

## **Supplemental Material:**

**1. Title:** Decreased Lung Function in 7-year-old Children with Early-Life Organophosphate Exposure

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## **Supplemental Methods:**

*Study setting and design.* Pregnant mothers were recruited to the CHAMACOS study during October 1999-October 2000. Women were eligible for the study if they were  $\geq 18$  years of age,  $<20$  weeks gestation who were planning to deliver at the county hospital, English or Spanish speaking, and Medi-Cal eligible. Medi-Cal is California's Medicaid health care program, and eligibility is based on economic need.

*Spirometry.* The children practiced blowing with a whistle before they practiced with the spirometer. They were instructed to blow into the whistle as loud and long as they can. Then, the technician would explain the purpose of the test and demonstrate the maneuver by blowing into the spirometer, and the children practiced blowing into the spirometer. Children were instructed to sit up straight on a stool with their feet flat on the floor, and take a deep breath and fill up their lungs with as much air as they can – till they feel like they cannot get any more in. The children were asked to place the mouthpiece in their mouth and seal it with their lips, and not to bite or stick their tongue in the hole, and then were coached to blast the air out as fast and as hard as they can, and not to stop until they are told. The technician kept encouraging the children to blow

until the test was completed. Children were instructed by demonstration not to lean forward when they blast out and to try to scrunch down instead.

After the practice, each child performed a maximum of eight expiratory maneuvers and up to three best acceptable tests were kept by the spirometric software. Each acceptable blow lasted at least three seconds. The children were coached to blow until the EasyOne signaled that the test has ended. All attempts were coached. Quality control was also achieved by verifying that the child did not lean forward; air did not leak out of the side; the child blew enough air in and took a deep breath right from the beginning; blew enough air out; did not stop blowing too soon; and took a big smooth breath. All maneuvers were reviewed again and verified by the two physicians to assure quality control.

***Data analysis.*** Season of birth corresponds generally to other potential exposures that might play a causal role in respiratory disease. We defined the seasons as follows: pollen (mid-January to mid-May 2000), dry (mid-May to mid-August 2000), mold (mid-August to mid-January 2001), wet (mid-January to mid-March 2001), pollen (mid-March to mid-May 2001) and dry (mid-May to October 2001). Discrete seasons of high spore and pollen concentrations were determined by ambient aeroallergen concentrations that were measured throughout the birth periods of the participants. Differences in the date of seasons across years are based on actual rainfall and measured pollen counts for that year. Detailed methods for the differentiation of the four seasons have been described elsewhere<sup>1</sup>. Data from the air monitoring station the Monterey Unified Air Pollution Control District (MBAPCD) was used to calculate the mean PM<sub>2.5</sub> concentration during the first three months of life. Measurements have been conducted every sixth day with high-volume Sierra-Andersen gravimetric samplers for 24 hours (Thermo

Scientific, Waltham, MA). The covariate pets at home (at ages 5 and 7) included indoor dogs, cats and other furry pets.

### **Supplemental Results:**

A total of 601 pregnant women were enrolled in the CHAMACOS cohort, of whom 347 children were followed when the children were approximately seven years of age<sup>2</sup>. 306 children attempted to complete the spirometry test. Of these, 27 children performed unacceptable maneuvers (either all spirometric measurements were unacceptable or only PEF measurements were acceptable). A total of 279 children (80.4% of the total number of children who were followed at seven years of age) completed the spirometry test. Families included in this analysis (n=279) did not differ significantly from families not included on most attributes, including urinary DAP concentrations during childhood (2,598 versus 2,337 (0.5-5 years; nmol/year/g crt)), maternal asthma (3.6 versus 6.5 percent), maternal education (78.9% versus 80.1% of mothers completed less than a high school education), marital status (marriage percentage—82% versus 80% ), poverty category (63.1% versus 60.1%), and child's birth weight (3,437 versus 3,440 g). However, mothers of children included in the present study were slightly older (mean age 26.5 versus 25.4, p=0.02), and breastfed the index child longer (9.1 months versus 4.9, p<0.01) than those from the initial cohort.

