United States
Consumer Product Safety Commission

September, 2024

CPSC Staff Statement on: Exposure Assessment of Polyhalogenated Organophosphate (PHOP) Flame Retardants Using Human Biomonitoring Data

The U.S. Consumer Product Safety Commission (CPSC or Commission) contracted with University of Cincinnati (UC) (Contract No. CPSC-D-17-0001, Order No. 61320622F01004) to complete an exposure assessment of Polyhalogenated Organophosphate (PHOP) Flame Retardants using Human Biomonitoring Data. This statement was prepared by the CPSC staff. UC produced the accompanying report for CPSC staff. The statement and report have not been reviewed or approved by, and may not represent the views of, the Commission.

UC's report consists of a main report that describes background, methods, and results from this analysis. This report follows the 2022 *Guidance Document for Use of Human Biomonitoring Data for Exposure Assessment* developed by UC for CPSC staff. The main report lists 22 supporting files in the Appendix (Report Section 8.0). These files document how underlying biomonitoring and toxicokinetic data were identified and processed. Files describing interim calculations, results files describing analyses of NHANES (National Human and Nutritional Examination Survey) and literature data, and the R statistical code used for all analyses are provided.

This report is an exposure assessment and does not make statements with regard to potential risks to human health. Human biomonitoring data can be used to estimate the total exposure across all pathways and can be used to calculate an estimated daily intake (DI). DIs for three PHOPs were calculated for four age groups (Ages 3-5, 6-11, 12-17, and 18+) using both deterministic and probabilistic methods based on urine biomonitoring data of corresponding metabolites, body weight, urine volumes, and fractional urinary excretion (F_{ue}). Biomonitoring data from four two-year cycles and a four-year cycle that includes the prior two-year cycle and the partial Covid-19 cycle of NHANES and other published literature were used.

The DIs for children were higher than DIs for adult age groups. There was not a clear increasing or decreasing trend over four NHANES cycles. Estimated DIs from deterministic and probabilistic calculations were generally in good agreement. Both deterministic and probabilistic analyses included correction for the intraclass correlation coefficient (ICC), to account for intra-individual variability relative to the time of exposure. To staff's knowledge, this is the first practical application of this ICC correction method for reverse dosimetry of these PHOPs. Thus, the current work may provide a better estimate of exposure, by better accounting for the relative contributions of inter-individual and intra-individual variability. This work includes new F_{ue} estimates compared to previous work on these PHOPs by estimating chemical-specific F_{ue} values. The non-uniqueness of metabolites relative to parent compounds and uncertainty related to F_{ue} estimates are acknowledged. This report will be used alongside other exposure estimation approaches to characterize exposures from specific sources relative to aggregate exposures.

Exposure Assessment of Polyhalogenated Organophosphate (PHOP) Flame Retardants Using Human Biomonitoring Data

Contract # CPSC-D-17-0001

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List of Abbreviations

AM = Arithmetic mean
ASD = Arithmetic standard deviation
BBP = Butylbenzyl phthalate
BCCP = Bis(2-chloroethyl) carboxymethyl phosphate
BCEP = Bis(2-chloroethyl) phosphate
BCIPHIPP = Bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate
BCIPP = Bis(1-chloro-2-propyl) phosphate (the preferred acronym)
BCPP = Bis(1-chloro-2-propyl) phosphate (a common alternative acronym)
BDCIPP = Bis(1,3-dichloroisopropyl) phosphate (the preferred acronym)
BDCPP = Bis(1,3-dichloroisopropyl) phosphate (a common alternative acronym)
C_{max} = Max concentration
CPSC = Consumer Product Safety Commission
DBP = Dibutyl phthalate
DEHP = Di(2-ethylhexyl) phthalate
DIDP = Diisodecyl phthalate
DINP = Diisononyl phthalate
DNTP (or DTT) = Division of Translational Toxicology
EPA (or US EPA) = Environmental Protection Agency
FR = Flame retardant
F_{ue} = Urinary excretion fraction
GM = Geometric mean
GSD = Geometric standard deviation
HBM = Human biomonitoring
Hr = hour
HTTK = High-Throughput Toxicokinetics
ICE = Integrated Chemical Environment
ICC = Intraclass Correlation Coefficient
ICRP = International Commission on Radiological Protection
Kg = kilogram
mL = milliliter
NCHS = National Center for Health Statistics
NHANES = National Health and Nutritional Examination Survey
OFR = Organohalogen flame retardant
PBPK = Physiologically-based pharmacokinetic
PHOP = Polyhalogenated organophosphate
TBBPA = Tetrabromobisphenol A
TCEP = Tris(2-chloroethyl) phosphate
TCIPP = Tris(1-chloro-2-propyl) phosphate (the preferred acronym)
TCPP = Tris(1-chloro-2-propyl) phosphate (a common alternative acronym)
TDCIPP = Tris(1,3-dichloroisopropyl) phosphate (the preferred acronym)
TDCPP = Tris(1,3-dichloroisopropyl) phosphate (a common alternative acronym)
UC = University of Cincinnati
UFR = Urinary Flow Rate
UFRBW = Body Weight Adjusted Urinary Flow Rate

1.0 Introduction

This report summarizes the approach and results of a project the University of Cincinnati (UC) conducted for the US Consumer Product Safety Commission (CPSC) under Contract #CPSC-D-17-0001, Task Order 61320622F1004. The purpose of this project was to apply the process guide, "Guidance Document for Use of Human Biomonitoring Data for Exposure Assessment," (Guidance Document henceforth) developed under U.S. Consumer Product Safety Commission (CPSC or Commission) Contract CPSC-D-17-0001, Task order 61320620F1013, as well as other sources, to identify human biomonitoring data for polyhalogenated organophosphate (PHOP) flame retardants (FRs) and estimate daily intake.

This was accomplished via three subtasks. (1) Because human fractional urinary exposure (F_{ue}) values are not available for PHOPs, the first task was to identify F_{ue} values based on human, animal and *in vitro* data for a group of phthalates. These phthalates are well-studied, and, like the PHOPs, are water-soluble and have relatively short half-lives for excretion from the body. The phthalate F_{ue} values were then compared with data on F_{ue} from PHOPs, where available. (2) The second task was to identify human biomonitoring data for PHOP FRs, focusing first on three "data-rich[1]" PHOPs, and then extending to the remaining PHOP FRs. Data for the three data rich PHOPs were also obtained from the National Health and Nutritional Examination Survey (NHANES). (3) The third task was to use the biomonitoring data to estimate daily intake. These estimates include evaluation of populations expected to have higher exposure or higher susceptibility, distributional analyses, and analyses of high-exposure individuals in NHANES.

The five phthalates considered in this task are dibutyl phthalate (DBP), butylbenzyl phthalate (BBP), di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), and diisodecyl phthalate (DIDP). These phthalate have molecular weights ranging from 278-447, have relatively short elimination half-lives, and were reviewed in both individual CPSC assessments and in the CHAP (2014) report.

The data-rich PHOPs identified by CPSC staff are shown in Table 1. The key metabolite(s) for each parent chemical is also shown. These are the three PHOP FRs evaluated as part of NHANES, based on the metabolites shown. However, as discussed further in the Discussion, we determined late in the project that these metabolites are shared by multiple PHOP FRs. Note also that one metabolite of TCIPP (BCIPHIPP) is not included in the NHANES biomonitoring.

[1] Data-rich PHOP chemicals are defined for the purposes of the present work as those listed as such in the Statement of Work.

Table 1. Data Rich PHOPs and Their Metabolites

Parent chemical	Acronym (s)	Parent CAS#	Metabolite	Metabo-lite Acronym	Metabo-lite CAS#
Tris(1-chloro-2-propyl) phosphate	TCPP/ TCIPP	13674-84-5	Bis(1-chloro-2-propyl) phosphate	BCPP/ BCIPP	789440-10-4
Tris(1-chloro-2-propyl) phosphate	TCPP/ TCIPP	13674-84-5	Bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate	BCIPHIPP	1477495-11-6
Tris(2-chloroethyl) phosphate	TCEtP/ TCEP	115-96-8	Bis(2-chloroethyl) phosphate	BCEtP/ BCEP	3040-56-0
Tris(1,3-dichloroisopropyl) phosphate/ Fyrol FR-2	TDCIPP	13674-87-8	Bis(1,3-dichloroisopropyl) phosphate	BDCPP/ BDCIPP	72236-72-7

2.0 Methods

2.1 Literature Search and Data Acquisition

2.1.1 PHOPs HBM and Toxicokinetic Data

Identifying references from previous literature searches and supplementing with updated searches

The literature searching for the subclass polyhalogenated organophosphates (PHOPs) built from the references identified as part of the DNTP (2021) (now Division of Translational Toxicology, DTT) comprehensive literature search for organohalogen flame retardants (OFRs). The full search and screening strategy is illustrated in Figure 1. From among the references of the DNTP search, CPSC provided a preliminary list of 164 references relevant to toxicokinetics and biomonitoring. All other references (n=**7799**[2]; n= 6532 unique) from the DNTP search that had passed Level 1 screening in the corresponding Distiller project were also included for screening (see below). Non-English language references were removed (n=77).

We updated the DNTP (2021) literature search to capture any recent relevant studies using *de novo* literature searches in two batches. The 3 most data-rich PHOPs (Primary 3 PHOPs; n=**583**; n=424 unique) were searched in PubMed and Web of Science covering dates from August 1, 2021 (just prior to the date the DNTP search was conducted) to June 14, 2022 (the date the updated searches were conducted). Non-English language references were removed (n=4). The data-poor PHOPs were searched in PubMed and Web of Science covering dates from August 1, 2021 to January 20, 2023 (the date the updated searches were conducted), (n=**980**; n=733 unique, after excluding any references found in the June

[2] Bolded numbers refer to entries on the Prisma flow diagram

14, 2022 search). Non-English language references (n=6) and conference proceedings (n=7) were removed. In light of the relatively short time period covered by the searches, the results were not limited by toxicokinetics or biomonitoring terms. *De novo* search terms are outlined in Table 2, and are based on the search terms used for the DNTP (2021) comprehensive literature search.

For both sets of de novo searches, terms returning no results in PubMed were removed from the PubMed searches. For the primary 3 PHOPs, these terms were not included in the Web of Science searches, while for the data poor PHOPs these terms were retained in the Web of Science searches. The difference in treatment of these terms for the Web of Science searches was based on a balance between number of references to screen and the likelihood of encountering "new" data (i.e. references for the primary 3 PHOPs obtained during de novo searches were far less likely to fill a gap in existing data compared to references for the data poor PHOPs).

Table 2. PubMed and Web of Science de novo Search Terms for PHOPs

Search set	Database	Search String
Primary 3 PHOPs	PubMed	("Tris(1-chloro-2-propyl) phosphate" OR "Tris(2-chloroisopropyl) phosphate" OR "Tris(2-chloroisopropyl)phosphate" OR TCPP OR TCIPP OR "13674-84-5" OR "2-chloroethanol phosphate" OR "Ethanol, 2-chloro-, phosphate (3:1) " OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(chloroethyl) phosphate" OR "Tris(-chloroethyl) phosphate" OR "Tris(chloroethyl)phosphate" OR TCEtP OR TCEP OR "115-96-8" OR "Tris(1,3-dichloro-2-propyl) phosphate" OR "Tris(1,3-dichloro-2-propyl)phosphate" OR "Tris(1,3-dichloroisopropyl) phosphate" OR "Tris(1,3-dichloroisopropyl)phosphate" OR "tris(1,3-dichloropropan-2-yl) phosphate" OR "Tris(2-chloro-1-(chloromethyl)ethyl) phosphate" OR TDCPP OR TDCIPP OR "13674-87-8" OR "polyhalogenated organophosphat*" OR "polybrominated organophosphat*" OR "polychlorinated organophosphat*") AND (("2021/08/01"[Date - Publication] : "2022/06/14"[Date - Publication]))
Primary 3 PHOPs	Web of Science*	ALL=("Tris(1-chloro-2-propyl) phosphate" OR "Tris(2-chloroisopropyl) phosphate" OR "Tris(2-chloroisopropyl)phosphate" OR TCPP OR TCIPP OR "13674-84-5" OR "2-chloroethanol phosphate" OR "Ethanol, 2-chloro-, phosphate (3:1) " OR "Tri(2-chloroethyl) phosphate" OR "Tri(2-chloroethyl)phosphate" OR "Tri(chloroethyl) phosphate" OR "Tri-beta-chloroethyl phosphate" OR "tris(2-chloroethyl) orthophosphate" OR "Tris(2-chloroethyl) phosphate" OR "Tris(chloroethyl) phosphate" OR "Tris(-chloroethyl) phosphate" OR "Tris(chloroethyl)phosphate" OR TCEtP OR TCEP OR "115-96-8" OR "Tris(1,3-dichloro-2-propyl) phosphate" OR "Tris(1,3-dichloro-2-propyl)phosphate" OR "Tris(1,3-dichloroisopropyl) phosphate" OR "Tris(1,3-dichloroisopropyl)phosphate" OR "tris(1,3-dichloropropan-2-yl) phosphate" OR "Tris(2-chloro-1-(chloromethyl)ethyl) phosphate" OR TDCPP OR TDCIPP OR "13674-87-8" OR "polyhalogenated organophosphat*" OR "polybrominated organophosphat*" OR "polychlorinated organophosphat*")
Data poor PHOPs	PubMed	("Tris(2,3-dichloropropyl)phosphate" OR "bis(2,3-dibromopropyl) phosphate" OR "Tris(2-chloropropyl) phosphate" OR "Bis(2-chloroethyl) 2-chloroethylphosphonate" OR "Tris(tribromoneopentyl)phosphate" OR

Search set	Database	Search String
		“Tris(dichloropropyl) phosphate” OR "2,3-Dibromopropylphosphate” OR “Tris(chloropropyl)phosphate” OR “Tris(chloroethyl) phosphate” OR “Tris(2-carboxyethyl)phosphine hydrochloride” OR TDBPP OR DDBPP OR TTBNPP OR TTBNP OR V6 OR BDCIPP OR BDCPP OR “78-43-3” OR “126-72-7” OR “5412-25-9” OR “6145-73-9” OR “6294-34-4” OR “19186-97-1” OR “66108-37-0” OR “34432-82-1” OR “36711-31-6” OR “64864-08-0” OR “5324-12-9” OR “26248-87-3” OR “72236-72-7” OR "Tris (2,3-dibromopropyl) phosphate” OR "Tris(2,3-dibromopropyl) phosphate” OR "Tris(2,3-dibromopropyl)phosphate” OR "Tris-(2,3-dibromopropyl)-phosphate” OR “Tris(-chloroethyl) phosphate” OR “Tris(chloroethyl)phosphate” OR "(2,3-Dibromopropyl) phosphate” OR ”Bis(2-chloroethyl) phosphate”) AND ("2021/08/01"[Date - Publication] : "2023/01/20"[Date - Publication])
Data poor PHOPs	Web of Science*^	ALL=("Tris(2,3-dichloropropyl)phosphate” OR “Bis(2-chloroethyl) vinylphosphonate” OR “Tris(2-chloroethyl) phosphite” OR "Phosphonic acid, P-[1-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]-, 1-[bis(2-chloroethoxy)phosphinyl]ethyl 2-chloroethyl ester” OR "Bis(2,3-dibromopropyl) hydrogen phosphate” OR "bis(2,3-dibromopropyl) phosphate” OR “Tris(2-chloropropyl) phosphate” OR “Bis(2-chloroethyl) 2-chloroethylphosphonate” OR "Tris(1,3-dichloropropan-2-yl) phosphite” OR "Tris(2,4,6-tribromophenyl) phosphate” OR “Tris(tribromoneopentyl)phosphate” OR "Tris [3-bromo-2,2-bis(bromomethyl)propyl] phosphate” OR "Phosphoric acid, 1,2-ethanediyl tetrakis(2-chloroethyl) ester” OR "Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester” OR "2,2-bis(chloromethyl)-1,3-propanediol bis[bis(2- chloroethyl)phosphate]” OR “Tris(dibromophenyl) phosphate” OR “Diethylene glycol bis[bis(2-chloroethyl)phosphate]” OR "2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-, 3,9-dioxide” OR "2,2-Bis(bromomethyl)-3-chloropropyl bis[2-chloro-1-(chloromethyl)ethyl] phosphate” OR "dimethyl {[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]methyl}phosphonate” OR “Tris(3-chloropropyl)phosphate” OR "Phosphoric acid, mixed 3-bromo-2,2-dimethylpropyl and 2-bromoethyl and 2-chloroethyl esters” OR "2,2-Bis(chloromethyl)-1,3-propanediyl tetrakis(1-chloro-2-propanyl) bis(phosphate)” OR “Tris(dichloropropyl) phosphate” OR "Bis(2,3-dibromopropyl) hydrogen phosphate--ammonia (1/1)” OR "Bis(2,3-dibromopropyl) phosphate, magnesium salt” OR "Sodium bis(2,3-dibromopropyl) phosphate” OR "potassium bis(2,3-dibromopropyl) phosphate” OR "2,3-Dibromopropylphosphate” OR “Tris(chloropropyl)phosphate” OR “Tris(chloroethyl) phosphate” OR "1,2-Diphenylpropan-2-yl diphenyl phosphate” OR “Tris(2-carboxyethyl)phosphine hydrochloride” OR "Bis(1,3-dichloropropan-2-yl) hydrogen phosphate” OR “Bis(2-chloro-1-methylethyl) 2-chloropropyl phosphate” OR “(2-Chloro-1-methylethyl) bis(2-chloropropyl) phosphate” OR "4-Bromo-2-chlorobutyl 3-bromo-2,2-dimethylpropyl phosphate” OR "Tris(2,4-dibromophenyl) phosphate” OR “2-Bromoethyl 5-bromopentyl 2-chloroethyl phosphate” OR "Ethanol, 2-bromo-, phosphate (3:1)” OR “Tris(2-bromo-4-methylphenyl) phosphate”) ALL=(TDBPP OR DDBPP OR TTBNPP OR TTBNP OR V6 OR “BCMP-BCEP” OR “U-OPFR” OR BDCIPP OR BDCPP OR “78-43-3” OR “115-98-0” OR “126-72-7” OR “140-08-9” OR “4351-70-6” OR “5412-25-9” OR “6145-73-9” OR “6294-34-4” OR “6749-73-1” OR “7046-64-2” OR “19186-97-1” OR “33125-86-9” OR “38051-10-4” OR “49690-63-3” OR “53461-82-8” OR “61090-89-9”)

Search set	Database	Search String
		ALL=(“66108-37-0” OR “1373346-90-7” OR “1067-98-7” OR “125997-20-8” OR “1047637-37-5” OR “26604-51-3” OR “34432-82-1” OR “36711-31-6” OR “64864-08-0” OR “66519-18-4” OR “5324-12-9” OR “26248-87-3” OR “29716-44-7” OR “34364-42-6” OR “51805-45-9” OR “72236-72-7” OR “76025-08-6” OR “76649-15-5” OR “98923-48-9” OR “2788-11-6” OR “84282-27-9” OR “27568-90-7” OR “35656-01-0” OR "Tris (2,3-dibromopropyl) phosphate” OR "Tris(2,3-dibromopropyl) phosphate” OR "Tris(2,3-dibromopropyl)phosphate” OR "Tris-(2,3-dibromopropyl)-phosphate” OR “Tris(2-chloroethyl)phosphite” OR “Tris(-chloroethyl) phosphate” OR “Tris(chloroethyl)phosphate” OR "(2,3-Dibromopropyl) phosphate” OR "2,2-Dichloroethyl dimethyl phosphate” OR ”Bis(2-chloroethyl) phosphate” OR “Diethylene glycol bis(bis(2-chloroethyl)phosphate)”)

**Note that date limitations in Web of Science were manually entered on the Advanced Search page. Dates used are the same as the corresponding PubMed search for each search type.*
^Note this search exceeded the Web of Science limits on number of search terms, so had to be split and searched separately.

Using the evidence maps produced as part of the literature survey conducted under Task Order 61320621F1001, we also identified additional peer-reviewed and grey literature sources with relevant toxicokinetic or biomonitoring data for the 3 primary PHOPs (n=**77**; n=38 unique) and for the data poor PHOPs (n=**25** ; n=10 unique). Finally, references specifically cited in the statement of work (n=**14**; n=3 unique) were added for screening.

References were deduplicated across the individual sources, leaving a total of **7321 unique** references that underwent Level 0 screening in Excel®.

Screening and prioritizing references for data extraction

References identified above were screened in two rounds. First, title and abstract were screened in Excel® for a) relevance to toxicokinetics and/or biomonitoring, and b) relevance to the PHOP subclass. Excel®-based screening used keywords and a formula to prioritize references for screening, but all references were manually screened. Title/abstract screening erred toward inclusion in cases of uncertainty. References were included if they possibly included: biomonitoring data (any medium), data on metabolism (a PHOP metabolite measured for biomonitoring, *in vitro/in vivo* studies of PHOP metabolism), data on other specific aspects of toxicokinetics (fractional urinary excretion [F_{ue}] or data that could be used to calculate F_{ue}, clearance or data that could be used to calculate clearance, physiologically based pharmacokinetic (PBPK) model that could provide toxicokinetic parameters, quantitative data on absorption or excretion). Based on this initial screen n=**6914** references were excluded.

Second, references deemed relevant to toxicokinetic and/or biomonitoring (n=**407**) were retrieved, and the full text screened in Distiller for relevance to toxicokinetics and/or biomonitoring and to the PHOP subclass. For PHOPs references, both levels of screening were conducted simultaneously for toxicokinetic data (Task 1) and biomonitoring data

(Task 2). A single reference could be identified as relevant to both biomonitoring and toxicokinetics, or to only one of the two.

One screener performed the first round of screening (Excel®), while two screeners performed the second round of screening (in Distiller®). Throughout this second round of screening and in later prioritization steps, studies containing intraclass correlation coefficients (ICCs) were flagged for later extraction (See Section 2.5).

References identified as relevant to PHOP toxicokinetics (n=**134**) proceeded directly to extraction in Excel®.

References identified as relevant to PHOP biomonitoring (n=**299**) proceeded to a "light extraction" round in Distiller®, to further screen and prioritize references for extraction of PHOP biomonitoring data in Excel®. Studies with only occupational exposure, and review articles/completed assessments that did not include value-added data (e.g., trend data or meta-analyses) were excluded at this point, as were conference proceedings, non-English articles and abstract-only references. In addition, studies that only included data from the National Health and Nutrition Examination Survey (NHANES) were also excluded, since the primary NHANES data are being analyzed in a separate element of this task. Factors considered for prioritization included: population/age group covered, inclusion of other vulnerable groups, US-based location, sample size ≥ 50, reporting of temporal trends, sample types (spot urine, 24-hour urine, blood/serum/plasma[3], breast milk, and/or other), and coverage of more than a single PHOP. One screener performed the light extraction, and one reviewer provided QA on all references. Of these 299, **170** proceeded to Excel® for prioritization for full extraction.

