United States
Consumer Product Safety Commission

July 22, 2025

CPSC Staff Statement on: PHOP Class-Based Dose-Response

The U.S. Consumer Product Safety Commission (CPSC or Commission) contracted with ICF (Contract BPA No. 61320622A0005, Order No. 61320623F2030) to complete a class-based dose-response assessment of Polyhalogenated Organophosphate (PHOP) Flame Retardants.[1] This statement was prepared by the CPSC staff. ICF produced the accompanying report, "PHOP Class-Based Dose-Response" (Subtask 2B in the contract), for CPSC staff. The statement and report have not been reviewed or approved by, and may not represent the views of, the Commission.

In Subtask 2A, ICF described approaches to perform class-based dose-response analyses, and in Subtask 4A they prepared a guidance document for performing class-base dose-response.[2] In the accompanying Subtask 2B report, ICF applied approaches identified in Subtasks 2A and 4A to derive quantitative toxicity reference value (TRV)[3] estimates for substances in the PHOP subclass.

Based on the available toxicity data for chemicals in the PHOP subclass, the contractor recommended a class-base dose-response approach that uses relative potency factor (RPF) analysis. In the RPF approach, one or more data-rich chemical(s) in a subclass may be the anchor or index chemical to which other chemicals are compared. The approach included: 1) describe the current availability of dose-response data for the PHOPs subclass; 2) perform a RPF assessment based on *in vivo* data and *in silico* data for different biomarkers; and 3) compare these outputs to traditionally determined TRVs to assess the viability of this approach and perform a semi-quantitative analysis of the PHOP chemicals for which only *in silico* data exist.

Based upon the availability of data, this report describes the calculation of RPFs for the 13 PHOP chemicals for which there has been an empirical determination of median lethal dose (LD50) in rats and 26 PHOP chemicals for which quantitative structure-activity relationship (QSAR) data provide a predicted LD50. The calculated RPFs based on LD50 data were compared to assess how well the points of departure (PODs) derived from *in silico* RPFs agreed with PODs derived from *in vivo* RPFs. Finally, these data were compared to the threshold of toxicological concern (TTC), which was then used to inform the confidence in the POD estimates for chemicals for which no empirical data are available. These data were then collated to produce TRV estimates for all chemicals within the PHOP subclass along with confidence levels for the estimates.

[1] The original contract also included a class-based dose-response assessment of the polyhalogenated bisphenol aliphatics and functionalized (PHBAF) subclass. For reasons explained in Section 2 of the accompanying report, the contract was modified to exclude the PHBAF subclass and provide more resources toward the class-based dose-response assessment of the PHOP subclass.

[2] The supporting documents cited in the Subtask 2B report from other subtasks of this contract as well as deliverables from an earlier call order (Contract BPA No. 61320622A0005, Order No. 61320622F2011) can be found at https://www.cpsc.gov/Business--Manufacturing/Organohalogen-Flame-Retardant-Chemicals-Assessment.

[3] "Toxicity reference value" or TRV quantifies the potency of a substance or estimates the dose level to which people can be exposed for a specified duration of time without experiencing an adverse health effect.

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: January 29, 2025

Re: Task 2B: Apply Class-based Dose-response Analyses to Develop Quantitative TRV Estimates for Two OFR Subclasses
(CPSC Contract Number 61320622A0005, CPSC Order Number 61320623F2030)

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1. Introduction

Under CO-9, Subtask 2B seeks to apply class-based dose-response analyses to develop quantitative toxicity reference value (TRV) estimates for the polyhalogenated organophosphate (PHOP) and polyhalogenated bisphenol aliphatics and functionalized (PHBAF) organohalogen flame retardants (OFRs) subclasses.

2. Overview of Class-based Dose-Response Approaches

In the Subtask 2A report, we describe methods that could be applied to perform class-based dose-response assessments and potential ways in which these methods may be applied to OFR chemicals in the PHOP and PHBAF subclasses. Briefly, we discussed how chemical classes are established based upon similarities among multiple chemicals that are usually structural or hazard based. Extrapolation methods informed by cumulative risk assessments, such as relative potency factors (RPFs), are applied to make inferences between data-rich and data-poor chemicals. Generally, one or more data-rich chemical(s) in a class may be the anchor or index chemical to which other chemicals are compared. Major takeaways of the report included:

- class-based assessments are of greater value when chemical classification is based on both biological and chemical properties,
- shared biology at the level of health outcomes, such as mode of action (MOA), or, ideally, adverse outcome pathways (AOPs), are important in transitioning from qualitative hazard characterization to quantitative dose-response assessment,
- the new approaches/alternative methods (NAMs) paradigm allows for the production of more data in a shorter time period and for less cost than conducting traditional animal toxicological studies *in vivo*.

We also noted the advantage of basing comparisons on biological mechanism during extrapolation from data–rich class members to data-poor chemicals with the possible need for different anchor chemicals to be used depending on available data.

Based on our findings in the Subtask 2A report, our overall proposal was to assess the PHOP subclass only. CO-1 (Call Order 61320622F2011, “Guidance Document for Conducting Class-based Hazard Assessment of Organohalogen Flame Retardants” under CPSC Blank Purchase Agreement (BPA 61320622A0005)) demonstrated a realignment of the subclass following the evaluation of the initial list of PHOP class members based on chemical and biological factors. In addition, under CO-1, hazard

characterization data was curated for the PHOP subclass from several databases (Section 3.1). Because neither this realignment nor hazard characterization was conducted for the PHBAF subclass in CO-1, we could not perform the same assessment for PHBAFs as done for PHOPs. Specifically, we proposed to perform a RPF dose-response analysis based on traditional *in vivo* data and NAMs data outputs and perform a semi-quantitative or qualitative analysis of chemicals with only *in silico data*. As such, in this report we

- describe the current availability of data,
- perform a RPF assessment based on *in vivo* data and *in silico* data for different biomarkers,
- compare these outputs to traditionally determined TRVs to assess the viability of this approach, and
- perform a semi-quantitative analysis of the PHOP chemicals for which only *in silico* data exists.

Based upon the availability of data, this report describes the calculation of RPFs for the 13 PHOP chemicals for which there has been an empirical determination of median lethal dose (LD_{50}) in rats and 26 PHOP chemicals for which quantitative structure-activity relationship (QSAR) data predicts a rat LD_{50}. Next, calculated RPFs, based on LD_{50} data, were compared to assess how well the points of departure (PODs) derived from *in silico* RPFs agreed with PODs derived from *in vivo* RPFs. These data were also compared to results from a recently published online dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024) that makes available surrogate/predicted PODs based on generic and reproductive/developmental endpoints through a probabilistic extrapolation method. Finally, these data were compared to the threshold of toxicological concern (TTC), which was then used to inform the confidence in the POD estimates for chemicals for which no empirical data are available. These data were then collated to produce TRV estimates for all chemicals within the PHOP subclass with affiliated confidence levels.

The chemicals in the PHOP class, including CASRNs, chemical names, and (when available) common abbreviations, can be found in Appendix Table A-1.

3. Overview of Availability of Hazard, Dose-response, and POD Data

To perform a class-based dose-response assessment, PHOP chemicals were first characterized by hazard profiles to determine whether all chemicals contained within the subclass shared similar hazard qualities. To do this for the 29 realigned PHOP chemicals, we turned to the CO-1 PHOP report and the CO-9 Subtask 1A, Subtask 1B, and Subtask 1C reports. Data were collated across these databases to classify chemicals based upon hazard (Section 3.1). These data were supplemented by checking the Environmental Protection Agency (EPA) Toxicity Value Database (ToxValDB) and Health Canada's Automated Workflow for Prioritization (HAWPr) database for data that could be used to derive additional TRVs and RPFs (Section 3.2).

3.1. Overview of Previously Collected PHOP PODs and TRVs

Data previously obtained under CO-1 and CO-9 Subtask 1A, Subtask 1B, and Subtask 1C were collated from the following databases: ToxValDB, CompTox Chemicals Dashboard, Danish (Q)SAR Database, European Chemicals Agency (ECHA), PubChem, Comparative Toxicogenomics Database (CTD), Integrated Chemical Environment (ICE), and Organization for Economic Co-operation and Development (OECD). The availability of hazard, cancer TRV, and non-cancer TRV data is described on a chemical-by-chemical basis in Table 1.

Overall, we found that these databases contained empirically determined hazard data for 14 PHOP chemicals, computational hazard data for 26 PHOP chemicals, and no hazard data for 3 PHOP chemicals. Additionally, 8 chemicals had published or newly derived TRV values identified in this project. Seven chemicals had non-cancer TRVs, and 4 had cancer TRVs. Of the cancer TRVs, 3 were linked to kidney cancer (TCEP (115-96-8), TDCIPP (13674-87-8), and TDBPP (126-72-7)), and for the noncancer

TRVs, 7 were linked to reproductive or developmental outcomes (Table 2). Additionally, when looking at hazard data more generally, we found that one additional chemical (TCIPP (13674-84-5)) had health effects affiliated with kidney tumors (n=4 total chemicals, Table 3). This led us to initially focus on the kidneys as the target tissue of interest for cancer outcomes and developmental and reproductive health effects as the targets of interest for non-cancer outcomes (See Section 3.2.1 and 3.2.2 for more information on how these choices coincided with critical effects).

There were 14 chemicals with empirically measured hazard data. Thirteen of these had empirically measured toxicity data (primarily rat LD_{50} values) that would allow for calculation of RPFs based on *in vivo* data (Appendix Table A-2). The 14th chemical, DDBPP (5412-25-9), had some assay specific molecular data available but nothing comparable to the other 13 chemicals that would allow for calculation of an RPF. The 13 chemicals with rat LD_{50} values plus an additional 13 chemicals, for a total of 26 chemicals, were identified to have QSAR data that would support the potential derivation of a RPF based on modeled data (Appendix Table A-2).

This information was integrated with TRVs identified in CO-9 Subtask 1A or derived in CO-9 Subtask 1B to identify available TRVs, available toxicity data, and data gaps (Table 1). During our query of ToxValDB, we identified additional TRV and POD data from animal toxicity studies. These data were investigated to determine the most accurate possible PODs and TRVs (Section 3.2).

Table 1. Hazard and Dose-response Data Availability for PHOP Chemicals

CASRN[a]	Abbreviation	Hazard Data	Noncancer TRV[b]	Cancer TRV[c]
115-96-8	TCEP	TV | CT | OECD | QSAR | PC | CTD | ECHA | ADME | ICE | WC | WO	1A | 1C | 2B	1A
13674-87-8	TDCIPP	TV | CT | OECD | QSAR | PC | CTD | ECHA | ADME | ICE | WC | WO	1A | 2B	1A | 2B
126-72-7	TDBPP	TV | CT | OECD | QSAR | PC | CTD | ADME | ICE | WC | WO	NA	1A | 2B
13674-84-5	TCIPP	TV | CT | OECD | QSAR | PC | CTD | ECHA | ICE | WC | WO	1A | 1C | 2B	1A | 1B | 1C[d]
6294-34-4	N/A	TV | CT | OECD | QSAR | PC | WO	2B	NA
38051-10-4	V6; BCMP-BCEP	TV | CT | QSAR | ECHA	1A | 1B	NA
19186-97-1	TTBNPP	TV | CT | QSAR | ECHA	2B	NA
1047637-37-5	BCMP-BCMEP	TV | CT | QSAR | ECHA	2B	NA
78-43-3	N/A	TV | CT | OECD | QSAR | WO	NA	NA
4351-70-6	N/A	TV | CT | OECD | QSAR | WO	NA	NA
140-08-9	N/A	TV | CT | OECD | QSAR | PC | WC | WO	NA	NA
6145-73-9	N/A	TV | CT | OECD | QSAR | PC	NA	NA
115-98-0	N/A	TV | CT | OECD | QSAR | PC | WO	NA	NA
5412-25-9	DDBPP	CT | QSAR | PC | CTD	NA	NA
6749-73-1	N/A	QSAR	NA	NA
66108-37-0	N/A	QSAR	NA	NA
33125-86-9	N/A	QSAR	NA	NA
76025-08-6	N/A	QSAR	NA	NA
76649-15-5	N/A	QSAR	NA	NA
5324-12-9	N/A	QSAR	NA	NA
27568-90-7	N/A	QSAR	NA	NA
84282-27-9	N/A	QSAR	NA	NA

CASRN[a]	Abbreviation	Hazard Data	Noncancer TRV[b]	Cancer TRV[c]
53461-82-8	N/A	QSAR	NA	NA
61090-89-9	N/A	QSAR	NA	NA
26604-51-3	N/A	QSAR	NA	NA
34621-99-3	N/A	QSAR	NA	NA
1067-98-7	N/A	NA	NA	NA
98923-48-9	N/A	NA	NA	NA
72236-72-7	N/A	NA	NA	NA

Dark blue shading = chemicals with experimentally determined data for hazard characterization; light blue shading = chemicals with QSAR data only for hazard characterization.
CASRN = CAS registry number; TRV = toxicity reference value; TV = data obtained from ToxValDB; CT = data obtained from CompTox Chemicals Dashboard; OECD = data obtained from Organization for Economic Co-operation and Development; QSAR = data obtained from Danish (Q)SAR Database; PC = data obtained from PubChem; CTD = data obtained from Comparative Toxicogenomics Database; ECHA = data obtained from European Chemicals Agency; ADME = data obtained from Integrated Chemical Environment Absorption Distribution Metabolism Excretion; ICE = data obtained from Integrated Chemical Environment Curve Surfer Tool; WC = Integrated Chemical Environment carcinogenicity data; WO = Integrated Chemical Environment acute oral data; NA – data not available.
[a] Five chemicals were removed from the PHOP class under CO-1 (2788-11-6, 1373346-90-7, 49690-63-3, 7046-64-2, 35656-01-0).
[b] Noncancer TRVs listed as 1A, 1B, and 1C were identified or derived during CO-9 Subtask 1A, Subtask 1B, or Subtask 1C, respectively. Noncancer TRVs listed as 2B were either derived based on ToxValDB data or a standardized point of departure (POD) was calculated in this subtask (Subtask 2B; see Table 2).
[C] Cancer TRVs listed as 1A, 1B, and 1C were identified or derived during CO-9 Subtask 1A, Subtask 1B, or Subtask 1C, respectively. Cancer TRVs listed as 2B, were derived from new PODs calculated in this subtask (Subtask 2B; see Table 3).
[d] A single assessment was identified in Subtask 1A (U.S. EPA, 2012) that made a qualitative conclusion only. During the time between the development of the Subtask 1A report and Subtask 1B report, a newly published cancer study was identified (NTP, 2023) for which we calculated cancer PODs and TRVs in Subtask 1B. In Subtask 1C, based on further evaluation of the mode of action for liver tumors and the accompanying qualitative evaluation of “some evidence” for uterine tumors, we determined that none of these cancer TRVs for TCIPP were appropriate for carrying forward.

