

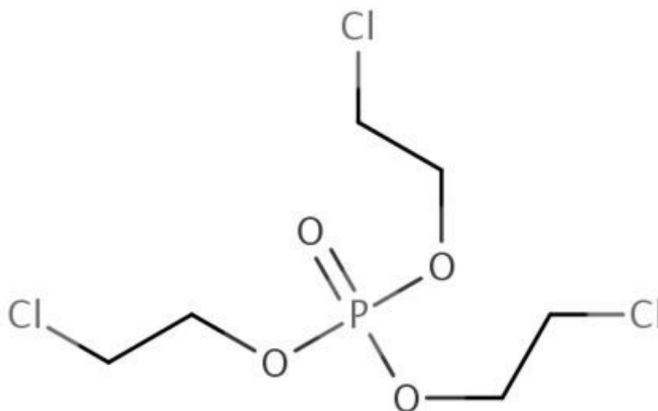
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## Draft Risk Evaluation for Tris(2-chloroethyl) phosphate (TCEP)

### Systematic Review Supplemental File:

#### Data Quality Evaluation Information for Human Health Hazard Epidemiology

CASRN: 115-96-8



*December 2023*

This supplemental file contains information regarding the data quality evaluation results for data sources that met the PECO screening criteria for the *Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)* and were used to characterize human health hazard. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (e.g., statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in *The Systematic Review Protocol for the Draft Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)*.

# Table of Contents

HERO ID	Reference	Page
<b>Tris(2-chloroethyl) phosphate (TCEP)</b>		
<b>Immune/Hematological</b>		
6957526	Araki, A., Bamai, Y. A., Bastiaensen, M., Van den Eede, N., Kawai, T., Tsuboi, T., Miyashita, C., Itoh, S., Goudarzi, H., Konno, S., Covaci, A., Kishi, R. (2020). Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. <i>Environmental Research</i> 183:109212.	4
2994738	Canbaz, D., van Velzen, M. J., Hallner, E., Zwinderman, A. H., Wickman, M., Leonards, P. E., van Ree, R., van Rijt, L. S. (2015). Exposure to organophosphate and polybrominated diphenyl ether flame retardants via indoor dust and childhood asthma. <i>Indoor Air</i> 26(3):403-413.	7
<b>Endocrine</b>		
4161719	Hoffman, K., Lorenzo, A., Butt, C. M., Hammel, S. C., Henderson, B. B., Roman, S. A., Scheri, R. P., Stapleton, H. M., Sosa, J. A. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. <i>Environment International</i> 107:235-242.	9
<b>Cancer/Carcinogenesis</b>		
4161719	Hoffman, K., Lorenzo, A., Butt, C. M., Hammel, S. C., Henderson, B. B., Roman, S. A., Scheri, R. P., Stapleton, H. M., Sosa, J. A. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. <i>Environment International</i> 107:235-242.	11
6747922	Li, Y., Fu, Y., Hu, K., Zhang, Y., Chen, J., Zhang, S., Zhang, B., Liu, Y. (2020). Positive correlation between human exposure to organophosphate esters and gastrointestinal cancer in patients from Wuhan, China. <i>Ecotoxicology and Environmental Safety</i> 196:110548.	13
<b>Lung/Respiratory</b>		
6957526	Araki, A., Bamai, Y. A., Bastiaensen, M., Van den Eede, N., Kawai, T., Tsuboi, T., Miyashita, C., Itoh, S., Goudarzi, H., Konno, S., Covaci, A., Kishi, R. (2020). Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. <i>Environmental Research</i> 183:109212.	16
<b>Metabolite: bis-2-chloroethyl phosphate (BCEP)</b>		
<b>Reproductive/Developmental</b>		
7274557	Crawford, K. A., Hawley, N., Calafat, A. M., Jayatilaka, N. K., Froehlich, R. J., Has, P., Gallagher, L. G., Savitz, D. A., Braun, J. M., Werner, E. F., Romano, M. E. (2020). Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. <i>Environmental Health: A Global Access Science Source</i> 19(1):97.	19
<b>Neurological/Behavioral</b>		
7274557	Crawford, K. A., Hawley, N., Calafat, A. M., Jayatilaka, N. K., Froehlich, R. J., Has, P., Gallagher, L. G., Savitz, D. A., Braun, J. M., Werner, E. F., Romano, M. E. (2020). Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. <i>Environmental Health: A Global Access Science Source</i> 19(1):97.	22

<b>Study Citation:</b>	Araki, A., Bamai, Y. A., Bastiaensen, M., Van den Eede, N., Kawai, T., Tsuboi, T., Miyashita, C., Itoh, S., Goudarzi, H., Konno, S., Covaci, A., Kishi, R. (2020). Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. <i>Environmental Research</i> 183:109212.		
<b>Health Outcome(s):</b>	Immune/Hematological		
<b>Reported Health Effect(s):</b>	eczema, allergic rhinoconjunctivitis		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	6957526		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	The study was conducted among elementary school students in Sapporo, Japan in 2008. The survey was sent to 6393 school children across 12 public elementary schools, and 44008 students responded, with 951 students interested in participating. Only 681 families were still at the same elementary school in 2009, of those only 128 families were able to be contacted for a home visit, meaning there was an overall participation rate of 2.9%. Despite a low participation rate, the reasons for exclusion are clearly defined at each step and are unlikely to introduce significant bias.
Metric 2:	Attrition	High	Of the final 128 participants, none were excluded from the data analysis after home visits/data collection occurred. There is no missing exposure or outcome data.
Metric 3:	Comparison Group	Medium	Participants in this cross-sectional study appear to be similar in terms of baseline characteristics. Most variables are controlled for in statistical analyses. Height and weight are not controlled for, but the listed mean + standard deviations imply that there is a somewhat large range.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	High	Exposure is reported as TCEP measured from urine.
Metric 5:	Exposure Levels	Medium	The study reports on a range of exposures from the LOQ to 1.13 nM of TCEP. In statistical analyses, TCEP concentrations are split into tertiles.
Metric 6:	Temporality	Medium	Exposure was measured after the onset of symptoms, so the temporality of the sum metabolites is not confirmed to be accurate. However, due to the ubiquity of TCEP in the environment, it is reasonable to assume that they were exposed to the same amount of TCEP prior to exposure assessment. However, the study does not check to see if children had moved recently, which could alter temporality.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Outcomes were assessed via the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, which was filled out by the parents. The questionnaire asks for symptoms common for wheeze, eczema, and allergic rhinoconjunctivitis. There was no medical diagnosis by a physician.
Metric 8:	Reporting Bias	High	A description of the the outcomes is clearly mentioned in the methods. Results are presented as odds ratios with 95% confidence intervals and p-values.
Domain 4: Potential Confounding / Variability Control			