A priority score was created allocating points for each of the above factors, with a focus on urine data (since that was the bulk of the data). All studies receiving a score of 5 or higher were manually screened to confirm the initial points, to determine whether data for vulnerable populations were reported separately (as opposed to being presented only in the context of a correlation analysis), and to identify the PHOPs evaluated. In addition, studies with the following tags were additionally screened for high-priority studies, regardless of total priority score: any 24-hour urine; temporal trends = yes; age <2 years; pregnant women; data poor PHOP. After the above prioritization for urine data, blood data were assessed for prioritization for extraction based on chemical and population coverage (without an explicit prioritization score). Studies that did not conduct appropriate adjustments to urine (specific gravity or creatinine) were excluded, unless they addressed a data gap. Blood studies were higher priority if they also included urine data, or were from North America or Europe. Studies from China were generally excluded (for any medium), unless there were other overriding considerations. Due to a smaller number of studies for blood than for urine, and a limited number of studies that contain data from both urine and blood in the same population, some studies from China that evaluated both media were also included.

[3] For the remainder of this report, "blood" refers to any blood fraction unless it is noted as specifically referring to whole blood.

When there were multiple published studies on the same cohort, only one was selected for extraction. There were some challenges to implementing this approach, such as when different studies used different subsets of people from the same cohort. Generally, the largest and/or best/most useful study was chosen. Demographic information and the quality of urine measurements were also used to determine the best/most useful study from a given cohort. If these factors did not meaningfully distinguish among studies, the study with the largest sample size was selected for extraction. In some cases (e.g., the HOME cohort), subsets of people used in different studies each contributed unique and high-quality information on different populations of interest (e.g., data on children broken down by race in one study, data on pregnant women in another study). In these cases, multiple studies from the same cohort were included. Based on this process, a prioritized group of studies (n=**31**) was identified for full extraction.

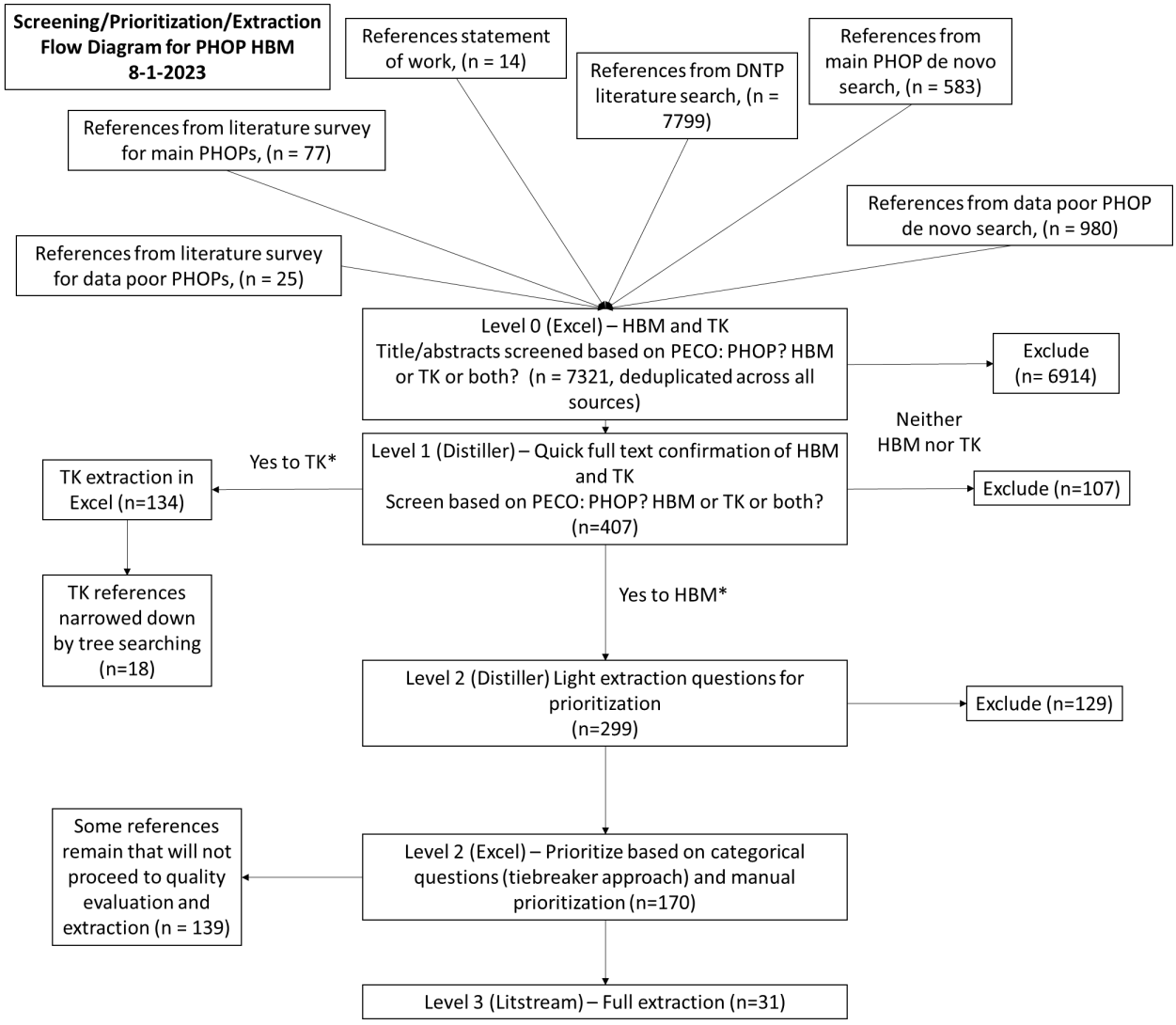
Studies flagged for toxicokinetic data were further reviewed for relevant data, and whether quantitative absorption, distribution, metabolism, or excretion data were available. From the studies with quantitative data, data were extracted into an Excel® spreadsheet on study conditions (exposed organism, exposure scenario (route, duration, frequency, doses), chemical dosed, biomarker monitored, duration of urine collection % label in urine, % label as biomarker, F_{ue} and basis, half-life, and clearance. A total of **11** PHOP toxicokinetic studies were extracted, covering both *in vivo* and *in vitro* data. Further details are provided in the PHOP TK Extraction and F_{ue} Estimation spreadsheet (see Appendix Table 1 for file name).

2.1.2 Phthalate Toxicokinetic Data

Identifying references from previous literature searches, and supplementing with updated searches

The literature searching for the phthalates of interest (dibutyl phthalate (DBP), butylbenzyl phthalate (BBP), di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), and diisodecyl phthalate (DIDP)) built from the CHAP report (CHAP, 2014). All references from the CHAP report (n=591) and the CHAP report itself (n=1) were included for screening (see below).

We conducted an updated search for literature published since the CHAP using *de novo* literature searches. The phthalates of interest (n= 4678; n=3460 unique) were searched in PubMed and Web of Science covering dates from January 1, 2013 (the year prior to the publication of the CHAP report) to June 14, 2022 (the date the updated searches were conducted). The updated searches for the phthalates covered a longer time period than those for the PHOPs (see Section 2.1.1), and so were additionally limited by terms related to toxicokinetics and biomonitoring. Biomonitoring was included as a search term because some biomonitoring studies use a value of fractional urinary excretion (F_{ue}) to estimate daily intake. In addition, the text word tag ([tw]) was used to further limit the fields searched, in order to further limit search hits to more relevant references. *De novo* search terms (including more detail on [tw]) are outlined in Table 3.



*Note that a single study may continue to Level 2 for HBM, for TK, or for both HBM and TK. All studies passing to Level 2 require Yes to PHOPs.

Figure 1. Prisma diagram for PHOP searching and screening

Table 3. PubMed and Web of Science de novo Search Terms for Phthalates

Search set	Database	Search String
Phthalates	PubMed^	("Dibutyl Phthalate"[Mesh] OR "Dibutyl Phthalate"[tw] OR "Di-n-Butyl Phthalate"[tw] OR "Di n Butyl Phthalate"[tw] OR "Butyl Phthalate"[tw] OR "d n butyl phthalate"[tw] OR "di nbutyl phthalate"[tw] OR "dibutyl phthalate"[tw] OR "dibutylphthalate"[tw] OR "phthalic acid di n butyl ester"[tw] OR "84-74-2"[tw] OR "butylbenzyl phthalate" [Supplementary Concept] OR "benzylbutyl phthalate"[tw] OR "bbp"[tw] OR "85-68-7"[tw] OR "Diethylhexyl Phthalate"[Mesh] OR "bis (2 ethylhexyl) phthalate"[tw] OR "bis (2 ethylhexyl) phthalate"[tw] OR "bis (2 ethylhexyl)phthalate"[tw] OR "bis (2 ethylhexylphthalate)"[tw] OR "Bis(2-ethylhexyl)phthalate"[tw] OR "DEHP"[tw] OR "di (2 ethylhexyl) phthalate"[tw] OR "di 2 ethylhexyl phthalate"[tw] OR "di 2 ethylhexylphthalate"[tw] OR "Di-2-Ethylhexylphthalate"[tw] OR "diethylhexyl phthalate"[tw] OR "Dioctyl Phthalate"[tw] OR "octoil"[tw] OR "phthalic acid di 2 ethylhexyl ester"[tw] OR "phthalic acid diethylhexyl ester"[tw] OR "117-81-7"[tw] OR "diisononyl phthalate" [Supplementary Concept] OR "di-isononylphthalate"[tw] OR "ENJ 2065"[tw] OR "ENJ-2065"[tw] OR "di-isononylphthalate"[tw] OR "di-iso-nonyl phthalate"[tw] OR "DINP"[tw] OR "28553-12-0"[tw] OR "diisodecyl phthalate" [Supplementary Concept] OR "diisodecyl phthalate"[tw] OR "DIDP"[tw] OR "26761-40-4"[tw]) AND (Toxicokinetics OR Absorption OR Distribution OR Metabolism OR Excretion OR ADME OR Urine OR Biomonitoring) AND (("2013/01/01"[Date - Publication] : "2022/06/14"[Date - Publication]))
Phthalates	Web of Science*	ALL=(("Dibutyl Phthalate" OR "Di-n-Butyl Phthalate" OR "Di n Butyl Phthalate" OR "Butyl Phthalate" OR "d n butyl phthalate" OR "di nbutyl phthalate" OR "dibutyl phthalate" OR "dibutylphthalate" OR "phthalic acid di n butyl ester" OR "84-74-2" OR "benzylbutyl phthalate" OR "bbp" OR "85-68-7" OR "Diethylhexyl Phthalate" OR "bis (2 ethylhexyl) phthalate" OR "bis (2 ethylhexyl) phthalate" OR "bis (2 ethylhexyl)phthalate" OR "bis (2 ethylhexylphthalate)" OR "Bis(2-ethylhexyl)phthalate" OR "DEHP" OR "di (2 ethylhexyl) phthalate" OR "di 2 ethylhexyl phthalate" OR "di 2 ethylhexylphthalate" OR "Di-2-Ethylhexylphthalate" OR "diethylhexyl phthalate" OR "Dioctyl Phthalate" OR "octoil" OR "phthalic acid di 2 ethylhexyl ester" OR "phthalic acid diethylhexyl ester" OR "117-81-7" OR "diisononyl phthalate" OR "di-isononylphthalate" OR "ENJ 2065" OR "ENJ-2065" OR "di-isononylphthalate" OR "di-iso-nonyl phthalate" OR "DINP" OR "28553-12-0" OR "diisodecyl phthalate" OR "DIDP" OR "26761-40-4") AND (Toxicokinetics OR Absorption OR Distribution OR Metabolism OR Excretion OR ADME OR Urine OR Biomonitoring))

^The [tw] tag (text word) "Includes all words and numbers in the title, abstract, other abstract, MeSH terms, MeSH Subheadings, Publication Types, Substance Names, Personal Name as Subject, Corporate Author, Secondary Source, Comment/Correction Notes, and Other Terms (see Other Term [OT] above) typically non-MeSH subject terms (keywords), including NASA Space Flight Mission, assigned by an organization other than NLM." (https://pubmed.ncbi.nlm.nih.gov/help/#tw)

**Note that date limitations in Web of Science were manually entered on the Advanced Search page. Dates used are the same as the corresponding PubMed search for each search type.*

References were deduplicated across the individual sources, and non-English (n=77) and meeting abstracts (n=7) were removed, leaving a total of 3,901 unique references that underwent Level 0 screening in Excel®.

Screening and prioritization of references for data extraction

References identified above were screened in two rounds. First, title and abstract were screened in Excel® for a) relevance to toxicokinetics and/or biomonitoring (focusing to the greatest extent possible on references that may have used an F_{ue}, for example to calculate a daily intake) , and b) relevance to the five phthalates of interest. Excel®-based screening used keywords and a formula to prioritize references for screening, but all references were manually screened. Title/abstract screening erred toward inclusion in cases of uncertainty. References were included if they potentially included: biomonitoring data (urine), data on other specific aspects of toxicokinetics (F_{ue} or data that could be used to calculate F_{ue}, PBPK model that could provide toxicokinetic parameters, quantitative data on absorption or excretion). Based on this initial screen n=3656 references were excluded.

After the initial screen in Excel®, references deemed potentially relevant to toxicokinetics as defined above (n=245) were retrieved, and the full text screened in Distiller to confirm relevance to toxicokinetics and to the five phthalates of interest. One screener performed both the first round of screening (Excel®) and the second round of screening (in Distiller®).

Of the references identified in Distiller® as relevant to phthalate toxicokinetics (n=195), only those identified as having animal data (n=44) proceeded directly to extraction in Excel®. Because the CHAP (2014) report provided a curated and peer-reviewed compilation of human F_{ue} values, studies with human data were not further evaluated. Based on this second screen, n=46 references were excluded entirely as not relevant to toxicokinetics in any model. In addition, a small number of references (n=4) were excluded because no full text could be found, even using interlibrary loan requests. At least one of these (by Hazleton Laboratories) was sufficiently described in a 2001 CPSC report that data from it could be included.

In screening and beginning to extract the animal toxicokinetic studies, it became apparent that much of the relevant primary animal F_{ue} data were from publications prior to the CHAP report, and thus the original studies had not been captured in the search strategy for the updated search. Therefore, the focus moved to tree searching, with the goal of tracing studies back to the primary data. In many situations this required multiple rounds of reviewing successively earlier studies in order to identify the original source of the F_{ue}. In the end, n=40 studies were extracted (n=13 of which were identified by tree searching), covering *in vivo* animal data. Further details are provided in the Phthalate TK Extraction and F_{ue} Estimation spreadsheet (see Appendix Table 1 for file name).

2.1.3 NHANES

Data were downloaded from the NHANES website and prepared for modeling as follows: XPT SAS transport files downloaded directly from the NHANES website were converted into analyzable SAS files using the 'xport' function. The NHANES files included the datasets

for urinary PHOP metabolites, demographics, body measures, urinary flow, and urinary pregnancy test results. All these datasets were merged by their unique NHANES identifier (SEQN) into a single dataset using the 'merge' function. In addition to the created overall SAS file dataset, a copy of the file was saved in EXCEL® (.xlsx) format using the SAS 'export' function.

Data were obtained for four complete 2-year NHANES cycles (2011-2012, 2013-2014, 2015-2016, and 2017-2018). In addition, the available data from NHANES 2019-2020 cycle are included in a combined cycle covering 2017-2020. As noted by the CDC, data collection was begun for NHANES 2019-2020, but was terminated due to Covid-19. Therefore, the collected 2019-2020 data are not nationally representative. NHANES has reweighted the combined 2017-2020 cycle to be nationally representative.

Table 4 shows the subpopulation analyses conducted for each NHANES cycle and each chemical. The one exception was that data for children 3-5 years old was not part of the 2011-2012 or 2013-2014 cycles. Further details about the which variables in each cycle were used for the analysis are provided in the NHANES Variables to Use spreadsheet ((see Appendix Table 1 for file name).

Table 4. NHANES Analyses Parameters and Categories

Parameter	**Categories**
Gender	Male, Female
Pregnancy Status	Pregnant, Not pregnant
Age Group	3-5 years[1], 6-11 years, 12-17 years, 18+ years
Race/ethnicity	Mexican-American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, Other Race – Including Multi-Racial
Adult Education Level	Less than high school degree, High school grad/GED or some college/AA degree, College graduate or above
Income to Poverty Ratio[2]	<1, 1-3, >3

[1]Except for the 2011-2012 and 2013-2014 cycles.
[2]Family income relative to the poverty level

2.2 Equations for Calculating Intake

2.2.1 Peer-Reviewed Studies of Urine Biomonitoring

As described in the Guidance Document, the concentration of the biomarker in urine can be converted to a daily intake using the following equation.

$$DI = \frac{C \times V}{BW \times F_{ue}} \qquad Eq.\ 1$$

Where: DI= Daily intake of the parent compound (mg/kg-day)
C= Biomarker concentration in urine (mg biomarker/L)
V= 24-hour urinary flow rate (L/day); also called UFR
BW= Body weight (kg)
F_{ue}= Urinary excretion fraction (mg biomarker excreted/mg parent compound intake)

However, many published F_{ue} values for PHOPs (for more detail, see Section 2.3.2) are reported on a molar basis (Eq. 2; or as % of dose, or % of administered radioactivity). This requires conversion into a mass-based F_{ue} before it can be used to calculate a mass-based daily intake (Eq. 3). This conversion requires converting moles of biomarker to mass of biomarker, and moles of parent to mass of parent.

$$Molar\ F_{ue} = \frac{mol\ biomarker\ in\ urine}{mol\ parent\ in\ dose} \qquad Eq.\ 2$$

$$Mass\ F_{ue} = Molar\ F_{ue} \times \frac{biomarker\ MW}{parent\ MW} = \frac{mol\ biomarker \times biomarker\ MW}{mol\ parent \times parent\ MW} \qquad Eq.\ 3$$

Where: MW = molecular weight (g/mol)
Mass F_{ue} = Urinary excretion fraction (mg biomarker excreted/mg parent compound intake)
Molar F_{ue} = Urinary excretion fraction (moles of biomarker excreted/moles of parent compound intake)

Combining Eq. 1 and 3, calculation of the daily intake based on the molar Fue becomes:

$$DI = \frac{C \times V}{BW \times Mass\ F_{ue}} = \frac{C \times V}{BW x Molar\ F_{ue} \times \frac{biomarker\ MW}{parent\ MW}} = \frac{C \times V \times parent\ MW}{BW \times Molar\ F_{ue} \times biomarker\ MW} \qquad Eq.\ 4$$

Where: DI = Daily intake of the parent compound (mg/kg-day)
C = Biomarker concentration in urine (mg biomarker/L)
V = 24-hour urinary flow rate (L/day); also called UFR
BW = Body weight (kg)
MW = molecular weight (g/mol)
Mass F_{ue} = Urinary excretion fraction (mg biomarker excreted/mg parent compound intake)
Molar F_{ue} = Urinary excretion fraction (moles of biomarker excreted/moles of parent compound intake)

Although Eq. 4 demonstrates the full relationship among molar-based F_{ue}, mass-based F_{ue}, and the calculation of DI, the molar to mass F_{ue} conversion (Eq. 3) and the DI calculation (Eq. 1) were treated as separate steps.

Some of the published studies measured urine concentrations of both BCIPP and BCIPHIPP (both metabolites of TCIPP). For these studies, the measured urine concentrations of BCIPP and BCIPHIPP were added, in order to determine the total excretion of these two metabolites, and then the daily intake was calculated based on the total of these two metabolites and the F_{ue} for total metabolites. Daily intake was also calculated for BCIPP and for BCIPHIPP individually for studies that reported both, using the individual F_{ue} values. This was for consideration of both the relative accuracy of the F_{ue} values and consideration of the potential for the biomarker metabolites to also reflect exposure to PHOPs other than the three data-rich PHOPs (see Discussion). For studies reporting only BCIPP, the F_{ue} for BCIPP was used. For studies only measuring BCIPHIPP, the F_{ue} for BCIPHIPP was calculated by subtracting the F_{ue} for BCIPP from the F_{ue} for total metabolites. For more detail on F_{ue}, see Section 2.3.2 and Table 9.

Daily intakes for published studies were calculated by two methods, to maximize the utility of inconsistently reported data. The first method (Method 1) calculated geometric mean (GM) and 95th percentile urinary biomarker concentrations for any studies that did not report them. Daily intake was then calculated from the reported/estimated GM and 95th percentile. Geometric standard deviation (GSD) was then calculated from the GM and 95th percentile. Estimated parameters assumed a lognormal distribution. For more detail on how parameters were estimated for Method 1, see Section 2.6. The second method (Method 2) directly calculated daily intake from whichever parameters were reported for each study/chemical/population combination. Thus, for example, if a study reported 25th and 75th percentile biomarker measurements, the corresponding intakes were estimated using Method 2, while Method 1 estimated *only* the GM and GSD. Arithmetic standard deviations (ASDs) and GSDs for daily intakes calculated by this method (i.e., calculated directly from the reported ASD and GSD) are less robust estimates than those calculated according to Method 1, since Method 2 used the spread, rather than the mathematical parameters describing the distribution (see Appendix Table 1 for file names).

Urinary volume and flow vary from individual to individual due to differences in hydration status. There are several approaches to account for differences in hydration status, including adjustments based on creatinine excretion, osmolality (a measure of how concentrated the urine is), specific gravity and urine flow rate (L/day). Of these, using specific gravity- adjusted data is preferred over data expressed relative to creatinine concentration, because specific gravity is a physical parameter of the urine, while creatinine excretion rate varies between individuals.

The database of biomonitoring studies for PHOPs was sufficiently large that it was possible to focus on only the studies reporting specific gravity-adjusted concentrations. Eq. 1 was applied to these concentrations without further adjustment.

2.2.2 NHANES – Urine Biomonitoring and Calculating Daily Intake

Due to the complexity of the calculations for NHANES, this section describes all of the calculations specific to NHANES, rather than separating them by topic, as done for the peer-reviewed literature.