Families included in the analysis of participants who had at least two acceptable measurements (n=212) did not differ significantly from families included in the analysis of participants who had only one acceptable measurement (n=19) on most attributes, including urinary DAP concentrations during childhood, maternal age, maternal asthma, maternal

education, marital status, and poverty category. However, children included in the analysis of participants who had at least two acceptable measurements had a higher birth weight (mean birth weight 3,474 kg versus 3,173 kg,  $p < 0.01$ ) than those included in the analysis of children who had only one acceptable measurement.

When BMI was considered as a covariate in sensitivity analyses, it was not found to alter the associations reported.

#### **References:**

1. Harley KG, Macher JM, Lipsett M, et al. Fungi and Pollen Exposure in the First Months of Life and Risk of Early Childhood Wheezing. *Thorax* 2009;64(4):353–58. DOI: 10.1136/thx.2007.090241.
2. Raanan R, Harley KG, Balmes JR, et al. Early-life exposure to organophosphate pesticides and pediatric respiratory symptoms in the CHAMACOS cohort. *Environ Health Perspect* 2015;123(2):179–85. DOI: 10.1289/ehp.1408235. Epub 2014 Nov 4.

**Supplemental Table E1.** DAP metabolite concentrations<sup>\*†</sup>, measured in maternal urine during pregnancy (nmol/L) and in children's urine at follow-up visits (nmol/g creatinine) between ages 0.5-5 years), CHAMACOS.

	n	DF (%)	GM (95% CI)	min	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	max
<b>Measurements of pregnancy (nmol/L)</b>									
First Half of Pregnancy									
Total DAPs	207	(89.4)	108 (89,131)	4	39	105	275	826	5026
DE	207	(74.5)	14 (12,18)	0.2	5	13	33	94	2436
DM	207	(83.6)	73 (59,90)	2	21	70	213	622	5019
Second Half of Pregnancy									
Total DAPs	258	(99.2)	123 (109,140)	6	64	120	229	515	2366
DE	258	(97.7)	19 (16,23)	0.7	6	22	51	120	630
DM	259	(99.2)	85	2	41	84	171	403	3175

(74,98)

Pregnancy Average

Total DAPs	275	(100)	145	10	72	132	285	585	2554
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(128,163)

DE	275	(100)	22	0.4	9	22	50	94	1245
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(19,25)

DM	276	(100)	105	6	51	97	225	530	3175
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(92,121)

**Measurements of childhood (nmol/g crt)**

At 6 Months

Total DAPs	251	(99.2)	229	2	88	190	674	1893	78235
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(188,280)

DE	251	(90.1)	43	0.2	14	67	147	307	78010
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(34,54)

DM	251	(88.1)	108	0.7	29	93	398	1679	10073
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(85,137)

At 1 Year

Total DAPs	262	(95.4)	237	4	86	229	647	1638	10552
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			(197,285)						
DE	262	(93.1)	61	0.8	31	69	148	258	1626
			(52,72)						
DM	262	(79.8)	115	0.8	28	121	484	1408	10298
			(91,147)						
At 2 Years									
Total DAPs	263	(96.6)	214	3	101	216	587	1324	5943
			(179,256)						
DE	263	(71.5)	22	0.0	3	47	117	302	1325
			(17,29)						
DM	263	(96.2)	149	2	56	164	423	1025	5843
			(124,179)						
At 3.5 Years									
Total DAPs	217	(94.5)	161	2	55	179	520	948	9240
			(130,198)						
DE	217	(63.1)	6	0.0	0.6	14	54	162	546
			(4,8)						

DM	217	(93.1)	132	2	44	143	361	929	8694
			(107,164)						

At 5 Years

Total DAPs	259	(91.2)	128	0.9	45	144	334	930	10085
			(105,155)						

DE	259	(50.1)	3	0.0	0.2	5	42	113	519
			(2,4)						

DM	259	(88)	101	0.8	39	97	288	840	10052
			(82,124)						

**AUC (0.5-5 years; nmol/year/g crt)**

Total DAPs	231	(90.9-	1687	118	861	1702	3095	6335	18927
		99.1)	(1493,1905)						

DE	231	(51.5-	258	14	137	255	525	812	16580
		92.5)	(227,293)						

DM	231	(78.3-	1311	79	608	1350	2598	5636	15460
		96.4)	(1150,1495)						

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Abbreviations: DF= detection frequency; GM= geometric mean; CI= Confidence Interval; crt=creatinine; diethyl (DE) phosphate, dimethyl (DM) phosphate and total dialkyl phosphate (DAP) metabolites.