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<b>Study Citation:</b>	Araki, A., Bamai, Y. A., Bastiaensen, M., Van den Eede, N., Kawai, T., Tsuboi, T., Miyashita, C., Itoh, S., Goudarzi, H., Konno, S., Covaci, A., Kishi, R. (2020). Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. Environmental Research 183:109212.			
<b>Health Outcome(s):</b>	Immune/Hematological			
<b>Reported Health Effect(s):</b>	eczema, allergic rhinoconjunctivitis			
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound			
<b>Linked HERO ID(s):</b>	No linked references.			
<b>HERO ID:</b>	6957526			
Domain	Metric	Rating	Comments	
	Metric 9: Covariate Adjustment	High	The results are reported as odds ratios that are adjusted for sex, grade, annual income, and the dampness index of the child's home. They were all included based on a priori evidence.	
	Metric 10: Covariate Characterization	Medium	Information on confounders were obtained via questionnaire. Sex and grade were measured via questionnaire and were unlikely to be reported incorrectly. Annual income is also self-reported, and could fall victim to desirability bias. There were also missing values for income (14.8% ) to which the mean annual household income was assigned. Finally, a "dampness" index was calculated by study investigator observation of dampness-related problems in each dwelling, such as condensation and visible mold.	
	Metric 11: Co-exposure Counfounding	Medium	The intent of this study was to measure co-exposures of phthalates and phosphate flame retardants and allergic outcomes. Statistical models were used in this study to examine in urine individual phthalates, combinations of phthalates, metabolites of PFRs and a combination of certain PFRs.	
Domain 5: Analysis				
	Metric 12: Study Design and Methods	High	The use of a cross-sectional design to understand the relationship between TCEP and wheeze/allergy symptoms is an appropriate study design, and calculating odds ratios via logistic regression is an appropriate method.	
	Metric 13: Statistical Power	Medium	The number of participants in each tertile is >20, which could be sufficiently large to detect an effect. The authors do not calculate statistical power, however they do mention that the power may not be enough to detect a significant effect. They may be referring to the multipollutant models in this case.	
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis is thorough and allows for replication given the study data.	
	Metric 15: Statistical Analysis	High	The model building is transparent and it is clear why variables were chosen.	
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)				
	Metric 16: Use of Biomarker of Exposure	High	TCEP is a parent compound.	
	Metric 17: Effect Biomarker	N/A	Not applicable - no biomarker of effect.	
	Metric 18: Method Sensitivity	Medium	The % of samples below the detection limit is stated to be 14.8% , which is not incredibly high but is sufficient to address the research hypothesis.	
	Metric 19: Biomarker Stability	Medium	There is no documented stability data, but is clarified that spot urine samples were collected in polypropylene containers and refrigerated until the study visit, and then stored a -20 deg C until the day of analysis.	
	Metric 20: Sample Contamination	Medium	There is no documentation of potential sample contamination.	
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<b>Study Citation:</b>	Araki, A., Bamai, Y. A., Bastiaensen, M., Van den Eede, N., Kawai, T., Tsuboi, T., Miyashita, C., Itoh, S., Goudarzi, H., Konno, S., Covaci, A., Kishi, R. (2020). Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. Environmental Research 183:109212.
<b>Health Outcome(s):</b>	Immune/Hematological
<b>Reported Health Effect(s):</b>	eczema, allergic rhinoconjunctivitis
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
<b>Linked HERO ID(s):</b>	No linked references.
<b>HERO ID:</b>	6957526

Domain	Metric	Rating	Comments
	Metric 21: Method Requirements	High	TCEP was measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS).
	Metric 22: Matrix Adjustment	Medium	TCEP concentrations were creatinine-adjusted, and ranges are reported without adjustment and with adjustment. However, the statistical model only uses adjusted concentrations of TCEP.

**Additional Comments:** This cross-sectional study measures the association between TCEP measured in spot urine samples and parent-reported symptoms of allergic rhinoconjunctivitis and eczema. Associations were analyzed using logistic regression and the study calculated odds ratios. No significant associations in single-pollutant models for TCEP were reported. The study has some deficiencies in outcome assessment, as there is no verifiable method used in this study.

**Overall Quality Determination** **High**

<b>Study Citation:</b>	Canbaz, D., van Velzen, M. J., Hallner, E., Zwinderman, A. H., Wickman, M., Leonards, P. E., van Ree, R., van Rijt, L. S. (2015). Exposure to organophosphate and polybrominated diphenyl ether flame retardants via indoor dust and childhood asthma. <i>Indoor Air</i> 26(3):403-413.			
<b>Health Outcome(s):</b>	Immune/Hematological			
<b>Reported Health Effect(s):</b>	Asthma			
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound			
<b>Linked HERO ID(s):</b>	No linked references.			
<b>HERO ID:</b>	2994738			
Domain	Metric	Rating	Comments	
Domain 1: Study Participation				
	Metric 1: Participant Selection	Medium	The authors reported participant selection in both this study and in Almqvist et al., 2003. However, not all of the elements were reported, such as participation rate at all phases of the study.	
	Metric 2: Attrition	Medium	Exclusion and missing values were reported in the Materials and Methods Section, Table 1, and Table S1.	
	Metric 3: Comparison Group	High	Study matches controls based on sex, atopic background of the parents, and socioeconomic status. Study states that the asthmatic children and their matched controls did not differ significantly according to several sociodemographic characteristics outlined in Table S1.	
Domain 2: Exposure Characterization				
	Metric 4: Measurement of Exposure	High	Samples were filtered, sealed, and stored appropriately. Analyzed by GC-EI-MS with QA detailed in Brandsma et al., 2014. Additional details in Almqvist et al., 2003	
	Metric 5: Exposure Levels	Medium	Table 3 provides the range and distribution of exposure for both cases and controls.	
	Metric 6: Temporality	High	House dust adequate to capture short half-life of TCEP. Dust was collected and analyzed when children were two months of age; exposure precedes disease.	
Domain 3: Outcome Assessment				
	Metric 7: Outcome Measurement or Characterization	High	Asthma defined according to set of criteria, including doctor's diagnosis and asthma medicine prescription.	
	Metric 8: Reporting Bias	Low	Not all data shown from analyses, including the multivariate linear regression analysis.	
Domain 4: Potential Confounding / Variability Control				
	Metric 9: Covariate Adjustment	Medium	Study reports multivariate linear regression analyses to adjust for covariates; however, the data was not shown in the main paper or supplemental. Study noted that the results did not differ from those reported.	
	Metric 10: Covariate Characterization	High	Questionnaire and doctors' diagnoses used.	
	Metric 11: Co-exposure Counfounding	Medium	Adjusted for in the multivariate linear regression analyses; data not shown but stated to not affect results.	
Domain 5: Analysis				
	Metric 12: Study Design and Methods	Low	Case-control used but no logistic regression conducted; no odds ratios.	
	Metric 13: Statistical Power	Medium	110 cases; 110 controls; adequate sample size	