NHANES does not measure specific gravity of the urine samples. While NHANES does measure creatinine as part of the standard biochemistry profile, it is limited to subjects 12 years or older, while biomarker measurements are available for ages 3 and up (or 6 and up, depending on the cycle). NHANES does collect information on the volume of the complete urinary void, as well as the time since last void, during urinary biomarker collection. This allows for the calculation of the urinary excretion rate of the analyte over the time period covered by the void, thus addressing the issue of hydration status without requiring the use of a surrogate such as creatinine concentration. Although multiple urine samples were collected from many of the subjects, PHOP concentration was measured in only one sample, and so that information was from a true spot sample regardless of the number of urine voids collected.

Urinary flow rate (UFR) was calculated from urine volume and collection time for each individual, according to NHANES guidelines and accounting for missing values. Briefly, NHANES collects urine for biomarker measurement in 3 collection times, and reports the volume and time for each separately. NHANES gives guidance on how to calculate UFR based on which collection times have a volume that is either 0 or missing (Table 5). In addition to this guidance, we evaluated the flow rate from the first collection time for outliers, since the beginning of that time interval is self-reported by each participant as the time since last urination. For the other collection times, the times since last collection time are used. By necessity, missing or 0 values of time were also excluded to avoid division by 0.

Downloaded data were recoded as needed to be consistent across cycles and to group continuous variables for tabular presentation. Age and income-poverty ratio were transformed from continuous values to the groups reported in Table 4, above. Earlier cycles (2011-2012, 2013-2014, and 2015-2016) have more granularity in the education level data than later cycles (2017-2018 and 2017-2020). Education levels from earlier cycles were condensed to match the education levels from the later cycles (as shown in Table 4). Units were converted as needed throughout.

When calculating any summary statistics, the complex survey design and sampling weights of NHANES were accounted for using the 'survey' and 'svrepmisc' R packages. The R codes for all calculations are provided as supplemental files. See Appendix Table 1 for the file name for the R code for the NHANES Deterministic Calculations.

Table 5. Logic and Equations for Calculating UFR in Different NHANES Scenarios.[4]

First collection Volume	Second collection Volume	Third collection Volume	Equation for UFR (urinary flow rate)	Term for UFR
Nonzero	0 or missing	0 or missing	UFR = URXVOL1/ URDTIME1 = URDFLOW1	URDFLOW1
Nonzero	Nonzero	0 or missing	UFR = (URXVOL1 + URXVOL2) / (URDTIME1 + URDTIME2)	Note that this is NOT URDFLOW2; that term is defined as URXVOL2/URDTIME2
0 or missing	Nonzero	0 or missing	UFR = (URXVOL1 + URXVOL2) / (URDTIME1 + URDTIME2)	Note that this is NOT URDFLOW2; that term is defined as URXVOL2/URDTIME2
Nonzero	Nonzero	Nonzero	UFR = (URXVOL1 + URXVOL2 + URXVOL3)/(URDTIME1 + URDTIME2 + URDTIME3)	Note that this is NOT URDFLOW3; that term is defined as URXVOL3/URDTIME3
0 or missing	0 or missing	Nonzero	UFR = (URXVOL1 + URXVOL2 + URXVOL3)/(URDTIME1 + URDTIME2 + URDTIME3)	Note that this is NOT URDFLOW3; that term is defined as URXVOL3/URDTIME3
0 or missing	Nonzero	Nonzero	UFR = (URXVOL1 + URXVOL2 + URXVOL3)/(URDTIME1 + URDTIME2 + URDTIME3)	Note that this is NOT URDFLOW3; that term is defined as URXVOL3/URDTIME3
Nonzero	0 or missing	Nonzero	UFR = (URXVOL1 + URXVOL2 + URXVOL3)/(URDTIME1 + URDTIME2 + URDTIME3)	Note that this is NOT URDFLOW3; that term is defined as URXVOL3/URDTIME3
0 or missing	0 or missing	0 or missing	None - no useful data	

As addressed further in Section 2.5, variability in the population distribution of chemical concentration in urine may be over-estimated when the half-life is short relative to the exposure frequency. To address this concern, the method of Pleil and Sobus (2016) was used to estimate the central tendency for an individual from a single spot sample, information on the intraclass correlation coefficient (ICC), and population summary statistics (geometric mean and geometric standard deviation), using the following equation:

[4] URXVOL = urine volume. URDTIME = time since last urine collection. URDFLOW = flow calculated at each collection time, which is not necessarily equivalent to the overall flow. Numbers as the end of any of these values indicate the first (1), second (2), or third (3) urine collection.

$$GM_i = \left(\frac{X_i}{GM}\right)^{ICC^y} \times GM \qquad Eq.\ 5$$

Where: GM_i = Predicted geometric mean for any single measurement (µg/L)
X_i = Single-spot measurement concentration (µg /L)
GM = Geometric mean for the population distribution (µg /L)
ICC = Intraclass correlation coefficient (see Table 6 below; unitless)
Y = slope factor (1/2: See Pleil and Sobus, 2016; unitless)

As part of the process of screening and prioritizing PHOP HBM and TK references (Section 2.1.1), references containing ICCs were flagged for later extraction. Table 6 shows the median of the ICCs reported for each chemical, based on urine biomonitoring studies, regardless of whether the study corrected urine concentration by specific gravity, by creatinine, or did not perform any correction. Details of this calculation are presented in the ICC Calculation spreadsheet (see Appendix Table 1 for the file name).

Table 6. Intraclass Correlation Coefficients for Data- Rich PHOPs

Parent // Metabolite	TCEP // BCEP	TCIPP // BCIPP	TDCIPP // BDCIPP
ICC	0.45	0.54	0.48

The GM_i was then used in daily intake calculations instead of the individual's reported exposure concentration, according to the following equation:

$$DI = GM_i \times \left(\frac{UFR}{BW \times F_{ue}}\right) \qquad Eq\ 6$$

Where: DI = daily intake (µg/kg-day)
GM_i= Predicted geometric mean for any single-spot measurement, after correcting for ICC in Eq. 5 (µg /L)
UFR = urinary flow rate calculated according to the logic in Table 5 (L/day)
BW = individual body weight (kg) from NHANES
F_{ue} = fractional urinary excretion (unitless). Values are specific to the metabolite measured in urine and are reported in Table 9.

Although the R code used includes the option to account for bioavailability, it was not used (bioavailability value is set to 1), because the F_{ue} values used already account for bioavailability. This may not always be the case.

2.2.3 Peer Reviewed Studies of Blood Biomonitoring

A few studies were available in which levels of PHOPs were monitored in blood or blood components (serum, plasma). If *in vivo* clearance data were available, these blood concentrations could be converted to daily intake using the following equation:

$$DI = C \times Cl \qquad \textit{Eq. 7}$$

Where: DI = Daily intake (absorbed dose) - mg/kg-day
C = concentration (serum, plasma, etc.) - mg/L
CL = clearance - L/kg-day

Unfortunately, no *in vivo* clearance data in humans or experimental animals were identified for any of the PHOPs. Therefore, the PBPK tool of the Integrated Chemical Environment (ICE) was used to calculate the steady state concentration (C_{ss})corresponding to a single human oral dose of 1 mg/kg, for each of the PHOPs with blood biomonitoring data (TDCIPP, TCIPP, TCEP, and BDCIPP). Blood biomonitoring data were also available for BCIPHIPP, but this chemical was not found in ICE by CASRN. Note that biomonitoring data were available for both parent PHOPs and two metabolites.

The ICE-PBPK tools use measured or estimated chemical-specific toxicokinetic parameters (intrinsic clearance and fraction unbound in blood) and physiological parameters, and the U.S. EPA httk package to estimate concentration. Two dosing durations (both using daily oral dosing of 1 µg/kg-day [0.001 mg/kg-day]) were run, because the default 3-day dosing returned one plasma C_{ss} value (for TDCIPP) that was greater than its respective predicted C_{max} (max concentration) in plasma. Running the model again with 30 days of dosing remedied this for TDCIPP by increasing the predicted plasma C_{max} for TDCIPP and left plasma C_{max} for the other 3 chemicals unchanged. For each of the four chemicals evaluated, the plasma C_{ss} value based on 3-day dosing and based on 30-day dosing were the same.

As described in the Guidance Document, the intake corresponding to the concentration of the biomarker measured in blood can be calculated using the equation:

$$DI = \frac{C \times 1\frac{\mu g}{kg}-day}{C_{ss}} \qquad \textit{Eq. 8}$$

Where: DI = Daily intake (µg/kg-day)
C = Biomarker concentration in blood (µg biomarker/mL)
C_{ss} = Steady state concentration of biomarker in blood at a dose of 1 µg/kg-day (µg/mL),

Note that the calculation of plasma C_{ss} (and therefore this calculation of the daily intake) is based on only metabolic and renal clearance; absorption is accounted for only if chemical-specific data are available. Based on our review of the httk default data, absorption was assumed to be 100% for the PHOPs. Therefore, the intake calculated using Eq. 8 was divided by a factor of 0.9 to account for bioavailability (see Appendix Table 1 for file name); the derivation of this factor is described in Section 2.3.2, in the context of the calculation of the PHOP F_{ue}.

The C_{SS} calculated for each of the biomarkers is shown in Table 7. The ICE PBPK tool always returns C_{ss} in mg/L, which is equivalent to µg/mL (units that are more convenient for the calculation of intake in units of µg/kg-day).

Table 7. C_{SS} Calculated Using ICE-PBPK for an Oral Human Dose of 1 µg/kg

Chemical	Css (µg/mL)
TCEP	2.069E-04
TDCIPP	3.227E-03
TCIPP	1.38E-04
BDCIPP	6.288E-05

A key aspect of this calculation is that the blood fraction used for biomonitoring (whole blood, plasma, or serum) needs to be the same as the fraction for which the clearance was determined. Unfortunately, there is no standard approach for converting between the concentration in one fraction and that in another fraction, because the ratio is a function of molecular weight, protein binding, and other parameters. This means that the relevant ratios need to be determined for each chemical. For the PHOPs, biomonitoring data were available for whole blood (TCEP, TCIPP, TDCIPP), serum (TCEP, TCIPP, BDCIPP, BCIPHIPP), and plasma (TCEP, TCIPP, TDCIPP), while the ICE-PBPK calculations estimate the concentration in plasma. Unfortunately, no data were located for PHOPs on the ratio between concentrations in whole blood, serum and plasma. In the absence of an alternative approach, the concentrations in the different blood fractions was assumed to be comparable, but this is an important uncertainty in the calculation.

Another uncertainty related to the units used for reporting of the concentration. Most of the studies of PHOPs in blood reported the biomarker concentration as ng/mL in the blood fraction, but one study (measuring TCEP and TCIPP in serum) normalized to the lipid content in the serum, reporting the results as ng/g lipid. These results were converted to concentration in the blood fraction using a conversion factor of 190 ng/g serum lipid weight : ng/g serum derived from data on tetrabromobisphenol A (TBBPA) in adults (ages 20-79) in a Health Canada (2020) report Since this conversion factor was derived based on TBBPA, it may not apply directly to PHOP chemicals. However, no data were identified that provided a way to calculate a similar ratio specific to PHOP chemicals. This introduces additional uncertainty to these calculations.

2.3 Determination of the Toxicokinetic Conversion

The key toxicokinetic factor for interpreting urine biomonitoring data is the F_{ue}, and the key parameter for interpreting blood biomonitoring data is the clearance for *in vivo* toxicokinetic studies or plasma concentration at steady state (C_{SS}) for *in vitro* toxicokinetic studies. No *in vivo* studies of clearance were identified, and so the C_{SS} was used for blood data, calculated as described in Section 2.2.3.

Because human F_{ue} data are not available for any of the PHOPs of interest, and because an F_{ue} is not available for every PHOP-related biomarker in urine, multiple approaches were

used to estimate the F_{ue}. This included both extrapolation from phthalate data and use of PHOP toxicokinetic data directly. The phthalates included in this review are well-studied, have human toxicokinetic data, cover a range of molecular weights comparable to that of the PHOPs, and are eliminated from the body in urine relatively quickly. Based on these considerations, they were considered reasonable potential surrogates, a hypothesis that was further investigated in the analysis.

It is important to make sure that the F_{ue} reflects the entirety of the chemical's elimination. If urine samples were not collected for a period of at least five times the half-life of elimination, it is necessary to extrapolate the urinary excretion to infinity, using the following equation (Poet et al., 2016).

$$Total\ mol\ excreted = \frac{mol_{urine}}{\left(1-exp^{\left(-ln(2)\times\frac{t_c}{t_{1/2}}\right)}\right)} \qquad Eq.\ 9$$

Where: t_c = total time of urine collection (hr)
mol_{urine} = total moles of parent chemical excreted in the urine (as parent or metabolite)

The F_{ue} can then be calculated as the ratio of moles biomarker excreted/moles parent compound intake. The mass-based F_{ue} can be calculated with the same equation, replacing the total moles in urine and total moles excreted with mg, or calculated from the molar F_{ue} using Eq. 4.

2.3.1 Phthalate Data for F_{ue}

The phthalate F_{ue} data were used to (1) evaluate how F_{ue} varies with molecular weight, and (2) compare the human and animal F_{ue}.

Both the human and rat phthalate F_{ue} values showed a strong relationship to molecular weight. Focusing on the total F_{ue} across all biomarkers, and the best rat studies (oral dosing, single dose administration, doses <1000 mg/kg), and eliminating outliers based on study design and visual judgement), the human and rat F_{ue} both showed a strong inverse correlation with molecular weight (R^2 = 0.70 for rats and 0.90 for humans). The regression equations for rats and humans also had very similar slopes and intercepts (Figures 2 and 3).

Additional documentation of the calculations is in the spreadsheet Phthalate TK Extraction and F_{ue} Calculation (see Appendix Table 1 for file name).

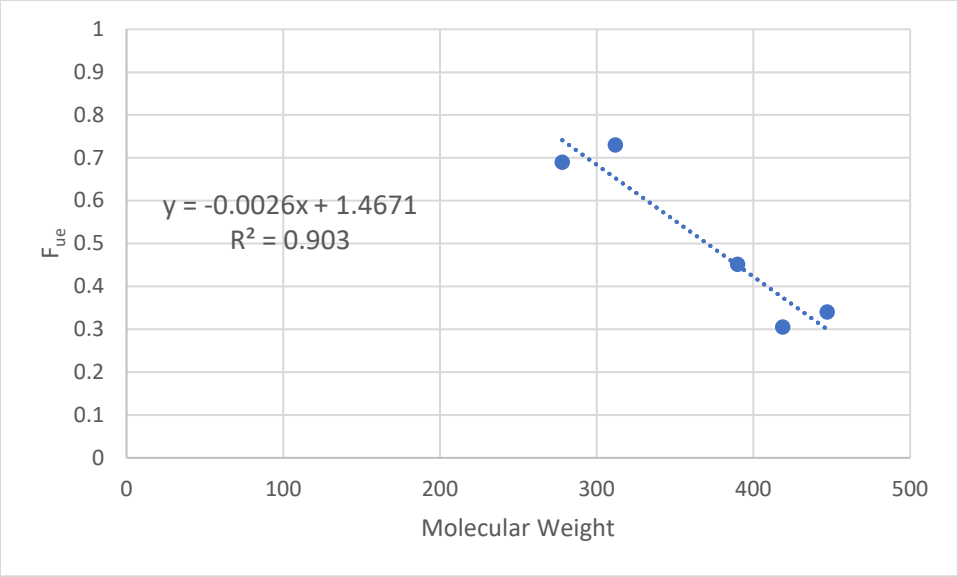


Figure 2. Human phthalate total F_{ue} vs. molecular weight

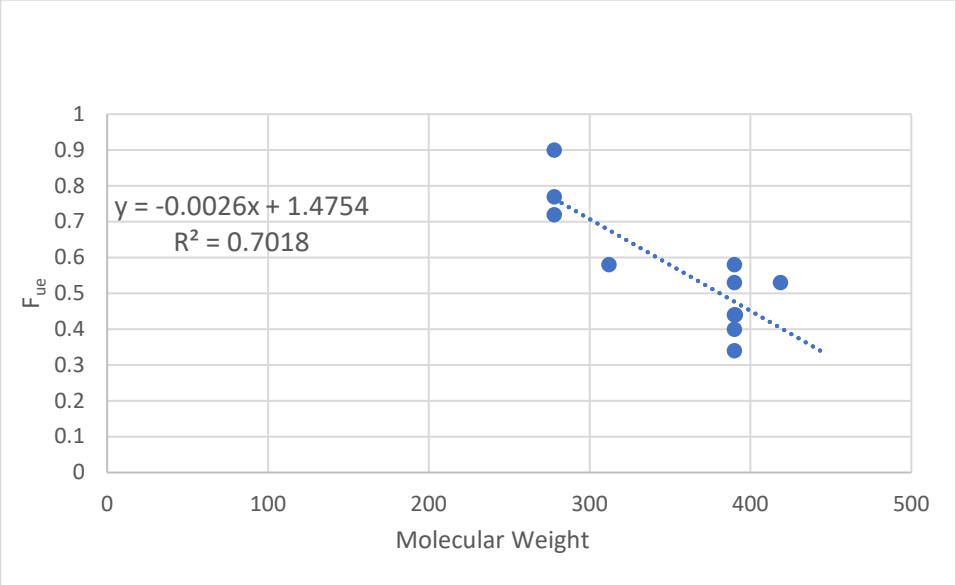


Figure 3. Rodent phthalate total F_{ue} vs. molecular weight (minus outliers)

2.3.2 PHOP Data for F_{ue}

As noted, multiple approaches were used to estimate the F_{ue} for the PHOPs, in light of the limited available data. Use of alternative approaches allowed the analysis to better reflect the uncertainties and potential range of the actual F_{ue} (see Appendix Table 1 for file names).

***In vitro* data to address interspecies differences**

Because human *in vivo* toxicokinetic data are not available for any of the PHOPs, a key question is how to extrapolate from the F_{ue} calculated using *in vivo* animal data to a human

F_{ue}. *In vitro* metabolism studies were used to attempt to quantify the difference between rats and humans in the rate of metabolism (and thus the rate of production of the metabolite used for biomonitoring). Four studies were identified with information on the degree of conversion of the parent PHOP to metabolites (Chapman et al., 1991; Nomeir et al., 1981; Van de Eede et al., 2013, 2016), but only the Chapman et al. (1991) study directly compared results for humans and rats. Due to the high variability in specific details of the study protocols, comparison between studies was considered to introduce too much uncertainty and variability.

Chapman et al. (1991) quantified conversion of TCEP to metabolite in cultured rat and human liver slices, and in rat and human liver microsomes. However, there were several internal inconsistencies in the paper that substantially reduced confidence in the results. For example, no activity was seen with microsomes from female rat livers, even though the activity in liver slices from male and female rats was roughly comparable. In addition, the fraction of metabolites that were not identified was zero in women, while in men the pmol of TCEP equivalents for other/nonidentified metabolites was comparable to that of BCEP produced (liver slice data); similar differences were seen for rats. It is possible that this latter difference reflects true sex-related differences in activity, but the female rat microsome data raise suspicions about the overall quality of the data in the study. Table 8 presents the fraction of metabolism to BCEP in human and rat liver slices, relative to the total of identified and unidentified metabolites. (Data were not available for expression of the formation of BCEP relative to total dose.)

Table 8. Conversion to BCEP as Fraction of Total Metabolites in Rat and Human Liver Slices (adapted from Chapman et al., 1991)

	Human - M	**Human - F**	**Interspecies ratios**	**Rat - M**	**Rat - F**
Molar % BCEP	0.27	0.09	See bottom rows	0.49	0.43
Average % BCEP by species	0.18		See bottom rows	0.46	
Ratio of average human: average rat	NA	NA	0.39	NA	NA
Ratio of male human: male rat	NA	NA	0.55	NA	NA
Ratio of female human: female rat	NA	NA	**0.20**	NA	NA

NA = Not applicable

Due to the overall low confidence in the Chapman study, it was not used as the primary basis for converting the rat F_{ue} to the human F_{ue}. However, the lowest interspecies ratio (0.20, for the ratio of female human: female rat; bolded in Table 8) was used as an estimate of the lower bound of the interspecies ratio. In the absence of good *in vitro* data for other PHOPs, this value was applied to all three data-rich PHOPs.

As a second approach for interspecies extrapolation, the comparison between humans and rats for the phthalate F_{ue} was considered. As noted in Section 2.3.1, the regression lines for the F_{ue} vs. molecular weight were remarkably similar for rats and humans (human, y = -

0.0026x + 1.4671; rat, y = -0.0026x + 1.4754). Recognizing that the regression could be comparable, but the specific F_{ue} could differ, the ratio between the rodent and human F_{ue} for total excretion of the five phthalates was determined. The ratio was between 0.8 and 1.2 for DBP, DEHP, and BBP; the ratio for DINP was 0.57. In the one available rat study on DIDP, the F_{ue} was reported only for a single metabolite, while the human F_{ue} was for all excreted material (see Phthalate TK Extraction and F_{ue} Estimation spreadsheet, compiled human and animal tab). Thus, considering the phthalate F_{ue} data both globally and on an individual chemical-specific basis, the human and rat F_{ue} for the phthalates were comparable.

Based on extrapolation from the well-studied phthalates, and considering the general similarity between the rodent F_{ue} for the PHOPs and phthalates (see the *in vivo* analysis, next subsection), a factor of 1 was used as the best estimate to extrapolate from the rat to human F_{ue} for all of the PHOPs.

***In vivo* data on PHOP F_{ue} in rats**

A total of seven studies had data that could be used to calculate a PHOP F_{ue} in rats. Data were available for TCEP, TDICPP, and TMCPP/TCIPP, and for the brominated PHOPs tris(2,3-dibromopropyl) phosphate (TDBP), tris(2,3-dibromopropyl) phosphate (TDBPP). One study (Minegishi et al., 1988) evaluated the F_{ue} for multiple PHOPs, but expressed the PHOP as the molar percent of the entire administered dose that was excreted in the urine. Regressing the F_{ue} from this study relative to molecular weight resulted in a moderately strong correlation coefficient (R^2 = 0.449), but the correlation was substantially improved when the brominated PHOP was excluded (R^2 = 0.93). The general similarity of the regression equation (y = -0.0032x + 1.8077) to that for the phthalates supports the conclusion that the phthalate F_{ue} data can be used to inform the PHOP F_{ue}. The brominated PHOPs were not further considered, in the absence of available HBM data above detection limits.

