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Estimated Tris(1,3-dichloro-2-propyl) Phosphate Exposure Levels for U.S. Infants Suggest Potential Health Risks

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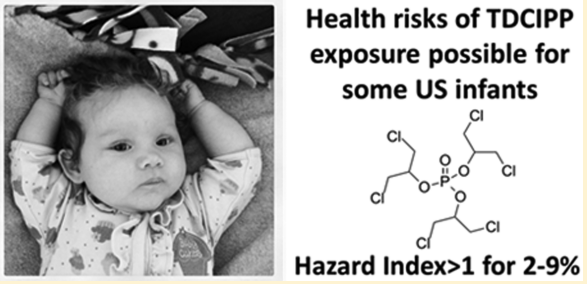
ABSTRACT: Tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) has been widely used as a flame retardant and is commonly detected in environmental samples. Biomonitoring studies relying on urinary metabolite levels [i.e., bis(1,3-dichloro-2-propyl) phosphate (BDCIPP)] demonstrate widespread exposure, but TDCIPP intake is unknown. Intake data are critical components 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 aged 2−18 months. Children were recruited from central North Carolina (n = 43, recruited in 2014 and 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 to 15.03 μg kg^{-1} day^{-1} for children included in our assessment, with some variation depending on model assumptions. The U.S. Consumer Products Safety Commission previously established an acceptable daily intake of 5 μg kg^{-1} day^{-1} 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 found 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.

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, on the basis of the 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 that previous research suggests might have higher levels of exposure.[11,15,24,25] Although the biological half-life of TDCIPP is likely on the order of hours, previous estimates of interclass correlation coefficients for BDCIPP suggest that a spot urine sample might 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 h 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.

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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 that 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 performed in accordance with a human subject 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 ref 15). Upon being collected, samples were transferred to polypropylene specimen containers and stored at −20 °C until analysis was performed. 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 d_{10}-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. The average recovery of d_{10}-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 3 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 (micrograms per liter) in the spot urine sample by an estimated 24 h urine output (liters) and calculating the micrograms per 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 (micrograms per day). Daily estimates were divided by each child's weight (kilograms), producing weight-adjusted intake rates in micrograms per kilogram per day (eq 1).

$$\mu\text{g of TDCIPP/kg/day} = \frac{\text{spot BDCIPP } (\mu\text{g/L}) \times \text{urine output (L/day)}}{\text{molar excretion fraction} \times \text{child weight (kg)}} \times \frac{\text{MW of TDCIPP (g/mol)}}{\text{MW of BDCIPP (g/mol)}} \quad (1)$$

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^{-1} h^{-1}).[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 conversion of TDCIPP 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.

Table 1. Parameter Estimates and Sources Used in Estimating TDCIPP Exposure

parameter	estimation method and species	value	ref
urine excretion rate		0.00125 L kg^{-1} h^{-1}	32
		0.001−0.002 L kg^{-1} h^{-1}	31
TDCIPP urinary excretion fraction	in vivo; rat	63%	36
TDCIPP metabolism	in vitro; human liver S9 fraction	68%	33
	in vitro; human liver microsome (HLM)	46%	33
	in vitro; rat liver homogenate	43%	35

Potential for Adverse Health Impacts. The CPSC calculated an acceptable daily intake (ADI) for TDCIPP based on previously published rodent data demonstrating histopathological effects in several organs [e.g., liver, kidney, spleen, and parathyroid; lowest observed adverse effect level (LOAEL) = 5 mg kg^{-1} day^{-1}].[17,18] Via incorporation of 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^{-1} day^{-1}. 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 of >1 indicates potential for health impacts at 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^{-1} day^{-1}.[37]