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<b>Study Citation:</b>	Canbaz, D., van Velzen, M. J., Hallner, E., Zwinderman, A. H., Wickman, M., Leonards, P. E., van Ree, R., van Rijt, L. S. (2015). Exposure to organophosphate and polybrominated diphenyl ether flame retardants via indoor dust and childhood asthma. Indoor Air 26(3):403-413.
<b>Health Outcome(s):</b>	Immune/Hematological
<b>Reported Health Effect(s):</b>	Asthma
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
<b>Linked HERO ID(s):</b>	No linked references.
<b>HERO ID:</b>	2994738

Domain	Metric	Rating	Comments
	Metric 14: Reproducibility of Analyses	Medium	Sufficient summary of analyses
	Metric 15: Statistical Analysis	High	Methods are transparent

Additional Comments: None

### Overall Quality Determination

**Medium**

\* No biomarkers were identified for this evaluation.



<b>Study Citation:</b>	Hoffman, K., Lorenzo, A., Butt, C. M., Hammel, S. C., Henderson, B. B., Roman, S. A., Scheri, R. P., Stapleton, H. M., Sosa, J. A. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. <i>Environment International</i> 107:235-242.		
<b>Health Outcome(s):</b>	Endocrine		
<b>Reported Health Effect(s):</b>	thyroid cancer (papillary)		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	4161719		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	High	Participant selection was well described, including timing of study, inclusion and exclusion criteria and case ascertainment.
	Metric 2: Attrition	High	Supplemental Figure 1 provides detailed information and shows only 1 of 71 cases excluded.
	Metric 3: Comparison Group	High	Cases and controls were recruited from the same Health Care Center during the same time period and were matched by age and gender.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	High	Flame retardants were measured in house dust. Collection methods and analysis of dust was fully reported. TCEP concentrations in household dust were measured by GC/EI-MS.
	Metric 5: Exposure Levels	Low	Only 2 levels of flame retardant exposure in the home were reported for cases and controls; TCEP concentrations above the median concentration were reported for both groups. Median TCEP concentrations were shown in the box plot in Fig. 1 but concentrations were not reported. Detection limits were not reported for organophosphate flame retardants.
	Metric 6: Temporality	Medium	Exposure at the same residence for at least 2 years prior to diagnosis; however, it is unclear whether exposure duration was sufficient for thyroid cancer.
Domain 3: Outcome Assessment			
	Metric 7: Outcome Measurement or Characterization	High	The thyroid cancer outcome was assessed by medical review of clinical and pathology data; pathological stage was assessed based on tumor size, location, metastasis.
	Metric 8: Reporting Bias	Medium	Health outcomes and exposures are reported, except for median exposure levels of each of the flame retardants. Adjusted ORs with CIs reported for overall incidence as well as measures of tumor aggressiveness (i.e., pathologic stage). Some data were reported for PBDEs but not the organophosphate flame retardants, such as number of detects, detection limits.
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	Covariate adjustments were described (age, income, BMI). Regression analyses were adjusted for participant age and household income. BMI was both included and excluded as a covariate. Other potential confounders were considered, but not applied because they did not alter effect estimates (race, employment status, and smoking). Ionizing radiation exposure was considered but no participants reported prior exposure.

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<b>Study Citation:</b>	Hoffman, K., Lorenzo, A., Butt, C. M., Hammel, S. C., Henderson, B. B., Roman, S. A., Scheri, R. P., Stapleton, H. M., Sosa, J. A. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. Environment International 107:235-242.			
<b>Health Outcome(s):</b>	Endocrine			
<b>Reported Health Effect(s):</b>	thyroid cancer (papillary)			
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound			
<b>Linked HERO ID(s):</b>	No linked references.			
<b>HERO ID:</b>	4161719			
Domain	Metric	Rating	Comments	
	Metric 10: Covariate Characterization	Medium	A questionnaire was administered to participants, but the method for assessing covariates was not described, although the study indicated that protocols were approved by an institutional review board. Did not report if the questionnaire was validated or the types of data collected in the questionnaire, but there is no evidence of confounding.	
	Metric 11: Co-exposure Counfounding	Low	Many flame retardants were measured in household dust samples. The authors acknowledge and provide data on those most highly correlated. Statistical analyses modeled each flame retardant separately. The authors indicate that component analyses were conducted to systematically assess FR mixtures but did not provide them in the article. They stated that they "did not provide any additional insights."	
Domain 5: Analysis	Metric 12: Study Design and Methods	High	The case-control study design was appropriate for the research question and applicable statistical methods were used (logistic regression models). However, the co-exposures were not accounted for in the analysis.	
	Metric 13: Statistical Power	Medium	The number of cases and controls was adequate to detect an effect.	
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was sufficient to be reproducible with access to the analytical data.	
	Metric 15: Statistical Analysis	High	Model assumptions were adequately described.	
Additional Comments:	For TCEP, dust levels in the home are used as surrogates for exposure, measured using MS/GC. PBDEs only were measured in serum (not organophosphate flame retardants). This case-control study used an adequate number of age- and gender-matched pairs. Multiple flame retardants were present in dust and in large ranges, depending on the flame retardant; adjustments were not made for multiple comparisons (separate models were assessed for each compound).			

**Overall Quality Determination**

**High**

\* No biomarkers were identified for this evaluation.

