MEMORANDUM

To: Eric Hooker, Matthew Cho, and Kristina Hatlelid, CPSC

From: Samantha Snow, Joei Robertson, and Elizabeth Martin, ICF
Mark Bradley and Lynne Haber, University of Cincinnati

Date: April 12, 2024

Re: Task 1B: Identify chemicals and studies that have sufficient information and quantify a toxicity reference value(s) in two subclasses
(CPSC Contract Number 61320622A0005, CPSC Order Number 61320623F2030)

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1. Introduction

Under CO-9, subtask 1B seeks to identify dose-response data for calculating screening-level toxicity reference values (TRVs) that can be used in class-based dose response and class-based risk assessment for two organohalogen flame retardant (OFR) subclasses (polyhalogenated organophosphates, PHOPs; and polyhalogenated bisphenol aliphatics and functionalized, PHBAF). This subtask was built on the review of agency assessments conducted for all PHOP and PHBAF OFRs under subtask 1A of this contract as well as the CPSC co-sponsored scoping review project with the National Institute of Environmental Health Sciences (NIEHS) Division of Translational Toxicology (DTT). This memo describes the data sources considered and a summary of the data found and TRVs calculated.

2. Identification of Chemicals and Studies with Quantitative Data for Screening-level TRV Derivation

2.1. Identification of Chemicals for Modeling

PHOP and PHBAF chemicals with an existing quantitative TRV from subtask 1A were excluded from this subtask. For the purpose of identifying chemicals to exclude, cancer and non-cancer endpoints were considered separately (i.e., if a chemical was found to have a non-cancer TRV in subtask 1A but no cancer TRV was identified, it was excluded from further non-cancer assessment but included for further cancer assessment). For the purpose of identifying chemicals that already have a quantitative TRV, margins of exposure (MOE, defined as the ratio of a point of departure [POD; e.g., BMDL or NOAEL] to some measure of exposure) identified in subtask 1A were treated as "non-quantitative." The existence of an assessment using an MOE approach did not exclude a chemical from subtask 1B (i.e., a chemical with an MOE but not a quantitative TRV was treated as not having a TRV and was included for looking for additional data to calculate a TRV). In addition to looking for new data for chemicals that had an MOE but not a quantitative TRV, the data used to derive the MOE were used in one of two ways. First, if the principal study used to identify the POD in the MOE assessment was available, the original data were used to model a BMDL (or to directly use the NOAEL or LOAEL if the data did not pass statistical checks for BMD modeling). Otherwise, if the principal study was not available, the POD as cited in the assessment was used directly. Uncertainty factors for data identified via MOE assessments were derived in the same manner as for any other study. The way that specific studies identified from MOE approaches were used is discussed in the following paragraphs, separated for PHOPs and PHBAFs.

Three PHOPs (TCEP/115-96-8, TDCIPP/13674-87-8, and TCIPP/13674-84-5; for full chemical names of these and other acronyms, see Appendix Table A-1) have existing quantitative non-cancer TRVs identified from subtask 1A

(TCEP has two existing TRVs, whereas TDCIPP and TCIPP have one each) and were thus excluded from this task for non-cancer endpoints. Additionally, for one PHOP (V6/38051-10-4), while there were no existing quantitative TRVs from subtask 1A, data on two studies were available from one MOE-based assessment (ECHA, 2008; Table 1) that can be used to derive a quantitative non-cancer TRV. Thus, this MOE assessment served as the basis for calculating a new TRV for V6, and V6 was included for looking for additional studies with data suitable for deriving a TRV. The principal studies cited in this MOE approach are unpublished reports (CIT, 2001; TNO Quality of Life, 2007)[1], and so the PODs as identified by ECHA (2008) were used directly to calculate a TRV. All other PHOPs were included when looking for additional data to derive non-cancer TRVs.

For cancer, three PHOPs (TCEP/115-96-8, TDCIPP/13674-87-8, and TDBPP/126-72-7) have existing quantitative TRVs identified from subtask 1A (TCEP has two existing cancer TRVs, whereas TDCIPP and TDBPP have one each), and were excluded from this task for cancer endpoints. One more PHOP (TCIPP/13674-84-5) has an existing publication (NTP, 2023; Table 1) with data available that can be used to derive a quantitative TRV. All other PHOPs were included when looking for additional data to derive cancer TRVs.

All PHBAFs were included for this subtask to look for additional studies that could be used to derive both cancer TRVs and non-cancer TRVs, because no PHBAF chemical had a quantitative TRV identified in subtask 1A. No cancer assessments were identified in subtask 1A for any PHBAF chemicals. Only one PHBAF (TBBPA/79-94-7) had any existing assessments available to be screened for non-cancer TRVs in subtask 1A; all three assessments used MOE approaches (principal studies: Fukuda et al., 2004; Tada et al., 2006; Van der Ven et al., 2008). All three principal studies were included in the references sourced from DTT. Two of these principal studies (Tada et al., 2007; Van der Ven et al., 2008) were selected for modeling and derivation of a TRV. The third of these principal studies (Fukuda et al., 2004) was not selected for modeling as it did not have a shared endpoint with other PHBAF chemicals and was thus deprioritized for this subtask (for more detail on study selection process, see Section 2.2).

2.2. Identification of Studies for Modeling

To identify studies for modeling, the provided output of 2,474 studies from the DTT screening project (incorporated as part of Attachment 1) was used to identify 333 studies that addressed PHOPs and PHBAFs (Figure 1). Three additional publications identified by experts as part of subtask 1A (as described above) were also included. The first was the NTP (2023) report on TCIPP, which was published after DTT conducted the screening literature search. The second and third studies were both unpublished studies summarized by ECHA (2008): a two-generation study of V6 in feed (TNO Quality of Life, 2007) and a 28-day gavage study of V6 (CIT, 2001). The DTT literature search would not have captured either of these studies since gray literature was not included in the DTT search and thus would not have captured ECHA assessments.

The identified studies were then progressively narrowed down to select studies for modeling (Figure 1). Studies with DTT-identified data on chemicals with a TRV identified in subtask 1A were excluded. Non-mammalian studies from the DTT-identified data were also excluded. Among the remaining species only rats, mice, and humans were available for the chemicals of interest. No data from other mammalian species were available. These studies were evaluated as described below to select studies and endpoints for modeling.

To further a class-based assessment, identifying shared health endpoints/targets is a critical step. To this end, key adverse effect types and target organ systems identified in subtask 1A for PHOPs and for PHBAFs were prioritized for derivation of TRVs for additional chemicals in subtask 1B. For PHOPs, these endpoints were developmental, endocrine, hepatic, renal, and reproductive. For PHBAFs, these endpoints were endocrine, hepatic, and renal (identified solely based on MOEs). In addition, while screening papers for one PHBAF chemical (TBBPA), several

[1] The two unpublished reports identified in ECHA, 2008 include "CIT (2001); 4 week toxicity study by oral route (gavage) in rats" and "TNO Quality of Life (2007); Oral two-generation reproduction toxicity study (including a dose-range finding study) with 2,2-Bis(chloromethyl)trimethylene bis[bis(2-chloroethyl)phosphate] (TL 10 ST) in rats".

studies repeatedly reported additional adverse effect types and target organ systems. These were subsequently included to evaluate for TRV derivation, and include reproductive, developmental, neurological, and immune.

Essential criteria to identify data suitable for modeling were confirmation of the correct chemical identity, studies containing at least 3 doses (including control), and studies containing a reasonable dose response (including a statistically significant difference from control in at least one dose). For papers with data suitable for modeling, additional criteria were used to select those endpoints to be modeled. These additional criteria were longer exposure duration (prefer chronic or subchronic, but shorter duration studies were included when no other options were available), oral route of exposure, and health effect data within a prioritized target organ system category. With regard to study duration, it was noted that EPA immunotoxicity test guidelines specify a 28-day exposure (US EPA, 2019), and so acute immunotoxicity studies were included. For route of exposure, studies where a relevant OFR chemical was injected (e.g., subcutaneous or intraperitoneal) were excluded as they were not environmentally relevant. For this report, only oral data are presented, as neither inhalation nor dermal studies that met inclusion criteria were found in the literature search. Each endpoint category was evaluated individually (i.e., all studies with liver effects were considered together to select the most suitable liver data for modeling). In light of this being a screening assessment and the complexity of neurotoxicity and immunotoxicity, the data available for modeling were often precursors of adverse endpoints (e.g. evaluation of decreased CD3+ cells instead of immunosuppression). While data quality was key, obtaining TRVs for overlapping/similar endpoints across chemicals in a subclass was also a consideration related to class-based assessment.

In general, biomonitoring studies were excluded. In most cases, the parent chemicals already had an existing TRV. Additionally, while the metabolite may be the primary source of the toxic effect, exposure assessments were provided for the parent and metabolite together making it difficult to disentangle the effect of co-exposures.

Data that were not suitable for BMD modeling but could provide a LOAEL/NOAEL were also included, for use as additional points of departure (PODs).

For most chemicals with available data, there were a minimal number of studies/endpoints such that all (or nearly all) with suitable data were selected for modeling. In contrast, there were 60 studies on TBBPA with data suitable for modeling, out of the identified 68 PHBAF studies from DTT. Endpoints that were available for other PHBAF chemicals were used to narrow down endpoints to model for TBBPA. This approach allowed for broader coverage of chemicals that had far fewer available studies for similar endpoints based on the charge to look at these chemicals in a class-based manner. These endpoints were endocrine, reproductive, neurodevelopmental, immune, and cancer/nonneoplastic effects. No renal endpoints were chosen for modeling because only TBBPA had any data on renal effects. Other endpoints that were shared between TBBPA and other PHBAF chemicals were prioritized for modeling instead.

