Evaluating the relative responsiveness of health endpoints to exposure to polychlorinated biphenyl (PCB) mixtures in mammalian model systems

United States Environmental Protection Agency

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Overview

Background: Polychlorinated biphenyls (PCBs) are a group of chemicals found in the environment as mixtures of individual congeners. Despite an expansive literature documenting the potential for adverse health effects from exposure to these mixtures, the relative sensitivity of various health endpoints (e.g., endocrine, developmental, respiratory) to PCB exposure, especially at low, environmentally relevant levels, remains unclear.

Methods: We used systematic review methods to compile dose-response information for noncancer health endpoints across a range of PCB mixtures, as reported in animal toxicology studies. However, these studies report effects by administered dose. Given the lipophilicity and biopersistence of PCBs, internal tissue levels continually increase with repeated dosing. We explored the effect of estimating internal tissue levels for studies administering Aroclor 1254 (most data-rich mixture), employing pharmacokinetic (PK) models that account for bioaccumulation.

Results: We identified 554 studies evaluating noncancer health endpoints in animal models and found that the relative responsiveness of specific health endpoints, based on the minimum lowest-observed-adverse-effect level (LOAEL), depends, to some extent, on the dose metrics considered.

Conclusions: Because many studies observed effects at the lowest dose tested, without no-observed-adverse-effect levels (NOAELs) our ability to assess whether there are true differences in endpoint responsiveness is limited.

Literature Search & Data Extraction

PECO Statement

Population
Nonhuman mammalian animal species exposed during any life stage. Studies including evaluations of transgenic animals only were considered "Potentially Relevant Supplemental Material."

Exposure
One or more oral, inhalation, dermal, or injected treatment(s) with any clearly quantified dosage of complex PCB mixtures administered to a whole animal (in vivo). Studies in which mammals were exposed only to individual PCB congeners or to mixtures comprising fewer than four congeners were considered "Potentially Relevant Supplemental Material".

Comparator
A concurrent control group exposed to vehicle-only treatment or untreated control.

Outcome
Any examination of survival, body weight, or development, or of the structure or function of dermatologic, cardiovascular, endocrine, gastrointestinal, hematopoietic, hepatic, immune, nervous, ocular, musculoskeletal, renal, respiratory or reproductive cells, tissues or systems. Endpoints such as observations of cellular structure, gene expression, cell signaling, or other similar biochemical measures are considered "Potentially Relevant Supplemental Material."

Literature Search
PubMed, Web of Science, and Toxline searched for references published through August 2016
Unique records identified = 52,127
Records prioritized for screening (natural language processing and machine learning) = 12,995

Title and Abstract Screening
Records included = TBD

Full-text Review
Records included = TBD

Literature Inventory
Literature inventories for included studies were created to develop summary-level, sortable lists that include basic study design information (e.g., species, PCB mixture(s) evaluated, doses administered, endpoints examined)
Records included = 554

Complete Data Extraction
Due to data availability and toxicological relevance, analysis focused on studies in rats, mice, and monkeys and mixtures tested in >1 study
Extracted parameters: complete study design information and NOAEL or LOAEL values
Records included = 542