3.2. Newly Identified PHOP Data for Points of Departure

TRVs identified and derived under CO-9 Subtask 1A and Subtask 1B relied on the literature search performed by the National Institute of Environmental Health Sciences (NIEHS) Division of Translational Toxicology (DTT) that was supplemented by additional grey literature searching. Neither of these methods specifically looked at online databases for TRVs or potential PODs. While looking at ToxValDB for data that could be used to derive RPFs in Subtask 2B (Section 4), a few potential PODs that were not previously identified but could be used to derive TRVs were noted for several PHOPs. Additionally, HAWPr was queried for data. Finally, PODs were pulled for comparison purposes from the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024). PODs in this dashboard were derived using machine learning methods that extrapolate PODs from surrogate chemicals to predict values for which no *in vivo* toxicity data exist.

For seven chemicals, our search yielded additional information on PODs related to noncancer endpoints (Table 2). For four chemicals, TCEP, TCIPP, TDCIPP, and V6 (115-96-8, 13674-84-5, 13674-87-8, and 38051-10-4, respectively), additional empirical PODs were identified that were higher than the PODs that were identified during Subtask 1A, so these new PODs were not further considered. For three chemicals (6294-34-4, 19186-97-1, 1047637-37-5) that did not yet have TRVs, potential PODs were identified in ToxValDB. These PODs had not been identified in prior steps because they were sourced from grey literature (ECHA Dossiers or High Production Volume Information System [HPVIS]) that would not have been captured during the DTT literature search and thus were not considered as part of Subtask 1B. These PODs were used to derive TRVs in Section 3.2.1 (Table 2, source ToxValDB). However, the PODs were one to two orders of magnitude higher than the PODs from authoritative sources identified in

Subtask 1A. Because the PODs from ToxValDB were based on incomplete documentation from secondary sources, it was uncertain whether the potency of these three chemicals is really that much lower than the potency of the chemicals with PODs from authoritative sources. Therefore, the new PODs from ToxValDB for 6294-34-4, 19186-97-1, and 1047637-37-5 were not used as the basis for TRVs (see Section 6.4).

Our consideration of potential new PODs included additional data evaluation for TCIPP (13674-84-5) and for TDCIPP (13674-87-8). As part of Subtask 1C, we noted that the NTP (2023) Report on TCIPP (13674-84-5) included data on nonneoplastic effects that might be used to derive an updated noncancer TRV. In the present subtask, the potential for deriving a TRV based on these nonneoplastic effects was investigated. Relatively few nonneoplastic effects were statistically different between control and exposed animals. In the two-year study of mice, exposed males had significantly more cytoplasmic alteration of the renal tubules (characterized by loss of cytoplasmic vacuoles) than control mice. These vacuoles are normally present in male but not female mice. However, neither these vacuoles nor their loss is associated with any adverse effect on kidney function, and thus the loss of vacuoles is not considered to be adverse. In the two-year study of rats, both male and female exposed animals had a higher incidence of bile duct hyperplasia than control animals. In the 3-month study of rats, bile duct hyperplasia was accompanied by minimal collagen deposition and inflammation, though no such accompanying changes were noted in the 2-year rat study. Bile duct hyperplasia is a common age-related change in rodents, especially in rats, in which accompanying fibrosis, inflammation, and/or spreading beyond the portal triad indicate increased severity, though these accompanying effects can be quite variable (Boorman et al., 1991; Wagner, 1999; WM et al., 2003). While more severe forms of this change can be adverse, when it is of minimal severity and remains in the portal triads (as was the case in the NTP study of TCIPP), it is of little or no concern to either rodents or human health (Hailey et al., 2014). Thus, the bile duct hyperplasia observed in these rats is also not considered to be adverse. Therefore, the noncancer TRV for TCIPP derived and selected in Subtask 1C (from a margin of exposure assessment identified in Subtask 1A) is retained in the present task.

The other chemical for which a new evaluation of all available data for TRVs and PODs was conducted was TDCIPP (13674-87-8). Because a TRV for TDCIPP was identified in Subtask 1A, it was not further investigated in Subtask 1B, and no additional data were identified in Subtask 1C. This meant that the TRVs identified in Subtask 1A had not yet been evaluated, and so they were evaluated in the context of the current Subtask. The most sensitive TRV for TDCIPP was derived from a LOAEL of 5 mg/kg/d for atrophy of seminal vesicles and other histological effects in testes of rats. This POD was used in MOE approaches by ECHA (2008c) and Health Canada (2016).

Lastly, for the remaining 3 PHOPs (6294-34-4, 19186-97-1, 1047637-37-5), PODs were identified in ToxValDB even though no PODs were identified as part of Task 1. This additional data on these three PHOPs were used to derive TRVs in Section 3.2.1. All 3 of these PODs identified in ToxValDB are sourced from grey literature (ECHA Dossiers or High Production Volume Information System [HPVIS]) that would not have been captured during the DTT literature search and thus were not considered as part of Subtask 1B.

No additional data were identified for cancer endpoints. In Section 3.2.2, we describe refinement of cancer TRVs.

3.2.1. Noncancer TRV Selection

Building on the discussion and selection of the most appropriate TRVs from the Subtask 1C report, and the additional information considered in Section 3.2, the present report considered new potential PODs based on the potential for shared health endpoints across different PHOPs, with the goal of determining empirical/literature-based noncancer PODs in a class-based assessment (Table 2). Note that when Subtask 1C was listed as the Subtask Source in Table 2, this reflects evaluation of various PODs across subtasks to select a “best” TRV. In no case were the tPODs the “best” TRV. The use of shared health endpoints is of importance for class-based assessment based on the assumption that members of the PHOPs subclass should act in a biologically similar manner and thus share similar critical effects. From this analysis of noncancer endpoints, PODs and TRVs were chosen for 7 PHOPs. In order to maintain comparability to published algorithms that derive PODs using machine learning methods (i.e., Chiu

Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024)) and the potential for TRVs to vary depending on the organization deriving them, the remainder of the report is presented as PODs, with TRV data contained in Appendix Table A-4.

Using the process described in Section 3.2, PODs for 5 of the 7 PHOPs in Table 2 were based on developmental effects. The sixth and seventh PHOPs (TDCIPP and TCEP) use PODs of reproductive endpoints instead, since 1) the reproductive endpoint for TDCIPP was more sensitive than developmental effects, and 2) no developmental studies of TCEP were available. The focus on developmental and reproductive endpoints also enables comparison based on similar endpoints with the predicted/surrogate reproductive/developmental PODs from the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024).

During POD selection, the most appropriate value was selected based upon critical effect (i.e., the adverse effect that occurs at the lowest dose identified in the most sensitive species). It is important to note that six of the seven selected PODs are from rat studies, while one (for TCEP) is from a mouse study. Additionally, while transcriptomic PODs (tPODs) were derived in Subtask 1C for TCEP and TCIPP, they were substantially lower than the PODs based on apical endpoints (tPOD = 0.014 mg/kg/d vs BMDL5[HED] = 2.73 mg/kg/d and tPOD = 0.03 mg/kg/d vs LOAEL = 99 mg/kg/d, respectively). These tPODs were based on transcriptomic data from a liver cell line, and liver is not the expected primary target tissue for these chemicals. Thus, after *in vitro* to *in vivo* extrapolation (IVIVE), the tPODs might be expected to be higher than the apical PODs, instead of lower. While the approach for the tPOD is designed to be conservative, that is, to be comparable to or somewhat lower than the *in vivo* POD, the goal is for there to be a maximum of about a 10-fold difference between the tPOD and apical POD. As noted in Subtask 1C, it is not clear why the tPODs were so much lower than the corresponding PODs based on apical endpoints.

To facilitate direct comparisons across chemicals, adjustments were made to the non-NOAEL PODs, resulting in the ‘standardized POD’. Specifically, LOAELs were divided by a factor of 10 as an approximation of a NOAEL, based on the standard uncertainty factor (UF) applied to adjust for a LOAEL in TRV calculations. Since all other data are in rodents, the BMDL5 for TCEP prior to conversion to the human equivalent dose (HED) was chosen as the standardized POD (21 mg/kg/d instead of 2.73 mg/kg/d). Table 2 presents both the original dose and HED to aid in comparison with previous Subtasks.

Table 2. Noncancer Points of Departure (PODs) from Task 1 and Subtask 2B

CASRN	Acronym	POD (mg/kg/d), POD Type; [Standardized POD]	Species, Critical Effect	Subtask Source	Uncertainty Factors Applied[a]	Selected Noncancer TRV (mg/kg/d)	Source
38051-10-4	V6; BCMP-BCEP	29, NOAEL	Rat, Increased number of runts	1A[b] 1B[c]	UFA = 10 UFH = 10	0.3	TNO Quality of Life, 2007, as cited in ECHA, (2008a)
13674-84-5	TCIPP	99, LOAEL [9.9 NOAEL]	Rat, Increased number of runts	1A | 1C | 2B	UFA = 10 UFH = 10 [UFL = 10]	0.1	TNO Quality of Life, 2007, as cited in Health Canada (2016), and ECHA, (2008b)
115-96-8	TCEP	2.73, BMDL5[HED]; [21, BMDL5]	Mouse, Decreased seminiferous tubules	1A | 1C | 2B	UFA = 3 UFH = 10	0.09	Chen et al. (2015), as cited in U.S. EPA, (2023)
13674-87-8	TDCIPP	5, LOAEL [0.5, NOAEL]	Rat, Atrophy of seminal vesicles and histological abnormalities in testes	1A[b] 2B[c]	UFA = 10 UFH = 10 [UFL = 10]	0.005	Stauffer Chemical Company (1981), as cited in ECHA (2008c) and Health Canada (2016)
6294-34-4	N/A	400, NOAEL	Rat, Maternal toxicity in a 14-day developmental study	2B	UFA = 10 UFH = 10	4	HPVIS, as curated in ToxValDB[d]
19186-97-1	TTBNPP	300, NOAEL	Rat, Guideline (not specified) compliant developmental study, specific	2B	UFA = 10 UFH = 10	3	ECHA Dossier, as curated inToxValDB[e]

CASRN	Acronym	POD (mg/kg/d), POD Type; [Standardized POD]	Species, Critical Effect	Subtask Source	Uncertainty Factors Applied[a]	Selected Noncancer TRV (mg/kg/d)	Source
			endpoint not clear				
1047637-37-5	BCMP-BCMEP	97, NOAEL	Rat, Maternal toxicity from a developmental guideline study (TG416)	2B	UFA = 10 UFH = 10	0.97	ECHA Dossier, as curated in ToxValDB[f]

CASRN = CAS registry number; POD = point of departure; TRV = toxicity reference value; NOAEL = no observed adverse effect level; UFA = interspecies uncertainty factor; UFH = intraspecies uncertainty factor; LOAEL = lowest observed adverse effect level; UFL = LOAEL to NOAEL uncertainty factor; BMDL = benchmark dose lower confidence limit; HED = human equivalent dose; N/A = not applicable.

[a] Any uncertainty factor not mentioned is equal to 1.

[b] Data identified from a margin of exposure approach.

[c] Toxicity reference value was calculated.