When papers were deemed not suitable for modeling, or were suitable but not chosen for modeling in favor of other data, the following reasons for exclusion were documented:

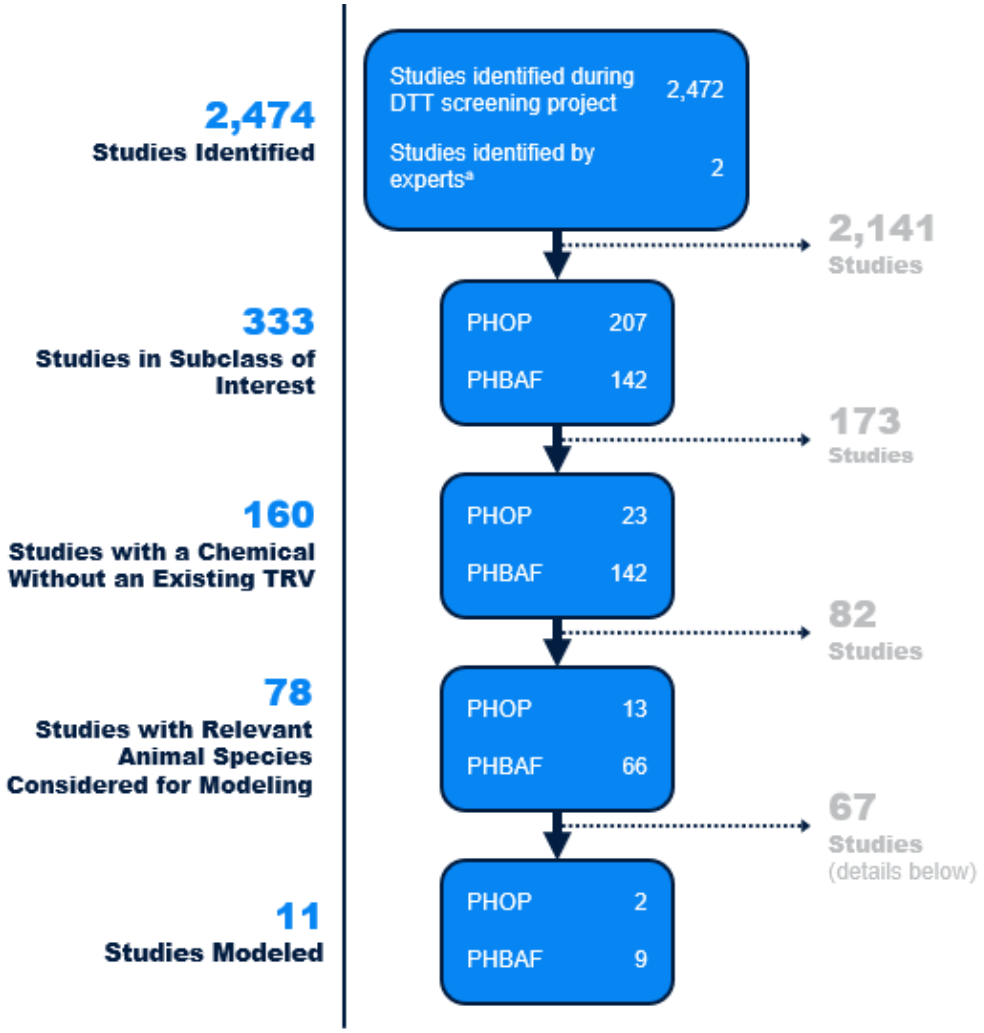
- Considered for Modeling but Other Data Selected to Model for this Chemical
- Data Presentation is Not Suitable for Modeling
- No Dose Response Effects Observed
- No Relevant Endpoints
- Not Relevant Chemical
- Only One Exposed Group
- Overlapping Dataset with NTP Study
- Parent Chemical Has Existing TRV
- Not an Environmentally Relevant Route

- PDF Not Found

It is possible that a single paper matched multiple criteria for exclusion. Such cases were identified by the first observed reason for exclusion, and not an exhaustive list of reasons (see Attachment 1).

These processes ultimately identified 2 PHOP and 9 PHBAF studies to extract and model (Table 1).

Figure 1. Decision Tree for Identifying Studies to Model



Studies Not Included for Modeling

Only one exposed group[b]	26	Data presentation is not suitable for modeling	3
No relevant endpoints	9	Overlapping dataset with NTP study	3
Considered for modeling but other data selected to model for these chemicals	8	Not relevant chemical	2
No dose response effects observed	7	PDF not found	2
Parent chemical has existing TRV[b]	6	Not an environmentally relevant route	2

[a] Studies identified by experts include a recent NTP report on TCIPP identified by CPSC clients that was published after the search was conducted for the DTT OFR screening project (NTP, 2023) and an assessment identified in subtask 1A on V6 that only listed margin of exposure data (ECHA, 2008) based on two unpublished reports (CIT, 2001; TNO Quality of Life, 2007).
[b] One study counted across two categories based on separate determination for PHOP and PHBAF chemicals included in study.

Table 12. Chemicals and Endpoints Identified for Modeling

Distiller ID	Study	Chemical Name (Acronym[a])	CASRN	Species, Strain (Sex)	Route of Exposure	Duration of Exposure	Exposure Scenario	Endpoints Selected for Modeling[b]
PHOPs								
Expert Identified 1	NTP, 2023	Tris(chloropropyl) phosphate[c] (TCIPP)	13674-84-5	Rats, Sprague Dawley (male, female considered separately)[d]	Oral — Feed	2yr	Exposed daily via feed for 2yr	*Increased Hepatocellular Adenoma or Carcinoma; Increased Uterine Adenoma or Adenocarcinoma*
				Mice, B6C3F1/N (male, female considered separately)[d]	Oral — Feed	2yr	Exposed daily via feed for 2yr	*Increased Hepatocellular Carcinoma; Increased Hepatocellular Adenoma or Carcinoma*
Expert Identified 2	ECHA, 2008	2,2-Bis(chloromethyl) trimethylene bis[bis(2-chloroethyl) phosphate] (BCMP-BCEP; also known as V6)	38051-10-4	Rats, Wistar outbred Crl:WI(WU) (both)	Oral — Feed	Two-Generation	Exposed via feed from the start of the study, during the premating period of at least 10 weeks, during mating, gestation, and lactation until sacrifice	Increased Number of Runts
				Rats, Sprague Dawley (both)	Oral — Gavage	28d	Exposed once daily via gavage for 28d	Increased Relative Liver Weight
PHBAFs								
60	Shockley et al., 2020	Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) (TBBPA-BDBPE)	21850-44-2	Rats, Sprague Dawley (male)	Oral — Gavage	5d	Exposed once daily via gavage for 5d	Decreased Serum T4 Concentrations
33254397	Wang et al., 2021	2,2',6,6'-Tetrachlorobisphenol A (TCBPA)	79-95-8	Mice, BALB/c (female)	Oral — Gavage	14d	Exposed once daily via gavage for 14d	Increased Treg Lymphocyte Percentage; Decreased $CD3^+$ T Lymphocyte Percentage

Distiller ID	Study	Chemical Name (Acronym[a])	CASRN	Species, Strain (Sex)	Route of Exposure	Duration of Exposure	Exposure Scenario	Endpoints Selected for Modeling[b]
33360189	Zhang et al., 2021	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	79-94-7	Mice, BALB/c (female)	Oral — Gavage	28d	Exposed once daily via gavage for 28d	Decreased $CD3^+$ T Lymphocyte Percentage; Treg Lymphocyte Percentage; Decreased $CD3^+$/Treg Ratio
24278553	Choi et al., 2011	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	79-94-7	Rats, Sprague Dawley (male)	Oral — Gavage	30d	Exposed once daily via gavage for 30d from PND 18 to PND 48	Decreased Relative Thyroid Gland Weight; Decreased Serum T4 Concentrations
18255212	Van de Ven et al., 2008	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	79-94-7	Rats, Wistar (male, female considered separately)[d]	Oral — Dietary	One-Generation	Exposed via feed starting 70 (males) or 14 (females) days prior to mating and continued during pregnancy and lactation	Decreased Serum T4 Concentrations
33546521	NTP, 2014	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	79-94-7	Rats, F344/NTac (male, female considered separately)[d]	Oral — Gavage	3mo	Exposed once daily via gavage 5d/wk for 3mo	Decreased Serum T4 Concentrations
				Rats, Wistar Han (female)	Oral — Gavage	2yr	Exposed once daily via gavage 5d/wk for 2yr	Increased Atypical Endometrium Hyperplasia; *Increased Adenoma, Adenocarcinoma, or Malignant Mixed Mullerian Tumor*
				Mice, B6C3F1/N (male)	Oral — Gavage	2yr	Exposed once daily via gavage 5d/wk for 2yr	Increased Eosinophilic Focus; *Increased Hepatocellular Adenoma*
21783755	Tada et al., 2007	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	79-94-7	Mice, ICR (male)	Oral — Gavage	14d	Exposed once daily via gavage for 14d	Increased Relative Liver Weight; Increased Hepatic Inflammatory Cell Infiltration; Increased Focal Necrosis of Hepatocytes

Distiller ID	Study	Chemical Name (Acronym[a])	CASRN	Species, Strain (Sex)	Route of Exposure	Duration of Exposure	Exposure Scenario	Endpoints Selected for Modeling[b]
28564613	Kim et al., 2017	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	79-94-7	Mice, C57BL/6 (male)	Oral — Gavage	14d	Exposed once daily via gavage for 14d	Decreased Survival and Neuronal Differentiation (BrdU Positive Cells); Increased Activation of Microglia (Anti-Iba-1 Immunostaining); Increased activation of Astrocyte (Anti-GFAP Immunostaining) Cells; Decreased Memory Retention (Latency Time in Passive Avoidance Test)
31541695	Rock et al., 2019	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	79-94-7	Rats, Wistar Han (male)	Oral — Gavage	GD 9 – PND 90	Exposed once daily via gavage from GD9 to PND 21 (Dam), and PND 22 – 90 (Offspring)	Decreased Latency to Enter Center; Decreased Open Arm Entries

PHOPs = polyhalogenated organophosphates; PHBAFs = polyhalogenated bisphenol aliphatics and functionalized; T4 = total thyroxine; PND = postnatal day; GD = gestation day

[a] Chemical acronyms were assigned from Bergman et al., 2012 when available. When not available, acronyms were assigned to align as closely as possible with Bergman et al., 2012 and to avoid potential confusion between different chemicals.

[b] Cancer endpoints are italicized.

[c] This NTP study used a commercial mixture identified as Tris(chloropropyl) phosphate. Chemical characterization of the mixture identified four isomers: ~65% tris(1-chloro-2-propyl) phosphate (CASRN 13674-84-5), ~25% bis(2-chloro-1-methylethyl) 2-chloropropyl, phosphate (isomer 2, CASRN 76025-08-6), ~4% bis(2-chloropropyl) 2-chloroisopropyl phosphate (isomer 3, CASRN 76649-15-5), and ~0.2% tris(2-chloropropyl) phosphate (isomer 4, CASRN 6145-73-9). Only cancer endpoints from this study were modeled, because an existing non-cancer TRV for this chemical was identified in subtask 1A.