<b>Study Citation:</b>	Hoffman, K., Lorenzo, A., Butt, C. M., Hammel, S. C., Henderson, B. B., Roman, S. A., Scheri, R. P., Stapleton, H. M., Sosa, J. A. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. <i>Environment International</i> 107:235-242.		
<b>Health Outcome(s):</b>	Cancer/Carcinogenesis		
<b>Reported Health Effect(s):</b>	papillary thyroid cancer		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	4161719		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	High	Participant selection was well described, including timing of study, inclusion and exclusion criteria and case ascertainment.
	Metric 2: Attrition	High	Supplemental Figure 1 shows only 1 of 71 cases excluded and shows only 1 of 71 cases excluded.
	Metric 3: Comparison Group	High	Cases and controls were recruited from the same Health Care Center during the same time period and were matched by age and gender.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	High	Flame retardants were measured in house dust. Collection methods and analysis of dust was fully reported. TCEP concentrations in household dust were measured by GC/EI-MS.
	Metric 5: Exposure Levels	Low	Levels of flame retardant exposure in the home were reported for cases and controls; TCEP concentrations above the median concentration were reported for both groups. Median TCEP concentrations were shown in the box plot in Fig. 1 but concentrations were not reported. Detection limits were not reported for organophosphate flame retardants.
	Metric 6: Temporality	Medium	Exposure at the same residence for at least 2 years prior to diagnosis; however, it is unclear whether exposure duration was sufficient for thyroid cancer.
Domain 3: Outcome Assessment			
	Metric 7: Outcome Measurement or Characterization	High	The thyroid cancer outcome was assessed by medical review of clinical and pathology data; pathological stage was assessed based on tumor size, location, metastasis.
	Metric 8: Reporting Bias	High	Health outcomes and exposures are reported, except for median exposure levels of each of the flame retardants. Adjusted ORs with CIs reported for overall incidence as well as measures of tumor aggressiveness (i.e., pathologic stage). Some data were reported for PBDEs but not the organophosphate flame retardants, such as number of detects, detection limits.
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	Covariate adjustments were described (age, income, BMI). Regression analyses were adjusted for participant age and household income. BMI was both included and excluded as a covariate. Other potential confounders were considered, but not applied because they did not alter effect estimates (race, employment status, and smoking). Ionizing radiation exposure was considered but no participants reported prior exposure.

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<b>Study Citation:</b>	Hoffman, K., Lorenzo, A., Butt, C. M., Hammel, S. C., Henderson, B. B., Roman, S. A., Scheri, R. P., Stapleton, H. M., Sosa, J. A. (2017). Exposure to flame retardant chemicals and occurrence and severity of papillary thyroid cancer: A case-control study. Environment International 107:235-242.			
<b>Health Outcome(s):</b>	Cancer/Carcinogenesis			
<b>Reported Health Effect(s):</b>	papillary thyroid cancer			
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound			
<b>Linked HERO ID(s):</b>	No linked references.			
<b>HERO ID:</b>	4161719			
Domain	Metric	Rating	Comments	
	Metric 10: Covariate Characterization	Medium	A questionnaire was administered to participants, but the method for assessing covariates was not described, although the study indicated that protocols were approved by an institutional review board. Did not report if the questionnaire was validated or the types of data collected in the questionnaire, but there is no evidence of confounding.	
	Metric 11: Co-exposure Counfounding	Low	Many flame retardants were measured in household dust samples. The authors acknowledge and provide data on those most highly correlated. Statistical analyses modeled each flame retardant separately. The authors indicate that component analyses were conducted to systematically assess FR mixtures but did not provide them in the article. They stated that they "did not provide any additional insights."	
Domain 5: Analysis	Metric 12: Study Design and Methods	High	The case-control study design was appropriate for the research question and applicable statistical methods were used (logistic regression models). However, the co-exposures were not accounted for in the analysis.	
	Metric 13: Statistical Power	Medium	The number of cases and controls was adequate to detect an effect.	
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis was sufficient to be reproducible with access to the analytical data.	
	Metric 15: Statistical Analysis	High	Model assumptions were adequately described.	
Additional Comments:	For TCEP, dust levels in the home are used as surrogates for exposure, measured using MS/GC. PBDEs only ere measured in serum (not organophosphate flame retardants). This case-control study used an adequate number of age- and gender-matched pairs. Multiple flame retardants were present in dust and in large ranges, depending on the flame retardant; adjustments were not made for multiple comparisons (separate models were assessed for each compound).			

**Overall Quality Determination****High**

\* No biomarkers were identified for this evaluation.

<b>Study Citation:</b>	Li, Y., Fu, Y., Hu, K., Zhang, Y., Chen, J., Zhang, S., Zhang, B., Liu, Y. (2020). Positive correlation between human exposure to organophosphate esters and gastrointestinal cancer in patients from Wuhan, China. <i>Ecotoxicology and Environmental Safety</i> 196:110548.		
<b>Health Outcome(s):</b>	Cancer/Carcinogenesis		
<b>Reported Health Effect(s):</b>	Gastrointestinal cancer.		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	6747922		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1: Participant Selection	Medium	Most key elements of study design and participation selection were described. Confirmed through pathology, cancer cases (n=74) were selected from a hospital in Wuhan, China. However, information on how controls (n=62) were selected was less transparent. It only mentions that they were "healthy enough to donate blood".
	Metric 2: Attrition	Medium	There was minimal subject withdrawal from the study, and the outcome and exposure data seem to have been largely complete.
	Metric 3: Comparison Group	Medium	There were some evidence that cases and controls were similar. For example, cases and controls on average had similar age and were recruited in the same time frame.
Domain 2: Exposure Characterization			
	Metric 4: Measurement of Exposure	High	Quantitative measurement of chemicals/organophosphate esters were measured in plasma using HPLC-MS/MS and electrospray positive ionization methods.
	Metric 5: Exposure Levels	Low	Range of exposure in the population were limited. Several chemicals, including TCEP, were not readily detected among cases and controls.
	Metric 6: Temporality	Low	Temporality was established, exposures were assessed after cancer was diagnosed. However, it was unclear whether exposures, including TCEP, fall within relevant exposures windows for the outcome of interest.
Domain 3: Outcome Assessment			
	Metric 7: Outcome Measurement or Characterization	Medium	Cases were assessed using appropriate methods; however, not enough information of how it was done is provided. Confirmed through pathology, cancer cases (n=74) were selected from a hospital in Wuhan, China.
	Metric 8: Reporting Bias	Medium	An appropriate description of the outcome was reported in the abstract, introduction and methods. The odds ratio as the main effect estimates were reported with their respective confidence intervals (CI). Numbers of cases and controls were detailed for the logistic regressions, but they seemed to be very low based on the reported odds ratio and 95% CI.
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	Low	There was some adjustments for potential confounders in the logistic regression models. To test the main hypothesis, the authors adjusted for age, gender and stage, not for smoking and other potential confounders.