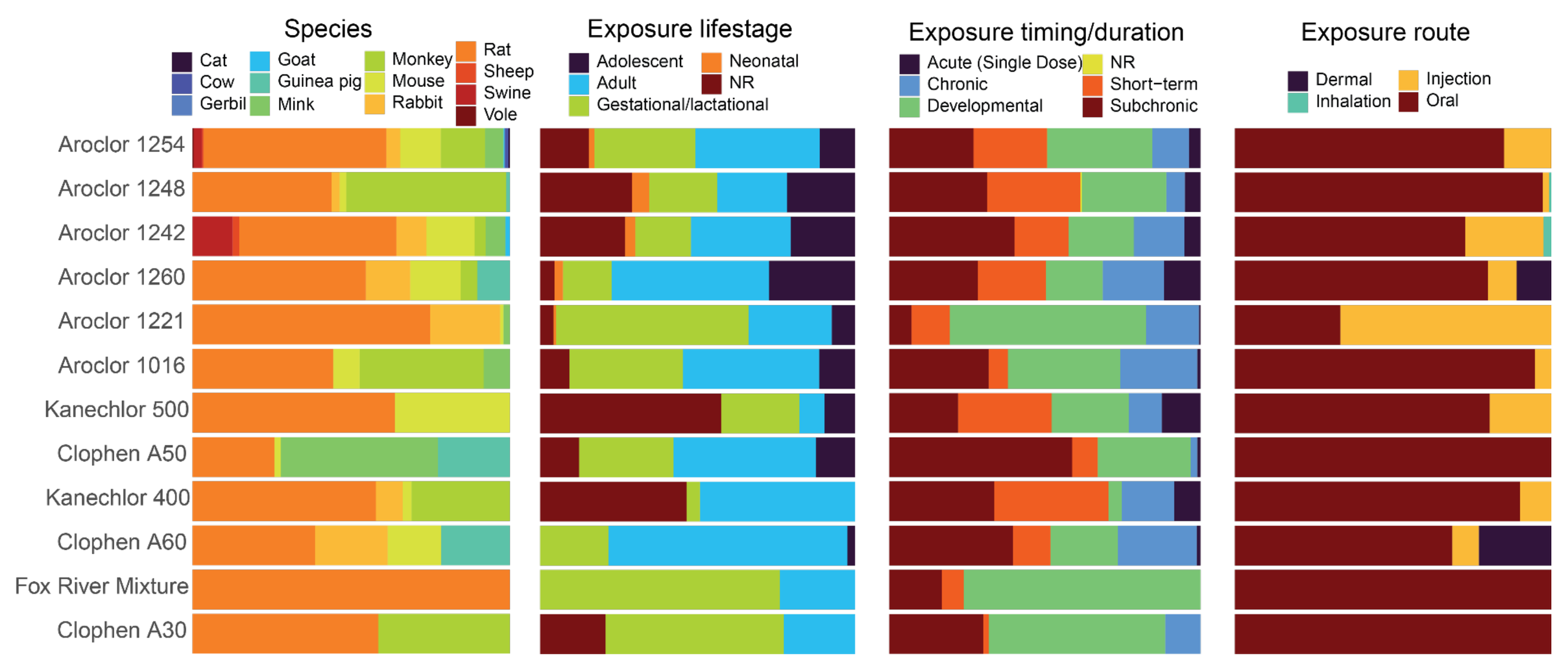
Figure 1. Literature screening and data extraction flow diagram.

Over 75% of all identified studies are for Aroclor 1254

	Unique studies	Hepato-biliary	Repro-ductive	Endocrine	Develop-mental	Immune System	Nervous System	Urinary System	Metabolic	Gastro-intestinal	Respir-atory	Hemato-poietic	Cardio-vascular	Dermal	Musculo-skeletal	Ocular
Aroclor 1254	290	150	114	95	85	63	80	55	37	28	24	21	26	20	15	9
Aroclor 1248	60	49	9	8	9	19	12	11	6	10	5	12	5	10	1	8
Aroclor 1242	57	37	23	24	13	24	8	12	9	8	9	10	7	4	2	3
Aroclor 1260	35	22	9	12	5	12	8	8	10	8	5	4	4	6	2	
Aroclor 1221	27	6	18	12	13	3	9	3	1	1	1	2	2		2	
Clophen A50	23	14	12	4	11	3	1	3	1		1	2	1	1		
Aroclor 1016	22	5	7	3	7	4	10	1	2			3		4	1	
Kanechlor 500	20	14	2	5	4	7	3	2	2		1	1	2	2		
Kanechlor 400	16	10		3	1	5		2	2	2	4	1	1	5		3
Fox River Mixture	12	6	7	3	8	6	10									
Clophen A60	11	6	8	3	4	3	4	3	2	1	2	1	1	1	1	
Phenochlor DP6	7	7	1	1		1		1	1	1	1	1	1	1	1	
Clophen A30	6	4	5	1	3	2	4	3	1	2	2		2		1	1

Figure 2. Number of publications in our database for PCB mixtures of known composition with ≥ 6 unique studies (showing 13 of 41 total mixtures).

