Estimated tris(1,3-dichloro-2-propyl) phosphate exposure levels for US infants suggest potential health risks

Kate Hoffman[1], **Larisa Gearhart-Serna**[1], **Matthew Lorber**[2], **Thomas F. Webster**[3], **Heather M. Stapleton**[1]

[1]Nicholas School of the Environment, Duke University, Durham, North Carolina, 27708 USA

[2]Retired, Unites States Environmental Protection Agency, Washington DC

[3]Boston University School of Public Health, Boston, MA, 02118 USA

Abstract

Tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) has been widely used as a flame retardant and is commonly detected in environmental samples. Biomonitoring studies relying on urinary metabolite levels (i.e. bis(1,3-dichloro-2-propyl) phosphate (BDCIPP)) demonstrate widespread exposure, but TDCIPP intake is unknown. Intake data area critical component of meaningful risk assessments and are needed to elucidate the potential health impacts of TDCIPP exposure. Using biomonitoring data, we estimated TDCIPP intake for infants.

Infants aged 2-18 months were recruited from central, North Carolina (n=43, recruited 2014-2015), and spot urine samples were analyzed for BDCIPP. TDCIPP intake rates were estimated using daily urine excretion and the fraction of TDCIPP excreted as BDCIPP in urine.

Daily TDCIPP intake estimates ranged from 0.01-15.03 μg/kg-day for children included in our assessment, with some variation depending on model assumptions. The U.S. Consumer Products Safety Commission (CPSC) previously established an acceptable daily intake of 5μg/kg-day for non-cancer health risks. Depending on modeling assumptions, we found that 2-9% percent of infants had TDCIPP intake estimates above this threshold. Our results indicate that current TDCIPP exposure levels could pose health risks for highly exposed infants.

Introduction

Tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) has been widely used as a flame retardant additive in consumer goods, including polyurethane foam used in residential furniture and baby products.[1-3] Research suggests that TDCIPP exposure is exceedingly common and varies considerably within the general population; however, exposure assessments have largely focused on measuring TDCIPP in various matrices (e.g. foam furniture, indoor air, or dust) [4-9] and on biomonitoring of urinary metabolites [i.e. bis(1,3-dichloro-2-propyl) phosphate (BDCIPP)],[10-15] rather than directly measuring human TDCIPP exposure.

Corresponding Author Heather M. Stapleton, Ph.D., Duke University, Nicholas School of the Environment, 9 Circuit Drive, Box 90328, Durham, NC 27708, Phone: 919-613-8717, heather.stapleton@duke.edu.

Although human health data are limited, TDCIPP is considered a probable human carcinogen based on animal studies.[16-18] Other, non-cancer health impacts have been observed in animal and in vitro studies, including disruption of endocrine function, adverse reproductive health, and neurotoxicity.[17-23] In 2006, the U.S. Consumer Products Safety Commission (CPSC) released a preliminary assessment of the potential health risks associated with the use of selected flame retardants, including TDCIPP, in upholstered foam furniture.[18] Although, human TDCIPP exposure was not directly assessed, based on use of TDCIPP in furniture, mathematical exposure models, and a review of toxicity data, the report suggested possible adverse health impacts associated with TDCIPP use in furniture foam.[18] Therefore, exposure estimates are needed to conduct risk assessments for TDCIPP.

Here, we use previously measured urinary BDCIPP levels and reverse dosimetry models to estimate daily TDCIPP intake for young infants, a group which previous research suggests may have higher levels of exposure.[11, 15, 24, 25] Although the biological half-life of TDCIPP is likely in the order of hours, previous estimates of interclass-correlation coefficients for BDCIPP suggest that a spot urine sample may provide a fairly reliable measure of average urinary levels of BDCIPP in adults.[5, 6, 26, 27] This is likely due to the fact that the primary routes of exposure to parent TDCIPP are chronic inhalation and inadvertent dust-ingestion, where air and dust have been impacted by use of products containing TDCIPP.[14, 28] Therefore, using urinary metabolite levels to estimate TDCIPP exposure is reasonable, particularly given the difficulty in collecting 24-hour urine samples from young children. In this study, we compare these values to relevant estimates from the CPSC report,[18] including the potential for non-cancer adverse health impacts and for increased cancer risk associated with exposure.