\*Limits of detection for all DE analytes ranged from 0.05-0.2 ug/L, and for all DM analytes 0.08-0.58 ug/L.

†Pregnancy measurements were specific gravity adjusted and childhood measurements were creatinine adjusted.

**Supplemental Table E2.** Associations<sup>\*†</sup> [ $\beta$  (95% CI)] of lung function<sup>‡</sup> at age 7 with average<sup>§</sup> prenatal concentrations of dialkyl phosphate (DAP) metabolites<sup>||</sup> measured in maternal urine collected twice during pregnancy.

	n	DEs	p- Value	DMs	p- Value	Total DAPs	p- Value
FEV <sub>1</sub> (L/s)	242	-0.02 (-0.12,0.08)	0.7	0.00 (-0.12,0.11)	1	-0.01 (0.14,0.11)	0.8
FVC (L)	205	-0.03 (-0.16,0.09)	0.6	-0.01 (-0.15,0.13)	0.9	-0.05 (-0.21,0.12)	0.6
FEF <sub>2575</sub> (L/s)	205	-0.06 (-0.27,0.15)	0.6	0.02 (-0.23,0.27)	0.9	-0.03 (-0.30,0.25)	0.9
FEV <sub>1</sub> /FVC	205	0.00 (-0.01,0.02)	0.7	0.01 (-0.01,0.02)	0.6	0.01 (-0.01,0.03)	0.5

\*Coefficients reflect change per 10-fold increase in specific-gravity adjusted metabolite concentrations.

†Adjusted for child's sex, age and age squared, log height, maternal smoking during pregnancy, season of birth (mold/wet/pollen/dry), mean daily PM<sub>2.5</sub> during first 3 months of life, breast feeding duration, signs of moderate/extensive mold at home visit (6 or 12 months), distance ( $\leq 150$ m) from highway (6 or 12 months), pets at home (5-7 years), household food insecurity score (7 years), maternal education, season of

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spirometry and technician. <sup>‡</sup>Highest lung function measurements of children that had at least two blows.

<sup>§</sup>Comprised from the average of the two measurements taken during pregnancy; for mothers who did not have both measurements, the average reflects the single measurement available. <sup>||</sup>Diethyl (DE) phosphate, dimethyl (DM) phosphate and total dialkyl phosphate (DAP) metabolites.

**Supplemental Table E3.** Associations<sup>\*†</sup> [ $\beta$  (95% CI)] of lung function<sup>‡</sup> at age 7, excluding children that took any medication 24 hours before the test who were prescribed respiratory medication during the last 12 months, with average<sup>§</sup> prenatal concentrations of dialkyl phosphate (DAP) metabolites<sup>||</sup> measured in maternal urine collected twice during pregnancy.

	n	DEs	p- Value	DMs	p- Value	Total DAPs	p- Value
FEV <sub>1</sub> (L/s)	236	0.00 (0.10,0.10)	1	0.03 (-0.09,0.14)	0.6	0.02 (-0.11,0.15)	0.8
FVC (L)	203	-0.03 (0.15,0.01)	0.7	0.01 (-0.14,0.15)	0.9	-0.03 (-0.19,0.14)	0.7
FEF <sub>2575</sub> (L/s)	203	-0.06 (-0.27,0.16)	0.6	0.03 (-0.22,0.28)	0.8	-0.02 (-0.30,0.27)	0.9
FEV <sub>1</sub> /FVC	203	0.00 (-0.01,0.02)	0.7	0.00 (-0.01,0.02)	0.7	0.01 (-0.01,0.03)	0.6

\*Coefficients reflect change per 10-fold increase in specific-gravity adjusted metabolite concentrations.