Exposure Designs Across Select Mixtures



Most identified studies are oral exposures in rats

Figure 3. Study design features shown by proportion of total for select PCB mixtures.

Inhalation of PCB contaminated air represents a significant exposure route – the lack of inhalation study designs is an important data gap

Studies with effects observed at the lowest dose (no NOAEL) make it difficult to assess potential differences in the relative responsiveness of health endpoints across mixtures

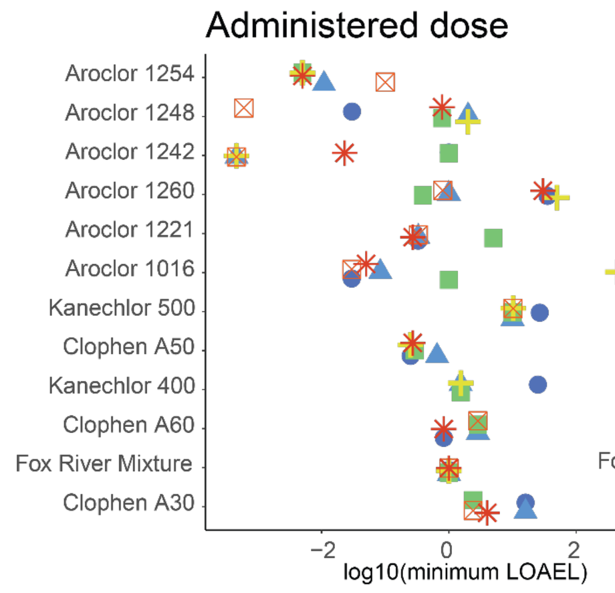


Figure 4. Comparison across select PCB mixtures for the minimum administered LOAEL (mg/kg-d) for six endpoint categories.