[d] For NPT, 2023, Van der Ven et al. 2008, and NTP, 2014, male and female outcomes were presented separately rather than together and were thus modeled separately and counted as separate endpoints in the text.

3. BMD Modeling and Deriving TRVs

3.1. Derivation of Point of Departures

Preparing the Data for Modeling

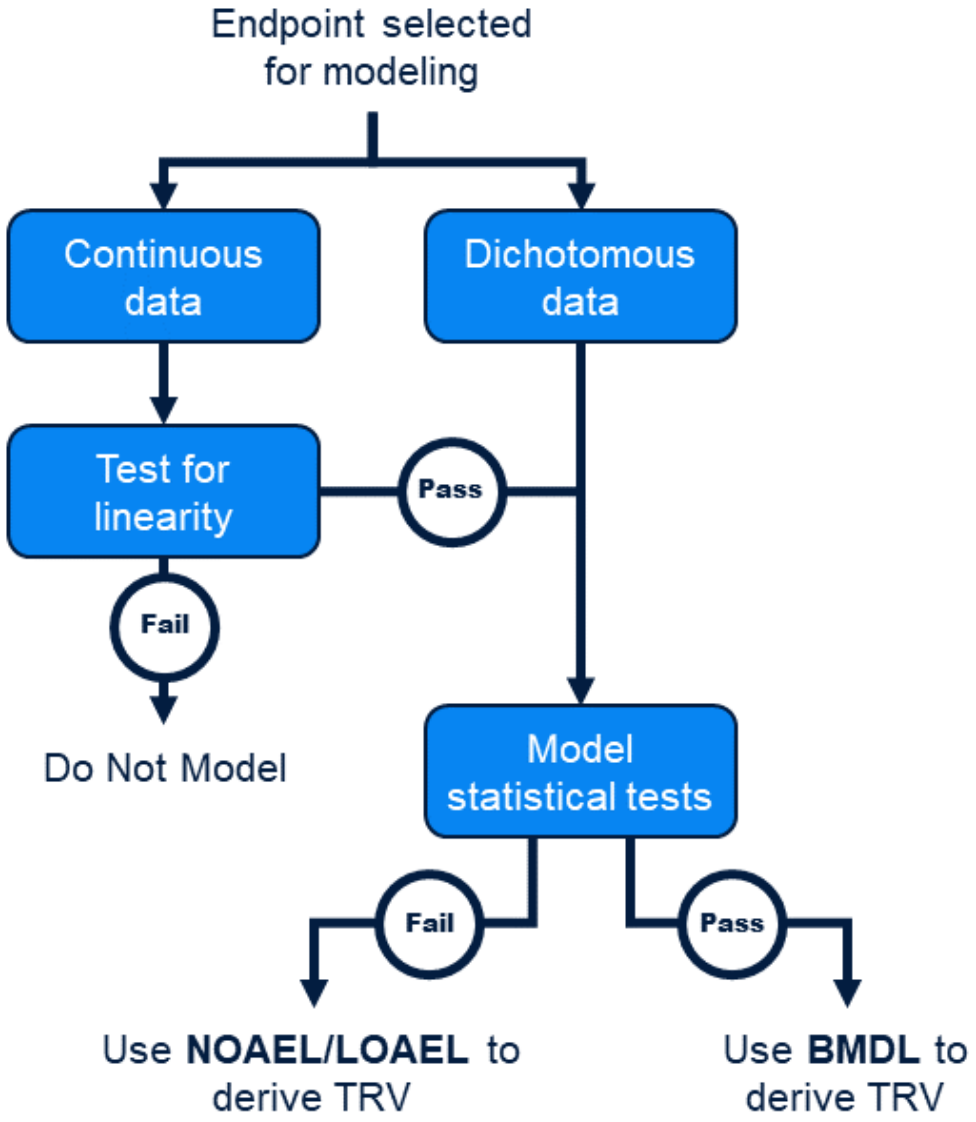
To model TRVs, data were extracted from 11 studies listed in Table 1. Specifically, 25 non-cancer endpoints and 6 cancer endpoints were extracted (when the same study presented the same endpoint data separately for males and females, that counts as 2 endpoints). To prepare data for point of departure (POD) modeling by benchmark dose modeling (BMD), data were extracted from papers into individual EXCEL® worksheets. Each endpoint was extracted into a separate sheet and each paper received a separate workbook. Table values were extracted directly into sheets, while WebPlotDigitizer was used to estimate the mean and standard deviation/standard error of the mean from figures. Data were then QC'd for correctness by senior staff.

Prior to modeling, incidence values were converted from values in proportion (%) to number of cases based on sample size, doses in µmol/kg/day were converted to mg/kg/day based on molecular weights, and standard error of the means were converted to standard deviation. No conversion from ppm in feed to mg/kg/day was needed because the studies in which dosing was in feed provided the corresponding doses in mg/kg/day. A total of 8 dichotomous endpoints (all cancer endpoints plus hepatic inflammatory cell infiltration and focal necrosis of hepatocytes from Tada et al., (2007)) and 23 continuous endpoints (all remaining non-cancer endpoints) were extracted for modeling. Among these are endpoints identified from MOE assessments reviewed in subtask 1A, including: two endpoints for V6 (increased number of runts and increased relative liver weight, from two unpublished studies cited by ECHA (2008)), and five endpoints for TBBPA (decreased serum T4 in both male and female rats, Van de Ven et al. (2008); increased relative liver weight, increased hepatic inflammatory cell infiltration, and increased focal necrosis of hepatocytes, Tada et al. (2007)). A third study on TBBPA (Fukuda et al., 2004) used as a principal study for an additional MOE assessment reviewed in subtask 1A is not included here, as data on the included endpoint (relative kidney weight) were not available for other PHBAF chemicals (see also Section 2). Since the original data from the unpublished studies on V6 were not available, TRVs for these endpoints were derived directly from the provided PODs instead of calculating a BMDL.

Testing Data to Verify Modeling Suitability

Once data were prepared, they were assessed to verify suitability for modeling (Figure 2). For dichotomous data, all data were graphed and determined to be suitable, given that each endpoint had an author reported statistically significant change for at least one dose group. Therefore, all 10 of 10 dichotomous endpoints were modeled using a Bayesian approach. For continuous endpoints, data were tested for linearity using the Cochran-Armitage test for trend. If the test was not statistically significant, data were not modeled at all. These data can be found in the following location on Teams: CPSC-ICF: Toxicological, Exposure, and Risk Assessments -> CO-9 Class-Based Dose-Response -> 01 – Deliverables -> Subtask 1B -> Attachment 2 – Graphs of Data Not Modeled. This resulted in 6 of 21 continuous endpoints (e.g., CD3+ T Lymphocyte Percentage in two studies, Treg Lymphocyte Percentage, Relative Thyroid Gland Weight, Activation of Microglia (Anti-Iba-1 Immunostaining), and Activation of Astrocyte (Anti-GFAP Immunostaining)) being dropped from further evaluation, for a total of 15 endpoints that were suitable for BMD modeling (Table 2, Table 3).

Figure 23. Decision Tree for Modeling Data



*Model statistical tests include Akaike information criteria (AIC), goodness of fit p-value, standard deviation of the model vs. input data, and BMD/BMDL ratio

Table 24. Summary of Modeling Statistical Checks for Non-Cancer Endpoints and Resulting Point of Departure Type for Derivation of TRV

Study Author	Chemical Name (Acronym[a])	Endpoint Modeled	Test of Linearity	Notes on BMD Modeling Fits	Type of Point of Departure Selected to Derive TRV
PHOPs					
ECHA, 2008	2,2-Bis(chloromethyl) trimethylene bis[bis(2-chloroethyl) phosphate] (BCMP-BCEP; also known as V6)	Number of Runts	N/A[b]	N/A	NOAEL
		Relative Liver Weight	N/A[b]	N/A	NOAEL
PHBAFs					
Shockley et al., 2020	Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) (TBBPA-BDBPE)	Serum T4 Concentrations	Pass	Model p>0.05, modeled control std dev>|1.5| actual response	NOAEL
Wang et al., 2021	2,2',6,6'-Tetrachlorobisphenol A (TCBPA)	Treg Lymphocyte Percentage	Pass	No models converged	LOAEL
		$CD3^+$ T Lymphocyte Percentage	Fail (p>0.05)	—[c]	None — Data failed trend test for linearity
Zhang et al., 2021	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	$CD3^+$ T Lymphocyte Percentage	Fail (p>0.05)	—[c]	None — Data failed trend test for linearity
		$CD3^+$/Treg Ratio	Pass	No models converged	LOAEL
		Treg Lymphocyte Percentage	Fail (p>0.05)	—[c]	None — Data failed trend test for linearity
Choi et al., 2011	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	Serum T4 Concentrations	Pass	Model p>0.05, modeled control std dev>|1.5| actual response	NOAEL
		Relative Thyroid Gland Weight	Fail (p>0.05)	—[c]	None — Data failed trend test for linearity
Van de Ven et al., 2008	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	Serum T4 Concentrations (Females)	Pass	model p>0.05, modeled control std dev>|1.5| actual response	NOAEL
		Serum T4 Concentrations (Males)	Pass	No models converged	LOAEL
NTP, 2014	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	Serum T4 Concentrations (Females)	Pass	Model passed — BMDL selected	BMDL[d] 1) BMDS — Hill (CV — normal) 2) BMDS — Average of BMDLs