Methods

Study Population:

A convenience sample of infants (2-18 months of age) was recruited from the Durham, North Carolina area between September 2014 and March 2015.[15] Children provided a spot urine sample and their parents completed a survey which included the child's age and weight. Weight was missing for one child and was imputed as the 50th percentile based on the child's age and sex.[29] Parents provided informed consent and all procedures were carried out in accordance with a human subjects research protocol approved by the Duke University Institutional Review Board.

Urine Collection and Analysis:

Urine samples were collected in pediatric urine collection bags (n=38) or via catheter (n=5; details of collection procedures are provided in Hoffman et al. 2015).[15] Upon collection, samples were transferred to polypropylene specimen containers and were stored at −20°C until analysis. Detailed descriptions of the extraction and analysis of BDCIPP have been published previously.[11, 30] Briefly, organophosphate flame retardant (PFR) metabolites were extracted using mixed mode anion exchange solid phase extraction with isotope dilution (d_{10} BDCIPP) and quantified using liquid chromatography coupled to electrospray ionization tandem mass spectrometry. We evaluated the recovery of d10-BDCIPP in all samples using

[13]C_2-DPHP, and measured levels of BDCIPP in laboratory blanks (n=6) analyzed alongside the samples for quality assurance purposes. Average recovery of d10-BDCIPP was 119 ± 4%. Very small amounts of BDCIPP were detected in laboratory blanks (0.04 ng/mL on average). Therefore, the method detection limit (MDL) was calculated using three times the standard deviation of the blanks normalized to the urine volume extracted (MDL=0.05 ng/mL). Analyte levels were blank corrected using the average levels in the laboratory blanks.

Estimation of daily TDCIPP intake:

To estimate daily TDCIPP intake we first predicted each participant's daily excretion of BDCIPP in urine using a volume-based approach; multiplying the concentration of BDCIPP (μg/L) in the spot urine sample by an estimated 24-hour urine output (L), calculating the μg/day of BDCIPP excreted.

To estimate TDCIPP intake from BDCIPP excretion, we then divided by the molar fraction (fraction of TDCIPP converted to BDCIPP and excreted in urine per day). This was assumed to be the daily mass intake of TDCIPP (μg/day). Daily estimates were divided by each child's weight (kg), producing weight-adjusted intake rates in μg/kg-day (Eq 1).

$$\mu g\, TDCIPP \ / \ kg - day = \frac{spot\ BDCIPP\, \mu g\ /\ L\ *\ urine\ output\ L\ /\ d}{molar\ fraction\ /\ d\ *\ child\ weight\ (kg)}\ *\ \frac{MW\ TDCIPP\ \frac{g}{mol}}{MW\ BDCIPP\ \frac{g}{mol}}$$

Models required the volume of urine excreted per day; however, this information was not collected for individual children. As such we used published estimates for children of this age from literature as a proxy (Table 1; 0.001-0.002 L/kg-hour).[31, 32] The urinary excretion fraction of TDCIPP converted to BDCIPP and excreted in urine has not been evaluated in a human population. We therefore reviewed past studies to estimate values for TDCIPP conversion to urinary BDCIPP (Table 1; 43-68%).[31, 33-36] Although these studies are based on both in vitro and in vivo work, we used their values as a range of possible values for the conversion of TDCIPP to BDCIPP and selected 45% and 65% as urinary excretion fractions for analyses. .

Potential for Adverse Health Impacts

The CPSC calculated an acceptable daily intake (ADI) for TDCIPP based on previous rodent data demonstrating histopathological effects in several organs (e.g. liver, kidney, spleen, and parathyroid; lowest-observed-adverse-effect level (LOAEL) =5 mg/kg-day).[17, 18] Incorporating an uncertainly factor (1000-fold), the ADI established by the CPSC for non-cancer health risks associated with TDCIPP exposure was set at 5 μg/kg-day. The CPSC document calculated a hazard index (HI; also known as a hazard quotient) associated with exposure as the ratio of the average daily dose to the ADI. An HI >1 indicates potential for health impacts at a particular levels of exposure. [18] The State of California proposed a similar no significant risk level for TDCIPP under Proposition 65 of 5.4 μg/kg-day.[37]