†Adjusted for child's sex, age and age squared, log height, maternal smoking during pregnancy, season of birth (mold/wet/pollen/dry), mean daily PM<sub>2.5</sub> during first 3 months of life, breast feeding duration, signs of moderate/extensive mold at home visit (6 or 12 months), distance ( $\leq$ 150m) from highway (6 or 12 months), pets at home (5-7 years), household food insecurity score (7 years), maternal education, season of spirometry and technician. ‡Highest lung function measurements of children that had at least two blows.

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<sup>§</sup>Comprised from the average of the two measurements taken during pregnancy; for mothers who did not have both measurements, the average reflects the single measurement available. <sup>||</sup>Diethyl (DE) phosphate, dimethyl (DM) phosphate and total dialkyl phosphate (DAP) metabolites.

**Supplemental Table E4.** Associations\*† [β (95% CI)] of lung function at age 7 with childhood concentrations of dialkyl phosphate (DAP) metabolites‡ measured at follow-up visits between 0.5-5 years of age.

	n	DEs	p- Value	DMs	p- Value	Total DAPs	p- Value
Highest FEV <sub>1</sub> for children who had one, two, or three maneuvers							
Minimally adjusted	231	-0.14 (-0.29,0.00)	0.06	-0.14 (0.28,0.01)	0.06	-0.16 (-0.31,0.01)	0.04
Adjusted	224	-0.18 (-0.32,-0.05)	0.009	-0.10 (-0.23,0.04)	0.1	-0.14 (-0.29, 0.00)	0.05
Highest FEV <sub>1</sub> for children who had at least two maneuvers							
Minimally adjusted	212	-0.12 (-0.27,0.02)	0.09	-0.15 (-0.29,0.01)	0.04	-0.17 (-0.32,0.03)	0.02
Adjusted	207	-0.16 (-0.30,-0.03)	0.02	-0.12 (-0.25,0.02)	0.08	-0.16 (-0.30,0.02)	0.03
Highest FVC for children who had one, two, or three maneuvers							
Minimally adjusted	206	-0.16 (-0.32,0.02)	0.07	-0.12 (-0.29,0.05)	0.2	-0.15 (-0.33,0.03)	0.1

Adjusted	203	-0.18 (-0.34,-0.02)	0.03	-0.08 (-0.24,0.09)	0.4	-0.12 (-0.29,0.05)	0.2
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Highest FVC for children who had at least two maneuvers

Minimally adjusted	178	-0.14 (-0.32,0.05)	0.1	-0.15 (-0.33,0.03)	0.1	-0.17 (-0.36,0.02)	0.07
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Adjusted	175	-0.17 (-0.33,0.00)	0.06	-0.13 (-0.29,0.04)	0.1	-0.17 (-0.34,0.01)	0.06
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Highest FEF<sub>2575</sub> for children who had one, two, or three maneuvers

Minimally adjusted	206	-0.30 (-0.80,-0.01)	0.04	-0.10 (-0.39,0.18)	0.5	-0.17 (-0.47,0.13)	0.3
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Adjusted	203	-0.36 (-0.64,-0.08)	0.01	-0.09 (-0.37,0.20)	0.6	-0.18 (-0.49,0.12)	0.2
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Highest FEF<sub>2575</sub> for children who had at least two maneuvers

Minimally adjusted	178	-0.22 (-0.51,0.07)	0.1	-0.07 (-0.35,0.21)	0.6	-0.12 (-0.42,0.18)	0.4
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Adjusted	175	-0.26 (-0.55,0.03)	0.08	-0.06 (-0.34,0.23)	0.7	-0.14 (-0.44,0.17)	0.4
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\*Coefficients reflect change per 10-fold increase in creatinine-adjusted (nmol/g creatinine) metabolite concentrations assessed by the Area Under Curve. †Minimally adjusted for child's sex, age, age squared, and log height. Fully adjusted models also include maternal smoking during pregnancy, season of birth

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(mold/wet/pollen/dry), mean daily PM<sub>2.5</sub> during first 3 months of life, breast feeding duration, signs of moderate/extensive mold at home visit (6 or 12 months), distance ( $\leq 150$ m) from highway (6 or 12 months), pets at home (5-7 years), household food insecurity score (7 years), maternal education, season of spirometry and technician. ‡Diethyl (DE) phosphate, dimethyl (DM) phosphate and total dialkyl phosphate (DAP) metabolites.