Unfortunately, the Minegishi et al. (1988) study evaluated an overall F_{ue} for total radioactivity in urine, while NHANES reported the urinary concentration of a single metabolite and the published HBM studies reported the concentration for a single metabolite, or occasionally two key metabolites. This meant that is was necessary to identify F_{ue} values for individual metabolites. The available studies included oral and intravenous administration. Nomeir et al. (1981) reported that 90% of an oral dose of TDCIPP was absorbed. Based on this percent absorption, and in the absence of other chemical-specific data, iv F_{ue} data were converted to oral F_{ue} by multiplying by 0.9. This meant that no additional correction for bioavailability was needed when calculating the daily intake from the urine concentrations. The molecular weight of the parent chemical and the metabolite of interest was used to convert from a molar-based F_{ue} to a mass-based F_{ue}. There were two studies each with F_{ue} calculations for BCEP and BDCPP; both results were quite similar and the average F_{ue} was used. No specific F_{ue} was identified for the parent chemicals in urine, but the large number of HBM studies meant that it was feasible to focus on studies that measured the metabolites.

Determining an F_{ue} for TCPP/TCIPP had two additional challenges. First, no toxicokinetic study provided an adequate F_{ue} for individual TCPP/TCIPP metabolites, although the Minegishi et al. (1988) study measured the F_{ue} for excretion of total TCIPP and metabolites in urine. Second, unlike the other data-rich PHOPs, TCIPP has two major metabolites – BCPP/BCIPP and BCIPHIPP. (See Table 1 for the full chemical names.) In order to estimate the F_{ue} for BCPP, the Minegishi et al. (1988) F_{ue} was adjusted by the average of the ratio of the key metabolite to the total F_{ue} for the other two major PHOPs. For studies with data on the total levels of BCIPP and BCIPHIPP, the total F_{ue} for TCIPP from Minegishi et al. (1988) was applied, recognizing that this may be an overestimate. All of these approximations added uncertainty to the dose calculation, but they allowed order-of-magnitude estimates of daily intake.

The distributional analysis focused initially on the uncertainty related to the interspecies extrapolation. The lowest human:rat ratio (in females – see Table 8) for the production of BCEP *in vitro* was used to estimate the low end of the F_{ue} for each chemical. That is, the best estimate of the F_{ue} was multiplied by 0.2 (Table 9). For the high end estimate, the highest ratio of human:rat F_{ue} on an individual phthalate basis was used. This ratio of 1.2 (for BBP) was applied to estimate the high end F_{ue} for BDCPP. For BCEP, there was some additional uncertainty in the study used to determine the F_{ue} (Burka et al., 1991). Although most sources identify BCEP as the primary metabolite, this source (Burka et al., 1991) identified bis(2-chloroethyl) carboxymethyl phosphate (BCCP) as the primary metabolite. Given this discrepancy, we increased the uncertainty (using a factor of 2 instead of 1.2) for estimating the high end F_{ue} for BCEP. We did not increase uncertainty on the low end, as the low end estimate of BCEP F_{ue} was already very low. The F_{ue} value for BCIPP and F_{ue} value for BCIPP/BCIPHIPP combined also have uncertainty related to the extrapolation from other chemicals. For BCIPP, a factor of 2 was used to estimate the high end F_{ue} from the best estimate. For the combined measurement of BCIPP and BCIPHIPP, the high end estimate was not further increased above the factor of 1.2 used to account for interspecies extrapolation uncertainties, because the F_{ue} is limited by the percent absorbed. Increasing the factor from 1.2 to 2 would have resulted in more excretion than there was absorption in the first place. Table 9 presents the final values for the F_{ue}, including both the best estimates and the ranges.

HBM data were available for one additional chemical without an F_{ue}, Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester (V6). No effort was made to estimate an F_{ue} for V6 for two reasons. First, in the only HBM study where V6 was evaluated, all results were below the detection limit. In addition, V6 has two phosphate groups, as opposed to one phosphate group for the data-rich PHOPs, and it differs from other PHOPs in its physicochemical properties, and so extrapolating an F_{ue} from other PHOPs would not be expected to be reliable.

Table 9. F_{ue} Estimate by Chemical (Mass Basis)

Chemical	Biomarker	Human F_{ue} Best Estimate	Human F_{ue} High End Estimate	Human F_{ue} Low End Estimate
tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), as Fyrol FR-2	BCDPP	**0.23**	0.28	0.05
Tris(2-chloroethyl) phosphate (TMCEP/TCEP)	BCEP	**0.13**	0.27	0.03
tris(1-chloro-2-propyl)phosphate (TCPP/TCIPP)	BCIPP	**0.23**	0.47	0.05
tris(1-chloro-2-propyl)phosphate (TCPP/TCIPP)	BCIPP + BCIPHIPP	**0.58**	0.90	0.12

2.4 Sources of Physiological Data

The sole piece of physiological data needed for the dose estimate was the ratio of the urinary flow rate (UFR) to the body weight. As discussed in Section 2.2.2, this parameter was calculated on an individual basis for the NHANES data and based on simulated individuals for probabilistic analyses of peer-reviewed data. Average and distributional values of UFR/BW derived from the 2017-2018 NHANES data were used as input for probabilistic analyses of peer-reviewed data (See Table 30 in Section 3.2.4).

For the main analyses of peer-reviewed data, the value for UFR/BW was built from the compilation prepared by Hays et al. (2015), based on NHANES 2009-2012 data. Table 10 presents the UFR/BW data used for calculations for individuals ages 6 and older, and for pregnant women. In the absence of specific UFR/BW for pregnant women in Hays et al. (2015), the "Low BMI" for 20-39 years UFR/BW value was chosen for pregnant women because it most closely matched a value of UFR-BW derived from the National Center for Health Statistics (NCHS, published as Fryar et al., 2021; for body weight) and the International Commission on Radiological Protection (ICRP, 2002; for UFR) default values discussed below.

Table 10. UFR/BW (mL/hr-kg) Data Used for Main Analyses of Peer-Reviewed Data

	6-11 years	12-19 years	20-39 years	40-59 years	≥60 years
	GM (95% CI)*	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)
For most population groups	1.01 (0.95, 1.07)	0.67 (0.63, 0.70)	0.65 (0.62, 0.69)	0.64 (0.62, 0.69)	0.56 (0.53, 0.58)
For pregnant women (from "Low BMI" group)	NA	NA	0.87 (0.75, 1.00)	NA	NA

*95% CI are presented as context, but were not used in main (deterministic) analyses.

Children under 6 were not included in the Hays et al. (2015) analysis, presumably because the NHANES cycles evaluated did not collect relevant data from children < 6 years of age. For these children ages 5 and younger, default values suggested by the NCHS and the ICRP were used to calculate UFR/BW, matching as closely as possible the age group for the default to the age group for the data. NCHS and ICRP provide their default values with a substantially different level of granularity. Thus, age groups were matched as closely as possible on a per study basis. Table 11 shows urinary flow rate data from ICRP, and Table 12 shows the body weight data from NCHS. Calculated UFR/BW ranged from 0.83 (5-year olds) to 1.63 (6-week olds) mL/hr-kg (0.021 to 0.039 L/kg-day). Overall these calculated UFR/BW values follow the same general pattern as those from Hays et al. (2015), with higher UFR/BW for younger age groups. However, the lowest calculated UFR/BW is lower than that for the 6-11 year group from Hays et al. (2015), reflecting some possible differences between the two methods of deriving UFR/BW. The combination of the lack of granularity in the UFR data from ICRP and the arbitrary age groups in individual studies adds uncertainty for the UFR/BW calculated for children ages 5 and younger.

Table 11. Urinary Flow Rate (UFR) in L/Day, as Reported by ICRP (2002)

Age group	UFR (L/Day)	Source
Newborn	0.3	ICRP (2002)
1 Year Old	0.4	ICRP (2002)
5-Year-Old	0.5	ICRP (2002)

Table 12. Weight in Kilograms for Children from Birth Through Age 5 years by Sex and Age: United States, 2015–2018, as Reported by Fryar et al. (2021)

Sex | Age	Mean body weight (kg)
Male | Birth–2 months	5.2
Male | 3–5 months	7.4
Male | 6–8 months	8.8
Male | 9–11 months	9.7

Sex | Age	Mean body weight (kg)
Male | 1 year	11.5
Male | 2 years	14
Male | 3 years	16.6
Male | 4 years	18.6
Male | 5 years	21.1
Female | Birth–2 months	5
Female | 3–5 months	6.7
Female | 6–8 months	8
Female | 9–11 months	9
Female | 1 year	11
Female | 2 years	13.2
Female | 3 years	15.4
Female | 4 years	18.1
Female | 5 years	21

2.5 Adjustment for Sampling for Less than a Day – the ICC

As discussed in the Guidance Document, variability in the population distribution may be over-estimated when the half-life is short relative to the exposure frequency. This over-estimation is of concern because exposure estimates often focus on the high end of the population distribution (e.g., the 95th percentile). The intraclass correlation coefficient (ICC) provides an approach for quantifying the relative contribution of intra-individual variability and inter-individual variability, and for calculating a better estimate of the overall population variability. The ICC is defined as the ratio of the logged variance between subjects and the total logged variance (Pleil and Sobus, 2013; Casas et al., 2018):

$$ICC = \frac{\sigma_\alpha^2}{\sigma_\alpha^2+\sigma_\varepsilon^2} \qquad \textit{Eq. 10}$$

Where: σ_α^2 = between subject logged variance
σ_ε^2 = within subject logged variance

An ICC can range between 0 and 1. An ICC of 0 means that all of the variability is due to *intra-individual* variability. In other words, biomarker measurements from spot sampling of any given individual may be any value across the entire distribution, and so a single spot sample is not a good estimate of the individual's mean exposure. Conversely, an ICC of 1 means that repeated measurements of an individual will stay the same, and so both the individual mean, as well as the population mean and distribution are well-characterized.

Pleil and Sobus (2013) described a method for estimating the distribution of long-term average exposures from a distribution of spot biomarker measurements using the ICC. They described three tiers of information for estimating the ICC. Because several of the PHOP HBM studies included multiple samples from the same individuals within a short

period of time, it was possible to calculate study-specific values of ICC, and then apply the Tier 2 correction.

In Tier 2, the GSD can be calculated using the following equation:

$$GSD = GM_g \times (ICC_{(m)} \times (X_{max} - X_{min}) + X_{min}) \quad \textit{Eq. 11}$$

Where: σ = standard deviation of logged data (used to calculate GSD_g, which is used to calculate X_{min} and X_{max})

μ = mean of logged data (used to calculate GM_g)

GSD_g = exp (σ) = "global" geometric standard deviation of the initial data set

GM_g = exp (μ) = "global" geometric mean of the initial data set

X_{min} = exp {ln[GSD_g]/sqrt(m)}/GM_g when ICC = 0

X_{max} = GSD_g/ GM_g when ICC = 1

As noted in section 2.2.2, studies with ICCs were flagged for later extraction as part of the screening and prioritization process. Ultimately 40 study/chemical/population combinations (29 unique studies) had ICC values that could be extracted. Relevant data were extracted from studies reporting one or more ICC values, regardless of correction method, so daily intake was not calculated for each of these studies. (Daily intake was calculated only for studies corrected for specific gravity, and the ICC correction was conducted on a subset of those, as described in Section 3.2.4). Studies with ICC evaluated data from adults and children, men and women, and pregnant women at various times across pregnancy. These data are summarized in Table 13.

Table 13. Range and Median ICC Values from Urine Studies (Regardless of Correction Method)

	BCEP	BCIPP	BCIPHIPP	BDCIPP
Max	0.68	0.74	0.746	0.88
Min	0.03	0.18	0.07	0.15
Median	0.45	0.54	0.345	0.48

As noted in the Guidance Document, the magnitude of the ICC also provides general information regarding the overall reliability for estimating long-term exposures. Table 14 shows an approach for using the ICC to categorize the reliability of using a sample to represent the average exposure (derived from Rosner, 2011 as cited in Casas et al., 2018). Based on the information in Tables 13 and 14, the available data indicate that the urine sampling data for the PHOPs is of "poor" to "fair" quality for estimating long-term exposures, though some of the better studies were "good" or even "excellent."

Table 14. Reliability of Urine Sample to Estimate Long Term Exposures

ICC	Reliability
<0.40	Poor
0.40-0.59	Fair
0.60-0.74	Good
≥0.75	Excellent

2.6 Calculating Missing Distributional Parameters.

As noted in Section 2.2.1, the reporting of distributional statistics was inconsistent across published studies. This section describes how missing distributional parameters (GM, 95th percentile, and GSD) of urine concentrations were calculated. For full details, see provided R code (see Appendix Table 1 for file name). All concentrations were log-transformed prior to calculations, and the result was again exponentiated to account for the assumed lognormal distribution.

For GM, the method of calculation depended on which parameters were reported. If the GM was reported by the study authors, that value was used without modification. If a median was present, the GM was assumed to be the median value. If no median was present, the GM was calculated based on a range determined by the maximum and some minimum value (either the minimum value or the detection limit). Generally, the natural log of the maximum and the natural log of the minimum (either divided by 2 for the method detection limit or the limit of quantification, or by the square root of 2 for the limit of detection) were summed, divided by two, and then exponentiated.

For 95th percentile, the method of calculation again depended on which parameters were reported. Generally, 95th percentiles were estimated by taking the ratios of two provided parameters, dividing by a relevant z score, multiplying by the z score for the 95th percentile, and adding the GM. Log transformations were used as appropriate.

GSD was calculated by dividing the 95th percentile by the GM, and then dividing by the z score for the 95th percentile. A subset of data from one study (Butt et al., 2016; BCIPP for women and for children) was a special case because of very limited information to use for estimation, having only a minimum less than the method detection limit and a maximum value. In this case, the GSD was calculated using the ratio of the maximum to the minimum and the z score for the 99.5th percentile.

2.7 Probabilistic analyses

A probabilistic analysis was conducted on the age-specific subsets of the NHANES 2017-2018 cycle. Separate analyses were conducted for each of five selected published studies (see Table 15). A Monte Carlo approach was used to randomly sample 1000 times for each parameter from the distributions described below using the rtri function (from EnvStats

package) for triangular distributions and the rlnorm function (part of base R) for lognormal distributions. For each set of randomly generated parameters, daily intake was calculated according to Eq. 1. To the greatest extent possible, parameters and distributions were derived from data.

For the analysis of NHANES data and data from published studies, the best estimate and high and low estimates for F_{ue} (Table 9) were used. Given a relative lack of data, F_{ue} was assumed to have a triangular distribution.

The UFR/BW distributions were derived from the NHANES 2017-2018 data for each age group used for the main NHANES analyses, and the distributional parameters (GM and GSD) were calculated based on the reported primary data (see Table 18 in Section 3.1.5). A log-normal distribution was assumed, a conclusion supported by visual inspection of the figures in Hays et al. (2015), and further supported by the results of the probabilistic analysis in Section 3.1.5. The same distributions were applied to the published studies chosen for probabilistic analyses. Table 15 shows how the age groupings for the NHANES analyses were mapped onto the published studies chosen for the distributional analysis.

Table 15. Age Groups from NHANES Chosen to Match Population Ages of Published Studies for Identifying UFR/BW Data.

Reference	Population, age group (cohort)	NHANES 2017-2018 age group for UFR/BW data
Phillips et al., (2018)	Children, ages 3-6 (NEST/TESIE cohort)	Ages 3-5
Hoffman et al., (2017)	Pregnant women, ages 26-35 (PINS cohort)	Ages 18+
Percy et al., (2022)	Children, age 5 (HOME cohort)	Ages 3-5
Percy et al., (2022)	Children, age 3 (HOME cohort)	Ages 3-5
Yang et al., (2023)	Pregnant women, 18-35+ (HOME cohort)*	Ages 18+
Hoffman et al., (2021)	Adults	Ages 18+

*83% were younger than 35 years old, no maximum age given

For the NHANES probabilistic analyses, distributional parameters (GM and GSD, after ICC correction) for urinary biomarker concentrations were calculated for each of the same age groups as used for the main NHANES analysis, and assumed to have a log-normal distribution. The calculated distributional parameters are presented in Table 18, in the Results.

For published study probabilistic analyses, the distributional parameters (GM and GSD) for urinary biomarker concentrations were obtained from the respective study. If these were not reported directly by the study, they were estimated. See the Results in Section 3.2.4. As with NHANES, urinary biomarker concentrations from published studies were assumed to have a log-normal distribution.

From the results of the Monte Carlo simulations for both NHANES and published studies, histograms were plotted to visually show the distribution, and descriptive statistics were calculated. The histograms are presented in Section 3.1.5 for NHANES and 3.2.4 for published studies (see also Appendix 1 for file names). Skewness and kurtosis were also evaluated. The fit of the distributions to the expected log-normal distribution was tested using the Shapiro–Wilk test (cutoff of p=0.05; p>0.05 indicates not significantly different from a log-normal distribution; using the function lnorm_test from the package goft).

3.0 Results

3.1 NHANES

NHANES provides a rich dataset on HBM data for the three major PHOPs, including the potential to conduct sub-analyses based on a variety of different variables (see Appendix Table 1 for file names).

3.1.1 NHANES Overall U.S. Population

Figures 4 through 9 present time trends for daily dose for each of the three PHOPs, based on the arithmetic mean (AM) and standard deviation (ASD), and based on the GM and GSD.

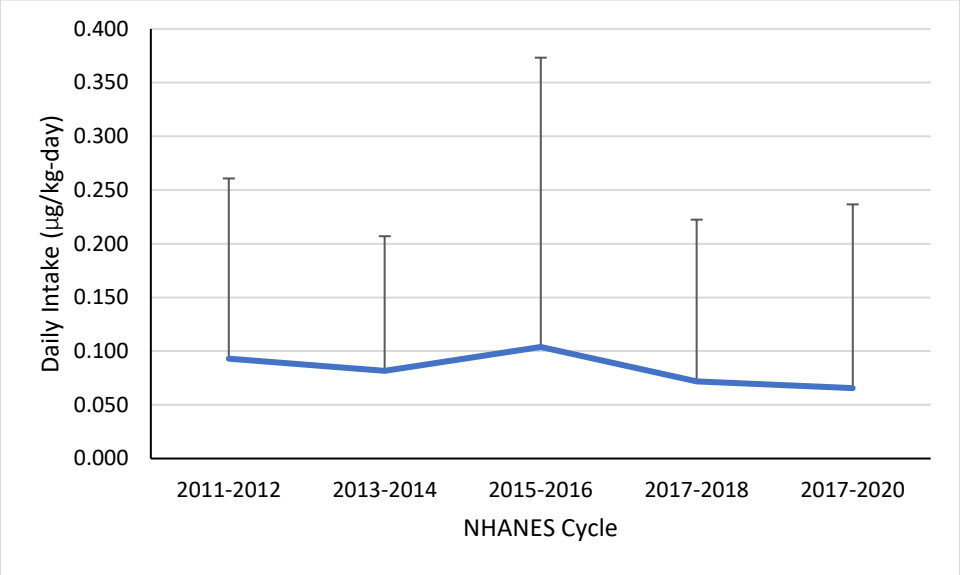


Figure 4. Arithmetic mean and standard deviation TCEP daily intake (µg/kg-day) for the overall NHANES population, by cycle.

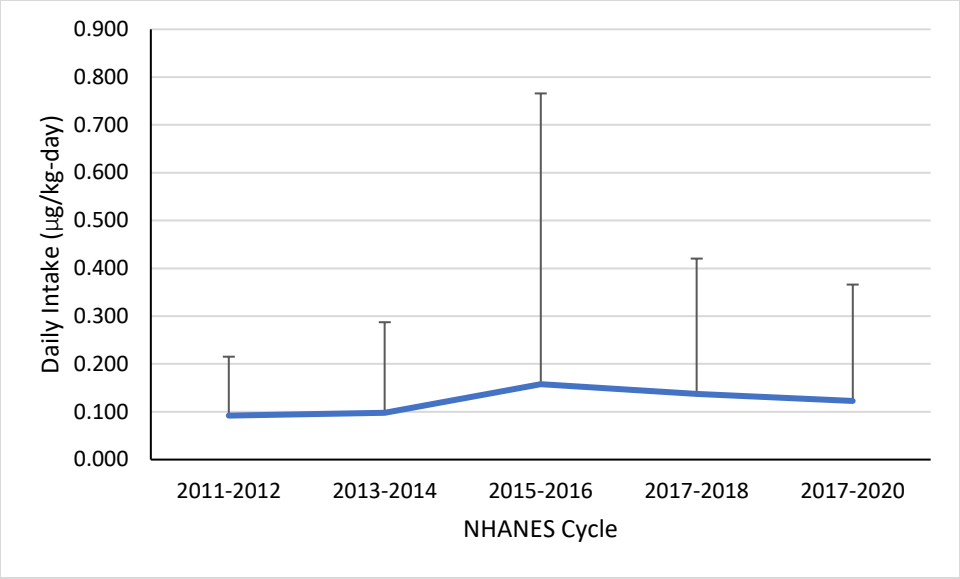


Figure 5. Arithmetic mean and standard deviation of TDCIPP daily intake (µg/kg-day) for the overall NHANES population, by cycle.

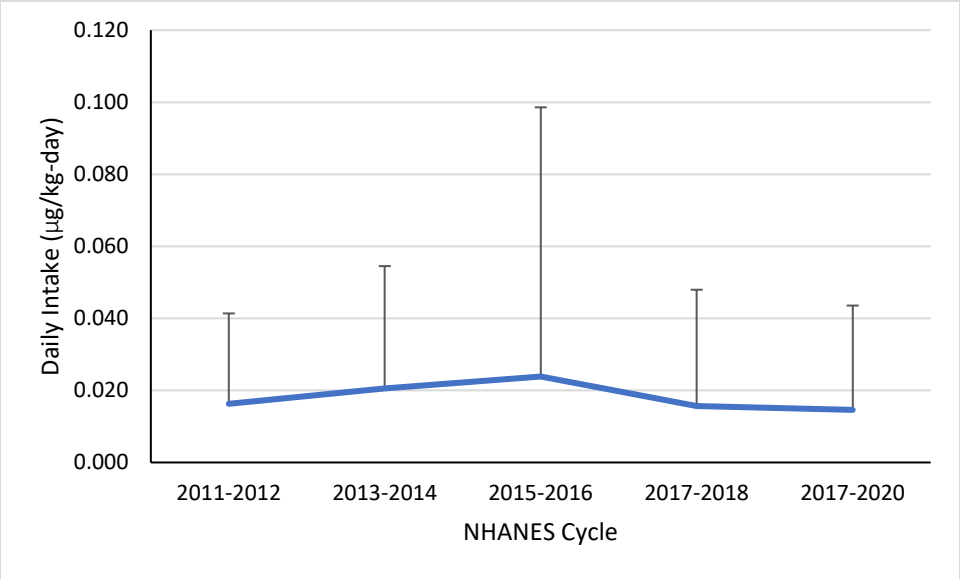


Figure 6. Arithmetic mean and standard deviation of TCIPP daily intake (µg/kg-day) for the overall NHANES population, by cycle.