Potential for Excess Cancer Risk

The CPSC calculated a cancer potency factor (i.e. the probability of incurring cancer in one's life time due to exposure) for TDCIPP using prior research indicating hepatocellular carcinoma and adenoma and tumors of the renal cortex: 0.031 $(mg/kg-d)^{-1}$.[17] Using the CPSC value, we estimated the lifetime excess cancer risk from exposure by multiplying the potency factor by the life time average daily dose (LADD). Following the CPSC, we first examine only infant exposure, assuming that the LADD is based on two years of exposure at the estimated rates. As this assumes zero exposure for the rest of the lifetime it likely represents an underestimate of exposure. As a sensitivity analysis, we also assumed a LADD equal to exposure during the first two years (i.e. constant exposure level equal to the level during infancy, likely overestimating exposure). We considered an additional exposure scenario which assumed that levels of exposure during the first 2 year of life were equal to those observed in our work and exposure thereafter equaled one-half of infant levels.

Results and Discussion

Children participating in this study were an average of 7.9 months of age (range 2-18 months) and there were slightly more males than females (Table 2). All urine samples had detectable levels of BDCIPP (geometric mean=2.29 μg/L; range=0.20-103.65 μg/L). As reported previously, urinary BDCIPP levels in this study population were higher than those found in studies of adults or older children conducted at similar time points,[6, 11] suggesting infants may have higher levels of exposure.

Using Equation 1, the estimated daily intake of TDCIPP ranged from 0.01-15.03 μg/kg-day for the individual children in our study population (Table 3). Among these children, the geometric mean intake was 0.11 μg/kg-day using assumptions that would result in the lowest estimated intakes (urine volume of 1 mL/kg-hr and 65% of TDCIPP excreted in urine as BDCIPP) and 0.33 μg/kg-day using assumptions that would result in the highest estimated intakes (urine volume of 2 mL/kg-hr and 45% of TDCIPP excreted in urine as BDCIPP). The average intake (average of the geometric means for each scenario) was 0.21 μg/kg-day.

It is important to point out that our work does not capture the relative importance of various exposure pathways. Our previous work in this study population suggests that the number of infant products that are present in the home is a particularly strong predictor of infants' urinary BDCIPP levels, as TDCIPP is the most common flame retardant used in foam-containing infant products.[2] Reasons for this association are unclear but could include hand-to-month contact, dermal absorption or inhalation.

Using these estimates, we calculated the HI for potential non-cancer health impacts as described by the CPSC.[18] Under every set of assumptions examined, a portion of children had HI > 1 (indicating potential health risks). Estimated percentages of children with an HI > 1 ranged from 2 to 9% (Table 3) under various assumptions of urine excretion rates and the fraction of TDCIPP excreted as BDCIPP in urine, indicating potential health risks at current levels of exposure.

Based on the cancer potency factor proposed by the CPSC (mg/kg-d)$^{-1}$,[18] we also calculated an estimated excess cancer risk based on the observed levels of TDCIPP exposure in our study population. Assuming exposure occurred only in the first two years of life (0.21 µg/kg-day for 2 years of a 75 year life time), we estimated cancer risk from exposure to TDCIPP to be 0.3 cases per million individuals; however, this is likely an under estimate. Assuming exposure during infancy continues at the same level throughout the life-course (0.21 µg/kg-day for 75 years), the estimated excess cancer risk was 10 per million, likely an over estimate. Finally, assuming exposure continues at half the level of infants' exposures (0.21 µg/kg-day for 2 years and 0.11 µg/kg-day for 73 years), results in an excess cancer risk of 5 per million. Our estimate is lower than that of the CPSC (300 cases per million), but under some assumptions surpasses the one in a million value used by CPSC to consider a substance hazardous.[17]

Certainly, there are some limitations of the methods used to estimate excess cancer risk in this study population. Assuming that there is no additional exposure after the first two years of life, the life time excess cancer risk does not exceed 1 per million (i.e. the CPSC threshold for hazardous substance classification); however, this exposure scenario seems highly implausible as exposure to TDCIPP has been measured in all age classes. [e.g. 25] Both alternative exposure scenarios considered suggest that life time excess cancer risk exceeds this threshold, particularly when infant exposure levels are assumed to continue throughout the life course (10 per million). A number of studies demonstrate that urinary BDCIPP levels decrease with age[25, 27, 38] and are higher among young children[11, 15, 39] suggesting that we may be over-estimating excess cancer risk. However, biomonitoring data also suggest that TDCIPP exposure may be increasing over time,[13] in which case our results using this assumption may more accurately reflect cancer burden among this cohort. It is not clear whether this trend will continue, particularly with the addition of TDCIPP to California's Proposition 65. Indeed, recent measurements of foam suggest that the use of TDCIPP in furniture may have declined since 2014.[3]