Potential for Excess Cancer Risk. The CPSC calculated a cancer potency factor (i.e., the probability of incurring cancer in one's lifetime because of exposure) for TDCIPP using prior research indicating hepatocellular carcinoma and adenoma and tumors of the renal cortex (0.031 mg kg^{-1} day^{-1}).[17] Using the CPSC value, we estimated the lifetime excess cancer risk from exposure by multiplying the potency factor by the lifetime average daily dose (LADD). Following the lead of the CPSC, we first examine only infant exposure, assuming that the LADD is based on exposure at the estimated rates for two years. 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 that assumed that levels of exposure during the first two years 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

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Table 2. Selected Characteristics of the Study Population (n = 43)

participant characteristic	mean ± STD or N (%)
age (months)	7.9 ± 4.7
weight (kg)[a]	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 races, including multiracial	5 (11.6)
income	
<50000	11 (25.5)
50000–99999	12 (27.9)
≥100000	17 (39.5)
missing	3 (7.0)

[a]Weight was imputed for one child missing this information as the age and sex specific 50th percentile based on CDC growth curves.

found in studies of adults or older children conducted at similar time points,[6,11] suggesting infants may have higher levels of exposure.

Using eq 1, the estimated daily intake of TDCIPP ranged from 0.01 to 15.03 μg kg^{-1} day^{-1} for the individual children in our study population (Table 3). Among these children, the geometric mean intake was 0.11 μg kg^{-1} day^{-1} using assumptions that would result in the lowest estimated intakes (urine volume of 1 mL kg^{-1} h^{-1} and 65% of TDCIPP excreted in urine as BDCIPP) and 0.33 μg kg^{-1} day^{-1} using assumptions that would result in the highest estimated intakes (urine volume of 2 mL kg^{-1} h^{-1} 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^{-1} day^{-1}.

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, and 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.

On the basis of the cancer potency factor proposed by the CPSC,[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^{-1} day^{-1} for 2 years of a 75 year lifetime), we estimated cancer risk from exposure to TDCIPP to be 0.3 case per 1 million individuals; however, this is likely an underestimate. Assuming exposure during infancy continues at the same level throughout the course of life (0.21 μg kg^{-1} day^{-1} for 75 years), the estimated excess cancer risk was 10 per 1 million, likely an overestimate. Finally, assuming exposure continues at half the level of infants' exposures (0.21 μg kg^{-1} day^{-1} for 2 years and 0.11 μg kg^{-1} day^{-1} for 73 years) results in an excess cancer risk of 5 per 1 million. Our estimate is lower than that of the CPSC (300 cases per 1 million) but under some assumptions surpasses the 1 in 1 million value used by the 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 lifetime excess cancer risk does not exceed 1 per 1 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., ref 25). Both alternative exposure scenarios considered suggest that lifetime excess cancer risk exceeds this threshold, particularly when infant exposure levels are assumed to continue throughout the course of life (10 per 1 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 overestimating 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 CPSC 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

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^{-1} day^{-1})	daily intake range (μg kg^{-1} day^{-1})	GM HI	N (%) for which HI > 1	maximal HI
urine volume, 1 mL kg^{-1} h^{-1}; fraction excreted in urine, 45%	0.17	0.01–7.51	0.03	1 (2)	1.50
urine volume, 1 mL kg^{-1} h^{-1}; fraction excreted in urine, 65%	0.11	0.01–5.20	0.02	1 (2)	1.04
urine volume, 2 mL kg^{-1} h^{-1}; fraction excreted in urine, 45%	0.33	0.03–15.03	0.07	4 (9)	3.01
urine volume, 2 mL kg^{-1} h^{-1}; fraction excreted in urine, 65%	0.23	0.02–10.4	0.05	2 (5)	2.08

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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] and 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. 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 the 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 on 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 BDCIPP over the course of five consecutive days (intraclass correlation coefficient of 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 United States.[14,43]

Our results suggest that infants' exposure to TDCIPP averages 0.33 μg kg^{-1} day^{-1}, 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 lifetime cancer risks of >1 in 1 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.

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Notes

The authors declare no competing financial interest.

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