[d] Direct link to HPVIS, summary via ChemView: https://chemview.epa.gov/chemview/?tf=0&ch=6294-34-4&su=2-5-6-7-37574985-56071369&as=3-10-9-8&ac=1-15-16-6378999&ma=4-11-1981377-4_16848473-4_16848474-4_49007566&gs=&tds=0&tdl=10&tas1=1&tas2=asc&tas3=undefined&tss=&modal=template&modalId=115164&modalSrc=3&modalDetailId=16336695&modalVae=0-0-2-1

[e] Direct link to ECHA Dossier: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/4427/7/9/3

[f] Direct link to ECHA Dossier: https://echa.europa.eu/de/registration-dossier/-/registered-dossier/7660/7/9/3/

3.2.2. Cancer POD Selection

Cancer PODs were based upon relationship to kidney tumors, as this is the most common effect observed among different members of the PHOPs subclass. Additionally, as discussed in depth in the Subtask 2A report, the general scientific consensus that the carcinogenic MOA of TCIPP leading to liver tumors via the constitutive androstane receptor (CAR), pregnane X receptor (PXR), and peroxisome proliferator-activated receptor alpha (PPARα) signaling pathways (NTP, 2023) is not relevant to humans (Felter et al., 2018). Specifically, neither activation of CAR, PXR, or PPARα are linked to tumor development in humans. Conversely, in rodents, the activation of these receptors is linked to tumor formation. Thus, carcinogenic outcomes that are linked to these MOAs are considered irrelevant for human health outcomes. For the uterine tumors observed in the TCIPP bioassay, a qualitative evaluation of "some evidence" would likely result in a categorization as a *possible human carcinogen*, for which cancer quantification is generally not done. Human relevance of uterine tumors was not discussed. Thus, based on questionable human relevance and the level of qualitative evaluation, no cancer quantitation is recommended for TCIPP. Therefore, there are three remaining cancer PODs available from Subtask 1A (Table 3). All three are based on kidney tumors. For TCEP, the U.S. EPA (2023) has determined the mechanism is unlikely to be via genotoxicity but may be from a variety of other changes including those related to cell cycle regulation and cell proliferation. OEHHA (2011) determined that TDCIPP is likely carcinogenic by a genotoxic mechanism, though it notes the exact mechanism is unknown. OEHHA (1992) based their cancer potency value for TDBPP on NCI (1978), which includes some evidence that TDBPP is mutagenic. The TDBPP slope factor reported in Subtask 1A was based on an "expedited" approach by CalEPA/OEHHA. This approach derives cancer potency values for California Proposition 65, by applying an existing literature search, automatically selecting a multistage model, and not making adjustments for pharmacokinetics. Additional assumptions include that the dose-response relationship for the most sensitive species reflects that for humans, interspecies extrapolation can be based on surface area scaling, tissue dose is proportional to administered dose, the multistage model can extrapolate outside experimental dose range, and cancer hazard increases with age to the third power. In order to make the cancer PODs more comparable, benchmark dose modeling of the male rat kidney data from NCI (1978) was conducted for the current task. Based on the best fitting model (log-logistic), a BMDL10 of 0.27 mg/kg/d and a cancer slope factor (CSF) of 0.37 $(mg/kg/d)^{-1}$ was calculated. In the absence of more complete documentation of the CalEPA calculation, it was unclear why this estimate differed by more than a factor of 6 from the CalEPA slope factor.

Table 3. Cancer Points of Departure (PODs) from Task 1 and Subtask 2B

CASRN	Acronym	POD (mg/kg/d), POD type	Species, Critical Effect	Subtask Source	Cancer Slope Factor $(mg/kg/d)^{-1}$	Source
115-96-8	TCEP	17.2, BMDL10	Rat, Kidney tumor (renal tubule adenomas or carcinomas)	1A[a]	0.0245 (human CSF) 0.0058 (rat CSF)	NTP (1991) as cited in U.S. EPA (2023)
13674-84-5	TCIPP	-[b]	Rat, Uterine adenoma or carcinoma	-	-	NTP (2023)
13674-87-8	TDCIPP	6.84, BMDL10	Rat, Renal cortical adenoma	1A 2B[c]	0.015	Stauffer Chemical Co. (1981) as cited in Health Canada (2016)
126-72-7	TDBPP	0.27, BMDL10[c]	Rat, Kidney tumor	1A 2B	2.3[d] 0.37[c]	NCI (1978) as cited in CalEPA/OEHHA (1992)

CASRN = CAS registry number; POD = point of departure; BMDL = benchmark dose lower confidence limit.
[a] Data was identified in Subtask 1A.
[b] Considering the qualitative evaluation of "some evidence of carcinogenicity" (U.S. EPA, 2012); (NTP, 2011) from Subtask 1A and the questionable mode of action relevance discussed in the Subtask 1C report, the quantification performed in Subtask 1B is not considered reliable.
[c] Data was calculated in the current Subtask
[d] Data was calculated by CalEPA/OEHHA.

4. Approach(es) Considered and Selected for Estimating PODs

4.1. Availability and Comparison of LD_{50}s/LC_{50}s/AC_{50}s by QSAR Data vs. Measured Data

One clear candidate for an approach to estimate PODs for chemicals with less or no data is the application of RPFs. This section describes and evaluates available data that could be used to derive RPFs. To address how LD_{50}s compare between different evidence streams, we compared:

(1) rat LD_{50}s captured from ToxValDB,

(2) mouse LD_{50}s from ToxValDB,

(3) zebrafish median lethal concentrations (LC_{50}s) from ToxValDB,

(4) IVIVE converted AC_{50}s for cell viability measurements from ICE,

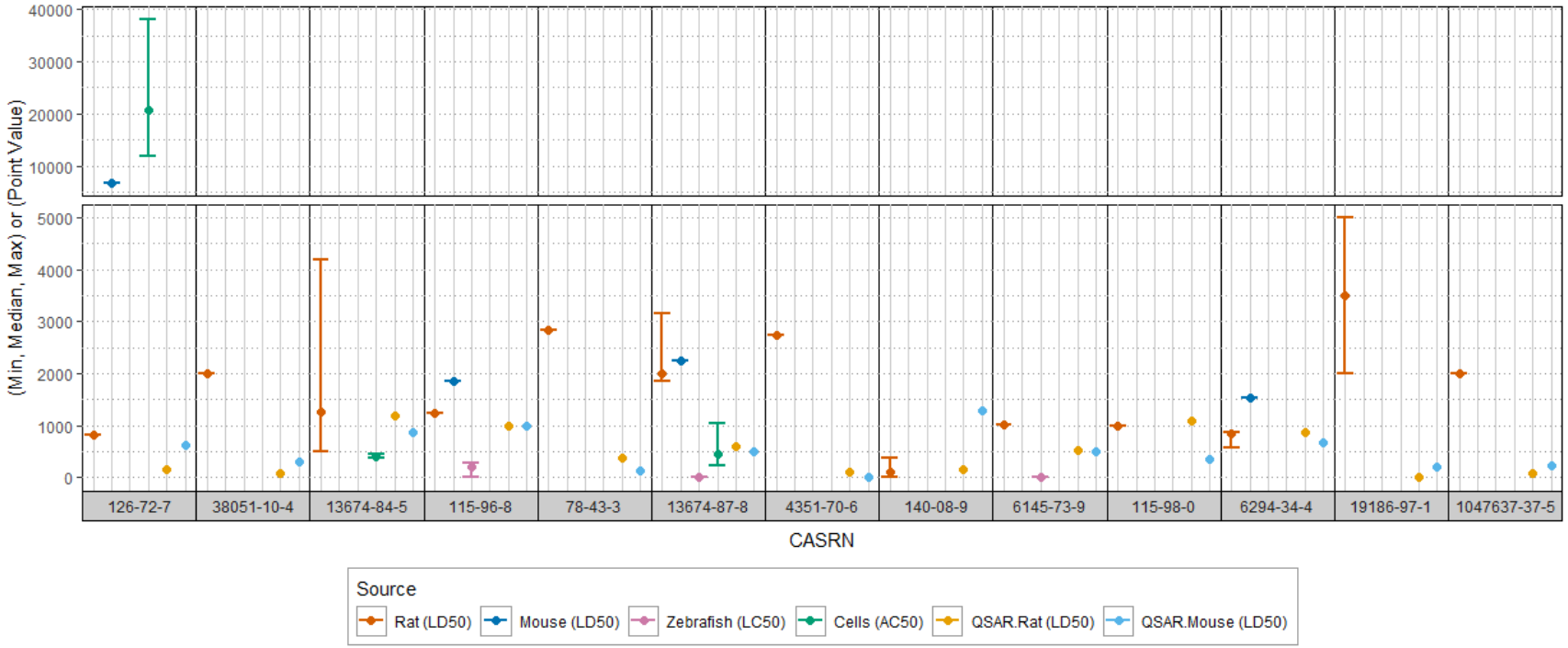
(5) LD_{50} estimates based upon QSAR data in rats, and

(6) LD_{50} estimates based upon QSAR data in mice.

Of the 29 PHOP chemicals, we found that 13 chemicals had experimental measurements that could be used to derive an RPF: 13 chemicals had LD_{50}s from rat data, 4 chemicals had LD_{50}s from mouse data, 3 chemicals had zebrafish LC_{50}s, and 3 chemicals had cell viability AC_{50}s (Appendix Table A-2). A much larger number of chemicals, 26, had QSAR data that was affiliated with a predicted LD_{50}. Importantly, both ToxValDB and ICE had multiple LD_{50}, LC_{50}, or AC_{50} values per chemical corresponding to different assays, while the Danish QSAR Database has only one predicted LD_{50} value for each chemical/species combination. Interestingly, the majority of empirical data exists for a small number of chemicals that already have TRVs with only limited data existing for chemicals that do not have TRVs (Appendix Table A-2).

To understand the concordance of the viability measurements with each other, we compared LD_{50}, LC_{50} (converted using the density of water and units to make comparable to LD_{50}s), and IVIVE converted AC_{50} values to each other. Figure 1 compares the empirical and QSAR-based viability data (including ranges when available) for the 13 chemicals with empirical data. We observed that among measurement systems, there was limited overlap in the values presented. Interestingly, even when just the rat and mouse data were compared, the respective LD_{50}s ranged from having significant overlap to differing by an order of magnitude. Generally, we noted that QSAR LD_{50}s were lower than those measured empirically. Data from mouse oral LD_{50}s, zebrafish LD_{50}s, and cell viability AC_{50}s were too sparse to be useful for deriving RPFs, and so were not analyzed further but are available in Appendix Table A-2. Given the lack of *in vivo* LD_{50} data for mice, the QSAR-based LD_{50} estimates for mice were also not analyzed further and are available in Appendix Table A-2.

Figure 1. Comparison of LD_{50}, LC_{50}, and AC_{50} Values across NAMs and Traditional Test Systems



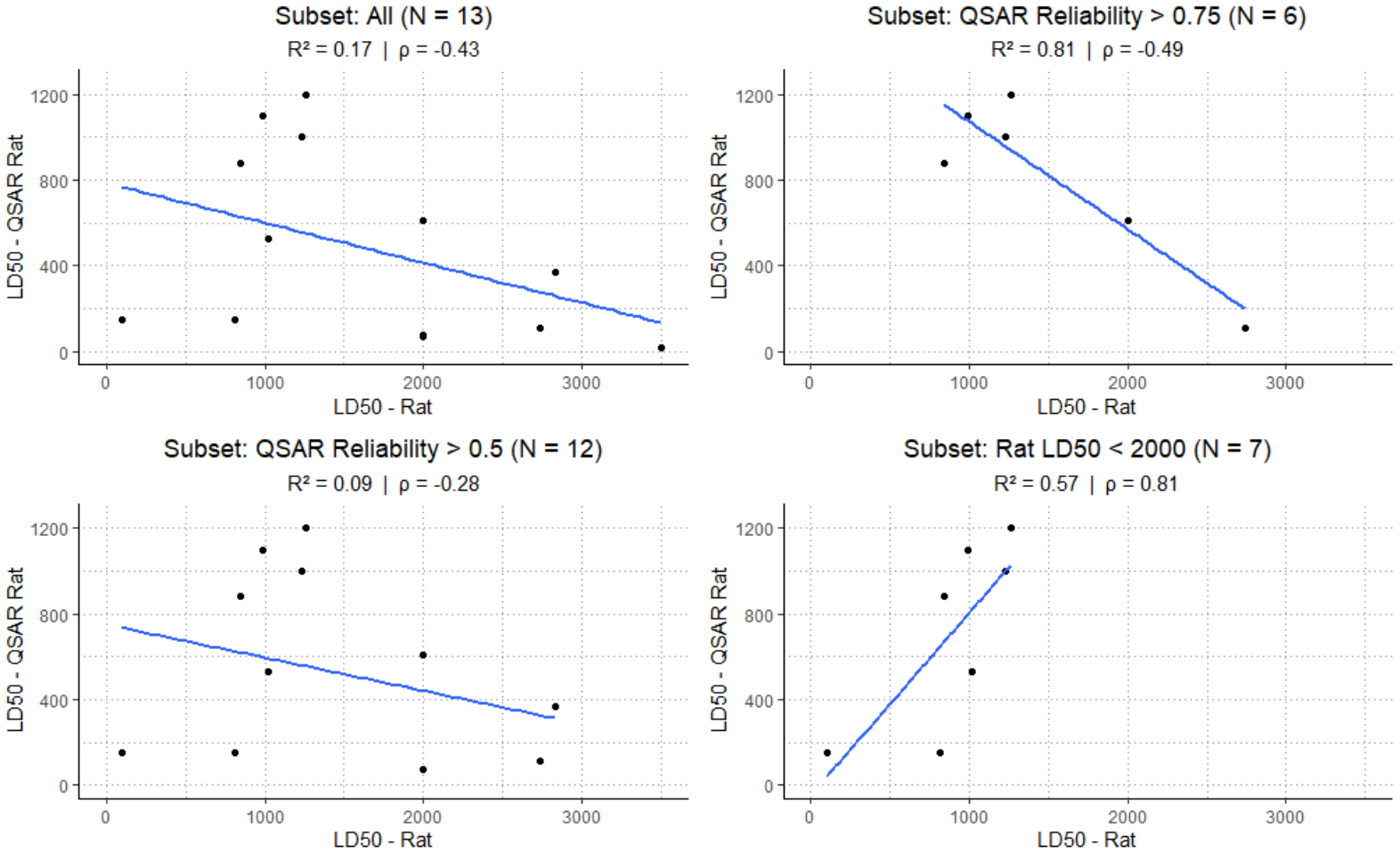
Range displayed are minimum and maximum of LD_{50}, LC_{50}, and AC_{50} values across assessments; median LD_{50}, LC_{50}, and AC_{50} values are presented as a dot. If only one assessment exists, data is presented as a single point.