Study Author	Chemical Name (Acronym[a])	Endpoint Modeled	Test of Linearity	Notes on BMD Modeling Fits	Type of Point of Departure Selected to Derive TRV
					3) BBMD — Bayesian Model Average
		Serum T4 Concentrations (Males)	Pass	Model passed — BMDL selected	BMDL[d] 1) BMDS — Hill (CV — normal) 2) BMDS — Average of BMDLs 3) BBMD — Bayesian Model Average
		Atypical Endometrium Hyperplasia	Pass	BMD/BMDL ratio > 3, BMDL 3x lower than lowest non-zero dose	LOAEL
		Eosinophilic Focus	Pass	Model passed — BMDL selected	BMDL[e] 1) BMDS — Bayesian Model Average
Tada et al., 2007	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	Relative Liver Weight	Pass	BMD/BMDL ratio > 3, BMDL 3x lower than lowest non-zero dose	NOAEL
		Inflammatory Cell Infiltration	Pass	BMDL 10x lower than lowest dose	LOAEL
		Focal Necrosis of Hepatocytes	Pass	BMD 3x lower than lowest non-zero dose, BMDL 3x lower than lowest non-zero dose	NOAEL
Kim et al., 2017	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	Decreased Survival and Neuronal Differentiation (BrdU Positive Cells)	Pass	No models converged	NOAEL
		Memory Retention (Latency Time)	Pass	Model p>0.05, BMDL 3x lower than lowest non-zero dose	NOAEL
		Activation of Microglia (Anti-Iba-1 Immunostaining)	Fail (p>0.05)	—[c]	None — Data failed trend test for linearity
		Astrocyte (Anti-GFAP Immunostaining)	Fail (p>0.05)	—[c]	None — Data failed trend test for linearity
Rock et al., 2019	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	Latency to Enter Center	Pass	No models converged	None — Data did not have a distribution suitable for NOAEL/LOAEL selection
		Open Arm Entries	Pass	Model p>0.05, BMD higher than maximum dose	LOAEL

BMD = benchmark dose; TRV = toxicity reference value; PHOPs = polyhalogenated organophosphates; PHBAFs = polyhalogenated bisphenol aliphatics and functionalized; NOAEL = no observed adverse effect level; N/A = not applicable; LOAEL = lowest observed adverse effect level; BMDL = benchmark dose (lower confidence limit); BMDS = EPA's

Benchmark Dose Software; BBMD = Bayesian BMD online tool.

[a] Chemical acronyms were assigned from Bergman et al., 2012 when available. When not available, acronyms were assigned to align as closely as possible with Bergman et al., 2012 and to avoid potential confusion between different chemicals.

[b] BMD modeling was not conducted on these endpoints; NOAEL was extracted from the assessment identified from subtask 1A (ECHA, 2008).

[C] Not applicable, endpoint did not move forward for BMD modeling.

[d] For continuous endpoints where a BMDL was recommended, three methods were used to derive a BMDL because BMDS does not yet include Bayesian model averaging for continuous endpoints.

[e] For dichotomous endpoints, BMDS includes Bayesian model averaging, so no additional methods were used to derive additional BMDLs.

Table 3. Summary of Modeling Statistical Checks for Cancer Endpoints and Resulting Point of Departure Type for Derivation of TRV

Study Name	Chemical Name (Acronym[a])	Endpoint Modeled	Test of Linearity	Notes on BMD Modeling Fits	Type of Point of Departure Selected to Derive TRV
PHOPs					
NTP, 2023	Tris(chloropropyl) phosphate (TCIPP)	Hepatocellular Adenoma or Carcinoma (Male Rats)	Pass	Model passed — BMDL selected	BMDL 1) BMDS — Bayesian Model Average
		Uterine Adenoma or Adenocarcinoma (Female Rats)	Pass	Model passed — BMDL selected	BMDL 1) BMDS — Bayesian Model Average
		Hepatocellular Carcinoma (Male Mice)	Pass	Model passed — BMDL selected	BMDL 1) BMDS — Bayesian Model Average
		Hepatocellular Adenoma or Carcinoma (Female Mice)	Pass	Model passed — BMDL selected	BMDL 1) BMDS — Bayesian Model Average
PHBAFs					
NTP, 2014	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	Adenoma, Adenocarcinoma, or Malignant Mixed Mullerian Tumor	Pass	Model passed — BMDL selected	BMDL 1) BMDS — Bayesian Model Average
		Hepatocellular Adenoma Multiple	Pass	Model passed — BMDL selected	BMDL 1) BMDS — Bayesian Model Average

BMD = benchmark dose; TRV = toxicity reference value; PHOPs = polyhalogenated organophosphates; BMDL = benchmark dose (lower confidence limit); BMDS = EPA's Benchmark Dose Software; PHBAFs = polyhalogenated bisphenol aliphatics and functionalized.

[a] Chemical acronyms were assigned from Bergman et al., 2012 when available. When not available, acronyms were assigned to align as closely as possible with Bergman et al., 2012 and to avoid potential confusion between different chemicals.

[b] For dichotomous endpoints, BMDS includes Bayesian model averaging, so no additional methods were used to derive additional BMDLs.

Dichotomous Data

For dichotomous data, Bayesian models were run using EPA's BMDS 3.3.2 under the following conditions: risk type= extra risk, benchmark response (BMR) = 0.1, and confidence level = 0.95. All possible models were enabled, and model averaging was conducted assuming equal prior weights. The maximum multistage was set to degree = 3. Bayesian model averaging was used, as it better reflects the uncertainty in the dose response data compared to using single models. One dichotomous endpoint (Atypical Endometrium Hyperplasia, Table 2) could not be adequately fit with the BMD modeling, as the BMDL was 3 times lower than the lowest dose in the study and the BMD/BMDL ratio was >3 (see Appendix B for full model results). In this case, a NOAEL/LOAEL approach was taken to estimate the point of departure.

Continuous Data

For continuous data, frequentist models were run using EPA's BMDS 3.3.2 under the following conditions: BMR Type = Std.Dev, BMRF = 1, Max polynomial = n-1, adverse direction = auto, distribution = normal, and variance = constant. All possible models were enabled. The recommended model is presented first as 1) BMDS – [Name of Recommended Model]. To better capture the uncertainty in the dose response data, two additional model outputs are reported: 2) BMDS — Average of BMDLs, which is the averaging of all viable models with acceptable residuals and p-values as well as similar Akaike information criteria (AICs); and 3) BBMD — Bayesian Model Average, which is the average of Bayesian models run using the online BBMD 2.2.1 tool. Unlike EPA's BMDS software, BBMD can conduct Bayesian model averaging for continuous endpoints, but BBMD and BMDS differ in their approach for priors. Table 4 presents the results for all three approaches to the modeling of continuous data.

It is important to note that a large percentage of the continuous endpoints did not move forward for modeling and/or TRV derivation. For continuous data, 7 of the 16 endpoints that were modeled did not converge, and so no BMDL could be calculated. Additionally, 5 of the 16 endpoints had models that did converge but were not recommended as they met two of the five exclusion criteria: (1) the p-value of the model was greater than 0.05, (2) BMDL was 3 times lower than the lowest presented dose in the study, (3) the BMD/BMDL ratio was >3 (4) modeled control std dev was >|1.5| the actual response, or (5) the modeled BMD was higher than maximum dose presented in the study. In the cases of failure to converge or model exclusion, a NOAEL/LOAEL approach was utilized. Specifically, the POD was set at the NOAEL if available. If no NOAEL was determinable, the LOAEL was used instead. For those endpoints for which POD derivation was attempted by BMD modeling, all possible models are presented in Appendix B. The original output files from BMDS can be found in the following location on Teams: CPSC-ICF: Toxicological, Exposure, and Risk Assessments -> CO-9 Class-Based Dose-Response -> 01 – Deliverables -> Subtask 1B -> Attachment 3 – BMDS Output Files.

Derivation of Toxicity Reference Values

Once the PODs were obtained using the guidelines listed above, TRVs (Table 4 and Table 5) were derived using the following approaches.

For non-cancer endpoints (Table 4) the following uncertainty factors were applied to all outcomes: Interspecies variability = 10 and Intraspecies variability = 10. When modeling did not result in a recommended BMDL, a NOAEL (or if necessary, a LOAEL) was used as a POD. For studies that utilized a LOAEL instead of a BMDL/NOAEL, an additional uncertainty factor of 10 was applied. When subchronic data were modeled, two TRVs were calculated, one with a duration uncertainty factor of 3 and another with this uncertainty factor set to 10; both of the resulting TRVs are shown in Table 4. The maximum total uncertainty factor used to derive a TRV is 3,000. In instances when all four uncertainty factors had a value of 10, a composite uncertainty factor of 3,000 was used instead of 10,000. When acute data were identified (here defined as ≤5 days), potential PODs are presented but TRVs were not derived for acute endpoints.

For studies that measured continuous outcomes and had statistically valid BMD models, three separate TRVs are presented in Table 4. The three TRVs in these cases were derived using the same set of uncertainty factors, but using PODs derived from three different modeling approaches: 1) the lowest AIC valid model (in BMDS), 2) BMDL averaging across all valid models (in BMDS), and 3) Bayesian BMD model averaging (in BBMD). As noted in Section

3.3.4, these three methods were used to better capture the uncertainty in the dose response data, in the absence of Bayesian model averaging capability for continuous data in EPA's BMDS.

For cancer outcomes (Table 5), a slope factor was calculated using the standard approach of 0.1/BMDL10. In addition, a risk-specific dose was calculated to estimate the dose that would lead to a one in one million lifetime excess cancer risk, as (10^{-6})/(slope factor).

Table 4. Points of Departure and Toxicity Reference Values (TRVs) for Non-Cancer Endpoints

Study Name	Chemical Name (Acronym[a])	Exposure Duration	Endpoint Modeled	POD Type	BMDL Model Used	POD (mg/kg/day)	Uncertainty Factors	TRV Value
PHOPs								
ECHA, 2008	2,2-Bis(chloromethyl) trimethylene bis[bis(2-chloroethyl) phosphate] (BCMP-BCEP; also known as V6)	Two-Generation	Number of Runts	NOAEL	N/A	29	Interspecies = 10 Intraspecies = 10 Subchronic = 1 LOAEL = 1	0.3
		28d	Relative Liver Weight	NOAEL	N/A	15	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10*[c] LOAEL = 1	0.02, 0.05
PHBAFs								
Shockley et al., 2020	Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) (TBBPA-BDBPE)	5d	Serum T4 Concentrations	NOAEL	N/A	0.94	N/A	—[b]
Wang et al., 2021	2,2',6,6'-Tetrachlorobisphenol A (TCBPA)	14d	Treg Lymphocyte Percentage	LOAEL	N/A	5	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 10	0.002, 0.002[d]
Zhang et al., 2021	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	28d	$CD3^+$/Treg Ratio	LOAEL	N/A	5	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 10	0.002, 0.002[d]
Choi et al., 2011	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	30d	Serum T4 Concentrations	NOAEL	N/A	125	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.1, 0.4
Van de Ven et al., 2008	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	One-Generation	Serum T4 Concentrations (Females)	NOAEL	N/A	100	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.1, 0.3
			Serum T4 Concentrations (Males)	LOAEL	N/A	3	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 10	0.001, 0.001[d]