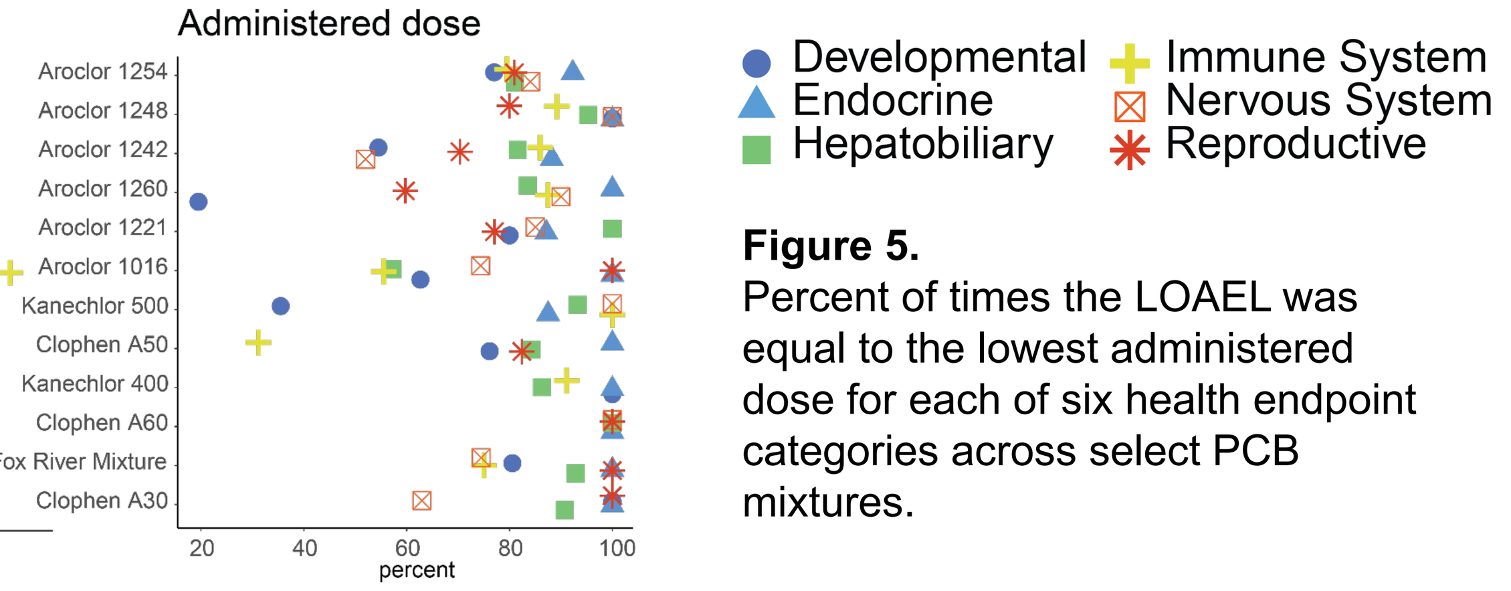


Figure 5. Percent of times the LOAEL was equal to the lowest administered dose for each of six health endpoint categories across select PCB mixtures.

Pharmacokinetic Modeling for Aroclor 1254

Internal tissue levels of PCBs may be more relevant for understanding potential exposure-response relationships compared with administered dose. Because tissue levels are highly dependent on study design features, we used the PK model described by Kapraun et al. (2022)* and a comparable PK model for non-pregnant adult animals, applied to monkey, mouse, and rat studies, to evaluate the effect of dose metric on the relative responsiveness of health endpoints for Aroclor 1254. We included all LOAELs, including those reported as food concentrations. Use of the model allowed us to translate the various dosing types, dose levels, and dosing regimens reported in each study into a common measure of internal dose (i.e., the average whole-body concentration of PCBs). Finally, the model allowed calculation of human equivalent doses (HEDs) by selecting model parameters that correspond to continuous exposure in humans. *Kapraun, Dustin F., et al. "A Generic Pharmacokinetic Model for Quantifying Mother-to-Offspring Transfer of Lipophilic Persistent Environmental Chemicals." *Toxicological Sciences* 189.2 (2022): 155-174. https://doi.org/10.1093/toxsci/kfac084

Accounting for study design can shift common assumptions about species sensitivity and exposure timing/duration

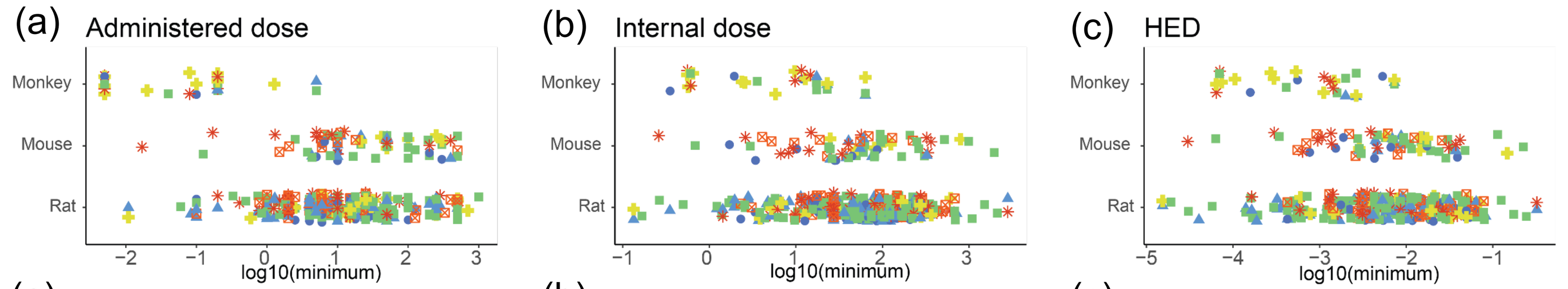


Figure 6. Effects of PK modeling on study level minimum LOAELs by species for (a) administered dose, (b) internal dose, and (c) human equivalent dose (HED).