Next, we sought to examine how concordant LD_{50} QSAR estimates were with LD_{50} measurements taken *in vivo* (Figure 2). To do this, we subset the data to rat LD_{50} data as this represented the largest subsample for which we had data. In this dataset, we found that when we looked at all data together, there was an extremely poor concordance (R^2=0.17, ρ=-0.43) between QSAR data and measured *in vivo* data. Perhaps more importantly, there was a negative correlation, with lower predicted values at high empirical LD_{50}s.

Sensitivity analyses were then conducted in an attempt to improve concordance between the LD_{50} *in vivo* measurements and LD_{50} QSAR estimates. We were able to improve the concordance substantially (R^2=0.81, ρ=-0.49) by using only high-quality QSAR estimates (Danish QSAR quality score $\geq$0.75), but there was still a negative slope. When we added in moderate estimates (Danish QSAR quality score $\geq$0.5), the concordance between measured and estimated values dropped substantially (R^2=0.09, ρ=-0.28), and the slope was still negative. Importantly, while the concordance improved significantly when focusing on only high-quality QSAR LD_{50} estimates, the QSAR data is generally two-fold lower than the measured data. Additionally, the negative correlation is highly problematic in using the QSAR data for predictions.

To determine whether we could provide better concordance with an appropriate direction and magnitude of effect, we subset measured data to those data that fell below the 2,000 mg/kg LD_{50}. An LD_{50} of 2,000 mg/kg was chosen because this is one commonly used cutoff when an LD_{50} is not seen even at the highest administered dose (i.e., an LD_{50} assigned a value of >2000 mg/kg). This provided both an improved correlation (R^2=0.57, ρ=0.81) and corrected the directionality of the relationship. This generally suggests that RPFs based on LD_{50} values that are less than 2,000 mg/kg may lead to better estimates for predicted PODs, and RPFs based on LD_{50} values that are greater than 2,000 mg/kg may not be reliable.

Figure 2. Comparison of *In Vivo* Rat LD_{50} Values to QSAR Predicted Rat LD_{50} Values with Various Sensitivity Analyses



LD_{50} *in vivo* data is on the x-axis, LD_{50} from QSAR is on the y-axis. After looking at all chemicals that had QSAR and $_{\text{in vivo}}$ data, sensitivity analyses were performed including (1) high-quality QSAR LD_{50} predictions (QSAR reliability >0.75), (2) high- and medium-quality QSAR LD_{50} predictions (QSAR reliability >0.5), and (3) measured LD_{50} values below 2,000 mg/kg. Concordance was examined by Pearson correlation (R^2, linear relationship) and Spearman correlation (ρ, monotonic relationship – qualitative rank-order comparison).

4.2. Availability and Comparison of Thyroid Binding Data

QSAR predictions for median inhibitory concentrations (IC_{50}) for thyroid receptor alpha and thyroid receptor beta binding were also identified in the Danish QSAR Database for 26 PHOPs (Appendix Table A-3). Thyroid receptor binding is plausibly related to developmental outcomes selected for the majority of PODs from *in vivo* data, and both thyroid and developmental outcomes have been implicated in earlier phases of the OFR assessment work.

Data availability was the same for both thyroid receptors alpha and beta: 20 PHOPs had predictions from all 3 models included in the database (i.e., CASE Ultra, Leadscope, and SciQSAR), 2 had predictions from only 2 of the models (i.e., CASE Ultra and Leadscope), while the remaining 4 had predictions from only one database (i.e., Leadscope). Importantly, all predictions were out of domain for all models and thus could not be used for derivation of RPFs.

Unfortunately, no quantitative experimental thyroid binding dose-response data were identified for comparison. In the absence of sufficient experimental thyroid data across chemicals and in light of all predictions being out of domain for all models, RPFs derived based on these QSAR-predicted data could not be reliably evaluated for confidence. While the PODs and TRVs based on these are presented in this report they could not be evaluated for correlation with similarly derived *in vivo* data. In contrast to the Danish QSAR Database predictions for LD_{50}s, thyroid receptor binding is predicted according to 3 separate models for each chemical. These estimates generally ranged across four orders of magnitude. In light of the large uncertainties, these data were not included in downstream analyses.

5. Derivation of Quantitative PODs

RPFs were derived for all PHOPs based on the data for cancer and noncancer endpoints separately. RPFs were derived by dividing the LD_{50} (*in vivo* or *in silico*) of the "target" chemical (the chemical for which we are predicting a POD) by the corresponding LD_{50} of the anchor chemical. Note that, using this approach, the interpretation of the RPF is the inverse of typical definitions. Since more toxic chemicals have *lower* LD_{50} values, an RPF <1 means that the chemical is *more* toxic than the anchor chemical. These RPFs were then applied by multiplying the anchor chemical POD by the derived RPF to arrive at a predicted POD for the target chemical. We applied these RPFs to derive PODs for all chemicals. Results for all chemicals can be found in Appendix Table A-4. Sixteen of the PHOPs (5412-25-9, 6749-73-1, 66108-37-0, 33125-86-9, 76025-08-6, 76649-15-5, 5342-12-9, 27568-90-7, 84282-27-9, 53461-82-8, 61090-89-9, 26604-51-3, 34621-99-3, 1067-98-7, 98923-48-9, 72236-72-7) had no empirical data, and so these were not evaluated further -. Three chemicals, 1067-98-7, 98923-48-9, 72236-72-7, did not have QSAR data and so were excluded from any analysis. In the main body of the report, we present data for the *in silico* RPF-POD derivations, *in vivo* RPF-POD derivations, and experimentally derived PODs based on apical effects, so as to focus the discussion on accuracy of these methods.

5.1. RPF Derivation

5.1.1. Noncancer RPF Derivation

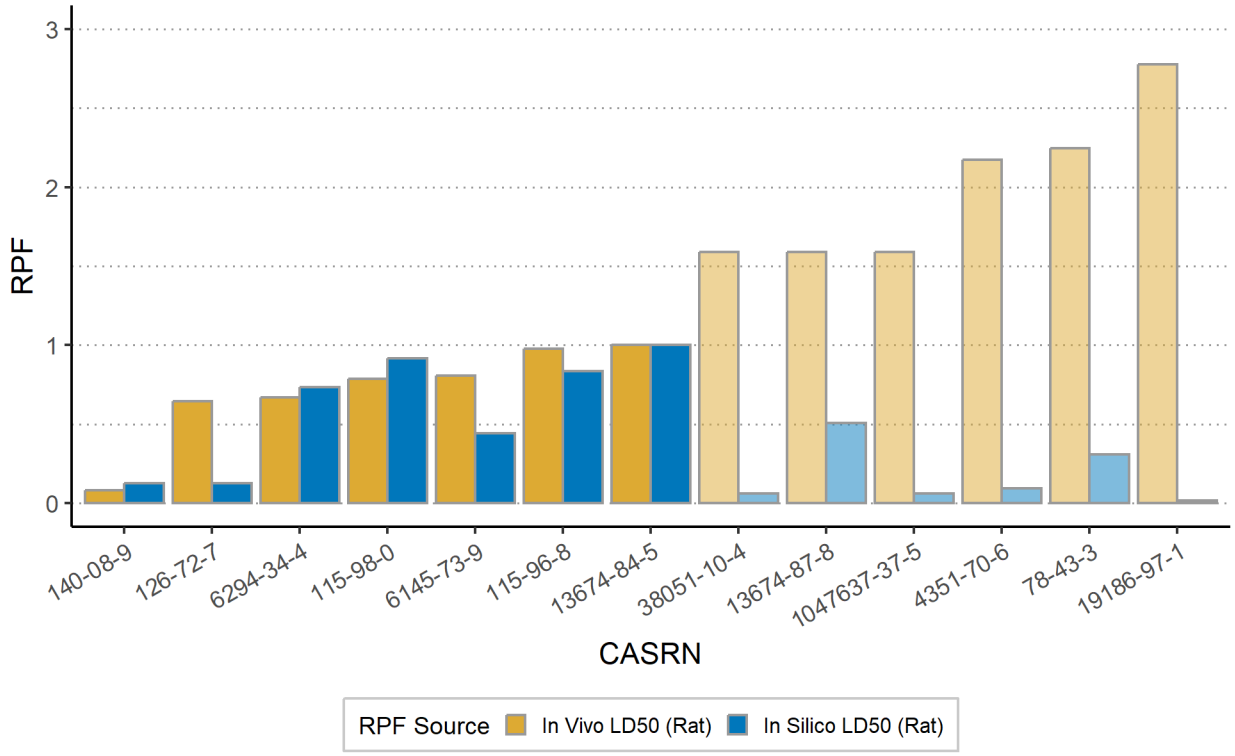
For the RPF approach for noncancer TRVs, TCIPP (13674-84-5) was chosen as the index chemical, because:

1) it has by far the most *in vivo* LD_{50} values (13) and a relatively large number of existing risk assessments,
2) its POD shares a developmental endpoint with most other PHOPs for which experimental data exist to derive a TRV, and
3) its Danish QSAR-predicted rat oral LD_{50} (1,200 mg/kg) is similar to the median *in vivo* rat oral LD_{50} (1,260 mg/kg).

For LD_{50}s from ToxValDB, the median LD_{50} was used to calculate the RPF. LD_{50}s from the Danish QSAR Database were used directly to calculate an RPF since this database provides only a single predicted value for each chemical/species combination. The results are presented in Figure 3.

Generally, we observed that the RPFs were well matched (i.e., the same order of magnitude) for 5 of the non-anchor chemicals with measured LD_{50}s below 2,000 mg/kg. (115-96-8, 126-72-7, 115-96-0, 6145-73-9, and 6294-34-4). One chemical with measured LD_{50} below 2,000 mg/kg, 126-72-7, had a substantial discrepancy between the predicted and measured LD_{50}. However, it should be noted that the more reliable RPFs were less than 1, meaning that the index chemical is the least toxic of this group (highest LD_{50}). The remaining RPFs had at least one order of magnitude difference between predicted and target LD_{50}s. Chemicals with LD_{50}s >2,000 mg/kg are shown in less saturated colors; all had large differences between the RPFs based on the predicted and empirical LD_{50}s, with much larger RPFs for the empirical data.

Figure 3. Relative Potency Factors for Noncancer Endpoints Based on *In Vivo* and QSAR Predicted Rat Oral LD_{50}s



5.1.2. Cancer RPF Derivation

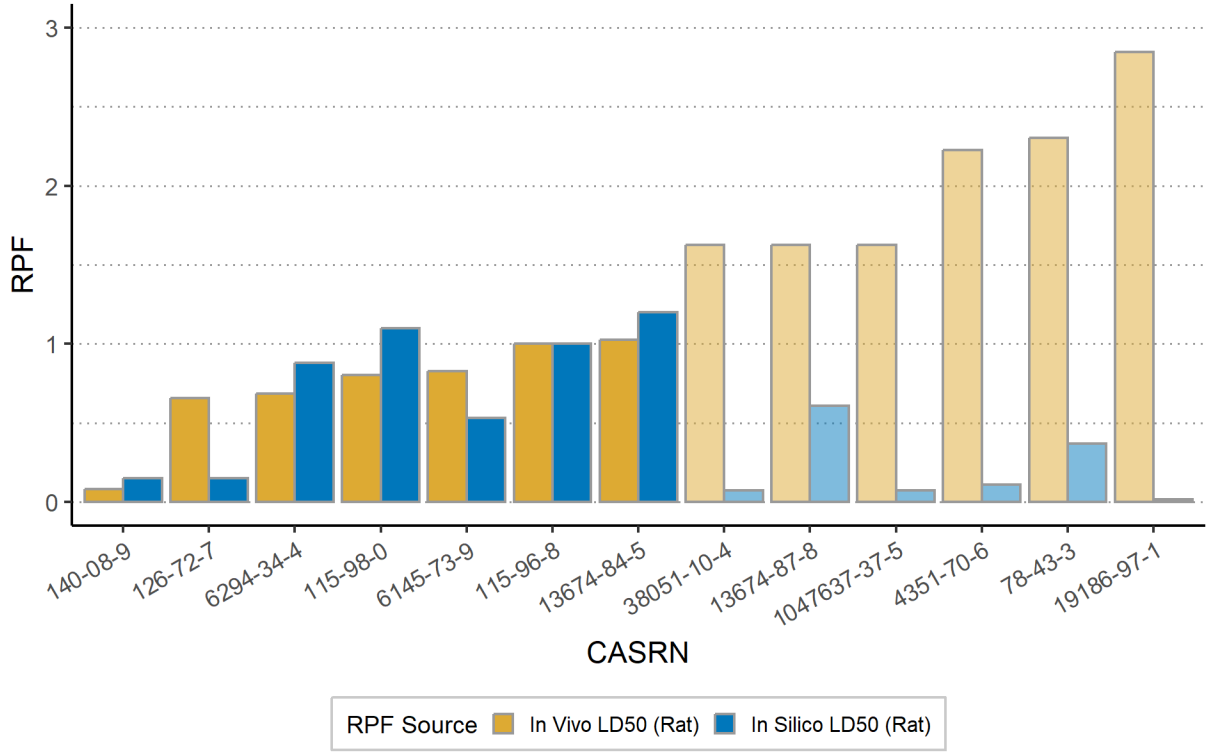
For the RPF approach for cancer TRVs, TCEP (115-96-8) was chosen as the index chemical because:

1) its POD comes from a recent assessment that uses BMD modeling instead of a LOAEL,
2) its POD based on the sole endpoint of kidney tumors in rats is shared with one other PHOP and in combination with other tumors for the third PHOP with *in vivo* data, and
3) its Danish QSAR-predicted rat oral LD_{50} (1,000 mg/kg) is at least somewhat similar to the median *in vivo* rat oral LD_{50} (1,230 mg/kg).