Additional data are needed to assess potential human health risks associated with exposure. It is important to note that values used in the CPSP document to assess risk are based on toxicological, rather than epidemiologic, data. Although these data suggest that there may be reason for concern, significantly more data about potential human health impacts are needed. Several recent studies, published since the release of the CPSC report, demonstrate associations between environmental TDCIPP measurements or urinary BDCIPP and health outcomes. Levels of exposure experienced by individuals in the general population, for example, have been associated with increased body mass index,[12] allergies and asthma,[40] decreased fertility and adverse reproductive outcomes.[41, 42]

We consider our work an important step in understanding human TDCIPP exposure; a single previous paper has used reverse dosimetry to estimate exposure to TDCIPP [38] and none have considered infants. In addition to the need for more information to estimate exposure over the lifetime for purposes of cancer risk assessment discussed above, our results should be interpreted in the context of several additional limitations. We did not have urine flow rates for individuals but rather used a range based on previous studies. In addition, estimates of molar fraction of TDCIPP converted to BDCIPP were based on animal and *in vitro* data,

and human excretion could vary considerably. Our results are also limited by our reliance on a single spot urine sample; data suggest that the biological half-life of TDCIPP is in the order of hours, indicating that BDCIPP concentrations vary over time. However, a number of previous studies in adults suggest that a spot urine sample is a reasonable proxy for longer-term exposure.[5, 6, 26] For example, we previously reported strong consistency in urinary TDCIPP over the course of five consecutive days (intraclass correlation coefficient=0.81 among adults), indicating that a spot urine sample may be a reasonable proxy for exposure over time.[6] No such data are available for young children. Interestingly, prior research suggests that TDCIPP exposure may vary seasonally, with higher levels of exposure in the summer.[12, 13] The samples in this analysis were largely collected during winter months suggesting that it is possible that our analyses underestimate average TDCIPP exposure. Finally, our sample consisted of a relatively small number of North Carolina infants. Patterns of exposure could be different in other populations and may be changing over time. Data from European countries, for example, suggest that exposure may be lower in Europe than in the US.[14, 43]

Our results suggest that infants' exposure to TDCIPP averages 0.33 μg/kg-day, a value under the threshold set by the CPSC for potential non-cancer health risks; however, a portion of infants included in our work had predicted exposures that could be associated with potential non-cancer health impacts (2-9%). In addition, under some assumptions, exposures were associated with increased life-time cancer risks over one in a million, the threshold for consideration as a hazardous substance. Cumulatively, our results, although limited to a relatively small population, suggest that current levels of exposure to TDCIPP experienced by some infants could be impacting their health. Confirmation of these results in a larger, more diverse cohort is needed.

Acknowledgements

References

1. Stapleton HM; Sharma S; Getzinger G; Ferguson PL; Gabriel M; Webster TF; Blum A, Novel and high volume use flame retardants in US couches reflective of the 2005 PentaBDE phase out. Environmental science & technology 2012, 46, (24), 13432–13439. [PubMed: 23186002]

2. Stapleton HM; Klosterhaus S; Keller A; Ferguson PL; van Bergen S; Cooper E; Webster TF; Blum A, Identification of flame retardants in polyurethane foam collected from baby products. Environ Sci Technol 2011, 45, (12), 5323–31. [PubMed: 21591615]

3. Cooper EM; Kroeger G; Davis K; Clark CR; Ferguson PL; Stapleton HM, Results from Screening Polyurethane Foam Based Consumer Products for Flame Retardant Chemicals: Assessing Impacts on the Change in the Furniture Flammability Standards. Environmental science & technology 2016, 50, (19), 10653–10660. [PubMed: 27552529]

4. Dodson RE; Perovich LJ; Covaci A; Van den Eede N; Ionas AC; Dirtu AC; Brody JG; Rudel RA, After the PBDE phase-out: a broad suite of flame retardants in repeat house dust samples from California. Environmental science & technology 2012, 46, (24), 13056–13066. [PubMed: 23185960]