**Supplemental Table E5.** Associations<sup>\*†</sup> [ $\beta$  (95% CI)] of FEV<sub>1</sub>/FVC ratio at age 7 with childhood concentrations of dialkyl phosphate (DAP) metabolites‡ measured at follow-up visits between 0.5-5 years of age.

	n	DEs	p- Value	DMs	p- Value	Total DAPs	p- Value
Highest FEV <sub>1</sub> /FVC ratio for children who had one, two, or three maneuvers							
Minimally adjusted	206	0.00 (-0.02,0.02)	0.9	0.01 (-0.01,0.03)	0.5	0.01 (-0.02,0.03)	0.6
Adjusted	203	0.00 (-0.02,0.01)	0.7	0.01 (-0.01,0.02)	0.6	0.00 (-0.02,0.02)	0.8
Highest FEV <sub>1</sub> /FVC ratio for children who had at least two maneuvers							
Minimally adjusted	178	-0.01 (-0.03,0.01)	0.6	0.01 (-0.01,0.03)	0.3	0.01 (-0.01,0.03)	0.5
Adjusted	175	-0.01 (-0.03,0.01)	0.5	0.01 (-0.01,0.03)	0.4	0.01 (-0.02,0.03)	0.6

\*Coefficients reflect change per 10-fold increase in creatinine-adjusted (nmol/g creatinine) metabolite

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concentrations assessed by the Area Under Curve. †Minimally adjusted for child's sex, age, age squared, and log height. Fully adjusted models also include maternal smoking during pregnancy, season of birth (mold/wet/pollen/dry), mean daily PM<sub>2.5</sub> during first 3 months of life, breast feeding duration, signs of moderate/extensive mold at home visit (6 or 12 months), distance ( $\leq 150\text{m}$ ) from highway (6 or 12 months), pets at home (5-7 years), household food insecurity score (7 years), maternal education, season of spirometry and technician. ‡Diethyl (DE) phosphate, dimethyl (DM) phosphate and total dialkyl phosphate (DAP) metabolites.

**Supplemental Table E6.** Associations<sup>\*†</sup> [ $\beta$  (95% CI)] of lung function at age 7, excluding children that took any medication 24 hours before the test who were prescribed respiratory medication during the last 12 months, with childhood concentrations of dialkyl phosphate (DAP) metabolites<sup>‡</sup> measured at follow-up visits between 0.5-5 years.

	n	DEs	p- Value	DMs	p- Value	Total DAPs	p- Value
Highest FEV <sub>1</sub> for children who had one, two, or three maneuvers							
Minimally adjusted	226	-0.13 (-0.28,0.02)	0.09	-0.13 (-0.28,0.02)	0.08	-0.16 (-0.31,0.00)	0.05
Adjusted	219	-0.17 (-0.31,-0.03)	0.02	-0.09 (-0.23,0.05)	0.2	-0.14 (-0.28,0.01)	0.07
Highest FEV <sub>1</sub> for children who had at least two maneuvers							
Minimally adjusted	207	-0.11 (-0.25,0.04)	0.2	-0.14 (-0.29,0.00)	0.05	-0.17 (-0.32,0.01)	0.04
Adjusted	202	-0.15 (-0.29,-0.01)	0.03	-0.11 (-0.25,0.03)	0.1	-0.15 (-0.30,0.01)	0.04
Highest FVC for children who had one, two, or three maneuvers							

Minimally adjusted	203	-0.14 (-0.32,0.03)	0.1	-0.11 (-0.29,0.06)	0.2	-0.14 (-0.33,0.05)	0.1
Adjusted	200	-0.18 (-0.34,-0.02)	0.03	-0.077 (-0.24,0.09)	0.4	-0.13 (-0.30,0.05)	0.2