For the other two PHOPs with existing *in vivo* cancer PODs, both have QSAR-predicted LD_{50}s that are more different from their *in vivo* LD_{50}s. Thus, TCEP is the most appropriate index chemical. The results are presented in Figure 4. It is important to note that it is possible that TCEP has a different MOA from the other PHOPs when it comes to carcinogenic effect, so the analysis offered here is more of a "proof of concept" rather than a definitive analysis.

The calculated RPFs were very similar to the calculated noncancer RPFs. This is not surprising, given that the LD_{50} for both anchor chemicals are in the range of 1,000 mg/kg. As with the noncancer RPFs, we observed that the RPFs were well matched (i.e., the same order of magnitude) for five of the of the non-anchor chemicals with measured LD_{50}s below 2,000 mg/kg (140-08-9, 115-98-0, 6145-73-9, 13674-84-5, and 6294-34-4). Of the six non-anchor chemicals that had measured LD_{50}s below 2,000 mg/kg, only 126-72-7 had more variability between the empirical and predicted LD_{50}s. The remaining RPFs were at least one order of magnitude different between predicted and empirical values; chemicals with LD_{50}s >2,000 mg/kg are shown in less saturated colors.

Figure 4. Relative Potency Factors for Cancer Based on *In Vivo* and QSAR Predicted Rat Oral LD_{50}s



5.2. POD Comparison

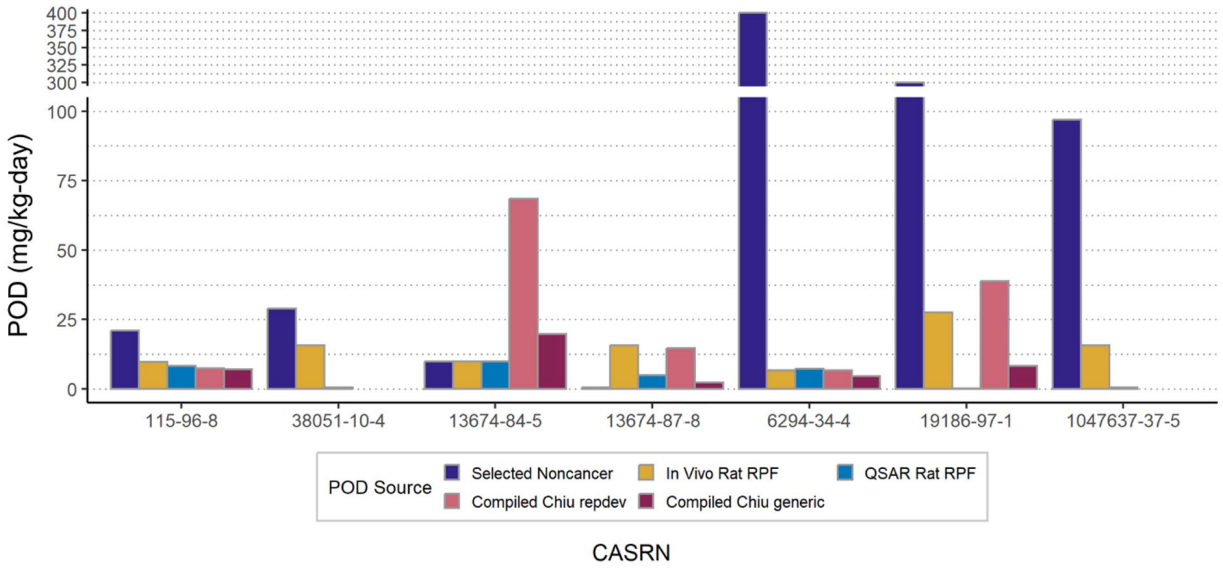
All PODs can be found in Appendix Table A-4. Here, we present the comparison among (1) values that were determined from the literature (selected PODs, Table 2 and 3), (2) values derived based upon RPFs from *in vivo* rat LD_{50} data, (3) values based on RPFs from QSAR rat LD_{50} data, and (4) values from the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024). The data from the Chiu Dashboard are referred to in Figure 5 as "compiled Chiu generic" and "compiled Chiu repdev" as data are from the lab of Dr. Weihsueh Chiu. The generic POD is a POD based on a generic health outcome while the repdev are PODs based upon reproductive and developmental outcomes. These PODs are benchmark doses (BMDs) and were calculated based on a continuous, quantal-deterministic, quantal-stochastic, or multiple conceptual model using probabilistic estimates of the reference dose. Here, we report only the median estimate for the sake of comparison with point estimates made using the RPF method.

5.2.1. Noncancer PODs

Noncancer endpoints were considered for seven chemicals. TCIPP was chosen as the index chemical (13674-84-5) as it has a robust literature base, the POD for it and other chemicals is relatively similar, and the predicted LD_{50} from *in silico* data is similar to the *in vivo* value. Each of these seven chemicals had a POD value that could be used to derive a TRV, either based on authoritative reviews or in ToxValDB based on either a reproductive or developmental endpoint of concern (Table 2). This allowed for comparison among empirically determined PODs, PODs predicted using RPFs derived from *in vivo* and *in silico* data, and those derived using a different methodology.

Predicted PODs from *in vivo* rat RPF data are within one order of magnitude of the selected POD for two of the non-index chemicals (115-96-8 and 38051-10-4), while the difference was much larger for the remaining 4 chemicals (6294-34-4, 19186-97-1, 1047637-37-5, and 13674-87-8) (Table 2, Figure 5). The larger difference for the latter 4 chemicals likely reflects two important sources of uncertainty. First, the selected noncancer PODs for all but 13674-87-8 were substantially higher than the selected noncancer PODs for the other chemicals. Importantly, the PODs for these 3 chemicals (6294-34-4, 19186-97-1, 1047637-37-5) were newly identified during this task from ToxValDB and have not been as completely vetted as the other PODs. Second, as noted in Section 5.1.1, the RPFs for chemicals with empirical LD_{50}s >2,000 mg/kg have lower reliability; this group includes 19186-97-1, 1047637-37-5, and 13674-87-8. For the 2 chemicals (115-96-8 and 38051-10-4) and the anchor chemical (13674-84-5) where there is general agreement between the empirical PODs and the RPF-based PODs, both reproductive and developmental and generic PODs based on the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024) are also roughly comparable.

Figure 5. Comparison of Noncancer Relative Potency Factor Derived Point of Departures and Measured Point of Departures for PHOP Chemicals



When comparing the data to the larger set of 13 chemicals for which *in vivo* rat LD_{50}s are available (Table 4), generally, we see the prior trend holding: PODs for chemicals with LD_{50}s that were less than 2,000 (highlighted in light blue) are within one order of magnitude of each other. Additionally, these values recapitulate the LD_{50}s presented in the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024). Similarly, the anchor chemical TCIPP (13674-84-5), highlighted in dark blue in Table 4, is within an order of magnitude of the Chiu Dashboard PODs. However, for LD_{50}s greater than 2,000 (no shading), *in vivo* rat PODs are generally higher than those predicted by the *in vivo* data. PODs calculated based on the *in vivo* RPFs are also within an order of magnitude to the Chiu Dashboard PODs, but the PODs calculated based on the *in silico* RPFs are generally more than an order of magnitude away from the Chiu Dashboard PODs.

Table 4. *In Vivo* and *In Silico* Noncancer Relative Potency Factor Derived Point of Departures for the 13 PHOP Chemicals with *In Vivo* Rodent LD_{50} Data

CASRN	Acronym	Rat LD_{50}	Standardized POD	POD *in vivo* RPF Rat LD_{50}	POD *in silico* RPF Rat LD_{50}	Chiu Dashboard		
						POD General	POD ReproDev	P or S
13674-84-5	TCIPP	1260	9.9	9.9	9.9	68	20	S
115-96-8	TCEP	1230	21	9.7	8.3	7.3	7.1	P
6294-34-4	N/A	845	400	6.6	7.2	6.8	4.6	P
126-72-7	TDBPP	810	-[a]	6.4	1.2	13	1.3	P
140-08-9	N/A	100	-	0.79	1.2	5.9	5.6	P
6145-73-9	N/A	1017	-	8.0	4.3	16	6.0	P
115-98-0	N/A	990	-	7.8	9.1	6.5	3.7	P

CASRN	Acronym	Rat LD_{50}	Standardized POD	POD *in vivo* RPF Rat LD_{50}	POD *in silico* RPF Rat LD_{50}	Chiu Dashboard		
						POD General	POD ReproDev	P or S
38051-10-4	V6; BCMP-BCEP	2000	29	16	0.61	-	-	-
13674-87-8	TDCIPP	2000	0.5	16	5.0	15	2.4	S
19186-97-1	TTBNPP	3500	300	28	0.15	39	8.3	P
1047637-37-5	BCMP-BCMEP	2000	97	16	0.61	-	-	-
78-43-3	N/A	2830	-	22	3.1	7.7	0.87	P
4351-70-6	N/A	2740	-	22	0.91	-	-	-

CASRN = CAS registry number; LD_{50} = median lethal dose; POD = point of departure; RPF = relative potency factor; P = predicted chemical value based on probabilistic reference dose calculation in the compiled database for either Aurisano et al. (2023) or Kvasnicka et al. (2024); S = surrogate chemical value in the compiled database for either Aurisano et al. (2023) or Kvasnicka et al. (2024); N/A = not applicable.
[a] = Data not available.
Units are all mg/kg/d, except LD_{50}s which are mg/kg.

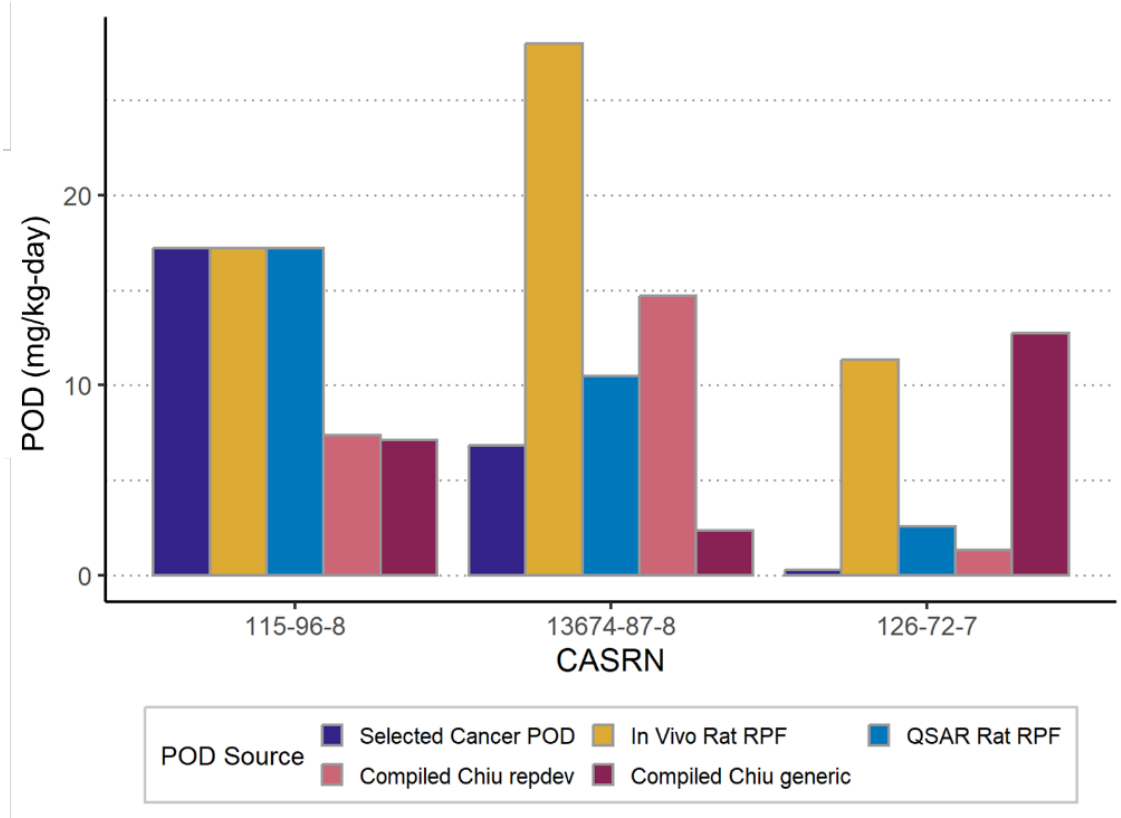
5.2.2. Cancer PODs

Cancer endpoints were considered for three chemicals. TCEP was chosen as the index chemical (115-96-8). It has a POD derived using current best practices, the POD is based upon kidney tumors, which were identified as a sensitive effect, and the LD_{50}s for the *in silico* and *in vivo* determined values are in general agreement.

There is good agreement (i.e., one order of magnitude difference or less) between the predicted PODs, regardless of source, and measured PODs for one of the two non-index chemicals (TDCIPP, 13674-87-8), while there were larger differences for TDBPP (126-72-7) (Table 3, Figure 6). TDBPP had a substantially lower cancer POD than the other subclass members with cancer PODs. The model that was closest to capturing the measured TDBPP POD was the reproductive and developmental POD (i.e., Compiled Chiu repdev) from the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024) and the *in silico* derived RFP-POD. The *in vivo* derived RPF-POD and generic Chiu POD for TDBPP were one order of magnitude higher than the *in silico* RPF-derived PODs.