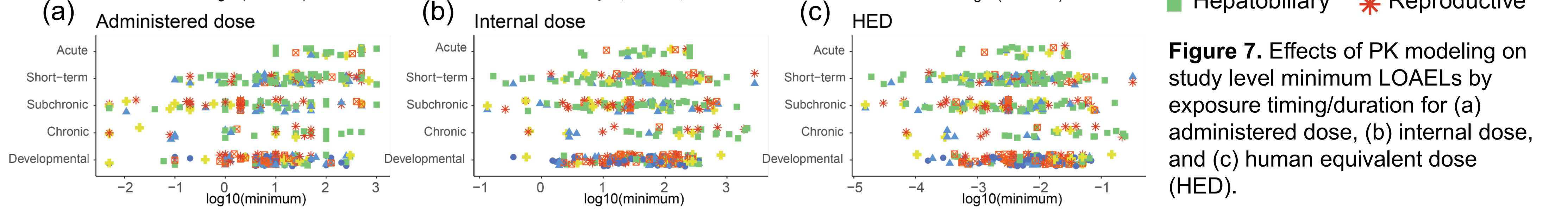


Figure 7. Effects of PK modeling on study level minimum LOAELs by exposure timing/duration for (a) administered dose, (b) internal dose, and (c) human equivalent dose (HED).

Aroclor 1254 Health Endpoint Responsiveness

PK modeling shifts the relative responsiveness ranking for health endpoint categories