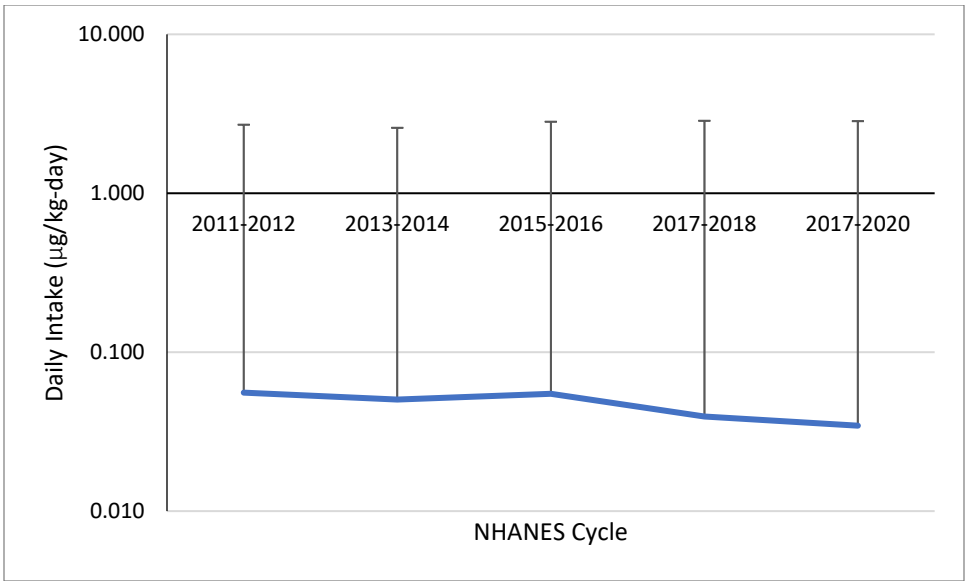


Figure 7. Geometric mean and GSD of TCEP daily intake (µg/kg-day) for the overall NHANES population, by cycle.

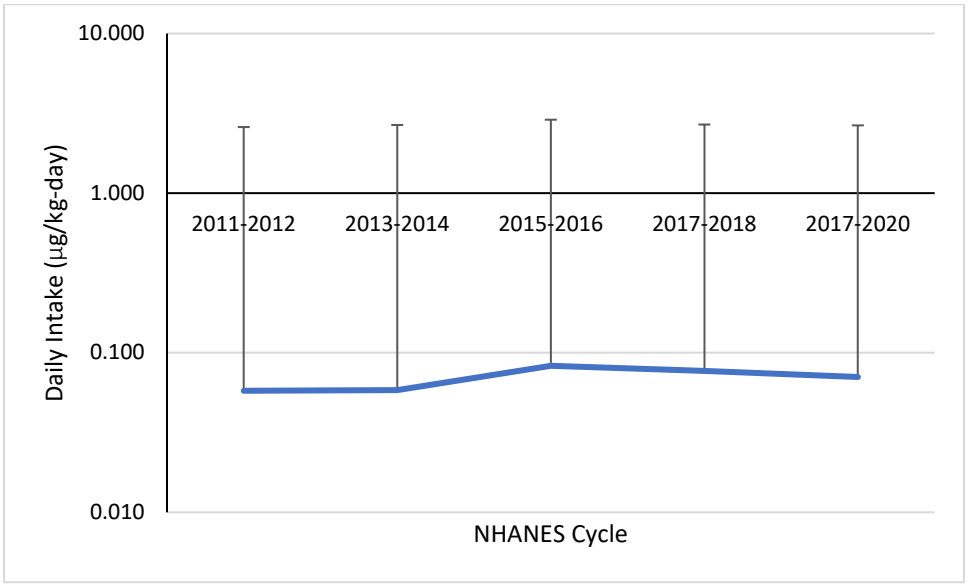


Figure 8. Geometric mean and GSD of TDCIPP daily intake (µg/kg-day) for the overall NHANES population, by cycle.

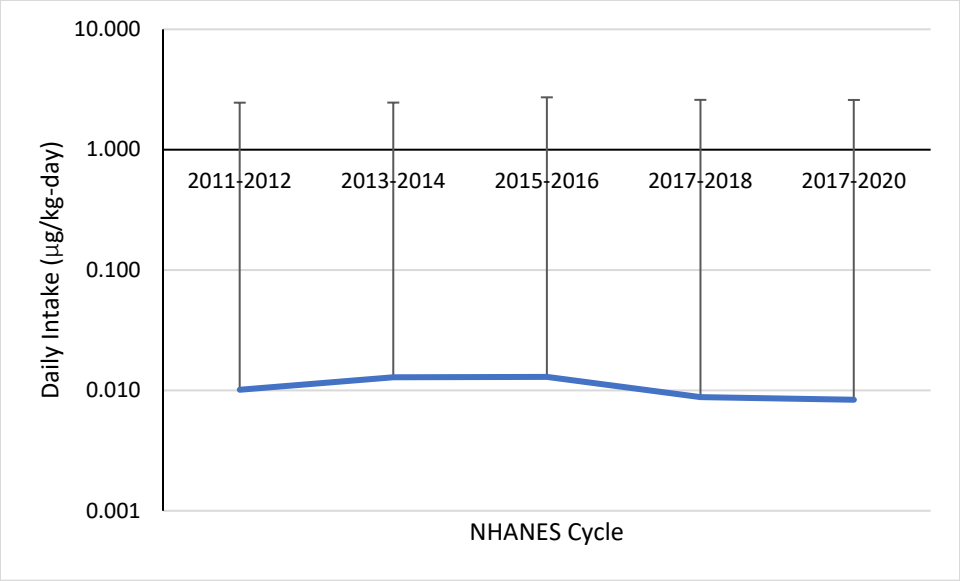


Figure 9. Geometric mean and GSD of TCIPP daily intake (µg/kg-day) for the overall NHANES population, by cycle.

There was no clear trend with time for any of the PHOPs. All three chemicals had the highest estimated dose in the 2015-2016 cycle, but variability was substantially higher in this cycle than in the other ones. The TCIPP dose was clearly lower than the dose of either of the other two PHOPs, on a population basis, and the daily dose of TCEP appears to be somewhat lower than that of TDICPP.

3.1.2 NHANES Age-Related Trends

Figures 10 - 12 show the trend in daily dose (arithmetic mean) with age for each of the cycles. Note that data were not collected on the 3-5 year olds during the 2011-2012 and 2013-2014 cycles. All three chemicals demonstrate a trend of increasing dose on a body weight basis with decreasing age. In particular, the 3-5 year olds received substantially higher doses, with doses more than twice that of the next youngest group of children. This result is not surprising, in light of the higher intake in this age group compared to other groups, and the greater amount of time spent near the floor.

As seen with the overall data, daily intake was highest in the 2015-2016 cycle, particularly for the 3-5 year olds. For the 6-11 year olds, daily intake of TCEP appeared to be lower in the 2017-2018 and 2017-2020 cycles than in prior years; a similar pattern was seen for TCIPP compared to the 2013-2014 and 2015-2016 cycles. In contrast, the TDCIPP intake for this age group appeared to be lowest in the 2011-2012 cycle. Daily intake for the 12-17 year olds appeared to trend downward at least slightly with time, with the most marked trend seen with TCEP.

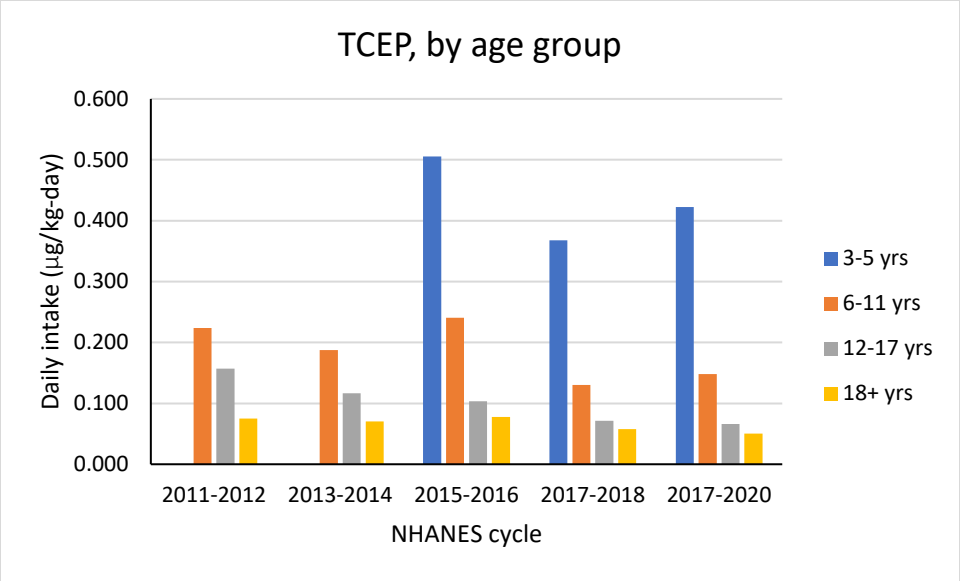


Figure 10. Arithmetic mean of TCEP daily intake (µg/kg-day) by age group, for each NHANES cycle.

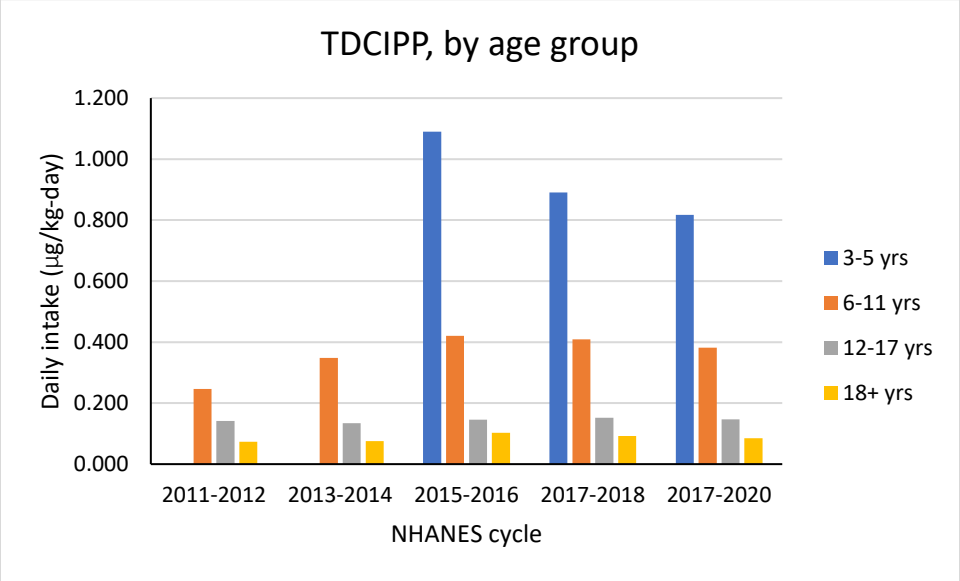


Figure 11. Arithmetic mean of TCIPP daily intake (µg/kg-day) by age group, for each NHANES cycle.

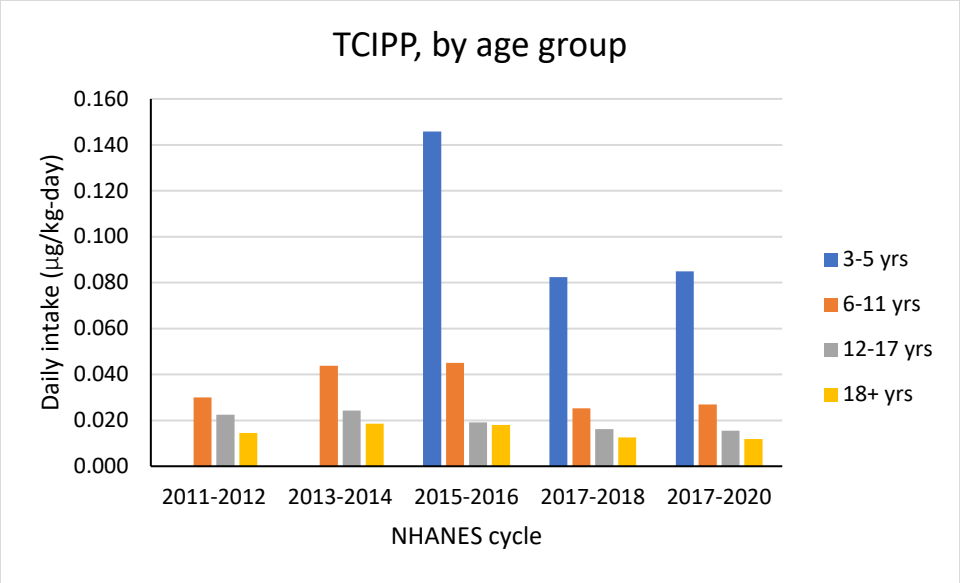


Figure 12. Arithmetic mean of TDCIPP daily intake (µg/kg-day) by age group, for each NHANES cycle.

3.1.3 Other NHANES Subgroups

Table 16 summarizes the distributional parameters for the remaining subgroups. Formal statistical tests were not conducted to compare specific groups, although the lowest income group (income:poverty ratio <1) tended to have slightly higher doses. In addition, the estimated daily intake was slightly higher for the nonpregnant than pregnant populations for all three chemicals. Non-Hispanic Black people tended to have slightly higher daily intakes of TCEP and TCIPP than other racial/ethnic groups, but intake of TCIPP was comparable.

Table 16. Estimated Daily Intakes (µg/kg-day) for TCEP, TDCIPP, and TCIPP from the 2017-2018 NHANES Cycle, by Various Sociodemographic Variables

	Arithmetic		Geometric		Percentiles				
TCEP // BCEP	**Mean**	**SD**	**Mean**	**SD**	**25th**	**50th**	**75th**	**90th**	**95th**
Sex									
Female	0.074	0.126	0.041	2.852	0.019	0.041	0.078	0.148	0.215
Male	0.070	0.172	0.038	2.786	0.019	0.037	0.078	0.141	0.187
Pregnancy status									
Pregnant	0.043	0.034	0.034	2.067	0.017	0.029	0.064	0.101	0.101
Not pregnant	0.064	0.077	0.041	2.606	0.021	0.046	0.081	0.146	0.187
Race/ethnicity									
Mexican American	0.080	0.273	0.038	2.808	0.019	0.036	0.079	0.125	0.186
Other Hispanic	0.066	0.094	0.039	2.811	0.020	0.040	0.075	0.116	0.187
Non-Hispanic White	0.067	0.103	0.039	2.763	0.019	0.040	0.077	0.149	0.195
Non-Hispanic Black	0.090	0.236	0.039	3.069	0.018	0.035	0.073	0.149	0.273

Non-Hispanic Asian	0.074	0.105	0.046	2.588	0.027	0.046	0.081	0.135	0.233
Other Race – Including Multi-Racial	0.084	0.150	0.040	3.328	0.016	0.041	0.089	0.160	0.216
Highest education level for an adult in the household									
Less than high school degree	0.068	0.115	0.035	3.006	0.015	0.032	0.079	0.134	0.209
High school grad/GED or some college/AA degree	0.075	0.129	0.041	2.850	0.019	0.041	0.079	0.169	0.199
College graduate or above	0.069	0.139	0.039	2.705	0.019	0.037	0.076	0.158	0.219
Ratio of income to poverty level									
<1	0.106	0.288	0.042	3.172	0.020	0.034	0.079	0.182	0.396
1 to 3	0.066	0.101	0.039	2.750	0.019	0.037	0.079	0.133	0.199
>3	0.065	0.098	0.038	2.746	0.018	0.041	0.072	0.138	0.195
	Arithmetic		**Geometric**		**Percentiles**				
TDCIPP // BDCIPP	**Mean**	**SD**	**Mean**	**SD**	**25th**	**50th**	**75th**	**90th**	**95th**
Sex									
Female	0.145	0.300	0.077	2.717	0.042	0.073	0.131	0.264	0.475
Male	0.130	0.266	0.077	2.513	0.043	0.073	0.137	0.214	0.371
Pregnancy status									
Pregnant	0.096	0.158	0.071	1.855	0.050	0.053	0.090	0.169	0.169
Not pregnant	0.119	0.113	0.087	2.184	0.056	0.081	0.133	0.246	0.336
Race/ethnicity									
Mexican American	0.146	0.387	0.076	2.588	0.042	0.073	0.122	0.210	0.388
Other Hispanic	0.149	0.336	0.080	2.667	0.038	0.079	0.147	0.219	0.478
Non-Hispanic White	0.130	0.235	0.076	2.550	0.043	0.073	0.135	0.221	0.405
Non-Hispanic Black	0.177	0.404	0.084	2.971	0.043	0.079	0.149	0.338	0.723
Non-Hispanic Asian	0.108	0.155	0.068	2.489	0.037	0.067	0.119	0.214	0.328
Other Race – Including Multi-Racial	0.139	0.272	0.077	2.745	0.043	0.075	0.123	0.343	0.435
Highest education level for an adult in the household									
Less than high school degree	0.115	0.207	0.063	2.654	0.032	0.059	0.118	0.188	0.247
High school grad/GED or some college/AA degree	0.150	0.334	0.083	2.546	0.045	0.074	0.144	0.260	0.425
College graduate or above	0.140	0.257	0.079	2.586	0.044	0.068	0.140	0.281	0.447
Ratio of income to poverty level									
<1	0.193	0.426	0.086	3.049	0.043	0.079	0.146	0.458	0.885
1 to 3	0.149	0.335	0.076	2.742	0.042	0.073	0.130	0.247	0.416
>3	0.119	0.168	0.077	2.420	0.044	0.074	0.136	0.210	0.371
	Arithmetic		**Geometric**		**Percentiles**				
TCIPP // BCIPP	**Mean**	**SD**	**Mean**	**SD**	**25th**	**50th**	**75th**	**90th**	**95th**
Sex									
Female	0.016	0.032	0.009	2.638	0.004	0.008	0.016	0.032	0.053

Male	0.015	0.032	0.009	2.533	0.004	0.008	0.014	0.029	0.050
Pregnancy status									
Pregnant	0.007	0.006	0.006	1.771	0.004	0.005	0.007	0.012	0.020
Not pregnant	0.012	0.015	0.008	2.371	0.005	0.008	0.015	0.027	0.035
Race/ethnicity									
Mexican American	0.015	0.038	0.009	2.372	0.005	0.008	0.015	0.022	0.040
Other Hispanic	0.018	0.031	0.010	2.672	0.005	0.009	0.016	0.041	0.064
Non-Hispanic White	0.015	0.030	0.009	2.521	0.004	0.008	0.014	0.030	0.050
Non-Hispanic Black	0.015	0.041	0.007	2.823	0.004	0.007	0.014	0.028	0.048
Non-Hispanic Asian	0.021	0.028	0.012	2.584	0.007	0.012	0.022	0.044	0.066
Other Race – Including Multi-Racial	0.016	0.033	0.008	2.948	0.003	0.007	0.018	0.033	0.050
Highest education level for an adult in the household									
Less than high school degree	0.015	0.024	0.008	2.809	0.004	0.009	0.016	0.030	0.048
High school grad/GED or some college/AA degree	0.020	0.048	0.010	2.734	0.005	0.010	0.018	0.039	0.073
College graduate or above	0.015	0.023	0.009	2.456	0.004	0.008	0.014	0.035	0.050
Ratio of income to poverty level									
<1	0.019	0.055	0.009	2.816	0.004	0.008	0.014	0.031	0.059
1 to 3	0.015	0.034	0.008	2.639	0.004	0.008	0.014	0.028	0.045
>3	0.016	0.023	0.010	2.526	0.005	0.009	0.016	0.035	0.060

3.1.4 NHANES High Exposure Analysis

Table 17 summarizes the results of the high-exposure analysis. Specifically, the individuals with daily intake greater than the GM daily intake was determined for each individual PHOP in the 2017-2018 cycle. Further analyses determined the overlap between these groups, that is, how many people had daily intake above the GM for two of the PHOPs, and for all three of the PHOPs. This provides context for the percent of the population who are likely co-exposed to multiple PHOP chemicals. As expected, about half of the population had intakes above the GM for each of the individual PHOPs. About a third had intake for two PHOPs above the respective GMs, and about a quarter of the population had intakes above the GM for all three PHOPs.

Table 17. Summary of Daily Intake (µg/kg-day) from "High-Exposure Individuals" (Intakes above the Geometric mean [GM]) in the NHANES 2017-2018 Cycle

PHOP(s) above GM	Number per category	Sample size	Percent of Sample Size
TCEP > GM	1005	1979	50.78
TCIPP > GM	952	1977	48.15
TDCIPP > GM	946	1977	47.85
TCEP & TDCIPP > GM	659	1975	33.37
TCIPP & TCEP > GM	658	1975	33.32
TCIPP & TDCPP > GM	624	1973	31.63
TCIPP & TCEP & TDCIPP > GM	494	1971	25.06

3.1.5 NHANES probabilistic analysis

Data from the NHANES 2017-2018 cycle by age, presented in Figures 10-12 in Section 3.1.2, were used for this analysis. The NHANES 2017-2018 cycle was chosen as the most recent complete cycle. It also includes the younger age group of 3-5 years that were not included in some earlier cycles.

Table 18 shows distributional parameters for each of four age groups for TCEP, TDCIPP, and TCIPP. As noted in Section 2.4, the distribution parameters for the UFR/BW data was obtained from the actual distributions for each age group in the 2017-2018 cycle. Table 9 shows the best estimate, and lower and upper bound values of F_{ue} for each biomarker. The ICC-corrected biomarker was the same as calculated for the main NHANES analysis according to Section 2.2.2 and Eq. 5. Uncertainty in the ICC was not included in the analysis, due to the complexity of the ICC correction, and the manner in which it builds on the population-estimated GM and GSD.

Figures 13-15 show the distributions of calculated daily intakes based on Monte Carlo simulations for each of the four age groups for TCEP, TDCIPP, and TCIPP, respectively. Only one distribution (for TCEP in 12-17 year olds; p=0.00065) was significantly different from the expected log-normal distribution based on results of Shapiro–Wilk tests (cutoff of p=0.05; p>0.05 indicates not significantly different from a log-normal distribution). Note that the descriptive statistics are specific to a given set of simulations.