Study Name	Chemical Name (Acronym[a])	Exposure Duration	Endpoint Modeled	POD Type	BMDL Model Used	POD (mg/kg/day)	Uncertainty Factors	TRV Value
NTP, 2014	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	3mo	Serum T4 Concentrations (Females)	BMDL	1) BMDS — Hill (CV — normal)	39.5	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.04, 0.1
					2) BMDS — Average of BMDLs	40.9	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.04, 0.1
					3) BBMD — Bayesian Model Average	25.3	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.03, 0.08
			Serum T4 Concentrations (Males)	BMDL	1) BMDS — Hill (CV — normal)	53.9	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.05, 0.2
					2) BMDS — Average of BMDLs	54.5	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.06, 0.2
					3) BBMD — Bayesian Model Average	34.5	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.04, 0.1
		2yr	Eosinophilic Focus	BMDL	BMDS — Bayesian Model Average	27.1	Interspecies = 10 Intraspecies = 10 Subchronic = 1 LOAEL = 1	0.3
			Atypical Endometrium Hyperplasia	LOAEL	N/A	250	Interspecies = 10 Intraspecies = 10 Subchronic = 1 LOAEL = 10	0.3
Tada et al., 2007	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	14d	Relative Liver Weight	LOAEL	N/A	700	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 10	0.2, 0.2[d]

Study Name	Chemical Name (Acronym[a])	Exposure Duration	Endpoint Modeled	POD Type	BMDL Model Used	POD (mg/kg/day)	Uncertainty Factors	TRV Value
			Inflammatory Cell Infiltration	LOAEL	N/A	350	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 10	0.1, 0.1[d]
			Focal Necrosis of Hepatocytes	NOAEL	N/A	700	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.7, 2
Kim et al., 2017	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	14d	Decreased Survival and Neuronal Differentiation (BrdU Positive Cells)	NOAEL	N/A	20	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.02, 0.07
			Memory Retention (Latency Time)	NOAEL	N/A	20	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 1	0.02, 0.07
Rock et al., 2019	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	GD 9 – PND 21 (Dam) PND 22 – 90 (Offspring)	Open Arm Entries	LOAEL	N/A	25	Interspecies = 10 Intraspecies = 10 *Subchronic = 3, 10* LOAEL = 10	0.008, 0.008[d]

POD = point of departure; TRV = toxicity reference value; PHOPs = polyhalogenated organophosphates; NOAEL = no observed adverse effect level; N/A = not applicable; LOAEL = lowest observed adverse effect level; PHBAFs = polyhalogenated bisphenol aliphatics and functionalized; T4 = thyroxine; BMDL = benchmark dose (lower confidence limit); BMDS = EPA's Benchmark Dose Software; BBMD = Bayesian BMD.

[a] Chemical acronyms were assigned from Bergman et al., 2012 when available. When not available, acronyms were assigned to align as closely as possible with Bergman et al., 2012 and to avoid potential confusion between different chemicals.

[b] Acute exposure duration, TRV was not derived.

[c] When an endpoint from a subchronic study was used to derive a TRV, an uncertainty factor of both 3 and 10 were used to calculate two separate TRVs (this uncertainty factor will be italicized in these instances).

[d] The maximum uncertainty factor total used to derive a TRV is 3,000. In instances when all four uncertainty factors had a value of 10, a composite UF of 3,000 was used instead of 10,000.

Table 5. Points of Departure and Toxicity Reference Values (TRVs) for Cancer Endpoints

Study Name	Chemical Name (Acronym[a])	Endpoint Modeled	BMDL Value (mg/kg/day)	Cancer Slope Factor (mg/kg/day)-1	Risk Specific Dose[b] (mg/kg/day)
PHOPs					
NTP, 2023	Tris(chloropropyl) phosphate (TCIPP)	Hepatocellular Adenoma or Carcinoma (Male Rats)	578	0.0002	0.006
		Uterine Adenoma or Adenocarcinoma (Female Rats)	426	0.0002	0.004
		Hepatocellular Carcinoma (Male Mice)	26	0.004	0.0003
		Hepatocellular Adenoma or Carcinoma (Female Mice)	253	0.0004	0.003
PHBAFs					
NTP, 2014	3,3',5,5'-Tetrabromobisphenol A (TBBPA)	Uterine Adenoma, Adenocarcinoma, or Malignant Mixed Mullerian Tumor (Female Rats)	162	0.0006	0.002
		Hepatocellular Adenoma Multiple (Male Mice)	65	0.002	0.0006

BMDL = benchmark dose (lower confidence limit); PHOPs = polyhalogenated organophosphates; PHBAFs = polyhalogenated bisphenol aliphatics and functionalized.

[a] Chemical acronyms were assigned from Bergman et al., 2012 when available. When not available, acronyms were assigned to align as closely as possible with Bergman et al., 2012 and to avoid potential confusion between different chemicals.

[b] Dose that would lead to a one in one million lifetime excess cancer risk.

4. Discussion

For PHOPs, the only new non-cancer TRVs were for V6, and the calculated TRVs ranged from 0.02 to 0.3 mg/kg/day, depending on the endpoint and choice of uncertainty factors. The only new PHOP cancer slope factors were for TCIPP, and ranged from 0.0002 to 0.004 $(mg/kg/day)^{-1}$, depending on the tumor type, sex, and species. These calculated TRVs are in addition to the three PHOPs with existing quantitative non-cancer TRVs identified in subtask 1A (which ranged from 0.007 to 0.2 mg/kg/day). The cancer slope factors derived in this subtask for TCIPP are in addition to the three PHOPs with existing cancer slope factors identified in subtask 1A (which ranged from 0.02 to 2 $(mg/kg/day)^{-1}$.

For PHBAFs, non-cancer TRVs ranged from 0.001 to 2 mg/kg/day, based on serum T4 concentrations in a subchronic study of TBBPA (Van de Ven et al., 2008) and focal necrosis of hepatocytes in a 14-day study of TBBPA (Tada et al., 2007), respectively. A TRV (0.002 mg/kg/day) was also calculated for TCBPA based on a specialized endpoint in an acute study (Treg lymphocyte percentage). This was the only study for this chemical with data that could be used to develop a TRV. While similar data (e.g., specialized endpoint, acute study) potentially suitable for modeling were identified for TBBPA-BDBPE (serum T4 concentration), these data were ultimately excluded from modeling due to shorter study duration (5 days, vs. 14 days for the TCBPA study). Repeated dose studies evaluating a range of target tissues were not available for either chemical.

Only one PHBAF study had quantitative cancer data: the NTP (2014) study of TBBPA. Two types of liver tumors in female rats and male mice were modeled. The cancer slope factors were 0.0006 $(mg/kg/day)^{-1}$ for one and 0.002 $(mg/kg/day)^{-1}$ for the other. There were no existing quantitative non-cancer TRVs or cancer slope factors identified for PBHAF chemicals in subtask 1A.

An important next step for moving beyond these screening-level TRVs to choosing final TRVs for a chemical and for moving forward with a class-based assessment is to consult experts in key endpoints (e.g., immunotoxicity, thyroid effects, and neurotoxicity). Such experts can more precisely determine the degree of change that is adverse, which is particularly important for continuous endpoints where the preferred definition of the benchmark response (BMR) is based on the adverse biological changes. In the current screening-level TRVs, a default BMR of a change in the mean of 1 standard deviation was used when deriving BMDLs for continuous endpoints. This may or may not be appropriate for final TRVs because this degree of change may not be adverse, such as for endpoints with minimal background variability. Using the default BMR introduces additional uncertainty in the calculation of the TRV for endpoints with low variability or that are not adverse of themselves.

Furthermore, with regards to the specific task of choosing TRVs leading into the class-based dose-response assessment, it will also be important to integrate the results across studies for a given chemical. In the present report, potential endpoints of interest are identified by looking for shared endpoints across chemicals in a subclass. However, the interpretation of the results of a given study must be informed by the results of other studies of that chemical with somewhat different study designs. For example, ECHA (2008) summarized a 28-day study (CIT, 2001) and a two-generation study (TNO Quality of Life, 2007) of V6, both of which evaluated liver weight. In the 28-day study, a NOAEL of 15 mg/kg/day and a LOAEL of 150 mg/kg/day were identified based on increased absolute and relative liver weights and histopathology changes (hepatocellular and centrilobular hypertrophy, in the absence of degenerative/necrotic changes). ECHA used this study and POD as the basis for its repeated dose MOE evaluation but noted that the dose spacing was large and the true NOAEL may be higher than 15 mg/kg/day. In support of this suggestion that the true NOAEL may be higher, the current assessment notes that the two-generation study included exposure of the animals for much longer than 28 days, but there was no effect on absolute or relative liver weight at the low dose (29 mg/kg/day), and the only effect at the mid dose (86 mg/kg/day) was increased relative liver weight (but not absolute liver weight) in males only, for both generations. Additional consideration of these data, together with guidance on interpretation of increased liver weight (U.S. EPA, (2002), pp 9-11; see also Hall et al., (2012)), will be useful prior to identification of a final TRV for V6. This example of V6 potency differences across studies supports the idea that data should be integrated on a chemical by chemical basis prior to a class-based dose-response analysis as study design will impact the potency assessment.

Lastly, when selecting a TRV, it is important to consider biologically related endpoints as part of the same assessment as seemingly disparate effects may be related by a single consistent mode of action (MOA). However, species differences must also be observed at the same time. As an example of this, induction of metabolic enzymes in the liver is also consistent with the observed decreases in T4 during TBBPA exposure and is a plausible mode of action that could integrate the observed liver and thyroid endpoints into one adverse outcome pathway. As explained by Dellarco et al. (2006), the mode of action begins with induction of hepatic T4-uridine diphosphate glucuronyl transfersase (UGT) activity, which leads to increased T4 hormone conjugation and increased excretion of the conjugated hormone, and decreased serum T4 levels. This results in a compensatory increase in thyroid stimulating hormone (TSH) and ultimately thyroid hyperplasia. Additionally, there are species considerations that must also be accounted for. In this case, in humans, decreased circulating T4 does not lead to increased TSH or thyroid hyperplasia, due to higher reserve capacity of thyroid hormones and longer half-life of T4 (Dellarco et al., 2006). Note that the MOA linking thyroid and liver effects is well-understood and well-documented in the literature, with the Dellarco et al. (2006) analysis being the seminal paper. The plausibility of this MOA is also consistent with the conclusions reached by NASEM (2019), which noted data in rats showing upregulation of clearance enzymes (including UGT) and increased expression of the gene for thyroid receptor alpha in the liver. The scoping document for the PHBAF class (CPSC, 2023) also discusses this as a potential MOA for TBBPA. However, these changes are not consistently demonstrated in rats, and are not concordant with observations in zebrafish (NASEM, 2019). Thus, while this is possibly a relevant MOA, a full MOA analysis would be required to confirm. This example demonstrates the power of the MOA analysis for linking related endpoints, while at the same time showcasing how species differences can impact interpretation of results.