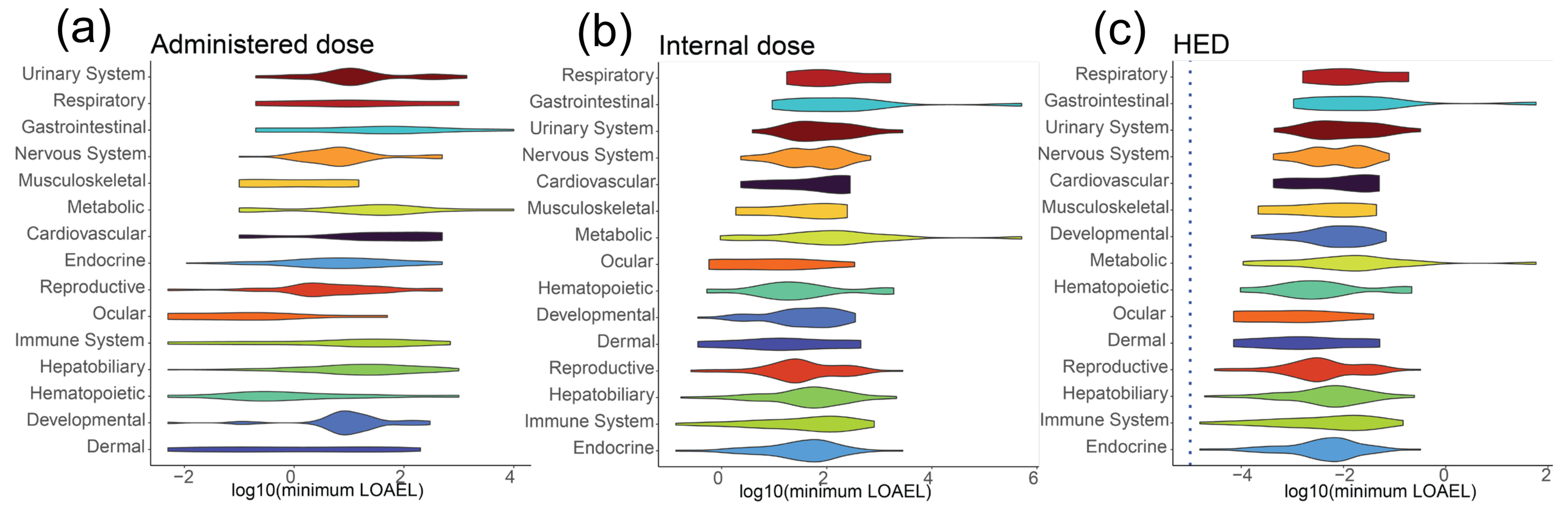


Figure 8. Responsiveness of health endpoint categories based on minimum LOAELs within each study for (a) administered dose, (b) internal dose, and (c) human equivalent dose (HED). Dashed line represents estimate of background human exposure levels (Weitekamp et al. 2021, 10.1016/j.scitotenv.2021.145912).

Benchmark dose modeling and/or lower dose studies might improve detection of potential differences in the responsiveness of health endpoints

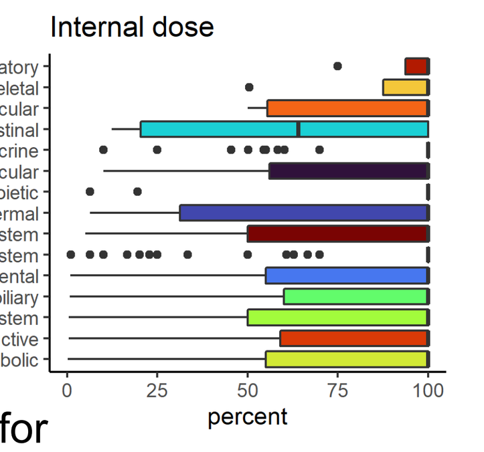


Figure 9. Boxplot showing percent of LOAELs at lowest tested dose in Figure 8. 100% indicates absence of NOAELs. Points are outliers.

Sensitivity of specific endpoints likely varies – comparisons between categories can depend on the relative sensitivity of the endpoints most frequently measured