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<b>Study Citation:</b>	Li, Y., Fu, Y., Hu, K., Zhang, Y., Chen, J., Zhang, S., Zhang, B., Liu, Y. (2020). Positive correlation between human exposure to organophosphate esters and gastrointestinal cancer in patients from Wuhan, China. <i>Ecotoxicology and Environmental Safety</i> 196:110548.			
<b>Health Outcome(s):</b>	Cancer/Carcinogenesis			
<b>Reported Health Effect(s):</b>	Gastrointestinal cancer.			
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound			
<b>Linked HERO ID(s):</b>	No linked references.			
<b>HERO ID:</b>	6747922			
Domain	Metric	Rating	Comments	
	Metric 10: Covariate Characterization	Medium	A few potential confounders were obtained and assessed through clinical records. However, the authors do not mention why other important potential confounders were included in the study.	
	Metric 11: Co-exposure Counfounding	Low	There were direct evidence of potential co-exposures, but were not were not appropriately adjusted for in the statistical approaches and/or in the logistic regression models.	
Domain 5: Analysis	Metric 12: Study Design and Methods	High	The study design chosen was appropriate for the research question to retrospectively investigate the associations between TCEP exposures and gastrointestinal cancer. The study used a variety of statistical approaches, including logistic regression models, appropriate to address the research question.	
	Metric 13: Statistical Power	Medium	The number of participants (cases, n=74; controls, n=62) was adequate to detect an effect in the population; however, not adequate for a comprehensive subgroup analysis.	
	Metric 14: Reproducibility of Analyses	Low	Description of statistical analyses is limited, thus it would be difficult to reproduce the authors' approach. Information about the treatment of missing values not provided, and the language discussing the Mann-Whitney U test is not entirely clear (unsure about "comparing the two groups" - cases and controls?).	
	Metric 15: Statistical Analysis	Low	The statistical models (logistic regression models) building process was appropriate and model assumptions were met (with respect to the outcome) to address the research question. However, the authors do not mentioned how they treated the independent variables and covariates in the models.	
Domain 6: Other (if applicable)	Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)			
	Metric 16: Use of Biomarker of Exposure	High	Biomarkers of exposure/organophosphate esters (including TCEP) were measured in plasma using HPLC-MS/MS and electrospray positive ionization methods.	
	Metric 17: Effect Biomarker	N/A	An effect biomarker was not assessed.	
	Metric 18: Method Sensitivity	Medium	Analytical methods to detect and measure biomarkers were sensitive.	
	Metric 19: Biomarker Stability	Medium	Some description of the sample collection and storage (at -20 degrees Celsius) until use for analytical purposes was provided.	
	Metric 20: Sample Contamination	High	Some information on sample handling to avoid or reduce potential contamination of the samples was described. Quality control measures were also taken into account to ensure reliable data.	
	Metric 21: Method Requirements	High	Information on instrumentation(s) that allowed for identification of the biomarkers, including TCEP, with a high degree of confidence and the required sensitivity was provided.	
	Metric 22: Matrix Adjustment	N/A	Matrix adjustment is not necessary for plasma biomarker samples.	

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<b>Study Citation:</b>	Li, Y., Fu, Y., Hu, K., Zhang, Y., Chen, J., Zhang, S., Zhang, B., Liu, Y. (2020). Positive correlation between human exposure to organophosphate esters and gastrointestinal cancer in patients from Wuhan, China. <i>Ecotoxicology and Environmental Safety</i> 196:110548.
<b>Health Outcome(s):</b>	Cancer/Carcinogenesis
<b>Reported Health Effect(s):</b>	Gastrointestinal cancer.
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
<b>Linked HERO ID(s):</b>	No linked references.
<b>HERO ID:</b>	6747922

Domain	Metric	Rating	Comments
Additional Comments:	In this study, the authors examined the associations between investigated the associations between organophosphate esters, including TCEP, and the increase risk for gastrointestinal cancer in a case-control study in Wuhan, China. Overall, most of the methodology used in this study were adequate. However, there were a number of chemicals that gave high frequencies of not detected values among the studied population and were not possible to be linked with the outcome of interest. In terms of the results, there was an increased risk for gastrointestinal cancer and exposure to organophosphate esters. Nonetheless, TCEP was not associated with gastrointestinal cancer due high frequencies of not detected values.		

**Overall Quality Determination**

**Medium**

<b>Study Citation:</b>	Araki, A., Bamai, Y. A., Bastiaensen, M., Van den Eede, N., Kawai, T., Tsuboi, T., Miyashita, C., Itoh, S., Goudarzi, H., Konno, S., Covaci, A., Kishi, R. (2020). Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. Environmental Research 183:109212.		
<b>Health Outcome(s):</b>	Lung/Respiratory		
<b>Reported Health Effect(s):</b>	wheeze		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	6957526		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	The study was conducted among elementary school students in Sapporo, Japan in 2008. The survey was sent to 6393 school children across 12 public elementary schools, and 44008 students responded, with 951 students interested in participating. Only 681 families were still at the same elementary school in 2009, of those only 128 families were able to be contacted for a home visit, meaning there was an overall participation rate of 2.9%. Despite a low participation rate, the reasons for exclusion are clearly defined at each step and are unlikely to introduce significant bias.
Metric 2:	Attrition	High	Of the final 128 participants, none were excluded from the data analysis after home visits/data collection occurred. There is no missing exposure or outcome data.
Metric 3:	Comparison Group	Medium	Participants in this cross-sectional study appear to be similar in terms of baseline characteristics. Most variables are controlled for in statistical analyses. Height and weight are not controlled for, but the listed mean + standard deviations imply that there is a somewhat large range.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	High	Exposure is reported as TCEP measured from urine.
Metric 5:	Exposure Levels	Medium	The study reports on a range of exposures from the LOQ to 1.13 nM of TCEP. In statistical analyses, TCEP concentrations are split into tertiles.
Metric 6:	Temporality	Medium	Exposure was measured after the onset of symptoms, so the temporality of the sum metabolites is not confirmed to be accurate. However, due to the ubiquity of TCEP in the environment, it is reasonable to assume that they were exposed to the same amount of TCEP prior to exposure assessment. However, the study does not check to see if children had moved recently, which could alter temporality.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Outcomes were assessed via the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, which was filled out by study investigators and the parents of children. The questionnaire asks for symptoms common for wheeze instead of actual medical diagnoses. Parents may also be impacted by the desirability bias. However, this is likely to have a non-differential effect.
Metric 8:	Reporting Bias	High	A description of the the outcomes is clearly mentioned in the methods. Results are presented as odds ratios with 95% confidence intervals and p-values.