5. Meeker JD; Cooper EM; Stapleton HM; Hauser R, Urinary metabolites of organophosphate flame retardants: temporal variability and correlations with house dust concentrations. Environ Health Perspect 2013, 121, (5), 580–5. [PubMed: 23461877]

6. Hoffman K; Garantziotis S; Birnbaum LS; Stapleton HM, Monitoring Indoor Exposure to Organophosphate Flame Retardants: Hand Wipes and House Dust. Environ Health Perspect 2015, 123, (2), 160–165. [PubMed: 25343780]

7. Abbasi G; Saini A; Goosey E; Diamond ML, Product screening for sources of halogenated flame retardants in Canadian house and office dust. The Science of the total environment 2016, 545-546, 299–307. [PubMed: 26747994]

8. Schreder ED; Uding N; La Guardia MJ, Inhalation a significant exposure route for chlorinated organophosphate flame retardants. Chemosphere 2016, 150, 499–504. [PubMed: 26775187]

9. Bergh C; Torgrip R; Emenius G; Ostman C, Organophosphate and phthalate esters in air and settled dust - a multi-location indoor study. Indoor Air 2011, 21, (1), 67–76. [PubMed: 21054550]

10. Dodson RE; Van den Eede N; Covaci A; Perovich LJ; Brody JG; Rudel RA, Urinary biomonitoring of phosphate flame retardants: levels in California adults and recommendations for future studies. Environmental science & technology 2014, 48, (23), 13625–33. [PubMed: 25388620]

11. Butt CM; Congleton J; Hoffman K; Fang M; Stapleton HM, Metabolites of organophosphate flame retardants and 2-ethylhexyl tetrabromobenzoate in urine from paired mothers and toddlers. Environmental science & technology 2014, 48, (17), 10432–10438. [PubMed: 25090580]

12. Hoffman K; Lorenzo A; Butt CM; Adair L; Herring AH; Stapleton HM; Daniels JL, Predictors of urinary flame retardant concentration among pregnant women. Environ Int 2017, 98, 96–101. [PubMed: 27745946]

13. Hoffman K; Butt CM; Webster TF; Preston EV; Hammel SC; Makey C; Lorenzo A; Cooper E; Carignan C; Meeker J; Hauser R; Soubry A; Murphy SK; Price T; Hoyo C; Mendelsohn E; Congleton J; Daniels JL; Stapleton HM, Temporal Trends in Exposure to Organophosphate Flame Retardants in the United States. Environmental Science and Technology Letters. 2017, (advanced publication).

14. Cequier E; Sakhi AK; Marce RM; Becher G; Thomsen C, Human exposure pathways to organophosphate triesters - a biomonitoring study of mother-child pairs. Environ Int 2015, 75, 159–65. [PubMed: 25461425]

15. Hoffman K; Butt CM; Chen A; Limkakeng AT Jr.; Stapleton HM, High Exposure to Organophosphate Flame Retardants in Infants: Associations with Baby Products. Environmental science & technology 2015, 49, (24), 14554–9. [PubMed: 26551726]

16. OEHHA. Evidence on the Carcinogenicity of Tris(1,3-Dichloro-2-Propyl) Phosphate. Sacramento, CA:Reproductive and Cancer Hazard Assessment Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (7 2011).

17. National Research Council (NRC), Toxicological Risks of Selected Flame-Retardant Chemicals. . 2000, (Subcommittee on Flame Retardant Chemicals, National Research Council, National Academy of Sciences. National Academy Press, Washington, DC.).

18. Babich MA CPSC Staff Preliminary Risk Assessment of Flame Retardants (FR) Chemicals in Upholstered Furniture Foam US Consumer Products Safety Commission: Bethesda, MD, 2006.

19. Dishaw LV; Powers CM; Ryde IT; Roberts SC; Seidler FJ; Slotkin TA; Stapleton HM, Is the PentaBDE replacement, tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. Toxicology and applied pharmacology 2011, 256, (3), 281–9. [PubMed: 21255595]

20. Farhat A; Crump D; Chiu S; Williams KL; Letcher RJ; Gauthier LT; Kennedy SW, In Ovo effects of two organophosphate flame retardants--TCPP and TDCPP--on pipping success, development, mRNA expression, and thyroid hormone levels in chicken embryos. Toxicol Sci 2013, 134, (1), 92–102. [PubMed: 23629516]