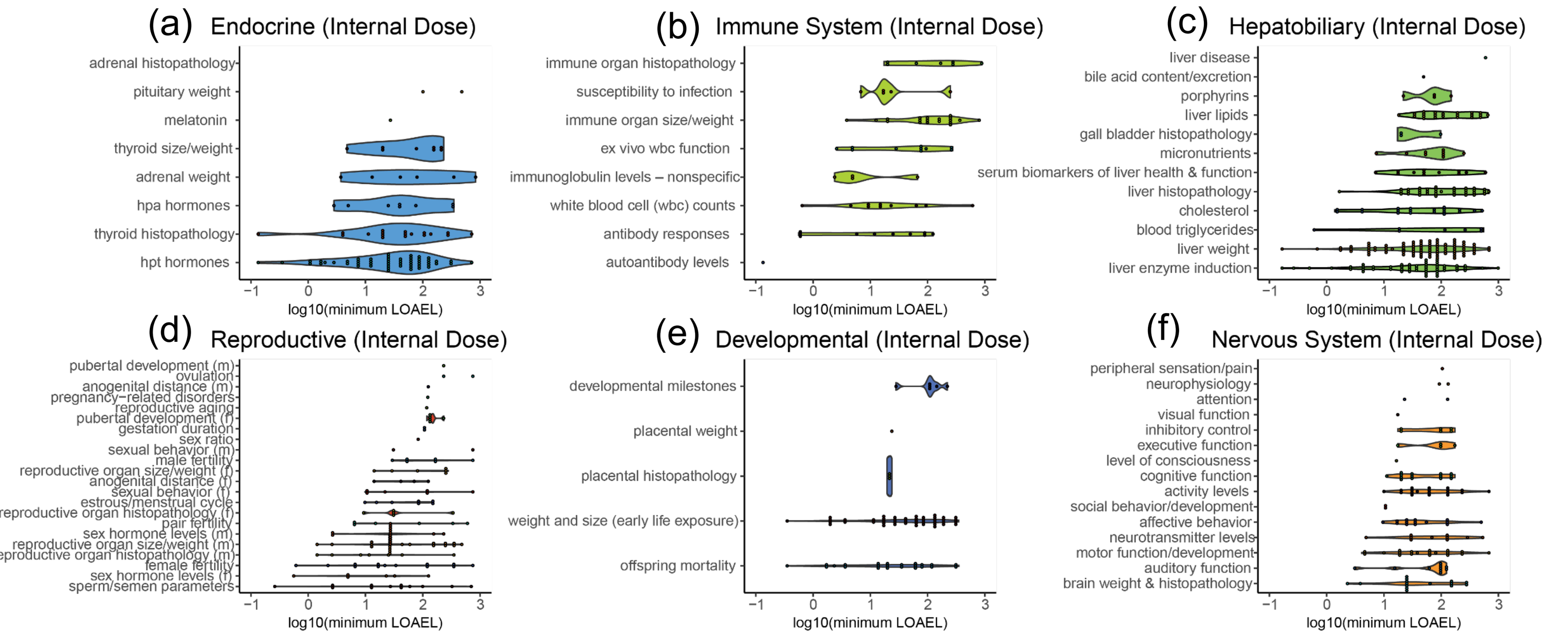


Figure 10. Responsiveness of specific endpoints based on minimum internal dose LOAELs within each study for (a) endocrine, (b) immune, (c) hepatobiliary, (d) reproductive, (e) developmental, and (f) nervous system endpoints. Points are study-level data.

Within study comparisons can illustrate consistent differences in endpoint sensitivity

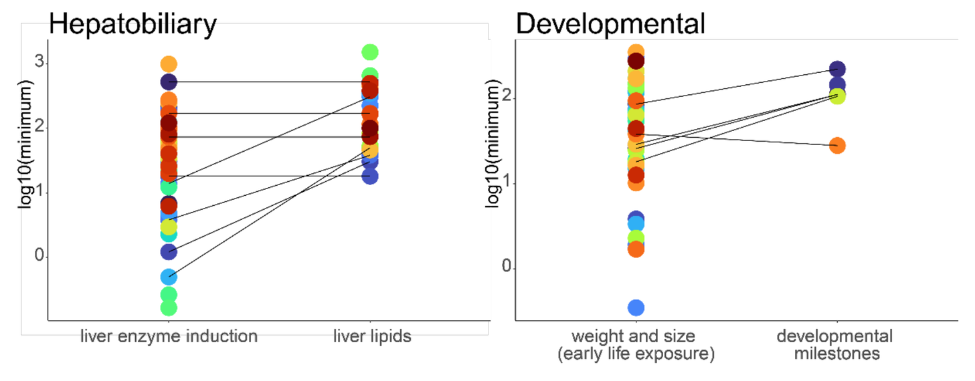


Figure 11. Responsiveness of select endpoints within (a) hepatobiliary and (b) developmental endpoint categories. Lines indicate endpoints measured within the same study.

Conclusions

- PCB exposures and noncancer health endpoints have been well-studied, particularly relative to other pollutants assessed for human health risk. Even with this relatively large database, there are limitations that make it challenging to assess differences in responsiveness between health endpoints or between PCB mixtures:
  - Many instances where the lowest administered dose is equal to the LOAEL (i.e., absence of within-study NOAELs)
  - Specific endpoints within each health endpoint category may vary in sensitivity and are not consistently measured between studies
- Commercial PCB mixtures are composed of 100-140 of the 209 PCB congeners. Because congeners can have different mechanisms of action, these mixtures may result in effects at similar dose levels across multiple endpoint categories.
- To protect public health, human health risk assessments aim to prioritize for evaluation the most sensitive health endpoints. Our study demonstrates the inherent challenges in this task for large and complex datasets.