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<b>Study Citation:</b>	Araki, A., Bamai, Y. A., Bastiaensen, M., Van den Eede, N., Kawai, T., Tsuboi, T., Miyashita, C., Itoh, S., Goudarzi, H., Konno, S., Covaci, A., Kishi, R. (2020). Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. Environmental Research 183:109212.		
<b>Health Outcome(s):</b>	Lung/Respiratory		
<b>Reported Health Effect(s):</b>	wheeze		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	6957526		
Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	The results are reported as odds ratios that are adjusted for sex, grade, annual income, and the dampness index of the child's home. They were all included based on a priori evidence.
	Metric 10: Covariate Characterization	Medium	Information on confounders were obtained via questionnaire. Sex and grade were measured via questionnaire and were unlikely to be reported incorrectly. Annual income is also self-reported, and could fall victim to desirability bias. There were also missing values for income (14.8% ) to which the mean annual household income was assigned. Finally, a "dampness" index was calculated by study investigator observation of dampness-related problems in each dwelling, such as condensation and visible mold.
	Metric 11: Co-exposure Counfounding	Medium	The intent of this study was to measure co-exposures of phthalates and phosphate flame retardants and allergic outcomes. Statistical models were used in this study to examine in urine individual phthalates, combinations of phthalates, metabolites of PFRs and a combination of certain PFRs.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The use of a cross-sectional design to understand the relationship between TCEP and wheeze/allergy symptoms is an appropriate study design, and calculating odds ratios via logistic regression is an appropriate method.
	Metric 13: Statistical Power	Medium	The number of participants in each tertile is >20, which could be sufficiently large to detect an effect. The authors do not calculate statistical power, however they do mention that the power may not be enough to detect a significant effect. They may be referring to the multipollutant models in this case.
	Metric 14: Reproducibility of Analyses	Medium	The description of the analysis is thorough and allows for replication given the study data.
	Metric 15: Statistical Analysis	High	The model building is transparent and it is clear why variables were chosen.
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)			
	Metric 16: Use of Biomarker of Exposure	High	TCEP is a parent compound.
	Metric 17: Effect Biomarker	N/A	Not applicable - no biomarker of effect.
	Metric 18: Method Sensitivity	Medium	The % of samples below the detection limit is stated to be 14.8% , which is not incredibly high but is sufficient to address the research hypothesis.
	Metric 19: Biomarker Stability	Medium	There is no documented stability data, but is clarified that spot urine samples were collected in polypropylene containers and refrigerated until the study visit, and then stored a -20 deg C until the day of analysis.
	Metric 20: Sample Contamination	Medium	There is no documentation of potential sample contamination.

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<b>Study Citation:</b>	Araki, A., Bamai, Y. A., Bastiaensen, M., Van den Eede, N., Kawai, T., Tsuboi, T., Miyashita, C., Itoh, S., Goudarzi, H., Konno, S., Covaci, A., Kishi, R. (2020). Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. Environmental Research 183:109212.
<b>Health Outcome(s):</b>	Lung/Respiratory
<b>Reported Health Effect(s):</b>	wheeze
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
<b>Linked HERO ID(s):</b>	No linked references.
<b>HERO ID:</b>	6957526

Domain	Metric	Rating	Comments
	Metric 21: Method Requirements	High	TCEP was measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS).
	Metric 22: Matrix Adjustment	Medium	TCEP concentrations were creatinine-adjusted, and ranges are reported without adjustment and with adjustment. However, the statistical model only uses adjusted concentrations of TCEP.

**Additional Comments:** This cross-sectional study measures the association between TCEP measured in spot urine samples and parent-reported symptoms of wheeze. Associations were analyzed using logistic regression and the study calculated odds ratios. No significant associations in single-pollutant models for TCEP were reported. The study has some deficiencies in outcome assessment, as there is no verifiable method used in this study.

**Overall Quality Determination** **High**

<b>Study Citation:</b>	Crawford, K. A., Hawley, N., Calafat, A. M., Jayatilaka, N. K., Froehlich, R. J., Has, P., Gallagher, L. G., Savitz, D. A., Braun, J. M., Werner, E. F., Romano, M. E. (2020). Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. <i>Environmental Health: A Global Access Science Source</i> 19(1):97.		
<b>Health Outcome(s):</b>	Reproductive/Developmental		
<b>Reported Health Effect(s):</b>	Gestational weight gain among pregnant women; infant gestational age at delivery; infant anthropometric measurements at birth and 6 weeks postpartum, including birth weight and length, head and abdominal circumference, and four body composition (iliac, subscapular, triceps, and thigh skinfold thickness).		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Metabolite: bis-2-chloroethyl phosphate (BCEP)		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	7274557		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	Overall, all key elements of study design and participation were reported. In this pilot study, 62 women and infants were recruited. Inclusion and exclusion criteria as well as participant selection were fully described.
Metric 2:	Attrition	High	A minimal number of subjects (6/62) were excluded from further analysis due to withdrawal, miscarriage, and lost to follow up. Exposure and outcome measurements were complete among pregnant women and infants. The exclusion or loss of follow up are not likely to introduce bias since the participated population is likely to represent the general eligible population.
Metric 3:	Comparison Group	High	Differences in baseline characteristics were reported and adequately considered and adjusted in the statistical analysis. Identified effect modification by infant sex were considered in further analysis. Participants were similar since they were recruited from the same setting using same inclusion criteria.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	High	Exposure levels of the target chemical were derived from metabolite concentrations in urine samples. Collection and quantification methods were fully described.
Metric 5:	Exposure Levels	Medium	Continuous individual exposure levels measured from OPE metabolite concentrations in pooled urine samples were used.
Metric 6:	Temporality	Medium	The authors reported that OPE metabolites in urine samples showed good reproducibility and good intraclass correlation. They used pooled urine samples collected at gestation weeks 12, 28 and 35 to represent the exposure window. OPE chemicals have relatively short half lives and very low bioaccumulation rate, so the OPE chemicals are commonly used to indicate persistent exposure. It is not clear whether the exposures fell within relevant exposure windows for the outcomes of interest.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Gestational weight gain (GWG) among nine pregnant women were substituted because of missing information. Newborn infants' anthropometry outcomes were measured twice by staff. A third measurement was applied if differences were out of pre-specified range. The same measurements were applied at 6 weeks postpartum. Significant measurement error is not likely to be present but not using the gold-standard.