21. Farhat A; Buick JK; Williams A; Yauk CL; O'Brien JM; Crump D; Williams KL; Chiu S; Kennedy SW, Tris(1,3-dichloro-2-propyl) phosphate perturbs the expression of genes involved in immune response and lipid and steroid metabolism in chicken embryos. Toxicology and applied pharmacology 2014, 275, (2), 104–12. [PubMed: 24407104]

22. Liu X; Ji K; Jo A; Moon HB; Choi K, Effects of TDCPP or TPP on gene transcriptions and hormones of HPG axis, and their consequences on reproduction in adult zebrafish (Danio rerio). Aquat Toxicol 2013, 134-135, 104–11. [PubMed: 23603146]

23. Liu X; Ji K; Choi K, Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in zebrafish. Aquat Toxicol 2012, 114-115, 173–81. [PubMed: 22446829]

24. Butt CM; Hoffman K; Chen A; Lorenzo A; Congleton J; Stapleton HM, Regional comparison of organophosphate flame retardant (PFR) urinary metabolites and tetrabromobenzoic acid (TBBA) in mother-toddler pairs from California and New Jersey. Environ Int 2016, 94, 627–34. [PubMed: 27397928]

25. Van den Eede N; Heffernan AL; Aylward LL; Hobson P; Neels H; Mueller JF; Covaci A, Age as a determinant of phosphate flame retardant exposure of the Australian population and identification of novel urinary PFR metabolites. Environ Int 2015, 74, 1–8. [PubMed: 25277340]

26. Hoffman K; Daniels JL; Stapleton HM, Urinary metabolites of organophosphate flame retardants and their variability in pregnant women. Environ Int 2014, 63, 169–72. [PubMed: 24316320]

27. Romano ME; Hawley NL; Eliot M; Calafat AM; Jayatilaka NK; Kelsey K; McGarvey S; Phipps MG; Savitz DA; Werner EF; Braun JM, Variability and predictors of urinary concentrations of organophosphate flame retardant metabolites among pregnant women in Rhode Island. Environ Health 2017, 16, (1), 40. [PubMed: 28399857]

28. Xu F; Giovanoulis G; van Waes S; Padilla-Sanchez JA; Papadopoulou E; Magner J; Haug LS; Neels H; Covaci A, Comprehensive Study of Human External Exposure to Organophosphate Flame Retardants via Air, Dust, and Hand Wipes: The Importance of Sampling and Assessment Strategy. Environmental science & technology 2016, 50, (14), 7752–60. [PubMed: 27350238]

29. Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES): Anthropometry Procedures Manual. http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf (11 12),

30. Cooper EM; Covaci A; van Nuijs AL; Webster TF; Stapleton HM, Analysis of the flame retardant metabolites bis(1,3-dichloro-2-propyl) phosphate (BDCPP) and diphenyl phosphate (DPP) in urine using liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem 2011, 401, (7), 2123–2132. [PubMed: 21830137]

31. Hazinski MF, Nursing care of the critically ill child. Third edition. . 2012.

32. Wittassek M; Koch HM; Angerer J; Bruning T, Assessing exposure to phthalates - the human biomonitoring approach. Mol Nutr Food Res 2011, 55, (1), 7–31. [PubMed: 20564479]

33. Van den Eede N; Maho W; Erratico C; Neels H; Covaci A, First insights in the metabolism of phosphate flame retardants and plasticizers using human liver fractions. Toxicol Lett 2013, 223, (1), 9–15. [PubMed: 23994729]

34. Hou R; Xu Y; Wang Z, Review of OPFRs in animals and humans: Absorption, bioaccumulation, metabolism, and internal exposure research. Chemosphere 2016, 153, 78–90. [PubMed: 27010170]

35. Sasaki K; Suzuki T; Takeda M; Uchiyama M, Metabolism of phosphoric acid triesters by rat liver homogenate. Bulletin of environmental contamination and toxicology 1984, 33, (3), 281–8. [PubMed: 6478075]

36. Lynn RK; Wong K; Garvie-Gould C; Kennish JM, Disposition of the flame retardant, tris(1,3-dichloro-2-propyl) phosphate, in the rat. Drug metabolism and disposition: the biological fate of chemicals 1981, 9, (5), 434–41. [PubMed: 6117442]

37. Faust JB; August LM, Evidence on the Carcinogenicity of Tris(1,3-Dichloro-2-Propyl) Phosphate. Sacramento, CA: Reproductive and Cancer Hazard Assessment Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency Available: http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/TDCPP070811.pdf [accessed 12 May 2015]. 2011.