In summary, we derived TRVs at a screening level for both cancer and non-cancer outcomes for chemicals currently lacking TRVs in two classes. Further consideration of study design, mode of action, and incorporation of expert input regarding the specific effects observed should be a part of the process to move from screening TRVs to final TRVs.

Chemical Identifiers

Table A-1. Chemical identifiers

Chemical Name	Chemical Acronym[a]	CASRN
Polyhalogenated Organophosphates (PHOPs)		
Tris(1,3-dichloroisopropyl) phosphate	TDCIPP (TDCPP)	13674-87-8
Tris(2-chloroethyl) phosphate	TCEP	115-96-8
Tris(2,3-dibromopropyl) phosphate	TDBPP	126-72-7
Tris(2-chloroisopropyl) phosphate; Tris(chloropropyl) phosphate (commercial mixture)	TCIPP (TCPP)	13674-84-5
2,2-Bis(chloromethyl) trimethylene bis[bis(2-chloroethyl) phosphate]	BCMP-BCEP; also known as V6	38051-10-4
Polyhalogenated Bisphenol Aliphatics and Functionalized (PHBAFs)		
Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)	TBBPA-BDBPE	21850-44-2
2,2',6,6'-Tetrachlorobisphenol A	TCBPA	79-95-8
3,3',5,5'-Tetrabromobisphenol A	TBBPA	79-94-7

[a] Chemical acronyms were assigned from Bergman et al., 2012 when available. When not available, acronyms were assigned to align as closely as possible with Bergman et al., 2012 and to avoid potential confusion between different chemicals. When other commonly used acronyms exist (including those used in assessments identified in Subtask 1A), they are identified in parentheses after the acronym from Bergman et al., 2012.

Appendix B Modeling Results

B.1. Endpoints Carried Forward for Toxicity Reference Value Derivation using BMDL as the Point of Departure

B.1.1. Continuous Endpoints — PHOPs

There were no continuous endpoints following exposure to PHOP chemicals that were carried forward for toxicity reference value derivation using BMDL as the point of departure.

B.1.2. Continuous Endpoints — PHBAFs

Table B-1. NTP, 2014 (33546521) — Serum Total Thyroxine Concentrations in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV — normal)	251.7647743	193.9648418	347.5496694	0.000366	118.4772	-3.05180957	0.70390436
Exponential 5 (CV — normal)	**78.33389938**	**55.11304444**	**98.41682451**	**0.428891**	**103.4895**	**0.000315715**	**-0.359253518**
Hill (CV — normal)	**75.61006048**	**53.88736181**	**91.93898823**	**0.431109**	**103.4792**	**-0.0061973**	**-0.366943184**
Polynomial Degree 3 (CV — normal)	331.9362402	266.1704923	438.1698905	<0.0001	122.2701	-2.1036594	0.967490673
Polynomial Degree 2 (CV — normal)	331.7677379	266.1677073	438.1847643	<0.0001	122.2701	-2.10344982	0.966860783
Power (CV — normal)	331.7395894	266.1685747	438.183738	<0.0001	122.2701	-2.10324002	0.966635865
Linear (CV — normal)	331.7395449	266.1665723	438.1844682	<0.0001	122.2701	-2.10324001	0.966635828

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.
Bolded data indicates model was viable.

Table B-2. NTP, 2014 (33546521) — Serum Total Thyroxine Concentrations in Females Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV — normal)	225.6586552	169.0949312	321.8170436	0.028728	105.9583	-1.35432879	0.315886317
Exponential 5 (CV — normal)	**76.51266456**	**42.31491582**	**153.1705564**	**0.390621**	**101.0237**	**-0.12416012**	**-0.749039839**
Hill (CV — normal)	**75.58405395**	**39.47517857**	**139.8639316**	**0.467961**	**100.6624**	**0.099029843**	**-0.697231241**
Polynomial Degree 3 (CV — normal)	336.2919092	268.7825905	447.0514565	0.003296	110.9462	-2.40425556	0.696550982
Polynomial Degree 2 (CV — normal)	336.7486596	268.9204965	447.044476	0.003296	110.9463	-2.40695666	0.700125592
Power (CV — normal)	336.6617237	268.9133817	447.0898935	0.003294	110.9474	-2.41366524	0.707816945
Linear (CV — normal)	336.2352848	268.7790421	447.0433989	0.003296	110.9462	-2.40393496	0.696209646

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.
Bolded data indicates model was viable.

B.1.2. Dichotomous Endpoints — PHOPs

Table B-3. NTP, 2023. (Expert Identified 1) — Male Hepatocellular Adenoma or Carcinoma Following Exposure to Tris(chloropropyl) phosphate

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	882.6921	531.0495	Infinity	-61.5921	1.559821	0.103489
Gamma	911.9048	626.5801	1562.437	-47.8626	-0.64449	-0.03081
Logistic	1108.558	801.9275	Infinity	-50.5944	-0.26181	-0.451
Log-Logistic	791.255	563.9497	1159.584	-58.2563	1.32275	0.105192
Log-Probit	829.475	600.7649	1228.01	-56.6664	1.603978	-0.02621
Multistage Degree 3	742.9006	575.3984	944.8778	-54.6314	1.199871	0.190162
Multistage Degree 2	769.7748	564.5992	1078.766	-54.129	1.194897	0.165154
Multistage Degree 1	868.0938	550.5304	1605.577	-54.2236	1.239976	0.105983
Probit	1011.283	757.0432	1876.815	-46.4543	-0.45841	-0.11757
Quantal Linear	868.0937	550.5311	1605.263	-47.1718	1.239976	0.105983

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Weibull	931.0311	616.9547	1915.839	-53.9751	-0.50807	-0.01396
Model Average	949.966	578.3785	1938.644	–	–	–

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit).

Table B-4. NTP, 2023. (Expert Identified 1) — Female Uterine Adenoma or Adenocarcinoma Following Exposure to Tris(chloropropyl) phosphate

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	1010.078	325.3891	Infinity	-98.8528	-0.33126	-0.50399
Gamma	1075.037	562.4137	3001.583	-84.6059	-0.39364	-0.64265
Logistic	1623.287	786.018	Infinity	-85.9639	0.255197	-0.91718
Log-Logistic	769.3736	382.3966	1385.045	-95.0339	0.256527	-0.29266
Log-Probit	1088.974	587.6748	1910.353	-94.5306	-0.69738	-0.81232
Multistage Degree 3	761.9527	532.0865	1028.805	-91.0943	0.330999	-0.2534
Multistage Degree 2	768.1631	505.0339	1181.723	-90.6127	0.29679	-0.25933
Multistage Degree 1	807.5595	471.0076	1850.068	-90.4645	0.299717	-0.27066
Probit	1133.25	712.2741	3217.378	-82.9026	-0.21437	-0.59562
Quantal Linear	807.5594	471.006	1849.937	-83.2982	0.299716	-0.27066
Weibull	1015.108	435.6635	4087.373	-90.6233	-0.28505	-0.48753
Model Average	1112.485	426.3561	3396.337	–	–	–

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit).

Table B-5. NTP, 2023. (Expert Identified 1) — Male Hepatocellular Carcinoma (mice) Following Exposure to Tris(chloropropyl) phosphate

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	74.15436749	4.55061437	410.8707946	-117.4388695	-0.248866025	-0.248866025

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Gamma	385.1980665	116.9522892	Infinity	-106.3478167	1.36490282	-1.587515947
Logistic	9581.228427	309.9359475	Infinity	-104.545855	0.416308214	-2.439106844
Log-Logistic	141.782521	30.27190365	466.4106194	-114.08391	0.927136481	-0.636791616
Log-Probit	282.3569962	67.72366828	1160.88591	-115.5643372	1.160868	-1.28463866
Multistage Degree 3	324.2744195	191.4281544	494.2777349	-111.9352375	1.382725842	-1.31555497
Multistage Degree 2	305.8115845	176.1369561	540.9686244	-111.4645799	1.293964939	-1.303675287
Multistage Degree 1	283.6225845	158.9039824	746.2210515	-111.1927578	1.21698005	-1.288507647
Probit	442.4818946	263.6051374	1346.400173	-104.5483148	1.40681532	-1.693291474
Quantal Linear	283.6226042	158.9039935	746.1848523	-104.6260952	1.21698005	-1.288507647
Weibull	190.730447	30.29872104	1506.16581	-111.1899143	0.893324927	-1.016574466
Model Average	284.4688445	26.15320305	1224.021806	-	-	-

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit).

Table B-6. NTP, 2023. (Expert Identified 1)— Hepatocellular Adenoma or Carcinoma (Female Mice) Following Exposure to Tris(chloropropyl) phosphate

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	555.8685	326.6584	855.9084	-123.381	0.210825	0.912761
Gamma	489.1849	291.1901	746.475	-110.708	-1.53677	0.94428
Logistic	423.6762	337.4714	601.9152	-111.359	-1.69016	1.089497
Log-Logistic	563.6373	330.6359	855.9775	-118.001	0.246274	0.892183
Log-Probit	640.7547	410.1501	960.3847	-116.667	0.470023	0.725434
Multistage Degree 3	524.2423	330.0771	721.4529	-114.799	0.279707	1.027998
Multistage Degree 2	465.0204	289.4251	651.4734	-115.51	-1.5648	1.073726
Multistage Degree 1	310.1812	213.8529	523.1019	-117.457	-1.99611	1.155577

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Probit	405.9616	323.1964	573.8278	-109.006	-1.68448	1.173792
Quantal Linear	310.1812	213.8537	523.0557	-110.15	-1.99611	1.155577
Weibull	553.5265	301.7599	863.1488	-117.157	0.250174	0.859153
Model Average	480.3287	252.5115	821.5875	–	–	–

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit).