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<b>Study Citation:</b>	Crawford, K. A., Hawley, N., Calafat, A. M., Jayatilaka, N. K., Froehlich, R. J., Has, P., Gallagher, L. G., Savitz, D. A., Braun, J. M., Werner, E. F., Romano, M. E. (2020). Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. <i>Environmental Health: A Global Access Science Source</i> 19(1):97.		
<b>Health Outcome(s):</b>	Reproductive/Developmental		
<b>Reported Health Effect(s):</b>	Gestational weight gain among pregnant women; infant gestational age at delivery; infant anthropometric measurements at birth and 6 weeks postpartum, including birth weight and length, head and abdominal circumference, and four body composition (iliac, subscapular, triceps, and thigh skinfold thickness).		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Metabolite: bis-2-chloroethyl phosphate (BCEP)		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	7274557		
Domain	Metric	Rating	Comments
	Metric 8: Reporting Bias	High	All of the measured outcomes were described in detail. Effect measurements with 95% CI and medians with interquartile ranges were reported. Continuous exposure levels were used and each analysis was tabulated or graphed for data extraction.
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	Covariates including maternal age at delivery, income, pre-pregnancy BMI, parity and infant sex were appropriately adjusted in the linear regression model and mixed effect model.
	Metric 10: Covariate Characterization	Medium	Covariate information was collected through a questionnaire at enrollment and medical records. Medical records are a well-established and reliable source, while the questionnaire is less-established. There is little to no concern about validity or confounding.
	Metric 11: Co-exposure Counfounding	Medium	Co-exposure of 2 other OPE metabolites in urine samples were evaluated and adjusted in this study. Even though the authors mentioned residual confounding by unmeasured co-exposure may be present, there is no direct evidence that it would introduce significant bias to the effect.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The study design and analytical models used were appropriate to analyze the relationship between exposure and outcomes. Up to 3 urine metabolite measurements were used to represent the exposure level in the pregnancy window. Linear regression models were used for the continuous variables.
	Metric 13: Statistical Power	Low	The authors reported that this pilot study with a smaller sample size (56 maternal-infant pairs) may not have sufficient statistical power to detect some effects. However, the power was sufficient to detect an association between OPE exposure and infant anthropometry by sex, which was also reported by Hoffman et al 2018.
	Metric 14: Reproducibility of Analyses	Medium	The analysis methods, model selection, and data processing methods were reported and sufficient to understand and reproduce.
	Metric 15: Statistical Analysis	High	Model assumptions were met and the method was transparent. Variable were appropriately transformed.
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)			
	Metric 16: Use of Biomarker of Exposure	Medium	BCEP is a metabolite of TCEP and used as a biomarker of TCEP exposure. There might be other parent compounds but TCEP is one of the most common OPE detected.
	Metric 17: Effect Biomarker	N/A	Not applicable - no biomarker of effect.
	Metric 18: Method Sensitivity	Medium	Analytical methods were fully described and appropriate. The LODs and detection frequency were reported in the supplemental table S1.

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<b>Study Citation:</b>	Crawford, K. A., Hawley, N., Calafat, A. M., Jayatilaka, N. K., Froehlich, R. J., Has, P., Gallagher, L. G., Savitz, D. A., Braun, J. M., Werner, E. F., Romano, M. E. (2020). Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. <i>Environmental Health: A Global Access Science Source</i> 19(1):97.
<b>Health Outcome(s):</b>	Reproductive/Developmental
<b>Reported Health Effect(s):</b>	Gestational weight gain among pregnant women; infant gestational age at delivery; infant anthropometric measurements at birth and 6 weeks postpartum, including birth weight and length, head and abdominal circumference, and four body composition (iliac, subscapular, triceps, and thigh skinfold thickness).
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Metabolite: bis-2-chloroethyl phosphate (BCEP)
<b>Linked HERO ID(s):</b>	No linked references.
<b>HERO ID:</b>	7274557

Domain	Metric	Rating	Comments
	Metric 19: Biomarker Stability	High	Sample storage and shipping condition was reported and no reported loss.
	Metric 20: Sample Contamination	High	There is no direct evidence to show the samples had contamination concerns. The analytical methods were described and the quality assurance used were within the lab limits, according to the authors.
	Metric 21: Method Requirements	High	Target analytes were separated on a ultra-high-performanceliquid chromatography system and quantified using mass spectrometry.
	Metric 22: Matrix Adjustment	N/A	The matrix adjustment information is not reported.

**Additional Comments:** Overall, this is a high-quality pilot study to evaluate the association between gestational exposure to target chemicals and reported health outcomes. The models and analytical methods applied were clear, fully described and appropriate. Strengths and limitations were discussed and not likely to introduce significant bias to the study.

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**Overall Quality Determination** **High**