38. Carignan CC; McClean MD; Cooper EM; Watkins DJ; Fraser AJ; Heiger-Bernays W; Stapleton HM; Webster TF, Predictors of tris(1,3-dichloro-2-propyl) phosphate metabolite in the urine of office workers. Environ Int 2013, 55, 56–61. [PubMed: 23523854]

39. Butt CM; Hoffman K; Chen A; Lorenzo A; Congleton J; Stapleton HM, Regional comparison of organophosphate flame retardant (PFR) urinary metabolites and tetrabromobenzoic acid (TBBA) in mother-toddler pairs from California and New Jersey. Environ Int 2016.

40. Araki A; Saito I; Kanazawa A; Morimoto K; Nakayama K; Shibata E; Tanaka M; Takigawa T; Yoshimura T; Chikara H; Saijo Y; Kishi R, Phosphorus flame retardants in indoor dust and their relation to asthma and allergies of inhabitants. Indoor Air 2014, 24, (1), 3–15. [PubMed: 23724807]

41. Carignan C; Mínguez-Alarcón L; Butt C; Williams P; Meeker J; Stapleton H; Toth T; Ford J; Hauser R, Urinary Concentrations of Organophosphate Flame Retardant Metabolites and Pregnancy Outcomes among Women Undergoing in Vitro Fertilization. **(Under Review).(Under Review)**

42. Meeker JD; Stapleton HM, House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. Environ Health Perspect 2010, 118, (3), 318–23. [PubMed: 20194068]

43. Van den Eede N; Neels H; Jorens PG; Covaci A, Analysis of organophosphate flame retardant diester metabolites in human urine by liquid chromatography electrospray ionisation tandem mass spectrometry. J Chromatogr A 2013, 1303, 48–53. [PubMed: 23849782]

Table 1:

Parameter estimates and sources used in estimating TDCIPP exposure.

Parameter	Estimation Method and Species	Value	Reference
Urine excretion rate			
		0.00125 L/kg-hour	Wittassek, 2011 [32]
		0.001-0.002 L/kg-hour	Hazinski, 2012 [31]
TDCIPP urinary excretion fraction			
	In vivo; rat	63%	Lynn, 1981 [36]
TDCIPP metabolism			
	In vitro; human liver S9 fraction	68%	Van den Eede, 2013 [33]
	In vitro; human liver microsome (HLM)	46%	Van den Eede, 2013 [33]
	In vitro; rat liver homogenate	43%	Sasaki, 1984 [35]

Table 2:

Selected characteristics of the study population (n=43).

Participant Characteristic	Mean ± STD or N (%)
Age (months)	7.9±4.7
Weight (kg) *	7.7±2.1
Sex	
Male	24 (55.8)
Female	19 (44.2)
Race/ Ethnicity	
Hispanic	4 (9.3)
Non-Hispanic White	32 (74.4)
Non-Hispanic Black	2 (4.6)
Other Race - Including Multi-Racial	5 (11.6)
Income	
<50,000	11 (25.5)
50,000-99,999	12 (27.9)
100,000	17 (39.5)
Missing	3 (7.0)

*Weight was imputed for one child missing this data as the age and sex specific 50th percentile based on WHO growth curves.

Table 3:

Estimated daily intake and hazard index under various assumptions of daily urine excretion and the fraction of TDCIPP excreted as BDCIPP in urine.

Input Assumptions	GM Daily Intake (μg/kg-day)	Range Daily Intake (μg/kg-day)	GM HI	N (%) HI>1	Max HI
Urine Volume 1 mL/kg-hr Fraction Excreted in Urine 45%	0.17	0.01-7.51	0.03	1 (2)	1.50
Urine Volume 1 mL/kg-hr Fraction Excreted in Urine 65%	0.11	0.01-5.20	0.02	1 (2)	1.04
Urine Volume 2 mL/kg-hr Fraction Excreted in Urine 45%	0.33	0.03-15.03	0.07	4 (9)	3.01
Urine Volume 2 mL/kg-hr Fraction Excreted in Urine 65%	0.23	0.02-10.4	0.05	2 (5)	2.08