic conjunctivitis during the preceding 2 years	TCIPP and TDCIPP in dust was positively associated with prevalence of atopic dermatitis; dust TBP was associated with asthma and allergic rhinitis
Canbaz et al. 2016	220 children 4-8 years of age in the BAMSE cohort	Sweden	nested case-control with exposure at age 2 months	mother's mattress dust	1994-2006	asthma at 4 or 8 years	TPHP and meta, meta, para-tricresyl phosphate (mmp-TMPP) for children that did not develop asthma
Araki et al. 2018	128 elementary school-aged children	Japan	cross-sectional	house dust and first-morning urine voids	2009-2010	parent-reported symptoms of wheeze, rhinoconjunctivitis, and eczema; evaluated using the International Study of Asthma and Allergies in Childhood questionnaire	TDCIPP in house dust, and metabolites of TDCIPP, TBOEP and TCIPP were associated with children's allergic symptoms
Bi et al. 2018	54 children approximately 10 years of age	Texas, USA	cross-sectional	HVAC filter dust and settled floor dust	2014-2015	asthma severity measured with the validated Severity of Chronic Asthma scale	no reported associations for OPEs
Neurodevelopment							
Castorina et al. 2017	248 to 282 children at age 7 years; CHAMACOS	California, USA	prospective pregnancy cohort	prenatal urine	1999-2000	neurodevelopment at age 7 years: Wechsler Intelligence Scale for Children, 4th ed. (WISC-IV); Behavior Assessment System for Children (BASC-2)	OPE metabolites positively associated with worse scores on the WISC-IV (particularly the Working Memory scale), and higher scores on the BASC-2 Hyperactivity scale
Lipscomb et al. 2017	72 preschool children	Oregon, USA	cross-sectional	silicone wristbands	2012-2013	Social Skills Improvement Rating Scale, a teacher-rated social behavior assessment	children with higher ΣOPFR were rated as having less responsible behavior and more externalizing behavior problems
Doherty et al. 2019a	149 to 227 children at age 2-3 years; PIN	North Carolina, USA	prospective pregnancy cohort	prenatal urine	2002-2005	cognitive development at age 2-3 years: MacArthur-Bates Communicative Development Inventories (MB-CDI) and the Mullen Scales of Early Learning (MSEL)	Higher levels ip-PPP associated with worse cognitive assessment scores on the MSEL and MB-CDI
Doherty et al. 2019b	199 children at age 3 years; PIN	North Carolina, USA	prospective pregnancy cohort	prenatal urine	2002-2005	behavioral development at age 3 years: Behavioral Assessment	BDCIPP associated with more withdrawal and attention problems;

Study Sample	Location	Study Design	Exposure Metric	Year of Sampling	Outcomes	Summary Findings
					System for Children 2nd Ed (BASC-2)	DPHP associated with greater hyperactivity and attention problems