B.1.2. Dichotomous Endpoints - PHBAFs

Table B-7. NTP, 2014 (33546521) — Adenoma, Adenocarcinoma, or Malignant Mixed Mullerian Tumor Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	262.7189	75.74767	673.3116	-118.161	0.084957	-0.26648
Gamma	356.1734	163.5413	773.3959	-104.897	0.209695	-0.6231
Logistic	448.3438	319.0367	1283.069	-106.105	0.832056	-1.01254
Log-Logistic	280.9586	100.232	583.9552	-113.289	0.161541	-0.29825
Log-Probit	398.7973	169.9383	807.9764	-113.435	0.709786	-0.70802
Multistage Degree 3	384.3435	236.363	576.8479	-110.221	0.843445	-0.53842
Multistage Degree 2	343.7554	212.4102	565.3338	-110.24	0.278222	-0.48789
Multistage Degree 1	283.8605	184.2349	558.1343	-110.379	0.070867	-0.40053
Probit	411.1844	299.9589	777.5715	-103.602	0.835362	-0.82908
Quantal Linear	283.8605	184.2378	558.0984	-103.471	0.070867	-0.40053
Weibull	290.4748	87.66954	732.4917	-111.034	0.034131	-0.47197
Model Average	325.4328	162.202	636.7922	–	–	–

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit).

Table B-8. NTP, 2014 (33546521) — Hepatocellular Adenoma Multiple Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	140.6936	34.90774	292.2589	-104.166	-0.01858	-0.07543
Gamma	144.2622	62.10561	288.6847	-91.6488	0.055217	-0.2136
Logistic	145.9538	106.9802	308.6053	-92.1983	0.057199	-0.39281
Log-Logistic	144.4974	43.56138	277.9637	-98.8904	0.02012	-0.04843
Log-Probit	201.4391	90.21998	351.709	-98.4139	0.419801	-0.2586
Multistage Degree 2	140.9289	82.23092	232.1856	-95.9658	0.115322	-0.07378
Multistage Degree 1	104.2488	68.10377	203.6438	-96.3781	-0.07811	-0.07811
Probit	138.6183	103.3294	243.0033	-89.9343	0.067009	-0.25246
Quantal Linear	104.2488	68.10464	203.6439	-90.1635	-0.07811	-0.07811
Weibull	135.1873	33.40611	294.5687	-97.4371	0.010026	-0.20629
Model Average	124.9569	64.58088	249.8952	–	–	–

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit).

Table B-9. NTP, 2014. (33546521) — Eosinophilic Focus Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	105.7055	5.96573	431.2838	-102.479	-0.40082	-0.40082
Gamma	419.2704	156.9619	1437.911	-91.059	0.139414	-1.49686
Logistic	764.0337	442.7492	Infinity	-92.3373	-0.09612	-2.1586
Log-Logistic	201.8032	53.66165	567.0927	-99.1527	1.588312	-0.74173
Log-Probit	301.6677	102.2535	1217.173	-100.175	1.971729	-1.09654
Multistage Degree 3	448.9726	275.4536	675.8053	-97.1461	0.229337	-1.47842

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Multistage Degree 2	415.151	252.5562	709.7325	-96.7331	0.140401	-1.42878
Multistage Degree 1	371.2465	227.2658	832.1266	-96.4738	1.964367	-1.35591
Probit	608.9975	404.0676	1550.385	-89.6987	0.353	-1.90303
Quantal Linear	371.2464	227.264	832.123	-89.5661	1.964367	-1.35591
Weibull	223.1536	47.93069	964.1353	-96.1092	1.579023	-0.95963
Model Average	370.3881	32.90353	1178.78	–	–	–

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit).

B.2. Endpoints Carried Forward for Toxicity Reference Value Derivation using NOAEL/LOAEL as the Point of Departure

B.2.1. Continuous Endpoints – PHOPs

There were no continuous endpoints following exposure to PHOP chemicals that were carried forward for toxicity reference value derivation using NOAEL/LOAEL as the point of departure.

B.2.2. Continuous Endpoints - PHBAFs

Table B-10. Shockley et al., 2020 (60) — Serum Total Thyroxine in Males Following Exposure to Tetrabromobisphenol A-bis(2,3-dibromopropyl ether)

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV – normal)	928.9610911	467.3252067	2800.322027	0.049783	108.1392	-3.3928E-08	2.065856619
Exponential 5 (CV – normal)	928.9610068	467.3251643	2800.321773	0.019996	110.1392	-6.9643E-08	2.065856605
Hill (CV – normal)	801.3532338	102.9825271	Infinity	0.019996	110.1392	-9.4057E-08	2.065856631

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Polynomial Degree 3 (CV – normal)	**911.0481216**	**503.1216437**	**2643.860406**	**0.166084**	**104.1409**	**0.000292204**	**2.065206208**
Polynomial Degree 2 (CV – normal)	895.1147206	502.6469685	2659.942582	0.09759	106.1555	-0.00301366	2.060493801
Power (CV – normal)	938.0982166	503.1739494	959.4352949	0.049783	108.1392	2.31349E-08	2.065856668
Linear (CV – normal)	845.8959281	497.8508241	2802.096954	0.092886	106.2793	-0.03652921	2.008435147

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.
Bolded data indicates model was viable.

Table B-11. Wang et al., 2021 (33254397) — Treg Lymphocyte Percentage in Females Following Exposure to 2,2',6,6'-Tetrachlorobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV – normal)	1431.255817	53.23307611	1464.706721	NA	73.35814	1.215292757	-3.199887832
Exponential 5 (CV – normal)	2.183736116	1.879804416	4.564571263	NA	46.4403	-6.0319E-10	-6.03193E-10
Hill (CV – normal)	–	–	–	–	–	–	–
Polynomial Degree 2 (CV — normal)	53.15448046	28.36234423	409.0832737	<0.0001	67.78432	-0.29956428	-2.539420715
Power (CV — normal)	53.0904499	28.36239736	409.0968423	<0.0001	67.78432	-0.30150831	-2.538316454
Linear (CV — normal)	53.09045315	28.36240883	409.0968674	<0.0001	67.78432	-0.30150828	-2.538316468

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.

Table B-12. Zhang et al., 2021 (33360189) — $CD3^+$/Treg Ratio Following Exposure to 2,2',6,6'-Tetrachlorobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV - normal)	26.12674236	16.20723851	26.66756593	<0.0001	32.43253452	-2.788435257	2.536093265
Exponential 5 (CV - normal)	1.376974583	0.137415847	4.68011447	NA	12.19853566	-5.22906E-09	-5.22906E-09
Hill (CV - normal)	0.367561961	0.001736223	3.848248986	NA	12.19853566	-1.93634E-07	-1.93634E-07

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Polynomial Degree 2 (CV - normal)	28.10359001	18.90418095	53.89325238	<0.0001	32.74913997	0.286092615	2.617844728
Power (CV - normal)	28.05439137	18.90416884	53.89433522	<0.0001	32.74945137	0.295837107	2.603184484
Linear (CV - normal)	28.06107998	18.90427107	53.89250323	<0.0001	32.74910897	0.29061445	2.615530259

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.

Table B-13. Choi et al., 2011 (24278553) — Serum Total Thyroxine Concentration in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV — normal)	419.0792143	228.6122783	1441.453083	0.047296	184.2847	0.885951885	0.294445429
Exponential 5 (CV — normal)	146.4683283	126.173975	Infinity	NA	183.0969	3.23584E-08	-5.45197E-08
Hill (CV — normal)	**150.3626687**	**126.4542095**	**Infinity**	**0.338786**	**181.0971**	**0.000184973**	**-0.000143944**
Polynomial Degree 3 (CV — normal)	452.085265	266.0175452	1488.739489	0.040817	184.5794	0.828572929	0.416614862
Polynomial Degree 2 (CV — normal)	453.3533454	266.0115643	1488.777071	0.040815	184.5794	0.823120392	0.42079857
Power (CV — normal)	451.5958475	266.0194596	1488.760944	0.040817	184.5794	0.830388474	0.415194234
Linear (CV — normal)	451.5958428	266.0194569	1488.662445	0.040817	184.5794	0.830388603	0.415194257

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.
Bolded data indicates model was viable.

Table B-14. Van de Ven et al., 2008 (18255212) — Serum T4 Concentrations in Females Following Exposure to 2,2',6,6'-Tetrachlorobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV - normal)	1026.19198	601.5156118	2086.119085	0.005035225	280.769292	-0.890447433	0.200302099
Exponential 5 (CV - normal)	**96.97498597**	**60.17186929**	**150.9542127**	**0.238457941**	**271.7536035**	**6.46275E-08**	**-0.743528321**
Hill (CV - normal)	**95.97093888**	**84.33797492**	**104.4635535**	**0.238457943**	**271.7536035**	**5.44759E-06**	**-0.743528835**

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Polynomial Degree 3 (CV - normal)	2096.370131	2053.400908	2139.293451	0.000223873	288.169796	0.646568945	0.484222397
Polynomial Degree 2 (CV - normal)	1483.44022	1030.446148	2635.675411	0.002398848	282.5889919	-1.328881123	0.347492492
Power (CV - normal)	1483.418525	1030.443082	2635.636864	0.002398848	282.5889919	-1.328866702	0.347477383
Linear (CV - normal)	1483.418539	1030.443092	2635.636889	0.002398848	282.5889919	-1.328866697	0.347477426

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.
Bolded data indicates model was viable.

Table B-15. Van de Ven et al., 2008 (18255212) — Serum T4 Concentrations in Males Following Exposure to 2,2',6,6'-Tetrachlorobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV - normal)	1155.938745	689.9374626	2382.727223	0.007281006	279.1091436	-1.828794734	1.961390679
Exponential 5 (CV - normal)	177.6401075	69.74619037	342.5959394	0.203627838	271.4385687	-0.07382746	1.654779001
Hill (CV - normal)	163.2264929	68.0534874	318.8501224	0.204247255	271.4304476	-0.055136611	1.663903637
Polynomial Degree 3 (CV - normal)	2198.95488	2153.818404	2243.978828	0.000480852	285.6924206	0.541820834	2.070349789
Polynomial Degree 2 (CV - normal)	1569.817454	1072.585156	2914.973173	0.003870311	280.6778892	-2.118315856	2.039874364
Power (CV - normal)	1569.813885	1072.595475	2914.96433	0.003870311	280.6778892	-2.118314635	2.039873043
Linear (CV - normal)	163.226547	145.6368653	332.0388108	0.204247255	271.4304476	-0.055137608	1.663903997

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.