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<b>Study Citation:</b>	Crawford, K. A., Hawley, N., Calafat, A. M., Jayatilaka, N. K., Froehlich, R. J., Has, P., Gallagher, L. G., Savitz, D. A., Braun, J. M., Werner, E. F., Romano, M. E. (2020). Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. Environmental Health: A Global Access Science Source 19(1):97.		
<b>Health Outcome(s):</b>	Neurological/Behavioral		
<b>Reported Health Effect(s):</b>	Infant feeding behaviors including general appetite, enjoyment of food, food responsiveness, slowness in eating, and satiety responsiveness.		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Metabolite: bis-2-chloroethyl phosphate (BCEP)		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	7274557		
Domain	Metric	Rating	Comments
Domain 1: Study Participation			
Metric 1:	Participant Selection	High	Overall, all key elements of study design and participation were reported. In this pilot study, 62 women were recruited. Inclusion and exclusion criteria as well as participant selection were fully described.
Metric 2:	Attrition	High	A minimal number of subjects (6/62) were excluded from further analysis due to withdrawal, miscarriage, and loss to follow up. Exposure and outcome measurements were complete among pregnant women and infants. The exclusion or loss to follow up are not likely to introduce bias since the participated population is likely to represent the general eligible population.
Metric 3:	Comparison Group	High	Differences in baseline characteristics were reported and adequately considered and adjusted in statistical analysis. Identified effect modification by infant sex was considered in further analysis. Participants were similar since they were recruited from the same setting using same inclusion criteria.
Domain 2: Exposure Characterization			
Metric 4:	Measurement of Exposure	High	Exposure levels of target chemical were derived from metabolite concentrations in urine samples. Collection and quantification methods were fully described.
Metric 5:	Exposure Levels	Medium	Continuous individual exposure levels were measured from OPE metabolite concentrations in pooled urine samples.
Metric 6:	Temporality	Medium	The authors reported that OPE metabolites in urine samples showed good reproducibility and good intraclass correlation. They used pooled urine samples collected at gestation weeks 12, 28 and 35 to represent the exposure window. OPE chemicals have relatively short half lives and very low bioaccumulation rates, so the OPE chemicals are commonly used to indicate persistent exposure. It is not clear whether the exposures fell within relevant exposure windows for the outcomes of interests.
Domain 3: Outcome Assessment			
Metric 7:	Outcome Measurement or Characterization	Medium	Infant feeding behaviors were evaluated by Baby Eating Behavior Questionnaire (BEBQ) completed by mothers. The validation is not reported but there is no direct evidence that the method has poor validity or significant misclassification.
Metric 8:	Reporting Bias	High	All of the measured outcomes were described in detail. Effect measurements with 95% CI and medians with interquartile range reported. Continuous exposure levels were used and each analysis was tabulated or graphed for data extraction.

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<b>Study Citation:</b>	Crawford, K. A., Hawley, N., Calafat, A. M., Jayatilaka, N. K., Froehlich, R. J., Has, P., Gallagher, L. G., Savitz, D. A., Braun, J. M., Werner, E. F., Romano, M. E. (2020). Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. <i>Environmental Health: A Global Access Science Source</i> 19(1):97.		
<b>Health Outcome(s):</b>	Neurological/Behavioral		
<b>Reported Health Effect(s):</b>	Infant feeding behaviors including general appetite, enjoyment of food, food responsiveness, slowness in eating, and satiety responsiveness.		
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Metabolite: bis-2-chloroethyl phosphate (BCEP)		
<b>Linked HERO ID(s):</b>	No linked references.		
<b>HERO ID:</b>	7274557		
Domain	Metric	Rating	Comments
Domain 4: Potential Confounding / Variability Control			
	Metric 9: Covariate Adjustment	High	Covariates including maternal age at delivery, income, pre-pregnancy BMI, parity and infant sex were appropriately adjusted in the linear regression model and mixed effect model.
	Metric 10: Covariate Characterization	Medium	Covariate information was collected through a questionnaire at enrollment and medical records. Medical records are a well-established and reliable source, while the questionnaire is less-established. There is little to no concern about validity or confounding.
	Metric 11: Co-exposure Confounding	Medium	Co-exposure of other 2 OPE metabolites in urine samples were evaluated and adjusted in this study. Even though the authors mentioned that residual confounding by unmeasured co-exposure may be present, there is no direct evidence that would introduce significant bias to the effect.
Domain 5: Analysis			
	Metric 12: Study Design and Methods	High	The study design and analytical models used were appropriate to catch the relationship between exposure and outcomes. Up to 3 urine metabolite measurements were applied to represent the exposure level during pregnancy. Linear regression models were used for the continuous variables.
	Metric 13: Statistical Power	Low	The authors reported that this pilot study with a smaller sample size (56 maternal-infant pairs) may not have sufficient statistical power to detect some effects. However, the power was sufficient to detect an association between OPE exposure and infant anthropometry by sex, which was also reported by Hoffman et al 2018.
	Metric 14: Reproducibility of Analyses	Medium	The description of analysis methods, model selection, and data processing methods were reported and sufficient to understand and reproduce.
	Metric 15: Statistical Analysis	High	Model assumptions were met and the method was transparent. Variable were appropriately transformed.
Domain 6: Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al. 2014)			
	Metric 16: Use of Biomarker of Exposure	Medium	BCEP is a metabolite of TCEP and used as a biomarker of TCEP exposure. There might be other parent compounds but TCEP is one of the most common OPE detected.
	Metric 17: Effect Biomarker	N/A	Not applicable - no biomarker of effect.
	Metric 18: Method Sensitivity	Medium	Analytical methods were fully described and appropriate. The LODs and detection frequency were reported in the supplemental table S1.
	Metric 19: Biomarker Stability	High	Sample storage and shipping condition was reported and no reported loss.
	Metric 20: Sample Contamination	High	There is no direct evidence to show the samples had contamination concerns. The analytical methods were described and the quality assurance used were within the lab limits, according to the authors.

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<b>Study Citation:</b>	Crawford, K. A., Hawley, N., Calafat, A. M., Jayatilaka, N. K., Froehlich, R. J., Has, P., Gallagher, L. G., Savitz, D. A., Braun, J. M., Werner, E. F., Romano, M. E. (2020). Maternal urinary concentrations of organophosphate ester metabolites: associations with gestational weight gain, early life anthropometry, and infant eating behaviors among mothers-infant pairs in Rhode Island. Environmental Health: A Global Access Science Source 19(1):97.
<b>Health Outcome(s):</b>	Neurological/Behavioral
<b>Reported Health Effect(s):</b>	Infant feeding behaviors including general appetite, enjoyment of food, food responsiveness, slowness in eating, and satiety responsiveness.
<b>Chemical:</b>	Tris(2-chloroethyl) phosphate (TCEP)- Metabolite: bis-2-chloroethyl phosphate (BCEP)
<b>Linked HERO ID(s):</b>	No linked references.
<b>HERO ID:</b>	7274557

Domain	Metric	Rating	Comments
	Metric 21: Method Requirements	High	Target analytes were separated on a ultra-high-performanceliquid chromatography system and quantified using mass spectrometry.
	Metric 22: Matrix Adjustment	N/A	The matrix adjustment information is not reported.

**Additional Comments:** Overall, this is a high-quality pilot study to evaluate the association between gestational exposure to target chemicals and reported health outcomes. Despite the small pilot-scale sample size, the samples are a good represent of eligible general population. The models and analytical methods applied were clear, fully described and appropriate. Strengths and limitations were discussed and not likely to introduce significant bias to the study.

**Overall Quality Determination** **High**