Table 18. Distributional Parameters for Body Weight Adjusted Urinary Flow Rate (UFR/BW) and ICC-corrected biomarker concentrations (µg/L) for Monte Carlo Analysis of NHANES Data

Age groups	UFR/BW (L/kg-day)		TCEP Metabolite BCEP (µg/L)		TCIPP Metabolite BCIPP (µg/L)		TDCIPP Metabolite BDCIPP (µg/L)	
Statistic	GM	GSD	GM	GSD	GM	GSD	GM	GSD
3-5 years	0.06	2.64	0.44	2.48	0.16	2.09	2.11	2.32
6-11 years	0.02	2.24	0.44	2.39	0.16	2.1	2.47	2.34
12-17 years	0.02	2.13	0.4	2.24	0.15	1.99	1.58	2.18
18+ years	0.01	2.07	0.34	2.31	0.14	2.05	1.09	2.34

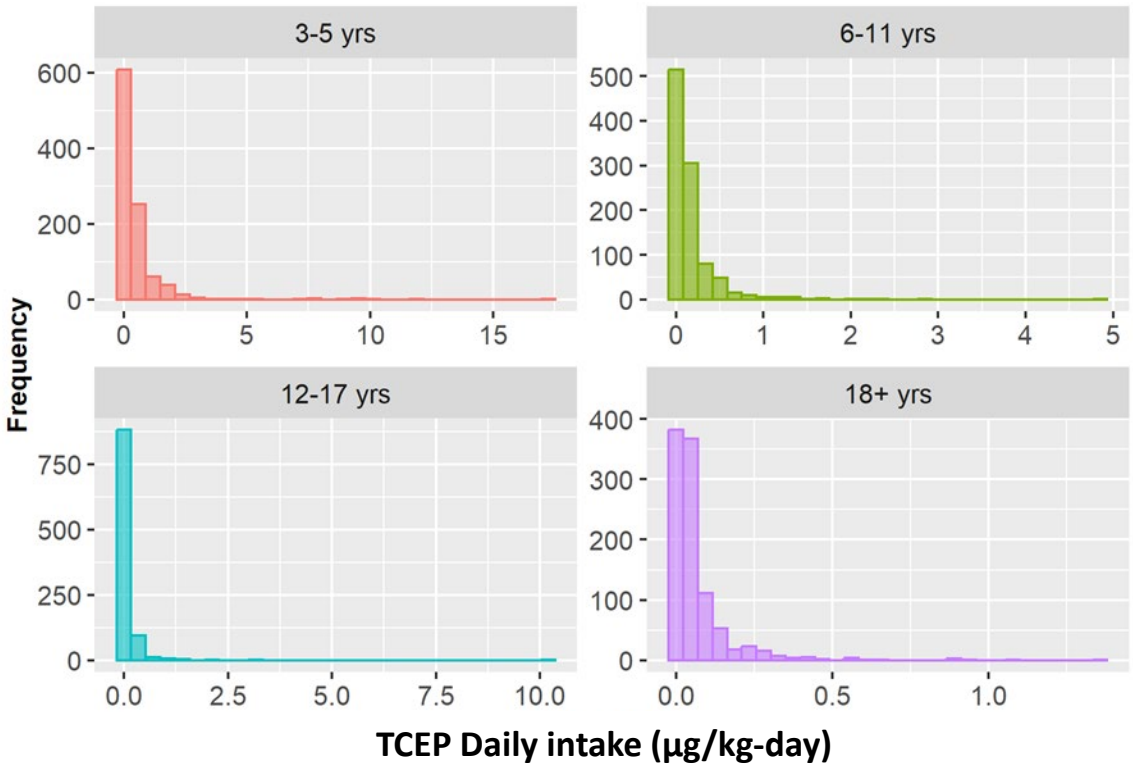


Figure 13. Predicted probabilistic distribution of TCEP daily intake (µg/kg-day) by age group, from NHANES 2017-2018.

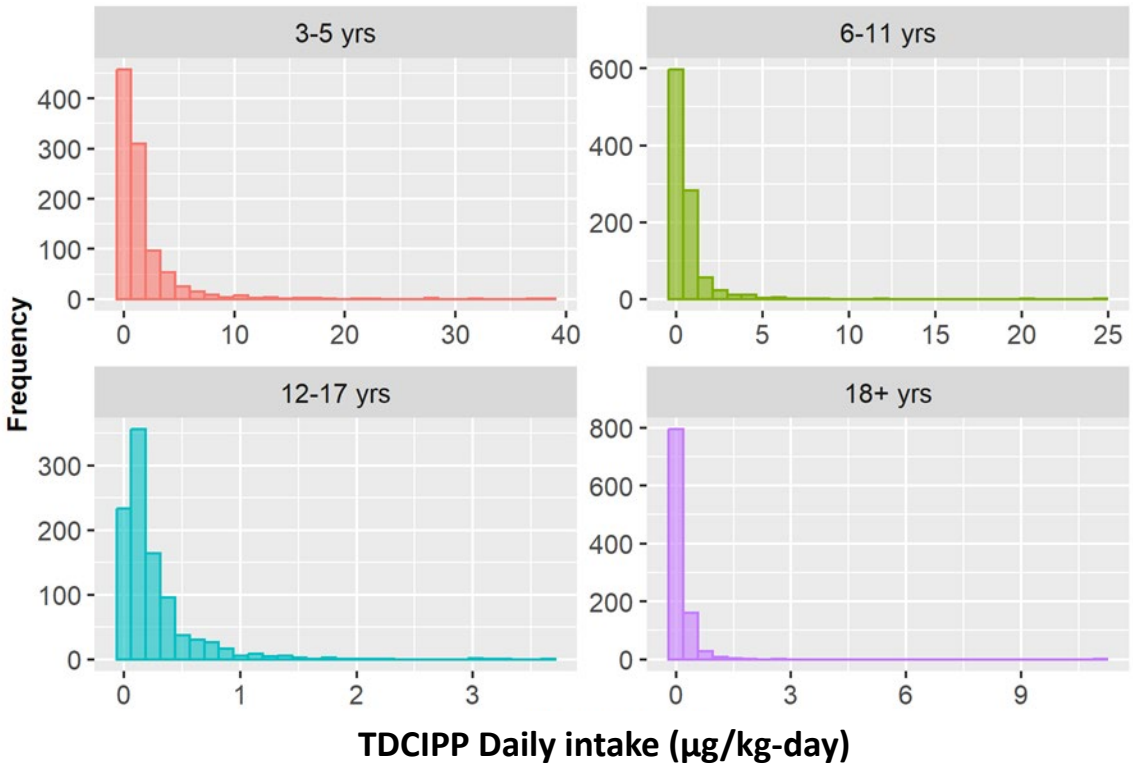


Figure 14. Predicted probabilistic distribution of TDCIPP daily intake (µg/kg-day) by age group, from NHANES 2017-2018.

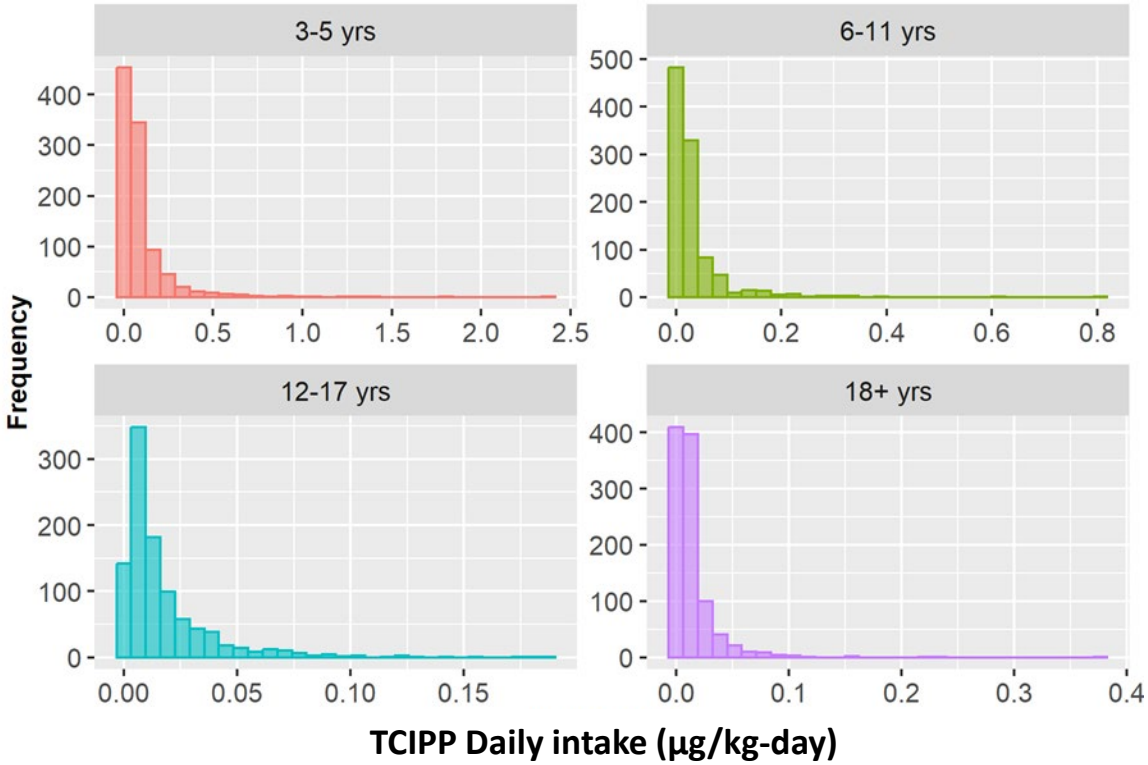


Figure 15. Predicted probabilistic distribution of TCIPP daily intake (µg/kg-day) by age group, from NHANES 2017-2018.

Table 19 shows skew and kurtosis for each of the four age groups for TCEP, TDCIPP, and TCIPP. Skew values greater than 1 indicate the data is highly positively skewed (reflecting the frequency in the tail of the distribution). Kurtosis values higher than 3 (the value expected for a symmetric distribution) indicate positive kurtosis (a high peak in the data).

Table 19. Skew and Kurtosis of Monte Carlo-Predicted Daily Intake (µg/kg-day) Distributions of TCEP, TDCIPP, and TCIPP by Age Group, from NHANES 2017-2018.

Age group	TCEP		TDCIPP		TCIPP	
Statistic	skew	kurtosis	skew	kurtosis	skew	kurtosis
3-5 yrs	7.1	65.3	5.7	44.1	6.2	57.7
6-11 yrs	6.4	65.0	9.0	122.0	6.3	64.3
12-17 yrs	21.4	560.7	4.1	24.9	3.3	15.0
18+ yrs	5.2	39.2	18.8	469.5	7.2	85.4

3.2 Peer-Reviewed Data

3.2.1 Urine HBM Data

As discussed in Section 2.2.1, two methods were used for calculating distributional parameters for intake. Method 1 was based on the mathematical properties of the GM and GSD. This method was applied to all data sets analyzed for urine biomarkers, and was considered more accurate than Method 2, which applied the conversion from biomarker to intake value to each individual available value of the biomarker distributional statistics. Method 2 was applied only as needed, where there were values (e.g., arithmetic mean, 25th percentile) not addressed by Method 1 These additional values are available in the calculation spreadsheet (see Appendix Table 1 for file name).

Because the studies evaluated for this report included a variety of populations and had varying sample sizes, it was not feasible to calculate an overall average. Instead, as a way of describing the central tendency, Table 20 summarizes the minimum and maximum values of the GM for each biomarker, and the number of rows of data (publication/ (sub)population/biomarker/chemical combination) that contributed to that range. Because Method 2 identified a GM only when reported by the authors, and Method 1 used the author-reported GMs as well as GMs estimated from other distributional parameters, the GM determined with method 2 are a subset of those determined with Method 1(although the GMs at the bounds could be the same for both approaches). Therefore, the range of GMs is presented here only for Method 1.

As shown in Table 20, there was a very wide range of GMs across studies and populations, making it very hard to interpret results in general. Comparing the median of the GMs across the different biomarkers is more informative. In calculating median, one study from Shanghai (Sun et al., 2018) that presented many "cuts" of the same data and had particularly low estimated daily intakes was limited to only the data on male and on female participants of all ages (two rows of data per chemical, instead of all 15 rows of data covering all ages and an additional 3 rows covering various ages of adults and another row covering children). Details are further described below. As shown in Table 20, the daily intake of TCIPP estimated based on the measured levels of BCIPHIPP or BCIPP was within a factor of two. The intake of TCIPP estimated based on the combined levels of BCIPP and BCIPHIPP was within a factor of four of that estimated based on the individual metabolites. This general similarity despite the uncertainties in both the F_{ue} values and physiological constants adds confidence to the overall assessment, although the comparison did not include high-end estimates.

Overall, the estimated intake for the three data-rich PHOPs was generally quite similar, ranging from 0.02 to 0.12 µg/kg-day.

Table 20. Range of Geometric Mean (GM) Daily Intakes (µg/kg-day) Calculated from Published Studies (Method 1)

Biomarker// Parent	Number of rows (Number for Median)	Min. GM	Max. GM	Median GM
BCEP //TCEP	67 (50)	1.57E-04	1.87E+00	1.17E-01
BCIPHIPP //TCIPP	19 (19)	7.13E-03	2.40E-01	2.22E-02
BCIPP & BCIPHIPP//TCIPP	8 (8)	4.32E-02	1.07E+00	7.72E-02
BCIPP //TCIPP	33 (16)	1.25E-03	2.35E+00	4.55E-02
BDCIPP //TDCIPP	131 (114)	1.73E-04	1.59E+00	9.68E-02

The central tendency estimates based on the published data were further investigated by comparing the results with NHANES. Table 21 compares the median of the GM daily intakes presented in Table 20 with the median daily intakes calculated based on the NHANES data. Figure 16 presents the same data in graphic form. As shown, the results for TCEP intake (based on BCEP data) and TDCIPP intake (based on BDCIPP data) are remarkably close for the NHANES and published data, differing by a factor of about 2 to <4 for TCEP (depending on the cycle) and by <70% for TDCIPP. The similarity in estimated intake is particularly noteworthy, in light of the range in years and populations addressed in the peer-reviewed literature.

The median intake of TCIPP estimated from the literature differed more substantially from the NHANES data. The TCIPP intake estimated from BCIPP was about a factor of 3 to <6 above the NHANES estimates, while the intake based on BCIPHIPP was a factor of <2 to <3 higher and the estimate based on the two metabolites combined was about a factor of <6 to <10 higher. Note that NHANES did not measure BCIPHIPP, and the same F_{ue} was used to calculate the intake based on the published literature and NHANES. This means that issues related to calculating the F_{ue} may have affected the differences in TCIPP intake estimates in Table 20, but not the calculation of TCIPP (based on BCIPP) from the literature vs. NHANES.

For all of the PHOPs, estimated intake was higher based on the median from the published studies than based on the GM in NHANES.

Table 21. Daily Intakes of Parent PHOP (µg/kg-day) from Published Studies Method 1 (Median GM by Biomarker) and NHANES (GM by Biomarker)

		NHANES cycle				
Biomarker //Parent	**Published Studies**	**2011-2012**	**2013-2014**	**2015-2016**	**2017-2018**	**2017-2020**
BCEP//TCEP	1.17E-01	5.57E-02	5.03E-02	5.47E-02	3.93E-02	3.45E-02
BCIPHIPP// TCIPP	2.22E-02	NA	NA	NA	NA	NA
BCIPP & BCIPHIPP// TCIPP	7.72E-02	NA	NA	NA	NA	NA
BCIPP//TCIPP	4.55E-02	1.02E-02	1.29E-02	1.30E-02	8.79E-03	8.36E-03
BDCIPP//TDCIPP	9.68E-02	5.78E-02	5.82E-02	8.28E-02	7.69E-02	7.06E-02

NA = Not applicable

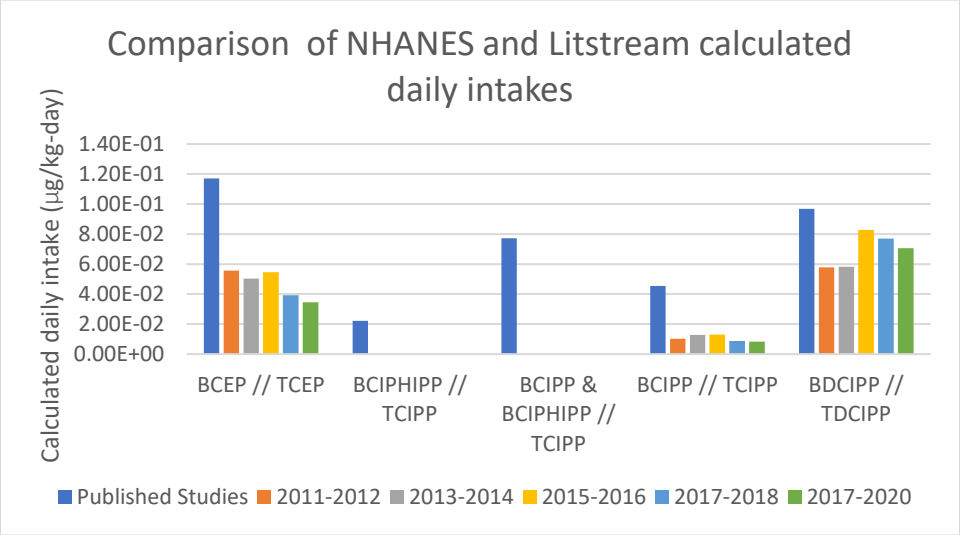


Figure 16. Comparison of daily intakes of parent PHOP (µg/kg-day) from published studies (median GM by biomarker) and NHANES (GM by biomarker) calculated daily intakes, based on various biomarkers

As an additional check on the methods of estimating F_{ue} for BCIPP, BCIPHIPP, and combined BCIPP&BCIPHIPP (See Section 2.3.2 and Table 9), daily intakes were calculated based on both metabolites individually and then combined for the studies that reported both metabolites. Table 22 presents these daily intakes. Calculated intakes are within a factor of 5 across the three calculations within a given study and population, and are often within a factor of 2-3.

Table 22. Daily Intake Summary Statistics (µg/kg-day) for TCIPP Metabolites Based on Published Studies (Method 1)

Study	Basic Population	Biomarker Abbreviation	GM | Daily intake parameters (µg/kg-day)	GSD | Daily intake parameters	95th Percentile | Daily intake parameters (µg/kg-day)
Hoffman et al., 2017	Pregnant women	BCIPP & BCIPHIPP	4.32E-02	2.52E+00	1.98E-01
		BCIPP	6.35E-02	2.32E+00	2.53E-01
		BCIPHIPP	2.98E-02	2.79E+00	1.62E-01
Hammel et al., 2020	Infants, 12 months	BCIPP & BCIPHIPP	7.42E-02	1.09E+01	3.80E+00
		BCIPP	1.11E-01	1.44E+01	8.98E+00
		BCIPHIPP	4.98E-02	3.49E+00	3.89E-01
	Infants, 6 weeks	BCIPP & BCIPHIPP	1.07E+00	8.87E+00	3.86E+01
		BCIPP	2.35E+00	9.49E+00	9.50E+01
		BCIPHIPP	2.25E-01	3.30E+00	1.61E+00
Phillips et al., 2018	Children	BCIPP & BCIPHIPP	8.03E-02	2.99E+00	4.86E-01
		BCIPP	5.06E-02	3.31E+00	3.63E-01
		BCIPHIPP	9.98E-02	2.87E+00	5.67E-01
Butt et al., 2016	Children	BCIPP & BCIPHIPP	1.66E-01	3.31E+00	1.19E+00
		BCIPP	5.38E-02	4.29E+00	5.90E-01
		BCIPHIPP	2.40E-01	3.15E+00	1.58E+00
	Women	BCIPP & BCIPHIPP	1.04E-01	6.61E+00	2.32E+00
		BCIPP	2.75E-02	4.57E+00	3.35E-01
		BCIPHIPP	1.54E-01	6.82E+00	3.62E+00
Gibson et al., 2019	Children	BCIPP & BCIPHIPP	6.14E-02	3.65E+00	5.17E-01
		BCIPP	9.29E-02	4.53E+00	1.11E+00
		BCIPHIPP	4.07E-02	1.97E+00	1.24E-01
	Women	BCIPP & BCIPHIPP	4.37E-02	2.74E+00	2.30E-01
		BCIPP	4.82E-02	3.30E+00	3.43E-01
		BCIPHIPP	4.07E-02	2.26E+00	1.55E-01

Table 23 shows calculated daily intakes by age group and pregnancy status. As for the overall summary of the GM data, only the results from Method 1 are presented, since Method 2 is a subset of these data. Some population/age/chemical combinations are not shown, because no studies evaluated that combination. For some combinations, only a single study/population/chemical/age/sex was identified (number of rows = 1), and so the minimum and maximum are the same.

The data in Table 23 generally reflect the pattern seen elsewhere of infants and children having higher daily intakes than older ages, and (less consistently) pregnant women having lower daily intakes than the adults as a whole. The "all ages" groups (including "all ages, male", and "all ages, female") for all chemicals in Table 23 are all different cuts of the same data from a single study in Shanghai, (Sun et al., 2018), so their lower daily intakes for each chemical relative to other age groups may be a result of the location of this study. Since this is likely to have a minimal impact on reported ranges, all rows for these groups are included in this analysis. For earlier analyses using medians, only the "all ages, male" and "all ages, female" groups were used, to prevent over-weighting this study. While there are other studies with multiple cuts of the same data, the low estimated daily intakes and the large number of data sets from the same data in this study in particular stand out, so it is the only one excluded.