Highest FVC for children who had at least two maneuvers

Minimally adjusted	176	-0.12 (-0.31,0.06)	0.2	-0.14 (-0.32,0.05)	0.1	-0.16 (-0.35,0.03)	0.1
Adjusted	173	-0.16 (-0.33,0.01)	0.07	-0.12 (-0.29,0.05)	0.2	-0.16 (-0.34,0.02)	0.08

Highest FEF<sub>2575</sub> for children who had one, two, or three maneuvers

Minimally adjusted	203	-0.29 (-0.57,-0.01)	0.05	-0.10 (-0.39,0.19)	0.5	-0.17 (-0.48,0.14)	0.3
Adjusted	200	-0.36 (-0.65,-0.08)	0.01	-0.10 (-0.39,0.19)	0.5	-0.20 (-0.51,0.11)	0.2

Highest FEF<sub>2575</sub> for children who had at least two maneuvers

Minimally adjusted	176	-0.21 (-0.50,0.08)	0.2	-0.05 (-0.34,0.24)	0.7	-0.10 (-0.41,0.21)	0.5
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Adjusted 173 -0.26 (-0.55,0.04) 0.09 -0.05 (-0.34,0.25) 0.8 -0.13 (-0.44,0.18) 0.4

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\*Coefficients reflect change per 10-fold increase in creatinine-adjusted (nmol/g creatinine) metabolite concentrations assessed by the Area Under Curve. †Minimally adjusted for child's sex, age, age squared, and log height. Fully adjusted models also include maternal smoking during pregnancy, season of birth (mold/wet/pollen/dry), mean daily PM2.5 during first 3 months of life, breast feeding duration, signs of moderate/extensive mold at home visit (6 or 12 months), distance ( $\leq 150$ m) from highway (6 or 12 months), pets at home (5-7 years), household food insecurity score (7 years), maternal education, season of spirometry and technician. ‡Diethyl (DE) phosphate, dimethyl (DM) phosphate and total dialkyl phosphate (DAP) metabolites.

**Supplemental Table E7.** Associations\*<sup>†</sup> [ $\beta$  (95% CI)] of FEV<sub>1</sub>/FVC ratio at age 7, excluding children that took any medication 24 hours before the test who were prescribed respiratory medication during the last 12 months, with childhood concentrations of dialkyl phosphate (DAP) metabolites<sup>‡</sup> measured at follow-up visits between 0.5-5 years.

	n	DEs	p- Value	DMs	p- Value	Total DAPs	p- Value
Highest FEV <sub>1</sub> /FVC ratio for children who had one, two, or three maneuvers							
Minimally adjusted	203	0.00 (-0.02,0.02)	0.7	0.01 (-0.01,0.02)	0.6	0.00 (-0.02,0.02)	0.8
Adjusted	200	-0.01 (-0.03,0.01)	0.5	0.00 (-0.02,0.02)	0.8	0.00 (-0.02,0.02)	1
Highest FEV <sub>1</sub> /FVC ratio for children who had at least two maneuvers							
Minimally adjusted	176	-0.01 (-0.03,0.01)	0.5	0.01 (-0.01,0.03)	0.4	0.01 (-0.02,0.03)	0.6
Adjusted	173	-0.01 (-0.03,0.01)	0.4	0.01 (-0.01,0.03)	0.5	0.00 (-0.02,0.03)	0.7

\*Coefficients reflect change per 10-fold increase in creatinine-adjusted (nmol/g creatinine) metabolite

concentrations assessed by the Area Under Curve. <sup>†</sup>Minimally adjusted for child's sex, age, age squared, and log height. Fully adjusted models also include maternal smoking during pregnancy, season of birth (mold/wet/pollen/dry), mean daily PM<sub>2.5</sub> during first 3 months of life, breast feeding duration, signs of moderate/extensive mold at home visit (6 or 12 months), distance ( $\leq 150$ m) from highway (6 or 12 months), pets at home (5-7 years), household food insecurity score (7 years), maternal education, season of spirometry and technician. <sup>‡</sup>Diethyl (DE) phosphate, dimethyl (DM) phosphate and total dialkyl phosphate (DAP) metabolites.