Table B-16. Tada et al., 2007 (21783755) — Relative Liver Weight in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV — normal)	**748.3121872**	**524.8131015**	**1343.290399**	**0.235345**	**34.75783**	**-0.02292858**	**-1.038585695**

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 5 (CV — normal)	**398.0545044**	**105.8773417**	**1065.410826**	**0.229138**	**35.31062**	**0.839008324**	**-0.313774806**
Hill (CV — normal)	**304.5478629**	**43.82549087**	**310.8520037**	**0.270333**	**35.07947**	**0.581604067**	**-0.080090824**
Polynomial Degree 3 (CV — normal)	**715.489006**	**487.5725208**	**1315.384786**	**0.255883**	**34.59049**	**-0.0764284**	**-0.977893338**
Polynomial Degree 2 (CV — normal)	**712.3383999**	**487.6192555**	**1315.351017**	**0.255914**	**34.59024**	**-0.07757374**	**-0.968261329**
Power (CV — normal)	**724.0995647**	**486.9110416**	**1319.433618**	**0.253499**	**34.60921**	**-0.07642156**	**-0.948519448**
Linear (CV — normal)	**712.5546932**	**487.6175807**	**1315.339886**	**0.255915**	**34.59024**	**-0.07749301**	**-0.968992335**

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.
Bolded data indicates model was viable.

Table B-17. Kim et al., 2017 (28564613) — Survival and Neuronal Differentiation (BrdU Positive Cells) in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV — normal)	145.9707051	83.54504377	Infinity	0.094817	292.7862	-1.64106428	1.015959803
Exponential 5 (CV — normal)	36.27208775	14.8212833	100.6261903	NA	292.0745	1.16944E-07	1.08188E-07
Hill (CV — normal)	34.41107522	10.53699866	95.97519623	NA	292.0745	4.50029E-07	-3.15726E-07
Polynomial Degree 3 (CV — normal)	359.2704168	127.2015475	366.6813806	NA	300.7635	0.180393645	1.471016542
Polynomial Degree 2 (CV — normal)	256.8064098	140.5314886	418.6765536	0.011165	296.5134	-1.73241339	1.288751788
Power (CV — normal)	211.1828831	143.9797434	390.7709618	0.050052	294.0639	-1.87217834	1.201931836
Linear (CV — normal)	211.182878	143.97974	390.7704171	0.050052	294.0639	-1.87217835	1.201931898

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.

Table B-18. Kim et al., 2017 (28564613) — Memory Retention (Latency Time) in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV — normal)	**379.7826478**	**178.3617632**	**1520.041505**	**0.144111**	**323.7835**	**0.425140237**	**1.272058654**
Exponential 5 (CV — normal)	23.45071232	6.537110638	26.35290495	NA	324.2307	5.47616E-09	-9.99399E-08
Hill (CV — normal)	**37.42673864**	**4.522660165**	**Infinity**	**0.987328**	**321.9094**	**-0.00725511**	**0.001928957**
Polynomial Degree 3 (CV — normal)	**440.8980161**	**257.1628828**	**1510.603083**	**0.118698**	**324.1715**	**0.2819584**	**1.379778415**
Polynomial Degree 2 (CV — normal)	**439.9135811**	**257.1762804**	**1510.631229**	**0.1187**	**324.1715**	**0.286247335**	**1.378152139**
Power (CV — normal)	**439.8748839**	**257.1662957**	**1510.634356**	**0.1187**	**324.1715**	**0.286450653**	**1.378047224**
Linear (CV — normal)	**439.8748819**	**257.1662945**	**1510.634349**	**0.1187**	**324.1715**	**0.286450642**	**1.378047223**

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.
Bolded data indicates model was viable.

Table B-19. Rock et al., 2019 (31541695) — Latency to Enter Center in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV - normal)	-	-	-	-	-	-	-
Exponential 5 (CV - normal)	-	-	-	-	-	-	-
Hill (CV - normal)	0.00454092	0.004125682	Infinity	NA	624.8837072	9.19657E-08	9.19657E-08
Polynomial Degree 3 (CV - normal)	561.4543114	259.6755211	600.6550282	0.01124698	629.3005928	0.067012563	1.963621451
Polynomial Degree 2 (CV - normal)	672.3179463	259.2118785	1720.381345	0.040721196	627.2767359	0.045662158	1.969048992
Power (CV - normal)	-	-	-	-	-	-	-
Linear (CV - normal)	650.9455368	258.9780813	Infinity	0.040745766	627.2755295	0.074760214	1.957215274

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.

Table B-20. Rock et al., 2019 (31541695) — Open Arm Entries in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Test for P-Value	AIC	Residual at BMD	Residual at Control
Exponential 3 (CV - normal)	**426.7330766**	**184.5922494**	**3571.550705**	**0.149652938**	**220.4825519**	**0.142320985**	**1.461196879**
Exponential 5 (CV - normal)	-	-	-	-	-	-	-
Hill (CV - normal)	-	-	-	-	-	-	-
Polynomial Degree 3 (CV - normal)	387.2096837	208.084856	2789.508928	0.143315779	220.5690888	0.102956625	1.483403208
Polynomial Degree 2 (CV - normal)	387.5337243	208.082619	2789.939326	0.143315833	220.569088	0.10156657	1.483914338
Power (CV - normal)	387.4172546	208.0848816	2789.738367	0.143315857	220.5690877	0.102065591	1.48373153
Linear (CV - normal)	387.4172568	208.0848828	2789.722916	0.143315857	220.5690877	0.10206559	1.483731552

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.
Bolded data indicates model was viable.

B.2.3. Dichotomous Endpoints - PHOPs

There were no dichotomous endpoints following exposure to PHOP chemicals that were carried forward for toxicity reference value derivation using NOAEL/LOAEL as the point of departure.

B.2.4. Dichotomous Endpoints - PHBAFs

Table B-21. NTP, 2014. (33546521) — Atypical Endometrium Hyperplasia Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	105.7054581	5.965730223	431.2838181	-102.4789382	-0.400816221	-0.400816221
Gamma	419.2704464	156.9618875	1437.910891	-91.05898596	0.139413767	-1.496855939
Logistic	764.0336827	442.7491622	Infinity	-92.33731644	-0.096116258	-2.158597518
Log-Logistic	201.8032404	53.66164513	567.0926978	-99.15266262	1.588311728	-0.741733719

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Log-Probit	301.667749	102.2534899	1217.172534	-100.1754396	1.971729401	-1.096543555
Multistage Degree 3	448.9726424	275.4535714	675.8053316	-97.1461194	0.229336589	-1.478419055
Multistage Degree 2	415.151	252.5562279	709.7325376	-96.73305389	0.140401357	-1.428780406
Multistage Degree 1	371.2464571	227.2657733	832.1265813	-96.47379589	1.964366979	-1.355910714
Probit	608.9974828	404.067642	1550.384918	-89.69866023	0.353000039	-1.903025879
Quantal Linear	371.2464301	227.2639904	832.1230076	-89.56606797	1.96436697	-1.355910721
Weibull	223.1536341	47.93068559	964.1353313	-96.10918185	1.579022722	-0.959630218
Model Average	370.3880845	32.90352848	1178.780226	-	-	-

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit).

Table B-22. Tada et al., 2007 (21783755) — Hepatic Inflammatory Cell Infiltration in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	8.726768	0.03179	83.731757	-18.46361908	-0.243169726	-0.243169726
Gamma	28.75612	4.255195	113.19482	-8.671882064	-0.562345837	-0.562345837
Logistic	27.54761	9.3962	58.979056	-7.66022271	-0.475996496	-0.475996496
Log-Logistic	16.01052	0.183285	195.61813	-14.66776284	-1.046286291	-1.046286291
Log-Probit	29.90863	1.114655	150.7969	-12.69831732	-0.489242253	-0.489242253
Multistage Degree 3	26.60157	10.86507	123.46731	-15.15667805	-0.589416445	-0.589416445
Multistage Degree 2	26.05683	10.78097	99.599716	-14.79840806	-0.579463112	-0.579463112
Multistage Degree 1	25.00851	10.57988	77.551465	-14.41899059	-0.563217049	-0.563217049
Probit	36.45597	16.63802	92.031742	-5.953579801	-0.910629869	-0.910629869
Quantal Linear	25.00851	10.57988	77.551466	-7.174757572	-0.563217049	-0.563217049

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Weibull	6.943412	0.060578	63.975591	-14.03445983	-0.326833308	-0.326833308
Model Average	26.37786	1.989868	82.084491	–	–	–

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.

Table B-23. Tada et al., 2007 (21783755) — Focal Necrosis of Hepatocytes in Males Following Exposure to 3,3',5,5'-Tetrabromobisphenol A

Model	BMD	BMDL	BMDU	Log Posterior Probability	Residual at BMD	Residual at Control
Dichotomous Hill	135.7015	7.304715	4605.7948	-27.59662898	-0.28029051	-0.28029051
Gamma	181.0742	34.67739	Infinity	-14.52174757	0.660519588	-0.602725526
Logistic	9306.945	71.17678	Infinity	-10.57935708	1.828087848	-1.572379407
Log-Logistic	209.0027	16.61646	722.68631	-21.66560262	0.665407302	-0.634606165
Log-Probit	374.2291	60.49682	931.03548	-21.31067574	0.882021361	-0.704110803
Multistage Degree 3	226.404	65.41241	526.85419	-20.4228647	0.775927439	-0.598865213
Multistage Degree 2	189.3568	58.18407	540.10218	-20.54009151	0.710224338	-0.59199044
Multistage Degree 1	119.7252	50.09832	771.16497	-20.12912397	-0.493202207	-0.493202207
Probit	135.763	75.34381	591.57449	-11.78119777	-0.522344744	-0.522344744
Quantal Linear	119.7252	50.09832	771.16689	-12.88489645	-0.493202207	-0.493202207
Weibull	159.8224	11.24534	4534.7233	-21.62248509	-0.499857059	-0.499857059
Model Average	143.8226	26.88233	866.21102	–	–	–

BMD = benchmark dose; BMDL = benchmark dose (lower confidence limit); BMDU = benchmark dose (upper confidence limit); AIC = Akaike information criteria.