Table 23. Geometric Mean Daily Intakes (µg/kg-day) Calculated Using Method 1, by Chemical and Population (Age Group and Pregnancy Status)

Chemical//Parent/ Population	Number of rows	Min	Max
BCEP//TCEP			
Children	18	1.95E-04	1.87E+00
All ages	13	1.64E-04	5.40E-04
All ages, female	1	3.24E-04	3.24E-04
All ages, male	1	2.51E-04	2.51E-04
Pregnant women	29	4.02E-02	1.77E-01
Adults	5	1.57E-04	1.69E-01
BCIPHIIPP//TCIPP			
Infants	2	4.98E-02	2.25E-01
Children	3	4.07E-02	2.40E-01
Teen/Young adult	9	1.58E-02	2.26E-02
Pregnant women	1	2.98E-02	2.98E-02

Chemical//Parent/ Population	Number of rows	Min	Max
Women	2	4.07E-02	1.54E-01
Adults	2	7.13E-03	9.36E-03
BCIPP & BCIPHIPP//TCIPP			
Infants	2	7.42E-02	1.07E+00
Children	3	6.14E-02	1.66E-01
Pregnant women	1	4.32E-02	4.32E-02
Women	2	4.37E-02	1.04E-01
BCIPP//TCIPP			
Infants	3	4.56E-02	2.35E+00
Children	4	1.75E-03	9.29E-02
All ages	13	1.25E-03	4.46E-03
All ages, female	1	1.40E-03	1.40E-03
All ages, male	1	1.90E-03	1.90E-03
Pregnant women	4	2.18E-02	6.35E-02
Women	2	2.75E-02	4.82E-02
Adults	5	1.34E-03	9.87E-03
BDCIPP//TDCIPP			
Infants	17	2.14E-01	1.22E+00
Infants, female	1	4.60E-01	4.60E-01
Infants, male	1	7.54E-01	7.54E-01
Children	26	4.18E-03	1.59E+00
Teen/Young adult	9	9.16E-03	1.61E-02
All ages	13	1.73E-04	5.04E-04
All ages, female	1	3.31E-04	3.31E-04
All ages, male	1	4.41E-04	4.41E-04
Pregnant women	37	4.63E-02	3.18E-01

Chemical//Parent/ Population	Number of rows	Min	Max
Women	3	4.75E-02	2.27E-01
Men	1	2.80E-02	2.80E-02
Adults	21	1.94E-04	3.02E-01

A bounding analysis for F_{ue} values was also conducted using high and low estimates of F_{ue}, for the studies reporting the highest and lowest urinary concentration of each metabolite (after conversion to μg/L). The results of this bounding analysis are shown in Tables 24 (using the upper bound F_{ue}) and 25 (using the lower bound F_{ue}). Since F_{ue} is in the denominator of the DI calculations, the upper bound F_{ue} and the minimum GM biomarker urinary concentration determine the lower end of the range, and the lower bound F_{ue} together with the maximum GM biomarker concentration represent the upper end of the intake range. The columns defining the extremes of the range are italicized.

Table 24. Daily Intakes (μg/kg-day) Calculated Using the Upper Bound F_{ue} Values for Each Chemical, for the Highest and Lowest Reported GM Urinary Biomarker Concentration (μg/L)

Biomarker Abbreviation// Parent	*Min. GM*	Max. GM
BCEP//TCEP	*7.91E-05*	1.50E-01
BCIPHIPP//TCIPP	*8.03E-03*	7.81E-02
BCIPP//TCIPP	*6.13E-04*	2.22E-02
BDCIPP//TDCIPP	*1.42E-04*	9.73E-01

Min GM column is italicized, as indicating the bottom end of the combined range.

Table 25. Daily Intakes (µg/kg-day) Calculated Using the Lower Bound F_{ue} Values for Each Chemical, for the Highest and Lowest Reported GM Urinary Biomarker Concentration (µg/L)

Biomarker Abbreviation// Parent	**Min. GM**	***Max. GM***
BCEP//TCEP	7.12E-04	*1.35E+00*
BCIPHIPP//TCIPP	7.91E-02	*7.69E-01*
BCIPP//TCIPP	5.76E-03	*2.09E-01*
BDCIPP//TDCIPP	7.96E-04	*5.45E+00*

Max GM column is italicized, as indicating the upper end of the combined range.

3.2.2 HBM Data in Blood Fractions

There were a limited number of studies with blood data, and studies reported different metrics for central tendency, so often there was only one study for a given combination of chemical/geography/central tendency metric (see Appendix Table 1 for file name). Average values of several measures of central tendency (median, arithmetic mean, and geometric mean) are presented by region (Asia or Europe) in Table 26. For TCIPP in Europe, there was only one study, so these "averages" are just reported values of each central tendency measure. Similarly, blood data for TDCIPP were available only in Asia; no studies in Europe measured TDCIPP in blood.

Table 26. Daily Intake Based on Blood Data

Averages of Central Tendencies (µg/kg-day)			
Region | Studies	**Avg. of 50th Percentile Median Daily Intake**	**Avg. of Arithmetic Mean Daily Intake**	**Avg. of Geometric Mean Daily Intake**
TCEP			
Asia (Hou et al., 2021; Zhao et al., 2017)	1.6	0.32	0.11
Europe (Xu et al., 2019; Henríquez-Hernández et al., 2017)	0.1	0.09	0.04
TCIPP			
Asia (Hou et al., 2021; Zhao et al., 2017)	5.12	3.38	0.48
Europe (Henríquez-Hernández et al., 2017)	3.98	3.54	1.23
TDCIPP			
Asia (Hou et al., 2021; Zhao et al., 2017)	NR	0.007	0.003
Europe	NR	NR	NR

There were two studies that reported biomarker concentrations in both blood and urine, one from Jinan, China (Hou et al., 2021) and the other from Oslo, Norway (Xu et al., 2019) . Only one (Hou et al., 2021) corrected urine measurements for specific gravity. The other (Xu et al., 2019) did not correct urine concentrations at all, and so was not included for further analysis. Table 27 presents daily intakes calculated from both matrices in the study that corrected by specific gravity. Comparison of the central tendencies between matrices is somewhat hampered by the fact that the study did not report central tendency estimates in both matrices for the same chemical. That is, central tendency was reported in blood for TCEP and TCIPP, but not TDCIPP, while in urine central tendencies were available only for TDCIPP. The central estimates of daily intakes of TCEP from the two matrices are within an order of magnitude. However, central estimates of daily intakes of TCIPP span 4 orders of magnitude. Central estimates of daily intake for TDCIPP could not be compared between the two methods, since no central tendencies were reported for TDCIPP in blood. The intake based on maximum concentration was more than one or two orders of magnitude

higher, respectively, based on blood than urine measurements (Method 2) for TCEP and TCIPP, but the two measurements were within an order of magnitude for TDCIPP. The reason for the large difference is not clear, but could be related to either measurement uncertainties or uncertainties in the toxicokinetic parameters used to estimate intake.

Table 27. Comparison of Calculated Daily Intakes (µg/kg-day) Based on Blood and Urine Measurements from the Same Study (Hou et al., 2021)

Bio-marker	Chem	50th Percentile / Median	Geometric Mean	GSD	95th percentile	Maximum
Blood	TCEP	1.60E+00	1.65E+00	Not Calculated	Not Calculated	2.72E+01
	TCIPP	5.98E+00	4.09E+00	Not Calculated	Not Calculated	3.58E+01
	TDCIPP	Not Calculated	Not Calculated	Not Calculated	Not Calculated	8.85E-01
Urine, Calculation Method 2	TCEP	Not Calculated	Not Calculated	Not Calculated	Not Calculated	8.82E-01
	TCIPP	Not Calculated	Not Calculated	Not Calculated	Not Calculated	7.60E-02
	TDCIPP	7.07E-03	6.19E-03	Not Calculated	Not Calculated	2.79E-01
Urine, Calculation Method 1	TCEP	Not Calculated	1.69E-01	1.90E+00	4.85E-01	Not Calculated
	TCIPP	Not Calculated	9.66E-03	2.23E+00	3.60E-02	Not Calculated
	TDCIPP	Not Calculated	6.19E-03	2.79E+00	3.36E-02	Not Calculated

3.2.3 Evaluation of the Impact of the ICC

As noted in Section 2.5, variability in the population distribution may be over-estimated when the half-life is short relative to the exposure frequency, because samples from different individuals may be taken at different points in the elimination curve. To evaluate the impact of the use of spot sampling, the ICC correction in Eq. 11was applied to two studies that are representative of the extremes on the available data (see Appendix Table 1 for file name), with one having a large number of samples per subject and a small sample size, and the other having a relatively large sample size and small number of samples per subject. Despite this difference, however, the ICCs for both studies were in the range of 0.5-

0.6, indicating that the variability was about evenly split between intra-individual and population variability.

One study (Bastiaensen et al., 2021) used an extensive sampling protocol to investigate the short-term variability of urinary biomarkers of OFRs. To do this, they collected all spot urine samples from 10 adults for 5 days, and a 24-hour pooled sample on an additional day. This intensive sampling regime allowed for a refined evaluation of the ICC for the sampled chemicals, but such intensive sampling was practical only for a relatively small sample size. Of the three data-rich PHOPs, only one metabolite of TCIPP (BCIPHIPP) and the major metabolite of TDCIPP (BDCIPP) were evaluated. The publication reported only the median and percentiles, and so the GM and GSD were estimating using the equations in Section 2.6.

The second study (Messerlian et al., 2018) collected 1-2 spot samples during the follicular stage of the women's cycle. Overall, 138 women provided 2 samples per cycle. Some women were evaluated during more than one pregnancy, and so the ICC reflects both sampling over the course of a week (during one cycle) and sampling separated by several months. Of the 3 data-rich PHOPs, only one metabolite (BDCIPP) was evaluated.

Table 28 shows the impact of the ICC on the estimated GSD for these studies. ICC correction reduced GSD to 88%,7 75%, and 71% of the original GSDs for BDCIPP (Messerlian et al., 2018), BCIPHIPP (Bastiaensen et al., 2021), and BDCIPP (Bastiaensen et al., 2021) respectively. The maximum possible reductions (if ICC=0) were 77%, 37%, and 29% of the original GSDs. In other words, consideration of the ICC would reduce the GSD by 23 – 71% (depending on the sample size and number of samples per subject) if all of the observed variability were due to intraindividual variability.

Table 28. Impact of the ICC on the Estimated GSD for Selected Studies

Study	Sample Size (# of Indivi-duals)	Average # of Samples Per Subject	ICC	Original GSD	ICC-corrected GSD	GSD Assuming ICC = 0)
Bastiaensen et al., 2021	10	30.9	BCIPHIPP: 0.599 BDCIPP: 0.588	BCIPHIPP: 3.33 BDCIPP: 4.53 (both estimated based on other distributional parameters reported by authors)	BCIPHIPP: 2.50 BDCIPP: 3.20	BCIPHIPP: 1.24 BDCIPP: 1.31
Messerlian et al., 2018	155	2.2	BDCIPP: 0.5	2.46 (estimated based on other distributional parameters reported by authors)	2.18	1.89

3.2.4 Probabilistic Analysis

Five published studies were selected for the probabilistic analysis. Key study and population characteristics are summarized in Table 29. Of the five, four (Phillips et al., 2018; Hoffman et al., 2017; Percy et al., 2022; Yang et al., 2023) were chosen to cover populations of interest (pregnant women and children) and metabolites of all three data-rich PHOPs, while simultaneously including a large enough sample size for reliable probabilistic analyses (all n>150). The fifth (Hoffman et al., 2021) was selected despite its small sample size (n=10) because it collected 24-hour urine samples, whereas the other four studies all collected urine via spot samples. This fifth study was also the only 24-hour urine study from the U.S. Despite the substantially smaller sample size, the more robust collection method provides greater confidence for use in distributional analyses. Further, it is not practical to do 24-hour analysis on a large cohort, so finding such a study with a large sample size is unlikely.

Table 30 shows the distributional parameters of input variables used for the probabilistic analyses (see Appendix Table 1 for file name). For each study/biomarker combination, the GM and GSD for the biomarker measurement was reported in the study. In order to make this probabilistic analysis as comparable as possible to the probabilistic analysis of the NHANES data, the age of the population was identified, and matched as closely as possible to the corresponding NHANES population. The UFR/BW GM and GSD for the identified NHANES population was determined from the 2017-2018 cycle of NHANES. The best estimate and high-and low estimates for F_{ue} were determined as described in Section 2.3.2 and Table 9. Note that, when urinary concentration data were available for both BCIPP and BCIPHIPP, the probabilistic analysis was conducted on the total concentration, using the F_{ue} for combined metabolites. However, because summary statistics were presented in the published papers only for the individual metabolites, the GM and GSD for the total concentration of BCIPHIPP and BCIPP needed to be calculated from the individual distributions. For Hoffman et al. (2021), BCIPP was measured without also measuring BCIPHIPP, and so daily intake was calculated directly from BCIPP using the F_{ue} for BCIPP.

Table 29. Study and Population Characteristics of Published Studies Selected for Probabilistic Analyses

Reference	Sampling location	Sampling years	Urine Sample Type	Population (cohort)	Biomarker	Sample Size	% Detection Frequency
Phillips et al., (2018)	North Carolina, USA	2014-2016	Spot urine	Children, ages 3-6 (NEST/TESIE cohort)	BCIPHIPP	181	97.2
					BCIPP		80.1
					BDCIPP		100
Hoffman et al., (2017)	North Carolina, USA	2001-2006	Spot urine	Pregnant women, ages 26-35 (PINS cohort)	BCIPHIPP	349	98.3
					BCIPP		48.7
					BDCIPP		92.8
Percy et al., (2022)	Cincinnati, OH, USA	2003-2006	Spot urine	Children, age 5 (HOME cohort)	BCEP	176	93.75
					BDCIPP	173	99.42
				Children, age 3 (HOME cohort)	BCEP	177	94.92
					BDCIPP	177	98.87
Yang et al., (2023)	Cincinnati, OH, USA	2003-2006	Spot urine	Pregnant women, 18-35+ (HOME cohort)*	BCEP	329	83.5
					BDCIPP		89.3
Hoffman et al., (2021)	North Carolina, USA	2018-2019	24-hour urine	Adults	BCIPHIPP	10	100
					BDCIPP		100

*83% were younger than 35 years old, no maximum age given

Table 30. Distributional Parameters of Input Variables Used for Probabilistic Analyses of Selected Peer-Reviewed Studies.

Reference	Population (cohort)	Biomarker	GM (μg/L)	Biomarker GSD	NHANES population	NHANES UFR/BW GM (L/kg-day)	NHANES UFR/BW GSD	F_{ue} (best, high, and low estimate)
Phillips et al., (2018)	Children, ages 3-6 (NEST/TESIE cohort)	BCIPHIPP	NA	NA	NA	NA	NA	NA
		BCIPP	NA	NA	NA	NA	NA	NA
		BCIPHIPP+ BCIPP	1.72	2.58	3-5 yrs	0.06	2.64	0.58 0.90 0.12
		BDCIPP	5.63	2.52	3-5 yrs	0.06	2.64	0.23 0.28 0.05
Hoffman et al., (2017)	Pregnant women, ages 26-35 (PINS cohort)	BCIPHIPP	NA	NA	NA	NA	NA	NA
		BCIPP	NA	NA	NA	NA	NA	NA
		BCIPHIPP+ BCIPP	1.2	2.21	18+ yrs	0.01	2.07	0.58 0.90 0.12
		BDCIPP	1.8	2.55	18+ yrs	0.01	2.07	0.23 0.28 0.05

Reference	Population (cohort)	Biomarker	GM (μg/L)	Biomarker GSD	NHANES population	NHANES UFR/BW GM (L/kg-day)	NHANES UFR/BW GSD	F_{ue} (best, high, and low estimate)
Percy et al., (2022)	Children, age 5 (HOME cohort)	BCEP	0.74	3.64	3-5 yrs	0.06	2.64	0.13 0.27 0.03
		BDCIPP	3.19	3.21	3-5 yrs	0.06	2.64	0.23 0.28 0.05
	Children, age 3 (HOME cohort)	BCEP	1	4.6	3-5 yrs	0.06	2.64	0.13 0.27 0.03
		BDCIPP	2.85	3.78	3-5 yrs	0.06	2.64	0.23 0.28 0.05
Yang et al., (2023)	Pregnant women, 18-35+ (HOME cohort)*	BCEP	0.51	4.33	18+ yrs	0.01	2.07	0.23 0.47 0.05
		BDCIPP	0.6	3.29	18+ yrs	0.01	2.07	0.23 0.28 0.05

Reference	Population (cohort)	Biomarker	GM (μg/L)	Biomarker GSD	NHANES population	NHANES UFR/BW GM (L/kg-day)	NHANES UFR/BW GSD	F_{ue} (best, high, and low estimate)
Hoffman et al., (2021)	Adults	BDCIPP	0.82	1.55	18+ yrs	0.01	2.07	0.23 0.28 0.05
		BCIPHIPP	0.16	1.94	18+ yrs	0.01	2.07	0.35 0.69 0.07

*83% were younger than 35 years old, no maximum age given
NA = Not applicable

Figures 17, 18 and 19 show the distributions of calculated daily intakes based on Monte Carlo simulations for each parent chemical and age group, for each study. Age groups are labeled based on the grouping used by the study authors, but the value of UFR/BW was based on the calculated distribution for NHANES (see Table 30). Note that both BCIPP and BCIPHIPP are metabolites of TCIPP, and there is more uncertainty in the derivation of the daily intake from the individual metabolite measurements than from the combined measurement of the two metabolites. Therefore, where data on both BCIPP and BCIPHIPP were available, probabilistic analyses were done only based on the total concentration of the two metabolites and the F_{ue} for the combined metabolites. No distributions were significantly different from a lognormal distribution, though one was borderline (BCIPHIPP+BCIPP in children ages 3-6; Phillips et al., 2018; p=0.051). Table 31 presents the skew and kurtosis for each combination of study, age group, and parent chemical.

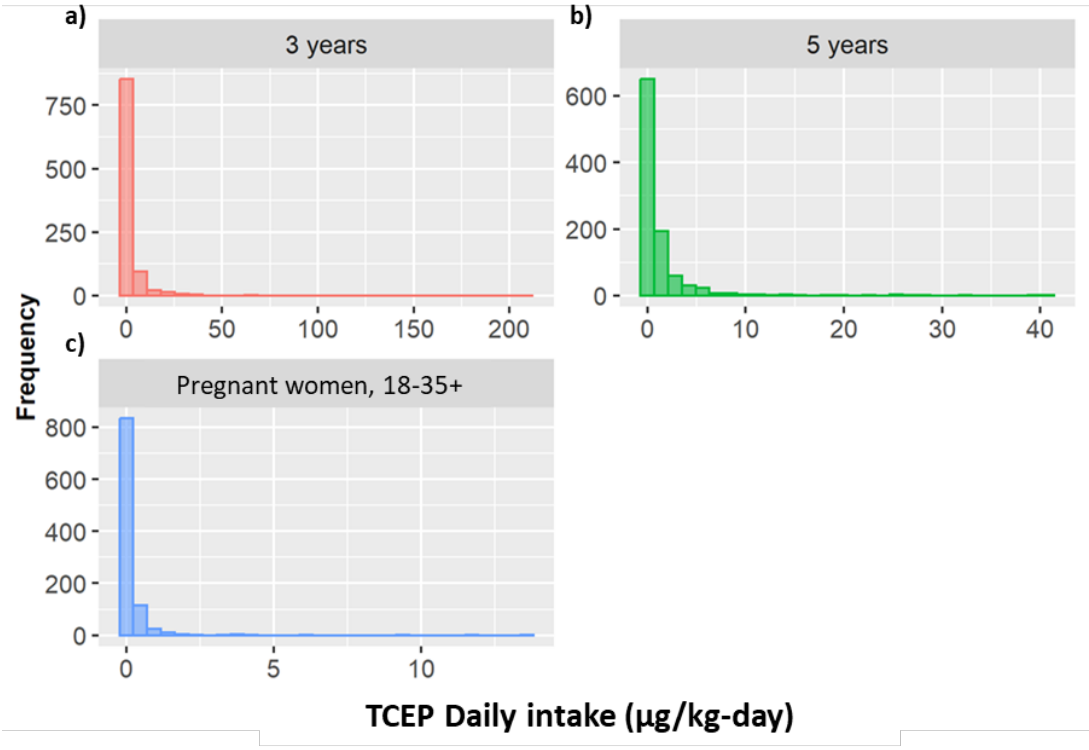


Figure 17. Predicted probabilistic distribution of TCEP daily intake (µg/kg-day) from published studies: a) Percy et al., 2022; b) Percy et al., 2022, c) Yang et al., 2023.

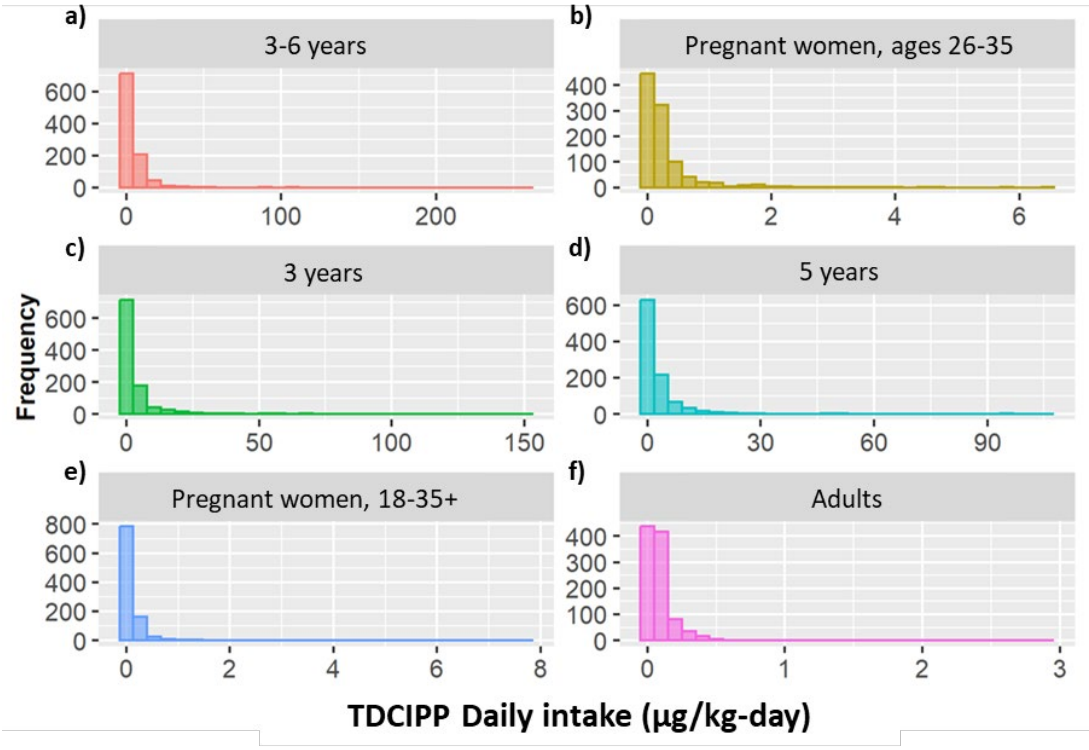


Figure 18. Predicted probabilistic distribution of TDCIPP daily intake (µg/kg-day) from published studies: a) Phillips et al., 2018; b) Hoffman et al., 2017 c) Percy et al., 2022; d) Percy et al., 2022; e) Yang et al., 2023; f) Hoffman et al., 2021.