As noted, this assessment is considered “proof of concept” rather than a definitive evaluation, in light of likely differences in cancer MOA. Based on assessments to date described in Section 3.2.2, the anchor chemical TCEP (115-96-8) is considered unlikely to be acting via a genotoxic MOA (U.S. EPA, 2023), while a genotoxic MOA is considered likely for TDCIPP (Faust & August, 2011) and TDBPP (California Office of Environmental Health Hazard Assessment (OEHHA), 1992; National Cancer Institute, 1978).

Figure 6. Comparison of Cancer Relative Potency Factor Derived Point of Departures and Measured Point of Departures for PHOP Chemicals



Next, PODs were compared across the larger set of 13 chemicals for which *in vivo* rat LD_{50}s are available (Table 5). Generally, we see the prior trend holding: PODs calculated using different methods for chemicals with LD_{50}s that were less than 2,000 (highlighted in light blue) are within one order of magnitude of each other. Additionally, these values roughly recapitulate the PODs presented in the Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024). Similarly, the POD for the anchor chemical TCEP (115-96-8), highlighted in dark blue in Table 5, is within an order of magnitude of the Chiu Dashboard PODs. However, for chemicals with LD_{50}s greater than 2,000 (no shading in Table 5), *in vivo* rat PODs are generally lower than those predicted by the *in vivo* data. Similarly, the Chiu Dashboard PODs are generally higher than the *in silico* derived RPF-PODs but lower than the *in vivo* derived RPF PODs.

Table 5. *In vivo* and *In Silico* Cancer Relative Potency Factor Derived Point of Departures for the 13 PHOP Chemicals with *In Vivo* Rodent LD_{50} Data

CASRN	Acronym	Rat LD_{50}	Standardized POD	POD *in vivo* RPF Rat LD_{50}	POD *in silico* RPF Rat LD_{50}	Chiu Dashboard		
						POD General	POD ReproDev	P or S
13674-84-5	TCIPP	1260	-[a]	18	21	68	20	S
115-96-8	TCEP	1230	17	17	17	7.3	7.1	P
6294-34-4	N/A	845	-	12	15	6.8	4.6	P
126-72-7	TDBPP	810	0.27	11	2.6	13	1.3	P
140-08-9	N/A	100	-	1.4	2.6	5.9	5.6	P

CASRN	Acronym	Rat LD_{50}	Standardized POD	POD *in vivo* RPF Rat LD_{50}	POD *in silico* RPF Rat LD_{50}	Chiu Dashboard		
						POD General	POD ReproDev	P or S
6145-73-9	N/A	1017	-	14	9.1	16	6.0	P
115-98-0	N/A	990	-	14	19	6.5	3.7	P
38051-10-4	V6; BCMP-BCEP	2000	-	28	1.2	-	-	-
13674-87-8	TDCIPP	2000	6.84	28	10.5	15	2.4	S
19186-97-1	TTBNPP	3500	-	49	0.30	39	8.3	P
1047637-37-5	BCMP-BCMEP	2000	-	28	1.3	-	-	-
78-43-3	N/A	2830	-	40	6.4	7.7	0.87	P
4351-70-6	N/A	2740	-	38	1.9	-	-	-

CASRN = CAS registry number; LD_{50} = median lethal dose; POD = point of departure; RPF = relative potency factor; P = predicted chemical value based on probabilistic reference dose calculation in the compiled database for either Aurisano et al. (2023) or Kvasnicka et al. (2024); S = surrogate chemical value in the compiled database for either Aurisano et al. (2023) or Kvasnicka et al. (2024); N/A = not applicable.
[a] = Data not available.
Units are all mg/kg/d, except LD_{50}s which are mg/kg.

6. Additional Considerations

6.1. Threshold of Toxicological Concern (TTC)

Threshold of Toxicological Concern (TTC) is defined as “a level of exposure for all chemicals below which there would be no appreciable risk to human health” (Patlewicz et al., 2008). This concept has not been formally accepted by all US regulatory agencies but is used in Europe (EFSA, n.d.). The primary reason to use this threshold in class-based dose response assessment is that the TTC (or its POD equivalent) can serve as a reasonable lower bound for estimated PODs. Secondarily, in the absence of other empirical or *in silico* bases for estimating PODs, the POD-equivalent of the TTC may be used as a POD for chemicals with little/no data.

All PHOPs considered in the current Subtask were also analyzed in ToxTree (Patlewicz et al., 2008), to identify an appropriate TTC. Under both the original and the revised Cramer rules, all PHOPs were Cramer Class III and are thus assigned a TTC of 1.5 µg/kg/d (0.0015 mg/kg/d) for noncancer effects (EFSA, 2019). In order to compare the TTCs with the values in Table 4 and Table 5, the TTC needed to be converted to an equivalent POD. The TTC is based on the 5th percentile of the Cramer Class III distribution for chronic studies, divided by an UF of 100 (UFA = 10 and UFH = 10). Thus, the corresponding POD is the TTC value multiplied by a factor of 100, which corresponds to a POD of 0.15 mg/kg/d (EFSA Scientific Committee et al., 2019). Generally, PODs above or in the range of the POD-equivalent of the TTC can be considered reasonable estimates. PODs that are notably lower than the POD-equivalent of the TTC would merit additional scrutiny regarding whether this is a reasonable result. Based on this analysis, all 13 noncancer PODs derived by *in vivo* RPFs and 12 of the 13 derived by *in silico* RPFs are above the TTC (Table 4). The exception is the *in silico*-RPF-derived POD for one chemical with an LD_{50} >2,000 mg/kg (TTBNPP, 19186-97-1), which is equal to the TTC. However, the *in vivo* LD_{50} for 19186-97-1 is the highest available (3,500 mg/kg), and thus the chemical is expected to have very low acute toxicity. The prediction of the very low POD (at the TTC) by *in silico* RPF for 19186-97-1 is inconsistent with available empirical evidence. Thus, based upon the available empirical data, all noncancer PODs for the PHOPs are considered reasonable. Further, for the chemicals with an *in vivo*

LD_{50} <2,000 mg/kg (the more reliable RPFs), most of the calculated PODs were at least an order of magnitude above the TTC. Thus, using the TTC as a TRV for the entire class would be overly conservative for many chemicals.

For cancer outcomes, the TTC for DNA reactive or mutagenic carcinogens is 0.0025 µg/kg/d (0.0000025 mg/kg/d). While it is not clear that all these chemicals work through a genotoxic mode of action, this level was considered as an illustration of how genotoxic chemicals might be included in a TTC analysis. In an assessment with greater confidence in the cancer PODs, the genotoxic carcinogens would be compared to this TTC and the nongenotoxic carcinogens would be compared to the TTC for the corresponding noncancer Cramer Class (in the case of PHOPs, Cramer Class III). The cancer TTC is based on a 1 in a million risk level. A corresponding POD (BMDL10) would be 0.25 mg/kg/d. That is, the TTC is multiplied by the response rate for the BMDL (10%) and divided by the target risk of 1 in a million = $0.0000025*0.1/10^{-6}$ = 0.25 mg/kg/d. This is lower than the empirical cancer PODs for TDCIPP (13674-87-8) and TCEP (115-96-8) by at least an order of magnitude, but comparable to the POD for TDBPP (126-72-7) (Table 3). The TTC POD is also 1-2 orders of magnitude lower than most cancer PODs derived by a variety of methods in Table 5. The major exception is 19186-97-1, with a POD of 0.3 mg/kg/d derived from an *in silico* RPF. However, as noted above for noncancer, this chemical has a particularly high *in vivo* LD_{50} (extremely low acute toxicity), and so such a low POD is not considered reasonable. Given the mechanistic differences among chemicals and general uncertainty in the methods used to estimate PODs for cancer endpoints, the usefulness of such comparisons is limited.

6.2. Applying the Most Sensitive POD/TRV Across the PHOP Subclass

One possible approach to a class-based assessment is to apply the most sensitive POD/TRV to all members of the class. However, this approach was not applied for PHOPs because while applying the most sensitive POD across the entire class would be health protective, it does not reflect the full range of high-quality PODs and would likely be overly conservative. Specifically, the existing “standardized” PODs range from 0.5 to 400 mg/kg/d, and the PODs based on the more reliable RPFs (derived from *in vivo* LD_{50}s) range from 0.79 to 9.9 mg/kg/d. For noncancer TRVs, the most sensitive (lowest numerical value) POD derived from *in vivo* data is for TDCIPP (13674-87-8) at 0.5 mg/kg/d for atrophy of seminal vesicles and a variety of histological changes in testes. This value is lower than all PODs predicted by any method in Table 4 except for 19186-97-1, which has a noted lack of confidence in this POD discussed above in Section 6.1. Thus, this approach is not recommended.

6.3. Ranking and Semi-quantitative Approach(es)

A semi-quantitative approach would group chemicals into more and less toxic categories without going to the next step of setting specific quantitative TRVs for data poor chemicals. To apply a semi-quantitative approach, it would first be necessary to establish some level of confidence in the rankings. Given the limited availability of empirical data, high confidence in *in silico* predictions would be needed to apply such an approach. Our analyses in Section 4.1 showed that for all available data, the R^2=0.09, indicating a severe lack of correlation. Thus, at this time, we cannot rely on *in silico* predictions, and chemical ranking is not possible for the whole subclass. As such, we pursued a quantitative analysis approach instead of a qualitative analysis.

6.4. Selecting the Class-based Approach for Deriving TRVs

6.4.1. Noncancer

The proposed approach for deriving TRVs for all PHOPs considers all of the available data, including TRVs, and the RPFs developed using the various approaches described above. The overall goal was to derive health-protective TRVs that reflect both the available data and the level of confidence for each category of chemicals. The general approach is described in Table 6. When relatively higher-confidence data exist (e.g., an existing high quality TRV, or a TRV derived using a higher-confidence RPF), using those TRVs instead would be best. On the other hand, when existing data used to identify PODs or derive

RPFs are themselves of low confidence, the greatest confidence was based on applying a conservative adjustment to the anchor chemical TRV, as described below. Particularly when there is low confidence in TRVs derived using the RPF method, an additional factor may need to be applied to the TRV from the index chemical to be sufficiently protective.

Table 6. Categories for Selecting the Class-based Approach to Derive Noncancer Toxicity Reference Value for PHOP Chemicals

Category Characteristics	TRV Approach	TRV Derivation Basis	Chemicals Included	Confidence
Available high-quality TRV based on published assessment	Use the available TRV	Selected TRVs were determined to have similar/related endpoints	38051-10-4 (V6; BCMP-BCEP), 13674-84-5 (TCIPP), 115-96-8 (TCEP), 13674-87-8 (TDCIPP)	High
TRVs from ToxValDB	Read across from anchor chemical (RPF = 1)	TRVs based on ToxValDB are based on similar/related endpoints but are less conservative than the anchor chemical and have very sparse data. Due to uncertainty that the most sensitive POD was identified, the more conservative approach to read across from the anchor chemical was selected.	6294-34-4, 19186-97-1 (TTBNPP), 1047637-37-5 (BCMP-BCMEP)	Medium
No TRV, empirical rat LD_{50} <2,000	Apply RPF based on *in vivo* rat LD_{50} to anchor chemical	RPF approach using the most confident RPF	126-72-7 (TDBPP), 140-08-9, 6145-73-9, 115-98-0	Low-medium because of uncertainty on how LD_{50} RPF relates to RPF for TRV
No TRV, empirical rat LD_{50} >2,000	Anchor chemical TRV/10	Consistent with the most sensitive chemicals with LD_{50}s <2,000, also generally consistent with Chiu ReproDev	78-43-3, 4351-70-6	Low
No empirical data	Anchor chemical TRV/10	Consistent with the most sensitive chemicals with LD_{50}s <2,000, also generally consistent with Chiu ReproDev	33125-86-9, 76025-08-6, 53461-82-8, 5412-25-9 (DDBPP), 6749-73-1, 66108-37-0, 76649-15-5, 5324-12-9 (BDBPP), 27568-90-7, 84282-27-9, 61090-89-9, 26604-51-3, 34621-99-3	Very low
No QSAR data	Anchor chemical TRV/10	Consistent with the most sensitive chemicals with LD_{50}s <2,000, also generally consistent with Chiu ReproDev	1067-98-7, 98923-48-9, 72236-72-7	Very low

TRV = toxicity reference value; RPF = relative potency factor; POD = point of departure; LD_{50} = median lethal dose; QSAR = quantitative structure-activity relationship.

As shown in Table 6 and Table 7, the first category is for chemicals that have high-quality TRVs, from authoritative assessments either identified or derived in Task 1 of this Call Order. Although this approach may not appear to be strictly class-based, it does reflect the similarity of endpoints across chemicals (all effects in reproductive or developmental studies, including both developmental and maternal effects). Because RPFs are available only for LD_{50} data, not for an endpoint or biomarker related to the apical effects of interest, applying RPFs was considered to introduce too much uncertainty when data exist for apical effects of interest.

The second category is those PHOP chemicals where PODs were identified in ToxValDB. These PODs were all higher than the POD of the index chemical, sometimes substantially higher (from nearly 10 times higher to over 40 times higher). However, the confidence in the PODs (and the resulting TRVs) is reduced because the primary data were available only in ECHA summaries, and these studies have not been rigorously considered in other authoritative assessments. To reflect this uncertainty, the TRV for the index chemical is adopted for this group of chemicals as a health-protective TRV.

The chemicals in the third category do not have any data appropriate for deriving a chemical-specific TRV, but they do have empirical rat LD_{50}s that are <2,000 mg/kg (and hence higher confidence than the LD_{50}s >2,000 mg/kg). For these chemicals, an RPF approach is recommended based on the most reliable RPF. This is the RPF based on the *in vivo* rat LD_{50}. Confidence in these estimated TRVs is low to medium due to uncertainty in how well RPFs based on the LD_{50} reflect RPFs that would be calculated for the apical effect of interest.