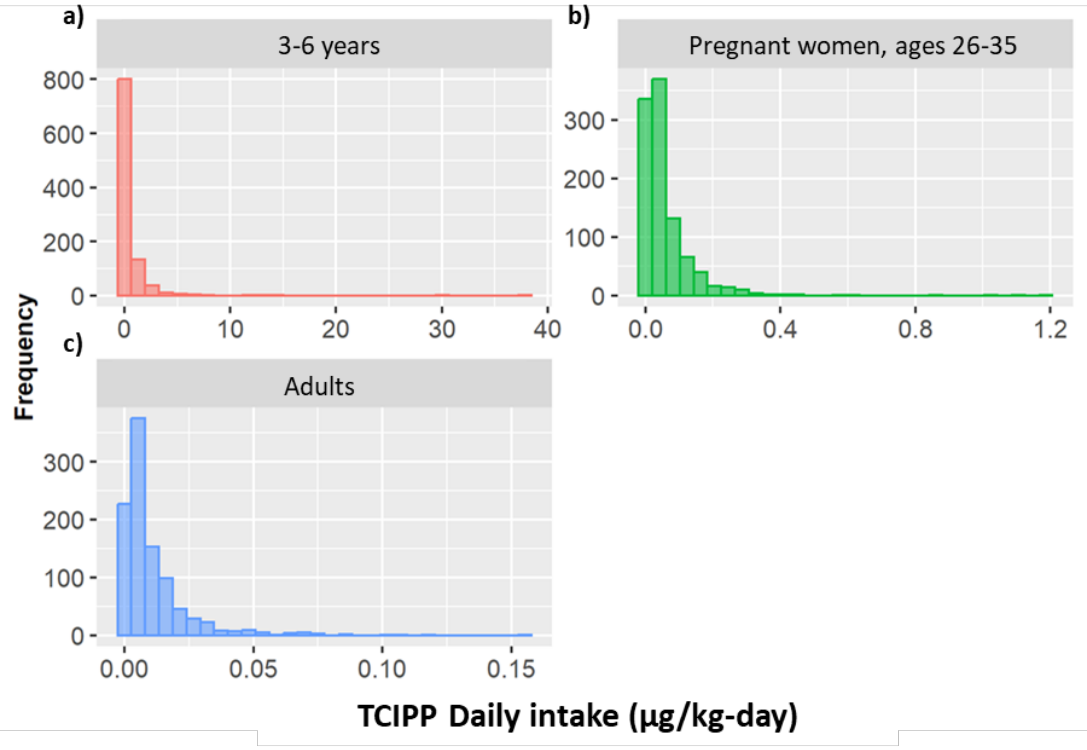


Figure 19. Predicted probabilistic distribution of TCIPP daily intake (µg/kg-day) from published studies: a) Phillips et al., 2018; b) Hoffman et al., 2017; c) Hoffman et al. 2021.

Table 31. Skew and Kurtosis for Distributions of Daily Intake Calculated in Probabilistic Analyses of Selected Peer-Reviewed Studies.

Reference	Population (cohort)	Biomarker	Skew	Kurtosis
Phillips et al., (2018)	Children, ages 3-6 (NEST/TESIE cohort)	BCIPHIPP + BCIPP	12.4	203.0
		BDCIPP	9.9	136.7
Hoffman et al., (2017)	Pregnant women, ages 26-35 (PINS cohort)	BCIPHIPP + BCIPP	6.1	56.8
		BDCIPP	4.8	31.4
Percy et al., (2022)	Children, age 5 (HOME cohort)	BCEP	6.2	179.4
		BDCIPP	6.9	59.0
	Children, age 3 (HOME cohort)	BCEP	13.2	218.8
		BDCIPP	7.2	74.3
Yang et al., (2023)	Pregnant women, 18-35+ (HOME cohort)*	BCEP	12.1	179.4
		BDCIPP	13.3	253.9

Hoffman et al., (2021)	Adults	BCIPHIPP	3.8	22.3
		BDCIPP	11.2	208.7

*83% were younger than 35 years old, no maximum age given

Compared to the distributions from the probabilistic analysis of NHANES data, the distributions from the probabilistic analysis of published studies overall appear generally similar. For TCEP and TDCIPP, GM daily intakes calculated from the published literature are in the same order of magnitude as those calculated from NHANES data for a given age group (data not shown; see Appendix Table 1 for file name). Though a direct comparison between published studies and NHANES for TCIPP metabolites is complicated by the fact that NHANES only measured BCIPP and not BCIPHIPP, the estimates from published studies for TCIPP still generally reflect intakes that are about an order of magnitude lower than the other PHOPs, with the exception of the 3-6 year-olds from the NEST/TESIE cohort (Phillips et al., 2018) which are in the same order of magnitude as other PHOPs.

Table 32 compares the GM and GSD estimated daily intake based on the published GM and GSD for each biomarker in urine for each study, with the GM and GSD of the intake estimated in the probabilistic analysis. For daily intake estimates of any PHOP for children, the probabilistic analysis increased the GM by a factor of 2-4 compared to the deterministic analysis. For adults, the probabilistic analysis decreased the GM by up to a factor of about 2, with one exception where it slightly increased.

Table 32. Comparison of Distributional Parameters for Daily Intakes (µg/kg-day) Calculated Directly from the Reported Data (Deterministic) vs. the Estimates from the Probabilistic Analysis

Reference	Population (cohort)	Biomarker // Parent	Deter-ministic GM	Deter-ministic GSD	Probab-ilistic GM	Probab-ilistic GSD
Phillips et al., (2018)	Children, ages 3-6 (NEST/TESIE cohort)	BCIPHIPP + BCIPP // TCIPP	8.03E-02	2.99E+00	2.14E-01	4.03E+00
		BDCIPP // TDCIPP	6.63E-01	3.01E+00	2.08E+00	3.90E+00
Hoffman et al., (2017)	Pregnant women, ages 26-35 (PINS cohort)	BCIPHIPP + BCIPP // TCIPP	4.32E-02	2.52E+00	3.26E-02	3.12E+00
		BDCIPP // TDCIPP	1.63E-01	3.05E+00	1.35E-01	3.65E+00

Percy et al., (2022)	Children, age 5 (HOME cohort)	BCEP // TCEP	1.22E-01	4.06E+00	3.67E-01	5.34E+00
		BDCIPP // TDCIPP	2.96E-01	3.63E+00	1.07E+00	4.93E+00
	Children, age 3 (HOME cohort)	BCEP // TCEP	2.16E-01	4.37E+00	5.14E-01	6.13E+00
		BDCIPP // TDCIPP	3.49E-01	3.37E+00	1.01E+00	5.28E+00
Yang et al., (2023)	Pregnant women, 18-35+ (HOME cohort)*	BCEP // TCEP	8.19E-02	4.33E+00	4.49E-02	5.42E+00
		BDCIPP // TDCIPP	5.45E-02	3.29E+00	4.60E-02	4.00E+00
Hoffman et al., (2021)	Adults	BCIPHIPP // TCIPP	7.13E-03	2.20E+00	6.15E-03	2.88E+00
		BDCIPP // TDCIPP	5.56E-02	1.68E+00	5.82E-02	2.51E+00

*83% were younger than 35 years old, no maximum age given

4.0 Discussion

In addition to collating a large body of data on PHOP biomonitoring data, this report contains a number of novel analyses and enhancements to prior work. Unlike a prior evaluation of TDCIPP by CPSC staff (Babich and Chen, 2019), which focused only on NHANES data from the 2013-2014 cycle, the current analysis included data from four complete two-year NHANES cycles and a four-year cycle that includes the prior two-year cycle and the partial Covid-19 cycle, as well as 31 studies from the published literature. These 31 studies were selected from a total of 299 PHOP HBM studies in the published literature, based on factors such as study relevance, sample size, study population (geography and vulnerable populations), and use of specific gravity-adjusted measurements.

A second difference from prior work was in the F_{ue}. Prior work by CPSC staff used a value of 0.63. We were not able to fully trace this value to its origin, although we noted that several secondary sources cited Lynn et al. (1981) for an F_{ue} for all three data-rich PHOPs. However, according to that study, 0.63 refers to the fraction of radiolabel in urine *and feces* present as the metabolite BDCPP. Our analysis used a combination of *in vivo* rat data for PHOPs and phthalates to derive the best and upper bound estimates of F_{ue} values for the three data-rich PHOPs and their metabolites, and supplemented these data with *in vitro* metabolic data from rat and human tissue slices for the lower bound estimates (see Table 9 and PHOP TK Extraction and F_{ue} Estimation spreadsheet). As shown in Table 9, the best

estimate of the F_{ue} for individual metabolites ranged from 0.13 to 0.23. These lower values for the F_{ue} result in higher estimated daily doses compared to prior work.

A novel aspect of the current analysis was incorporation of the ICC into both the analyses of the NHANES data and a selected number of published studies, to account for the impact of intraindividual variability on distributional estimates. As shown by Aylward et al. (2017), the use of urine spot sample data can lead to over-estimation of the population variability for short half-life chemicals, because people are sampled at different points are their elimination curve relative to the most recent exposure. Use of the ICC aids in separating the population and intraindividual variability related to the sampling time. For the published studies where the impact of the ICC was evaluated, adjustment of the GSD by the ICC reduced it to 71-88% of the published GSD**.** A challenge with approaches based on specific ICC values or the variation in a specific study is that the variability measure is tied to a specific study population, sampling scheme and method used to standardize urine concentrations.

There were also a number of elements contributing to the uncertainty in the calculations. Perhaps the greatest uncertainty was in the estimates of the F_{ue}, and this uncertainty was reflected in the wide distribution used for the F_{ue} in the probabilistic analysis. Uncertainties related to the calculation of the F_{ue} values included interspecies extrapolation, accounting for bioavailability, the need to estimate an F_{ue} when data were available for total excretion, and, for TCIPP, the need to extrapolate from other chemicals. While two studies with similar results were available with similar F_{ue} estimates for BDCPP in urine from TDCIPP, many of the components of the calculations were based on single studies. Estimates of daily intake of TCIPP are further complicated because studies measured different metabolites as biomarkers – BCIPP, BCIPHIPP, or the combination of the two. The F_{ue} calculation assumed that both metabolites together account for the entire urinary excretion of ingested TCIPP, which may not be the case. Further, the relative amount of BCIPP and BCIPHIPP produced varies with age and sex (Hammel et al., 2020). As noted above, ICC values are tied to specific study populations and methods. Applying the same overall median ICC values from published studies to NHANES data, without consideration of population or study characteristics, adds uncertainty to the calculations. An additional uncertainty in the calculations based on urinary concentrations was the difficulty of calculating the UFR/BW ratio for the published studies, particularly for children, and in matching UFR and BW for granularity of data from different sources.

There were also uncertainties in the estimation of daily intake from the more limited blood data. No data were available on the relative partitioning of the PHOPs into different blood fractions, and so the plasma clearance estimated from httk was assumed to apply to all blood fractions. In addition, in the absence of any data comparing different normalizing approaches, the conversion from lipid adjusted levels to measurements based on concentration in the blood fraction was based on the data for TBBPA. It was not possible to quantify the degree of error introduced by either of these work-arounds. However, it was noted that the daily intake estimates based on blood biomonitoring and based on urine biomonitoring in the same study often differed by more than an order of magnitude. In light of the general agreement between the intake estimates based on published studies of

urine biomonitoring and the intake estimates based on the NHANES urine data, it seems likely that the difference between extrapolation from blood and from urine relates to the toxicokinetic parameters used for the extrapolation. However, insufficient data are available to determine whether the primary error is in the F_{ue}, the clearance, or both. Since the discrepancy between the urine and blood results was seen with multiple different populations, it appears that the discrepancy is not related to the physiological parameter of UFR/BW.

It was noted that both BCIPP and BCIPHIPP are metabolites of TCIPP, and data on these metabolites in urine, both alone and in combination, were available from several studies; NHANES had data only on BCIPP. The median TCIPP intake calculated from the published data was substantially higher than the TCIPP intake calculated from NHANES, regardless of which metabolites were used for the published data, although the difference was smallest when estimating TCIPP intake based on BCIPHIPP published data. The source of this difference is not clear. The same F_{ue}, was used for BCIPP for both NHANES and the published data, but the proportion of excretion in each of the two metabolites varies with age, and the approach used here may not have adequately addressed this variation. The median GM intake estimated for TCEP and TDCIPP from published data was also higher than the corresponding GMs from NHANES. It is not clear why there was a systematic tendency for intakes estimated from the published studies to be higher than the corresponding intakes estimated for NHANES, although it should be noted that this comparison was only for the central tendencies, and not for the upper percentiles.

An uncertainty related to broader interpretation of the results was identified late in the project. The published biomonitoring literature describes the biomarkers listed in Table 1 of this report as being unique and diagnostic for their respective parent chemicals. However, as part of another OFR project (CO-1 under ICF BPA # 61320622A0005 Call Order # 61320622F2011), we determined that each of the measured metabolites (except BCIPHIPP) is also an empirical or predicted metabolite of multiple other PHOPs (Table 33). In the absence of F_{ue} values for these alternative parent/metabolite calculations, it is not possible to determine the daily intake of the three data-rich compounds vs. alternative parent compounds. However, the estimates provided in this report may still be reasonable estimates for the data-rich PHOPs, if exposure is primarily to these three chemicals. In addition, the overlap of metabolites supports the use of a class-based analysis in other parts of the overall OFR project.

Table 33. Major Empirical or Predicted Metabolites of PHOPs and Their Shared Parents

Metabolite CAS#	Metabolite Name/ Abbreviation	Parents
789440-10-4	Bis(1-Chloropropan-2-yl) phosphate/ BCPP/ BCIPP	• Tris(1,3-dichloro-2-propyl) phosphate* • Tris(2-chloroisopropyl)phosphate* • Bis(2-chloro-1-methylethyl) 2-chloropropyl phosphate • Tetrakis(1-chloropropan-2-yl) ethane-1,2-diyl bis(phosphate) • 2,2-Bis(chloromethyl)-1,3-propanediyl tetrakis(1-chloro-2-propanyl) bis(phosphate)
3040-56-0	Bis(2-chloroethyl) phosphate/ BCEP	• Tris(2-chloroethyl) phosphate* • Phosphoric acid, 1,2-ethanediyl tetrakis(2-chloroethyl) ester • Diethylene glycol bis[bis(2-chloroethyl)phosphate] • Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester (V6)* • Tris(chloroethyl) phosphate
72236-72-7	Bis(1,3-dichloro-2-propyl) phosphaten (BDCIPP)	• Tris(1,3-dichloro-2-propyl) phosphate* • 2,2-Bis(bromomethyl)-3-chloropropyl bis(2-chloro-1-(chloromethyl)ethyl) phosphate
1477495-11-6	Bis(1-chloro-2-propyl) 1-hydroxy-2-propyl phosphate (BCIPHIPP)	• Tris(1-chloro-2-propyl) phosphate* (not shared)

*Indicates relationships empirically identified

5.0 Conclusions

This report evaluated daily intake of three data-rich PHOPs, TCEP, TCIPP, and TDCIPP, based on biomonitoring data in NHANES and published literature. The overall central tendency results from the two data sources were within an order of magnitude (Table 21 and Figure 16). For most of the NHANES cycles, comparable intake was estimated for TCEP and TDCIPP, with TCIPP intake about an order of magnitude lower. Based on the NHANES data, the GM intakes were 0.034 to 0.056 µg/kg-day, 0.0083 to 0.013 µg/kg-day, and 0.058 to 0.083 µg/kg-day for TCEP, TCIPP, and TDCIPP, respectively.

Comparing the NHANES data with the results from published studies is complicated by the wide range of study designs, study populations, and sampling years (2001-2019), as well as the variety of statistical measures used by different studies (e.g., arithmetic mean, geometric mean, 50th percentile, etc.) To reflect these differences, the median of the GMs across studies (henceforth median intake) was compared with the GM from NHANES, recognizing that these are not identical measures of central tendency. The median intake estimate from the literature for each PHOP was higher than the estimate from NHANES, but the differences were within the uncertainty expected for this sort of analysis. The median intake for TCEP and TDCIPP estimated from the literature was 0.117 and 0.097 μg/kg-day, respectively, or about 2-4 fold and <2 fold the estimate from NHANES. Interpreting the estimated TCIPP intake based on the published literature is more complicated, because TCIPP intake can be estimated based on the metabolites BCIPP and BCIPHIPP each separately (with the corresponding F_{ue} values), or based on the total concentration of the two metabolites combined. The estimated intake of TCIPP from published studies was similar to that from NHANES when based on BCIPHIPP (0.022 μg/kg-day), was about a factor of 2 higher than NHANES when based on BCIPP (0.046 μg/kg-day) and the estimated intake based on the sum of the two metabolites was higher again by nearly a factor of two, at 0.077 μg/kg-day. This difference was likely related to uncertainties in the respective F_{ue} values (and was not due to double-counting). Properly estimating the F_{ue} for the TCIPP metabolites was challenging due to data gaps in the toxicokinetic data, as well as variability in the ratios of the two metabolites. Overall, the TCIPP intake estimated from literature data was about a factor of 3 to <6 or <2 to <3 above the NHANES estimates (based on BCIPP and BCIPHIPP, respectively), while the estimate based on the two metabolites combined was about a factor of <6 to <10 higher.

A few studies with blood biomonitoring data were also evaluated. However, for the one study where intake could be estimated based on both blood and urine biomarker levels, the intake estimates varied by multiple orders of magnitude. In light of the richness of the urinary biomarker data and the uncertainties associated with the blood biomarker data, the latter were not further investigated.

In the evaluation by age, the NHANES data had a trend toward decreasing intake with increasing age, and intake for the 3-5 year-olds was
several fold higher than that of the 6-11 year olds. No data were available from NHANES for the children under 3 years old. Comparison by age was harder with the published data, but young children tended to have somewhat higher estimated daily intake (Table 32 and see the analysis of individual studies from LitStream (see Appendix Table 1 for file name)).

For all three PHOPs, the estimated daily intake of pregnant women based on NHANES data was slightly lower than that of non-pregnant women, but the variability was high, with the ASD comparable to the mean. (No formal statistical comparisons were conducted.) Individual data were used to calculate the UFR/BW for NHANES, and so this apparent difference is not due to error in estimating this parameter.

The analysis of the high exposure individuals from NHANES found that about half of the population had intakes above the GM for each of the individual PHOPs. About a third had

intake for two PHOPs above the respective GMs, and about a quarter of the population had intakes above the GM for all three PHOPs.

Probabilistic analyses were conducted for each of the PHOPs and age ranges on NHANES for the most recent complete cycle, and for five selected published studies (with all of the PHOP/population combinations in those publications). As expected, almost all of the daily intake distributions were lognormal. The distributions from the NHANES and literature data were all right-skewed.

Of the biomarkers evaluated in this report, only BCIPHIPP is likely to be unique to the parent for which intake was estimated; all others are (measured or predicted) metabolites of multiple PHOPs. However, the intake of TCIPP estimated from concentrations of BCIPHIPP were similar to that estimated from the other TCIPP metabolite, BCIPP, even though three other PHOPs may be metabolized to BCIPP. The suggests that the current analysis provides reasonable estimates of the intake of TCIPP, despite the uncertainties listed in the discussion. Similarly, BDCIPP and BCEP may be providing reasonable estimates of TDCIPP and TCEP, respectively, even though these chemicals are also (or may be) metabolites of other PHOPs, if much of the exposure is to TDCIPP and TCEP.

Overall, the analyses described in this report can support further exposure analyses by CPSC staff of the subject PHOPs, with the NHANES results supported by published data.

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8.0 Appendix

Table A1. Titles of Supporting Documents and File Names

Title Name	File Name
PHOP TK Extraction and F_{ue} Estimation	PHOP tk extraction and Fue estimation-3.20.24.xlsx
Raw extracted data from Litstream for full extraction	Task 16 PHOP Full extraction results from Litstream_8.1.23 submit.xlsx
Phthalate TK Extraction and F_{ue} Estimation	Phthalate Fue data and calculations-3.20.24.xlsx
R code for NHANES Deterministic Calculations	1.NHANES_v14.R
R code for NHANES Probabilistic Calculations	3.Probablistic results_NHANES_v4.R
R code for data cleaning of Litstream blood/plasma/serum data	Litstream analysis_blood.R
R code for Litstream Deterministic Calculations	2.Urine_Litstream analysis_v7.R
R code for Litstream Probabilistic Calculations (BCEP)	4.Probablistic results_litstream_1.BCEP_v5.R
R code for Litstream Probabilistic Calculations (BCIPP)	4.Probablistic results_litstream_2.BCIPP_v5.R
R code for Litstream Probabilistic Calculations (BDCIPP)	4.Probablistic results_litstream_3.BDCIPP_v5.R
ICC Calculation and ICC-modified GSD calculations	PHOP ICCs_extracted data and GSD analyses.xlsx
Documentation of columns to keep during data cleanup of raw Litstream output for urine analyses	PHOP Litstream columns to keep_Urine.xlsx
Documentation of columns to keep during data cleanup of raw Litstream output for blood/serum/plasma analyses	PHOP Litstream columns to keep_Blood.xlsx
NHANES Variables to Use	NHANES Variables to use - all cycles 3.20.24.xlsx
Litstream variables for analysis	Literature Variables to use 3.20.24.xlsx

Additional parameters to be used for probabilistic analyses, including shapes of distributions	Distributional parameters to use 3.20.24.xlsx
NHANES deterministic results	NHANES_result_tables 2.24.24.xlsx
NHANES deterministic results with figures	NHANES_result_tables_FIGURES_6.7.24.xlsx
NHANES probabilistic results with figures	Distributional_data_results_NHANES_final_3.20.24.xlsx
Litstream deterministic results with figures	Litstream_data_wide_results_final-3.20.24.xlsx
Litstream probabilistic results with figures	Distributional_data_results_LitStream_final-3.20.24.xlsx
Litstream deterministic results for blood/serum/plasma measurements	PHOP blood-serum-plasma based daily intake calculations 12.4.23.xlsx

All cycles of NHANES data were directly downloaded from NHANES (.XPT) format. These datasets are already publicly available. These raw data were transformed using SAS and further processed using excel and R (see Section 2.1.3).