Chemicals in the fourth category lack data suitable for deriving a chemical-specific TRV. These chemicals have an empirical LD_{50} but that LD_{50} is >2,000 mg/kg, indicating low acute toxicity (and potentially low chronic toxicity). In contrast to this expected low acute toxicity, as shown in Figure 2, the QSAR-estimated LD_{50}s for these chemicals are often so much lower than the *in vivo* LD_{50}s as to cause a negative correlation between QSAR and *in vivo* LD_{50}s. Thus, our confidence in the QSAR-estimated LD_{50}s for these chemicals was very low. In the absence of a clear reliable basis for an RPF, the TRV for all of these chemicals is estimated as the anchor chemical TRV divided by 10. The factor of 10 was chosen based on the phrase in the RfD definition that the RfD is an estimate with "uncertainty spanning perhaps an order of magnitude." This phrase has been interpreted to mean that the RfD is at the upper end, the lower end, or the middle of the range of an order of magnitude (U.S. EPA, 2002). Based on a desire to express the TRVs relative to the anchor chemical, but be more conservative, a factor of 10 seemed reasonable. This choice is supported by some level of consistency with other empirical data and predictions from the Chiu Dashboard. Within the empirically identified standardized PODs, TCIPP (the anchor chemical) has a NOAEL of approximately 10 mg/kg/d. Dividing this by a factor of 10 results in a value of 1 mg/kg/d, which is slightly higher than but within the range of uncertainty of the lowest standardized POD (TDCIPP at 0.5 mg/kg/d), and clearly lower than any other standardized POD. Further, for chemicals with an LD_{50} <2,000 mg/kg, this factor of 10 covers 5 of the 6 PODs calculated using the RPF based on *in vivo* rat data, with the exception (140-08-9) being within an additional factor of 2. The higher quality *in silico*-based POD predictions are all >1. Some of the lower-confidence *in silico*-based predictions are indeed lower than this, but three of them are within a factor of 2 and one more (the lowest) is in the range of the TTC. In addition, the PODs calculated by this method for this category are in the range of the ReproDev PODs from the Chiu Dashboard. Confidence in the resulting PODs and TRVs is low.

Chemicals in the fifth category lack empirical data but have an estimated LD_{50}. However, as discussed, confidence in the estimated LD_{50}s in the absence of empirical data is very low. Therefore, estimates for these chemicals follow the same approach as for chemicals in the fourth category, but confidence is very low. Values based on this approach are found in Table 7.

The same approach could be applied for chemicals in the sixth category that do not even have estimated QSAR LD_{50}s values, again with very low confidence.

Table 7. Class-based Derived Noncancer Toxicity Reference Values for PHOP Chemicals

CASRN (Acronym, if available)	Confidence	TRV	POD Derivation Method
38051-10-4 (V6; BCMP-BCEP)	High	0.3	Available high-quality TRV
13674-84-5 (TCIPP)	**High**	**0.1**	**Available high-quality TRV (Anchor chemical)**
115-96-8 (TCEP)	High	0.09	Available high-quality TRV
13674-87-8 (TDCIPP)	High	0.005	Available high-quality TRV
6294-34-4	Medium	0.1	Read across from anchor chemical (RPF = 1)
19186-97-1 (TTBNPP)	Medium	0.1	Read across from anchor chemical (RPF = 1)
1047637-37-5 (BCMP-BCMEP)	Medium	0.1	Read across from anchor chemical (RPF = 1)
126-72-7 (TDBPP)	Low-medium	0.06	Apply RPF based on *in vivo* rat LD_{50} to anchor chemical
140-08-9	Low-medium	0.008	Apply RPF based on *in vivo* rat LD_{50} to anchor chemical
6145-73-9	Low-medium	0.08	Apply RPF based on *in vivo* rat LD_{50} to anchor chemical
115-98-0	Low-medium	0.08	Apply RPF based on *in vivo* rat LD_{50} to anchor chemical
78-43-3	Low	0.01	Anchor chemical TRV/10
4351-70-6	Low	0.01	Anchor chemical TRV/10
33125-86-9	Very low	0.01	Anchor chemical TRV/10
76025-08-6	Very low	0.01	Anchor chemical TRV/10
53461-82-8	Very low	0.01	Anchor chemical TRV/10
1067-98-7	Very low	0.01	Anchor chemical TRV/10
5412-25-9 (DDBPP)	Very low	0.01	Anchor chemical TRV/10
6749-73-1	Very low	0.01	Anchor chemical TRV/10
66108-37-0	Very low	0.01	Anchor chemical TRV/10
76649-15-5	Very low	0.01	Anchor chemical TRV/10
5324-12-9 (BDBPP)	Very low	0.01	Anchor chemical TRV/10

CASRN (Acronym, if available)	Confidence	TRV	POD Derivation Method
27568-90-7	Very low	0.01	Anchor chemical TRV/10
84282-27-9	Very low	0.01	Anchor chemical TRV/10
61090-89-9	Very low	0.01	Anchor chemical TRV/10
26604-51-3	Very low	0.01	Anchor chemical TRV/10
34621-99-3	Very low	0.01	Anchor chemical TRV/10
98923-48-9	Very low	0.01	Anchor chemical TRV/10
72236-72-7	Very low	0.01	Anchor chemical TRV/10

6.4.2. Cancer

Theoretically, a similar matrix could be developed for the PHOP cancer assessments. However, as noted, the cancer RPFs developed in this document should be thought of as a proof of concept since the cancer database includes one chemical thought to act via a nongenotoxic MOA, two chemicals thought to act via a genotoxic MOA, and one chemical for which the only high-confidence rodent tumors appear to be induced by a MOA not relevant to humans. This database is not large enough to develop or test any hypotheses on relative potency.

7. Discussion

In this report we compiled existing and newly derived TRVs, along with measured and predicted data for deriving RPFs, to calculate TRVs for as many chemicals in the PHOP class as possible. We were able to identify data covering enough chemicals for *in vivo* rat oral LD_{50}s and QSAR-predicted rat oral LD_{50}s to evaluate the quality of the QSAR predictions. This is in contrast to the situation for *in vitro* data addressed in Subtask 1C, where *in vitro* data were available only for chemicals that already have TRVs. The lack of broader *in vitro* testing is likely because NAMs efforts to date have been largely toward validation rather than developing new data to assess new chemicals. This highlights the need for testing a broader range of chemicals in *in vitro* NAMs models.

Using the available data to derive RPFs highlighted a number of limitations that exist for the RPF approach to POD/TRV derivation. One key challenge for the RPF approach was the limited concordance between measured and predicted data, limiting the confidence in this data for deriving RPF estimates. The directionality of this concordance was appropriate only when the measured LD_{50}s were limited to <2,000 mg/kg. The use of LD_{50}s to derive RPFs is also an uncertainty as this may be based on a different MOA from the critical effect/endpoint of interest, which would result in a different relative potency.

We also considered approaches beyond the RPF approach, including TTC, applying the most sensitive existing TRV to all chemicals in the subclass, and a ranking-based or other semi-quantitative approach. As a point of comparison to the estimated PODs calculated in this report, we also identified available predicted/surrogate PODs from the recently published online Chiu Dashboard (Aurisano et al., 2023; Kvasnicka et al., 2024). Although the results of these endpoint agnostic models were not used as the primary basis for any TRVs, it was noted that the results of the endpoint agnostic repdev model was generally consistent with the final recommended approach for the three chemical categories with the least amount of available data. Endpoint agnostic methods hold promise for being able to evaluate large numbers of chemicals at once, but in the absence of a biological connection, it will be necessary for toxicologists and risk assessors to develop greater familiarity with such models.

Importantly for cancer TRVs, the limited set of available data prevented hypothesis testing and confidence assurance in the estimates. Additionally, the differences in MOAs (i.e., genotoxic vs. non-genotoxic) further prevented confident extrapolation. As such, cancer TRVs were not derived for cancer outcomes.

Overall, the final class-based approach chosen for developing the PHOP TRVs attempted to make maximal use of the available data, taking into account the uncertainties associated with each data stream. The goal is to be health protective to the degree that a health-protective approach could be identified in the absence of further data. It is likely that systematic testing with a selected group of NAMs relevant to the expected MOAs could further enhance the confidence in the calculated TRVs, as well as moving the science forward for class-based assessments of data poor chemicals.

Appendix A.

Table A-1. PHOP Chemicals

CASRN	Chemical Name	Common Acronym
5324-12-9	2,3-Dibromopropylphosphate	BDBPP
1047637-37-5	2,2-Bis(chloromethyl)-1,3-propanediyl tetrakis(1-chloro-2-propanyl) bis(phosphate)	BCMP-BCMEP
1067-98-7	Tris(3-chloropropyl)phosphate	N/A
115-96-8	Tris(2-chloroethyl) phosphate	TCEP
115-98-0	Bis(2-chloroethyl) vinylphosphonate	N/A
126-72-7	Tris(2,3-dibromopropyl) phosphate	TDBPP
13674-84-5	Tris(2-chloroisopropyl)phosphate	TCIPP
13674-87-8	Tris(1,3-dichloro-2-propyl) phosphate	TDCIPP
140-08-9	Tris(2-chloroethyl) phosphite	N/A
19186-97-1	Tris(tribromoneopentyl)phosphate	TTBNPP
26604-51-3	Tris(dichloropropyl) phosphate	N/A
27568-90-7	Ethanol, 2-bromo-, phosphate (3:1)	N/A
33125-86-9	Phosphoric acid, 1,2-ethanediyl tetrakis(2-chloroethyl) ester	N/A
34621-99-3	Tetrakis(1-chloropropan-2-yl) ethane-1,2-diyl bis(phosphate)	N/A
38051-10-4	Phosphoric acid, 2,2-bis(chloromethyl)-1,3-propanediyl tetrakis(2-chloroethyl) ester	V6; BCMP-BCEP
4351-70-6	Phosphonic acid, P-[1-[[(2-chloroethoxy)(2-chloroethyl)phosphinyl]oxy]ethyl]-, 1-[bis(2-chloroethoxy)phosphinyl]ethyl 2-chloroethyl ester	N/A
53461-82-8	Diethylene glycol bis[bis(2-chloroethyl)phosphate]	N/A
5412-25-9	Bis(2,3-dibromopropyl) hydrogen phosphate	DDBPP
61090-89-9	2,4,8,10-Tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[3-bromo-2,2-bis(bromomethyl)propoxy]-, 3,9-dioxide	N/A
6145-73-9	Tris(2-chloropropyl) phosphate	N/A
6294-34-4	Bis(2-chloroethyl) 2-chloroethylphosphonate	N/A
66108-37-0	2,2-Bis(bromomethyl)-3-chloropropyl bis[2-chloro-1-(chloromethyl)ethyl] phosphate	N/A
6749-73-1	Tris(1,3-dichloropropan-2-yl) phosphite	N/A
72236-72-7	Bis(1,3-dichloropropan-2-yl) hydrogen phosphate	N/A
76025-08-6	Bis(2-chloro-1-methylethyl) 2-chloropropyl phosphate	N/A
76649-15-5	(2-Chloro-1-methylethyl) bis(2-chloropropyl) phosphate	N/A
78-43-3	Tris(2,3-dichloropropyl)phosphate	N/A
84282-27-9	2-Bromoethyl 5-bromopentyl 2-chloroethyl phosphate	N/A
98923-48-9	4-Bromo-2-chlorobutyl 3-bromo-2,2-dimethylpropyl phosphate	N/A

N/A = not applicable.
Five chemicals were removed from the PHOP class under CO-1 (2788-11-6, 1373346-90-7, 49690-63-3, 7046-64-2,

35656-01-0).

Table A-2. Data Availability for PHOP Chemicals

CASRN	CompTox Chemicals Dashboard												Integrated Chemical Environment (ICE)				Danish (Q)SAR Database			
	Rat				Mouse				Zebrafish				Cells							
	LD_{50} median	LD_{50} min	LD_{50} max	N	LD_{50} median	LD_{50} min	LD_{50} max	N	LC_{50} median	LC_{50} min	LC_{50} max	N	AC_{50} median	AC_{50} min	AC_{50} max	N	LD_{50}, rat oral (mg/kg)	Reliability index [a], rat	LD_{50}, mouse oral (mg/kg)	Reliability index, mouse
115-96-8	1230	1230	1230	2	1866	1866	1866	1	202	3.74846	285.492	5	-[b]	-	-	-	1000	0.82	1000	0.65
13674-87-8	2000	1850	3160	6	2250	2250	2250	1	3.66271	0.418	7	9	445.3575	233.745	1036.243	30	610	0.86	510	0.67
126-72-7	810	810	810	2	6800	6800	6800	1	-	-	-	-	20654.379	11762.084	38256.745	18	150	0.73	630	0.79
13674-84-5	1260	500	4200	17	-	-	-	-	-	-	-	-	401.395	374.504	455.819	4	1200	0.78	880	0.63
6294-34-4	845	580	880	4	1530	1530	1530	1	-	-	-	-	-	-	-	-	880	0.79	670	0.57
38051-10-4	2000	2000	2000	2	-	-	-	-	-	-	-	-	-	-	-	-	73.36	0.54	300	0.63
19186-97-1	3500	2000	5000	2	-	-	-	-	-	-	-	-	-	-	-	-	-	0.48	220	0.34
1047637-37-5	2000	2000	2000	2	-	-	-	-	-	-	-	-	-	-	-	-	-	0.54	230	0.61
78-43-3	2830	2830	2830	2	-	-	-	-	-	-	-	-	-	-	-	-	-	0.71	130	0.5
4351-70-6	2740	2740	2740	2	-	-	-	-	-	-	-	-	-	-	-	-	-	0.77	5.63	0.08
140-08-9	100	7.5	370	5	-	-	-	-	-	-	-	-	-	-	-	-	-	0.73	1300	0.37
6145-73-9	1017	1017	1017	2	-	-	-	-	13.5	13.5	13.5	1	-	-	-	-	530	0.59	500	0.29
115-98-0	990	990	990	2	-	-	-	-	-	-	-	-	-	-	-	-	1100	0.78	350	0.45
5412-25-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	560	0.71	2000	0.14
6749-73-1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	97.87	0.41	1000	0.48
66108-37-0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	270	0.77	560	0.62

CASRN	CompTox Chemicals Dashboard												Integrated Chemical Environment (ICE)				Danish (Q)SAR Database			
	Rat				Mouse				Zebrafish				Cells							
	LD_{50} median	LD_{50} min	LD_{50} max	N	LD_{50} median	LD_{50} min	LD_{50} max	N	LC_{50} median	LC_{50} min	LC_{50} max	N	AC_{50} median	AC_{50} min	AC_{50} max	N	LD_{50}, rat oral (mg/kg)	Reliability index [a], rat	LD_{50}, mouse oral (mg/kg)	Reliability index, mouse
33125-86-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	120	0.62	280	0.69
76025-08-6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	950	0.62	700	0.52
76649-15-5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	500	0.52	350	0.19
5324-12-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	920	0.57	2400	0.29
27568-90-7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	600	0.69	550	0.49
84282-27-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	250	0.48	250	0.34
53461-82-8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	150	0.64	310	0.7
61090-89-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7.93	0.35	48.39	0.31
26604-51-3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	360	0.31	270	0.46
34621-99-3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	120	0.65	210	0.66
1067-98-7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
98923-48-9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72236-72-7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

CASRN = CAS registry number; LD_{50} = median lethal dose; AC_{50} = median activity concentration.
[a] Reliability index: <0.3 = not a reliable prediction quality; 0.3-0.5 = borderline prediction quality; 0.5-0.75 = moderate prediction quality; >0.75 = high prediction quality.
[b] Data not available.

Table A-3. Thyroid Receptor Data Availability for PHOP Chemicals

CASRN	Abbreviation	IC_{50} (mg/L) Thyroid Receptor Alpha			IC_{50} (mg/L) Thyroid Receptor Beta		
		CASE Ultra[a]	Leadscope	SciQSAR	CASE Ultra	Leadscope	SciQSAR
115-96-8	TCEP	45665.78	3631.71	1248.51	9238.28	42.65	165.57
13674-87-8	TDCIPP	68926.55	3253.24	577.55	13943.98	38.51	3.19
126-72-7	TDBPP	111588.4	2470.24	11003.19	22574.55	44.57	146.63
13674-84-5	TCIPP	52396.72	3021.44	1246.53	10599.96	40.32	243.17
6294-34-4	N/A	43106.49	3186.79	1177.45	8720.53	37.9	255.59
38051-10-4	V6; BCMP-BCEP	93254.23	6588.38	9558.04	18865.52	71.67	12.49
19186-97-1	TTBNPP	-[b]	1203.49	-	-	16.86	-
1047637-37-5	BCMP-BCMEP	102229.4	4131.67	-	20681.21	40.16	-
78-43-3	N/A	68926.55	3253.24	2836.52	13943.98	38.51	22.35
4351-70-6	N/A	97662.62	9843.47	4793.23	19757.34	82.37	17.07
140-08-9	N/A	43106.49	1899.43	11522.39	8720.53	18.57	702.33
6145-73-9	N/A	52396.72	3021.44	436.92	10599.96	40.32	27.1
115-98-0	N/A	37274.5	2874.83	275.49	7540.71	34.98	97.08
5412-25-9	DDBPP	79616.4	5274.39	1793.09	16106.56	112.24	254.1
6749-73-1	N/A	66367.27	1735.58	3540.41	13426.23	17.1	15
66108-37-0	N/A	93143.86	2515.85	410.16	18843.19	31.37	1.05
33125-86-9	N/A	75503.94	8999.53	3190.58	15274.6	82.84	14.66
76025-08-6	N/A	-	3021.44	-	-	40.32	-
76649-15-5	N/A	52396.72	3021.44	-	10599.96	40.32	-
5324-12-9	N/A	-	-	-	-	-	-
27568-90-7	N/A	66997.49	3898.42	2883.09	13553.73	52.91	362.71
84282-27-9	N/A	66618.39	2444.19	13200.61	13477.04	89.95	2906.66
53461-82-8	N/A	82549.99	12005.14	11890.97	16700.03	156.1	23.55
61090-89-9	N/A	139758.2	4039.68	331.57	28273.36	72.4	16.94
26604-51-3	N/A	-	2676.37	-	-	29.99	-

CASRN	Abbreviation	IC_{50} (mg/L) Thyroid Receptor Alpha			IC_{50} (mg/L) Thyroid Receptor Beta		
		CASE Ultra[a]	Leadscope	SciQSAR	CASE Ultra	Leadscope	SciQSAR
34621-99-3	N/A	84477.46	5759.98	1633.58	17089.96	64.75	10.62
1067-98-7	N/A	-	-	-	-	-	-
98923-48-9	N/A	-	-	-	-	-	-
72236-72-7	N/A	-	-	-	-	-	-

CASRN = CAS registry number; IC_{50} = median inhibitory concentration; N/A = not applicable.
[a] CASE Ultra, Leadscope, and SciQSAR are three separate models that provide IC_{50} QSAR predictions for thyroid receptor alpha and thyroid receptor beta from the Danish QSAR Database.
[a] Data not available.

Table A-4. Relative Potency Factors and Point of Departures for PHOP Chemicals Based on oral LD_{50}s from *In Vivo* and QSAR-predicted Data

CASRN	Non-Cancer								Cancer							Chiu Dashboard		
	Rodent LD_{50}	POD[a]	RPF *in vivo* LD_{50} (rodent)	RPF *in silico* LD_{50} (rodent)	POD *in vivo* RPF Rat LD_{50}	POD *in silico* RPF Rat LD_{50}	TRV *in vivo* RPF Rat LD_{50}	TRV *in silico* RPF Rat LD_{50}	POD[a]	RPF *in vivo* LD_{50} (rodent)	RPF *in silico* LD_{50} (rodent)	POD *in vivo* RPF Rat LD_{50}	POD *in silico* RPF Rat LD_{50}	CSF *in vivo* RPF Rat LD_{50}	CSF *in silico* RPF Rat LD_{50}	POD General	POD ReproDev	P or S
13674-84-5	1260	9.9	1	1	9.9	9.9	0.10	0.099	-[b]	1.0	1.2	18	21	0.0057	0.0048	68	20	S
115-96-8	1230	21	0.98	0.83	9.7	8.25	0.097	0.083	17.2	1	1	17	17	0.0059	0.0058	7.3	7.1	P
6294-34-4	845	400	0.67	0.73	6.6	7.26	0.066	0.073	-	0.69	0.88	12	15	0.0085	0.0066	6.8	4.6	P
126-72-7	810	-	0.64	0.125	6.4	1.2375	0.064	0.012	0.27	0.66	0.15	11	2.6	0.0088	0.039	13	1.3	P
140-08-9	100	-	0.079	0.125	0.79	1.2375	0.0079	0.012	-	0.081	0.15	1.4	2.6	0.072	0.039	5.9	5.6	P
6145-73-9	1017	-	0.81	0.44	8.0	4.4	0.080	0.044	-	0.83	0.53	14	9.1	0.0070	0.011	16	6.0	P
115-98-0	990	-	0.79	0.92	7.8	9.1	0.078	0.091	-	0.80	1.1	14	19	0.0072	0.0053	6.5	3.7	P
38051-10-4	2000	29	1.6	0.061	16	0.61	0.16	0.0061	-	1.6	0.073	28	1.3	0.0036	0.079	-	-	-
13674-87-8	2000	0.5	1.6	0.51	16	5.0	0.16	0.050	6.84	1.6	0.61	28	10	0.0036	0.0095	15	2.3	S
19186-97-1	3500	300	2.8	0.015	28	0.15	0.28	0.0015	-	2.8	0.018	49	0.30	0.0020	0.33	39	8.3	P
1047637-37-5	2000	97	1.6	0.062	16	0.62	0.16	0.0062	-	1.6	0.075	28	1.3	0.0036	0.078	-	-	-
78-43-3	2830	-	2.2	0.31	22	3.1	0.22	0.031	-	2.3	0.37	40	6.4	0.0025	0.016	7.7	0.87	P
4351-70-6	2740	-	2.2	0.092	22	0.91	0.21	0.0091	-	2.2	0.11	38	1.9	0.0026	0.053	-	-	-
33125-86-9	-	-	-	0.1	-	0.99	-	0.0099	-	-	0.12	-	2.064	-	0.048	12	4.0	P

CASRN	Non-Cancer								Cancer							Chiu Dashboard		
	Rodent LD_{50}	POD[a]	RPF *in vivo* LD_{50} (rodent)	RPF *in silico* LD_{50} (rodent)	POD *in vivo* RPF Rat LD_{50}	POD *in silico* RPF Rat LD_{50}	TRV *in vivo* RPF Rat LD_{50}	TRV *in silico* RPF Rat LD_{50}	POD[a]	RPF *in vivo* LD_{50} (rodent)	RPF *in silico* LD_{50} (rodent)	POD *in vivo* RPF Rat LD_{50}	POD *in silico* RPF Rat LD_{50}	CSF *in vivo* RPF Rat LD_{50}	CSF *in silico* RPF Rat LD_{50}	POD General	POD ReproDev	P or S
76025-08-6	-	-	-	0.79	-	7.8	-	0.0784	-	-	0.95	-	16.34	-	0.0061	15	7.6	P
53461-82-8	-	-	-	0.13	-	1.2	-	0.0124	-	-	0.15	-	2.58	-	0.039	15	2.6	P
1067-98-7	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	14	6.5	P
5412-25-9	-	-	-	0.47	-	4.62	-	0.046	-	-	0.56	-	9.6	-	0.010	-	-	-
6749-73-1	-	-	-	0.082	-	0.8074275	-	0.0081	-	-	0.09787	-	1.7	-	0.059	-	-	-
66108-37-0	-	-	-	0.23	-	2.2275	-	0.022	-	-	0.27	-	4.6	-	0.022	-	-	-
76649-15-5	-	-	-	0.42	-	4.125	-	0.041	-	-	0.5	-	8.6	-	0.012	-	-	-
5324-12-9	-	-	-	0.77	-	7.59	-	0.076	-	-	0.92	-	16	-	0.0063	-	-	-
27568-90-7	-	-	-	0.5	-	4.95	-	0.050	-	-	0.6	-	10	-	0.0097	-	-	-
84282-27-9	-	-	-	0.21	-	2.0625	-	0.021	-	-	0.25	-	4.3	-	0.023	-	-	-
61090-89-9	-	-	-	0.0066	-	0.0654225	-	0.0007	-	-	0.00793	-	0.14	-	0.73	-	-	-
26604-51-3	-	-	-	0.3	-	2.97	-	0.030	-	-	0.36	-	6.2	-	0.016	-	-	-
34621-99-3	-	-	-	0.1	-	0.99	-	0.0099	-	-	0.12	-	2.1	-	0.048	-	-	-
98923-48-9	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-
72236-72-7	-	-	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-

CASRN = CAS registry number; LD_{50} = median lethal dose; POD = point of departure; RPF = relative potency factor; TRV = toxicity reference value; CSF = cancer slope factor; P = predicted chemical value based on probabilistic reference dose calculation in the compiled database for either Aurisano et al. (2023) or Kvasnicka

et al. (2024); S = surrogate chemical value in the compiled database for either Aurisano et al. (2023) or Kvasnicka et al. (2024).
[a] Point of departure is standardized.
[b] Data not available.
Units are all mg/kg/d, except LD_{50}s which are mg/kg

Appendix B. Glossary

Definitions were adapted from the EPA Terminology Services Website.

Adverse Outcome Pathway: Model that identifies the sequence or molecular and cellular events required to produce a toxic effect when an organism is exposed to a substance.

Dose Response Assessment: A determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response. Response can be expressed as measured or observed incidence or change in level of response, percent response in groups of subjects (or populations), or the probability of occurrence or change in level of response within a population.

Hazard Characterization: A description of the potential adverse health effects attributable to a specific environmental agent, the mechanisms by which agents exert their toxic effects, and the associated dose, route, duration, and timing of exposure.

Lethal Dose 50: The dose of a chemical taken by mouth or absorbed by the skin which is expected to cause death in 50% of the test animals so treated.

Mode of Action: Understanding how chemicals perturb normal biological function; the key steps in the toxic response after chemical interaction at the target site that is responsible for the physiological outcome or pathology of the chemical.

Point of Departure: The dose-response point that marks the beginning of a low-dose extrapolation. This point can be a BMDL (the lower bound on dose for an estimated incidence or a change in response level from a dose-response model), or a NOAEL or LOAEL for an observed incidence or change in level of response.

Relative Potency Factor: The ratio of the toxic potency of a given chemical to that of an index chemical in the chemical class. Relative potency factors are used to convert exposures of all chemicals in the chemical class into their exposure equivalents of the index chemical.

Toxicity Reference Value: An estimate of an exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a BMDL, a NOAEL, a LOAEL, or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. Reference value is a term proposed in the report, "A Review of the Reference Dose and Reference Concentration Processes" (U.S. Environmental Protection Agency (U.S. EPA), 2002), and is a generic term not specific to a given route of exposure.

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